AN UNIDENTIFIED VIRUS PRODUCING ACUTE MENINGITIS AND PNEUMONITIS IN EXPERIMENTAL ANIMALS

By THOMAS FRANCIS, Jr., M.D., and T. P. MAGILL, M.D.

(From the Laboratories of the International Health Division, The Rockefeller Foundation, New York)

Plates 2 and 3

(Received for publication, April 27, 1938)

In the winter of 1934, during the course of studies with the virus of epidemic influenza, throat washings from a patient suspected of epidemic influenza were inoculated into ferrets. With repeated passages in ferrets a disease was produced which in the gross resembled influenza virus infection (1, 2). Cross immunity between experimental influenza and the disease in question, however, did not obtain. Furthermore, the pulmonary lesions produced by the agent when introduced intranasally into mice were seen to differ strikingly from those produced by influenza virus. Instead of the edematous bluish red consolidation of influenza in mice (2, 3), the lesions were firm, rubbery, and of a pink pearly grey appearance resembling marble. No difficulty was encountered in maintaining the agent in mouse passage with suspensions of lungs of infected mice, but attempts to perform passive protection tests in mice with serum of ferrets recovered from infection with the homologous agent or from influenza virus infection were unsuccessful. While it was thus impossible to determine with certainty the source of the infectious agent, it seemed most likely to have been derived in the course of passage from a supposedly normal ferret and, consequently, to be of animal origin.

In 1936 an epidemic of respiratory disease clinically resembling epidemic influenza was widespread throughout the United States. An extensive study of material obtained during the outbreak in California (4) was made in these laboratories. Influenza virus was not demonstrated, nor did antibodies to influenza virus develop in the serum of convalescent patients. During the period of the epi-

demic, however, an infectious agent identical with that isolated in 1934 was repeatedly recovered from ferrets inoculated with throat washings of the patients. Fresh washings obtained from patients along the Atlantic seaboard as well as washings shipped in 50 per cent glycerine from California and other parts of the country were used. With fresh washings a clinical illness not infrequently occurred in the first ferret inoculated and from the first ferret was without difficulty transferred to mice. Attempts to recover the same agent from normal ferrets were unsuccessful. Attempts to demonstrate the virus in normal mice were also unsuccessful. Moreover, the agent has not been encountered since the spring of 1936 although large numbers of ferrets were inoculated with throat washings the following year in the study of an epidemic of influenza (5, 6).

Regardless of its origin, the frequent occurrence of the infectious agent during the period of study in 1936 made it imperative to determine characteristics which would serve to differentiate the agent from, or to identify it with, known viruses, a class in which it appears to belong. The present report deals with the observations which have been made in these respects.

General Characteristics

The agent to be described belongs, on the basis of information available, in the class of filtrable viruses. Repeated cultures in a wide variety of liquid and solid media, under aerobic and anaerobic conditions, have failed in our hands to reveal a microscopically visible bacterium which would reproduce the experimental disease. Furthermore, careful study of sections of affected organs or impression smears stained by a variety of methods have not ordinarily disclosed recognizable bacteria or parasites. In fixed preparations, however, bodies resembling elementary bodies have been observed.

The agent usually passes a Berkefeld V filter with comparative ease, passes a Seitz filter rarely or in but small amounts, and fails to pass a Berkefeld N filter. The agent filters through graded collodion membranes of 430 mμ average pore diameter but has not penetrated membranes of 250 mμ average pore diameter or less.

With centrifugation in the horizontal centrifuge at 3,000 R.P.M. for 1 hour some slight reduction in titer may occur, but in the high

speed centrifuge (7) at 13,000 R.P.M. almost complete sedimentation occurs in the same length of time.

The agent remains viable in 50 per cent glycerine for 3 to 4 months and rapidly regains full virulence with animal passage.

TABLE I

Pathogenicity of the Virus in Different Animal Species

Animal species	Route of inoculation	Pulmonary consolidation	Paralysis	Fever	Glandular enlargement	Death
Ferret	i.n.	+	0	+	0	+
	s.c. or i.p.	0	0	+	0	0
Mouse	i.n.	+	0		0	+
	i.c.	0	+		0	+
	s.c. or i.p.	0	+		0	+
Rabbit	i.n.					
	i.c.	0	0	+	0	0
	s.c. or i.p.	0	0	+	0	0
	Corneal	0	0	0	0	0
	i. test.	0	0	0	0	0
	i. cut.	0	0	0	0	0
Monkey	i.n.	Negative with throat washings of human patients				
	i.c.	0	+	+	0	0
	s.c. or i.p.	0	0	+	+(s.c.)	0
Guinea pig	i.c.	0	0	+	0	±
	s.c.	0	0	+	+	±
	i.p.	0	0	+	0	±

i.c. = intracerebral.
i.p. = intraperitoneal.
i.n. = intranasal.
i. cut. = intracutaneous.
i. test. = intratesticular.
s.c. = subcutaneous.

Attempts to maintain the agent in chick embryo-Tyrode's tissue culture medium have not been fruitful, but it is readily maintained by passage on the chorio-allantoic membrane of the developing egg.

The virus is pathogenic for ferrets, mice, monkeys, and within certain limits for guinea pigs and rabbits. These effects are summarized in Table I.

Infection of Animals

Experimental Disease in Ferrets.—Ferrets of all ages have been found to be susceptible. Passage of the virus in ferrets has ordinarily been carried out by the intranasal route.

A 10 per cent suspension of the lung and turbinate tissue of an infected ferret is inoculated intranasally into a normal ferret anesthetized with ether. After an incubation period of 24 to 48 hours, a sharp rise in temperature to 105–106°F. or higher may be observed. The temperature may be sustained for 4 to 5 days and is accompanied by weakness, loss of appetite, irritability, nasal discharge, and labored breathing. The majority of animals have been sacrificed on the 4th or 5th day and not infrequently the animal is moribund at this time. In others, fever may persist for 7 to 10 days with continuation of respiratory distress during the entire period but with ultimate recovery. At other times little fever or few signs of infection are observed, but autopsy reveals pulmonary involvement. Thus it is seen that considerable variation in the disease picture occurs. No evidence of involvement of the central nervous system has been observed following intranasal infection. Diarrhea is not uncommon and considerable dehydration occurs.

The most prominent pathological feature of the disease following intranasal infection of ferrets is an extensive edematous pulmonary involvement resembling in many respects that produced by influenza virus (2, 8). In general, however, the parenchyma of the lung is firmer than in the case of experimental influenza. Cultures of the lung are usually bacteriologically sterile. There is, in addition, congestion of the nasal tissues and a moderate amount of mucoid exudate. No marked abnormality of the remaining organs has been observed.

Following intraperitoneal inoculation of virus the ferret may exhibit marked weakness, sustained fever, and diarrhea for 3 to 10 days, but recovery has always resulted.

Large doses of infectious material given subcutaneously to the ferret have failed to produce objective evidence of infection other than a febrile response of 2 to 3 days' duration.

Experimental Disease in Mice.—Intranasal inoculation: The experimental infection is readily transferred to mice of all ages by the intranasal inoculation of suspensions of infected ferret lung. It requires little adaptation and can be transmitted serially in mice with little or no difficulty.

With a 10 per cent suspension of infected mouse lung as inoculum death of the inoculated mice occurs in 2 to 4 days; but when the dosage is decreased to 0.01

per cent or less, death is delayed for as long as 15 to 21 days and only rarely is there full recovery. Infected mice exhibit ruffled fur, respiratory distress, sticky eyes, and audible, wet respirations. No neurological signs occur.

The typical lesion occurs in the lungs which present a firm, rubbery, pinkish grey pneumonia involving most of the lung. At times the lung has an almost cartilaginous consistency when cut, and considerable edema fluid exudes. After intranasal inoculation the virus is recovered not only from the lung but from the blood, spleen, and liver as well.

Intracerebral inoculation: When the virus is introduced into the brains of mice an entirely different disease picture is produced. In a dilution of 1:1,000,000, virus injected intracerebrally causes paralysis and death of the animal in 6 to 10 days. Following infection with 10 per cent or 1 per cent suspensions of virus material, death ordinarily occurs in 2 to 3 days.

The first evidence of infection after intracerebral inoculation is a decrease in the activity of the mouse and the assumption of a crouching attitude. The animal scratches its nose constantly. The eyelids become tightly glued. The tail becomes hypersensitive, and shortly there is noted a flaccid paralysis of the hind limbs which drag along to one side while the animal walks with its fore legs. The hair over the posterior half of the body lies flat, in contrast to the erect state of the hair over the anterior portion of the body. Soon the animal becomes prostrate, struggling feebly and unable to right itself if placed in the supine position although the fore limbs are usually not paralyzed. Terminal convulsions may occur. The rate of development of symptoms varies with the infecting dose and the more typical progress of the disease is observed in animals which receive the smaller doses. An occasional mouse recovers after paralysis of indefinite duration. In contrast to the results of intranasal inoculation no pulmonary lesions are seen following intracerebral infection. The brain, however, is swollen and edematous and the characteristic lesion is a generalized meningitis.

Intraperitoneal and subcutaneous inoculation: The intraperitoneal inoculation of mice results in a somewhat varied disease. The animal becomes sick, and the abdomen is swollen and contains a fair amount of cloudy fluid and considerable fibrin. With large intraperitoneal doses of virus 50 per cent or more of the mice die with paralysis similar to that which occurs following intracerebral inoculation. If broth or starch is injected into the brain at the time virus is given intraperitoneally, only the exceptional mouse survives. Pulmonary lesions are not usually seen.

The subcutaneous inoculation of mice with strong virus suspensions

usually results in the depilation of the skin over the site of injection and the development of a firm granulomatous subcutaneous swelling. The skin may become contracted and break down. Approximately 10 to 15 per cent of mice so inoculated develop typical paralysis of the posterior quarters and die. A certain number recover from the paralysis while the majority reveal no clear evidence of central nervous system involvement. They do not develop pneumonia.

Experimental Disease in Monkeys.—Two monkeys (one *M. rhesus* and one *M. cynomolgos*) were inoculated intracerebrally with mouse passage virus. The course of the disease was quite similar in both instances. After an interval of 48 hours a brisk rise of temperature to 104°F. occurred. At the same time a flaccid paresis of one arm was noted. Fever and paralysis persisted for little more than 48 hours after which the animals rapidly recovered.

Cerebrospinal fluids obtained at the height of the disease by cisternal puncture contained, respectively, 500 and 1,000 cells, practically all of which were lymphocytic in type. Virus was recovered from the spinal fluid upon the intracerebral inoculation of the fluid into mice.

One of the animals which recovered after intracerebral inoculation was tested for immunity to infection with poliomyelitis virus and succumbed.

The virus was given to one monkey (*M. cynomolgos*) subcutaneously in the groin. On the 2nd day following inoculation there was slight enlargement of the inguinal gland, loss of appetite, and listlessness. On the 3rd day the temperature reached 105°F., then within 12 hours rapidly returned to normal limits. The animal recovered completely without evidence of involvement of the central nervous system.

Experimental Disease in Guinea Pigs and Rabbits.—The intracerebral inoculation of guinea pigs with the virus usually elicits fever and loss of weight as the only objective evidence of infection. Following a quiescent period of 48 to 72 hours a sharp rise of temperature to 105° or 106°F. is observed. The fever persists for 4 to 5 days after which relatively prompt recovery usually ensues. A small percentage of the animals die 5 to 6 days after inoculation, without paralysis.

When the virus is given subcutaneously to guinea pigs, thickening of the skin and induration of the regional lymph nodes occur. These

observations are somewhat obscured, however, by the frequent appearance of intercurrent infection in the stock of guinea pigs employed. Plantar inoculations were uniformly negative.

In rabbits the intracerebral inoculation of virus also causes a peak of fever, usually without paralysis or other evidence of disease. Following intraperitoneal inoculation a brief febrile reaction may occur but no other characteristic signs of infection are observed. Subcutaneous injection may cause fever and local cutaneous infiltration. Inoculation of virus on the scarified cornea, into the testicles, and into the skin has elicited no significant changes.

Pathology

In the ferret significant pathological changes have been primarily limited to the lungs and have been studied only after intranasal infection.

As previously mentioned, a pneumonia of variable extent occurs. The involved lobes are plum-colored, firm, and distended with edema fluid which flows freely from the cut surface of the bronchi. At times a clear albuminous fluid is present in the pleural cavity.

Microscopic examination reveals a pneumonia similar to that produced by the viruses of influenza (2, 8), psittacosis (9), or Rift Valley fever (10). There is edema of the bronchial walls but little or no desquamation of the bronchial epithelium; in fact, it appears somewhat hyperplastic. Exudate may be formed in the lumen of the bronchus. The vascular endothelium appears swollen and unusually prominent but hyperemia is not an outstanding feature. The alveolar walls are edematous and densely infiltrated with large mononuclear cells containing large pale nuclei (Figs. 1 and 2). These cells seem almost to form a lining of the alveolar spaces and the appearance of the lung in places approaches the adenomatous.

The alveolar spaces are distended and contain a moderate cellular exudate consisting primarily of large pale-staining mononuclear cells. Polymorphonuclear leukocytes are not prominent. Fibrin is usually not observed, and edema fluid, despite the large amount which seeps from the cut lung, is relatively scanty. In general, however, the lung presents a picture of a more proliferative type than that observed in infection with the virus of influenza.

The pathology in mice varies with the route of inoculation of the virus.

The pulmonary lesions are the outstanding feature after intranasal inoculation (Fig. 3). The early lesions are characterized by a certain degree of hyperemia

but especially by a rich effusion of edema fluid which fills the alveolar spaces over a comparatively large area. While edema of the alveolar walls is of moderate extent a few large mononuclear cells are observed. A rich cellular exudate resembling true consolidation later appears diffusely throughout the lung. The cells are predominantly large mononuclear in type but lymphocytes and polymorphonuclear leukocytes are scattered throughout. Fibrin deposits may occur. Hyperemia and extravasation of erythrocytes may appear. At times the exudate is so extensive as to make identification of the alveolar walls difficult. The latter, however, are swollen and infiltrated with large cells. Still later the lung shows dense infiltration of the parenchyma throughout and the alveoli are densely packed with cellular exudate. The appearance of the mouse lung is in general quite different from that observed in infection with influenza virus.

In mice which develop paralysis following intracerebral or intraperitoneal inoculation, an extensive meningitis and choroiditis is observed over the brain and spinal cord (Fig. 4). No perivascular cuffing or other evidence of infection is seen in the parenchyma of the brain or spinal cord. Because of the type of paralysis it was thought that damage to anterior horn cells of the spinal cord should be detectable, and in some sections alterations suggesting cytolysis in these cells were observed. Later studies, however, and examination of normal spinal cords did not substantiate these impressions (Fig. 5). The meningeal and choroidal reaction is of a mixed mononuclear and polynuclear type, the proportion of the latter cells being apparently related somewhat to the acuteness of the disease. The meningitis is diffuse over the dorsal and basilar aspects of the central nervous system. The ganglion cells do not appear to be damaged. Inclusion bodies have not been detected.

In the peritoneal exudate of mice which are inoculated intraperitoneally a rich collection of large mononuclear cells is found. Search for inclusion bodies in these cells has been unsuccessful.

The brains of monkeys infected with the virus were not examined.

In rabbits and guinea pigs a subcutaneous granulomatous lesion may develop after subcutaneous injection. There may also be hemorrhagic extravasation into the indurated tissue. Regional lymph nodes become swollen, hyperplastic, and firm.

Immunity

Ferrets which recover from intranasal infection are usually resistant to reinoculation.

Mice which recover after intranasal infection are resistant to reinoculation by the same route. Mice which recover after intraperitoneal or subcutaneous inoculation of virus are firmly immune

to subsequent intracerebral inoculation, regardless of whether or not they exhibited any evidence of infection as a result of the primary inoculation, but these mice are fully susceptible to the virus administered intranasally. However, efforts to recover virus from the brain or spinal cord of immune animals have proved unsuccessful. The immunity developed to one strain of virus is fully effective against all other strains of the same virus.

Attempts to study serological immunity by means of passive protection tests in mice have been somewhat difficult. Serum from recovered animals or from rabbits immunized by intraperitoneal inoculation fails to protect test animals when serum-virus mixtures are injected intracerebrally or intranasally. When serum-virus mixtures containing 10 per cent virus are given intraperitoneally the mortality is high, while with weaker concentrations of virus the percentage of survivors is high. When broth is given intracerebrally to mice before the administration of virus intraperitoneally, a uniformly high mortality occurs with the weaker dilutions of virus. Consequently the following procedure was adopted. A 3 per cent suspension by weight of infected mouse brain was made in 10 per cent horse serum-saline. To 1 volume of the virus suspension were added 2 volumes of the serum to be tested, and 0.3 cc. of the mixture (final concentration of virus equals 1 per cent) was injected intraperitoneally into mice which had 1 hour previously been given intracerebrally 0.03 cc. of sterile broth. The mice were observed for 10 days and survival or death of the animals was recorded. In Table II are presented results typifying those which have been obtained.

It has been possible to show by this means that the serum of known immune animals contains antibodies which protect the test mice from fatal infection. The margin of safety is narrow, however, since it is not always possible to obtain duplicate results with the same serum in different tests. Nevertheless, the sera of recovered ferrets and rabbits immunized by intraperitoneal inoculation have been shown to possess protective antibodies, whereas normal ferret and rabbit sera have usually been devoid of any protective capacity. In no instance, however, has serum from a human individual been found to exert more than a suggestive effect. This is true of convalescent sera from the patients studied during the respiratory epidemic in

the early months of 1936 (4). Since it has so far been possible clearly to demonstrate immune substances only in the serum of animals recovering from rather severe infections or repeated inoculations, the difficulty in evaluating minor effects is obvious. As a result, the procedure has failed to yield significant information as to the origin of the infectious agent.

TABLE II

Protection Test in Mice with Sera from Various Sources

Serum		Mouse No.								Protection
Source	Nature of immunity	1	2	3	4	5	6	7	8	
Ferret 4-14	Influenza	d5	d5	d6	d6	d6	d9	d10	d10	None
Ferret 5-96	M-P virus	d5	d5	d5	d6	d9	S	S	S	Suggestive
Ferret 3-30	M-P virus	S	S	S	S	S	S	S	S	Complete
Ferret 4-06	M-P virus	S	S	S	S	S	S	S	S	Complete
Rabbit	Normal	d7	d7	d7	d7	d8	d8	d9	d9	None
Rabbit 1-35	M-P virus	d6	S	S	S	S	S	S	S	Good
Ferret 4-01	Influenza	d5	d5	d6	d6	d8	d8	d9	S	None
Ferret 6-11	M-P virus	d9	S	S	S	S	S	S	S	Good
Ferret 5-99	Influenza	d5	d7	d7	d8	d8	d9	d9	S	None
Ferret 2-64	M-P virus	S	S	S	S	S	S	S	S	Complete
Human	S.S.* acute	d5	d5	d6	d6	d6	d7	d8	d9	None
Human	S.S.* convalescent	d7	d7	d7	d8	d8	S	S	S	Suggestive
Culture broth		d6	d6	d7	d7	d8	d8	d10	S	None

d5 = mouse died 5th day; S = survived.

M-P = the virus described in this report, meningo-pneumonitis.

* Human serum from patient whose throat washings were given to ferret from which original M-P virus was obtained.

Differential Diagnosis of the Virus

It has not been possible to identify the virus reported in this paper with viruses already known. It most closely resembles 4 viruses which have been described: (*a*) encephalomyelitis of mice, described by Theiler (11); (*b*) psittacosis (9, 12, 13); (*c*) lymphocytic choriomeningitis (14, 15, 16); and (*d*) lymphogranuloma inguinale (17).

From encephalomyelitis of mice the virus is distinguished by its much larger size and by differences in the pathological findings in mice, as well as by its pathogenicity for monkeys.

The agent is differentiated from that of psittacosis by the absence of the typical hepatic necrosis produced in mice and guinea pigs infected with psittacosis. Furthermore, the characteristic picture of the nervous disease in mice following intraperitoneal or subcutaneous inoculation of the virus has never been reported in psittacosis. Nevertheless, certain of the features of psittacosis in rabbits, guinea pigs, and monkeys bear suggestive resemblances to the picture herein reported, while the size of the psittacosis agent is in the same general range as that observed in the present instance.

The virus has many resemblances to the virus of lymphocytic choriomeningitis. The disease produced by the new virus after intracerebral inoculation in mice, although much more rapidly fatal, produces a choriomeningitis very similar to that of lymphocytic choriomeningitis. The pulmonary lesions produced in mice by the former have, however, no counterpart in reported studies with the virus of lymphocytic choriomeningitis. The latter produces a more uniformly fatal infection in guinea pigs. Both viruses are capable of producing a meningeal infection in mice. It has been possible[1] on two occasions to test cross immunity in mice with the two viruses. Mice known to be immune to lymphocytic choriomeningitis have not been immune to the unknown virus, nor have mice immune to the latter virus been resistant to lymphocytic choriomeningitis. Thus, while resemblances exist between the two viruses, the evidence indicates that they are different.

Many characteristic effects of the virus in question resemble those produced by the virus of lymphogranuloma inguinale (17). The pathology in the central nervous system of mice is similar with the two viruses. Paralysis and death of mice after subcutaneous inoculation have not been reported with lymphogranuloma inguinale nor have the typical pulmonary lesions which occur in mice and ferrets after intranasal inoculation of the new virus been observed with lymphogranuloma inguinale virus. The virulence of strains of lymphogranuloma inguinale virus obtained in America is much lower and the immunity produced less striking. Nauck and Malamos (18) have reported the recovery of strains of virus of lymphogranuloma inguinale which more nearly approach the virulence of the virus here

[1] Through the courtesy of Dr. T. F. McN. Scott and Dr. T. M. Rivers.

described. Even these strains, however, survive only a few days in 50 per cent glycerine and produce neither nervous symptoms nor immunity with subcutaneous or intraperitoneal inoculation of mice. They do produce a typical disease in *M. rhesus*. The size of the two viruses is similar. Moreover, granulomatous infiltrations in the skin of mice, guinea pigs, and rabbits are produced by both. The granules observed in lymphogranuloma infection (19) have not, however, been detected in the present studies.

It has been possible[2] to test cross immunity in mice immune to the respective viruses. None was detectable. Mice immune to lymphogranuloma inguinale were fully susceptible to the new virus and *vice versa*. Furthermore, the type of paralysis produced by the unknown virus was recognized to be decidedly different from that seen in the disease produced by lymphogranuloma inguinale virus. It was interesting to observe that, when tested with lymphogranuloma inguinale, mice immune to the unknown virus died with a paralysis exactly similar to that produced by the new virus in susceptible animals. This suggests that the sites damaged by the virus at the time of immunization were again attacked by the heterologous test virus to produce a clinical disease picture more closely resembling the original than the test infection.

Further cross immunity tests were conducted by Dr. Marion Howard of Yale University Medical School, who found that her mice immunized to strains of lymphogranuloma inguinale were completely susceptible to the unknown virus. In addition, Dr. Howard prepared antigen from infected mouse brains for Frei tests. The material failed to elicit the Frei reaction in patients known to be positive reactors, while tests with lymphogranuloma inguinale virus preparations were typically positive. This evidence seems almost conclusively to eliminate lymphogranuloma inguinale from further consideration unless antigenically distinct strains exist.

It is quite possible, of course, that despite the negative results in cross immunity tests, the virus herein described is related either to lymphocytic choriomeningitis or to lymphogranuloma inguinale. If so, it possesses certain striking pathogenic differences from the known strains of the two viruses as well as sharply different im-

[2] Through the kindness of Dr. A. W. Grace and Mrs. F. H. Suskind of The New York Hospital.

munological characters. In any event, it must be noted that the virus was not obtained from the usual source of lymphocytic choriomeningitis virus, *i.e.*, the spinal fluid; nor of lymphogranuloma inguinale, *i.e.*, buboes. Its exact source is at present uncertain, but it is possible to assert that the new virus was derived either from the throat washings of patients suffering from an epidemic disease clinically resembling epidemic influenza or from ferrets inoculated with this material. In the present state of the studies the virus described in this report appears to possess more characteristics in common with lymphogranuloma inguinale than with lymphocytic choriomeningitis. Because of the two most prominent pathological effects which it produces in experimental animals, it is suggested that for purposes of identification the agent be called the *virus of acute meningo-pneumonitis*.

SUMMARY

An infectious agent is described which belongs apparently to the class of filtrable viruses, but which, on the basis of the evidence at hand, is not to be identified with any virus previously described.

The virus has multiple tropisms and is pathogenic for mice, ferrets, and monkeys of both *M. rhesus* and *M. cynomolgos* species. Intranasal infection of mice and ferrets causes extensive pneumonic lesions of fatal severity. Intracerebral inoculation of the virus produces in monkeys a lymphocytic choriomeningitis from which the animal recovers, while in mice a rapidly fatal choriomeningitis is produced. Fatal paralysis occurs in a moderate proportion of mice which receive the virus by intraperitoneal or subcutaneous routes, while the remainder become immune to the intracerebral test but not to the intranasal test. Subcutaneous inoculation of mice, monkeys, ferrets, rabbits, and guinea pigs causes local granulomatous induration of the skin with enlargement of the regional lymph nodes.

The virus was repeatedly recovered in 1936 from ferrets inoculated with throat washings of patients suffering from an epidemic disease clinically indistinguishable from epidemic influenza. It is impossible, however, to conclude whether the virus is of ferret or human origin.

Although possessing many features in common with the virus of lymphocytic choriomeningitis and the virus of lymphogranuloma inguinale, cross immunity tests have failed to yield any evidence that

the new agent is immunologically related to either of the aforementioned viruses.

For purposes of identification the name *virus of acute meningopneumonitis* is suggested.

BIBLIOGRAPHY

1. Smith, W., Andrewes, C. H., and Laidlaw, P. P., *Lancet*, 1933, **2**, 66.
2. Francis, T., Jr., *Science*, 1934, **80**, 457.
3. Andrewes, C. H., Laidlaw, P. P., and Smith, W., *Lancet*, 1934, **2**, 859.
4. Francis, T., Jr., *Am. J. Pub. Health*, 1937, **27**, 211.
5. Francis, T., Jr., Magill, T. P., Beck, M. D., and Rickard, E. R., *J. Am. Med. Assn.*, 1937, **109**, 566.
6. Francis, T., Jr., Magill, T. P., Rickard, E. R., and Beck, M. D., *Am. J. Pub. Health*, 1937, **27**, 1141.
7. Bauer, J. H., and Pickels, E. G., *J. Bact.*, 1936, **31**, 53.
8. Shope, R. E., *J. Exp. Med.*, 1934, **60**, 49.
9. Rivers, T. M., and Berry, G. P., *J. Exp. Med.*, 1931, **54**, 129.
10. Francis, T., Jr., and Magill, T. P., *J. Exp. Med.*, 1935, **62**, 433.
11. Theiler, M., *J. Exp. Med.*, 1937, **65**, 705.
12. Rivers, T. M., and Berry, G. P., *J. Exp. Med.*, 1931, **54**, 105.
13. Rivers, T. M., and Berry, G. P., *J. Exp. Med.*, 1931, **54**, 119.
14. Armstrong, C., and Wooley, J. G., *Pub. Health Rep., U. S. P. H. S.*, 1934, **49**, 1019.
15. Traub, E., *J. Exp. Med.*, 1936, **63**, 533.
16. Rivers, T. M., and Scott, T. F. McN., *J. Exp. Med.*, 1936, **63**, 415.
17. Grace, A. W., and Suskind, F. H., *Proc. Soc. Exp. Biol. and Med.*, 1934, **32**, 71.
18. Nauck, E. G., and Malamos, B., *Arch. Schiffs- u. Tropen-Hyg.*, 1937, **41**, 537.
19. Miyagawa, Y., *et al.*, *Japan. J. Exp. Med.*, 1935, **13**, 1.

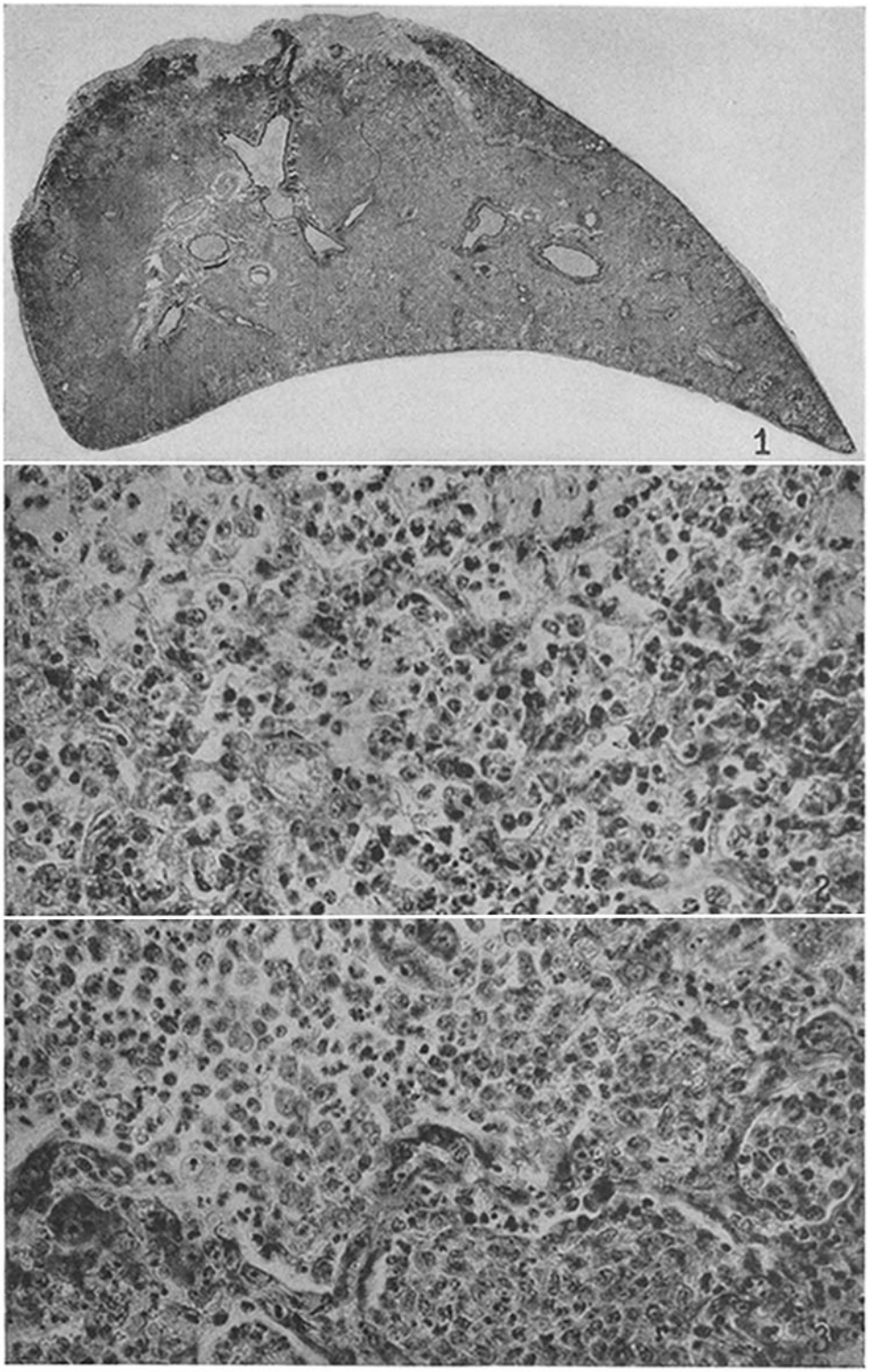
EXPLANATION OF PLATES

PLATE 2

FIG. 1. Cross section of lung of ferret 4 days after intranasal infection with virus. There is almost complete consolidation of the lobe, especially dense in the rounded aspect. Giemsa. × 8.

FIG. 2. High power magnification of lung shown in Fig. 1. There is thickening and infiltration of the alveolar walls which are somewhat obscured by the cellular exudate. The pneumonic exudate is composed primarily of large and small mononuclear cells interspersed with polymorphonuclear leukocytes. Giemsa. × 450.

FIG. 3. Lung of mouse sacrificed 4 days after intranasal infection with virus. The marked induration and thickening of the alveolar walls is apparent. The rich cellular exudate is characterized by large pale-staining mononuclear cells although other types of cells are numerous. Giemsa. × 450.



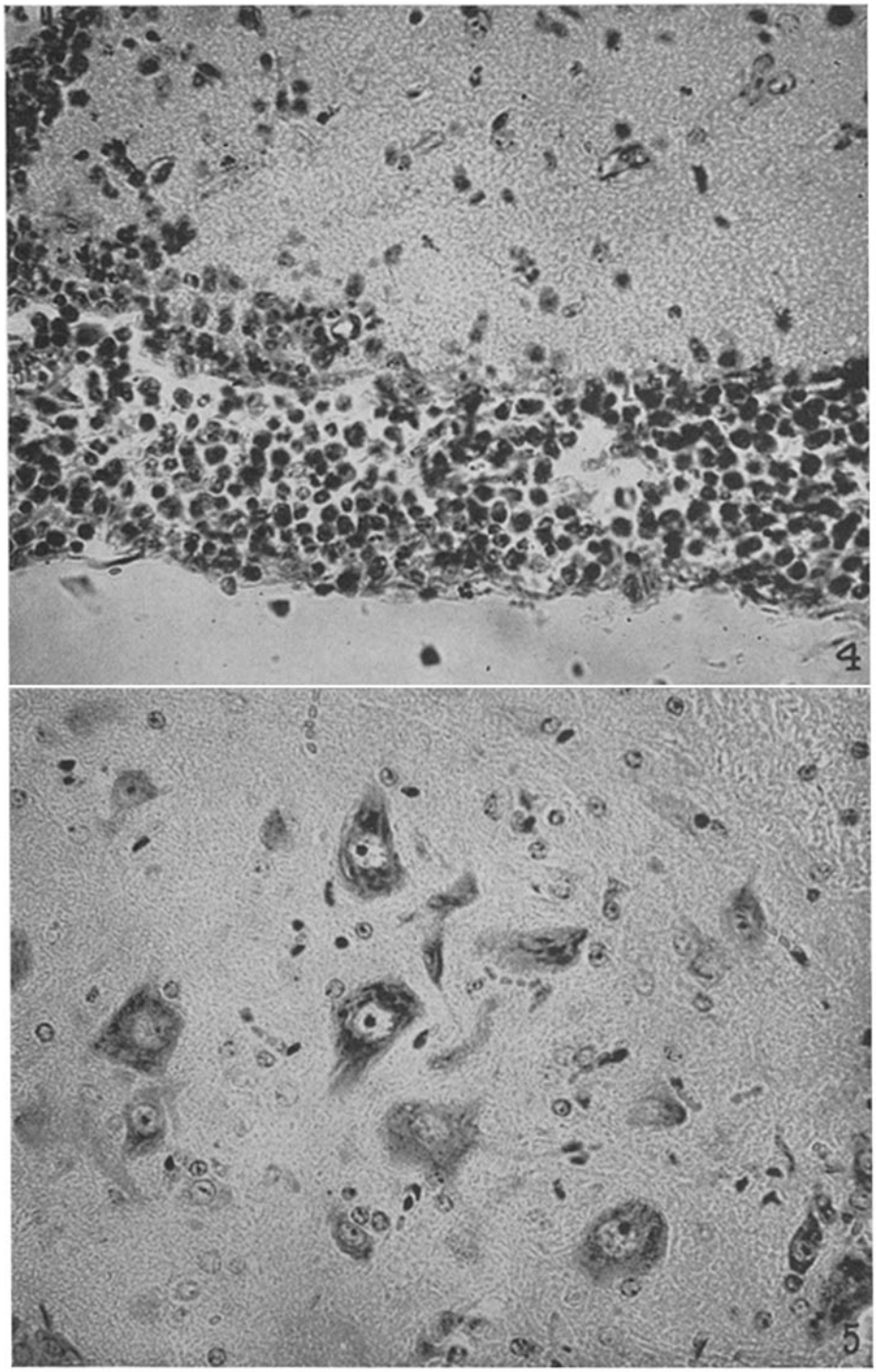
Photographed by Joseph B. Haulenbeek

(Francis and Magill: Virus of meningitis and pneumonitis)

PLATE 3

FIG. 4. Section of brain of mouse sacrificed 3 days after intracerebral inoculation of virus. There is a marked leptomeningitis predominantly mononuclear in type but a sprinkling of polymorphonuclear leukocytes is also present. Note the absence of parenchymal lesions. Giemsa. × 450.

FIG. 5. Anterior horn of lumbar portion of spinal cord of mouse which died with paralysis of hind quarters 3 days after intracerebral inoculation of virus. The pyramidal cells are apparently undamaged nor is there any evidence of parenchymal injury to the cord. Giemsa. × 450.



Photographed by Joseph B. Haulenbeek

(Francis and Magill: Virus of meningitis and pneumonitis)