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A Study of the Etiology of Influenza.

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In a previous communication¹ we have announced the cultivation of a filterable virus from 2 cases of typical influenza, one occurring in an epidemic of the interpandemic type in 1930 and the other during an outbreak of similar character in 1932. These 2 cultures when inoculated intranasally in human volunteers produced respiratory infections of the general type of the common cold but of considerable severity and with a tendency to greater constitutional reaction than is commonly observed after inoculation of cultures of common cold virus.

In March, 1934, there occurred in a small convalescent home for rheumatic children a local outbreak of influenza. The symptoms of the early cases were almost identical, consisting of malaise followed by fever as high as 104°F. and lasting for 3 days. During the height of the disease there was headache, general aching, nausea and vomiting. This was followed by marked weakness for several days. In the later stages of the epidemic the picture was that of a severe cold with only a slight rise in temperature. The leucocyte count was elevated rather than lowered as in some outbreaks of influenza.

Chick embryo tissue cultures were made from filtered nasopharyngeal washings obtained from 2 of the early cases of the disease. One of these cultures in the 18th generation, 2 months after isolation, was inoculated intranasally into 3 human volunteers under rigid quarantine. The results are presented in the following protocols.

Volunteer 93, a heavy, muscular man with no recent history of respiratory disease was inoculated intranasally with 3 cc. of culture R18. The inoculation was repeated 5 hours later. The next morning, 18 hours after the first inoculation, the subject manifested nasal obstruction, sneezing, mucoid nasal discharge, a productive cough and a slight malaise. Later the malaise increased and was accompanied by headache and pain in the back of the neck. The pharynx became sore and inflamed. There was no fever and the maximum leucocyte count was 9000.

¹ Dochez, A. R., Mills, K. C., and Kneeland, Yale, Jr., *Proc. Soc. Exp. Biol. and Med.*, 1933, **30**, 1017.

Volunteer 94, a short, heavy set man with no recent history of respiratory infection, was inoculated intranasally with culture R18 at the same time and in the same manner as Volunteer 93. Subject awoke the next morning, 18 hours after the first inoculation, with slight nasal obstruction, mild headache and soreness of back and shoulders. The symptoms became more pronounced during the day and cough, nasal discharge and general malaise developed. On the second day headache and pain in the back were pronounced and there were dizziness, anorexia, and vomiting. The throat was red and swollen. Most of the day was spent in bed. The symptoms lasted for 6 days, there was no fever, the maximum leucocyte count was 12,100.

Volunteer 95, a rather thin man with no history of upper respiratory infection for 6 months. Inoculated intranasally with culture R18 at the same time and in the same manner as Volunteers 93 and 94. The next morning, 18 hours after inoculation, nasal obstruction was present. There was nasal discharge and productive cough. There was general malaise and severe headache. The tonsils showed a few whitish spots and the pharynx was acutely inflamed. Subject became much worse in the afternoon and went to bed complaining of bad pain in neck and back and of feeling dizzy. The subject vomited throughout the night and the next morning appeared acutely ill. There was marked nausea and retching, the chest felt sore and the cough was pronounced and frequent. The face was flushed and the eyes suffused. The temperature reached 101°F. by mouth and the leucocyte count was 10,900. On the third day the fever had subsided but cough and general malaise were still marked. On the fourth day the subject again became worse, complete anorexia was present and vomiting reappeared. The pharynx was diffusely red. Headache and malaise were vary marked and coughing was severe. By the fifth day all the symptoms had abated markedly and he was discharged from quarantine on the seventh day, feeling weak and still slightly dizzy. The maximum leucocyte count was 12,600. The subject likened the experience to an attack of influenza suffered in Germany in 1918.

From these experiments the conclusion seems justified that a filterable agent has been cultivated from clinical influenza which after being carried for 18 transplants in chick embryo medium produced in experimental subjects a picture similar to that seen in the natural outbreak, in which individual attacks ranged from the appearance of common cold to that of typical clinical influenza. The

leucocytes were elevated rather than lowered, a finding, however, which is quite common in natural outbreaks.

No visible organisms of any kind could be cultivated either aerobically or anaerobically from the cultures used for inoculation. With the exception of occasional contaminating diphtheroid organisms nothing was visible microscopically in the cultures at any time nor was there any recognizable visible change in the medium.