RIFT VALLEY FEVER

A Report of Three Cases of Laboratory Infection and the Experimental Transmission of the Disease to Ferrets

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Plates 16 and 17

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Rift Valley fever, a disease of sheep and cattle, was first studied and described in the Kenya Colony, British East Africa, by Daubney, Hudson, and Garnham (1), who showed that the specific causative agent of the disease is a filterable virus. Findlay and Daubney (2) found that the virus is infectious for a wide variety of animal hosts, and especially for rodents. That the virus is infectious for man as well, was noted by Daubney, Hudson, and Garnham (1), who reported the prevalence of the disease among sheep herders during the epizootic. Moreover, these investigators transmitted the disease directly to man by the intramuscular inoculation of the blood of infected sheep. The disease in man has been described as dengue-like (1), or influenza-like (3), and is characterized by sudden onset, fever, and severe pains in the back and extremities.

Further evidence of the infectiousness of the virus for man has been obtained from the high incidence of the disease among laboratory workers engaged in studying the experimental disease. Kitchen (4) has recently summarized thirteen cases of Rift Valley fever of laboratory origin. In each instance the diagnosis was based upon the recovery of the virus from the blood of the patient during the acute illness, the demonstration of specific neutralizing antibodies in the convalescent serum, or both. The presence of the virus of Rift Valley fever in human blood is most readily demonstrated by the inoculation of the blood into mice, in which a rapidly fatal disease of a septicemic nature is produced (5). Marked hepatic necrosis is an outstanding feature of the infection in mice, and acidophilic intranuclear inclusion bodies are found in great numbers in the damaged liver cells.

The actual mode of infection of the human individual with Rift Valley fever has not been established, although Findlay (5) suggests the possibility that infection

occurs through an abrasion of the skin, through the conjunctival sac, or through the nasal mucous membranes. Furthermore, by the instillation of Rift Valley fever virus into the nostrils of monkeys, he induced a febrile disease in those animals similar to that occurring spontaneously in man.

All the previously reported cases of laboratory infection occurred during a period of active study of the virus, so that the diagnosis of Rift Valley fever was readily suspected. The present report deals with three cases of Rift Valley fever in human individuals, in the first of which the source of the infection is obscure. The disease in the other two cases appears to have been related directly to the handling of infectious material. The virus was shown to be present in the upper respiratory tracts of two of the individuals, as demonstrated by the intranasal inoculation of ferrets with nasopharyngeal washings of both patients. In these ferrets a disease was produced in which pulmonary involvement was the outstanding feature.

Report of Cases

Case 1, E. H.—The patient, a male laboratory assistant, during the early morning of Oct. 6, 1934, felt chilly and experienced generalized aching. He was seen that afternoon by a physician, who noted no abnormal physical findings except mild injection of the throat. His temperature by mouth was 103°F. On the following day, after antipyretics, the temperature was 99.5°, and the next day was normal. The aches and pains were less severe. Recovery was uneventful except that the patient complained for some time of shooting pains in his muscles.

Because of the similarity of the clinical symptoms to those of influenza, pharyngeal washings obtained on the 2nd day of illness were inoculated intranasally into a ferret. The ferret became ill 2 days later, and with material obtained from this ferret, sacrificed on the 4th day of illness, it was possible to transmit the disease to other ferrets.

Case 2, T. F.—The patient, a member of the staff, working with the virus obtained from the previous case, was suddenly awakened at 2 a.m. Nov. 10, 1934, with severe chills. During the day his temperature rose to 104.5°, and was accompanied by headache, generalized bodily pains, moderate nasal congestion, tenderness of the eyeballs, and mental confusion. The leukocyte count in the morning was 4880; in the afternoon 3720. The urine showed no abnormalities. The patient was considered to be suffering from a typical attack of influenza. The following day, after the administration of antipyretics, the fever was lower, but

marked backache persisted. The leukocyte count was 4780 with 48 per cent polymorphonuclear leukocytes. On the 3rd day the patient's temperature returned to normal and remained so. Convalescence proceeded rapidly without complications. There persisted for some time, however, pain on motion of the eyes, and a sense of imbalance.

Throat washings obtained from the patient on the 1st day of illness were inoculated into the nasal passages of a ferret. The animal became ill, and the course of the infection was similar to that of the ferret inoculated with the washings from the previous case. Pharyngeal washings obtained from the patient on the 7th day after the onset of infection failed to produce the disease in a ferret. The blood of this patient, taken on the 1st day of illness, was also found to contain active virus.

TABLE I

Recovery of Virus from Human Cases of Rift Valley Fever

Case No.	Material from which virus was isolated	
	Throat washings	Blood
1. E. H., Oct. 6, 1934	+	Not done
2. T. F., Nov. 10, 1934	+	+
3. S. S., Dec. 12, 1934	−	+

+ = virus recovered from the indicated material.
− = virus not recovered from the indicated material.

Case 3, S. S.—The patient, a male laboratory assistant, actively engaged in the studies of the two previous strains of virus, was taken sick suddenly on Dec. 12, 1934. The onset was marked by a severe chill, at which time his temperature was 99.8°F. by mouth. There was a slight cough. His throat was red and a throat culture taken at this time revealed a heavy growth of hemolytic *Hemophilus influenzae.* The leukocyte count was 9700. During the night his temperature was reported to have risen to 105.6°F. There was sleeplessness, some epistaxis, nausea and vomiting, a distinct sense of anxiety, and generalized aches and pains. The latter, the patient described as not being as severe as those of influenza which he had experienced 3 months previously. He was admitted to the hospital on Dec. 13, 1934, with a temperature of 103°F. and white blood cell count of 5650 with 80 per cent polymorphonuclears. The urine showed no abnormalities. There was a mild but persistent nosebleed. The patient's temperature fell rapidly and he apparently had recovered completely when discharged from the hospital on the 8th day after admission. 2 days later he again developed fever, severe

headache, nausea and some vomiting, and experienced dizziness for several days. Recovery proceeded uninterruptedly thereafter.

The pharyngeal washings taken from the patient at the onset of the illness did not contain demonstrable virus, but the blood obtained on the 2nd day of illness was found to be infectious for mice.

The course of the disease in this individual resembles the previously reported cases of Rift Valley fever with febrile relapses (1, 5). In none of the present cases was there any evidence of visceral damage. In fact, the clinical diagnosis of influenza was made unhesitatingly in each instance.

The Transmission of Rift Valley Fever to Ferrets

The pharyngeal washings of Cases 1 and 2 were inoculated into the nasal passages of ferrets anesthetized with ether. The subsequent course of events in both instances was so similar that they can be considered together. After an interval of 48 hours, the temperature of the ferrets rose abruptly to 106°F., the animals became apathetic, displayed no interest in food, and respirations were rapid. The course of the temperature is shown in Chart 1. The animals were sacrificed on the 4th day of fever. At autopsy, a bluish edematous consolidation of the lower lobe of the left lung was observed. The liver was pale and rather brown. There was distinct hyperemia of the lower two-thirds of the intestines. The spleen was somewhat enlarged. The adrenal glands and kidneys showed no gross abnormalities.

With the intranasal inoculation of suspensions of finely ground lung tissue from an infected ferret, or with Berkefeld filtrates of such suspensions, it was possible to transmit the disease serially in these animals. With successive transfers the infection became more severe, and when allowed to continue was generally fatal. The pulmonary lesions became more extensive so as to involve almost the entire lung. Copious amounts of blood-stained mucus collected in the trachea. At times hemorrhagic diarrhea occurred and dark, changed blood was found in the intestines. On one or two occasions gross hemorrhages were noted about the adrenal glands. The spleen was usually enlarged. The liver was light brown, and in some instances gross areas of necrosis were visible to the naked eye.

It was subsequently found that the subcutaneous injection of

emulsions of infected ferret lung into normal ferrets also caused death; in the two instances observed, pulmonary lesions were present even after subcutaneous inoculations.

Pathology of Rift Valley Fever in the Ferret

In describing the pathological changes which were observed in infected ferrets, it must be borne in mind that the majority of the animals were sacrificed on the 4th or 5th day of illness, and that the size of the infecting dose of virus was progressively decreased. The

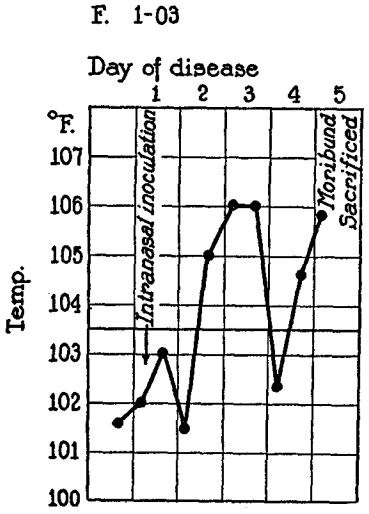

CHART 1. Temperature chart of a ferret infected with Rift Valley fever virus.

most severe intestinal and hepatic lesions were observed in the animals of the early passages.

Lungs.—The lungs of ferrets which die or are sacrificed after intranasal inoculation present in the gross a massive bluish gray consolidation of lobar distribution. The consolidation usually involves all of the basal lobes, the cardiac and right middle lobes, and, less completely, the upper lobes. When the infected lung is cut, a large amount of thin serous fluid exudes, and the size of the lobe decreases considerably. Cultures of the involved lungs are almost invariably bacteria-free.

Microscopically, the outstanding features of the pneumonia are a moderate edema and cellular proliferation in the alveolar walls, the great amount of edema fluid and the comparatively scanty cellular exudate in the alveoli. The cells comprising the exudate are primarily of the large acidophilic mononuclear variety

similar to those seen in the lungs of ferrets infected with influenza virus (7, 8). Inclusion bodies were not observed. No noteworthy changes were seen in the walls of the bronchi or bronchioles, although a moderate amount of exudate, containing polymorphonuclear leukocytes, was not infrequently present in the lumen. The peribronchial lymphatic channels are, at times, quite dilated. Vascular hyperemia is usually noted. The walls of the blood vessels may be very edematous, the cells of the endothelium are swollen, and a moderate perivascular round cell infiltration is commonly present. (Fig. 1.)

Liver.—The lesions in the liver are of irregular severity. At times the entire organ is light brown in color with nodular areas of necrosis 0.5 cm. in diameter. At other times there is little gross change except increased friability. The liver is usually swollen. Microscopic study, in the majority of instances, revealed very mild, if any, damage to the liver. On the other hand, in the livers of the early passage ferrets, marked hemorrhagic necrosis of zonal distribution was seen. At other times all the hepatic cells appeared to be undergoing fatty degenerative changes. The nuclei were distinct, but no inclusion bodies were seen. Some infiltration of small mononuclear cells about the portal radicals was observed. The Kupffer cells were not obviously affected. (Figs. 3 and 4.)

Spleen.—The spleen is usually enlarged and exhibits active hematopoiesis. Apart from moderate hyperemia or edema, significant changes were not observed.

Intestines.—In the gross, hyperemia of most of the large intestine is frequently present, and at times either fresh blood or blackened, changed blood may be found in the lumen. No gross ulcerations were observed. Microscopically, in the majority of instances, little of significance is seen except hyperemia of the capillaries of the villi. In one instance, in which fresh blood was present in the intestine, the sections revealed distinct hemorrhage in the villi, and, in some areas, desquamation of the lining epithelium. These changes resemble those described in the intestinal canal of infected sheep (1, 5). (Fig. 2.)

Adrenals.—The adrenals were examined only in those instances in which gross hemorrhage was observed. The hemorrhage was limited to the subcapsular tissue, while the glandular structure was entirely normal.

Kidneys.—The kidneys usually show no gross changes other than cloudy swelling. In one animal a few small hemorrhages were noted in the cortex. Microscopically, in this case, marked congestion of the glomerular capillaries and intertubular vessels was seen. Albuminous exudate was present in the tubules and in the glomerular spaces.

The most consistent pathological changes, apart from those in the lungs of the ferrets, were the hemorrhagic extravasations in different organs. These lesions are apparently related to an increased permeability of the blood vessels or to marked congestion rather than to destructive changes in the vascular walls. In contrast to the disease in sheep and mice, the extensive, almost complete hepatic necrosis is

not commonly seen in ferrets. Furthermore, in sections of the ferret organs, acidophilic intranuclear inclusion bodies have not been observed.

Rift Valley Fever in Mice

When bacteria-free suspensions of lung from the infected ferrets were inoculated into the nasal passages of anesthetized mice, death of the mice occurred in 3–4 days. Pulmonary lesions were not observed, but the livers of the mice so infected presented the extensive necrosis and acidophilic intranuclear inclusions characteristic of Rift Valley fever. It was possible to continue to transmit the infection to normal mice by the intranasal, intraperitoneal, subcutaneous, or intracerebral inoculation of the blood, or suspensions of lung or liver from infected mice.

Furthermore, serum of the second and third patients taken at the height of the disease was found to contain active virus which produced the characteristic disease in mice. After standing in the ice box 10 weeks, the serum still contained considerable virus. On the other hand, the direct intranasal inoculation of mice with washings from the throats of the patients did not induce Rift Valley fever in these animals.

Identification of the Virus

It was found that convalescent serum from Patients 1 and 2 reciprocally neutralized in ferrets the activity of the strains of virus recovered from the throats of these two patients. The ferrets receiving mixtures of convalescent serum and active virus developed neither fever nor pulmonary lesions.

The serum of ferrets after recovery from the disease was found to contain antibodies which specifically neutralized the infectivity of the virus. Nevertheless, two of these animals, reinoculated intranasally after an interval of 2 months, again became sick with fever and respiratory symptoms.

Neutralization tests were also carried out in mice. The livers of mice infected with the E. H. strain were used as the source of virus. Weighed amounts of liver were ground with 10 per cent normal rabbit serum in distilled water. After centrifugation at high speed for 15 minutes the material was further diluted serially to

make 10^{-3}, 10^{-4}, 10^{-5}, and 10^{-6} concentrations, in terms of the original liver weight. In dilutions as high as 1:10 million, 0.2 cc. of the material injected into the peritoneal cavity of a mouse caused death in 2–3 days. 0.5 cc. portions of the respective dilutions were mixed with 1.0 cc. amounts of the serum to be tested and incubated at 37°C. for 30 minutes. Each of a group of three mice was then inoculated intraperitoneally with 0.4 cc. of the serum-virus mixture.

TABLE II

Identification of Virus as Rift Valley Fever by Neutralization Tests in Mice

Human sera	Dilution of virus suspension											
	10^{-3}			10^{-4}			10^{-5}			10^{-6}		
Normal												
E. M.	D2	D2	D2	D2	D2	D2	D2	D2	D2	D2	D2	D2
R. P.*	D2	D3	D3	D3	D3	D3	D3	D3	D3			
T. M.*	D2	D2	D3	D2	D2	D2	D2	D2	D2			
M. T.*	D2	D2	D3	D2	D2	D2	D2	D2	D2			
Convalescent												
1. E. H.	S	S	S	S	S	S	S	S	S			
2. T. F.	S	S	S	S	S	S	S	S	S			
3. S. S.	S	S	S	S	S	S	S	S	S			
Known Rift Valley immune (N.O.)	S	S	S	S	S	S	S	S	S			
Animal sera												
Normal ferret	D2	D2	D2	D2	D2	D2	D2	D2	D2	D3	D3	D3
Convalescent ferret												
Rift Valley fever virus												
Strain 1	S	S	S	S	S	S	S	S	S			
Strain 2	S	S	S	S	S	S	S	S	S			
Influenza virus												
Strain P. R. 5	D2	D2	D3	D2	D2	D2	D2	D2	D2			
Strain P. R. 8	D2	D2	D2	D2	D2	D2	D1	D2	D2			
Known Rift Valley immune monkey	S	S	S	S	S	S	S	S	S			

D = died. Numerals indicate day after infection on which death occurred.

S = survived without evidence of infection.

Strains 1 and 2 are those recovered from Case 1 (E.H.) and Case 2 (T.F.) respectively.

Strains P.R. 5 and P.R. 8 are strains of human influenza virus obtained from influenza patients in Puerto Rico.

* Normal individuals who had been exposed to infection, but had experienced no illness.

It was found that the convalescent sera of all three patients, and the serum from recovered ferrets, protected mice against at least 1000 fatal doses of the virus. The serum of a human individual previously shown to neutralize Rift Valley fever virus, and the serum of a monkey immunized[1] against Rift Valley fever virus, were also found to afford complete protection to mice against the virus recovered from the three cases of human infection reported in the present study.

The serum of normal men and of three individuals who had been exposed to infection with the virus contained no neutralizing antibodies. The serum of ferrets recovered from infection with the virus of influenza likewise failed to protect mice against infection with the Rift Valley fever virus.

The evidence which led to the conclusion that the disease which had been encountered was Rift Valley fever may be briefly summarized: The virus obtained from the pharyngeal washings or from the blood of the patients induced an experimental disease in mice which was identical with that produced in these animals by the virus of Rift Valley fever. The infectivity of the virus was neutralized not only by the serum of the convalescent patients and of ferrets which had recovered from the experimental disease, but also by the serum of a human individual who was known to have had Rift Valley fever, and by the serum of a monkey which had been immunized with the virus of Rift Valley fever. Both sera were known to contain neutralizing antibodies for Rift Valley fever virus. From the experimental evidence, therefore, it may be concluded that the virus recovered from the three patients reported in this paper is the virus of Rift Valley fever.

Differential Diagnosis of Rift Valley Fever and Influenza

The difficulty of differentiating Rift Valley fever from influenza on purely clinical grounds is emphasized in the cases here reported. In only the third case was the diagnosis of influenza questioned, and, in this case, only because the patient had experienced a proven attack of influenza but 3 months previously. A second attack of the same infection within so short a time seemed unlikely. Nevertheless, there was no distinct clinical feature which served to differentiate one infec-

[1] The monkey was immunized by Dr. T. M. Rivers.

tion from the other. The blood of this patient taken during the acute stage of his second illness was found to cause a fatal, non-bacterial disease in mice. Since results of this nature have not been obtained with the blood of influenza patients, it was suggested that the two illnesses were unrelated and of different etiology. Chart 2 presents the temperature curves of the patient during the attack of influenza and during the later illness which was shown to be Rift Valley fever.

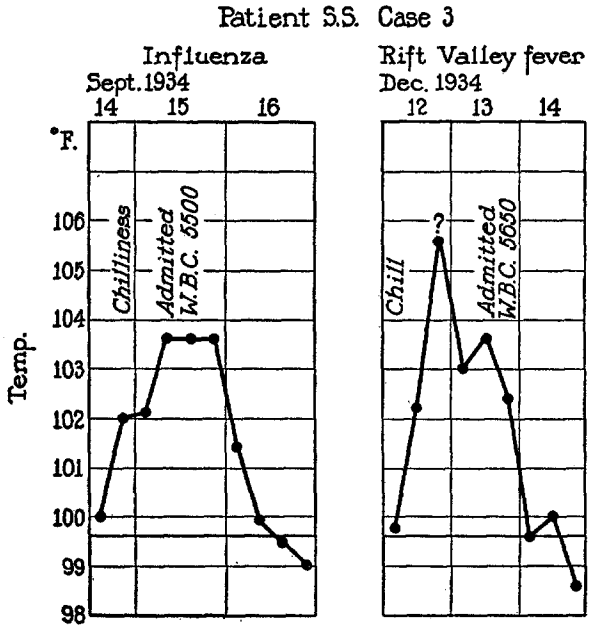

CHART 2. Temperature charts of the same patient (S. S.) during an attack of influenza and a subsequent attack of Rift Valley fever.

A comparison of the two curves again illustrates the close similarity of the clinical course in the two diseases.

The susceptibility of ferrets to infection with the virus of Rift Valley fever has not previously been reported. The susceptibility of these animals to the virus of influenza (6) and the pulmonary involvement which follows the intranasal inoculation of human (7) or swine (8) influenza virus was known. The febrile reaction and the pulmonary lesions produced by Rift Valley fever virus in ferrets differ only in

severity from those caused by the viruses of human and swine influenza. The virus of Rift Valley fever is infective for ferrets by the subcutaneous, as well as by the intranasal route, and produces lesions in organs other than the lungs. These facts serve to differentiate it from the virus of influenza.

TABLE III

Differential Diagnosis of Rift Valley Fever and Influenza

	Influenza	Rift Valley fever
Man		
Onset	Abrupt with chills	Same
Symptoms	Generalized aches, etc., mild respiratory	Same
Course	Short and sharp	Same
Complications	Usually none	Same
W. B. C	Leukopenia	Same
Virus in	Respiratory tract	Respiratory tract and blood
Ferret		
Incubation	24 to 72 hrs.	Same
Lung lesions	Only after several passages	First passage. More extensive
Liver lesions	Cloudy swelling	Focal necrosis. At times very marked
Intestinal lesions	None	Hemorrhagic enteritis
Outcome	Recovery	Usually death
Mouse		
Lung lesions	Marked	None
Liver lesions	None	Marked. Acidophilic nuclear inclusions
Virus in	Lungs	Blood, liver, lungs, others
Effective route of inoculation	Intranasal	All routes

The results of mouse inoculation, however, afforded the most striking evidence of the differences in the two diseases. In mice, the disease produced by the virus of influenza is apparently limited to involvement of the respiratory tract, with bluish red pulmonary consolidation. Rift Valley fever virus is infectious in high titer for mice by all routes, and invades the blood and all other organs. Pulmonary lesions were not observed even after intranasal infection. Extensive hepatic

necrosis, with acidophilic intranuclear inclusions, occurs no matter by what route the virus is introduced.

Immunization of Rabbits

Although they considered the rabbit an insusceptible host, Findlay and Daubney (2) reported that the virus of Rift Valley fever could be demonstrated in the blood of these animals for several days after intravenous administration. No reference is made, however, to the development of specific immune bodies in the serum of rabbits which were inoculated with the virus.

In the present study, large doses of the suspensions of lung of infected ferrets were inoculated into rabbits intracerebrally, intracutaneously, and intraperitoneally. In no case did the animal become sick or even exhibit a febrile reaction. In spite of the lack of evidence of active infection, it was of interest to determine whether neutralizing antibodies developed in the serum of rabbits inoculated with virus-containing material. To test this possibility, rabbits were given two intraperitoneal injections 4 weeks apart, of suspensions of lungs of infected ferrets, and were bled 15 days after the last injection. The serum of these rabbits was found to contain a high titer of neutralizing antibodies for Rift Valley fever virus as measured by the mouse protection test. The results are similar to those reported by Whitman (9) with the virus of yellow fever.

The Effect of the Route of Administration of Serum-Virus Mixtures upon the Protective Action of Immune Serum

When the neutralization test in mice is performed by the intraperitoneal inoculation of mixtures of serum and Rift Valley fever virus, the results are usually quite sharp. All mice receiving normal serum and virus die in 2–3 days, while the mice injected with mixtures of virus and immune serum survive without evidence of infection.

If the mixtures are given by the intranasal route to mice under ether anesthesia, certain sera fully effective by the intraperitoneal route may exhibit little or no protective action. In other instances, after 8–10 days, irregular deaths may occur among the mice receiving mixtures of immune serum and virus, suggesting that during the interval the neutralizing action of the serum has been dissipated and

has merely delayed the fatal outcome. From the animals which succumb to the delayed infection, fully active virus may be recovered. In Table IV are presented the results of comparative tests done by the intranasal and intraperitoneal routes.

These results indicate that the protective action of immune serum is not exerted directly upon the virus, since the period of exposure of virus to immune serum *in vitro* was the same in both series of tests. The neutralizing efficiency of the immune serum appears rather to be influenced by the route by which the serum-virus mixture is administered.

TABLE IV

The Influence of the Route of Administration upon the Neutralizing Capacity of Serum

Serum	Route of inoculation	Dilutions of virus								
		10^{-3}			10^{-4}			10^{-5}		
Normal human	i.n.	D3	D3	D3	D3	D3	D3	D4	D4	S
	i.p.	D2	D2	D2	D2	D2	D2	D2	D2	D2
Convalescent human	i.n.	D3	D3	D6	D4	D4	D4	D5	S	S
	i.p.	S	S	S	S	S	S	S	S	S
Normal ferret	i.n.	D2	D3	D3	D2	D3	D3	D4	D4	D4
	i.p.	D2	D2	D2	D2	D2	D2	D2	D2	D2
Convalescent ferret	i.n.	D8	S	S	D8	D9	S	S	S	S
	i.p.	S	S	S	S	S	S	S	S	S

i.n. = intranasal.
i.p. = intraperitoneal.
D = died. Numerals indicate day after infection on which death occurred.
S = survived.

DISCUSSION

The unusual feature in this outbreak of Rift Valley fever in man is that the source of infection of the first case (E.H.) was not definitely established. No Rift Valley fever virus had been used for study in these laboratories for 4 months prior to the onset of the illness. Furthermore, this patient had never assisted with the actual investigative work, nor had he ever been exposed to animals used in the study. The mice which had been employed were constantly kept in a room

under strict quarantine. The jars in which they were placed stood in pans of lysol, and the legs of the table on which the jars rested stood in lysol.

3 months after all animals had been removed from the room, the patient assisted in scraping and painting the walls and floor. So far as can be determined, that task was completed 15 days before the onset of the disease. If the infection in the present instance was acquired by exposure to virus persisting in this room, the virus must have withstood very adverse conditions for over 3 months, remaining not only viable but infectious. Similarly, the incubation period of the resultant infection, if thus acquired, was considerably prolonged, since all other records indicate that the period of incubation in Rift Valley fever in man is 6 days or less (5).

Another interesting aspect of the study of the human cases of the disease is that the virus of Rift Valley fever was readily recovered from the upper respiratory tract of two of the patients during the first 3 days of the disease, whereas on the 8th day after onset the virus could not be demonstrated in the throat washings of the one individual studied (Case 2). These observations clearly indicate that the virus of Rift Valley fever belongs to the group of filterable viruses which may effect their entry to the human body through the respiratory tract. Further evidence of the capacity of the virus to invade by way of the respiratory tract was obtained by the inoculation of the virus into the nasal passages of ferrets. The experimental disease in the ferret is characterized by the development of extensive edematous pulmonary consolidation with a scanty exudate of large mononuclear cells. The pulmonary lesion resembles that produced in experimental animals by other virus diseases, for example influenza (7, 8) and psittacosis (10).

In addition to the pathological features of the disease in mice, which were identical with those of Rift Valley fever, the virus recovered from patients in the present study was identified as that of Rift Valley fever by means of neutralization tests in mice. Not only was the infectivity of the virus neutralized by the serum of all three patients during convalescence, and by the serum of recovered ferrets, but by known Rift Valley fever immune serum as well. It was therefore established that the disease was Rift Valley fever.

An interesting observation was made regarding the influence of the route of administration upon the specific protective action of immune serum in mice. When given alone by the intranasal or intraperitoneal route, the virus of Rift Valley fever invades the blood of mice and profoundly damages the liver. When given together with immune serum by the intraperitoneal route, no evidence of infection is observed, but when immune serum and virus are administered by the intranasal route there may be little detectable difference between the protective effects of immune and normal serum. The difference in the protective action of the same serum administered by two different routes must, therefore, be related to a difference in the responses of the tissues into which the serum-virus mixtures are introduced.

These results offer support to the views of other investigators who have indicated that immune serum does not act directly upon the virus with a virucidal effect (11–13). Furthermore, the results suggest that the reaction of the tissue which first encounters the serum-virus mixture may be an important factor in determining the neutralizing efficiency of immune serum. A somewhat similar concept has been discussed recently by Sabin (13).

In the presence of an epidemic of influenza, it may be difficult clinically to differentiate Rift Valley fever from influenza. In the ferret the gross aspects of the experimental disease differ from those of influenza only in their severity. The chief aid in differential diagnosis is the presence of the virus of Rift Valley fever in the circulating blood of the patient during the acute illness. The virus can be recovered by the inoculation of the blood into mice, in which animals characteristic pathological lesions are produced.

SUMMARY

Three cases of Rift Valley fever in human individuals are reported. The virus was recovered from the respiratory tract of the patients and was transmitted to ferrets by the intranasal route. The experimental disease so produced in ferrets is characterized by fever, marked pulmonary lesions, and hemorrhagic phenomena.

The results indicate that the virus of Rift Valley fever belongs to the group of filterable viruses which may gain entrance to the human body through the respiratory tract.

The differential diagnosis of Rift Valley fever and influenza is discussed. While, clinically, this is a difficult problem, the diagnosis may be readily established through animal experimentation.

Certain observations concerning the influence of the route of administration on the protective action of immune serum in serum-virus mixtures are presented.

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EXPLANATION OF PLATES

PLATE 16

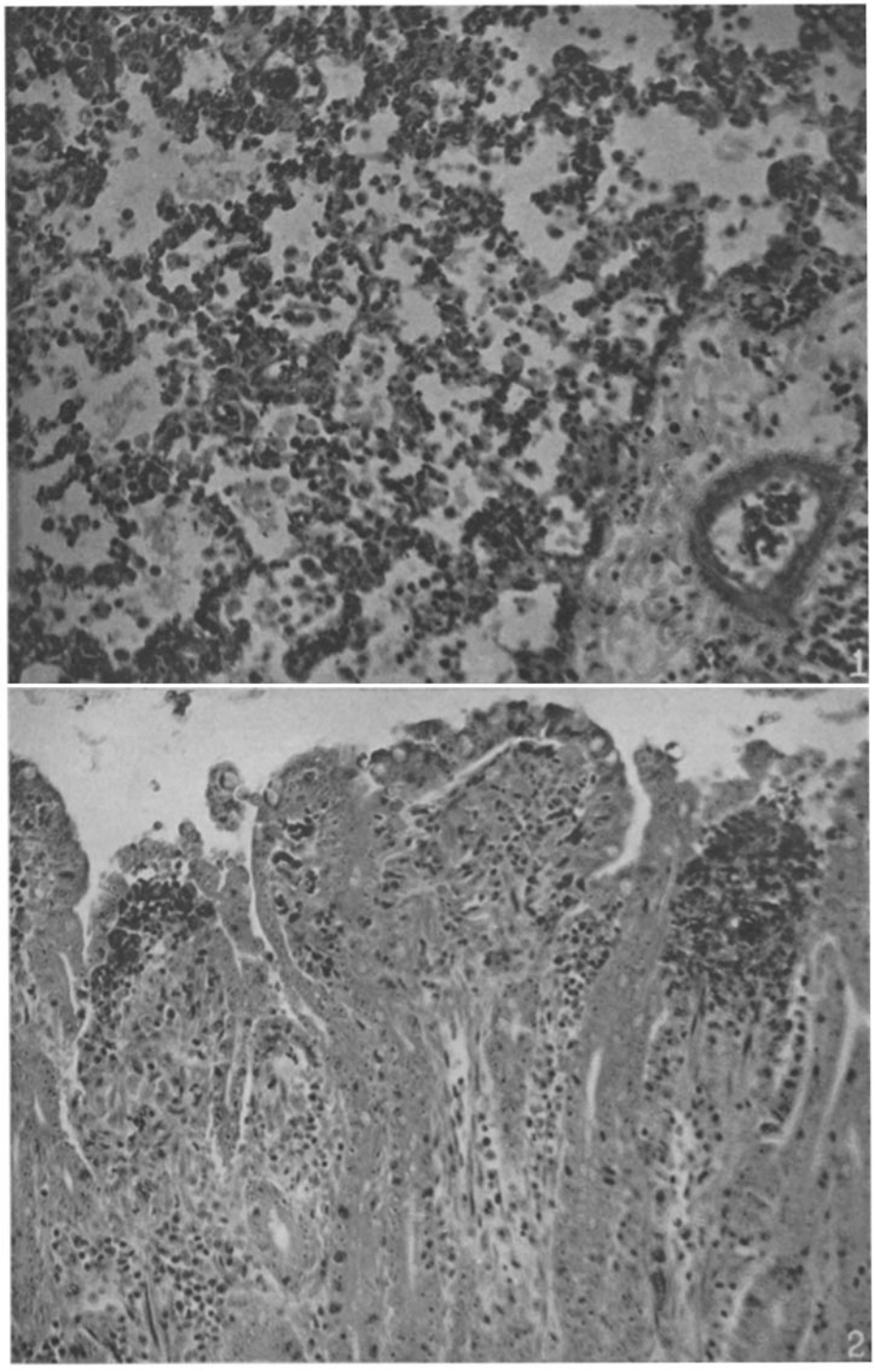
FIG. 1. Section through lung of ferret infected intranasally with Rift Valley fever virus. The organ appeared consolidated in the gross. There are thickening and hyperemia of the alveolar walls. The alveoli contain edema fluid and a scanty exudate of large mononuclear cells. Edema of the arterial wall is pronounced. (Eosin-methylene blue. M plate, B filter. × 210.)

FIG. 2. Section of the mucosa of the small intestine of an infected ferret in which hemorrhagic enteritis was present at autopsy. There is hyperemia of the vessels and extravasation of erythrocytes into the villi. (Eosin-methylene blue. M plate, 2 G filters. × 210.)

PLATE 17

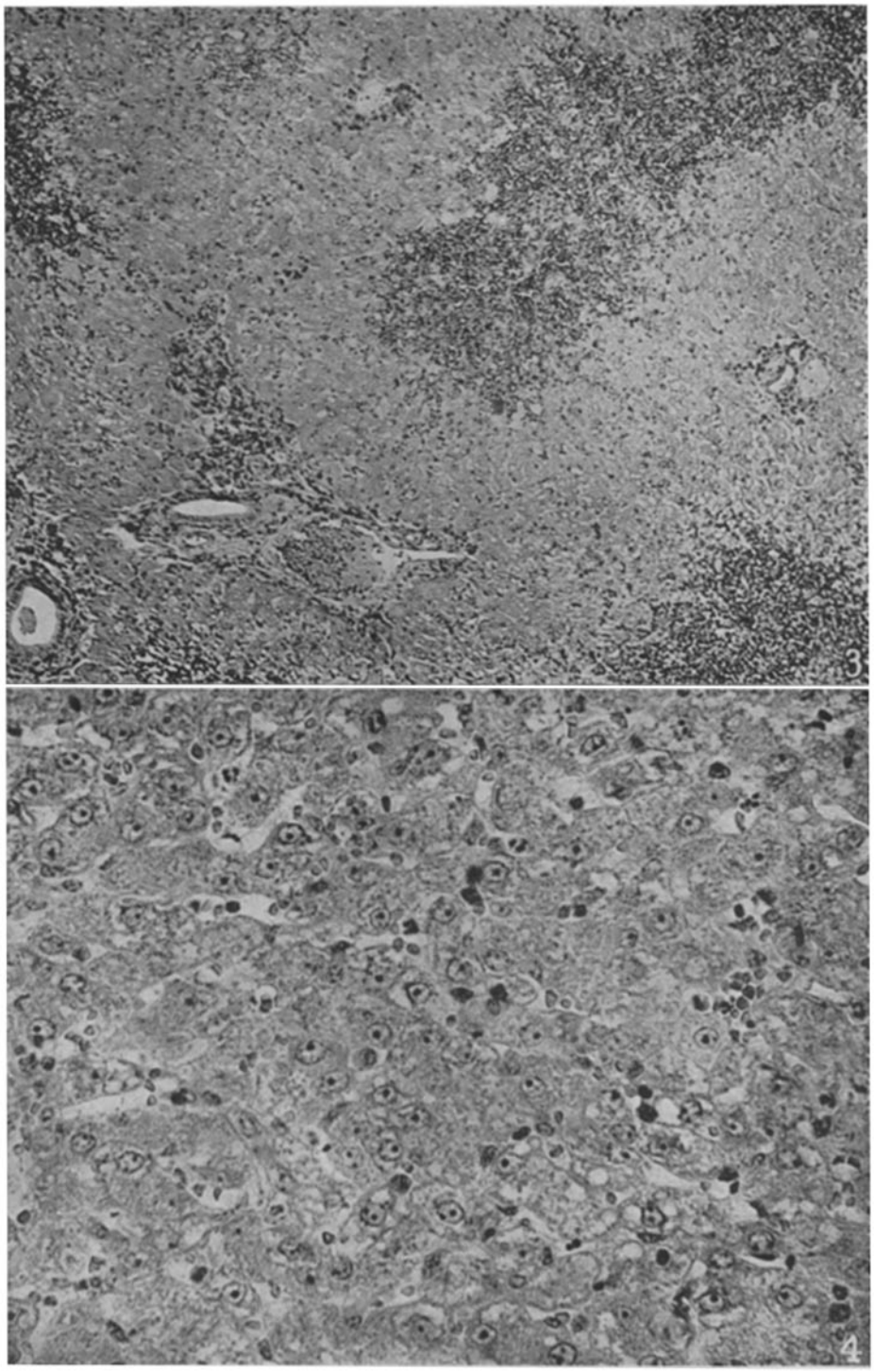
FIG. 3. Section of liver of an infected ferret showing mid-zonal hemorrhagic necrosis. (Eosin-methylene blue. M plate, 2 G filters. × 110.)

FIG. 4. Section of the liver of an infected ferret in which a rather uniform cytoplasmic lesion is present. The cells are pale, granular, and contain many vacuoles. (Eosin-methylene blue. M plate, 2 G filters. × 460.)



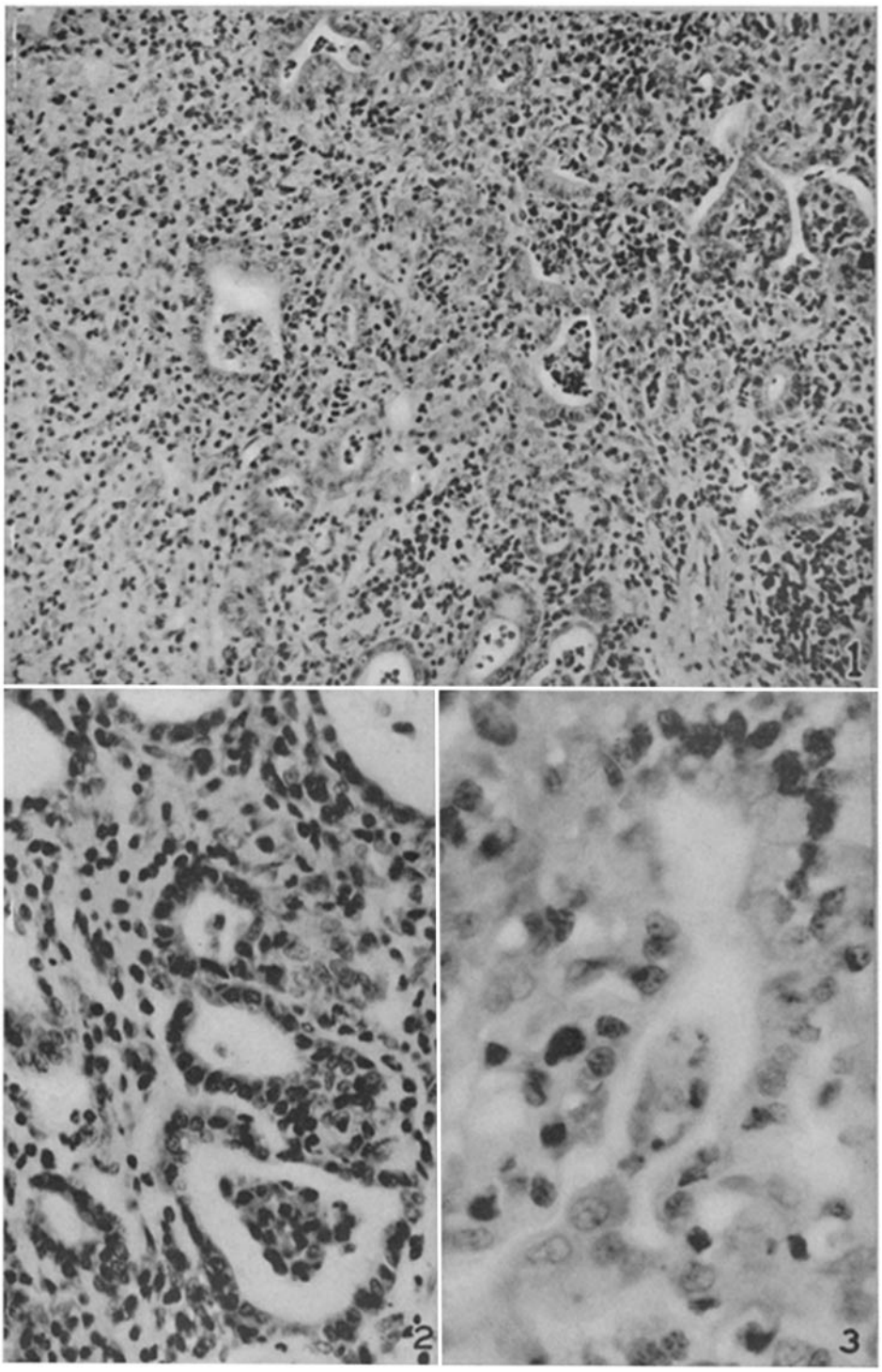
Photographed by Louis Schmidt

(Francis and Magill: Rift Valley fever)



Photographed by Louis Schmidt

(Francis and Magill: Rift Valley fever)



(Sprunt *et al.*: Interstitial bronchopneumonia. II)