level of histamine concentration in the blood and the lowest point of blood pressure fall (Fig. 1). As the graph indicates, following this fall in blood pressure there occurs a marked compensation within an hour that exceeds the normal pressure at the beginning of the experiment. Although there is no satisfactory explanation for this change in blood pressure after the marked fall, it should be mentioned that when this rise does occur there is no measurable histamine present in the blood stream.

In a limited number of experiments in which the rats were followed for a longer time after irradiation than those just described, it was interesting to find that following the first 4 or 5 hours period after mid-lethal dosage of X-rays, even though the histamine in the blood was not measurable, the animals' blood pressure remained relatively low compared with normal, and continued to fall slowly to levels of 60 to 70 mm of Hg by the 4th to 6th day after irradiation. There also occurred in all the animals studied a marked loss in appetite and weight during this same period.

From this critical point, however, the rats either became progressively more depressed and died at the end of about 10 days, or showed a marked recovery in appetite, weight, blood pressure, and general appearance and survived the 600 units of X-irradiation. It was also interesting to note that if histamine assays were run on rats in these experiments there occurred a gradual increase in assayable histamine starting the 2nd day after irradiation, until on the 5th day, the rats showed nearly 1.0 $\gamma$ of histamine (by assay) per 2 cc of blood plasma extracted. If the rats survived this critical 4 to 6 day period and showed signs of recovery, there was no evidence of histamine present in the blood by the 9th or 10th day after irradiation.

From these experiments it would appear that the low blood pressure correlates with high levels of histamine in the blood plasma which is very suggestive of the theory that the cause of death after irradiation is of the nature of circulatory failure or a condition simulating shock, an observation that was earlier suggested by Prosser, Painter and Moore.[4] Although no explanation can be advanced concerning the mechanism responsible for the appearance of histamine after irradiation, it is believed that the cyclic appearance of histamine at a 2 hour and a 5 day period after irradiation offers suggestions for further investigation of the problem in question.

*Summary.* 1. Rats, after X-irradiation with mid-lethal dosage (600 r) show assayable histamine in concentrations of 1 to 2 $\gamma$ per 2 cc of blood plasma at 2 hour and 5 day intervals following the irradiation.

2. Rats irradiated similarly to those used in the histamine assay experiments show a fall in blood pressure that correlates with the appearance of histamine in blood plasma and strongly suggests that histamine is responsible for the lowered blood pressure.

3. Rats, from 4 to 6 days after a mid-lethal dosage of irradiation show a loss in appetite and weight, and a critical fall in blood pressure from which only 50% will recover. The rest die within 9 or 10 days after the irradiation was given.

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## Chorio-meningo-encephalitis Following Inoculation of Newcastle Disease Virus in Rhesus Monkeys.*

HERBERT A. WENNER AND BEVERLY LASH.

*From the Departments of Pediatrics and Bacteriology, and the Hixon Memorial Laboratory, School of Medicine, University of Kansas, Kansas City, Kansas.*

Newcastle Disease Virus (NDV), commonly the cause of a disease of fowl, patently, may, because of intimate association with man, cause human disease. Recognized syndromes in man caused by NDV include conjuncti-

* Aided by a grant from the United States Public Health Service.

vitis,[1] and an influenza-like illness.[2] Recently, Howitt, Bishop, and Kissling[2] have pointed out that NDV may cause a mild CNS disease indistinguishable from abortive poliomyelitis in infants and children. In view of this last mentioned observation a study was made and Newcastle Disease Virus has been found to cause a CNS disease in rhesus monkeys. The results of this study are reported herein.

*Materials and methods. Virus.* The "Manhattan" strain of NDV† was grown in 10 day old embryonated eggs. A pool of infected allantoic fluid (12th passage) was made and stored at −70°C. The infected fluid had an embryo MLD in dilution 0.1 cc $\times$ $10^{8.5}$. The hemagglutinin titer (fowl RBC) was 1:640. The hemagglutinin and hemagglutinin-inhibition tests were done with modifications as described by Florman.[3]

*Monkeys.* Rhesus (*Macaca mulatta*) monkeys were used. Each monkey received 0.8 cc of infected, undiluted allantoic fluid in the brain. Monkeys were observed twice daily. Temperature records were kept. Whole blood, serum and cerebrospinal fluid were obtained before and at intervals following inoculation. The CNS obtained from monkeys was examined histologically; fresh material was passaged to monkeys, rodents and embryonated eggs.

*Results.* Five monkeys were inoculated with infected allantoic fluid. All became sick. One died on the 6th day (following inoculation): one other was sacrificed on the 7th day. The remaining 3 monkeys recovered.

*Clinical course.* The clinical course of one monkey appears in Fig. 1. Following an incubation period of 2 to 5 days fever (104 to 105°F) occurred. With the onset of fever monkeys became agitated, and tremulous. They were grossly awkward in locomotion. The fever lasted 2 to 7 days. Convalescence was slow; symptoms lasted 7 to 10 days following abatement of fever. Cerebrospinal fluid obtained from 3 monkeys in the acute phase of illness was cloudy. The cell count ranged from 37 to 250/mm³. Mononuclear cells predominated.

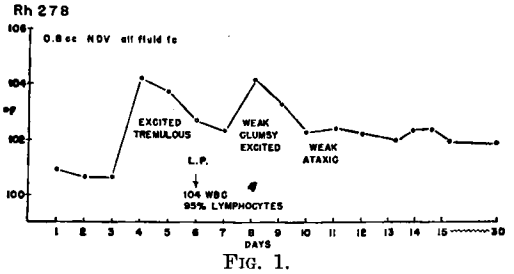



FIG. 1.
Response of a rhesus monkey following intracerebral inoculation of Newcastle Disease virus.

*Serologic Studies.* Hemagglutinin-inhibition tests with pre-inoculation, acute and convalescent serums showed an 8 to 32 fold rise in NDV antibody level. Specific complement-fixation was obtained with NDV infected allantoic fluid. No complement-fixation was obtained with lymphocytic choriomeningitis infected mouse brain.[6]

*Passage.* The CNS of a rhesus monkey sacrificed during the acute phase of illness was inoculated intracerebrally into 2 rhesus monkeys, Swiss mice, hamsters, guinea pigs, cotton rats and embryonated eggs. Chick embryos died; NDV was recovered from them. A monkey sickened. The sick monkey was unable to sit up on the 30th day. There was ipsilateral weakness of the right arm and leg. All other animals remained well (31 days).

*Pathology.* The CNS histology was characterized by (a) encephalitis, (b) focal meningitis, and (2) inconstant and intense inflam-

[1] Burnet, F. M., *Med. J. Australia*, 1943, **2**, 313.

[2] Howitt, B. F., Bishop, L. K., and Kissling, R. E., *Am. J. Pub. Health*, 1948, **38**, 1263.

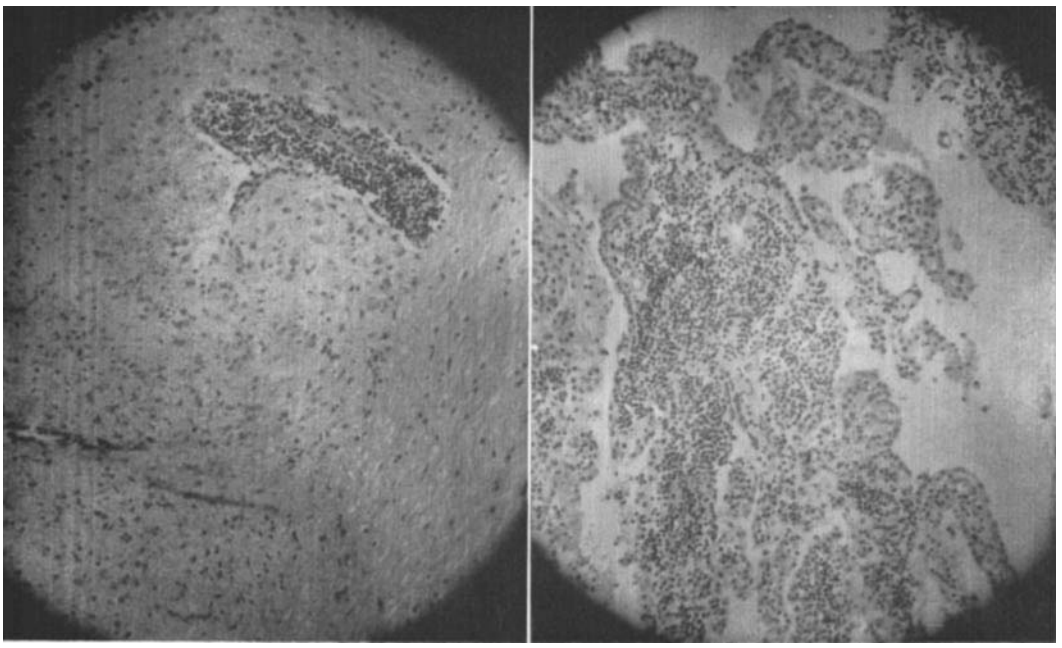
† We are indebted to Dr. L. D. Bushnell, Department of Bacteriology, Kansas State College, Manhattan, Kansas, for the "Manhattan" strain of Newcastle Disease Virus. On its receipt, the virus was in the 8th passage in the embryonated egg. Infected allantoic fluid (12th passage) inoculated intracerebrally in Swiss mice, guinea pigs, hamsters, and cotton rats, caused illness in cotton rats[4] and hamsters.[5]

[3] Florman, A. L., PROC. SOC. EXP. BIOL. AND MED., 1947, **64**, 548.

[4] Wenner, H. A., unpublished observations.

[5] Reagan, R. L., Lillie, N. E., Hauser, J. E., and Brueckner, A. L., PROC. SOC. EXP. BIOL. AND MED., 1948, **68**, 293.

[6] Espana, C., and Hammon, W. McD., *J. Immunol.*, 1948, **59**, 31.



(1) (2)

FIG. 2.

Lesions in the (1) rhombencephalon and (2) choroid plexus of a rhesus monkey following intracerebral inoculation with Newcastle Disease virus.

mation of choroid plexus (Fig. 2). Perivascular cuffing, neuronecrosis and neuronophagia were best seen in the rhombencephalon, particularly in juxtaposition to the 4th ventricle. No changes were seen in the spinal cord of the monkeys inoculated with NDV infected allantoic fluid. In the passage monkey additional pathologic changes were found. These changes consisted of extensive inflammatory and degenerative changes in the gray matter, particularly in the anterior horns of the spinal cord.

*Discussion.* Heretofore, fowl and hamsters have been found susceptible to Newcastle Disease Virus. Now another host, the *rhesus* monkey has been found susceptible to NDV.‡ The pathogenesis of NDV in rhesus monkeys requires additional clarification. At the height of illness NDV can be detected in CNS tissue and occasionally in the blood, but not in cerebrospinal fluid. If the pathological lesions only are considered it would appear that NDV may have been disseminated in cerebrospinal fluid. (CSF) The apparent absence of virus in CSF, in contrast to the presence of it in blood and CNS tissue may indicate widespread proliferation of virus. Further study is necessary in order to determine whether NDV resembles in pathogenesis experimental lymphocytic choriomeningitis or possibly poliomyelitis.

*Summary.* The "Manhattan" Strain of Newcastle Disease Virus produced in rhesus monkeys a chorio-meningo-encephalitis.

‡ This virus causes encephalitis in cotton rats also.[4]