Facts and problems of rabies / by A.M. Stimson.

TREASURY DEPARTMENT
Public Health and Marine-Hospital Service of the United States

HYGIENIC LABORATORY.—BULLETIN NO. 65

JUNE, 1910

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United States Public Health and Marine-Hospital Service.

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FACTS AND PROBLEMS OF RABIES.[a]

By A. M. Stimson,

Passed Assistant Surgeon, United States Public Health and Marine-Hospital Service, Washington, D. C.[b]

INTRODUCTION.

There has existed since ancient times a disease which, on account of its peculiar method of transmission, its unusually long period of incubation or latency after exposure, the violent and terrifying symptoms, the extreme suffering endured by its victims, and its uniformly fatal termination, has come, in spite of its comparative rarity, to be widely known to the general public and to be extensively investigated by scientists. At the same time there has been handed down from the ages when superstition and ignorance had as yet received but little counterbalancing check from the influence of reasonable or scientific investigation, a mass of erroneous belief which, in its extent and fantastic distortions, probably exceeds that to which any other malady has fallen heir.

Nomenclature.—This disease has been given various names indicating some real or fancied feature of prominence. These names may be classified as follows:

Language.	Meaning madness.	Indicating canine association.	Meaning fear of water.
Greek	λυσσα, λυττα	κύων-λυσσας	ὑδροφοβία.
Latin	Rabies, furor	Rabies canina	Aquifuga, horror aquæ.
French	Rage		
German	Wuth, Tollwuth, Lyssa.	Hundswuth	Wasserscheu.
English	Rabies, madness	Canine madness	Hydrophobia.
Italian	Rabbia		Idrofobia.
Spanish	Rabia		
Hollandish		Hondsdolheid	

Other names have been suggested, but little used. The Latin "rabies" would seem to be the best general term for the disease in both man and animals.

[a] Submitted for publication May 18, 1910.

[b] Dr. Walter D. Cannon assisted in the work of translation and preparation of the bibliography, and the author desires to make grateful acknowledgment of his help.

Importance.—Compared with the great scourges from which man has suffered, such as tuberculosis, smallpox, plague, cholera, and yellow fever, rabies has played a very small part in the mortality of the human race; but it has annually claimed a number of victims, it has caused much suffering and anxiety in those exposed persons who have feared its onset, and it has entailed a very significant monetary loss from the death of valuable domesticated animals. If this disease were among those for which the most intelligently directed and efficiently executed measures of suppression which man can devise have proved thus far of little avail, it would be of less relative importance than even its comparative incidence would indicate. But since it has been demonstrated that, by comparatively simple measures, the disease can be reduced to a minimum or even wholly eradicated, it is raised to an importance disproportionately great to the frequency of its occurrence compared with that of less remediable maladies. The continued existence, not to say increase, of rabies in animals and man is a reproach upon the efficiency of organized medical bodies for the suppression of disease.

Study of rabies.—The fact that rabies is a well-defined entity as a disease has led to its extensive investigation from the standpoint of a purely scientific interest, as well as from that of preventive and curative medicine. And the great extent to which it has been studied is indicated by the fact that several thousands of articles on various phases of the subject have been collected from the archives of medical literature.

The literature upon the subject can, of course, be found in the Index Catalogue of the Surgeon-General's Library and the Index Medicus, but excellent bibliographies covering the most important publications will be found in the following: Högyes (49), E. Marx (69), Marie (68), Heller (45).

The Surgeon-General of the United States Public Health and Marine-Hospital Service frequently receives inquiries concerning rabies, which it is hoped may for the most part be answered in this publication.

There still remain persons who are skeptical concerning, or even deny the existence of, rabies as a distinct disease. No attempt will be made to enter into controversy with them. If they are fair-minded and possess an average amount of intelligence, a visit to a laboratory where scientific work in this direction is being done will suffice to dispel their objections even if their faith in human nature is so slight that they are able to regard those investigators who have devoted years of disinterested study to the subject as untruthful or very badly mistaken.

A BRIEF DESCRIPTION OF THE SALIENT FEATURES OF RABIES.

Before taking up in detail the study of the phenomena of rabies it is well to review briefly the salient features which combine to distinguish it.

Rabies is an ancient and widespread disorder perpetuated among the lower animals, chiefly the dog family, transmitted in nature to other animals and to man by the inoculation of virulent saliva through bites. It is undoubtedly caused by a living microorganism, as yet not positively identified, which invades the nervous system, rendering it virulent and inducing the symptoms. The period of incubation is variable, but relatively long, usually between one and two months. The symptoms are referable to excitation and finally depression of the central nervous system by the microorganism or its products, with ultimate destruction of its functionating power. A general increase of reflex excitability is early noted. The centers for respiration and deglutition are especially severely attacked, with spasm or paralysis as a result. General convulsions of central origin frequently occur, paralysis of spinal origin may attack the extremities. The psychical functions are disturbed in degrees varying in their manifestations from morbid anxiety to delirium and mania. Pathological changes of a characteristic nature are confined principally to the nervous system. The disease is essentially the same in all of the many species of animals that are susceptible. Protection is afforded by inoculation with attenuated rabies virus and to some extent by antirabic serum and, so far as known, by no other means. The blood serum of immunized persons and animals possesses specific properties against rabies virus. Once developed, the disease is almost uniformly fatal. No other disease presents these characters in combination.

HISTORY OF RABIES.

No detailed discussion of this phase of the subject is intended here. The references cited are well known and inserted merely to illustrate the ancient existence and recognition of the disease.

The earliest reference to rabies is said to be that of Aristotle in the fourth century, B. C., or possibly Democritus in the fifth century. Hippocrates, who preceded Aristotle by about a half century, is said to have made no mention of the disease. It is natural, however, that in those days of very crude methods of diagnosis, the disease was confused with other nervous affections and that because of its long period of incubation, its outbreak in man was not connected with injuries received from animals. Other ancient writers mention it, but the first extended description was given by Celsus in the first century, A. D. Cælius Aurelianus and Galen in the second century gave very good descriptions.

Cælius Aurelianus, in his description of hydrophobia in man, makes mention of the following symptoms, which are sufficiently distinctive to show that he was familiar with the same disease which we recognize to-day:

In the beginning of the attack, anxiety with no reason for it, irritability and malaise, restless movements, sleep light and disturbed, insomnia, stretching and continual gaping, and an unremitting desire to vomit, an unusual susceptibility to air, no matter how quietly the patient may have been resting, intoleration and loathing of liquids, little desire to drink. When the disease is established, there is thirst and at the same time dread of water, at first at the sight of it, later of the very sound or mention of it. This fear extends to oily preparations. The pulse is small, hard, and irregular; in certain cases there is a light fever. There are eructations; heaviness of the limbs. The diaphragm is displaced upward and the functions of the intestines suppressed. Urination becomes frequent and of small amounts. There is nervous spasm and trembling. The voice is hoarse like the bark of a dog; breathing is difficult, the body drawn up. Generalized convulsions are occasioned by the entry of persons for fear that they may be bringing water. The face and eyes are congested, the body emaciated. Pallor and sweating of the upper parts. Frequent erections and seminal emissions. The tongue is protruded, there is hiccough, bilious vomiting, frequently black, fear of drink, the hands being held before the eyes on the approach of the drinking vessel, etc.

The Arabian physicians and philosophers transmit, without significant additions, the opinions of their predecessors. The middle ages contribute nothing to our knowledge of the disease. The disease appears again in the medical writings of the fifteenth, sixteenth, and seventeenth centuries, although in the interval in other literature indisputable references were made to it. That a paralytic form occurs in man appears to have been first recognized by van Swieten (114) in 1771. Experiments on the virulence of the saliva were first successfully carried out by Zinke, 1804, on dogs and other animals, and he also showed the destructive action of phosphorus and arsenious acid on the virus.

Gruner, 1813, recommended inoculation of test animals with the saliva of suspected dogs to establish the diagnosis.

Count de Salm-Reifersheid, 1813, made numerous successful inoculations. The first actual demonstration of the identity of the disease in man and animals is accredited to Magendie and Breschet (63), who transmitted it from man to dogs through the saliva. This important demonstration is reported in a footnote, but is clear in detail.

Following Hertwig, in 1829, very many observers have conducted experiments under various conditions, which demonstrated the disease to be an infection as we now understand it, transmitted by the saliva of rabid animals through bites.

It remained for Pasteur to devise the method of subdural inoculation of material from the central nervous system, and from him the modern study of the disease may be said to date.

The importance of this means of inoculation is appreciated on reading an article like that, for instance, of Bollinger, 1875, characterized throughout by good sense, who says that inoculation (i. e., subcutaneous) would be of little value in diagnosis and only so in positive cases. Subdural inoculation is, however, very certain and remains the only reliable means of settling the diagnosis beyond doubt. A perusal of some of the literature on rabies of the period before the infectious nature of many diseases had become known, puts us in a position to understand how the mistaken hypotheses originated in the attempt to explain the paradoxical features of the disease. These questions are, to a large extent, explained by the assumption of specific infection by a living micro-organism.

The history of rabies, as shown by its literature, is extremely instructive, as showing how much and how little was known in past ages. For instance, in Krügelstein's work in 1826 we learn that the following observations had already been made, some of them centuries before: That long-haired dogs had rabies less frequently than short-haired ones, an observation easily explained by the mechanical removal of the infectious saliva by the hair; that young dogs were susceptible, a fact which has since been doubted, but is now well established; that the saliva of dogs may be virulent before the symptoms have appeared; that the fear of water is rarely observed in rabid animals; that rabid dogs are frequently more playful at first; that mad dogs are not necessarily wild eyed, nor do they always froth at the mouth or carry the tail between the legs.

Among the superstitious and erroneous beliefs anciently entertained, and in some regions reverenced to the present day, may be mentioned that of Avicenna that the little figures of dogs, in reality blood clots, passed in the urine of a hydrophobia patient after the administration of cantharides, were the cause of rabies and that their elimination in this manner would result in a cure.

The belief that the removal of the "mad worm," which proves to be a normal cartilage in the tongue, would prevent dogs from taking rabies, was honored by an edict from Frederick the Great providing for the carrying out of the measure. The same medical authority paid a large sum for the secret of a cure for rabies, which turned out to be an emulsion of "may worms" in honey.

A popular means of diagnosis at one period consisted of stripping the feathers from the breast of a living fowl and applying the denuded area to the wound. If the dog was rabid, the fowl would die; but if the fowl remained well, no anxiety need be felt.

The modern "mad stone," still believed in and patronized in portions of the United States, is composed, according to White (118), chiefly of tricalcium-phosphate. "Mad stones" are usually calculi obtained from various portions of the alimentary tract of the lower

animals. Superstition holds that they adhere to poisoned wounds (dog bites, snake bites, etc.) and remove the virus, which is evidenced by the discoloration produced when the stone is subsequently boiled in milk. The belief in these " stones " is a positive danger, since they possess none of the powers attributed to them, and their employment to the exclusion of scientific means of protection has been the cause of many deaths (Brawner).

The spontaneous origin of rabies in the dog was held in some quarters up to comparatively recent years and is still a popular belief, and various causes now disproved were assigned for it, for example: Deprivation of animal food in dogs accustomed to meat diet, ungratified sexual instinct in male dogs, sudden suppression of lactation in female dogs, extremes of temperature, especially heat, eating of putrified materials, or drinking foul water.

The chief stumbling block seems to have been this belief in spontaneous origin, which held in check experimental observations and discouraged the institution of preventive measures. The demonstration that rabies is an infectious disease, dependent for its outbreak on preceding infection, has opened up an inexhaustible field for experimental research and rendered possible those preventive measures which are effective if properly carried out.

The criticism has been made of general articles upon rabies that they exhibit a great similarity, one critic claiming that the informaton contained in them had its common source in van Swieten's commentaries on the writings of Boerhaeve. It is evident that true writings on any subject must resemble each other to a certain extent, and it is hoped that sufficient original observation by modern workers will be reported in these pages to dispel any suspicion that present-day writers are beholden to past centuries for the bulk of their information.

A perspective view of the history of rabies may be gained from the following: Rougemont (108), Krügelstein (56), Faber (29), Marx, K. F. H. (70), Fleming (34), Högyes (48), Marx, E. (69), Bollinger (14).

GEOGRAPHICAL DISTRIBUTION AND PREVALENCE.

The general statement may be made that there is no portion of the globe where man and other terrestrial mammals can live which is not potentially capable of harboring rabies. Climatic influences never operate directly to the extinction of the disease, once it has appeared. Rabies is relatively rare in sparsely settled districts unless rabid wild animals are prevalent, as, for instance, in parts of Russia, where the disease occurs among wolves to a considerable extent. The great continents all harbor rabies to a greater or less extent. It seems to be nearly stationary in some places, in others decreasing, and in some increasing. Increasing density of popula-

tion, human and canine, of an infected region results in an increase in the prevalence of rabies unless rigid measures for its check are carried out.

Rabies occurs from Greenland to the Philippine Islands, where Dudley (28) reports 158 deaths in man collected by him. The disease as it occurs in the Arctic seems not to correspond exactly with that observed elsewhere and deserves special study. Colan (22) refers to it, and interesting descriptions are given by Nansen in "Farthest North." Rabies was formerly believed not to exist in Constantinople, where the dog population is very large, but Remlinger has dispelled this belief. It is, however, relatively rare there when the dog population is considered, which is explained by the great prevalence of the paralytic type.

Australia is said to be free from the disease by Bruce and Loir (17), who ascribe this condition to the peculiar fauna and the rigid quarantine on dogs which has been practiced for many years.

There seems little doubt that different strains of virus have various degrees of pathogenicity, which may explain local differences in the disease.

Rabies in America.—Rabies was observed on this continent early in the latter half of the eighteenth century. Accounts appear in the lay press as early as 1768. It appears to have occurred first in the Northern Atlantic States, but to have spread southward within a few years. Attempts have been made from time to time to secure data approaching exactness as to its prevalence in the United States, but in the past and present condition of mortality statistics in this country no accurate results can be obtained. If this is true of man, it is still more so of the lower animals. The positive results at hand, however, indicate that nearly every State in the Union has at one time or another harbored this disease in man or animals.

An inquiry (Kerr and Stimson (51)) recently made by direction of the Surgeon-General of the Public Health and Marine-Hospital Service showed the disease to be largely confined to the eastern half of the country during 1908. It is the general opinion of observers of the disease that it is on the increase in this section. Certainly more cases are recognized; but it must be borne in mind that there has been increasing activity in state and municipal agencies in securing and examining material for diagnosis.

In the survey above referred to (51) it appeared that during 1908 only ten States or territories were free from the disease in man or animals, namely, California,[a] Idaho, Maine, Montana, Nevada, New Mexico, Oregon, Utah, Washington, and Wyoming. Reports were received of 111 deaths in man during this year, an inconsiderable number compared with the deaths from tuberculosis; but when we

[a] An outbreak occurred in California in the latter part of 1909. (Month. Bull. Calif. St. Bd. Health, Nov., 1909.)

consider the suffering involved and that these deaths could have been for the most part prevented by intelligent action, the need of increasing activity in preventive measures is apparent.

The loss of valuable live stock can not be estimated from any data which we have, but judging from the loss in certain localities, it was very considerable and enough to extend a ray of hope that activity would be stimulated by it, although the death of a few children in the same localities would not be sufficient to arouse it.

The progress of the disease in various countries is thus summarized:

In Great Britain the disease is now extinct, as the result of well applied suppressive measures. It is practically so in the Scandinavian countries.

These figures from Doebert (27) show the conditions in some other European countries:

Country.	Basis.	1902.	1903.	1904.	1905.	1906.	1907.
Prussia	Persons bitten by mad or suspected animals.	250	307	365	368	373	405
Do	Rabid animals	534	795	945	749	614	728
Belgium	do	15	35	25	94	68	237
France	Rabid dogs	2,355	2,391	2,392	2,368	2,043	1,892
Austria	Infected towns	970	1,109	1,011	1,252	1,331	1,008
European Russia	do				3,360	4,035	5,844
Holland	Rabid animals		25	1	1	51	41
Italy	Rabid domesticated animals	428	33	329	310	792	701

The increasing strictness of inquiry must be considered in some of the above countries before an increased prevalence as indicated in the figures can be assumed. And again, it must be remembered that, while a total increase may appear, marked reductions have resulted in areas where rigid measures have been carried out.

As is the case with many other diseases, rabies may be quite prevalent in a territory without coming to official cognizance or gaining public notice unless attention is drawn to the condition by the death of some person from hydrophobia. This is well illustrated by the conditions reported by Salmon (111) in the District of Columbia, where an investigation, stimulated by such a death, revealed a quite unsuspected prevalence among dogs. We believe that there are comparatively few cities in the eastern portion of the United States where a careful investigation extending over a year's time would fail to reveal the presence of rabies in dogs.

ANIMALS AFFECTED AND SUSCEPTIBLE.

While nearly or quite all warm-blooded animals are susceptible under favorable conditions to experimental inoculation of the virus of rabies, it is more commonly met with in nature in those mammalians which are subjected most often to the bites of dogs, wolves, coyotes, etc. Some species are relatively seldom infected because they are seldom subjected to bites or because they are provided with

a thick fur which tends to mechanically prevent the introduction of the virus, or possibly because of some natural relative immunity.

There is some reason to believe that skunks may propagate the disease widely among their own kind as the dog does, and cases are know of infection of man by this animal; but as a rule animals other than the dog or his kind do not transmit the disease another remove. This may be explained by their relative lack of ability, opportunity, and tendency to bite when rabid.

The demonstrated susceptibility of rats and other rodents to subcutaneous inoculation has led to the opinion, entertained by a few, that these animals might be capable of perpetuating rabies without the mediation of the dog. Their limited contact with man, however, argues little danger from this source, and the success of the measures directed against the dog alone, as for instance in England, shows that this fear is unfounded. It has been shown that rats may acquire fixed virus infection by ingestion of rabic brains. Perpetuation of the disease in this manner among animals dangerous to man seems far from probable.

The domesticated animals are affected with something like the following relative frequency, subject, of course, to variation according to conditions:

Animals sickened and died, or killed on account of rabies in Prussia.

Animals.	Doebert's figures, 1902-1907.		Schüder's figures, 1886.	
	Number.	Percentage.	Number.	Percentage.
Dogs	3,715	85.1	.....	80.2
Cattle	467	10.7	.....	14.7
Horses	63	1.44	.....	1.0
Swine	49	1.12	.....	1.6
Cats	35	.81	.....	.7
Sheep	32	.7	.....	1.7
Goats	4	.09	.....	.1
Other animals	.....	.....	.....	.02
Total	4,365	.....	11,306	.....

Biting animals rabid or supposedly rabid, in cases from Paris and Budapest institutes.

[From table by Högyes.]

Animals.	Paris percentages.	Budapest percentages.	Animals.	Paris percentages.	Budapest percentages.
Dogs	93.13	90.32	Man	0.04	0.26
Cats	5.75	7.80	Jackals	.03	.....
Cattle	.37	.52	Sheep	.02	.....
Horses	.22	.28	Foxes	.02	.02
Asses and mules	.18	.06	Rabbits	.....	.02
Wolves	.12	.38			
Swine	.07	.32	Total number of cases	14,296	4,961

Considering now the animals which have been successfully inoculated experimentally, it may be stated that all mammals so far tried

(a large number of species) have proved capable of taking the disease. Birds also are susceptible of inoculation, but seem to have a relative immunity, as old fowls and pigeons if they take the disease at all frequently recover and their nervous system is innocuous to rabbits, although it may transmit the disease to other fowls. This relative immunity is possibly due to their high body temperature, 108° F.

Frogs are said by von Lote to be susceptible, but to exhibit such a long incubation period that many experiments have been reported negatively because not continued long enough. Marie also found that frogs are susceptible; but Dammann and Hasenkamp, and Galli-Valerio obtained only negative results.

Remlinger states that the tortoise is refractory to rabies, an observation confirmed by Carowgean (20).

SEASONAL PREVALENCE.

The disproportionate prevalence of rabies during certain seasons of the year, long a matter of belief, seems to have little foundation in fact. What foundation it may have is either a matter of local coincidence or is due to the fact that more men and animals are likely to be abroad and liable to meet with infections at some seasons, notably the warm months, than at others, and not to any increased susceptibility.

The following statistics show that the seasonal variations are not marked or constant in any direction, except that the last quarter of the year usually shows relatively fewer cases:

Based on—	Author.	Place.	Years.	Jan.	Feb.	Mar.	Apr.	May.	June.
Rabid animals	Schüder	Germany	1886–1901	24.4 per cent.			27.6 per cent.		
Rabid dogs	do	France	1897–1901	24.2 per cent.			27.4 per cent.		
Persons treated	do	Berlin	1898–1902	25.9 per cent.			26.7 per cent.		
Persons bitten	Doebert	Prussia	1907	25.8 per cent.			25.5 per cent.		
				168	171	194	197	186	144
Rabid dogs	do	France	1903–1907	24.8 per cent.			30.2 per cent.		
				773	866	1,051	1,086	1,035	1,153
Persons bitten	Blatchford	United States.	To 1856.[a]	33.3 per cent.			25.3 per cent.		
Rabies in dogs	Salmon	Various		20.9 per cent.			29.2 per cent.		
				943	1,045	960	1,323	1,419	1,467
Total average				25.0 per cent.			27.4 per cent.		

Based on—	Author.	Place.	Years.	July.	Aug.	Sept.	Oct.	Nov.	Dec.
Rabid animals	Schüder	Germany	1886–1901	25.5 per cent.			22.5 per cent.		
Rabid dogs	do	France	1897–1901	25.4 per cent.			23.0 per cent.		
Persons treated	do	Berlin	1898–1902	26.5 per cent.			20.9 per cent.		
Persons bitten	Doebert	Prussia	1907	22.8 per cent.			25.7 per cent.		
				171	148	152	226	150	155
Rabid dogs	do	France	1903–1907	24.8 per cent.			20.4 per cent.		
				1,044	807	802	782	728	704
Persons bitten	Blatchford	United States.	To 1856.[a]	24.3 per cent.			15.3 per cent.		
Rabies in dogs	Salmon	Various		27.5 per cent.			21.5 per cent.		
				1,435	1,294	1,145	965	933	1,137
Total average				25.2 per cent.			21.3 per cent.		

[a] 101 cases.

The symptoms of rabies all point to a disturbance of the nervous system, and the anatomical changes abundantly confirm the idea that this is the part of the body primarily affected. Certain glandular organs share in the affection to the extent of disturbance of function and of containing the infecting agent. That the disease is an infectious one, i. e., produced by the invasion of a pathogenic microorganism emanating from a previous case of the diseases, is strongly suggested by the symptoms and the manner of conveyance, and is proved by the fact that all the parts of the nervous system, as well as some glandular structures and secretions, produce the same symptoms and results when inoculated experimentally into a healthy animal.

The most generally accepted view as to the manner of the pathogenesis of the microorganism causing rabies is that upon its introduction beneath the epidermis or mucosa it finds its most favorable or perhaps its only favorable medium for propagation in the nerve endings or torn fibers of the region. Along the course of these it develops, not disturbing their function although rendering them infective, until the central nervous system is reached. Here the nerve cells are attacked, the first effect being a hyperstimulation of their activity, the final result a destruction. At the same time, as certain authorities maintain, there occurs the production of a toxin, extra or intracellular, which is responsible for some of the symptoms. This latter view is opposed by others, and the elucidation of the question constitutes an important problem with a bearing on methods of treatment.

There is good experimental evidence that the explanation as above briefly outlined is correct. Nerves leading up from the site of the inoculation to the central nervous system have been shown to become progressively infectious in ascending segments, while their section previous to inoculation confines the infectious agent to the lower segment. The blood and lymph streams seem to be almost entirely incapable of taking up the microorganism from the site of inoculation and presenting it in a pathogenic condition to the cells of the brain and the cord. The blood of rabic animals has usually been found nonpathogenic when directly inoculated, but a few successful inoculations are recorded (Marie (64), Koch, J. (52)).

If we except for the time being the Negri bodies, the anatomical changes, gross and microscopic, can not be said to be characteristic of and confined to rabies, as they have been found in other conditions. They are, however, for the most part fairly constant and may be considered as directly connected with the disease in a specific manner. Many of them are produced during the prolonged death agony and

are consequently not peculiar to this disease. To review these changes:

Meninges.—These are usually congested and the vessels stand out in a very evidently dilated manner. There are punctate hemorrhages here and there over the surface. These changes may be mechanical and due to the convulsive seizures, although they are found in the paralytic type of the disease where generalized spasms are infrequent. The meninges are frequently edematous.

The *cerebrospinal fluid* is said to be increased in amount and consequently under high pressure.

The *brain* and *cord* show the same vascular changes to a less extent than the meninges. Areas of softening have been observed, visible sometimes to the naked eye, but often microscopic in size. A perivascular infiltration with lymphocytes and embryonal cells may be noted throughout the central nervous system, and cellular proliferation in the vascular tunics, even to the extent of occlusion, is described. These changes are similar to those observed in progessive paralysis and sleeping sickness (Achúcarro (1)). An infiltration with embryonal elements is observed around the motor nuclei of the bulb and cord, constituting the "rabic tubercles" of Babes (2).

The nerve cells themselves, especially in certain regions, may show marked changes, those in the interior of the "rabic tubercles" being degenerated.

In the *peripheral ganglia*, especially the pneumogastric fusiform ganglia, the cells are in a majority of the cases much degenerated, the capsules in which they lie are thickened through proliferation of their cellular elements, and the connective tissue is infiltrated with round cells. This condition is sufficiently constant and characteristic to be of considerable diagnostic importance, although not conclusive. The nerve cells in rabies are usually degenerated in some portion of the brain and not in others. The changes seen are irregular distribution of the chromatophilic elements, vacuolization, shrinkage of the cell as a whole, and eccentric disposition of the degenerated nucleus. Changes in the neuro-fibrillar network have been shown by Cajal's method. The brain cells in rabies are frequently not found markedly degenerated when the coarser histologic methods are used in routine examinations.

The great majority of observers are agreed upon the specificity of the changes described by Negri, but there is a division of opinion as to whether they are the parasites themselves which cause the disease, whether they contain the much smaller parasite in their interiors, or whether they represent a specific reaction of the nerve cells to the poison. They consist of sharply defined round or oval structures occurring within the nerve cells of the brain and cord, taking the stain in a manner very distinct from the cell structures, and contain-

ing minute granules which stain differently from the rest of the body. They are very constantly found in rabies at all stages of the disease after the onset of the symptoms, and have a predilection for certain portions of the brain, although found at times in nearly all portions of the central axis. They have been described by Stefanescu in the parotid gland of one dog dead of rabies. (See under Diagnosis, p. 34.)

Outside of the nervous system there are few changes not secondary to its involvement. The fauces, pharynx, and larynx are usually deeply congested. The tongue (in dogs) is dry and may be blackened. The salivary glands are inflamed and their secretion before death is much increased. Retention cysts under the tongue of carnivorous animals may sometimes be formed, due to the undue activity of the glands and to swelling and occlusion by desquamated epithelium of the ducts.

One of the exploded hypotheses of rabies is that of Maroschetti, who claimed that these "vesicles" appeared in man before the development of rabies; that the virus was contained in them, and that its liberation by incision followed by cauterization was a sure preventive of hydrophobia. The pancreas, adrenals, spleen, and kidneys show engorgement, as may other glandular structures. Babes and Jonnesco (5) have recently described at some length the lesions of the pancreas and the salivary glands.

In the lower animals, especially dogs, the gastro-intestinal tract is frequently devoid of normal contents, food or chyme, and instead are found a variety of unusual foreign bodies—sticks, stones, straw, splinters of wood, feathers, etc. This constitutes a finding of doubtful diagnostic value, as it is known that dogs suffering from diseases other than rabies, sometimes swallow such objects, as do also wandering dogs when suffering from hunger; but it was relied upon before subdural inoculations became depended upon for making the diagnosis certain.

It must be admitted that, with the exception of the Negri bodies, the microscopic anatomy of rabies offers nothing which is constant or characteristic, although the changes above briefly described are met with in a majority of the cases. There is one, however, not demonstrated by the microscope, which is absolutely constant for the nervous system and frequently present in certain of the glands, chiefly the salivary, and is absolutely characteristic. This is the acquisition of the property of causing rabies in fresh animals when suitably inoculated. For a discussion of the findings of different observers of the pathological anatomy of rabies, see Högyes (49), Remlinger (96), Marie (68).

The *blood* is stated by Courmont and Lesieur (23) to present from the early stages until after death a relative polynucleosis which is constantly found. The lung juice also presents this condition. Other observers describe leucocytosis.

The *urine* sometimes contains albumin, but glycosuria is a more striking phenomenon, although apparently uncommon in man. Acetonuria sometimes occurs.

RABIES VIRUS.

As ordinarily used this term now applies almost exclusively to the virulent nervous substance of an animal suffering or dead from rabies. It comprises the specific cause of the disease and the medium in which it is found, i. e., the nervous substance. The nature and properties of the virus will be discussed under the subject of *immunity*, but it may be well to point out here certain differences between "street" and "fixed" virus, as they will be frequently referred to in the following pages.

Street virus (virus des rues, Strassenvirus) is the virulent nervous tissue as met with in the natural disease. Its virulence is very variable and when inoculated into rabbits subdurally it causes the symptoms of rabies to appear at a variable period of more than fourteen days as a rule. There have been exceptions to this noted in several instances when the incubation was as low as eight days. Instances of this kind are collected from the literature by Nitsch (79). Consequently the incubation period can not be taken as an absolute criterion as to whether a given virus is of natural or laboratory origin. This question is sometimes raised when a person has died of rabies after having taken the Pasteur treatment. It has been suggested that dogs are more reliable test animals for this purpose than are rabbits. Again the inoculations should be carried on for several passages when the nature of the virus should become clear.

Fixed virus (virus fixe) is modified from the street virus by passing it through a long series of rabbits. In this way its virulence becomes greater for these animals, so that they finally take the disease after a constant "fixed" period of incubation. No amount of passage can reduce the incubation period below this point, so the virulence is said to be fixed. Other considerations in this connection will be taken up later.

INCUBATION PERIOD.

The incubation period of rabies is remarkable for its length and variability. Its length is in nature seldom under ten days, and may extend over many months. It is difficult to say what the longest period has been; but it is generally admitted that a year or more is not impossible. The majority of cases occur before the end of the third month. Extremely long periods as reported always lead to the suspicion of a mistake or the occurrence of an unobserved or forgotten intermediate exposure. The fact that the saliva of animals may possess infective properties several days before the outbreak of

significant symptoms may explain the occurrence of unsuspected infections within the supposed incubation period, since trifling bites or licking of abraded surfaces by an apparently healthy dog would be likely to escape attention or be forgotten.

The length of incubation is influenced by certain known factors:

(1) The species of animal affected. From a review of the statistics on this subject it would appear to be longer in man than in the lower animals, and among them, in a general way, proportionate to the size of the animal.

(2) The site of inoculation. The shorter period in cases of bites near the brain accords with the accepted views on the transmission of the virus along nerve trunks. The shorter the distance to be traversed the shorter will be the period of latency, other factors being equal.

(3) Sex. Females, at least in the human species, exhibit a shorter period than males.

(4) Children usually have a shorter period of incubation than adults, but this may be because bites in children are frequently severe and about the head.

(5) Severity of wound. Wounds in which nerve trunks or muscles are torn result in a relatively short period of incubation, both because of the large amount of virus introduced and because it is brought into immediate contact with the nerve tissue.

(6) It is probably true that early onset of the disease may be induced by certain causes which tend to weaken the resistance of the nervous system. Alcoholic indulgences, sudden shocks as from cold baths or falling into the water, excessive fright or other nervous excitement, and certain diseases affecting the nervous system, e. g., syphilis, antecedent meningitis, have in many instances seemed to determine an early onset.

(7) Treatment. Nitsch has pointed out that in a large series of cases the deaths, in spite of the Pasteur treatment, occurred on an average earlier than in untreated persons (sixty-four and one-half days to ninety days), and that this would naturally be expected when the rationale of the treatment is understood, since cases in which the incubation would have been long, if untreated, are those which afford the most time for the establishment of immunity if treated.

(8) There is some reason to believe that rabies virus, as it occurs in nature, varies much in virulence, and that this is in some way related to the geographical distribution. Thus, the short incubation periods of the cases reported in Egypt by Bain and Maloney may have relation to an especially potent virus in this region, as compared with that commonly prevalent in Europe.

During the period of incubation no unusual symptoms are complained of. The wound heals as other wounds do without any specific

phenomena. Some persons are very anxious about the outcome, and may get into a condition of nervous excitement; but they are as likely to do so after harmless as after infected wounds.

A general idea of the duration of the period of incubation in man and various animals may be gained from the following statistics and figures:

Incubation period in man.—Bauer (11), in 1886, published the results of an inquiry into the incubation period of 537 cases of human rabies, representing all the material available to him at that time. Seventeen of these cases had an incubation period of over one and one-fourth years, and 10 of the remaining cases were regarded as doubtful. The average period in the remaining 510 cases was seventy-two days. In *males* the average was eighty days, in *females* sixty-five days. The period was influenced by *age* as follows:

Number of persons.	Age.	Average period.
	Years.	*Days.*
120	2 to 14	57.0
182	15 to 50	77.5
45	51 to 78	70.0

The location of the bite was determined in 252 cases, the average periods being—

	Days.
For 73 cases of head and neck bites	55
For 3 cases of buttock bites	26
For 144 cases of upper extremity bites	81½
For 17 cases of lower extremity bites	74
For 15 cases of bites on several parts of body, many being on the head	55

Bites on the buttocks are not ordinarily followed by as short a period as indicated.

According to the biting animal, modifying virulence and severity of bite—

	Days.		Days.
49 wolf bites	39	2 fox bites	33
293 dog bites	73½	1 cow bite	30
31 cat bites	80		

No effect of local treatment was noted, nor any relation between the incubation period and the duration of illness.

The percentage of Bauer's total number of cases developing rabies at specified periods—

	Per cent.		Per cent.
1 to 19 days	8.24	100 to 149 days	7.65
20 to 39 days	28.43	150 to 199 days	5.69
40 to 59 days	21.18	200 to 249 days	.98
60 to 79 days	15.30	250 to 330 days	2.35
80 to 99 days	9.22	1 to 1¼ years	1.18

Incubation period in animals.—Friedberger and Frohner (35) give the following figures for the incubation in animals:

Ox, 4 to 8 weeks average. Shortest, 1 week; longest, 2 years.
Horse, 4 to 8 weeks average. Longest, 12 weeks; 2 cases—283 days, 20 months.
Cat, 2 to 4 weeks average.
Pig, 2 to 3 weeks average. Shortest, 6 days; longest, 179 days.
Sheep, 3 to 4 weeks.
Poultry, 6 weeks to 11 months.

Nocard and Leclainche (82) give the following figures:

Dog and cat, 15 to 60 days average. Shortest, 8 days; longest, 1 year.
Horses, 15 to 60 days average. Cases as high as 10, 14, and 20 months (four-fifths of cases under 60 days).
Cows, 1 to 3 months average. Cases as high as 20 and 23 months.
Sheep and goats, 15 to 30 days average.
Swine, 15 to 30 days average. Extremes 6 days (?); 6 months.

Högyes says, concerning the incubation period in dogs, that 60 days' average is usually given, but that under experimental conditions at Budapest it is considerably shorter, e. g.:

	Days.
By bites	9 to 33
By subcutaneous infection	13 to 19
By subdural infection	10 to 15

SYMPTOMS AND CLINICAL COURSE.

Rabies presents at least two clinical types. These are the furious or excited, and the quiet, silent or paralytic. Paviot and Lesieur (88), distinguish, according to the portion of the nervous system most involved, four types of the disease: Cerebral, medullary, cerebellar, and sympathetic.

The study upon which this classification was made was very thorough, but embraced too few cases to generalize from. The authors apparently trace a connection between the type of clinical manifestations and the localization of the most pronounced lesions.

These variations, however, are all within the theoretical limits of a specific involvement of the nervous system by a microorganism or its products. The disease is essentially the same in all animals, although there is a predominance of certain symptoms or of one form or another in different species.

The excited or furious type in man.—The onset of rabies is usually rapid. The patient usually shows some psychical change very early, becoming anxious, melancholy, and oppressed with a strange presentiment of harm. Insomnia is complained of. Such symptoms, however, are in many cases absent at first, and local numbness, tingling, itching, and formication in and progressing centrally from the wound may be the only disturbance. The wound or scar may

become somewhat engorged and tender. Sometimes the first symptom complained of is a strange sensation in the throat, difficulty or discomfort in swallowing, a sense of constriction of the fauces.

Bain and Maloney (7) record a case in which the first symptom was difficulty in walking, and another in which cardiac irregularity was the first sign. There are many cases recorded where the onset was apparently determined by some severe mental shock, and the initial symptoms may be apparently purely hysterical. In fact, hysterical manifestations are not unusual and may lead to a favorable diagnosis and prognosis. These symptoms are in some of the cases part of the psychological pathology of rabies, an aggravation of the usually less violent aberrations. The state of mind induced by the beginning disease often renders the patient susceptible to excitement on exposure to impressions which ordinarily would not produce it. Fright and terror may, therefore, be regarded in many instances as a manifestation of the disease, not as the determining cause of its outbreak. It is conceivable, however, that any influence causing over excitement of the nervous system with subsequent fatigue or exhaustion might predispose to the more rapid invasion of a microorganism, or increase the susceptibility to a toxin. An initial rise of temperature is perhaps the most constant early sign, the elevation being moderate as a rule.

The symptoms usually progress without delay after the preliminary signs are observed. The forewarning symptoms may last several days before the decided outbreak, but usually only twenty-four to forty-eight hours. The "grand symptom," hydrophobia, is present in the majority of cases, although influenced by the patient's disposition and surroundings to a considerable extent. It arises from the extremely painful spasms of the organs of deglutition and respiration, which are induced by attempts to eat or especially to drink. These spasms are often of such an agonizing character that the thought of them causes a mental anguish not exceeded in the possibilities of human suffering of physical origin. Consequently the sight, smell, or sound of liquids suggests the act of swallowing and is sufficient to bring on an attack in many cases. The patient, if a person of exceptional self-control, may sometimes be diverted from the subject for a considerable time and be free from the painful seizures. Sometimes the patient goes through an elaborate formula in preparing to drink, like a child insisting upon a special arrangement of all accessories in an effort to protract the time before taking an unpleasant dose of medicine. Then an effort is made to gulp down a swallow of the liquid only to have it forcibly expelled with an accompanying anguishing spasm of the throat and larynx.

The condition consists, therefore, of a hypersusceptibility of the nerve cells to external stimuli. If these stimuli can be removed, cell

action may be kept temporarily in abeyance. The cell explosions may be evoked by phychical stimuli and through the special senses. Drafts of air, lights, sounds, and even smells, may bring on a convulsive seizure. Skin and tendon reflexes are exaggerated. The respiratory spasm involves the thoracic muscles and can not be relieved by intubation. In fact, the glottis may be open during an attack. Solid food is usually more readily taken than are the fluids.

Whatever the onset the disease usually progresses rapidly. In a minority of cases there may be periods of absence of symptoms which cause the hope of recovery and doubts of the diagnosis to be entertained. Remissions always occur except in the extremely rapid cases. As the disease progresses the symptoms become more severe. The mind is usually clear, questions being answered with understanding until the voice becomes indistinct and the words unintelligible. In a large number of cases the patient is very talkative, speaking incessantly about himself and his disease until interrupted by a spasm.

There are periods of excitement which may be truly maniacal, the patient raging about the room, destroying furniture, and trying to escape. There is seldom, however, any tendency to injure other persons, much less to bite them as popularly supposed. After a violent period the patient may realize his acts and be sorry for them. He frequently seems to know when an attack is coming on, and begs to be restrained lest he injure someone. Sexual excitement, accompanied by priapism, is a frequent symptom. The voice becomes hoarse with a peculiar quality. The strange sounds emitted during expectoration or on the onset of the seizure have given rise to the popular statement that the patient "barks like a dog."

The convulsive seizures become more frequent and severe and distributed over a larger area. Sometimes the muscular contractions are so severe as to cause rupture of the muscles. Small hemorrhages from mucous surfaces and elsewhere may occur. Vomiting is a rather frequent symptom, and the vomitus is often black. The color is said to be due to regurgitated bile, but blood also is sometimes found.

Death may occur during the convulsive stage, but more frequently a condition of paralysis mercifully leads the patient on to death. The spasmodic seizures become less severe and frequent and less readily evoked. The muscles, racked to the limit of human endurance, become limp. The face, which had expressed terror and extreme suffering, becomes smooth and expressionless. The jaw drops and the mouth hangs open. There is commonly an excessive secretion of saliva of a ropy character which the patient is unable to expel and which flows out of the corner of the mouth in large quantities; but where this is not abundant, the tongue becomes dry and hard. The breathing becomes irregular and feeble, and finally stops. The temperature

ascends before, and it is said immediately after death in some cases; but where this stage is prolonged the temperature is more likely to be subnormal. Sugar and acetone are sometimes found in the urine, although not as constantly in man as in some of the lower animals, especially the herbivores.

The eye symptoms described are photophobia, mystagmus, and sometimes strabismus. In the paralytic stage the pupil is dilated from paralysis of the iris.

In a general way, then, the symptoms may be grouped into three stages: That of prodromata, the excited stage, and the paralytic. They often merge into each other, so that their limits are uncertain.

The paralytic type in man.—This was early described by van Swieten. Because its symptoms are less marked than the violent type it has undoubtedly been unrecognized in many cases, and the disease has been incorrectly diagnosed. In fact, its existence seems to have been lost sight of for a time.

In 1887 Gamaleia (39) caused renewed interest to be taken in the matter by his publication of a number of cases taken from medical literature and his own observations, and it must now be regarded as a rather common form of the disease in man, as it is undoubtedly in dogs and other animals. Pathologically it has been attributed to infection with a large amount of virus and to involvment of the spinal cord rather than the brain. The symptoms are those of the last stage of the excited form, without any pronounced antecedent symptoms of excitement. They bespeak a transitional form between the paralytic rabies of the smaller animals and the convulsive form of hydrophobia in man. Gamaleia sums up the manifestations in the cases reviewed by him as follows:

Onset with high fever, general malaise, cramps, headache, and vomiting much as in the ordinary convulsive form. Afterwards, localized pains, ordinarily in the bitten parts, but rarely so when these are in the lower extremities. A heaviness and numbness of these parts follow, then ataxia and weakness followed by more or less complete paralysis. A girdle sensation is frequently complained of. Anæsthesia is uncommon. Consciousness is ordinarily retained, at least until late in the disease.

The paralysis spreads with preceding or accompanying pains of the affected parts, invading the limbs, trunk, rectum and bladder, face, tongue, and eye muscles. Respiratory involvement is variable in the time of its appearance and severity. Inspiration is more affected than expiration. Dyspnoic convulsions may result when the condition is severe.

More or less difficulty in swallowing liquids results from the respiratory embarrassment, but the symptom "hydrophobia" is caused more by the imagination than by the disease. Frequently

normal respiration may be restored for a time. Death occurs by cardiac paralysis, according to this author.

This form of the disease is more prolonged than the furious type, lasting up to seven and one-half days, while in the latter the average duration is three or four days.

RABIES IN THE LOWER ANIMALS.

Rabies is the same disease pathologically and clinically in whatever animal it occurs. It is true, however, that one clinical type or the other predominates, according to the species affected, and that different animals have various ways of showing the symptoms.

The dog is almost an intellectual anomaly among animals. By centuries of association with man, of a kind more intimate than any other enjoys, it has acquired a mental development far in advance of most of the domesticated animals. It is natural that psychical disturbances should be marked in this animal. When a dog shows a marked and apparently causeless change of its habitual disposition, suspicion of rabic infection should be entertained, especially if an opportunity for such is known to have occurred. This change may be either in the direction of becoming more morose, sullen, and irritable, or of showing unusual affection and desiring to be petted more than usual. Fatal infections of man have occurred during this stage through licking of abraded or scratched surfaces by an overaffectionate animal, or by bites received in a period of unnatural playfulness.

A very characteristic symptom is the change in the character of the voice. It has been aptly described as resembling the belling of a tired hound which has been chasing game for a long time. Instead of the normal succession of sharp barks, there is a hoarse howl followed by an unequal series of barks, lower in pitch than is normal, the jaws not being completely closed between them as is normally the case.

The rabic dog, whatever his initial symptoms, soon becomes restless, lying down and getting up again repeatedly. He is easily startled, and growls and barks on slight provocation. In the furious type, after a few days or less of inquietude, he may suddenly leave home, wandering off for many miles perhaps, to return in a day or two, emaciated, wounded, and utterly changed. During the period of "running mad" he may have bitten many persons and other animals. He may bite and tear his own flesh at the site of the wound, and seems impelled to bite anything that comes in his way, as if some relief could be gained in that way. He can not be said, as a rule, to fight with other dogs. He bites them and passes on, but does not go out of his way very much to attack them. His main object seems to be to keep moving, as if to escape something.

The popular idea of a mad dog is a raging animal with glaring red eyes, the froth flying from his jaws, and the tail carried between the legs. A picture of such a dog appears as the frontispiece to Rougemont's treatise on rabies (1798). This is an unusual picture in actual experience. The dog looks sick, takes no interest in his surroundings, but trots ahead, perhaps with wavering gait. The conjunctivæ are, it is true, usually injected, but frequently not enough to attract attention, and the tail may be carried over the back. It is the rule that dogs in this condition have no appetite for their accustomed food and frequently swallow indigestible objects, such as sticks, stones, straw, etc. Swallowing is difficult and, later in the disease, impossible.

Convulsions of greater or less distribution now appear, and the animal may die in one. More frequently a paralytic stage supervenes. The dog drags himself to a secluded place. The hind legs are usually paralyzed first. It is often thought by the observers that his spine has been injured. The jaw drops from paralysis of its muscles. The tongue is apt to be dry and may be blackened. A black discoloration of the roof of the mouth is no criterion whatever for rabies, as it occurs in healthy dogs. Salivation may be profuse, the saliva drooling from the mouth. This is not incompatible with the dried condition of the tongue. The animal becomes much emaciated. Death is caused by the ascent of the paralysis to the respiratory centers.

The *paralytic form* is quite frequent among dogs and offers peculiar danger to man. These are the cases where the owner or sympathetic bystander endeavors to remove an imaginary bone from the throat and becomes bitten or scratched. Spasms of deglutition and the animal's actions during them, and paralysis of the throat muscles, strongly suggest an obstruction in the throat. It is a mistake to suppose that rabid dogs have any fear of water. They are intensely thirsty and desire to drink, but when the paralytic condition affects the throat muscles they are unable to swallow. They are so far from having a fear of water that they sometimes swim rivers while in the furious stage, as observed in ancient and modern times. Young puppies have been thought to enjoy an immunity to rabies, but this has been shown to be incorrect by Remlinger (103).

Glycosuria as a symptom of rabies has been described by Nocard, Rabieaux and Nicolas (95), and others. It is stated to be very constant in herbivores, less so in carnivorous animals. It is not of renal origin, since the blood contains sugar in excess.

A detailed account of the symptoms of natural rabies in other animals does not seem to be called for, as they are but modifications of type or intensity of the disease in dogs. The paralytic form is very frequently in herbivores, but horses frequently have the furious

type in its most agonizing form. Fowls are said to have the furious form by Friedberger and Frohner (35), but other observers are almost unanimous in describing a slow paralysis in them, both the incubation and duration being prolonged.

Experimental rabies in the rabbit requires special description, because it is this animal which is now most used for diagnostic inoculations of material from man, dogs, or other animals.

After subdural inoculation the animal evidences no symptoms whatever for several days to two or three weeks, depending on the nature of the virus, i. e., fixed or street virus, virus of high or low virulence. The first sign to be noted, if the animal is examined for it, is an elevation of temperature. v. Löte (60) states that this transient premonitory fever is seen in rabbits inoculated with virus of medium virulence. The animal appears sleepy, does not eat; its movements are incoordinated and it is apt to fall. The appearance of the face is quite characteristic, the eyes having a staring expression, and frequently one ear hangs down while the other remains erect. The animal urinates much more frequently and copiously than normally, and this, coupled with the decreased consumption of food, results in a very evident emaciation. Rarely there is a brief furious stage in which the animal throws itself against the cage and tries to escape. Gritting of the teeth is frequently observed. Convulsive seizures are frequently seen, involving the legs, back, and jaws. They persist after the animal can no longer sit up and lies on its side, so that the litter in the cage is scraped in a segment of a circle where the legs move. Paralysis usually begins in the hind legs and proceeds forward, but may be reversed. The usual position in this stage is on the side with the head drawn sharply backward; anterior flexion is rare. Movements become weaker until only a feeble respiratory movement is visible and the animal dies. Abortion in pregnant females is very common.

DIAGNOSIS.

The diagnosis of rabies rests upon the consideration of as many of the following factors as are available: (1) History of exposure, (2) the length of the period of incubation, (3) the clinical symptoms and course, (4) the termination, (5) the post-mortem findings, gross and microscopic, and (6) inoculation tests upon animals. These will be considered in detail.

(1) *The history of exposure.*—While the great majority of patients suffering from rabies will give an account of being bitten or scratched by an animal, or having an abraded surface exposed to the saliva of one at some time previously, there are some cases where this is lacking. Such cases were formerly described as "spontaneous" or "idiopathic," but it is a fundamental doctrine that infectious disease does not

originate *de novo*, but is always derived from previous disease in another host. It is not surprising that in a disease like rabies, the incubation period of which often extends over many weeks, slight scratches received from dogs or other animals, or licking of the hands on which there were trifling wounds, might be forgotten at the time of onset. This is the more apt to occur since the saliva of animals has been shown experimentally to be infectious several days before the appearance of noticeable symptoms in them. Again, it sometimes happens that a patient realizing the character of the disease with which he is beset, attempts to deceive and reassure himself by denying any knowledge of infection. The evidence of other persons will often clear up such cases. It sometimes happens that no history of infection may be obtained until late in the disease or after death, when some acquaintance furnishes the information. There are some recorded instances where the patient died apparently of rabies but where the biting animal has after a period of illness recovered. Dogs have, under experimental conditions, recovered from developed rabies, so that their recovery can not be regarded as positive proof of the nonrabic character of the disease. The fate of the animals biting or being bitten by them should be inquired into. At any rate, the history of a bite by an animal known or thought to be rabid is only suggestive and does not rule out other diseases. In animals evidence of infection is frequently lacking. Opportunity for it should be considered and scars looked for if it can be done with safety.

(2) *The length of the period of incubation.*—There are some apparently well-authenticated cases of development of rabies in man as early as ten days after exposure. This probably is the lower limit of this variable period. Hysterical manifestations simulating rabies usually come on within a few hours or days after the assumed exposures, or if appearing late are induced by seeing, hearing, or reading of some real case of the disease.

The occurrence of symptoms like those of rabies at a period less than two weeks or more than one year after the exposure should be regarded with suspicion, and every effort made to clear up the other factors bearing upon diagnosis.

The mental behavior of the patient during the period may be of assistance in making a diagnosis, or on the other hand lead to confusion. Many cases show no disturbance whatever until the unmistakable signs develop. Others from the time of the bite are in such a state of anxiety that it is difficult to tell at first whether the new symptoms are a product of hysteria or due to rabic infection.

(3) *The clinical symptoms and course.*—While the symptoms and course of rabies are usually sufficiently distinctive clinically to rest a diagnosis upon as firm a basis as obtains in other infections, such

a diagnosis nowadays should be confirmed both in man and in the lower animals by laboratory methods where these are available. It must be admitted, however, that there are occasional cases which are difficult or impossible of clinical diagnosis. Confusion may be caused by hysterical symptoms. In this connection witness the interesting case reported by Calabrese (18), in which the onset seemed to be determined by reading an account of a case of hydrophobia and the symptoms were markedly hysteroid, and a period of amelioration of the symptoms made a diagnosis of hysteria seem permissible. Death occurred, and the brain substance caused rabies in rabbits, two removes. Where these hysterical manifestations appear within a week of exposure (provided there have been no previous exposures) rabies can be excluded, so far as present experience teaches. In the condition called lyssophobia the symptoms popularly ascribed to rabies may be closely simulated. They are apt to be exaggerated and ill timed. For instance, the first signs may be the symptom hydrophobia and a good imitation of a dog's bark and to some extent its actions, the patient going about on all fours and biting at the furniture. The hysterical stigmata are present, and the patient may be cured by suggestion.

Once a patient came to the Hygienic Laboratory a few days after handling a dog thought to be mad. He complained of a sense of constriction in the throat, pains in his head, and was visibly nervous and excited. He thought himself to be in the grip of the dread malady. His symptoms subsided promptly upon being emphatically reassured. Such cases could be multiplied. It is stated that hypersensitiveness to drafts of air, which is very common and pronounced in true rabies, is not simulated in hysteria. This may be tested by stepping unobserved behind the patient and fanning him. A convulsive seizure induced in this way would serve to strengthen a diagnosis of rabies. Tetanus and mania may simulate rabies. The absence of trismus and continuous spasm serve to differentiate rabies from the former, as do also the long period of incubation and other factors mentioned in this discussion. Mania seldom takes the form of rabies, and can be differentiated by etiologic considerations. Simple throat infections with fever, pain, and difficulty in swallowing occurring after exposure to rabic infection are sometimes indistinguishable from incipient rabies; but the course of the disease will differentiate it within a short time.

It is to be emphasized that upon clinical evidence alone the diagnosis will sometimes, but not often, be uncertain. Remlinger (100) considers some cases diagnosed as Landry's paralysis as true paralytic rabies and advocates special investigation of such cases with this point in view.

In the lower animals there is a variety of diseases which may be mistaken for rabies, and undoubtedly often are. Experienced veterinarians, however, are correct in their diagnoses in the great majority of cases. Friedberger and Frohner mention a large number of conditions in the dog which may resemble rabies clinically.

It seems necessary to refer especially to the nervous form of dog distemper. In this disease there is sometimes a train of symptoms closely resembling those of certain cases of rabies. There may be the same convulsions and paralysis. The involvement of nasal and ocular mucosæ, the intestinal symptoms, and eruption may be looked for in vain. However, a dog with distemper is said not to have the aggressive tendencies of a rabid one. An ugly dog with distemper would certainly *appear* more aggressive than a paralyzed and helpless rabid dog. There is some evidence that the resemblance between these two diseases extends further than the clinical features, and that their pathogenesis may be similar, although it certainly is not identical (see microscopic findings and inoculation tests). In the case of the dog the matter can be cleared up by microscopic examination and inoculation, when suitable post-mortem material can be obtained.

It is necessary to reiterate that the rabid dog is sick; is not necessarily running wild and furious; is frequently obedient up to a late stage; and often seems to have a "bone in his throat," or to have sustained injury to the back.

(4) *Termination.*—The great majority of persons and animals die of rabies after the first symptoms have developed. Therefore, if recovery occurs after the onset of the suspicious symptoms, the disease almost surely was not rabies. The statement that the disease is uniformly fatal does not, however, seem to be quite justified. Dogs are known to have recovered from rabies acquired under experimental conditions (Damman and Hasenkamp (25) and Högyes). There are not lacking reports of recovery in man; and, while the diagnosis is often found not to be justified beyond a doubt upon examination of the records, there still remains a probability in some cases that the disease was true rabies.

Josef Koch (52) adds new weight to the view that recovery from rabies is not impossible. He cites the varying and sometimes very long incubation period in animals experimentally inoculated as evidence that there are strains of virus of attenuated virulence from which recovery is possible, and gives instances of such recovery in dogs from *street virus inoculations* in his own experience. He cites four cases from Paltauf that died of intercurrent disease—alcoholism, apoplexy, and pulmonary embolism—after they had been bitten by rabid animals and whose brains conveyed rabies to inoculated

animals, as indicating that the brain of a human being might actually be rabific without there being at the time any symptoms of the disease. Koch thinks, furthermore, that the cases of paralysis occurring during antirabic treatment are really cases of myelitis caused by the street virus infection.

No case must be regarded then as hopeless, and effort to effect a cure it not absolutely discouraged.

The duration of the disease is usually only a few days, and patients who survive a week or longer are probably suffering from another disease.

(5) *The post-mortem findings.*—As has been stated, these are for the most part inconstant and not absolutely characteristic. The absence of any other adequate cause of death should be determined. In the case of dogs, emaciation, foreign bodies in the alimentary tract, injection of the meninges and pharyngeal mucosa, and small hemorrhages in the central nervous system are extremely suggestive but not conclusive. It has long been hoped to determine a definite organism as the causal agent of the disease which by its demonstration in the tissues and isolation therefrom would render the diagnosis certain. This can not be said positively to have been accomplished, but the demonstration by Negri of certain bodies named after him has been a great advance in this direction.

Negri (74) has recently summed up his work upon the "parasite of rabies," *Neuroryctes hydrophobiæ* Calkins. He traces a developmental cycle for the organism, which he classifies with the Sporozoa. The bodies consist of a groundwork of protoplasm which contains "inner bodies." These latter are of two general types with transitional forms between them. The types are (1) small roundish and highly refracting; (2) larger, less refracting, roundish, or oval, or irregular. Both types are found in the same body. They are not artefacts, being found in unstained fresh tissues. In the smallest Negri bodies they are united and form a nuclear mass. As the parasite grows this nucleus increases in size and then becomes distributed throughout the protoplasm of the organism in the form of the smaller and larger inner bodies. These bodies then undergo a differentiation of their chromatin, which latter becomes separated and inclosed in a feebly staining capsule, constituting a "spore." The Negri body now consists of a mass of these spores. These are extremely minute—small enough to pass a bacterial filter. They may become dispersed throughout the nervous system, and when isolated would not be certainly differentiated from the granular structure of the latter. This explains why the parts of the brain which are very virulent may not contain Negri bodies in the cells. Golgi and Grassi confirm Negri's findings and concur in his interpretation of them.

These bodies are very generally admitted to be very constant in rabies and peculiar to it. Their availability for diagnosis is therefore assured in the majority of cases, but their exact significance is in dispute. The views of their significance are grouped as follows:

(a) *That they are the parasites causing rabies.*—This view is held by Negri himself and by a great many other observers. An able presentation of this attitude and very complete references to the literature on Negri bodies will be found in the articles of Williams and Lowden (119), and Williams. The supporters of this view urge the constancy (some 98 per cent) and specificity of the bodies to rabies, their morphology, which they consider that of the Protozoa, and the occurrence of various forms or stages which they regard as evidence of vital development.

(b) *That they are specific reactions of the invaded cells against the real parasites which are contained in the interior of the bodies and appear as granules differentiated by staining.*—This reaction is in the nature of an effort to isolate or sequestrate the offending microorganisms. The reason why they are found in greatest numbers in parts of the brain which are not especially virulent is that the cells of these parts are especially resistant and capable of exciting the limiting action. This view is held by Babes and his followers.

(c) *That they are cell degenerations or inclusions not connected necessarily with parasitic invasion.*—Achúcarro (1) claims to have shown that the glia cells of nerve centers undergo a degeneration in rabies which cause them to appear, when properly stained, identical with Negri bodies, and that these glia cells become incorporated into the larger cells and their processes and give rise to appearances indistinguishable from the Negri bodies.

Bearing upon the nature of these bodies are the following considerations:

Size.—It has been urged that they can not be the causal agent of rabies, as they are too large to pass the filters which fail to restrain the infective principle. This is hardly a valid objection, however, since it is not claimed that the visible forms are the only ones, but merely a stage of the development of the organism. Small plastic forms are assumed which are small enough to pass the filters.

Location.—The fact that they occur in great numbers in comparatively nonvirulent parts of the brain and are rare in the most virulent portions has been taken as evidence that they are not causative parasites; but Negri's explanation of this should be considered. If Stefanescu's (114) observation of these bodies in the parotid gland of a dog is confirmed in other cases, an important link will be added to the chain of evidence as to the parasitic nature of the bodies.

Morphology.—On morphological grounds alone they are regarded by many, including Calkins, as Protozoa, and stages of development

are described; but others have claimed that their staining reactions are not those of typical Protozoa.

Standfuss (113) states that the mere finding of Negri bodies is not sufficient to establish the diagnosis. He found bodies almost indistinguishable from Negri bodies in "dog sickness."

Bodies somewhat similar to Negri bodies have been described in dog distemper and other conditions, but their differentiation is said by those who have described them not to be a difficult matter, except those described by Standfuss, already referred to.

Poor (92) has described such forms in a tetanic guinea pig; Lina Luzzani (62) in normal cats; Pace (86) in persons dying of old age, cerebral embolism, and aortic insufficiency; Babes (3) in a case of arsenic poisoning; Schiffmann (116) in Hühnerpest; Lentz (59) and Mazzei (71) in distemper; Pinzani (91) in a guinea pig dead of diphtheria toxin; Goffi (40) in the testicles of a healthy animal.

Before granting that indistinguishable or even similar forms may be found in distemper we must be sure that we are dealing with this disease. Text-book descriptions of distemper, and especially of the "nervous form," do not furnish us with any absolute criteria for the detection of the disease, which is alleged to be protean in its manifestations. It seems more reasonable to suppose that the bodies described came from cases of true rabies incorrectly diagnosed on clinical grounds as distemper, than to believe that bodies as definite in their structure and relations as the Negri bodies can be the result of more than one cause.

Marie apparently considers the Negri bodies as evidence of non-specific cellular reactions against certain microorganisms and toxins and other poisonous agents.

In expressing our own views regarding these bodies and their value for diagnostic purposes, it may be said that we have, so far, found them specific for the disease, and, when unmistakably present, diagnostic of rabies. They are not, however, always present or at least demonstrable in cases of rabies. When a person has been bitten by an animal having symptoms suspicious of rabies it is our custom to institute at once the preventive treatment, although we may not have been able to demonstrate the presence of the Negri bodies in the nervous system of the biting animal. Inoculation tests have shown this to be sound practice in a few cases where the Negri bodies were not found, since the inoculated animals have developed rabies. Again, the personal equation of the examiner must be taken into account. A person undertaking this work should be thoroughly familiar with the technic of demonstration and the appearance of these bodies before expressing an opinion as to their presence.

The custom of killing suspected animals immediately after they have bitten some one operates against the demonstration of Negri bodies, which may not be present in the early stage of the disease.

We believe that an experienced examiner may rely upon his diagnosis of rabies based on the presence of Negri bodies, but in their absence inoculation tests must be made before rabies can be excluded.

Among the changes, for which more or less diagnostic value has been claimed, must be mentioned the rabic tubercles of Babes, the ganglion changes of van Gehuchten and Nelis, the polynucleosis of Courmont and Lesieur, and the glycosuria of Rabieaux and Nicolas.

Babes, while admitting the diagnostic value of the Negri bodies, claims that the embryonal cell infiltration into the nerve tissue in the particular manner described by him is more constant and appears earlier. It is not, however, according to other observers confined to rabies. The same criticism applies to the lesions of van Gehuchten and Nelis, an embryonal cell infiltration of the connective tissue of the nerve ganglia, especially demonstrable in the plexiform ganglion of the vagus, with outgrowth of the endothelial lining of the ganglion cell capsules, and destruction of the large ganglion cells.

Courmont and Lesieur claim that in the dog there is always present a relative polynucleosis of the blood and lung juice. Whereas in this animal the polynuclears constitute normally 53 per cent of the leucocytes, in the rabid animal they form 90 per cent. In the absence of this condition they claim that rabies can be excluded.

These three microscopic lesions undoubtedly have some value from a diagnostic standpoint, and since they require no extraordinary technical methods for their demonstration they should be employed where time will permit; but they have been overshadowed of late by the search for Negri bodies which have largely occupied the attention of investigators.

Glycosuria as a symptom of rabies has been studied especially by Rabieaux and Nicolas. They examined the urine of a large number of animals, including dogs, cats, goats, and asses. They used the phenylhydrazin test and Fehling's solution, and identified the sugar by the polariscope. They concluded that while glycosuria is frequently encountered in the rabies of Carnivora, it is more pronounced, appears earlier, and is contant in herbivorous animals, constituting in the latter class a valuable aid to diagnosis. We have been unable to confirm their findings in the case of rabbits, in which they report finding sugar in all of 19 animals examined.

(6) *Inoculation tests upon animals.*—This remains the final resort in determining the diagnosis post-mortem. While the discovery of Negri bodies is regarded in many laboratories as conclusive evidence of rabies, rendering test inoculations superfluous, workers along these lines will do well to confirm their microscopic findings by ani-

mal inoculation until sure of their technic and satisfied of their ability to make a diagnosis from these findings. In the absence of Negri bodies test inoculation must be resorted to in all cases. For technique see page 63.

Irregularities may occur occasionally among inoculated animals, due to techical errors or relative immunity, but as a rule, the results will be at least as satisfactory as with the inoculation of any other pathogenic micro-organism.

Rabbits subdurally inoculated usually come down during the third week; guinea pigs often as early as the twelfth day or earlier. Sometimes, however, the period is much prolonged, as in a case mentioned by di Mattei, when the rabbits developed rabies after two hundred and seventy days, the delay being attributed to a loss of virulence dependent upon putrefaction of the material. We have observed an incubation period of one hundred and forty-six days in a rabbit inoculated in the muscles of the neck with putrefied material placed two days in glycerin. Many Negri bodies were found in the brain of this rabbit.

Schüder (112) gives the following figures relating to the incubation period in rabbits:

Method.	Virus.	First and second week.	Third week.	Fourth week.	Fifth week.	Sixth week.
		Per cent.	*Per cent.*	*Per cent.*	*Per cent.*	*Per cent.*
Subdural	Street	10.5	83.2	5.0	1.0	0.3
Intramuscular	Phenolated	8.0	52.0	20.0	14.0	6.0

Inoculation with spinal fluid obtained during life is wholly unreliable, as it usually fails even in true cases of rabies.

The *Wassermann reaction*, deviation of complement, is said to have been obtained in a few experimental cases. It has not come into use up to the present time because of the uncertain state of the test and the difficulties attending its execution.

Heller and Tomarkin (47) show that the expressed juice of brains of rabid animals has in certain proportions when combined with antirabic serum (obtained from rabbits immunized with fixed virus) the power of deviating the complement so that hemolysis does not occur. The same, however, occurred when juice from normal rabbits was used. Normal rabbit *serum*, however, failed to restrain hemolysis in combination with normal or rabic material.

Baroni, Ciuca, and Ionescu-Mihaiesti (10) got completely negative results with the serum of rabbits subjected to Pasteur immunization, with the serum of a rabbit immunized by intravenous injections of fixed virus, and with Marie's sheep serum. They used as antigen a 10 per cent emulsion of fixed virus, as complement guinea-pig serum, and blood corpuscles from a dog.

Centanni (21) found that no reliance could be placed upon complement deviation tests with rabic antigen and antirabic serum, since the antigen alone had the power to fix the complement, as had also normal nerve tissue. The antirabic serum alone likewise fixed the complement in certain cases. The neurotoxic reaction takes precedence and obscures the specific reaction.

IMMUNITY.

The subject of immunity in rabies, as in many other infectious diseases, is one of great complexity, entailing the study of all the phenomena bearing upon the rationale of the disease, natural and experimental.

Natural immunity is enjoyed by certain of the lower vertebrata, the reptiles, for example; but in the amphibia (frogs) the immunity is not absolute, but relative, and is evidenced by an extremely long period of incubation and protracted course of the disease. Birds exhibit a less marked relative immunity, while there is not known to be a mammalian species that is immune.

Individual immunity does occur, however, in animals; and occasionally dogs and other animals are found which appear to be refractory to inoculation by the severest methods. The same, it would seem, might be reasonably predicated of human beings.

The occurrence of *hereditary immunity*, passive and transient in character and transmitted only through the immunized mother to her offspring, is indicated by the experiments of Remlinger (104). Konradi (54) states that this immunity extends only to the first generation, but endures for a long time.

Two important facts are known with regard to *acquired immunity:* First, that man and animals may be rendered immune by inoculations with the modified virus of rabies; second, that their blood acquires "rabicidal" properties, i. e., the power to render inert the virulent material exposed to its action *in vitro*. There are many other facts bearing on the modus of immunity, some of which have served only to introduce new problems, other to throw some light on the main question of how immunity is established.

Any conception of immunity in rabies necessitates a knowledge of the properties of rabies virus. The essential difference between street and fixed virus has already been pointed out (p. 20), but other changes of the virus in its course of modification from street to fixed virus remain to be considered.

Virus in its fixed condition, as indicated by its constant and irreducible incubation period, is in several ways different from street virus. It is generally considered to be *more virulent* for rabbits, inasmuch as it causes the disease so much more quickly. At the same time it has to some extent lost virulence for other animals higher in

the scale, at least when injected subcutaneously. This is explained by perhaps a majority of observers upon the assumption of a toxin, i. e., a substance immediately poisonous and the product of the growth of the causative micro-organism, comparable to the toxins of *B. diphtheriæ* (a soluble toxin) or *B. pestis* (an insoluble or intracellular toxin). It is assumed that by the passage through rabbits the toxin element has been increased, hence the early onset and the paralytic symptoms; and at the same time the vegetative or reproductive power of the micro-organism has been increased (Marx). Its resistance to the inimical action of the body juices, however, is thought to be reduced, hence the innocuity upon subcutaneous injection. The toxins, according to this theory, are supposed to call forth the production of antibodies, which destroy the micro-organism and render its products inert before it has had opportunity, because of its lowered resistance, to injure the organism by its advancing growth.

This brings us to a consideration of the "toxin," which constitutes an important problem, since the demonstration of such a body has so far been insufficient for general acceptance. If no such substance exists, the present methods in general use of producing immunity in man may be advantageously modified, since it is really the fear of the effects of this hypothetical substance which at present prevents the general use of a more potent virus for immunization, which may confidently be expected to give a more rapid and intense immunity and be the means of reducing very materially the mortality after protective treatment.

The arguments advanced for and against the existence of a rabies toxin may be thus summarized:

IN FAVOR OF A TOXIN.	AGAINST A TOXIN.
The production of symptoms of fever, protracted emaciation, cachexia, and paralysis by virus filtered or otherwise treated so as to eliminate infection by a micro-organism.	That these symptoms are not typically rabiform and may be ascribed to other causes, notably the introduction of foreign nerve substance. Normal brain substance similarly treated has same action, but less marked. That these toxic symptoms are not constant. Heller and Bertarelli, 1904, observed none.
The occasional occurrence of paralytic symptoms apparently not due to rabic infection, occurring during or soon after antirabic inoculations.	Same as above, and that these symptoms are due to real street rabies, modified by the treatment to a mild or atypical course, or they are the manifestations of anaphylaxis due to the introduction of foreign proteid.
	That enormous amounts of fixed virus can be administered subcutaneously without toxic symptoms.

That the assumption of a toxin explains the difference between street and fixed rabies above described.

That *immunity* to rabies may be conferred by increasing doses of filtered emulsions and those exposed to a high temperature.

No immunity in certain experiments.

Babes reports that by the use of filtration, alcohol precipitation, and dialysis a substance can be prepared which in a fresh condition and large doses induces in dogs, rabbits, and guinea pigs fever, hyperesthesia, paresis, marasmus, and death. The substance is complex and may well be an enzyme (Marx). Mechanically subdivided frozen virus is noninfective, but is toxic (Heller, Barratt).

That no specific toxic substance has been isolated in a pure condition, and that the products described may originate in the nerve tissue rather than in the micro-organism.

That rabbit cord dried until it has lost infectious properties has lost also immunizing properties (Harvey and McKendrick).

That large doses of fixed virus do not induce symptoms more quickly than small ones.

That these symptoms are as well explained by the mechanical action of a micro-organism as by the action of a toxin (Harvey and McKendrick).

That some of the symptoms of rabies: fever, leucocytosis, hemorrhages, are those which we have come to recognize in other diseases as toxic (Babes).

That the conditions are in some respects parallel with those in smallpox where no toxin has been invoked to explain immunity, i. e., fixed virus: man-vaccine: man.

That the specific activity of antirabic serum seems to be fully explained by its *antimicrobial* properties without assuming any antitoxic action.

Heller and Bertarelli (46) believe that the production of a poisonous substance does accompany the growth of the micro-organism in nerve tissue; but, like the toxin of tetanus, it is fixed by the nervous matter. Consequently it would play no dangerous part were fixed virus to be used for human immunization unless the combination were sufficiently unstable not to withstand certain unforeseen reactions (perhaps of a neurolytic nature) within the economy.

Högyes (49) explains artificial immunity conferred by the injection of fixed virus as follows:

It appears that the action of successive injections of dilutions of fixed virus, increasing from weak to strong, or of the emulsions of

dried cord, is primarily this: that the rabies toxin contained in these arrives earlier at the cells of the central nervous system by way of the blood and lymph circulations than does the slowly progressing growth of the rabies microbe along the nerves. So that upon their arrival at the nerve centers the protoplasm of the nerve cells has already become accustomed to the action of rabies toxin and consequently the virus, introduced during the preventive inoculations or introduced for purposes of (experimental) infection, can no longer affect the nerves and cause the above-described chromatolytic changes in them. "The microbe finds only toxin-proof elements."

Marie calls attention to the fact that in immunization with dried cords a relatively high proportion of toxin to living micro-organisms may be expected in the earlier doses administered, since the drying at 22° can have had little influence upon the toxin, while it is known to gradually reduce the infectious properties of the cord, presumably by a numerical decrease of the micro-organisms. Applying to this supposition, however, the idea of fixation of liberated toxin by the nerve tissue, would it not be reasonable to suppose that the toxin contained in the dead parasites would be fixed by the surrounding nerve elements in the virus itself and thus rendered innocuous to the cells of the person or animal to be immunized?

To return to the fixed virus: Whether or not this contains a dangerous toxin, it is the fear of such a substance that has to a great extent deterred Pasteur institutes from using fresh (unattenuated) fixed virus for the production of immunity, inasmuch as it is now widely accepted that there is little to fear in the way of rabic *infection* from the subcutaneous exhibition of this substance. This belief is supported not only by actual experiment which certain observers have made upon their own persons, but by the apparent success of a method which is actually based upon the use of fresh fixed virus, namely, Ferran's method (q. v. under treatment). Ferran has stated that there is a toxin which excites the production of antibodies which destroy the virus. Hence, he claims large doses are less likely to cause *infection* than small ones, since in the latter there is proportionately little of this antibody-evoking substance, while the living virus capable of growth is just as potential of producing the disease as it would be in larger doses.

While Ferran's results are reported to be good, it was not so with one of his would-be followers, Bareggi (9), who, in an earnest effort to improve upon the Pasteur method as generally employed, adopted that of Ferran, *as he understood it*, with the result that five of his patients died within ten days of each other, and that in consequence his institute was closed by the Italian Government. The symptoms of these persons were those of the paralytic form, and their brain material, when inoculated into animals, produced rabies in the normal

period for fixed virus. This, then, constituted an infection, and not an intoxication. These cases have undoubtedly dampened the ardor of many who have wished to improve upon the usual Pasteur treatment in the direction of intensification; but it should be remembered that they are unique and counterbalanced by thousands of cases in which fresh fixed virus has been used with impunity. They are probably explained by the fact that *fixed virus, so called, is not a substance of uniform virulence.* It is true that a given strain of virus comes by repeated passage to a state beyond which there is no apparent change, and that all strains of virus thus treated arrive apparently about the same stage when finally "fixed." But these strains do differ among themselves considerably.

If we examine a large number of original descriptions of the properties of fixed virus we shall find that one author will say that in rabbits inoculated subdurally with fixed virus the animals show decided symptoms on the sixth day; another will say after six days or on the seventh; another, on the fifth day (Ivo Novi) (83); not a great difference, to be sure. But in describing the duration of the disease a greater difference is apparent, death being said to occur all the way from the sixth to the twelfth day.

In a verbal communication from a physician formerly in charge of the Pasteur treatment in Mexico, it was learned that the strain of fixed virus employed there induces symptoms in rabbits in three or four days, and deaths on the sixth day. This virus came originally from a rabbit inoculated personally by Pasteur. When originally received, some sixteen years ago, its incubation period was eight days. This steadily decreased for seven or eight years, since which time it has been fixed at the present degree of virulence.

Marie states that the virus of Santiago, Chile, kills rabbits regularly in six or seven days.

Passage of virus in animals other than the rabbit.—It is generally stated on early authority that serial experimental passage of virus in *dogs* results in diminution and final loss of virulence. If this were true the disease would disappear spontaneously from among these animals unless it were reenforced from time to time by passage through some susceptible species. The experiments of Marie (65) have shown, however, that the virus does not lose it potency when passed serially through dogs, but, on the contrary, tends to become fixed with an incubation period, when transferred to rabbits, of eight or nine days.

In rats, street virus becomes rapidly exalted in virulence, even with a few passages.

In foxes, cats, and the herbivivores also an augmentation of virulence is said to occur.

An *attenuation* and *final loss* of virulence is observed when monkeys, frogs, and birds are serially inoculated. In fact, the monkey

was utilized by Pasteur to attenuate the virus in the first attempts to obtain a noninfectious vaccinal material.

Location of the virus within the body.—The central nervous system and peripheral nerves harbor the virus with great constancy, and it was the appreciation of this fact that led to the opening up by Pasteur of the whole field of modern research on rabies.

The infectiousness is variable in different parts of the nervous system, the peripheral nerves being less virulent than the centers.

Nitsch (79) found that 0.1 mg. of the cortex of the brain (fixed virus) was lethal for rabbits in seven to nine days, while 0.5 mg. from the middle of the cord was not so, but 1.0 mg. was lethal. The medulla he found to be some five times more virulent than the middle of the cord. Later he (81) states that the brain is almost one hundred times as virulent as the cord. He claims that the gray matter is much more virulent than the white during life, but that this difference diminishes after death, due, it is assumed, to a post-mortem diffusion of the micro-organism. The cortex is somewhat more virulent than the cornu ammonis and corpora quadrigemina, which are equivalent. The sympathetic ganglia are stated to be very little virulent and the retina not at all so.

There is a widespread conviction that after death a diffusion of the virus takes place so that organs which during life would not contain it are found virulent after removal at autopsy.

The *cerebrospinal fluid* has proved avirulent in the great majority of cases where it has been investigated.

The *skin* may possibly contain the virus at the point of inoculation, the evidence of this resting upon the experiments of Pace (85), who transmitted rabies to rabbits by inoculation with the cicatrix from a fatal case of human rabies.

Certain glands contain the virus with considerable constancy if certain animal species be considered. The *salivary glands* of dogs are very constantly infectious, much less often those of rabbits, and very rarely those of man. Roux and Nocard (110) found that the saliva of a dog was virulent some three days before the onset of definite symptoms, and Rabieaux (94) claimed that the submaxillary gland could become virulent before the brain and cord. This is against the accepted idea that the virus proceeds from the brain to the salivary glands by way of the nerves.

According to Remlinger (101) the saliva of a dog may remain virulent five days after recovery from rabies, which sometimes although rarely happens. This animal had been inoculated with fixed virus.

In *man* the salivary glands are, it appears, seldom invaded by the virus except perhaps by a post-mortem diffusion of the virus. The positive results obtained by Bardach have not been obtained by

later observers in the majority of cases. However, successful inoculations with the saliva of persons suffering from rabies are reported by Bertarelli (12), and by Nicolle and Chaltiel (78), and also Magendie's original transmission of rabies from man to dogs was by means of saliva. Bertarelli, in his last-mentioned work, seems to have shown that the virus is conveyed to the salivary glands by way of the nerves.

Aqueous humor of the eye.—This fluid is generally considered avirulent, but positive results from its inoculation are reported by Courmont and Nicolas (24).

Blood.—If the virus could be demonstrated in the blood stream, it would be reasonable to expect the same result in any blood-containing organ. Results of the experiments with blood of persons and animals suffering from rabies have, however, been for the most part negative. Marie (64) was able to demonstrate virulence of the blood serum of animals artificially inoculated even before their symptoms had developed. He makes no claim that this is the general rule.

Joseph Koch states that he also has demonstrated the infectivity of the blood.

We consider it extremely likely that the period at which the blood is drawn for examination has much to do with the presence or absence of infectious properties and that the same is true of other tissues.

In this connection must be considered the question as to whether the blood stream may convey the virus to the fœtus. Evidence of such conveyance would be gained by the development of rabies in the new born if other possible means of infection, such as nursing, licking of the offspring by the mother animal, etc., could be excluded. So far as we know, no placental transmission of rabies in the human species has been published, but several instances of it have been observed in animals under experimental conditions, (Loir (61), Konradi (53), Perroncito and Carità (89), and recently Damman and Hasenkamp (25).)

Negative results of experiments along the same lines are recorded by Bombicci, Zagari, and Repetto.

There are a number of clinical observations of placental transmission in the lower animals. (Bollinger (14) cites Callicac's case; Friedberger and Frohner (35).)

Milk.—As in the blood, the virus seems to be found in the milk of rabid animals with great infrequency, but there are sufficient instances on record of the virulence of milk to cause us to regard this fluid as dangerous when taken from a cow suffering from rabies.

Bardach (8) records the case of a woman suffering from hydrophobia whose milk was demonstrated to contain the virus by inoculation of animals. A child which she had been nursing remained well.

Nocard also obtained positive results with milk from a rabid bitch. Nicolas (76) had only negative results from his experiments with herbivores.

The danger would, of course, be greater through contamination of abraded surfaces upon the hands of the milker than through ingestion of the milk.

The *liver*, *spleen*, and *spermatic fluid* appear never to harbor the virus. The *pancreas*, *lachrymal glands*, and *suprarenal capsules*, however, seem to be virulent in a large number of instances.

Resistance of the virus to physical and chemical agents.—Grinding: Experiments with virus subjected to grinding in a frozen condition (MacFadyean's apparatus) have shown that *infectiousness* may be destroyed by mechanical subdivision. The ground substance, however, had toxic properties.

Pressure: Heller (45) has shown that rabic virus resists a pressure of 200 to 350 atmospheres (Buchner press).

Centrifugalization: This is competent to render the supernatant fluid of an emulsion avirulent. The sediment, of course, is virulent.

Heat: Variations in the results of the action of heat upon rabies virus obtain just as in the determination of the thermal death point of bacteria. Marie quotes Celli to the effect that the virus is destroyed in one hour at 60° C.; Roux, in a few minutes at 60°; Högyes, in thirty minutes at 52° to 58°. Marie found that a centesimal emulsion was rendered avirulent by exposure to 60° for thirty minutes.

The following figures indicate the results of heating, as observed by Babes and by Puscariu (from Marx (69)):

Minutes.	Degrees.	Cord kills rabbits in—
		Days.
40	58	(*a*)
32	58	20
24	58	16
24	56	16
16	58	12
8	58	12
4	58	11
2	58	9

a Not killed.

Puscariu says that heating ten minutes 80°, 70°, and 60°, the animals live; 50°, animals die after eleven to twelve days; 45°, animals die after eleven days; 40°, animals die after ten days; 35°, animals die after nine days; 30°, animals die after nine days; unheated, animals die after eight days.

Cold.—Barratt subjected rabies virus to the temperature of liquid air (—190° C.) for three months without destroying its virulence.

Desiccation.—At 23° C., the virulence is usually lost in five or six days; at lower temperatures, the loss is more slowly effected; at higher temperatures, more rapidly, for example, at 35° C., *in vacuo*, the virulence is retained for 121 hours; in carbonic acid gas, 198 hours; in air, only 56 hours. Rapid dessication, however, under certain conditions is not destructive of the virulence, since Vansteenberghe (117) found that a rabic brain, reduced to a pulp and spread in a very thin layer, *in vacuo*, and rapidly desiccated for twenty-four hours in the presence of sulphuric acid, furnished a product which was capable of causing the disease in rabbits, with the same incubation period that was required for the same virus in the fresh state. Rabic virus prepared in this way is not susceptible of attenuation under the conditions usually obtaining in laboratories for the attenuation of virulent cords, even at the end of several months; in the form of powder this rapidly desiccated virus, preserved in stoppered tubes in the dark for nine months, was still capable of causing rabies in rabbits on the seventh day when subdurally inoculated. These findings were confirmed by Remlinger and Nouri (105) and Marie. The former state that it is immaterial whether the desiccation is effected in the presence of H_2SO_4, KOH, or atmospheric air; they seem to think that the rapidity of desiccation is dependent rather upon the thinness of the layer of brain pulp exposed to the drying action. In their experience, under the most favorable conditions, the powdered virus did not retain its virulence longer than three months. It is not applicable for treatment by the method of Högyes.

Harvey and McKendrick (43) claim that the loss of virulence is nearly proportionate to the loss of water extracted through drying.

Light.—This is said by Celli to destroy the virulence in forty hours (i. e., sunlight).

Rontgen rays.—These appear to have no significant action upon the virus, according to the experience of Högyes, Frantzius, Calabrese, and Ceni.

Radium.—It is claimed by Tizzoni and Bongiovanni that radium exerts a rabicidal action upon the virus *in vitro* and a curative action upon animals even after the onset of the symptoms. These claims have not been substantiated by other observers, and are contested by Calabrese, Rhens, J. Danysz, and Ivo Novi.

Dilution.—It is possible to dilute emulsions of rabies virus until a small amount will no longer transmit the disease when inoculated subdurally in rabbits. According to Högyes, this degree is attained with a dilution of 1:10,000. Nitsch (79) found that larger amounts (1 to 3 c. c.) of this dilution nearly always caused rabies.

Filtration.—Emulsified rabies virus is stated to pass the pores of certain Berkefeld filters, but not the finer Chamberland filters. Bertarelli and Volpino claim that fixed virus passes finer pores than

street virus, and direct attention to the corresponding size of the Negri bodies in these two forms of the virus. Experiments upon the filterability of virulent suspensions must be made and interpreted with caution. Imperfections of the filter itself are difficult to exclude. At the Hygienic Laboratory we have never succeeded in obtaining a virulent filtrate of fixed virus emulsions, using a Berkefeld candle and the ordinary water-pump vacuum. Marie states that no bodies can be discovered in the filtrate by the new ultramicroscopic methods.

Chemical agents.—Rabies virus is sensitive to the action of acids and alkalies, but is more resistant to chemical disinfectants than are bacterial emulsions. The difficulty in estimating the susceptibility of virus to chemical agents is that we can not note the effect of these substances upon the growth of the organism in a test tube as in the case of bacteria which may be cultivated, but must introduce mixtures containing the chemical into the body of an animal, and, to be sure of results, under the cerebral dura. Results are thus vitiated by the action of the chemical upon the animal. Fermi (32) has sought to avoid this objection by injecting the mixtures subcutaneously into rats, which are very susceptible to the virus which he employs in this manner. Until his results shall have been more fully tried out it is deemed inadvisable to accept as accurate any data as to the rabicidal action of chemical substances.

The resistance of rabies virus to biological influences.—Putrefaction of rabic nerve substance may proceed to the extent of liquefaction without completely destroying the virus. There is reason to believe, however, that the virulence may be reduced by putrefaction so that the incubation period in inoculated animals will be much prolonged.

When rabies virus is introduced into a vertebrate host it meets with conditions inimical to its growth which vary in intensity according to the site of inoculation, the species, and the amount and character of the virus. Thus, virus injected into the lymph sac of the frog is said to lose its virulence in a short time. The peritoneum exerts an unfavorable action on the virus, and attempts to inoculate animals by this route are generally unsuccessful (Remlinger (99)).

The gastric juice is so destructive of the virus that infection would hardly seem possible were it not that Fermi (33) and Remlinger (102) have succeeded in causing the disease in rats by this means.

When we consider the subcutaneous injection of virus we must distinguish the comparatively greater resistance of street virus from that of fixed virus. Apparently there are agencies at work in the subcutaneous tissues which are capable of destroying the virus under certain conditions. In the work of Kraus, Eisler, and Fukuhara (55), leucocytes or cells of organs were capable of, as they say, *adsorbing* the virus of rabies from an emulsion *in vitro* if digested

with it at 37°. Carbon and certain acids and alkaline substances possessed the same properties. All these substances had a similar action on the vaccines of Hühnerpest and cowpox.

This furnishes a hint that the formed elements in the subcutaneous tissues cooperate with the serum in the destruction of virus introduced under the skin. Since leucocytosis is known to occur during immunization with fixed virus (Nicolas and Bancel (77)), there is an abundant supply of formed elements ready to exert whatever inimical action they are capable of upon the newly introduced virus. This leucocytosis is caused also by the introduction of normal nervous substance, so that whatever fraction of the total immunity is to be attributed to leucocytic action is due probably to the nervous tissue *per se* and not to the specific elements of the virus.

A consideration of these properties leaves no doubt that the virus contains a living morphological entity which is the cause of rabies.

Having described in brief some of the properties of rabies virus it is necessary to discuss the properties of the serum which are induced by immunization with this substance. The most striking property not possessed by normal serum is that of being able to destroy the activity of the virus of rabies *in vitro* by contact with it. The blood serum of a person or other mammal subjected to a course of injections by Pasteur's method, when mixed in certain proportions with an emulsion of fixed or street virus, will cause the virus to become inert when injected subdurally into a test animal. This property is not possessed by the serum of animals suffering from rabies. Some time is necessary for the development of this property. Kraus and Heller were unable to detect it until twenty-two days after the termination of Pasteur treatment in five persons examined. Its duration is, however, of considerable length, since the same observers were able to demonstrate it in the same patients eighty-five days later. In a patient whose serum was examined at the Hygienic Laboratory two years after treatment at a Pasteur Institute very little antirabic activity was shown. All the animals injected with the virus-serum mixtures died of rabies, but there was a relative retardation of the time of onset and death corresponding to the amount of serum used.

According to Marie (68) the action of the serum upon the virus appears to be of the nature of a fixation of some component upon some specific body in the virus. Serum "saturated" with a portion of virus is deprived of the property of destroying the virulence of another portion after its recovery from the mixture by centrifugation. Normal nerve tissue, however, does not remove the antirabic property. The union between the hypothetical antibodies and antigen is instable, since virus so neutralized may regain its virulence after washing with salt solution. There is no evidence that antirabic serum

posseses a neurotoxic action, which might account for its antirabic properties.

An interesting fact in connection with the study of antirabic serum is that its activity is sometimes confined within narrow limits, and this is especially true in case the treatment of the animal producing the serum has been of long duration. To illustrate: A serum active against a definite emulsion of virus—say 1 per cent—when added in the amount of 1 c. c. might be inactive in the amounts of 0.1 and 5 c. c. The explanation given of this phenomenon is that the smaller amount was insufficient to neutralize all the virulent units, while the larger amount (5 c. c.) was hampered in its action by the excess of immune bodies over the complement which is necessary to effect the destruction of the microörganism through their mediation. Marie has noted an increase of potency of serum subjected to a temperature of 56° C.

While the serum of normal mammals has been found inactive against rabies virus by nearly all observers, the serum of some especially resistant nonmammalian species has been shown to be active when added to fixed virus in large amounts. Marie found the serum of fowls to be active in the proportion of 3 parts of serum to 1 part of fixed virus (1:100).

From immunized sheep a serum having a titre of 1:40 F. V. $\frac{1}{100}$ has been obtained.

Notwithstanding the marked antirabic properties which may be demonstrated in a serum *in vitro*, its action within the body experimentally has not given us reason to expect much usefulness in a therapeutic way. This apparently depends upon the following facts: (1) That the action of the serum is probably purely microbicidal; hence, if a toxin plays a part in the pathology of rabies no antagonism to this substance could be expected from the serum; and again, in developed rabies where the nerve cells have already been destroyed, a mere killing off of the causative organism would not result in *restitutio ad integrum*. (2) That the immunity conferred during the period of incubation is, like all passive immunity, transient in character. The microörganism might be temporarily held in check by an injection of serum; but after the rapid disappearance of the immune properties of the serum it is reasonable to suppose that it would proliferate again and produce the disease. Animal experimentation has borne out this supposition to some extent, since in the majority of tests a prolongation of the incubation period only has resulted from the injection of antirabic serum. The wonderful results reported by Tizzoni and his coworkers have unfortunately not been reduplicated by other investigators.

Literature.—Most of the important articles on serum therapy are referred to in Marie's "Etude experimentale de la rage," Paris, 1909. We would refer also to the articles by Poor and Friedmann, Collected Studies from the Research Laboratory, Department of Health, City of New York, volume 2, and Semple, in the Lancet, 1908.

In summing up the data on the modus of active immunization against rabies virus the following facts seem to be established:

1. That rabicidal properties appear in the blood serum.
2. That the brain cells in high degrees of immunity resist the action of virus directly applied to them.
3. That there is evidence that leucocytosis is induced and that leucocytes have the property of at least temporarily rendering the virus inert.

On these data we advance the hypothesis that the first step in the establishment of immunity is the production of leucocytosis. That the next is the production of antibodies in the blood serum, and that finally the nerve cells themselves may in some cases acquire resistance to the invasion or at least to the pathogenic action of the microörganism.

We do not know the relations of these factors one with another. They must be to a certain extent independent, at least as regards serum and cellular immunity, since animals which after treatment may furnish a serum of high antirabic potency, may nevertheless at the same time be susceptible to subdural infection.

TREATMENT OF RABIES.

A. *Of the developed disease.*—Up to the present time no cure for the developed disease has been discovered. From time immemorial there have been advocated various drugs and procedures for which their discoverers have claimed curative properties, but none have stood the test of time. Nearly all the drugs of the pharmacopœias have been used at one time or another in this malady, besides a great number of weird and noxious combinations. Cures are reported from the use of diaphoretic drugs and measures, especially the Russian bath, but the diagnosis in many of these cases rests upon very insecure foundation. However, it must in fairness be admitted that it is possible or even probable that recovery has taken place in man, since it is well known to have occurred in dogs; but to what extent this result has been due to treatment remains undetermined.

In recent years we have come to look to serum therapy for the cure of acute infectious diseases, but the results in the cases of diphtheria and cerebro-spinal meningitis obtained with immune sera, brilliant as they are, are no better than those obtained in malaria

and sleeping sickness, for example, with quinine and the arsenical preparations. The former are bacterial infections; the latter, protozoan. What rabies is, is undetermined, but the weight of evidence seems to favor its inclusion among the latter. Hence, from our experience in the treatment of other infections, we may as well expect the specific for rabies to be a mineral or a vegetable drug as a serum or other substance specifically related in its origin to the ultimate cause of the disease.

Antirabic serum alone has not so far saved a human being after the development of rabies, although it has undoubted prophylactic properties with definite limitations and is capable of destroying rabies virus *in vitro*.

For the present we must treat developed rabies in man symptomatically. Chloroform inhalations, prolonged if necessary, for the control of painful spasm; chloral and the bromides *per rectum*, or, possibly, curare subcutaneously. Morphine is recommended in large doses by some authors, but this may increase the nervous excitement and mental suffering. Hypnotic drugs are usually, even in very large doses, without appreciable effect. Where the patient can not swallow food, rectal alimentation is probably to be preferred to feeding by the stomach tube, the introduction of which is painful, difficult, or impossible.

Intubation or tracheotomy is probably useless for the relief of dyspnœa and suffocation, as there is generalized spasm of the respiratory muscles and the glottis may be patent all the time.

Mechanical restraint is generally unnecessary and should not be resorted to except in the violent maniacal forms. The sick room should be quiet, warm, and free from drafts. Admission to it should be as limited as possible. Attendants should preserve a calm and cheerful demeanor, and should only speak of the patient's disease to reassure him. Undoubtedly the suffering is often increased by nervous excitement and by the relation by an indiscreet attendant in the patient's hearing of dismal tales of suffering in similar cases.

B. *Prophylactic treatment of exposed persons—Local treatment of the wound.*—Cauterization has been advocated and practiced since the time of Celsus, and probably longer, since he undoubtedly took his descriptions of the process from an earlier source. When properly carried out it is undoubtedly of some benefit. It has been shown by experiment to prolong the incubation period, even when it did not prevent the extension of the infection; and in this way would allow more time for the establishment of immunity by the antirabic inoculations. It should be practiced as soon after the injuries as possible, but may be employed at any time while the wound remains open.

Actual cautery is efficient only if immediate and thorough. It involves too much suffering and destruction of tissue to be of general use. Another objection to the actual cautery is that it is difficult to reach all depths of the wound and that unreached pockets may exist where the virus is not destroyed.

The best method is to thoroughly touch all parts of the wound down to its depths with nitric acid. Carbolic acid is probably less effective. Silver nitrate is said to be very inefficient, and its use is not advised. Aside from cauterization, this wound is to be treated along the general principles of surgery. Promising experimental results with Bier's method have recently been reported by Cano (19).

Cauterization of wounds does not in the least supplant the antirabic inoculations.

General treatment.—The patient should endeavor to keep himself in good general health. Nervous excitement, fatigue, and all forms of excess, especially alcoholic, are to be avoided. Cold bathing and exposure to wet and cold are unfavorable.

Preventive inoculations.—The Pasteur treatment for the prevention of rabies in exposed persons is designed to confer immunity during the period of incubation. The production of this immunity, as at present practiced, is a long process, but fortunately the period of incubation in the majority of cases is longer. In persons in whom from a combination of the factors already mentioned (p. 21) the incubation period would be very short the Pasteur treatment fails. It also fails in certain individuals who can not be immunized, from some unknown peculiarity of their constitutional make-up. This condition is paralleled in other diseases. To this extent the present method of preventive inoculation is not ideal. It can undoubtedly be improved, but just how to do this with safety is a problem which has long been before us.

The principle upon which the Pasteur treatment is based is the production of immunity by the inoculation of rabies virus so modified as to render it innocuous. Pasteur first accomplished this by serial inoculation of monkeys, in which animal the virus loses its potency. Test animals inoculated with the spinal cord of these monkeys become immune to subsequent infection with virulent rabies virus. This method was, however, obviously inapplicable to man on a large scale. He finally devised the method at present in use, which involves the treatment of the virus in two steps: First, the serial passage of the virus in rabbits until a fixed degree of virulence is reached; second, the attenuation of this rabbit virus by desiccation.

The first of these processes is, in the light of our present knowledge, the more important, since the fixed virus is so modified as to be relatively innocuous to man. The second of these processes has been modified in various ways, or even dispensed with.

The modifications proposed or in use will be briefly indicated:

(1) *The use of unmodified fixed virus* was advocated and introduced by Ferran, of Barcelona. The results are stated to be good, but the selection of patients for treatment is stated by Remlinger to be favorable to a low mortality, inasmuch as no patient is admitted to treatment who has been bitten as long as ten days before application. Ferran emulsifies 0.08 gm. of the cord of a rabbit dead of fixed virus infection, with the aid of sand to comminute it thoroughly and to produce a fine emulsion, using 8 c. c. of fluid, apparently salt solution or bouillon. Six c. c. of the top fluid are immediately injected subcutaneously into three different portions of the body, 2 c. c. in each. These injections are repeated on five successive days. In severe cases the treatment is repeated after an interval of five to ten days (Frosch (36)).

A similar treatment has recently been employed by Proescher (93), in Pittsburg. He states that he uses does fifty times as great as those of Ferran, and has had no death from rabies in forty persons treated. He first demonstrated the innocuousness of his particular strain of fixed virus, which he designates "Pittsburg," by injecting a whole brain of a rabbit, dead of its infection, into each of two persons intramuscularly, no ill effects following. He had reduced the number of injections from two daily for ten days to one daily for six days, and contemplated a further reduction.

(2) *The dilution of fresh fixed virus.*—This method was devised by Högyes. He claims that in Pasteur's method the so-called attenuation was in reality but a numerical diminution of the rabies organisms present, a view entertained by Pasteur, and that this could be more accurately controlled by simply diluting the fresh virus with salt solution, increasing the dosage as the treatment progressed by increasing the strength of the emulsion. Högyes claims that more accurate dosage is possible by this method, and that the method employed experimentally on dogs gave more favorable results. An advantage pointed out by Harvey and McKendrick is that smaller amounts of nerve tissue in proportion to the amount of virus *per se* are inoculated, inasmuch as a large proportion of the nerve tissue of dried cords is inert as regards its power to immunize. These authors ascribe the paralytic symptoms which sometimes occur during or after immunization with dried cords to anaphylaxis induced by the repeated injection of this foreign nerve substance, and state that these symptoms are not observed with the dilution method of immunization.

The method is briefly as follows: An original emulsion of fixed virus is prepared from the spinal cord of a rabbit killed or dead of fixed virus infection, by rubbing it up with sterile salt solution (0.7 per cent) in the proportions of 1 to 100. By appropriate additions

dilutions are then prepared varying from 1:200 to 1:10,000. These dilutions are now to be used for immunizing according to the following formulæ, injecting them subcutaneously:

Simple cases: Slight hand or foot wounds.

Day.	Time.	Dilution.	Cubic centimeter.	Day.	Time.	Dilution.	Cubic centimeter.
First	a. m.	1:10,000 & 1:8,000	3 3	Eighth	a. m.	1:1,000	1.5
	p. m.	1:6,000 & 1:5,000	3 3		p. m.	1:500	1
Second	a. m.	1:5,000	3	Ninth	a. m.	1:200	1
	p. m.	1:2,000	2	Tenth	a. m.	1:6,000 & 1:5,000	3 3
Third	a. m.	1:2,000	2		p. m.	1:2,000	2
	p. m.	1:1,000	1.5	Eleventh	a. m.	1:2,000	2
Fourth	a. m.	1:1,000	1		p. m.	1:1,000	1.5
	p. m.	1:500	1	Twelfth	a. m.	1:1,000	1.5
Fifth	a. m.	1:200	1		p. m.	1:500	1
Sixth	a. m.	1:6,000 & 1:5,000	3 3	Thirteenth	a. m.	1:200	1
	p. m.	1:2,000	2	Fourteenth	a. m.	1:100	1
Seventh	a. m.	1:2,000	2				
	p. m.	1:1,000	1.5				

Severe cases: Head and face wounds.

Day.	Time.	Dilution.	Cubic centimeter.	Day.	Time.	Dilution.	Cubic centimeter.
First	a. m.	1:10,000 & 1:8,000 & 1:6,000	3 3 3	Tenth	a. m.	1:1,000	1.5
	p. m.	1:5,000 & 1:2,000	3 2		p. m.	1:500	1
Second	a. m.	1:5,000 & 1:2,000	3 2	Eleventh	a. m.	1:200	1
	p. m.	1:1,000 & 1:500	1.5 1	Twelfth	a. m.	1:6,000 & 1:5,000	3 3
Third	a. m.	1:200	1		p. m.	1:2,000 & 1:1,000	2 1.5
Fourth	a. m.	1:6,000 & 1:5,000	3 3	Thirteenth	a. m.	1:1,000 & 1:500	1.5 1
	p. m.	1:2,000 & 1:1,000	2 1.5		p. m.	1:200	1
Fifth	a. m.	1:1,000 & 1:500	1.5 1	Fourteenth	a. m.	1:6,000 & 1:5,000	3 3
	p. m.	1:200	1		p. m.	1:2,000 & 1:1,000	2 1.5
Sixth	a. m.	1:6,000 & 1:5,000	3 3	Fifteenth	a. m.	1:1,000	1
	p. m.	1:2,000 & 1:1,000	2 1.5		p. m.	1:500	1
Seventh	a. m.	1:1,000	1.5	Sixteenth	a. m.	1:200	1
	p. m.	1:500	1	Seventeenth	a. m.	1:6,000 & 1:5,000	3 3
Eighth	a. m.	1:200	1		p. m.	1:2,000 & 1:1,000	2 1.5
Ninth	a. m.	1:6,000 & 1:5,000	3 3	Eighteenth	a. m.	1:1,000	1.5
	p. m.	1:2,000 & 1:1,000	2 1.5		p. m.	1:500	1
				Nineteenth	a. m.	1:200	1
				Twentieth	a. m.	1:100	1

Between these formulæ gradations may be arranged to suit individual cases.

This method has been extensively employed with good results at Budapest, and the same principle has been adopted in India.

(3) *Fixed virus attenuated by drying.*—The original method of Pasteur, the one most extensively practiced, has the advantage that it may be administered by private physicians at a distance from the laboratory, since the dried virus can be preserved for some time by glycerinization and shipped in this condition from the laboratory. Again, its wide application has created a confidence in its use which the less extensive experience with other methods, however worthy they may be, has not begotten.

The original schema of its employment has been modified from time to time, so that scarcely two institutions now follow identical procedures. This modification has been effected along three lines: (1) With regard to the time consumed by the treatment, either lengthening or shortening the original period of fifteen days; (2) dispensing with some of the more attenuated cords; (3) increasing or diminishing the dosage given at individual injections. In addition must be mentioned the unintentional modifications caused by the use of small rabbits, the relatively smaller cords of which desiccate, and consequently attenuate more rapidly than do those of rabbits of standard weight (2,000 grams); and by drying cords at temperatures other than 23° C. At lower temperatures the cords attenuate in virulence less rapidly.

The schemata devised by Pasteur and until recently followed at the Institute at Paris are three, the least intense of which is rarely employed. The other two, together with modified schemata advocated by other authorities, are inserted here to illustrate the direction and extent of the modifications:

Pasteur's original schemata (Marx).

Light schema.			Intense schema.		
Day of treatment.	Age of dried cord.	Amount of injected emulsion.	Day of treatment.	Age of dried cord.	Amount of injected emulsion.
	Days.	*c. c.*		*Days.*	*c. c.*
First	14	3	First	14	3
	13	3		13	3
Second	12	3		12	3
	11	3		11	3
Third	10	3	Second	10	3
	9	3		9	3
Fourth	8	3		8	3
	7	3		7	3
Fifth	6	2	Third	6	2
	6	2		6	2
Sixth	5	2	Fourth	5	2
Seventh	5	2	Fifth	5	2
Eighth	4	2	Sixth	4	2
Ninth	3	1	Seventh	3	1
Tenth	5	2	Eighth	4	2
Eleventh	5	2	Ninth	3	1
Twelfth	4	2	Tenth	5	2
Thirteenth	4	2	Eleventh	5	2
Fourteenth	3	2	Twelfth	4	2
Fifteenth	3	2	Thirteenth	4	2
Sixteenth	5	2	Fourteenth	3	2
Seventeenth	4	2	Fifteenth	3	2
Eighteenth	3	2	Sixteenth	5	2
			Seventeenth	4	2
			Eighteenth	3	2
			Nineteenth	5	2
			Twentieth	4	2
			Twenty-first	3	2

According to this schema, head injuries require twenty-one days of treatment.

Babes's modification for a man who applied for treatment six days after having received a finger bite.

Day of treatment.	Age of dried cord.	Amount of injected emulsion.	Day of treatment.	Age of dried cord.	Amount of injected emulsion.
	Days.	*c. c.*		*Days.*	*c. c.*
	12	4	Eighth	5	3
	11	4		4	3
First	12	4	Ninth	3	2
	10	4		2	2
	10	4	Tenth	2	2
	9	4		1	2
Second	9	4	Eleventh	Pause.	.....
	8	4	Twelfth	8	2
	8	4		7	2
	7	4	Thirteenth	7	2
Third	7	4		6	2
	6	4	Fourteenth	6	2
	6	4		5	2
	5	4	Fifteenth	5	2
Fourth	5	3		4	2
	4	3	Sixteenth	4	2
	4	2		3	2
	3	2	Seventeenth	3	2
Fifth	3	2		2	2
	2	2	Eighteenth	2	2
Sixth	Pause.	.....			
Seventh	7	4			
	6	4			

Nitsch uses 5 to 1 day cord; 0.1 to 0.15 gm. of cord to 2 c. c. physiological solution. Treatment lasts but ten days, two injections daily. Each patient receives 2.5 gm. of cord during treatment. Very severe cases are treated sixteen days.

Of 1,424 cases treated, 6 died=0.42 per cent. One case stopped treatment before its completion, and 5 died before fifteen days after completion. These results are very favorable.

Nitsch suggests, as has also been suggested by Babes, the concomitant use of serum therapy with the use of cerebral cortex. Rabic cerebral cortex is shown to be fifty times as virulent as rabic cord.

The technic of the Pasteur method will be more fully considered later (p. 65).

The method in use at the Hygienic Laboratory is given on page 68.

(4) *Fixed virus attenuated by heat.*—This method advocated and used by Puscariu and Vesesco at Jassy, and by Babes, seems to be merely a more difficult manner of attaining the same end accomplished by the desiccation and dilution methods. It is said, however, to have been more recently adopted in Japan. Babes defends the method inasmuch as his mortality since employing it has been very low. He combines this method in severe cases with the use of antirabic serum.

It is claimed that by heating emulsions of fixed virus to 80° C. for fifteen minutes the organism of rabies is killed, but that a relatively thermo-stabile substance, capable of provoking immunity, is left unaltered. Paralytic symptoms (see *ill effects from treatment*) are said to be more frequent after this form of treatment.

(5) *Fixed virus modified by partial digestion.*—This so-called Italian method consists in exposing the virus before injection to the action of artificial gastric juice. It is claimed that in this way an actual attenuation is accomplished; not merely a numerical reduction of the exciting organisms, and that virus so treated can not be restored to its original virulence by passage through animals.

(6) *Fixed virus acted upon by bile.*—Has been suggested for treatment following the experiments of Frantzius, Vallée, and Solomon, and Kraus, but so far as known has not been applied to man.

(7) *Fixed virus acted upon by glycerin.*—While glycerin has the power to conserve rabies virus in an active condition for a month or more (Calmette), on prolonged exposure this virulence is suddenly lost (two and one-half months, Loir; five months, Rodet and Galavielle (107)), although the immunizing power is, to some extent at least, retained. Rodet and Galavielle note the immunizing action of rabic nerve matter which has lost its virulence through prolonged conservation in glycerin. Rarely is this immunity sufficiently substantial to withstand subdural-test inoculation with fixed virus,

but it constantly resists subcutaneous inoculation. Galavielle and Martin (38) tested the same immunity with the subdural inoculation of street virus in rabbits and found it to be considerably more marked than when tested in the same way with fixed virus, since out of 13 rabbits subcutaneously immunized only 6 developed rabies, and 2 of these only after prolonged incubations. They suggest the possibility of glycerinized virus treatment for persons exposed to rabies.

(8) *Fixed virus acted upon by antirabic serum.*—Marie (67) claims that by treating, at least for the preliminary injections, with fixed virus partially neutralized with antirabic sheep serum *in vitro*, a rapid immunity is conferred, inasmuch as the lysis ordinarily accomplished in the tissues is partially effected *in vitro* by the antirabic serum. He claims that in this way virus of high immunizing power, but of diminished infectious properties, can be administered. He states that since 1904 nearly three hundred patients have been treated in this manner with excellent results.

The method is described as follows:

One gm. of the bulb of a passage rabbit (f. v.) is rubbed up with 9 c. c. of weak broth or physiological salt solution and the emulsion strained through cloth. To 2 c. c. of this decimal emulsion is added 4 c. c. of antirabic sheep serum, previously heated for thirty minutes at 56° C. The 6 c. c. mixture, containing an excess of virus (i. e., unneutralized), is injected into two places under the skin of the abdomen. The same injections are repeated on the three following days, after which the patient receives inoculations of dried cord, beginning with that of the sixth day. The serum used was of insufficient strength to neutralize the virus in the proportions given.

This treatment he considers especially applicable to severe bites and to belated cases. The mortality in treated persons is said to have been lowered since the introduction of this treatment.

(9) *Fixed virus acted upon by carbolic acid.*—Fermi (31) has had better success by this method, he claims, than is attained by the Pasteur method. He claims that the Pasteur method does not invariably protect the Muridæ against one and two day cords and claims that a virulent strain of fixed virus might cause rabies in man, and that his 5 per cent emulsion of fixed virus acted upon by 1 per cent carbolic acid is free from these objections.

(10) *Fixed virus acted upon by mechanical disintegration.*—The experiments of Barratt and of Heller have shown that by prolonged rubbing in the frozen condition the infectiousness of fixed virus can be destroyed, and, further, that this destruction is not due to the low temperature but to an actual breaking up of the micro-organisms, which is readily effected in the congealed state. While this comminuted material is not infectious and can not therefore reproduce the disease, it is toxic and capable of inducing a prolonged

cachexia, marasmus, and sometimes paralysis, which can only be attributed to a poison contained within or elaborated by the micro-organism. Heller has also shown that animals may be immunized to this substance by the administration of progressively increasing doses, and that this immunity is active also against rabies infection. Of 10 rabbits so treated, only 1 developed rabies after subcutaneous inoculation with passage virus, while all of the control animals died of rabies. This method has not thus far been applied to the treatment of man.

Serum therapy.—Great hopes that a cure for developed rabies was at hand were entertained when it was learned that the blood of immunized persons and animals possessed the power to destroy the infectious principle of rabies virus *in vitro*. It was hoped to establish an immediate passive immunity, comparable to that caused by antidiphtheric serum, as distinguished from the delayed active immunity conferred by the older methods and comparable to that induced by vaccination against smallpox. Although encouraging results have been obtained in the lower animals with respect to their immunization with antirabic serum, with regard to its curative effects serum therapy has been very disappointing. Marie advises the dried and pulverized serum as a local application to wounds caused by animals suspected of rabies, and employs the serum in the fresh state to partially neutralize the fixed virus used in the first injections of the course of antirabic treatment as above given in detail. The properties of antirabic serum are discussed under the subject of Immunity.

Who shall receive the Pasteur treatment?—Persons who have been bitten by rabid animals or who have had open wounds or scratches contaminated with the saliva of such animals should receive the treatment. At times the question has been raised whether persons who have drunk of the milk of rabid cows should be subjected to the preventive inoculations. While the possibility of infection by this means is extremely remote, there is some evidence that the virus can sometimes be present in the milk. On the other hand, infection through the intact mucosa of the alimentary tract is highly improbable, since the action of the gastric juice is destructive to the virus.

Persons bitten by animals presenting symptoms strongly suggestive of rabies should receive the antirabic treatment whether or not the suspicion is confirmed by histological examination and pending the result of the inoculation test, if such is made. The necessity for treatment arises from the fact that rabies is really much more prevalent among animals than is generally suspected, and too much valuable time will be lost by delaying treatment for the result of animal inoculation.

Persons bitten by animals not showing any of the symptoms of rabies are not exempt from the necessity for treatment until the biting animal, which should be closely confined and carefully observed for certainly not less than two weeks, shall be shown to be free from the disease, since the saliva is known to be virulent sometimes several days before the onset of the symptoms; four to five days according to Roux and Nocard (110); Zagarro (120), twelve days.

In this connection it is deemed pertinent to repeat that the histological examination is conclusive only when positive; that Negri bodies (p. 33) when demonstrable in the central nervous system are positive indication, according to present knowledge, that the animal was rabid; but the failure to find them does not exclude rabies, since they may not have developed to a demonstrable condition at the time the animal was killed, or they may have escaped detection through technical imperfections, or, finally, they may not be present even in well-developed rabies in the portions examined.

The results of the Pasteur treatment and its modifications.—In order to determine the value of the method it is necessary to compare the mortalities of treated and untreated persons. We believe that no exact comparison can be made, but that there is ample evidence to show that an enormous saving of life has resulted from the timely administration of the treatment.

The inaccuracy of this comparison arises from the difficulty of determining its latter factor, namely, the mortality of untreated persons. It is hardly to be supposed, even in countries where official supervision is the most intimate, that every dog bite or even every case of human rabies has come to official notice, or that the existence of rabies in the biting animal can have been accurately determined in every case. The severity and site of the injury must also be considered as a variable and in many cases unrecorded quantity. Sources of error are found also in the determination of the mortality of treated persons, but to a much less extent. Patients can, for the most part, be accounted for during the year following the treatment; and, thanks to the present state of knowledge, the diagnosis of rabies in the biting animal can be accurately established in many cases. Then, too, the arrangement of the records of patients into categories (see p. 70) according to the basis of diagnosis lends additional accuracy to treatment statistics.

Estimations of mortality in untreated persons.—In Prussia statistics are collected with as much care, probably, as in any other country. The recent statistics of Doebert (1909), based on official records, show a mortality of 14.8 per cent in 122 untreated persons who were significantly bitten by rabid animals within the period from 1902 to 1907. Cases of insignificant bruises, etc., and of bites by

animals not proved to have been rabid were excluded in the computing of these statistics. He quotes the estimates of other observers, as follows: Horsley, 16 per cent; Reifer, 15 per cent; Dujardin-Beaumetz, 14 per cent; Högyes, 15 to 16 per cent.

Schüder (112) collected statistics of 14,959 persons bitten by rabid or suspected animals and untreated, and found that the mortality varied greatly in different countries, but averaged 8.9 per cent. We should of course expect Schüder's figures to be lower than those of Doebert, since the character of the injury and the proof of rabies in the biting animal were not considered in the former's estimate.

Marx (1904) thinks that the older figures were, as a rule, too high, and that a mortality of 6 to 10 per cent of untreated bitten persons would approximate the truth.

In the United States there are no available statistics of a general scope upon which a mortality estimate of untreated persons can be based. Among the isolated attempts to form such an estimate is that of Brawner (15), who followed in the newspapers such cases of bites and deaths as were reported to have occurred within the Southern States. Of 80 persons untreated, except by the "madstone," there were 16 deaths reported=20 per cent, while of 170 treated at the Pasteur Institute only 1 died.

Mortality in treated persons.—Doebert reports a mortality of 1.3 per cent among 1,741 persons having received *significant bites* from *rabid* animals and taken the Pasteur treatment during the period of 1902–1907. Only 0.85 per cent, however, died more than fifteen days after the end of the treatment, and hence are regarded as flat failures of the treatment, for which no claim is made that immunity can be invariably established by it before that time.

In general, it may be stated that the total mortality of bitten persons having received the antirabic inoculations is pretty constantly about 1 per cent, of which one-half could not, from the nature of the treatment, have been expected to live, on account of the short time permitted for the establishment of immunity. In other words, 0.5 per cent die of rabies within fifteen days after the completion of the treatment that can not be charged to its failure, but to a want of time to establish immunity.

Remlinger (97) gives the mortality of treated persons in twenty institutes, which shows an average mortality of 0.5895 per cent occurring within fifteen days of the end of the treatment. These figures cover various periods of time, the latest year reported being 1903.

Results are always poorest where the bites are the most severe, for example, where wolves abound, and where from the lack of transportation facilities a long time has elapsed before the patient is received for treatment. Results are better as the older formulæ of treatment are replaced by those in which more virulent material is administered.

This is illustrated by the experience at Cracow (Nitsch (80)) where, with the use of a mild form of treatment lasting but ten days, the mortality was 1.05 per cent; but since the adoption of a more intensive treatment it has been reduced to 0.42 per cent; or, eliminating the deaths occurring within fifteen days after treatment, nil. There were 1,424 cases treated.

These two facts taken together, namely, the increased mortality with severe bites and the decreased mortality with greater intensity of treatment, furnish a powerful argument for the reality of rabies and for the innocuousness and the value of preventive inoculations.

THE TECHNIC OF CERTAIN OPERATIONS CONCERNED IN THE MANAGEMENT OF THE ANTIRABIC LABORATORY.

(1) *Examination of suspected material for evidence of rabies.*—This material consists ordinarily of the head of some animal, oftenest the dog. It should be shipped packed in ice if practicable; if not, it may be wrapped in cloths soaked in bichloride of mercury or other germicidal solution. For microscopical examination, material may be sent already fixed and placed in weak alcohol. For inoculation tests, the fresh material or the medulla placed in glycerine is suitable.

Many methods have been employed for the demonstration of the Negri bodies. The individual examiner must determine the method which gives uniform results in his hands.

In our experience, the rapid methods, while often giving brilliant results, and undoubtedly time saving when positive, have been less reliable in the end than the sections. It is our practice to make smears from Ammon's horn and examine them immediately. Failing in the search for the bodies, other portions of the brain are examined: the cerebral cortex, cerebellum, and medulla. If the search is still unsuccessful, sections are made in which the cells are found in their normal relations and the search is facilitated by their proximity.

Both histological examination and inoculation tests should be made, at least until one's technic is assured, and even then the inoculation tests should always be applied when the histological examination is negative or doubtful. For this purpose the medulla should be preserved in glycerine pending the result of the histological examination.

Removal of the brain of animals for examination.—The head is held by an assistant by means of a pair of lion-jawed forceps attached to the snout and held in one hand, while the other hand, protected with several folds of a towel wet with antiseptic solution, is employed to steady the head at appropriate points. The skin is divided down the median line and the muscles dissected away from the bone. The outer tables of the skull are then sawed through in a line running from the foramen magnum to the frontal sinus on each side. Division

of the bone is completed with the chisel and mallet, and the calvaria torn off. The membranes are divided and the brain removed by shelling it out whole with closed curved scissors, cutting off the cranial nerves as they appear. Where the tentorium is osseous, it may be divided with bone shears if it does not pull out readily. It is advisable to remove the brain intact if possible in order that the different portions, especially the hippocampus major, may be recognized and specimens taken from them.

Locating the hippocampus or cornu ammonis.—The brain is placed base upward and the temporal lobe lifted outward away from the median line until the cornu comes into view as a long cylindrical whitish body tapering at its uppermost end. It is further identified by sectioning it transversely when the characteristic concentric light and dark zones will be seen. This peculiar structure also serves to distinguish the cornu if a horizontal section is made with a sharp knife through the hemisphere. The cornu can be recognized even in softened brains if the parts be not too much disturbed by handling.

Locating the plexiform ganglion.—This may be accomplished by following up the course of the pnumogastric nerve, which will be found in relation to the carotid artery, to a point one-half inch or less from the base of the brain where the enlargement will be encountered and may be removed for sectioning and examination to demonstrate the changes described by Van Gehuchten and Nelis.

Staining Negri bodies.—We have found the Mallory eosinmethylene-blue method, early recommended by Williams and Lowden, to be the most dependable one. It may be shortened considerably without serious detriment.

Smears are made on slides or cover glasses by crushing a small section of the brain matter between two of them and drawing them out under gentle pressure to produce a fairly thin film.

(*a*) Fixation in Zenker's solution for fifteen minutes.

(*b*) Wash in tap water.

(*c*) Ninety-five per cent alcohol tinted with iodine.

(*d*) Absolute alcohol five minutes.

(*e*) Five to 10 per cent watery solution of eosin (Grubler, W. g.) five minutes.

(*f*) Stain in Unna's polychrome methylene-blue two to three minutes.

(*g*) Wash in water.

(*h*) Differentiate in 95 per cent alcohol.

(*i*) Blot off, dry, and examine with oil immersion lens.

Sections.—Fix thin pieces in Zenker's solution for two and one-half to three hours. Wash well. Ninety-five per cent alcohol, two changes, one hour each. Absolute alcohol, two changes, one hour each. In cedar oil until cleared. Cedar oil and paraffine equal

parts, one hour. Paraffine, two changes, one hour each. Embed, section and stain as above, but increase time somewhat, especially in iodine-alcohol where the sections should remain until the mercury granules disappear.

Negri bodies stained in this way take a magenta color, easily distinguished from the bright eosin tint of the red-blood corpuscles, and dark-bluish granules are distinguishable in their interior. The nerve cells and the nuclei of the glia and the endotheliad cells are blue (*see* Pl. I).

This method of staining is less successful following more rapid methods of fixation, but fairly good pictures are obtained with sections fixed in acetone.

The material is placed in acetone for forty-five minutes, then in several changes of paraffine; embedded and sectioned. The iodine-alcohol step is omitted.

Williams secures beautiful specimens by a modification of Mann's method, which has the advantage of being rapid and easy. Our results with this modification, while sometimes very satisfactory, have been irregular and have necessitated in some instances a resort to the longer methods. The method is as follows:

For smears: Make smears as usual. Fix for ten seconds in neutralized methyl alcohol (500 c. c. alcohol+0.25 gm. Na_2CO_3), to which 0.1 per cent of picric acid has been added. Stain over the flame until steamed in methylene blue (sat. alc. sol.), 30 c. c.; fuchsin (sat. alc. sol.), 5 c. c.; distilled water, 300 c. c. Wash. blot, and examine.

Frothingham's method of making touch preparations is designed to preserve the natural relations of the cells, and in this way facilitate the search for the Negri bodies.

Other methods are those of Harris (42), which is very good; Giemsa, as employed by Negri (74); Neri (75), a modified Gram's stain; Hematoxylin and fuchsin; Lentz (58), eosin and Lœffler's alkaline methylene blue; Borel's eosin-methylene blue-silver oxide, given in detail in Laveran and Mesnil's "Trypanosomes et trypanosomiasis," Paris, 1904, pages 10 and 11; and numerous others devised and employed by various observers. Bohne (13) gives a number in full.

Heyman (44) reports no results of practical value with the use of the so-called rapid methods, stained or unstained smears, Negri, Luzzani, or Van Gieson's method, dark field illumination and frozen sections. He uses paraffine sections and Lentz's modification of Mann's method almost exclusively.

The search for the rabic tubercles of Babes and the ganglion changes of Van Gehuchten and Nelis involve only the ordinary histological procedures which require no special descriptions.

(2) *Animal inoculations.—Animals used:* For this purpose rabbits have the advantage of exhibiting the symptoms in a more characteristic manner than the smaller animals, and the disadvantage of having a longer incubation period, which is rarely less than fourteen days, and frequently much longer.

Guinea pigs are much cheaper and exhibit symptoms several days earlier than do rabbits, but frequently the disease is of such short duration that little opportunity is afforded for observation.

Rats have been used to some extent, but they require a special holder and are difficult to handle. They are suitable for the intramuscular injection only.

In default of rabbits and guinea pigs, in emergency almost any small mammal may be utilized for subdural inoculation.

Material.—Portions of the medulla, or failing in this the cerebral cortex, are the most suitable for inoculation. In the case of man where autopsy is denied, the saliva or aspirated cerebro-spinal fluid may be used; but the results have significance only when positive, since these secretions are frequently noninfectious in positive cases.

Fresh material is of course preferable, but old and putrefied material may still be employed if emulsified in glycerine and permitted to stand twenty-four to forty-eight hours before its injection. Some of the emulsion should be kept for further inoculation in case acute death occurs in the first inoculated animals. Or the material may be rubbed up with sufficient quantity of 1 per cent solution of carbolic acid and injected.

Method of inoculation.—With fresh material the subdural inoculation is to be preferred, but with putrid material deep injection into the muscles of the neck will result in nearly as large a percentage of "takes," with fewer deaths from intoxication or sepsis. The incubation period, however, is likely to be prolonged.

The emulsion is made by rubbing up a small piece of brain tissue (size of a pea) in a sterile mortar, and then adding a few cubic centimeters of salt solution and reducing it to a uniform consistency.

Subdural inoculation.—This method of inoculation is performed most satisfactorily by etherizing the animal. Make a one-fourth inch incision through the skin just back of the eyes and to one side of the median line, draw the skin back over the parietal bone, and with the aid of a stylet or a small trephine or jeweler's drill effect an opening through the skull large enough to readily admit the needle, which, attached to a small syringe, is now passed through the opening and 0.2 c. c. of the emulsion injected. The needle should be bent forward one-fourth inch from its tip so that the fluid may get well under the dura. The skin is then allowed to slip forward and the opening is closed with collodion and a little cotton. The operation re-

quires but a few seconds, and as soon as the animal recovers from the anesthetic it resumes feeding with no apparent inconvenience.

The old method of removing a button is unnecessarily laborious. Sutures are not required, since only a small incision is made, and moreover are sometimes followed by stitch abscesses.

The illustration (Pl. II) shows a convenient form of head holder for rabbits, which is easily constructed.

This method is applicable for routine inoculation of passage animals with fixed virus in the production of antirabic vaccine.

(3) *Removal of the cord.*—The method of Oshida (84) has many advantages over the older method of laminectomy, which it has wholly superseded at the Hygienic Laboratory. As improved by us, it is carried out in the following manner:

The rabbit, when completely paralyzed, is killed with chloroform and nailed to a board, back uppermost, and thoroughly wetted down with an antiseptic solution (1 per cent tricresol). An incision is made through the skin from the forehead nearly to the tail and the skin laid back on each side, the ears being cut close to the head. An area 1 inch wide is seared with a hot iron around the occiput and nuchal region and ear openings, and another across the spine just above the sacrum. The spine is then divided transversely in the center of the seared areas by means of bone-cutting forceps. The neck is dissected loose from the skin, etc., and a large square of sterile gauze is inserted beneath it. The lumbar region is dissected up for a few inches and a similar piece of gauze placed beneath it. Then a piece of telegraph wire about 14 inches long, bent into a handle at one end and having a small wisp of cotton twisted about the other end, is used to push the cord out of its canal. The spine is steadied by a pair of lion jawed forceps (Pl. III).

An assistant catches the cord with forceps as it emerges from the cervical opening and lifts it out. The spinal nerves are torn off during this procedure and the membranes stripped off, leaving a clean sterile cord. A silk ligature, with one long end, is placed around the upper end and another just below the middle of the cord, which is then cut in two just above the lower ligature. A small piece is cut off the lower end of the upper portion and placed in a tube of bouillon, which is incubated as a test of sterility. The cords are then hung in a drying bottle (see illustration). All manipulations are under aseptic conditions.

Drying the cord.—The cords are hung in the drying bottles (Pl. IV) by their attached ligatures, which are retained by the cotton plug. Sticks of caustic potash are previously placed in the bottom of the bottle, as shown. The bottles are properly labeled with the number of the rabbit and the date, and placed in the incubator having a constant temperature of 22° to 23° C. This may consist of

the ordinary gelatine incubator maintained in a cold room by gas, or one of the more elaborate cabinets designed for this purpose.

Use of the cord.—After one day drying the cord is known as "1-day cord," after two days as "2-day cord," etc. Pieces may be cut off each day and used immediately, in which case rabbits will have to be killed daily in order to have cords of all degrees of virulence always at hand; or, as is the practice at the Hygienic Laboratory, 1-centimeter pieces are cut off daily up to the eighth day and placed immediately in glycerine. Cords in glycerine and kept in a cold place will retain their potency at the point where it was when they were cut, little if any diminished, for several weeks and a constant supply may thus be kept on hand without the daily killing of rabbits. The material conserved in this way is available for shipment and use at a distance from the laboratory. It is first cut into one-half centimeter pieces, each of which serves, when emulsified with 2½ c. c. of salt solution, for one injection.

Titration of the serum of persons or animals for the determination of antirabic properties in vitro.—The conditions of experiments of this kind should always be carefully recorded. The method employed at the Hygienic Laboratory is similar to that used by Marie, and is carried out as follows: Virus is taken immediately after death from the medulla of a series rabbit which has been inoculated subdurally with fixed virus, has shown definite symptoms on the seventh day thereafter, has become completely paralyzed, and has been killed on the eighth day by chloroform. A weighed amount of this virus is rubbed up by hand very finely in a porcelain mortar, and enough 0.8 per cent sodium chloride solution added gradually without interrupting the trituration to make 100 parts. To 1 gram of bulb, 99 c. c. of salt solution would be added. When thoroughly emulsified the fluid is filtered through a paper filter (Schleicher and Schüll No. 588 Faltenfilter). Equal amounts (1 c. c.) are now added to each of a series of small conical test glasses. The serum to be tested is now added to all but one of these glasses in different amounts (e. g., 0.01, 0.02, 0.05, 0.1, 0.2, 0.5, 1.0 c. c.). The mixture is stirred up with a sterile platinum needle, and placed in the cold room or ice box for twenty-four hours. During this time they should be stirred up once or twice. Now sufficient salt solution is added to each glass to bring the total quantity contained by each up to the maximum contained by any, including, of course, the control to which no serum has been added. Equal amounts (0.2 c. c.) are now injected into a series of test animals, rabbits or guinea pigs, corresponding to the series of dilutions. Accuracy of dosage is secured by making the injections intracerebrally rather than subdurally. The antirabic property of the serum is indicated by the period of incubation and of death of the animals.

TREATMENT OF PATIENTS BY THE HYGIENIC LABORATORY.

Patients coming to the Hygienic Laboratory for the preventive inoculations are treated according to the following formula, which corresponds closely to that in use at Berlin. All formulæ are more or less arbitrary, and this one is no exception. It was adopted for the following reasons:

(1) That cords dried for a longer period than eight days are devoid of infectious properties and presumably are also lacking in immunizing properties. Their use may therefore be regarded as a waste of valuable time, since the average incubation is all too short to consume any part of it with superfluous procedure.

(2) On the other hand, the use of cords of greater virulence than eight-day cord to begin with was set aside as having a less widely demonstrated innocuousness and less authoritive support, although we believe that it can be done without danger. So far as our experience has gone, no advantage would have accrued, since up to the present time (January, 1910) no deaths have occurred after treatment.

(3) Following the custom established by Pasteur, the injections of more virulent material are spaced through the treatment and increased in number near its termination.

Scheme for mild treatment.

Day.	Cord.	Amount injected.			Day.	Cord.	Amount injected.		
		Adult.	Five to ten years.	One to five years.			Adult.	Five to ten years.	One to five years.
	Injections.	c. c.	c. c.	c. c.		*Injections.*	c. c.	c. c.	c. c.
1	8-7-6=3	2.5	2.5	2.0	12	4=1	2.5	2.5	2.5
2	5-4=2	2.5	2.5	1.5	13	4=1	2.5	2.5	2.5
3	4-3=2	2.5	2.5	2.0	14	3=1	2.5	2.5	2.0
4	5=1	2.5	2.5	2.5	15	3=1	2.5	2.5	2.0
5	4=1	2.5	2.5	2.5	16	2=1	2.5	2.0	1.5
6	3=1	2.5	2.5	2.0	17	2=1	2.5	2.0	1.5
7	3=1	2.5	2.5	2.0	18	4=1	2.5	2.5	2.5
8	2=1	2.5	1.5	1.0	19	3=1	2.5	2.5	2.5
9	2=1	2.5	2.0	1.5	20	2=1	2.5	2.5	2.0
10	5=1	2.5	2.5	2.5	21	2=1	2.5	2.5	2.0
11	5=1	2.5	2.5	2.5					

Scheme for intensive treatment.

Day.	Cord.	Amount injected.			Day.	Cord.	Amount injected.		
		Adult.	Five to ten years.	One to five years.			Adult.	Five to ten years.	One to five years.
	Injections.	c. c.	c. c.	c. c.		*Injections.*	c. c.	c. c.	c. c.
1	8-7-6=3	2.5	2.5	2.5	12	3=1	2.5	2.5	2.0
2	4-3=2	2.5	2.5	2.0	13	3=1	2.5	2.5	2.0
3	5-4=2	2.5	2.5	2.5	14	2=1	2.5	2.5	2.0
4	3=1	2.5	2.5	2.0	15	2=1	2.5	2.5	2.0
5	3=1	2.5	2.5	2.0	16	4=1	2.5	2.5	2.5
6	2=1	2.5	2.0	1.5	17	3=1	2.5	2.5	2.5
7	2=1	2.5	2.5	2.0	18	2=1	2.5	2.5	2.0
8	1=1	2.5	1.5	1.0	19	3=1	2.5	2.5	2.0
9	5=1	2.5	2.5	2.5	20	2=1	2.5	2.5	2.5
10	4=1	2.5	2.5	2.5	21	1=1	2.5	2.5	2.0
11	4=1	2.5	2.5	2.5					

Treatment at a distance from the laboratory.—This has been rendered possible in recent years through the use of glycerinated virus. Glycerine may be added to the emulsion, and this shipped in a special container; or the rabbit cord itself, cut into pieces representing single doses, may be sent in bottles containing glycerine. These pieces of cord must be emulsified by the physician using them. This latter method has been used in shipping virus from the Hygienic Laboratory to state health officials, upon their requests to the Surgeon-General, United States Public Health and Marine-Hospital Service, Washington, D. C. It necessitates some technical skill in its preparation and use, and for this reason it is stipulated that the virus shall be administered under the immediate supervision of the state health authorities.

The bottles containing the virus are accompanied by the following directions and copies of the schemata of injections:

Directions for the use of rabies virus shipped from the Hygienic Laboratory, U. S. P. H. & M. H. S., Washington, D. C.

The virus should be kept, until used up, in an ice box or other cold place. This material is perishable, and must not be kept on hand for future use. Each bottle contains the number of doses required, until further shipments are made, of cord dried for the number of days indicated on the label. Further shipments of cord to complete treatment already begun are made without further request.

Dose.—Each small section of cord (about one-half cm.) constitutes one dose.

The following equipment is necessary for making and using the emulsion:

Physiological salt solution.

Alcohol.

Absorbent cotton or gauze.

Glass or porcelain mortar and pestle (capacity, 10 to 20 c. c.).

Thumb forceps.

Hypodermatic syringe (at least 3 c. c. capacity) with large needle.

Glass pipette, 5 c. c., graduated at least to 0.5 c. c.

Small conical test glass or beaker or other small container.

These must be sterilized, and then the instruments, etc., rinsed in sterile salt solution. Aseptic technique throughout.

To make the emulsion.—Remove one section of cord from the bottle with the thumb forceps, and rinse it free of glycerin with sterile salt solution in the small glass container, place it in the empty mortar, and, without the addition of any fluid, rub up as finely as possible. Then 2½ c. c. of the salt solution are gradually added by means of the pipette, taking care between the additions of salt solution to rub to a uniform consistency. Draw the full amount of the emulsion into the syringe.

To use.—Scrub the skin at site of inoculation with alcohol and inject the emulsion into the subcutaneous tissue, being careful not to injure muscular layers or visible veins. Alternate successive injections on the two sides of the anterior abdominal wall.

For the schemes of injections see accompanying sheets.

A record should be kept of each case, giving essential particulars concerning the patient, his injury, treatment, and subsequent history, with dates; and also concerning the biting animal and the basis upon which the diagnosis of rabies was made in it.

For the purpose of accurately determining the value of the Pasteur or other preventive treatment of rabies, the plan adopted at the Pasteur Institute at Paris should be followed.

Patients receiving the treatment are classified according to the evidence of rabies in the biting animal as follows:

Group A. Rabies demonstrated by animal inoculation.

Group B. Rabies diagnosed by a competent veterinarian.

Group C. Cases in which, from the evidence at hand, it is supposed that the biting animal was rabid.

To this may now be added another group in which the diagnosis is based upon the demonstration of Negri bodies.

Contraindications for treatment.—No specific contraindications exist. It is true, in a small percentage of syphilitics, alcoholics, and neurasthenics, and probably in some apparently healthy persons, a transient paralysis may occur or even death from ascending paralysis. These cases, however, are not definitely proven to be due to the treatment, and in any event they are outweighed by the total saving of life. Pregnant women have taken the treatment without disturbance. A boy severely affected with chorea seemed improved rather than otherwise by the treatment.

Ill effects from the treatment.—The statement is frequently seen that the Pasteur treatment is without danger *per se*. This statement is not strictly true. There are on record a small number of fatal cases in which the treatment was apparently responsible, and a larger, but still small, number in which a serious but temporary paralysis occurred during or immediately after the treatment, and could reasonably be attributed to it.

These cases can not be considered as seriously impairing the value of the treatment any more than deaths from the administration of anesthetics, fat embolism in the reduction of fractures, or from anaphylaxis in the administration of diphtheria antitoxin, respectively, occurring in a very small percentage of cases, can be considered to favor the general abandonment of these procedures. The rarity of this accident will be appreciated when we consider that Remlinger (98), upon searching the records of 107,712 persons that had received the treatment, found but 40 cases of treatment paralysis, 2 of which resulted fatally. Subsequent reports have increased the total number of reported cases to about 76 with 2 additional fatal ones (Müller, Pampoukis, Fabricius, Jones).

The principal explanations that have been advanced for the phenomenon of treatment paralysis are as follows:

(1) That the symptoms are due to the street virus received from the biting animal which becomes so modified by treatment that the disease runs an atypical and usually a mild course with recovery as a common result. This view was supported by Roux, Laveran, and a

majority of the early observers of the condition. Against this view are the facts that the accident occurs as frequently, if not more so, after slight injuries as after severe bites; that several cases have occurred in which the biting animal was not rabid (Nedrigailoff und Ostrjanin (73), Fabricius (30), Torini, see Müller, p. 269); that pain at the site of injury is rarely experienced; that the period of incubation is too short for infection with street virus; and finally that paralytic rabies is usually considered an intense rather than an attenuated form of rabic infection. Babes and Marinesco (6) describe the lesions, which are not those of rabies, in a fatal case, and state that the animals inoculated with the brain matter failed to take rabies. Josef Koch (52) expresses himself in favor of the view that these cases are abortive street virus infections.

(2) That the condition is due to infection introduced with the virus, in the form of contaminating microorganisms, during the treatment. Several observers have claimed to have isolated such organisms, but they were of different kinds in each case, while the symptoms were the same. Again, myelitis of bacterial origin is a very fatal disease, while these cases of treatment paralysis having symptoms of myelitis, or at least congestion of the cord or bulb, recover spontaneously in the great majority of instances.

(3) That treatment paralyses are instances of fixed-virus infection. The early appearance of the symptoms in many cases is against this view, since virulent emulsion is not commonly injected during the first days of treatment, and the paralytic phenomena have been known to appear from the first to the seventh day after the administration of the first virulent injection.

(4) That the rabies "toxin" is the cause of the paralysis. While some authors (Babes, Remlinger, Marie, etc.) seem confident of the existence of such a substance *in active form*, discussion elsewhere given (p. 39) appears to leave room for reasonable doubt. However, the transient nature of the disorder is adduced as an argument in favor of an intoxication.

(5) That hysteria is competent to explain the phenomena. Evidently this is not so, since the stigmata of hysteria are not commonly found and the sphincteric involvement speaks against it.

(6) That the phenomenon is one of anaphylaxis, due to the repeated injection of a foreign proteid represented by the rabbit cord employed for the preventive inoculations. This idea, advanced by Harvey and McKendrick and entertained by Müller, seems to have much to recommend it. It is stated that these phenomena have never followed treatment with diluted fixed virus as used by Högyes, and it is in this form of treatment that the proportion of nerve substance to active virus is at a minimum.

Marinesco adverts to the cytotoxic action of foreign nerve substance as a possible explanation of the phenomena.

Whichever, if any, of these explanations may prove to be the true one, it is evident that a special individual susceptibility must exist, otherwise the paralysis would occur much more frequently among those who have received the preventive inoculations.

Certain authors have claimed that in the majority of their cases of treatment paralysis, a neurotic personal or family history could be traced, which might argue a peculiar susceptibility of the nervous system. Alcoholism and sudden chilling of the body are likewise supposed, and apparently with good reason, to render the nervous system hypersensitive to the exciting cause, whatever that may be. The phenomenon is said not to have occurred after treatment by Högyes's method, and to have been most common after treatment according to the Roumanian practice.

The symptoms usually appear from a week after the commencement of the treatment to shortly after its termination. There is usually insomnia, headache, and a feeling of numbness in one or more extremities, oftener in the lower. Sometimes pain or itching at the site of the injection is complained of. The affected member becomes weak and finally paralyzed and the paralysis extends in a day or two to other portions of the body. The patient becomes helpless. The rectum and bladder are frequently more or less paralyzed. Bulbar symptoms are not rare; there may be difficulty in swallowing, but there is no hydrophobia. The special senses are frequently affected, especially vision. The paralysis is flaccid, the reflexes being diminished or lost as a rule. The Babinski phenomenon is sometimes observed. The condition of the patient may become most alarming, but usually a rapid improvement takes place and health is regained in a few weeks, although months are sometimes required for complete restoration. In some instances the condition is apparently a myelitis; in others the peripheral nerves appear to be involved. Pfeilschmidt records a case in which the paralysis involved chiefly the facial muscles.

No special treatment is indicated. The preventive inoculations should be discontinued, although in several reported cases they have been persisted in without apparent detriment.

Some benefit has been claimed by Remlinger from the use of antirabic serum. Cystitis, bedsores, and inhalation pneumonia are to be guarded against.

There appears to be no criterion by which this condition can be differentiated from paralytic rabies at its inception, but a few observations may be of value in this connection: The initial fever is usually slight, that in rabies is higher; the pains are not referred to the bitten parts, but rather, if at all, to the site of the injection;

the period of incubation is usually too short for that of true rabies; the mental symptoms of rabies are usually absent. The termination is by recovery as a rule, frequently at a surprisingly rapid rate, sometimes much longer deferred.

Among 180 persons treated at the Hygienic Laboratory there occurred one case of treatment paralysis in a man who had had meningitis in childhood. The paralysis was rapid in its progress, and the patient's condition became rather alarming, but he made a good although somewhat tedious recovery. (For references to treatment paralysis see Bibliography Nos. 4, 6, 16, 26, 30, 37, 41, 43, 44, 48, 50, 52, 57, 72, 73, 87, 90, 93, 98, 106, 109.)

Other ill effects from the treatment are, as a rule, of minor importance. The patient usually complains of some discomfort at the site of inoculation, and may be nervous or sleepless, or, on the other hand, drowsy for the first few days. Except the local discomfort, there is no reason to think that these symptoms are specific manifestations of any action of the virus. They are probably psychical manifestations induced by the novelty of the situation. A local reaction of the tissues to the virus is commonly observed in our experience during the second week. Rarely it is observed during the entire treatment. It seems to have no relation to the potency of the virus used. It has seemed to us that children and thin people exhibited it less markedly than others. So far as we know no relation between the local reaction and the establishment of immunity has been worked out. We regard the phenomenon as a manifestation of hypersusceptibility to foreign nerve tissue. Patients have been observed to develop the reaction simultaneously in several inoculation sites after about a week's treatment, during which none had appeared. Marie (66) mentions indurations following the second of two injections, seventeen days apart, and due to the wide separation of the species (dog and rabbit). The reaction consists of a slightly raised and edematous area from 1 to 3 inches in diameter with an erythematous blush occurring around the needle puncture and appearing several hours after injection. There is usually considerable itching and some pain and tenderness. The appearance is shown in Plate V. This subsides in the course of a day, leaving a palpable " knot " under the skin, which is slowly absorbed. The lymph nodes associated with the region are commonly a little enlarged and tender.

Abscesses have not been observed at the Hygienic Laboratory, although they were reported some time after treatment in some marines who came from Panama for treatment. A considerable number of these men also developed malarial attacks. It has been observed that dormant malaria appears to be awakened to activity by the treatment. However, this condition is so frequently observed

in persons recently removed from the Tropics that a recrudescence of malaria can hardly be definitely attributed to the treatment.

Various skin rashes are sometimes observed. These have in our experience taken the form of mild urticaria, which disappeared in a few days.

SUPPRESSIVE MEASURES AGAINST RABIES.[a]

The suppression of rabies wherever it exists is worth undertaking seriously from the view point of the sanitarian, the dog owner, and those who own valuable stock. The annual toll of human death is not very great, but a single death from a terrible disease which is preventable is a reproach to the sanitary administration. The loss of time and money to those exposed persons who are obliged to take the Pasteur treatment, frequently through no fault or neglect of their own, is very considerable. Their mental suffering can not be expressed in dollars and cents. During 1908 at least two large hunt clubs were obliged to destroy their entire kennels because of infection with rabies, and many hundreds of valuable dogs were sacrificed for the same reason. The loss of stock—cattle, horses, sheep, and swine—from rabies mounts up to thousands of dollars annually in some areas of the United States.

The measures by which rabies can be exterminated, or at least reduced to a minimum, are well known. It is their application which causes the difficulty, and the crux of this difficulty is popular sentiment and popular apathy. The average citizen either does not believe in the existence of rabies, or takes no active interest in the matter until a personal experience affects his pocketbook or his personal comfort, and then the active interest which he suddenly develops extends no further than his personal affairs. Measures to be effective must be state wide in their application, and a uniformity of legislative and executive action in contiguous States is necessary if any lasting benefit is to be secured.

The history of the fight against rabies in certain sections of Europe is especially instructive in this connection. Great Britain, an island, had little difficulty in completely eradicating rabies where the suppressive measures were administered centrally by the board of agriculture and fisheries in 1897, and in preventing its introduction by adequate quarantine. The same result was obtained in the Scandinavian countries, which are peninsular and have little connection with the mainland. Holland, less isolated, has been less successful, and Belgium, with an extensive French boundary line, still less so.

[a] This section is practically identical with the Report of the Committee on the Prevention and Suppression of Rabies, approved as a basis for the formulation of regulations by the conference of state health officers with the United States Public Health and Marine-Hospital Service, April 30, 1910.

In France the popular opposition to measures against the liberty of dogs, and especially muzzling, has prevented any considerable reduction in the prevalence of rabies except in certain parts where these measures have been well carried out. Germany points with justifiable pride to the extermination of the disease in certain parts where it was formerly very prevalent, but it has been powerless to prevent its persistence and even increase in certain border States, notably Silesia, where infection is continually received from Austria, and where the racial and philological differences in the inhabitants tend to impair the effectiveness of measures.

The States of the Union are for the most part not separated by natural barriers competent to prevent the spread of rabies from one to another. Consequently a uniformity of method must be adopted in order to combat the disease successfully. Antirabic regulations must have an areal distribution as wide as that of the disease, and must persist until, as in England, the disease is completely eradicated. Otherwise local and periodic outbreaks are bound to occur and a condition as bad as, or worse than the present one will ensue.

Without indicating an exact form of regulations for the prevention of the spread of rabies, it may be well to discuss the measures which have proven valuable, what their limitations and the special indications for their employment are. In introduction, it may be stated that the domestic dog and his wild congeners are the principal disseminators of rabies, and it is to prevent the possibility of transmission by these animals that measures must be directed. The wild animals—wolf, coyote, and in certain sections the skunk—are now fast being reduced to negligible numbers in the United States, and consequently require only local measures such as are maintained against any noxious wild beast to prevent their being a danger to man. As has been previously pointed out, the idea entertained by Sime and others that an intermediate host, such as the wild rabbit, is required for the reinforcement of rabies virus is probably erroneous and at any rate without epidemiological significance.

(1) *Destruction of ownerless dogs.*—This is perhaps the most effectual single measure against rabies. It should obtain at all times and in all places, irrespective of the prevalence of rabies. It implies the maintenance of an official dog-catching force and a pound equipped for the detention and humane destruction of dogs. The personnel of the dog-catching force should be carefully selected with regard to probity and good judgment, since these qualities are necessary in those who have an unpopular duty to perform, and the lack of them soon leads to antagonism and even abuse on the part of the public. The ownerless dog, for the purposes of sanitary law, should be defined as a dog unprovided with a collar and license tag of the current year. Impounded dogs may be kept for a few days to permit

of their redemption upon the payment of tax and costs. The sale of impounded dogs is to be discountenanced.

(2) *License fee.*—This is also a permanent measure. All owned dogs should be licensed yearly. Payment of fee secures a license for one year and a tag to be worn continuously, attached to the dog's collar. The tag bears the license number corresponding to the entry on the official register, the number of the year during which it is good, and the name of the place in which it is issued. Changing the form of the tag from year to year renders obsolete tags more readily detectable.

A shield on the collar bearing the name and address of the owner, is a convenience but not a necessity, since these data can be obtained from the register by referring to the license number.

It is suggested in towns of such size and concentration of population that in the opinion of the authorities it would be practicable, to have the tag affixed by the licensing officer or his assistants, in order that it may be securely attached, that the identification of the dog may be complete, that the condition of health of the animal may be observed and its sex ascertained.

The license fee operates in the control of rabies by (*a*) rendering ownerless dogs recognizable by the absence of the tag of the current year, (*b*) reducing the total number of dogs kept, and (*c*) restricting the ownership of dogs to those who have some sense of their value and will, consequently, take better care of them.

The fee should be sufficiently high to accomplish the last two ends. Dog license moneys should be expended in the administration of the dog laws, and not used for unrelated purposes. Unspayed female dogs should be licensed at a higher rate than spayed females or male dogs, with a view to limiting the natural increase of the dog population. Evasion of this provision by deception should be punishable by fine or forfeiture of the dog or the right to keep dogs. In case the licensing officer or his assistant personally affixes the tag, evasion of this fee is precluded.

(3) *Dog owners should be made legally responsible for damage inflicted by their dogs.*—The absurd practice now obtaining in some places of the public assumption of such damages and their defrayal out of the dog license funds by the community should be discontinued. Damage by ownerless dogs may, however, be compensated out of public funds.

(4) *The education of the dog-owning public in matters relating to the care of dogs as affecting the spread of communicable diseases.*—Since public sentiment is such an important factor in the control of rabies, it should be intelligently directed by the authorities charged with this duty through their periodical official publications and leaflets, and cordial cooperation of the officials with the public directly.

(5) *Muzzling.*—This measure should be in constant application wherever rabies exists. It should be abandoned only when the disease has been absent from a region a sufficiently long time to warrant a feeling of security that it has been eradicated and is not merely in abeyance. This time varies much in different regulations now in vogue, but the opinion of many competent observers is that it should not be less than six months. Even this period can not be regarded as absolutely safe, since incubation periods in excess of this time are known to have obtained. Muzzling ordinances for certain months or seasons of the year, when based on a supposed seasonal prevalence, are, in the face of facts, illogical. They should be issued and maintained *pro re nata.* These regulations should involve not only the immediate vicinity concerned, but a sufficient zone about it to insure safety. From the known tendency of mad dogs to wander far, this zone should be commensurately wide.

Muzzling ordinances should prescribe that muzzles be constructed of metal, should prevent biting, should be humane, and permit of the dog's opening its mouth, and should be fitted to the animal, being changed from time to time if necessary, with the animal's growth.

Efficient muzzling stands second only to the destruction of ownerless dogs in efficiency in reducing the prevalence of rabies, and in extensive epizootics takes first place. Unfortunately it is always opposed by a considerable portion of the population, and in many places is not rigidly enforced. Popular enlightenment only can improve this condition. The chief objection against muzzling comes from the dog lover, who claims that it is cruel. There is some justice in this, inasmuch as an ill-constructed or ill-fitting muzzle undoubtedly causes suffering to the animal. A well-made metal muzzle of the basket type, permitting the dog to open its mouth but not to bite, and fitted to its head, is at least as humane as the bit which these critics place in the horse's mouth. Dogs soon become accustomed to wearing them and soon show their appreciation when they are applied, since they know it means an outing for them.

It has been suggested that licensing authorities prescribe the exact type of muzzle to be employed, or even supply the muzzles themselves to secure a suitable article.

Where muzzling is prescribed for the fiscal license year it is recommended that the license tag be firmly affixed to the muzzle itself, so that an unmuzzled dog would be amenable to the rules applying to unlicensed animals.

Muzzling is effective by preventing dogs possibly afflicted with rabies from transmitting the disease by bites, by necessitating the frequent observation of dogs at feeding times, etc., and by indicating an ownerless dog by its absence. When a muzzle is removed from a dog during the period of the ordinance the animal should be re-

strained by chaining up or by confinement in a suitable inclosure to prevent its running at large.

(6) *Restraint of dogs.*—The compulsory confinement of dogs by their owners on their private premises is a temporary measure employed with success in heavily infected regions. Its duration should not be less than three months and its efficacy increases with a longer period of enforcement. The area of the application should be the same as that in the case of muzzling, upon which measure it may be superimposed if considered necessary. To provide for the exercise necessary to dogs which are thus confined it should be permitted that they be led muzzled in leash at public places. In England special provisions against the night wandering of dogs were found useful.

Special provisions at all times should be made against the running at large of owned female dogs while in heat. Owners of such dogs who allow them at large at such times, even though properly tagged and muzzled, should be made subject to penalty. Female dogs in heat and at large cause the congregation of many dogs together, fights arise among them, and an opportunity for the transmission of rabies occurs if the disease be present in any stage of infectiousness among them. The progeny of such dogs is usually of an undesirable mongrel kind and if not destroyed is soon turned loose to swell the wandering dog population.

(7) *Leading in leash.*—This measure is not advised except the dog at the same time be muzzled. Evasions are so readily and frequently effected that provisions must be made so that if the animal is temporarily released by its owner it will be powerless to inflict bites.

(8) Compulsory notification of the authorities by dog owners and veterinarians of cases of rabies or suspected rabies in dogs or other animals is a useful measure in the early discovery of foci of infection. It should be followed by immediate official veterinary investigation and the destruction of the animal if the diagnosis be confirmed. In case of doubt, especially where a person has been bitten by the animal, effective isolation and observation for at least ten days if necessary should be instituted, to allow time for the development of pronounced symptoms and the confirmation or disproval of the suspicion. The heads of animals so destroyed should be sent for examination to a laboratory maintained by the authorities in charge of antirabic work. Disinfection under official supervision of kennels, stalls, etc., occupied by rabid animals is advisable.

Pending official investigation of suspected cases, the animal should be safely confined, and curative measures should not be attempted on account of the danger of infection.

Bitten animals should also be reported, and in the case of dogs and cats it is wisest that they be destroyed. In the case of valuable

stock it should be permitted that they be isolated or quarantined for at least six months from the time of the bite. It should be provided that if dogs, on account of their value, are ever permitted to be quarantined rather than immediately destroyed after being bitten by a rabid animal, this quarantine be carried out by the authorities, or under their supervision, and that the expense be borne by the owner.

The commercial use of any part, including the hide, of an animal killed for rabies must be prohibited unless such parts have previously been rendered innocuous to the satisfaction of the authorities. Proper disposal of carcasses must be enjoined.

Rabies or hydrophobia in man should be made "reportable" throughout the country.

(9) *Quarantine.*—To prevent the introduction of rabies, a quarantine of at least six months should be imposed upon imported dogs. One year would be a safer but scarcely more effectual period, since there are few enthusiasts who would submit to a six months' detention of their dogs, or attempt to import them were this enforced. Quarantine has been effectual in preventing the introduction of rabies in Australia, where the long journey is a strong adjunct, and in England. In the latter country special provisions are made for performing dogs, which permit their introduction into the country under strict police supervision. In Germany dogs may not be moved from one section to another without a certificate from an official veterinarian and other provisions. The expense of quarantine must be borne by the owner.

(10) Immunization of the lower animals has been suggested and even carried out to a slight extent. It is not applicable to dogs, since it is evident that no large proportion of a dog population can be reached by any such method. Valuable dogs should be so cared for that no danger of infection exists. In the event of such a dog being bitten, protective inoculations may be given, if commenced with little delay, to save the life of the animal, but not as a general sanitary measure.

Herds of cattle have been successfully protected by inoculating them; but it is reported that in the method employed—intravenous injection—there was some loss from infection. In our opinion this method of preventing the spread of rabies in the lower animals is not worthy of serious consideration.

CONCLUSIONS.

In conclusion it may be well to summarize briefly what we know about rabies and what we would like most to know.

It is apparent that the disease is quite prevalent in the lower animals and not as rare in man as has been supposed. Exact informa-

tion as to its prevalence in the United States is not available and its acquisition is necessary. Concerning the species of animals susceptible to experimental infection, we know that all mammals with which man comes in contact can be successfully inoculated, but that those which play a significant part in the perpetuation of the disease are few in number and largely confined to the dog tribe. We now know that outbreaks of rabies in animals are not confined to any particular season of the year.

We have a good deal of data on the pathological findings of the disease, but there are many points concerning its essential pathology that require elucidation. We know that rabies is caused by a living microorganism which invades the nervous system and can be thrown off in the saliva. The exact nature of this organism is still unknown, as is also the nature of its activities and products within the body. The isolation of this parasite, be it animal or vegetable; its cultivation upon artificial media, so that it may be observed under conditions favorable for the determination of its characters, and especially the extraction of its toxic products, if there are such, would seem to offer the greatest opportunity for the discovery of a means of curing the developed disease. Our knowledge of the symptoms of rabies is sufficient to enable us to make a diagnosis in the majority of cases, yet we lack a laboratory test which is applicable during the life of the patient or animal. Inoculation tests enable us to make sure the postmortem diagnosis when suitable material is available, but in practice they require so much time that their value is restricted. The Negri bodies appear to be specific for rabies, but the determination of their exact significance, and their relations to somewhat similar bodies found in other diseases, is still a problem and a most important one.

Until our information concerning the causative organism and the essential pathology of rabies is made definite, our ideas concerning its immunity must necessarily be somewhat vague. We do know, however, that artificial immunity can be conferred during the usual incubation period, and this knowledge has been of great service to us. The possibilities of antirabic serum have not been exhausted by trial. It deserves further investigation, but our present data do not warrant us to expect very much benefit from this source. The treatment of developed rabies by means of drugs, while it has received considerable attention in the past, perhaps because of the discouraging outcome of the earlier attempts at treatment, has received but little attention in recent years. In view of the facts that the balance of evidence leans toward the protozoan nature of rabies, and that certain protozoan infections are amenable to cure by specific drugs, it is our opinion that research in this direction should not be abandoned. The most promising line of investigation in this connection would appear to be based not upon the physiological action of the

drug but upon its action upon the parasite. Here we are limited at once by our lack of knowledge. Administration by the intraspinal method should not be neglected.

Attempts to improve upon the methods of the immunization of exposed persons are desirable, in order to eliminate the small percentage of failures and the very much smaller proportion of injurious results. In making such attempts, however, we must not jeopardize human life by the use of methods which are without experimental basis. The ill effects which have occurred in a very small proportion of treated cases should be traced, if possible, to their source, to determine whether they are really attributable to the treatment, and if so to what element thereof, so that it may be remedied; or whether they really represent a benign influence of the treatment in modifying an otherwise fatal case of rabies into a mild form.

Finally, as regards the eradication of rabies, we have now and have had for a long time all the knowledge of rabies necessary to effect its entire suppression. This knowledge can be summed up in a single sentence, to wit: Rabies is perpetuated in the dog through the infliction of bites by a rabid dog and does not arise spontaneously. If all rabid dogs could be prevented from biting other animals, rabies would in the course of a year be a mere historical curiosity of medicine, an illegitimate field of research for the investigator in pure pathology, a plaything for the controversialist. There are few infectious diseases the prevention of which rests, as in rabies, upon a single definite measure. The public can not say with reference to rabies, "Let the medical profession or scientist show us the cause of this disease and how it may be prevented, and we will do the rest." This information has been furnished, and it is incumbent upon the public, once it has been informed, to bestir itself. Otherwise, the patient work of "patching a bad job" must go on, the slow searching out of better "patches" must continue, and more experimental animals must be sacrificed for the protection of human life.

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LIST OF HYGIENIC LABORATORY BULLETINS OF THE PUBLIC HEALTH AND MARINE-HOSPITAL SERVICE.

The Hygienic Laboratory was established in New York, at the Marine Hospital on Staten Island, August, 1887. It was transferred to Washington, with quarters in the Butler Building, June 11, 1891, and a new laboratory building, located in Washington, was authorized by act of Congress, March 3, 1901.

The following *bulletins* [Bulls. Nos. 1–7, 1900 to 1902, Hyg. Lab., U. S. Mar.-Hosp. Serv., Wash.] have been issued:

*No. 1.—Preliminary note on the viability of the *Bacillus pestis*. By M. J. Rosenau.

No. 2.—Formalin disinfection of baggage without apparatus. By M. J. Rosenau.

*No. 3.—Sulphur dioxid as a germicidal agent. By H. D. Geddings.

*No. 4.—Viability of the *Bacillus pestis*. By M. J. Rosenau.

No. 5.—An investigation of a pathogenic microbe (*B. typhi murium* Danyz) applied to the destruction of rats. By M. J. Rosenau.

*No. 6.—Disinfection against mosquitoes with formaldehyde and sulphur dioxid. By M. J. Rosenau.

No. 7.—Laboratory technique: Ring test for indol, by S. B. Grubbs and Edward Francis; Collodium sacs, by S. B. Grubbs and Edward Francis; Microphotography with simple apparatus, by H. B. Parker.

By act of Congress approved July 1, 1902, the name of the "United States Marine-Hospital Service" was changed to the "Public Health and Marine-Hospital Service of the United States," and three new divisions were added to the Hygienic Laboratory.

Since the change of name of the service the bulletins of the Hygienic Laboratory have been continued in the same numerical order, as follows:

*No. 8.—Laboratory course in pathology and bacteriology. By M. J. Rosenau. (Revised edition, March, 1904.)

*No. 9.—Presence of tetanus in commercial gelatin. By John F. Anderson.

No. 10.—Report upon the prevalence and geographic distribution of hookworm disease (uncinariasis or anchylostomiasis) in the United States. By Ch. Wardell Stiles.

*No. 11.—An experimental investigation of *Trypanosoma lewisi*. By Edward Francis.

*No. 12.—The bacteriological impurities of vaccine virus; an experimental study. By M. J. Rosenau.

*No. 13.—A statistical study of the intestinal parasites of 500 white male patients at the United States Government Hospital for the Insane; by Philip E. Garrison, Brayton H. Ransom, and Earle C. Stevenson. A parasitic roundworm (*Agamomermis culicis* n. g., n. sp.) in American mosquitoes (*Culex sollicitans*); by Ch. Wardell Stiles. The type species of the cestode genus *Hymenolepis;* by Ch. Wardell Stiles.

No. 14.—Spotted fever (tick fever) of the Rocky Mountains; a new disease. By John F. Anderson.

No. 15.—Inefficiency of ferrous sulphate as an antiseptic and germicide. By Allan J. McLaughlin.

*No. 16.—The antiseptic and germicidal properties of glycerin. By M. J. Rosenau.

*No. 17.—Illustrated key to the trematode parasites of man. By Ch. Wardell Stiles.

*No. 18.—An account of the tapeworms of the genus *Hymenolepis* parasitic in man, including reports of several new cases of the dwarf tapeworm (*H. nana*) in the United States. By Brayton H. Ransom.

*No. 19.—A method for inoculating animals with precise amounts. By M. J. Rosenau.

*No. 20.—A zoological investigation into the cause, transmission, and source of Rocky Mountain "spotted fever." By Ch. Wardell Stiles.

No. 21.—The immunity unit for standardizing diphtheria antitoxin (based on Ehrlich's normal serum). Official standard prepared under the act approved July 1, 1902. By M. J. Rosenau.

*No. 22.—Chloride of zinc as a deodorant, antiseptic, and germicide. By T. B. McClintic.

*No. 23.—Changes in the Pharmacopœia of the United States of America. Eighth decennial revision. By Reid Hunt and Murray Galt Motter.

No. 24.—The International Code of Zoological Nomenclature as applied to medicine. By Ch. Wardell Stiles.

No. 25.—Illustrated key to the cestode parasites of man. By Ch. Wardell Stiles.

No. 26.—On the stability of the oxidases and their conduct toward various reagents. The conduct of phenolphthalein in the animal organism. A test for saccharin, and a simple method of distinguishing between cumarin and vanillin. The toxicity of ozone and other oxidizing agents to lipase. The influence of chemical constitution on the lipolytic hydrolysis of etheral salts. By J. H. Kastle.

No. 27.—The limitations of formaldehyde gas as a disinfectant with special reference to car sanitation. By Thomas B. McClintic.

*No. 28.—A statistical study of the prevalence of intestinal worms in man. By Ch. Wardell Stiles and Philip E. Garrison.

*No. 29.—A study of the cause of sudden death following the injection of horse serum. By M. J. Rosenau and John F. Anderson.

No. 30.—I. Maternal transmission of immunity to diphtheria toxine. II. Maternal transmission of immunity to diphtheria toxine and hypersusceptibility to horse serum in the same animal. By John F. Anderson.

No. 31.—Variations in the peroxidase activity of the blood in health and disease. By Joseph H. Kastle and Harold L. Amoss.

No. 32.—A stomach lesion in guinea pigs caused by diphtheria toxine and its bearing upon experimental gastric ulcer. By M. J. Rosenau and John F. Anderson.

No. 33.—Studies in experimental alcoholism. By Reid Hunt.

No. 34.—I. *Agamofilaria georgiana* n. sp., an apparently new roundworm parasite from the ankle of a negress. II. The zoological characters of the roundworm genus *Filaria* Mueller, 1787. III. Three new American cases of infection of man with horsehair worms (species *Paragordius varius*), with summary of all cases reported to date. By Ch. Wardell Stiles.

*No. 35.—Report on the origin and prevalence of typhoid fever in the District of Columbia. By M. J. Rosenau, L. L. Lumsden, and Joseph H. Kastle. (Including articles contributed by Ch. Wardell Stiles, Joseph Goldberger, and A. M. Stimson.)

No. 36.—Further studies upon hypersusceptibility and immunity. By M. J. Rosenau and John F. Anderson.

No. 37.—Index-catalogue of medical and veterinary zoology. Subjects: Trematoda and trematode diseases. By Ch. Wardell Stiles and Albert Hassall.

No. 38.—The influence of antitoxin upon post-diphtheritic paralysis. By M. J. Rosenau and John F. Anderson.

No. 39.—The antiseptic and germicidal properties of solutions of formaldehyde and their action upon toxines. By John F. Anderson.

No. 40.—1. The occurrence of a proliferating cestode larva (*Sparganum proliferum*) in man in Florida, by Ch. Wardell Stiles. 2. A reexamination of the type specimen of *Filaria restiformis* Leidy, 1880=*Agamomermis restiformis*, by Ch. Wardell Stiles. 3. Observations on two new parasitic trematode worms: *Homalogaster philippinensis* n. sp., *Agamodistomum nanus* n. sp., by Ch. Wardell Stiles and Joseph Goldberger. 4. A reexamination of the original specimen of *Tænia saginata abietina* (Weinland, 1858), by Ch. Wardell Stiles and Joseph Goldberger.

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No. 43.—The standardization of tetanus antitoxin (an American unit established under authority of the act of July 1, 1902). By M. J. Rosenau and John F. Anderson.

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No. 45—Further studies upon anaphylaxis. By M. J. Rosenau and John F. Anderson.

No. 46.—*Hepatozoon perniciosum* (n. g., n. sp.); a hæmogregarine pathogenic for white rats; with a description of the sexual cycle in the intermediate host, a mite (*Lelaps echidninus*). By W. W. Miller.

No. 47.—Studies on Thyroid: I. The relation of iodine to the physiological activity of thyroid preparations. By Reid Hunt and Atherton Seidell.

No. 48.—The physiological standardization of digitalis. By Charles Wallis Edmunds and Worth Hale.

No. 49.—Digest of comments on the United States Pharmacopœia. Eighth decennial revision for the period ending December 31, 1905. By Murray Galt Motter and Martin I. Wilbert.

No. 50.—Further studies upon the phenomenon of anaphylaxis. By M. J. Rosenau and John F. Anderson.

No. 51.—Chemical tests for blood. By Joseph H. Kastle.

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No. 58.—Digest of comments on the Pharmacopœia of the United States of America (eighth decennial revision) and the National Formulary for the period ending December 31, 1906. By Murray Galt Motter and Martin I. Wilbert.

No. 59.—The oxidases and other oxygen catalysts concerned in biological oxidation. By Joseph Hoeing Kastle.

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○

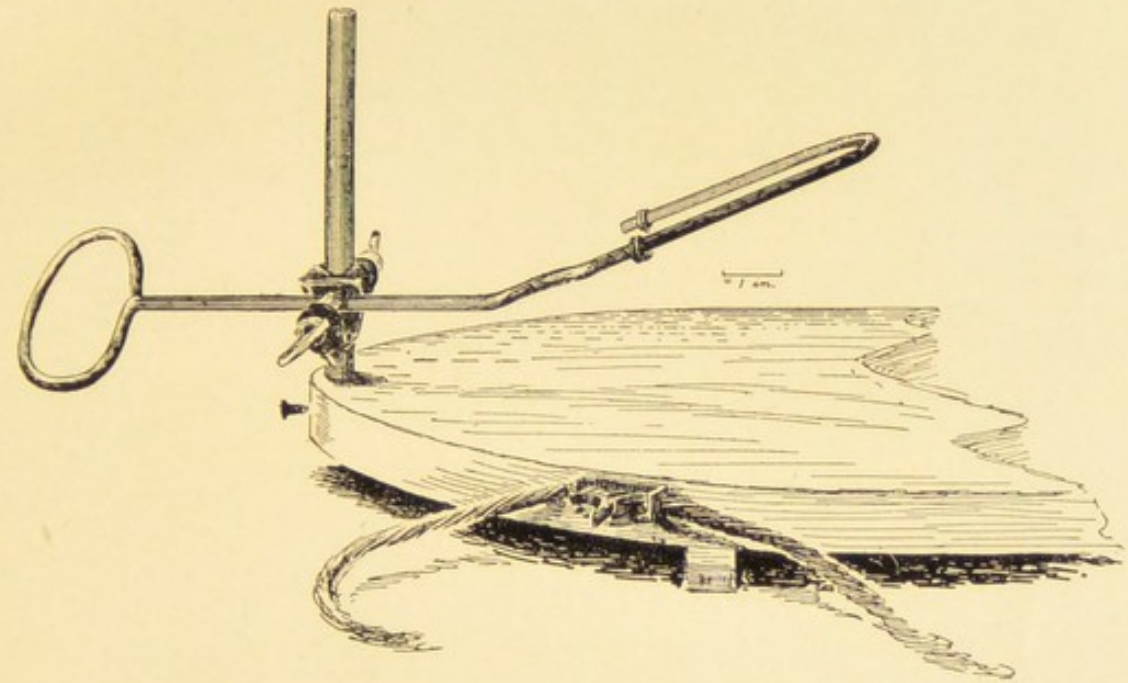
PLATE I.

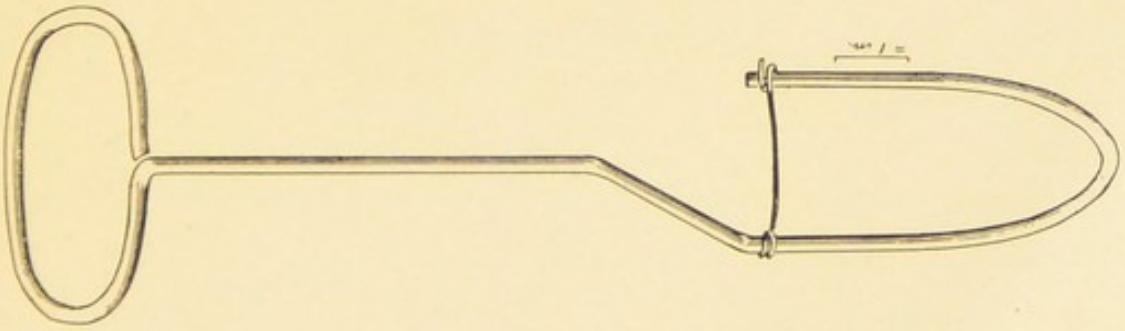
L. H. Wilder

LEGEND.

1, 2, 3.—NEGRI BODIES IN GANGLION CELLS FROM AMMON'S HORN.

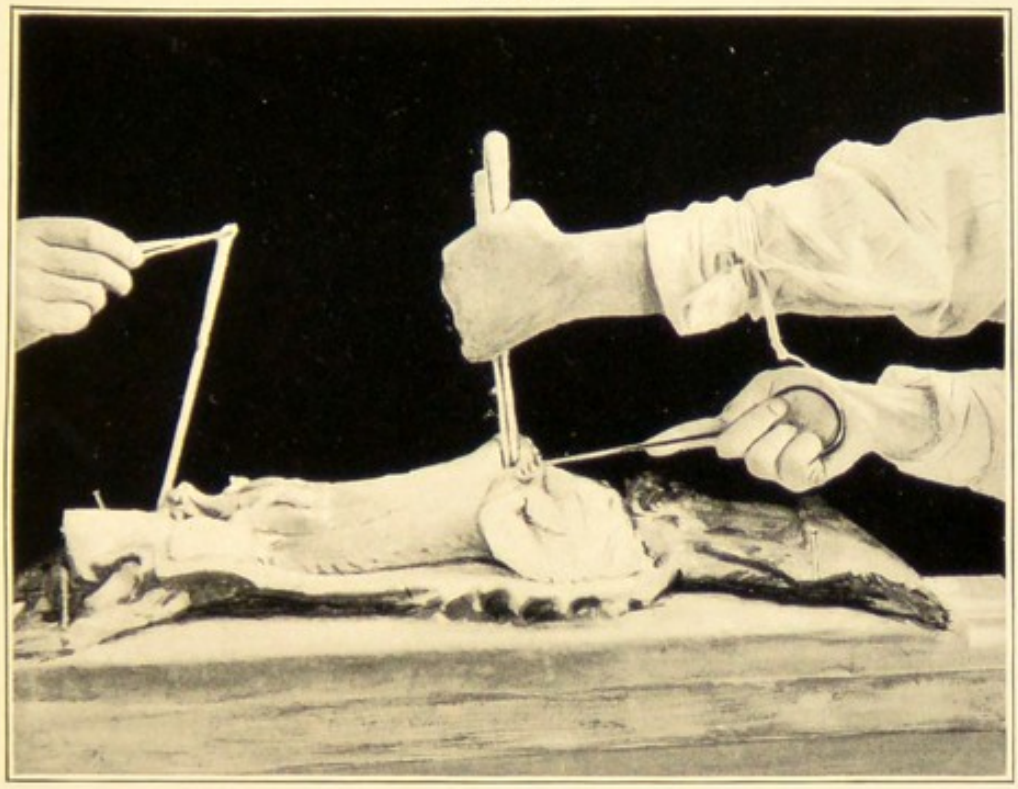
4, 5, 6.—BODIES FOUND IN DOG DISTEMPER, AFTER LENTZ.





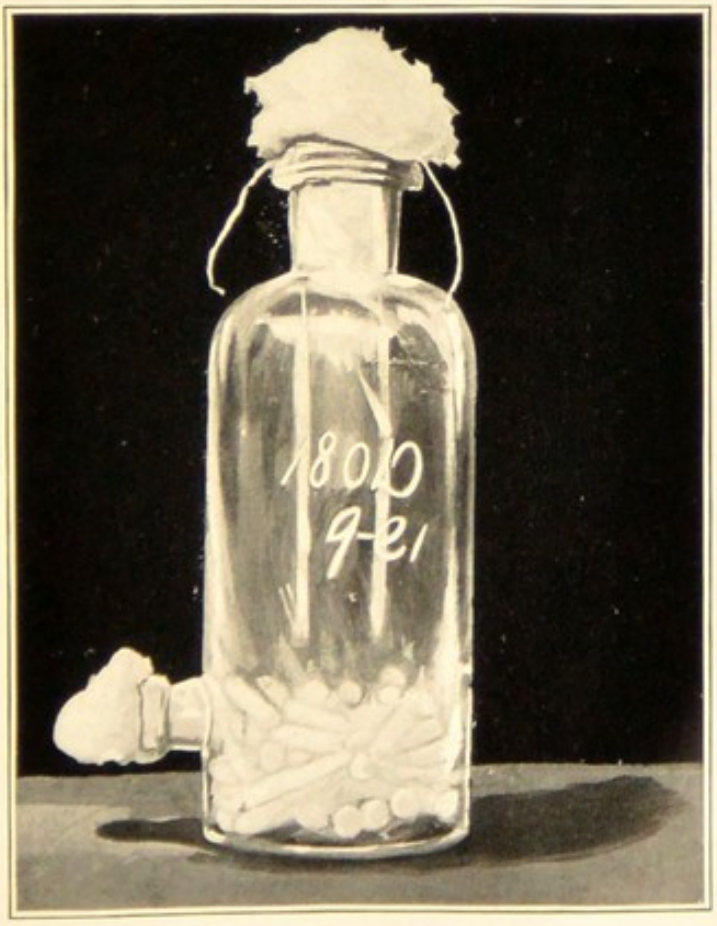
CONVENIENT HOLDER FOR SUBDURAL INOCULATION.

PLATE III.



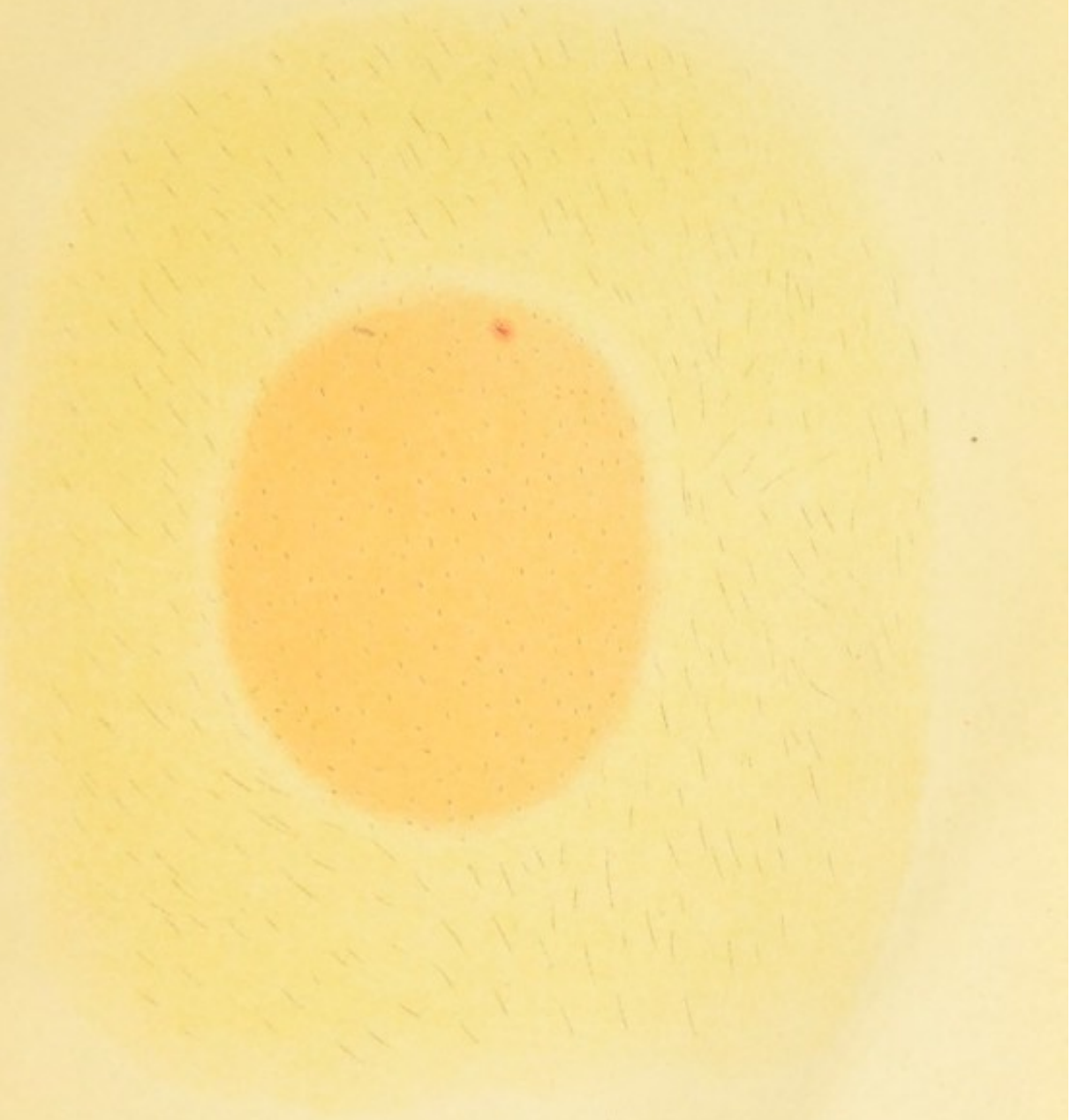
REMOVAL OF THE SPINAL CORD BY THE IMPROVED OSHIDA METHOD.

PLATE IV.



METHOD OF DRYING SPINAL CORDS.

PLATE V.



L. H. Wilder

LEGEND.

APPEARANCE OF A MODERATELY SEVERE REACTION AT THE SITE OF AN INJECTION.