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# EXPERIMENTAL TOXIC PULMONARY EDEMA IN ALBINO MICE WITH INFLUENZA

V. N. Parusov and V. V. Zhunko

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Toxic edema of the lungs during influenza develops 3 h after infection of mice with concentrated influenza viruses adapted to lung tissue. The toxic action of the viruses is manifested by filling of the alveoli with a liquid exudate, by the development of stasis in the pulmonary vessels, by eosinophilic necrosis of the epithelium of the bronchioles, and also by destruction of cells of the cortical layer of the thymus. The model thus developed can aid with the understanding of fulminating forms of influenzal infection in man terminating in death.

KEY WORDS: *influenza*; *pulmonary edema*.

The toxicity of influenza virus has so far been studied in experiments on volunteers or in mice by intravenous, intracerebral, or parenteral methods of infection [1, 3, 5, 7]. Under these conditions no severe lung lesions develop. Yet we know that one of the leading manifestations of the toxicosis with severe influenza in man is toxic hemorrhagic edema of the lungs [2, 4, 6].

The object of this investigation was to develop a model of experimental toxic pulmonary edema in albino mice with influenza.

## EXPERIMENTAL METHOD

Two hundred mice were infected intranasally, under ether anesthesia, with one of the following strains of influenza virus in a dose of $10^{-3}$ in 0.05 ml: A/Hong Kong/68 ($H_3N_2$), A/Victoria/72 ($H_3N_2$), A/Leningrad/72 ($H_3N_2$), all avirulent for mice, and A/37/11 ($H_1N_0$), A/Hong Kong/68 ($H_3N_2$), and A/Leningrad/32/49 viruses adapted to mouse lungs. The animals were killed 3 days after infection, the trachea and lungs were removed with sterile precautions, cut into small pieces and disintegrated by ultrasonic treatment, and the virus was

Laboratory of the Pathogenesis and Pathomorphology of Acute Respiratory Virus Diseases, All-Union Research Institute of Influenza, Ministry of Health of the USSR, Leningrad. (Presented by Academician of the Academy of Medical Sciences of the USSR A. A. Smorodintsev.)
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Fig. 1

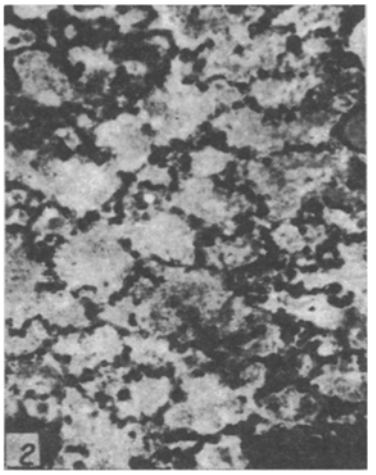

Fig. 2

Fig. 1. Total eosinophilic necrosis of epithelium of a bronchiole. Hematoxylin–eosin, 900×.

Fig. 2. Slightle eosinophilic fluid in lumen of most alveoli. Stasis. Hematoxylin–eosin, 320×.

concentrated by differential centrifugation. The resulting suspension of each virus, containing $5 \cdot 10^8$–$5 \cdot 10^9$ $EID_{50}$ in 0.05 ml, was used to infect 30 animals, anesthetized with ether, intranasally. The respiratory organs, liver, and thymus of the mice were taken at once or 3, 6, and 9 h after infection for histological and virological investigation.

## EXPERIMENTAL RESULTS

The concentration of virus in the lungs of the mice 3 h after infection had fallen to 4.5-5.5 log EID.

On histological investigation 3 h after injection of the concentrated influenza viruses adapted to lung tissue into the mice, condensation and, in some cases, hypersecretion of the epithelium of the trachea and larger bronchi were observed. In some of the small bronchi and bronchioles total eosinophilic necrosis of the epithelium developed (Fig. 1). The walls of the vessels were thickened as a result of imbibition of serous fluid and evidence of stasis was well marked. Many alveoli in the juxtahilar and apical regions of the lungs contained much of a slightly eosinophilic exudate contaminated with erythrocytes (Fig. 2). The alveolar septa were thin and the alveolar epithelium hyperplastic.

After 6-9 h the epithelium of the trachea and bronchi was in a state of hypersecretion; foci with grossly thickened alveolar septa and a serous exudate in the alveoli were found only occasionally, however, in the lung tissue. Destruction of lymphocytes was observed in the cortical layer of the thymus.

Phenomena of hypersecretion of the epithelium of the respiratory tract and congestion of the lungs were found 3 and 6 h after infection of the mice with concentrated viruses not adapted to mouse lungs. In mice receiving allantoic fluid, physiological saline, or concentrated homogenates of lungs from 200 intact mice by intranasal injection as the control, congestion of the lungs was observed at the same times of the experiments.

Toxic hemorrhagic edema of the lungs thus arose 3 h after intranasal infection of mice with concentrated strains of influenza A virus adapted to lung tissue. Strains of influenza virus not adapted to lung tissue did not possess these properties. This suggests that toxic edema of the lungs associated with a malignant course of influenza in man is attributable to intensive reproduction and accumulation of the virus in the respiratory organs in high concentrations.

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