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The pathology of human rabies, with a case report

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THE PATHOLOGY OF HUMAN RABIES,
WITH A CASE REPORT.

A THESIS
SUBMITTED TO THE FACULTY OF THE GRADUATE COLLEGE
OF THE
UNIVERSITY OF IOWA,
IN PARTIAL FULFILLMENT OF THE REQUIREMENTS
FOR THE DEGREE OF
MASTER OF SCIENCE IN MEDICINE.

BY
MARK FREDERICK BOYD, M. D.

OSKALOOSA, IOWA,
JULY, 1913
OUTLINE OF THESIS

1. Introduction. Distribution of rabies in Iowa.

2. Case Report
   b. Development and course of disease.
   c. Post mortem findings, gross and microscopical, results of animal inoculations.

3. Review of current literature upon pathology of the disease.
   a. Knowledge of properties of virus.
   b. Pathological changes described.


5. Success with different methods of staining Negri bodies.

6. Conclusions.

7. Literature consulted.
Rabies is becoming widespread in Iowa. Along the Des Moines river valley between the cities of Des Moines and Boone, the disease is endemic. Another focus of infection is the territory in and around the city of Davenport. Within the last two years cases of the disease in dogs have been reported from the north east and south central portions of the state. Statistics as to the number of human deaths from rabies in this state are not available, but the case here reported is the fourth human case in this state within the last ten years, to the writer's knowledge. Two of these human cases have occurred in the Des Moines-Boone territory. With the exception of the present case, none of these four had received the prophylactic treatment. In these human cases dogs as the carriers of the infection. In addition to these human cases, numerous cases in cattle, horses and hogs, came to my attention. It is possible that some of the wild carnivorous animals may assist in keeping the disease endemic, since foxes, coyotes and skunks are common in the state.

Late in July, 1911, a strange dog appeared on the premises of Mr. E. B., a farmer living near Shannon City, in the south central portion of Iowa. The dog appeared
friendly and was tolerated about the place. On August 1st it attacked some of Mr. B's stock and when Mr. B. and his twelve year old son attempted to drive the dog away, it attacked them both. Mr. B. was bitten on the anterior aspect of the right wrist, and his son on the calf of the right leg, the dog's gang penetrating the boy's overalls. The dog's teeth penetrated the skin of both father and son. A few hours later, suspecting the dog to be rabid, the wounds of both father and son were cauterized with carbolic acid. A search was made for the dog in the neighborhood; it was killed and its head sent to the Bacteriological Laboratory of the Iowa State Board of Health for examination. At the laboratory Negri bodies were found in the hippocampus. A diagnosis of rabies was reported and father and son advised to take the Pasteur treatment. Five days after being bitten they appeared at the laboratory for treatment. The intensive treatment was immediately instituted, using cord attenuated after the method of Pasteur, furnished by the Hygienic Laboratory of the U. S. Public Health Service. During the course of the treatments no untoward events occurred in either patient. Twenty one days later both were discharged in good health and returned to their home. Nothing further was heard from either of them until November 21st,
1911, when Mr. B. was brought to the University Hospital at Iowa City, in the convulsive stages of rabies. This was one hundred and thirteen days from the day he was bitten.

His relatives who accompanied him stated that his health had been apparently good until four or five days previous to his admission to the hospital. He then complained for a couple of days of pain in the scar of the bite on his right wrist. This caused the family some apprehension. On the day before admission he developed a spasm of the muscles of deglutition whenever he attempted to swallow. Suspecting rabies, his family urged him to return to Iowa City. Accompanied by the son who previously received the treatment and a neighbor, he walked six miles to the railroad station at night. He walked because the jarring of the buggy started convulsive seizures. He was in a cheerful frame of mind. After boarding the train the convulsions increased in frequency, so that at Des Moines it was necessary to call a physician and administer opiates to control the convulsions. Fifteen hours after he left his home he was admitted to the hospital. He was conscious up to the time morphine was administered, and would realize when a convolution was impending and endeavor to control himself and prevent injury to those with him.
The following account is taken from the bedside notes made at the Hospital. When admitted at 5:40 P. M. on November 21st, Mr. B. was very restless and suffered paroxysms of "terror" about every five minutes, lasting from ten to thirty seconds. At these times the pupils would dilate and remain so through the paroxysm. The general expression of his face, together with his movements suggested an evident hallucination which terrified him. He would throw his head and shoulders to one side of the pillow and with his hands would clutch the bedding and seemingly grasp at imaginary objects. The fingers were partially flexed in a claw-like position. Throughout the paroxysm he would murmur incoherently, sometimes loud and sometimes in an ordinary tone of voice.

He was given Morphine gr. $\frac{1}{4}$ and Hyoscine Hydrochloride $\frac{1}{100}$, per hypo, and fifteen minutes Chloral Hydrate, gr. xxx, and Potassium Bromide, gr. xxx per rectum. This would quiet him for about an hour and a half. These were repeated every two hours until death.

8. P. M. The muscles of the neck would be rigid during a paroxysm. The pupils were dilated except when under the influence of sedatives. The eyes were constant-
ly moving between paroxysms. They reacted slightly to light. Rectal temperature 104.1; pulse 108, full, strong and regular. Later the cornea were noted to be dry and somewhat opaque.

11:45 P. M. A lumbar puncture was performed by the house doctor, and 10. c. c. of clear cerebro-spinal fluid obtained. The eye grounds were examined and found normal. Priapism present. Sphincter ani muscle set in spasmodic contraction upon passage of rectal tube. The muscles generally very rigid. Pulse 140, weaker.


1:40 A. M. Paroxysms commenced, about two minutes apart. The patient yelled loudly and incoherently, except once when he distinctly said, "Oh! Hell, take it away, take it away". At times he seemed to be driving cattle, and once said "Back" and held hands as if pulling on lines. Face flushed, neck stiff. Eyes open, staring cornea dull and dry. Facial muscles twitch between paroxysms. Evidently swallowed without much difficulty. Re-
flexes unchanged. Pulse 140; Respiration 15, irregular.

4: A. M. Bladder catherized and xxxi\v ounces of urine obtained. Urine clear, amber, sp. gr. 1. 023. Contained no sugar or albumin. Eyes partially closed. No movements of facial muscles. Rectal temperature 105.4°; Pulse 148, weak; Respiration 17, irregular.

6: A. M. Paroxysms continue.

9: A. M. Eyelids cyanotic. Hands edematous. Hallucinations continue. Lower extremities have very little motion in paroxysms. Pupils react to light. Temperature 105.6°; Pulse 142; Respiration 16.

12: M. Difficulty in breathing. Face and ears becoming cyanotic. Patient acts as if nauseated and did some straining, as if a foreign object was in the esophagus. After respiration became re-established his face became flushed. Temperature 105.8°; Pulse 142; Respiration 16.

1: P. M. The patient suddenly, without warning,
regurgitated three to four ounces of dark brown fluid from mouth. A second regurgitation occurred three quarters of an hour later. The hands moved towards the throat several times. Following regurgitation the patient seemed relieved. Pulse 144; Respiration 17.

2:15 P. M. Blood count taken. 37% hemoglobin (Sahli), Reds 5, 220, 000, and whites 11, 200. All reflexes absent except a doubtful reaction to light. Anal sphincter relaxed. Pulse 148, very weak; Respiration 24.

The respirations became shallower, the regurgitations of dark brown fluid became more frequent, the pupils dilated and at 2:50 P. M. of the 22nd, the patient died.

All members of the family and friends who came in contact with Mr. B. were given the Pasteur treatment. The treatment was repeated in the boy who was bitten at the same time his father became infected. No further cases developed to our knowledge.

At 4:00 P. M. a post mortem was performed by Doctors Edlavitch and Boyd. The autopsy protocol follows.
Body is that of a well-built and fairly well nourished old man. Length 172 cm.; weight approximately 160 pounds. Body is still warm, there is no rigor mortis and no livor mortis anywhere. There is a small linear scar about 1 ½ c. m long, just above the right wrist on the outer side. Nowhere else on the body is there any evidence of any bites, cuts or other forms of trauma. A few spider angiomata are present here and there over the body. The eyes are slightly prominent. The pupils are equal and widely dilated. The lips and conjunctivae are very pale. The mouth can be easily opened, and on being opened a small amount of a dark-brownish fluid dribbles out.

On cutting into there is found a moderate amount of subcutaneous fat. The muscles everywhere appear of a dark-reddish color, they have their characteristic soft and elastic consistency, and cut with no increased resistance. The peritoneal cavity contains no free fluid, and the peritoneal surface is everywhere smooth and glistening. Diaphragm reaches up to the 4th rib on right and to 5th rib on left side. The pleural cavities contain no free fluid, and the pericardial cavity contains no excess of free fluid. The pleural and pericardial surfaces are everywhere smooth and shiny.
The heart weighs 290 gms. It is not enlarged or distended. The valves are all delicate, and the heart muscle appears to have its uniform dark-reddish color throughout. At the mouths of both coronary arteries there several small, grayish, rather hard and distinctly elevated patches, the coronary arteries themselves show no sclerotic changes anywhere throughout their course. The aorta has lost considerable elasticity, and 
maxi everywhere throughout its lumen there found grayish-yellow patches and long streaks of subintimal thickening. These seem to be most numerous at the openings of the branches of the aorta. In one or two places these patches are hard and calcareous in consistency.

The lungs are voluminous, they feel soft, elastic, and are every crepitant and air containing. Cut surfaces have a smooth and uniform pinkish white red color, except one rather large area in the posterior part of the right lower lobe, which has a distinctly dark-reddish color. This area when cut appears moist and bleeds abundantly. The bronchi are not congested and are not covered by any exudate. Glands at the hilum are not enlarged. Weight of left lung, 430 gm.; weight of right lung, 515 gm.
The liver is not enlarged, weighing 1330 gms. Its surface is smooth and regular. It has a dark, rather bluish-red color, it feels a little firm but elastic, and cuts easily. On section the cut surface bleeds quite profusely, and on the slightest pressure a large amount of dark red blood can be squeezed out. The liver lobules are everywhere well preserved. The gall bladder is tense, being filled with a dark-brown bile. The biliary ducts are patent, and the ampulla of Vater is also patent.

The spleen weighs 140 gms. Its surface is smooth and the capsule is nowhere roughened or thickened. The organ cuts easily, and on section presents a uniform dark-reddish pulp in which the Malpighian bodies can be plainly made out, and in which there is found no increase in the fibrous tissue trabeculae. The blood vessels are not particularly engorged.

The pancreas weighs 110 gms. It has a light yellowish color and nowhere does it feel hard or indurated. Cut sections show a uniform yellowish surface in which the characteristic glandular structure is easily made out. The duct of Wirsung is patent.
The mucous membrane of the pharynx and aesophagus is smooth, very pale and moist. It is covered with a small amount of the dark brown fluid found in the mouth.

The parotid and sub-maxillary glands present no appreciable gross changes.

The stomach is enormously distended, being filled with a very large amount of gas and a moderate amount of dark-brown fluid. The gastric wall is nowhere thickened and its mucosa is smooth and regular. The proximal third of the small intestine is also greatly distended, being filled with an odorless gas. The remainder of the small intestine appears collapsed and contains a very small amount of thin yellowish fecal material. The caecum and appendix show nothing of any interest. The large intestines are distended, being filled with pultaceous, brownish, semi-fluid fecal matter. The rectum is greatly distended, being filled with the fluid administered by enema. Nowhere throughout the gastro-intestinal tract is there found any change worthy of note. The mesenteric glands are not enlarged.

The kidneys weigh together 290 gms. They have a
somewhat bluish color, and feel soft and elastic. Capsule is not thickened, and strips easily, leaving a surface which is everywhere smooth and regular. They cut with an increased resistance, and on section leave a surface which bleeds easily. The pyramids are all very well preserved, the striations are distinct, the cortex is not thickened, and the glomeruli can be plainly made out. The vessels are unusually distended, slight pressure causing a good deal of bleeding.

The bladder is slightly distended and contains a small amount of clear yellowish urine. The bladder shows no thickening or irregularities, and its mucosa is well preserved throughout. The prostate is not especially enlarged, but feels a little hard and not quite so elastic. However it is definitely encapsulated. The Seminal vesicles and testes show nothing of interest.

The brain weighs 1250 gms. The internal surface of the dura is perfectly smooth and glistening throughout, and there is no thickening of the meninges anywhere. There is however, quite a marked congestion of the pia-arachnoid all over the convexity of the brain. The cortex of the brain
also shows considerable congestion, particularly over the area directly adjacent to the great longitudinal fissure. The cord shows some congestion of the pia-arachnoid, and some congestion of the surface of the cord substance, similar to what was found over the cortex of the brain.

Pieces of tissue were promptly removed; some were fixed in Zenker's solution and some in 4% formalin. Blocks were embedded in both celloidin and paraffin and sectioned as thin as the consistency of the tissue would permit. Ehrlich's acid hematoxylin was used a general stain, Pappenheim's pyronin-methyl green stain for the differentiation of fibroblasts, and various methods of staining, to be discussed later, were used for the differentiation of the Negri bodies.

The following is a description of the pathological histological findings.

Skin from scar. No visible contraction of connective tissue in the scar. The different layers of the epithelium and the corium are apparently normal.

Biceps muscle. Muscle fibers normal. A slight in-
crease is noted in the amount of connective tissue between the muscle fibers.

Heart muscle. Heart muscle fibers have undergone brown atrophy.

Lungs. The alveoli are emphysematous. The blood vessels in the thickened alveolar walls are hyperemic. Some of the alveoli contain desquamated epithelial cells. The alveoli in tissue removed from the dark red area in the posterior part of the right lower lobe are filled with a serous exudate containing small numbers of red and white blood cells.

Parotid glands. No increase in the amount of interstitial connective tissue. No apparent degeneration of the serous cells. The epithelium lining the inter and intra-lobular ducts is extensively denuded from the duct walls, and lies within the lumen. A few small areas of fibroblastic infiltration were noted in the connective tissue surrounding the ducts. Negri bodies were not found.

Sub-maxillary glands. The epithelium of the inter-lobular ducts is denuded in many places, but not nearly as
extensively as in the parotid ducts. Small centers of proliferation of the epithelial cells of the ducts are noted in both the intra and inter-lobular ducts. The serous cells are apparently normal. The mucous cells are swollen, their nuclei cannot be discerned. The serous cells of the demilunes are apparently normal. Centers of fibroblastic infiltration are noted in the connective tissue surrounding the excretory ducts and also in the walls of the smaller arteries. Negri bodies were not found.

Stomach. The gastric mucosa and muscular walls are apparently normal. No post-mortem digestion of the mucosa has taken place.

Liver. The central veins of the lobules are distended with blood and the capillaries between the chains of hepatic cells are congested. The liver cells contain considerable hepatogenous pigment. Extensive areas of fatty degeneration of the liver cells are found.

Pancreas. The glandular tissue of the pancreas and Islands of Langerhans is apparently normal. The blood vessels in the connective tissue are hyperemic, and petechial hemorrhages into the septae are
noted. The connective tissue is necrotic in these areas. In the connective tissue septae are a few centers of fibroblastic infiltration. Negri bodies were not found.

Spleen. The splenic pulp is hyperemic. The Malpighian follicles are hyperplastic. At the centers of some follicles are seen cells whose cytoplasm is apparently homogenous and glassy, taking a diffuse stain with eosin. The nuclei of these cells cannot be seen.

Kidneys. The epithelial cells of the glomeruli appear normal. The capillaries of the glomeruli are hyperemic. Most of the epithelial cells lining the convoluted tubules are swollen, their outlines indistinct, and their cytoplasm has a granular appearance. Many epithelial nuclei do not stain. The capillaries in the interstitial tissue are hyperemic. Towards the apex of the medullary pyramid the connective tissue appears edematous. In places the epithelium of the collecting tubules has been completely denuded. These areas are hemorrhagic, the blood infiltrating the lumen of the denuded tubule and the tissue surrounding it.

Adrenal glands. An atrophy of the medullary mm por-
tion and a hypertrophy of the cortical portion is apparent. The capillaries between the cells of the zona glomerulosa are congested. Outlines of the cells of the cortex are indistinct and their cytoplasm appears vacuolated. The ganglionic cells are apparently normal and none were found containing Negri bodies. At one point in the connective tissue surrounding the gland is an area of lymphocytic infiltration.

Hypophysis. In the anterior portion of the gland, a few of the chief cells show amitotic division. The chief and acidophile cells are apparently normal. The glial tissue of the posterior lobe is granular and stains poorly. The blood vessels of the capsule of the gland and interlobular septum are congested. A marked lymphocytic infiltration is seen in and around the blood vessels of the posterior lobe and septum. Negri bodies were not found.

Throughout the entire central nervous system more or less alteration of the nerve cells was noted. These changes were most marked in the hippocampus, the medulla and cord, and least so in the cells of the cerebral cortex. A few ganglionic cells even in these locations appeared normal, but the majority were altered. The changes noted are as follows: The tigroid
bodies are lacking in portions of some cells, in others entirely so. Some cells present the bodies grouped to-gether in large irregular masses distributed throughout the cell or in a single massive group. The nuclei of many cells from which the tigroid bodies are absent are shrunken and distorted, with irregular outlines. The nucleoli are absent from such nuclei. Some nerve cells are shrunken, their internal structure is not discernable and the cell appears as a shadow.

Across the Fissure of Rolando. Capillaries congested. Nuclei of glial cells in numerous compact groups of from four to six nuclei. A few small Negri bodies in the pyramidal cells.

Under surface of the Temporal lobe. Capillary congestion. Glial cell nuclei in similar groups as previously described. A few small Negri bodies are present.

Hippocampus major. Capillary congestion. Negri bodies abundant in ganglionic cells. The Negri bodies vary in size from less than 1 micron to four or five micra in diameter. The smaller bodies are round and the larger ones round or oval. A single ganglionic cell may contain as high as four or five bodies.
Cerebellum. Capillaries congested. Cells of the molecular layer apparently normal. Many of the Purkinje cells contain Negri bodies, some cells containing more than one body.

Pons. Capillary congestion. No Negri bodies found.

Medulla, through the 4th ventricle and Olivary nuclei. Capillary congestion, and small hemorrhagic areas around some capillaries. In places the epithelium of the 4th ventricle is thickened and consists of two or three layers of cells. Underneath these thickened areas is an area of fibroblastic proliferation. Some of the smaller blood vessels have a round cell infiltration in and around their walls.

Medulla at the Pyramidal decussation. Capillary congestion. Around the central canal is an eccentric proliferation of connective tissue, in which are epithelial cells from the epithelial lining of the canal, lying singly or in groups. The remaining epithelium does not completely surround the canal lumen. At one place the epithelium is proliferating into the canal lumen.
The spinal cord; Sections were examined from the cervical, dorsal and lumbar regions. The changes described as having taken place around the central canal in the medulla continue throughout the entire cord. In the dorsal region the canal is obliterated by this proliferation. The capillaries are congested. Negri bodies were not found in the ganglionic cells. A few small petichial hemorrhages were noted in the cervical region.

Gasserian ganglia. Congested. Some of the ganglionic cells are shrunken and retracted from their capsular wall. They stain poorly. There is a marked fibroblastic infiltration into the connective tissue between the ganglionic cells. Many of these cells are proliferating into vacant spaces left by the shrunken ganglionic cells.

Animal inoculations: The following inoculations were made:

No. 1 Rabbit, inoculated sub-durally with an emulsion of the medulla. The animal succumbed in twelve days to rabies. Negri bodies were found in its hippocampus. The virus from the medulla of this animal was passed successively through two guinea pigs.

No. 2 Guinea pig, inoculated sub-durally with an emulsion of hippocampus. Succumbed to rabies in eighteen days, Negri bodies in its hippocampus.

No. 3. Guinea pig, inoculated sub-durally with emulsified nervous tissue from the right brachial plexus. The animal survived.
No. guinea 4, Guinea pig, inoculated sub-durally with emulsion of nervous tissue from left brachial brachial plexus. The animal survived.

No. 5, Guinea pig, inoculated sub-durally with emulsion of skin from scar on right wrist. The animal survived. (N. B. Lack of available animals prevented the virulence of other tissues being determined.)

Since the classic researches of Pasteur on the sub-dural inoculation of rabies and his application of a form of vaccine therapy to its prophylaxis, comparatively little of importance has been added to our knowledge of this disease. His studies form the basis of our present ideas of rabies and subsequent workers in this field have uniformly corroborated his results. Previous to his researches Zäncke in 1804 had demonstrated the virulence of the saliva of rabid dogs, the identity of the disease in man and animals had been established by Count de Salm-Reifferscheid in 1813 (1), and the inoculation of susceptible animals with the saliva of supposedly rabid animals was recommended as an aid to diagnosis by Gruner in 1813 (3). Practically the entire literature of this field was a confused mixture of ignorance and superstition. The existence of rabies as an infectious disease was doubted by many, and fanciful ideas prevailed, some of which are still current,
about the origin and cure of rabies.

Its existence as an infectious disease may be established by the demonstration of two distinct properties, common to and characteristic of all infectious diseases; namely its transmissibility and the period of incubation following inoculation before the manifestation of symptoms. The transmissibility may be demonstrated either by the natural inoculation of susceptible animals through the saliva of rabid animals or artificially by the inoculation of susceptible animals with tissue from a rabid animal. In either case the inoculated animal will, after the lapse of a variable period of time, (the incubation period) depending upon the site of inoculation and the character of the virus, develop rabies. Suitable tissue from the body of an animal dying of rabies, inoculated into the body of a susceptible animal will cause the development of rabies in the animal so inoculated, and the tissues of this second animal will in turn, be found as capable of causing the death of other animals as was that of the first. There has been a multiplication of the rabid virus in the body of the inoculated animal.

After the establishment of bacteriological technique upon its present foundation, many workers endeavored
to discover the causative organism of rabies, and various cocci were described from stained sections of rabid tissue. Fol (4) believed that he was able to cultivate some cocci from rabid tissue, which he believed to be the specific organism. Subsequent workers have significantly failed to corroborate his findings. Recently Proescher (5) has demonstrated a pleomorphic bacillus in brain substance infected with fixed virus, digested with antiformin, and also by direct staining of smears and sections. As yet he has not cultivated his organism or shown its pathogenesis. Several able workers are of the opinion that the Negri bodies, to be later described, are the causative organism. But they have not isolated the bodies or demonstrated their pathogenesis. For the present, then, it may be considered that the relationship of any specific micro-organism to rabies has not been demonstrated.

A possible explanation of these failures to isolate the organism of rabies may be given in the results of Remlinger (6) with filtration experiments. He states that he has successfully passed rabid virus through the pores of a No. 5 Berkefeld filter, but did not succeed with the Chamberland filter. Several other workers, notably Bertarelli and Volpino (36) have reported similar results. More recently Poor and Stienhall (41) have succeeded in obtain-
ing the virus free from the cells of the host and contaminating organisms. They use two methods. In the first they extract the salivary glands with glycerin and remove the glycerin by dialysis. By their second method they aspirate the glands under a vacuum of twenty-nine inches of Mercury and then press the glands in a meat press and centrifugalize the fluid. The fluid is then filtered through a Berkefeld candle, freeing it from tissue cells and contaminating bacteria. However Stimson (7) at the Hygienic Laboratory has never succeeded in obtaining a virulent filtrate of fixed virus emulsion, using a Berkefeld candle and a water pump vacuum. Emulsions of the virus may be so diluted so highly that small amounts will not prove fatal on sub-dural inoculation into rabbits. Hogyes (8) states that this obtained with a 1:10,000 dilution. Larger amounts of such diluted emulsion are however, still infectious.

The virulence of rami a strain of rabic virus may be greatly enhanced by successive passages through a large series of susceptible animals by subdural inoculation. If very susceptible animals, such as rabbits be used, the period of incubation may be shortened to six days. It appears that such a strain of virus, whose virulence for rabbits is so greatly enhanced, is less virulent for human beings, for
it is used untreated in some methods of immunization, and with good results. As a rule the period of incubation cannot be reduced below six days by any further passage through susceptible animals, though a single instance is reported where the incubation period was still further reduced. Virus of this character is known as fixed virus (virus fixe). Passage of virus through animals of a low degree of susceptibility, such as monkeys, is stated to lengthen the period of incubation. The virus which has been transmitted from animal to animal through the bites of rabid animals in known as street virus. Here the varying susceptibility of different species and races of animals, together with the varying length of the pathway the virus may have to travel before it reaches the central nervous system, makes the duration of the incubation period of street virus subject of a great deal of variation. The following table by Bauer (37) gives the percentage of cases with incubation periods of different duration in 537 cases of human rabies.

<table>
<thead>
<tr>
<th>No. days incubation</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 -19 days in</td>
<td>8.24</td>
</tr>
<tr>
<td>23 -39</td>
<td>28.43</td>
</tr>
<tr>
<td>40 -59</td>
<td>21.18</td>
</tr>
<tr>
<td>69 -79</td>
<td>15.30</td>
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<tr>
<td>80 -99</td>
<td>9.22</td>
</tr>
<tr>
<td>100-149</td>
<td>7.65</td>
</tr>
<tr>
<td>150-199</td>
<td>5.69</td>
</tr>
<tr>
<td>200-249</td>
<td>93</td>
</tr>
<tr>
<td>250-339</td>
<td>2.35</td>
</tr>
<tr>
<td>12 -15 mos.</td>
<td>1.18</td>
</tr>
</tbody>
</table>
Our knowledge of the properties of the rabic virus is only that of the virus contained in emulsified nervous tissue. Opinions of the susceptibility of rabic virus to various chemical and physical agents have to be formed from observations of their effect upon the virulence of the virus, since at present it cannot be cultivated outside of the animal body.

Practically all mammals are susceptible, especially the carnivores and rodentiae. Birds are capable of being inoculated, but frequently recover. A difference of opinion exists as to the susceptibility of frgms frogs, and the tortoise is said to be refractory. The tissues of an infected animal are not uniformly infectious; blood and lymph seem almost incapable of taking up the virus. Its particular affinity is for the central nervous system and glands, of which the salivary are the most virulent. It is also present in the secretions of these glands. It may be thrown down as sediment upon the centrifugation of an emulsion so as to render the supernatant fluid avirulent. According to the experience of different observers, exposure to 60° C. for thirty minutes is fatal to the virus. On the other hand, it resists extremes of cold, even that of liquid air. Dessication for five or six days at room temperature destroys the virulence. At higher temperatures the loss of virulence is
more rapid. Harris and Shackell (9) were able to dessicate rabic virus in from 24-36 hours without loss of virulence, using a freezing temperature and vacuum. Mechanical subdivision of the virus by grinding in a frozen condition destroys its virulence. In general it may be said that emulsions of the virus are more resistant to chemical disinfectants than are bacterial emulsions. This is probably because the virus is surrounded by a protecting layer of nervous tissue, which protects it from the destructive action of the disinfectant. Proescher (10) has shown that street virus is resistant to the action of the antiformin. Sautchenco (11) states that street virus resists the action of 5% solutions of phenol, and Semple (13) finds that emulsions of fixed virus, which resist the action of 1% phenol at room temperature for several days, succumb in 24 hours at 37'. C. Glycerine is commonly used as a preserving agent for the virus, as it gradually destroys contaminating organisms, and finally the virus itself. Corrosive acids or alkalies will destroy the virus with certainty, if applied so that all portions of the emulsion are subject to the action of the chemical. The destructive changes produced during the putrefaction of nervous tissue does not destroy the virus, even if the tissue be reduced to a pulp.

The symptoms manifested during the progress of the disease are indicative of severe irritation of the central nervous system. The changes found in the nervous tissue are
more pronounced than those found elsewhere in the body, and are the only ones which may be said to be typical of the disease. Practically all changes present in other tissues are secondary to the involvement of the nervous system.

The gastro-intestinal tract and its accessory organs are the only other tissues in which any constant changes are found. The fauces, pharynx and larynx are usually found to be deeply congested and the secretions of the mucusous surfaces are decreased. Babes and Jonnesco (30) have described well defined changes in the salivary glands and pancreas. These changes are more pronounced in the pancreas than in the salivary glands, and more marked in the sub-maxillary gland than in the parotid. The glandular portion of the pancreas is only slightly modified. The epithelium of the pancreatic duct is desquamating, the duct walls contain centers of embryonal cells. These changes affect both the larger and the smaller ducts. The gland is always hyperemic. Small centers of embryonic cells are found in the interstitial tissue. In the dog the parotid is frequently altered, while only occasionally affected in man. There may be an embryonic infiltration of the interstitial tissue of the parotid, with a dilation of the blood vessels. The acini of the
of the sub-maxillary gland are dilated, the cells swollen, edematous and confluent and many of the nuclei do not stain. The demilunes of Gianuzzi may be distinguished by their nuclei. The ducts may have nests of embryonic cells in their walls and the interstitial tissue shows embryonic infiltration. The entire gland is hyperemic. They were unable to find Negri bodies in any of these glands in five cases of human rabies. The stomach and intestines are usually devoid of their normal contents. It frequently happens that rabid dogs swallow a variety of foreign objects, and sticks, stones, feathers, straw and similar material may be found. The presence of these foreign materials was at one time considered of diagnostic value.

Babes and Jonesco (31) have described the lesions in the spleen in rabies. In animals which have been inoculated through the blood stream with either fixed or street virus the spleen is frequently virulent, as determined by inoculation. The organ is generally somewhat hypertrophied, the follicles are very apparent. The splenic pulp is hyperemic and often hemorrhagic. There is often a swelling of the endothelial cells of the small vessel. They note centers of degeneration and of hyaline necrosis in the centers of the follicles. These changes are more marked in young indiv-
iduals of the human species.

The same writers have also described changes in the kidney in human rabies (32). They found evidence of irritation of the parenchyma. The epithelial cells are swollen and desquamated, and more or less hyperemic areas are present. The lesions in man are not identical with those in the dog or rabbit.

In the nervous tissue are found the most striking changes of the disease, and it is tissue which evidently offers the virus most favorable opportunities for multiplication. After the virus has been introduced underneath the epithelial covering of the body, it gains access to the nerve filaments and develops centrally along the nerve fibers. Stimson (16) states that "nerves leading up from the site of 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 segments". Ordinarily blood and lymph do not seem to participate in the transportation of the virus to the brain as shown upon direct inoculation, but Marie has succeeded in performing inoculations in this
manner, using large quantities of blood and lymph.

Grossly examination of the brain and cord presents no striking changes. The meninges are congested, punctate hemorrhages may be present and not infrequently the meninges are edematous. The same changes, but to a lesser extent are visible in the brain and cord. Small areas of softening have been observed. An increase in the amount of cerebrospinal fluid is reported by Maloney (18).

The nerve cells may be altered in some portions of the brain and not in others. These lesions consist of atrophy, vacuolation and granular or fibrinous degeneration of nerve cells associated with degenerations of the processes. Golgi has described irritative and regressive changes in the nucleus, characterized by increase and subsequent fragmentation of the chromatin with karyolysis, bladder like swelling vacuolation and granular degeneration of the cell body; atrophy and loss of the processes and eventually destruction of the entire cell. These changes apparently do not affect in all the cells, some apparently remaining normal. Bailey (50) describes shrinking, displacement and dissapearence of the tigroid nerve bodies of the cells in rabies.
A perivascular round cell infiltration is found in the cord and medullar, somewhat similar to that of poliomyelitis. Babes (49) describes a proliferation of the epithelium of the cerebrospinal canal. In the gray matter surrounding the canal, hemorrhages, sometimes symmetrical are found. He frequently found thromboses of the small vessels by reticulated, hyaline, pigmented material, or by leucocytes or hyaline globules and sometimes a hyaline degeneration or even inflammation of the vascular tunic. The hemorrhages are often limited to the lymphatic sheath of the vessels. At the same time the epithelium of the ventricles and central canal may be partially lost. These areas are occasionally filled with blood or hyaline material. The most constant changes Babes found are especially in the gray matter surrounding the cerebro-spinal and in the motor centers of the medulla and spinal cord. These lesions consist of at first a hyperemia and accumulation of embryonic cells around the smaller vessels. Proliferative changes are present, several small cells are present in the place of a large one. Round, unicellular, rarely multinuclear elements of a lymphatic origin often invade the protoplasm, even of the cells, and fill out the dilated pericellular lymphatic spaces by a multiplication of small nuclei. Babes calls these pericellular and perivascular focal accumulations of round cells "rabic tubercles", and considers...
them to be so constant as to be of considerable value in diagnosis. He also notes an edematous condition of the medullary sheath of the nerve fibers.

Van Gehuchten and Nelis (47) described changes in the peripheral ganglia which are sufficiently constant to be of diagnostic value. Frothingham (48) finds these lesions are not pathognomonic of rabies, but rarely occur in other disorders, and in a study of more than 700 hundred Gasserian ganglia—mostly from dogs—he finds the percentages of error very small. He states there is a “multiplication of cells within the capsule of the ganglion cell, the ganglion cell itself becoming gradually destroyed and its place being finally occupied by the invading cells, thus forming a focus suggesting a tubercle. Such lesions may be extensive, invading most of the ganglia, or only a few ganglion cells may attacked in this, the typical form. Another, the atypical form, consists of a more or less general infiltration of cells without such characteristic grouping, although usually and especially when the lesions are extensive, the two forms exist together”.

Pirone (27) describes a perivascular infiltration and diffusion of lymphoid elements and plasma cells in the
posterior lobe of the hypophysis. In places the lymphoid tissue may have a nodular arrangement. Later (29) he states that the epithelial cells of the anterior portion are in a state of reproductive hyperactivity. The capillaries and small blood vessels of the periphery of the anterior lobe are congested and small hemorrhages are present. He states that parallel changes take place in the suprarenal glands, and that he has demonstrated (28) that both the hypophysis and suprarenal gland are virulent. A hyperplasia

(Continued on page 34)
of the cortical portion of the suprarenal gland with an atrophy of the medullary portion has been described by Austoni (34) and a lymphocytic infiltration of the connective tissue capsule has been described by Moschini (35).

Negri in 1903 (19) described the presence of well-defined round or oval bodies within the cytoplasm of the nerve cells of the brain and cord, varying in size from less than half a micron to those as large as three micra in diameter. They never appear within the nucleus. A single cell may contain from one to six or more of these bodies, of varying shapes and sizes. These bodies take an acid stain, while the nerve cell itself is stained by basic dyes. Within the bodies lie minute granules, varying in number with the size of the body and which take a basic stain. The Negri bodies are not found before the onset of symptoms and may not be found in the brains of animals which have been killed shortly after the manifestations of the earliest symptoms. Some brains will contain them in large numbers, while in others prolonged search will reveal only a few. Their distribution is not uniform. They are most constantly found in the ganglion cells of the Hippocampus.
major and in the Purkinje cells of the cerebellum. They will be present in these locations even if not present elsewhere in the central nervous system. The portions of the brain and cord which contain them in largest numbers are less virulent upon inoculation than are those portions in which the bodies are less abundant. Stefanescu (20) has reported their presence in frozen sections from the parotid gland of a rabid dog, but her findings have not been corroborated. Marinsisco (33) has found them in the ganglionic cells of the suprarenal glands. Moschini (35) and Pirone (29) have never found the bodies in the suprarenal glands or hypophysis. More recently Lentz (39) has described minute bodies in the hippocampus of animals dying from fixed virus infection. They are smaller than the smallest Negri bodies, of either a round or oval shape. They are composed of an acid staining ground substance in which are massive basophile granulations. These are both extra and intra cellular. They may be found even in the extremities of the pyramidal cells where the Negri bodies are rarely found. They stain with the same stains used for the differentiation of Negri bodies. Lentz has found them in 36% of rabbits inoculated with the Berlin strain of virus and in 73.3% of those infected with the Sassari strain. Search for their presence has been advocated as a means of differentiation between fixed and
street virus, but reported results of their value for this purpose seems to be doubtful.

The nature of these cell inclusions has been the source of considerable controversy, as yet not settled. Williams and Lowden (22) maintain that the bodies are the true causative agent of the disease. They are of this opinion because of the morphology of the bodies, which resembles that of certain Protozoa, and because they have traced what they describe as the life cycle of the organisms. Calkins has given the bodies the name of Neuroryctes hydrophobiae, and assigned them a place in the Sporozoa. Their staining reactions resembles that of other known Protozoa, and because they are iodin resistant, Nerl (23) considers them to belong to this sub-kingdom. Negri was also of this opinion, and described their life cycle in great detail. Babes believes that the bodies are due to an effort on the part of the nerve cell to isolate the invading organism. Proescher is of this opinion and regards them as representing a reaction against the antiformin resistant he has described. These workers explain the preponderence of these bodies in those parts of the brain which are of the least virulence on the grounds of the greater resistance on the part of those cells and consequent greater ability to isolate the virus. Lentz con-
siders his fixed virus bodies as due to max fragmentation of the nucleolus, with a fusion of the nuclear elements. He traces an analogy between the fixed virus bodies and the Negri bodies and concludes that since the fixed virus bodies are degenerative products, the Negri bodies are of the same nature. Achucarro claims that the glia cells of nerve centers undergo a degeneration in rabies and that these glia cells become incorporated in the ganglia cells and their processes, from Negri bodies, and cannot be distinguished. He considers them to be unconnected with any parasitic invasion. Other observers have described somewhat similar bodies in the brains of animals dying from widely different causes.

The most constant property of the disease, which may be demonstrated even in the absence of Negri bodies and other visible changes, is the ability of tissue from the central nervous system and salivary glands to reproduce the disease in susceptible animals upon inoculation. Thus these tissues may be shown to contain the virus from the onset of symptoms and before the Negri bodies are demonstrable. The virus is either more abundant in certain portions of the central nervous system or else the virus in these localities is more virulent than that present elsewhere. The peripheral nerves are less virulent than the centers. Nitsch (24)
found that the medulla was some five times more virulent than the middle of the cord and 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 to an assumed post-mortem diminution of the micro-organisms. He states that the cortex has a slight increase of virulence over the hippocampus and quadrigeminal bodies, which are of the same degree of virulence. The sympathetic ganglia are only slightly virulent, while the retina is avirulent. The cerebro-spinal fluid was found to be avirulent. Pace (25) claims to have transmitted rabies to rabbits by inoculation with the cicatrix of the inoculation wound in a fatal human case. Pirone (26) was unable to confirm this in a case under his observation. Pirone's experience is in accordance with our own in the present case.

An active protective immunity against rabies may be developed by inoculation with attenuated forms of the virus. This was first applied by Pasteur. In his method the attenuation was produced by dehydration over caustic potash of the spinal cord of an animal dying from fixed virus infection. Harris (12) uses virus desiccated in vacuo at a low
temperature. Semple at Kasauli (13) uses as a vaccine an 3% emulsion of nerve tissue in normal saline, which has been killed by 1% phenol at 37.0C. for twenty four hours. This is practically identical with the method of Fermi of Sassari, who uses a 5% emulsion of rabid nerve tissue treated in the same manner as that of Semple. The advantages claimed for this method are facility and ease of preparation; ability to preserve the activity and aseptic condition for some time; increased efficiency as shown by immunization experiments; and absence of mortality during the cure. Proescher (14, 15) reports good results by inoculating with untreated, fresh, fixed virus. The principles of this method were first introduced by Ferran of Barcelona. Proescher uses a strain of fixed virus, which, while virulent for rabbits, is not virulent for human beings, as proven by inoculation. Marie obtains his material for treatment by partially neutralizing fixed virus with an anti-rabid sheep serum in vitro. Cummings of Ann Arbor (38) attenuates the fixed virus by dialyzing a standard suspension of rabid tissue in running distilled water. Högyes of Budapest uses a series of very high dilutions of untreated fixed virus in saline solution. Among other
methods in use for the attenuation of fixed virus are the attenuation by heat; by partial digestion with artificial gastric juice; by contact with bile; by glycerine and by grinding. It is considered that the attenuation does not act by lowering the virulence of the virus contained in the nervous tissue, but by destroying most of the rabic organisms present, in reality on a par with the dilution method. Probably the greatest results will be achieved by using virus which has not been treated in any way to the action of destructive agents, but whose virulence for man has been lessened by passage through especially susceptible animals. For this reason the methods of Ferran and of Proescher probably have the greatest future. The blood of immunized persons and animals contains antibodies capable of destroying the virulence of nerve emulsions in vitro. The use of serum from immunized animals in the establishment of a passive immunity has not met with success in practical application. The duration of active immunity appears to be from three to five years, as determined by the susceptibility to rabies of animals previously immunized.

"Pasteur at the International Medical Congress held at Copenhagen in 1884 stated that complete immunity against
street virus is not established until two weeks after the treatment is discontinued or five weeks after the treatment is instituted. Those patients in whom the incubation period is less than thirty days are only partially if at all protected by the treatment. Practically the entire .5% or less of mortality occurring during or shortly after the completion of the treatment may be explained by the above statement. The mortality varies somewhat with the different methods of treatment and the following table from Fermi gives the percentages of mortality at some of the principle institutes over the world.

<table>
<thead>
<tr>
<th>Institute</th>
<th>Method of Immunization</th>
<th>% Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Algiers</td>
<td>Calmette's method</td>
<td>.34%</td>
</tr>
<tr>
<td>Baltimore</td>
<td>Pastuer's and Högyes' methods</td>
<td>.14%</td>
</tr>
<tr>
<td>Berlin</td>
<td>Modified Pastuer</td>
<td>.75%</td>
</tr>
<tr>
<td>Bordeaux</td>
<td>Pastuer's method</td>
<td>.283%</td>
</tr>
<tr>
<td>Breslau</td>
<td>&quot;</td>
<td>.45%</td>
</tr>
<tr>
<td>Budapest</td>
<td>Högyes method</td>
<td>.96%</td>
</tr>
<tr>
<td>Buenos Ayers</td>
<td>Pastuer's method</td>
<td>.47%</td>
</tr>
<tr>
<td>Chicago</td>
<td>&quot;</td>
<td>.19%</td>
</tr>
<tr>
<td>Constantinople</td>
<td>&quot;</td>
<td>.45%</td>
</tr>
<tr>
<td>Charkow</td>
<td>&quot;</td>
<td>.67%</td>
</tr>
<tr>
<td>Florence</td>
<td>&quot;</td>
<td>.09%</td>
</tr>
<tr>
<td>Hanoi</td>
<td>Calmette's method</td>
<td>.65%</td>
</tr>
<tr>
<td>Kasauli</td>
<td>Högyes method</td>
<td>.60%</td>
</tr>
<tr>
<td>Marseille</td>
<td>Pastuer's method</td>
<td>.36%</td>
</tr>
<tr>
<td>Milan</td>
<td>&quot;</td>
<td>.70%</td>
</tr>
<tr>
<td>Minneapolis</td>
<td>&quot;</td>
<td>.04%</td>
</tr>
<tr>
<td>Montpellier</td>
<td>&quot;</td>
<td>.07%</td>
</tr>
<tr>
<td>Moscow</td>
<td>&quot;</td>
<td>.6%</td>
</tr>
<tr>
<td>Naples</td>
<td>&quot;</td>
<td>.5%</td>
</tr>
</tbody>
</table>
The mortality from rabies has generally been considered to be 100%, though the percentage of cases resulting from bites of rabid animals is much less, depending on the species of animal inflicting the wound; the location of the wound with regard to the abundance of nerve supply and to the protection afforded by clothing. About 16% of individuals bitten by rabid dogs develop rabies, while from the bites of rabid wolves the percentage is very much higher. Remlinger (43) concludes that an animal bitten by a rabid animal is not always killed when the virus reaches the brain. The virus may be destroyed by the effects of vaccination; or be latent, to revive suddenly after traumatism to the brain, lively emotion and local and general cold. Palettau
(40) found that the medulla was virulent in four human cases who were receiving the Pasteur treatment and died from intercurrent diseases, without manifesting any symptoms of rabies. He believes that in a person infected with rabies the virus usually reaches the central nervous system, but in most cases is destroyed by the natural defensive processes without causing symptoms. Viala (45) reports a female rabbit which resisted four sub-dural inoculations with rabic virus, while her progeny all succumbed. Koch (44) has had dogs recover which were experimentally infected with street virus. The opinion is expressed that the occasional cord complications during the treatment may be due to rabies and not to the treatment.

In the search for Negri bodies in the different organs and tissues we experimented with several different stains recommended especially for Negri bodies. Lentz's stain gives very good differentiation, but the staining process is very complicated and the results are not constant. The results we obtained with the Harris, Van Giezen, and Williams and Lowden stains were similar. Some sections would give a satisfactory picture, while in others the contrast would be poor. We found that von Krogh's stain
as described by Koch (46) gave very satisfactory results. The results with each section stained were const-
tant, the differentiation and contrast excellent. Accord-
ing to Koch paraffin sections are stained for five minutes
in polychrome methylene blue. They are given a brief wash
in water and placed in 2% chromic acid solution for from
two to five minutes, then washed in water and differentiated
in 5% tannic acid solution. The section is then washed, de-
hydrated, cleared and mounted. With this stain the ganglion-
ic cells and glial tissue take a fairly uniform bluish
tint. The Negri bodies (and Lentz corpuscles) appear of
a brilliant reddish violet color and stand out from the
nerve cells in very marked contrast.

Conclusions:

(1) In this case of human rabies pathological
changes occurred in the spleen, kidneys, pancreas, salivary
glands, hypophysis, adrenals, peripheral ganglia and cen-
tral nervous system corresponding with those already described
as occurring in this disease.

(2) The scar of inoculation wound in this case
was not virulent. The same may be said of the brachial
plexuses of both sides.
The patient was an individual in whom antirabic anti-bodies could not be developed, since, from the length of the incubation period in this case a protective immunity should have been developed.

(4) In our hands von Krogh's stain has given the most satisfactory results for the staining of Negri bodies.

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Fig. 1. Sub-maxillary gland. Interstitial tissue surrounding interlobular duct.
   a, e, serous cells.
   b, lumen of large duct, the epithelium of which is desquamating.
   d, smaller duct.
   c, area of fibroblastic infiltration.

Fig. 2. Portion of Malpighian body of spleen.
   a, cells with homogenous and glassy cytoplasm.
   b, lymphocytes.
Fig. 1 Around the central canal of lumbar cord.
   a epithelial cells penetrating the tissues below
   the basement membrane
   b place where cells commence their aberrant growth.
   c lumen of canal

Fig. 2 Section through the medulla at the fourth ventricle and olivary bodies. Perivascular round cell infiltration in a vascular in the roof of the fourth ventricle.

Fig. 3 Temporal lobe of the cerebrum. Glial cells in groups of three and four.
Plate III

Fig. 1. Gasserian ganglia
   a, a, area of fibroblastic infiltration.
   b, b, atrophied and shrunken ganglionic cells

Fig. 2. Group of ganglia cells from Hippocampus major
   a, a. Negrê bodies, stained with von Krogh's stain.
THE PATHOLOGICAL BASIS OF THE THROAT SYMPTOMS OF RABIES.

A THESIS
PRESENTED TO THE FACULTY
OF THE
GRADUATE COLLEGE OF THE UNIVERSITY OF IOWA,
IN PARTIAL FULFILLMENT
OF THE
REQUIREMENTS FOR THE DEGREE
OF
MASTER OF SCIENCE IN MEDICINE.

BY
MARK FREDERICK BOYD, M. D.

OSKALOOSA, IA.
July, 1913
THE PATHOLOGICAL BASIS OF THE THROAT SYMPTOMS OF RABIES.

OUTLINE OF THESIS

1. Introduction
2. Throat symptoms on a human case.
3. Post mortem findings in relation to throat symptoms.
4. Animal inoculations: observed symptoms and post mortem findings.
5. Description of throat symptoms as given by authorities.
7. Conclusions.
8. References to literature

SCOPE OF STUDY

This study was undertaken that an opinion might be formed, if possible, of the pathological changes responsible for the throat symptoms of rabies: whether they are caused by pathological changes present in the throat serving as a peripheral irritant, or whether the symptoms are due to alteration of the nerve cells whose fibers supply the pharynx and larynx.
THE PATHOLOGICAL BASIS OF THE THROAT SYMPTOMS OF RABIES.

The rather rare infectious disease known as rabies has many synonyms in the English as well as foreign languages indicative of the frequency which all observers have noted symptoms referable to the throat. They practically all refer to the difficulty in swallowing caused by muscular spasms of the pharynx and larynx. For instance the ancient Greek name ιφασφιλία; the Latin Aquifuga or horror aquae; the German Wasserschau; the English Hydrophobia and the Italian Idrophobia, all refer to the prominence of these symptoms in the course of the disease.

The following is a brief history of a case of human rabies recently under observation in the University Hospital, noting particularly the symptoms referable to the throat. Mr. E. B. of Shannon City, Iowa, was bitten by a strange dog on the 1st of August, 1911. Subsequent laboratory examination of the dog's brain proved it to have been rabid. Five days after having been bitten he appeared at the Laboratory of the Iowa State Board of Health and received the Pasteur treatment. The course of the treatment was uneventful and he was discharged at the end of twenty one days in good health. He returned to his home and nothing further was heard of him until November 21st, 191
when he was brought to the University Hospital at 5:40 P.M. in the exciting stages of rabies. His relatives who accompanied him stated that his health had been apparently good until four or five days previous to his admission to the hospital. He then complained for a couple of days of pain in the scar of the bite on his right wrist. Two days previous to his admission he developed a spasm of the muscles of deglutition whenever he attempted to swallow, the spasms preventing his swallowing any liquid or solid food. His family suspected rabies and prevailed on him to return to Iowa City. His mental attitude was cheerful. He walked from his home in the country to the railroad station as the jarring of the buggy started general convulsive seizures. After he developed the general convulsions it was impossible to get any history of any convulsions affecting the throat muscles alone. After boarding the train the convulsions increased in frequency so that Des Moines it was necessary to call a physician to administer opiates. He was conscious up to the time opiates were administered and realized when a convulsion was impending and endeavored to prevent himself injuring those with him.

The following account is extracted from the bedside notes made at the hospital after admission.

Nov. 22 1:40 A.M. Paroxysms commenced, about two minutes apart. The patient yelled loudly and incoherently except once, when he distinctly said "Oh! Hell, take it away, take it away." Face flush-
ed, neck stiff; Eyes open, staring, cornea dull and dry. Facial muscles twitch between paroxysms. Evidently swallowed without much difficulty. Pulse 140; Resp. 15, irregular.

Nov. 22 12M. Difficulty in breathing. Face and ears becoming cyanotic. Patient acts as if nauseated and did some straining as if a foreign object was in the throat. After respiration became re-established his face became flushed. Temp. 105.5°; Pulse 142; Resp. 16.

Nov. 22, 1 P. M. The patient suddenly, without warning regurgitated three to four ounces of dark brown fluid. A second regurgitation occurred at 1:45 P. M. The hands moved towards the throat several times. Following regurgitation the patient seemed relieved. Pulse 144; Resp. 17.

Nov. 22, 2:15 P. M. All reflexes absent except a doubtful reaction to light. The respirations became shallower, the regurgitations of fluid became more frequent, the pupils dilated and at 2:50 the patient died.

In this case the spasms of the muscles of the pharynx and larynx alone had ceased before entering the hospital and the convulsive seizures involved the entire body.

At 4: P. M. a complete post mortem was performed by Drs.
Edlavitch and Boyd. The following extracts are from the autopsy protocol, and refer to the larynx, pharynx, asophagus, ganglia and medulla.

The mucosa of the larynx, pharynx and asophagus was smooth, very pale and moist. The mucosa of the pharynx was covered with a small amount of the dark brown fluid found in the mouth.

The Gasserian ganglia were removed as it was not possible to dissect the fusiform ganglia from the vagus without mutilating the neck.

The medulla and cord showed some congestion of the pia-arachnoid and some congestion of the cord substance.

The medulla was sectioned through the 4th ventricle and above the decussation, olivary bodies, and through the closed portion. Tissue was imbedded in paraffin and sections were stained with Ehrlich’s acid hematoxylin and eosin, Pappenheim’s pyrinnion and methyl-grün, and thionin.

The pharynx and larynx presented no gross changes and were not sectioned.

Gasserian ganglia. Congested. Some of the ganglionic cells are shrunken and retracted from their capsular wall. They stain poorly
There is a marked fibroblastic infiltration into the connective tissue between the ganglionic cells. Many of the fibroblasts are proliferating into vacant spaces left by the shrunken ganglionic cells.

Medulla through the 4th ventricle and olivary bodies. Capillary congestion and small hemorrhagic areas around some capillaries. In places the epithelium of the 4th ventricle is thickened and consists of two or three layers of cells. Underneath these areas is an area of fibroblastic proliferation. Some of the smaller blood vessels have a round cell infiltration in and around their walls. The cells in the dorsal nucleus of the IX and X nerves, in the nucleus of the XII, and the nucleus ambiguous are altered. The Nissl bodies of the cells are entirely absent from many cells; in others they are shrunken and absent from portions of the cell. Some nuclear walls are shrunken, with irregular outlines, their nucleoli absent. A few cells appear normal and some entire cells appear shrunken and are only visible as shadows.

Medulla slightly above the pyramidal decussation. Capillary congestion. Around the central canal is an eccentric proliferation of connective tissue in which are epithelial cells from the epithelial lining of the canal, lying singly or in groups. The remaining epithelium does not completely surround the lumen
of the canal. At one place the epithelium is proliferating into the canal lumen.

On April 18th four guinea pigs were inoculated sub-cutaneously on the back of the neck with an emulsion of nervous tissue containing rabic fixed/virus. Each pig was given about four drops of the emulsion, a rather small dose for a subcutaneous inoculation.

Their subsequent history follows:

Guinea pig #1. April 26th the pig was very nervous and excited, running continuously about its cage, and frequently biting and scratching at itself. It remained in this condition for two days. On the 29th it was unable to sustain its weight on its left fore leg, though able to move that extremity. It would cough frequently and act as if some foreign body was sticking in its throat which it was trying to dislodge. From the onset of symptoms of the 26th it was not noticed to eat or drink. In the evening of the 29th it was unable to sustain its own weight and lay on its left side, its head extended, due to extreme contraction of the muscles of the back of neck. Squealed frequently. If touched the animal had a general convolution. On the 30th its convulsions were frequent, the breathing shallow and rapid. Died on the afternoon of the 30th. Very emaciated.

Guinea pigs #2 and 3 survived.

Guinea pig #4. April 27th the pig was very nervous and restless, knawing and biting at the walls of the cage. Not observed to eat.
Apparently had spasmodic contractions of muscles of throat, as would sit on haunches and elevate head, the muscles of the throat meanwhile violently contracting. Breathing difficult during such a spasm. On the 1st of May the posterior extremities were paralyzed. The animal became comatose and died on the 2nd.

Post mortem findings: #1. Pharynx and larynx normal. Mucous membranes were pale, but moist. Muscles red and pliable. The meninges of brain and cord were congested. The medulla and Gasserian ganglia were removed, fixed in formalin and sectioned. The ganglionic cells of the medulla presented the same features as described from the medulla of the human case. The Gasserian ganglia presented similar changes to those in the human case.

#2. Conditions identical with those described for guinea pig #1.

Three stages are described in the progress of rabies, namely the premonitory stage, the stage of excitement and the paralytic stage. The symptoms of the throat are manifested during the stage of excitement. Osler describes the throat symptoms as follows—"Stage of Excitement—This is characterized by a great excitability and restlessness, and an extreme degree of hyperaesthesia. Any afferent stimulus—i.e., an sound or draught of air, or the mere association of a verbal suggestion will cause a violent reflex spasm. The spasms, which affect particularly the muscles of the
larynx and mouth, are exceedingly painful and are accompanied by an intense sense of dyspnoea, even when the glottis is widely opened or when tracheotomy has been performed. Any attempt to take water is followed by an intensely painful spasm of the muscles of the larynx and elevators of the hyoid bone. It is this which makes the patient dread the very sight of water and gives the name of hydrophobia to the disease. Stimson in Facts and Problems of Rabies (2) gives this description—"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. Subsequently smell the sight, sound or sound of liquids suggests the act of swallowing and is sufficient to bring on an attack in many cases."

Striking pathological changes in the pharynx and larynx have never been noted in the disease. It very frequently happens that the condition of congestion, present elsewhere in the body, is also manifested in the pharynx, but was not noted either in the human or experimental cases here discussed.
found in all the peripheral ganglia; in both the cerebro-spinal and sympathetic. These alterations are more pronounced in the cerebro-spinal than in the sympathetic ganglia. They were first described by Van Gehuchten and Nelis (3) who believed them specific for rabies. Frothingham (4) states that he has found them in over 700 Gasserian ganglia, mostly from, and that while they are not specific for rabies, they are so rarely found in other conditions as to be a valuable diagnostic aid. The changes inevitably result in a greater or less destruction of the nerve cells. This destruction is brought about by an active proliferation of the cells of the capsule in which each of the nerve cells is lodged. The new cells multiply actively by direct division and finally completely fill the corresponding capsule. Many nerve cells are completely destroyed and their places occupied by the new cells. When the destructive process is very intense it manifests a tendency to pass the limits of the capsule and all the ganglia is formed of new tissue, of small placed very close to each other, in which are seen the remains of nerve cells and blood vessels. Without any chances of error, the changes which have taken place in the Gasserian ganglia of this human case may be assumed to have been present in the fusiform ganglia of the vagus, which Van Gehuchten and Nelis state is the most sensitive to these changes.

These destructive changes are present in the nerve cells whose processes are the afferent fibers from the pharynx and larynx. Van Gehuchten and Nelis consider these changes to be responsible for the
extreme hypersusceptibility to external stimuli. This hypersusceptibility gives place to anesthesia and the above authors find that in the dog the anesthesia is often complete, and that reflex movements cannot be produced by the faradic current.

The nerve cells may be altered in some portions of the central nervous system and not in others. These lesions consist of atrophy, vacuolation and granular or fibrinous degeneration of nerve cells associated with degeneration of the processes. Golgi has demonstrated irritative and regressive changes in the nucleus, characterized by increase and subsequent fragmentation of the chromatin with karyolysis, bladder like swelling, vacuolation and granular degeneration of the cell body; atrophy and loss of the processes and eventually destruction of the entire cell. These changes apparently do not affect all the cells, some apparently remaining normal. Bailey (8) describes shrinking, displacement and disappearance of the Nissl bodies of the nerve cells in rabies. Babes (5) describes hemorrhages from the small blood vessels of the medulla, frequently limited to the lymphatic sheath of the vessel. He constantly finds in the motor centers of the medulla and cord a hyperemia and accumulation of embryonic cells around the smaller vessels. Round unicellular elements of a lymphatic origin often invade the protoplasm and fill out the dilated pericellular lymphatic spaces by a multiplication of small nuclei. These pericellular and perivascular accumulations are known as the rabic tubercles of Babes.
The above cellular changes have been found in the cell groups constituting the nuclei of origen of the nerves whose fibers supply the mucosa and musculature of the pharynx and larynx in the human case, and in various cells from the medulla in the experimental cases, namely the dorsal nucleus of the IX and X nerves and the nucleus ambiguous of the IX, X and XI nerves. The ganglionic changes were present in both the human and experimental cases.

The post mortem findings do not indicate that any pathological changes in the pharynx or larynx were responsible for the spasms of their musculature. The spasms were not caused by reflex action from a peripheral irritant situated on the mucosa of the pharynx or larynx, but were caused by a central irritation of the nerves supplying the pharynx and larynx, i.e., the vagus, glosso-pharyngeal and spinal accessory. The condition of the nerve cells in the nuclei of origen of both the vagus and spinal accessory nerves indicate that these cells have been profoundly altered and destroyed, presumably by the virus of rabies.

From this data we must conclude that the pathological basis of the throat symptoms of rabies is nervous in origen; that the origen changes in the afferent fibers render them hypersusceptible to stimuli, leading to their paralysis and death; and that spasms taking place after the destruction of the cells of the afferent fibers are due to central irritation of the motor cells of the nerves supplying the pharynx and larynx.