which would deal directly with physical reality. Logically the problem seems to offer two possibilities, between which we are in principle given a choice. In the end the choice will be made according to which kind of description yields the formulation of the simplest foundation, logically speaking. At the present, we are quite without any deterministic theory directly describing the events themselves and in consonance with the facts.

For the time being, we have to admit that we do not possess any general theoretical basis for physics, which can be regarded as its logical foundation. The field theory, so far, has failed in the molecular sphere. It is agreed on all hands that the only principle which could serve as the basis of quantum theory would be one that constituted a translation of the field theory into the scheme of quantum statistics. Whether this will actually come about in a satisfactory manner, nobody can venture to say.

Some physicists, among them myself, can not believe that we must abandon, actually and forever, the idea of direct representation of physical reality in space and time; or that we must accept the view that events in nature are analogous to a game of chance. It is open to every man to choose the direction of his striving; and also every man may draw comfort from Lessing's fine saying, that the search for truth is more precious than its possession.

A COMPLEX VACCINE EFFECTIVE AGAINST DIFFERENT STRAINS OF INFLUENZA VIRUS

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IN November, 1939, during the course of certain experiments, four normal ferrets were inoculated intranasally with a strain of epidemic influenza virus obtained during a 1939 epidemic[1] These ferrets developed typical symptoms of experimental influenza, but during convalescence, unexpectedly they began to manifest evidences of a distemper-like infection, and subsequently one died. On the eleventh day after the original inoculation the remaining 3 sick animals were killed. To prevent the spread of the epizootic in the normal ferret colony, a vaccine was prepared from a suspension of the lungs and spleens of these ferrets and was inactivated by the addition of 1:1000 formaldehyde and stored at 4° C. Similar vaccines had been found effective in preventing the spread of ferret distemper on previous occasions.

After inactivation in the icebox for 6 to 10 days, 2 cc of this vaccine was injected subcutaneously into each of 157 normal ferrets. Two days after the vaccination, groups of these animals were inoculated intranasally with the PR8, W.S., or 399 strains of influenza virus. To our great surprise, none of the inoculated ferrets developed experimental influenza. Serum obtained 4 days after vaccination from ferrets which had not been inoculated with influenza virus neutralized both the PR8 and W.S. strains in high dilutions. Serum taken from a number of ferrets prior to vaccination possessed no neutralizing antibodies. These very unexpected findings suggested that the injection of the so-called distemper vaccine had resulted in an inadvertent immunization of almost all the normal ferrets in the laboratory against influenza virus.

Since this vaccine had been inactivated with formaldehyde and because it appeared to have produced a much broader immunity than resulted from an actual infection with the influenza virus,[2] it seemed of importance to study this phenomenon more thoroughly. One group of vaccinated ferrets was held for repeated bleedings in order to determine the persistence of antibodies after vaccination. Another group was held for active immunity tests at different intervals following vaccination.

At various intervals during the first 3 months after vaccination sera were obtained from the first group consisting of 15 animals. The neutralizing capacities of the sera from each ferret were determined, and the results are shown graphically in Fig. 1. For purposes of comparison, the results of similar tests on multiple sera from a group of 16 ferrets convalescent from experimental influenza are also shown. The sera from both groups of ferrets were tested against the PR8 strain, since an indication of the extent and the duration of heterologous strain immunity was desired. Line I connects the mean neutralizing capacities of sera obtained from the 15 ferrets at various intervals after vaccination. Line II connects similar values for sera obtained from certain of 16 ferrets at various periods during convalescence from experimental influenza. It will be noted that the serum of vaccinated ferrets possessed almost as much antibody as that of the convalescent animals during the first month. During the second and third months the antibody titers of the convalescent ferrets' sera decreased rapidly, whereas the titers of the sera from the vaccinated ferrets re-

[1] F. L. Horsfall, Jr., R. G. Hahn and E. R. Rickard, *Jour. Clin. Invest.*, 19: 379, 1940.

[2] F. L. Horsfall, Jr. and E. H. Lennette, *Jour. Bact.*, 39: 56, 1940.

mained almost constant. At the end of the third month sera of the vaccinated ferrets were capable of neutralizing 40 times more virus than were the sera of the convalescent animals.

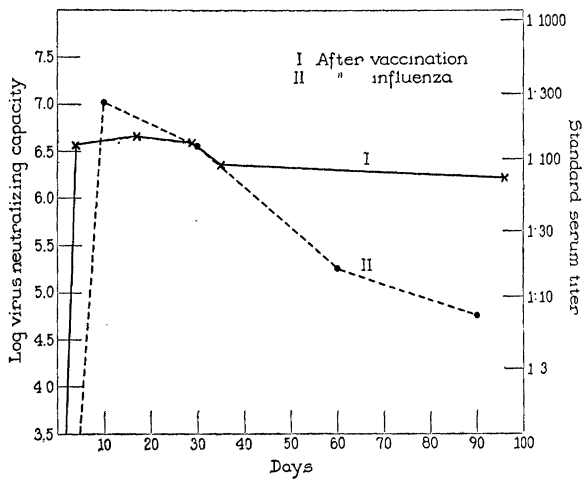

FIG. 1. Mean neutralizing capacities against the PR8 strain of influenza virus of ferret sera taken at various intervals. Line I = sera from 15 ferrets after vaccination. Line II = sera from 16 ferrets after experimental influenza.

The active immunity of vaccinated ferrets was tested by the intranasal inoculation of approximately 1000 infectious doses of the PR8, W.S., or 399 strains of influenza virus. In ferrets these strains had been found to be sufficiently different from each other antigenically to fail to produce reciprocal cross immunity.[3] Groups of vaccinated ferrets were tested for the presence of active immunity, 2, 5, 12, 20, 30, and 97 days after vaccination. In most instances serum was obtained before the immunity test and in all cases 10 days afterwards for the determination of neutralizing capacity. The results are summarized in Table I. Ferrets were

TABLE I

IMMUNITY IN VACCINATED FERRETS TO INFLUENZA VIRUS

Number of ferrets in test group	Strain of virus used for immunity test*	Results			
		C. P.	N. C.	Solidly immune	
		Number	Number	Number	Per cent.
14	PR8	0	0	14	100
14	W.S.	1	3	11	78
9	399	0	1	8	89

* 1000 infectious doses given to each ferret.
C.P. Clinical and pathological signs of influenza.
N.C. Increase in virus-neutralizing capacity of serum.

considered to be immune when they failed to manifest typical clinical and pathological signs of ferret influenza and when there was no significant increase in the virus-neutralizing capacity of their sera following inoculation. It will be seen that of 14 ferrets tested for immunity against the PR8 strain at various intervals after vaccination, all were immune; of an equal number of vaccinated ferrets tested for immunity against the W.S. strain, 11 were immune; and of 9 ferrets tested for immunity against the 399 strain, 8 were immune. Thus of a total of 37 vaccinated ferrets tested for the presence of active immunity to infection by one or another of three different strains of influenza virus, 33 were solidly immune.

Although this vaccine was found to be surprisingly effective in producing immunity to influenza virus when used relatively soon after preparation, after storage in the icebox for two months it had become entirely ineffective.

Since the symptoms of the secondary infection in the ferrets from which the vaccine was prepared suggested distemper, the vaccinated ferrets were also inoculated with canine distemper virus obtained from the spleen of an infected dog and were found to be immune. This demonstrated that the ferrets from which the vaccine was originally prepared had suffered from a mixed infection of influenza and canine distemper viruses.

The fundamental elements entering into the vaccine were thus established, and the next step in the study was to determine the immunizing efficacy of each of the two virus components alone, following the procedures employed in the preparation of the first vaccine as closely as possible.

Although it was known that during early convalescence from influenza active virus could not be recovered from consolidated ferret lungs, vaccines, both formalinized and non-inactivated, were prepared from the lungs and the spleens of ferrets which had been infected from 8 to 11 days previously with influenza virus. The subcutaneous injection of these vaccines into normal ferrets resulted in neither the production of neutralizing antibodies nor the development of immunity against influenza virus. It therefore seemed unlikely that the effectiveness of the original vaccine could be attributed to influenza virus alone.

Formalinized vaccines were also prepared from the lungs and the spleens of ferrets which had been infected with canine distemper virus alone 12 days previously. Normal ferrets which were given these vaccines subcutaneously did not produce neutralizing antibodies against, or become immune to, influenza virus, although they proved to be immune to dog distemper.

Finally, formalinized vaccines were made from suspensions of the tissues from two ferrets mixed *in vitro*. One of these animals had been infected with influenza virus, while the other had been infected with distemper virus. These vaccines also failed to stimulate either the development of neutralizing antibodies or active immunity to influenza virus in normal ferrets.

[3] *Ibid.*

These experiments indicated that neither of these two viruses alone was capable of producing effective vaccines and that *in vitro* mixtures of the two were ineffective. The evidence suggested, therefore, that, in order to have effective vaccines, it was essential for both viruses to produce infections in the same host concurrently.

In order to ascertain whether a vaccine possessing an immunizing efficacy equal to that of the original preparation could be reproduced at will, ferrets were inoculated with mixtures of both influenza and distemper viruses and were killed at various intervals thereafter. Formalinized vaccines were prepared from their lungs and spleens, repeating the original procedure. These vaccines were tested in normal ferrets, and at various intervals thereafter the serum of the vaccinated animals was tested for the presence of neutralizing antibodies. The animals themselves were also tested for active immunity to influenza virus.

It soon became apparent that it was not easy to prepare vaccines as effective as the original preparation. A large number of different vaccines were prepared from the tissues of ferrets which had been infected with both viruses. The duration and the severity of the two infections were varied. Separate tissues or mixtures of tissues were used in preparing the vaccines, and the procedure of inactivation was altered in a number of ways. Most of these preparations proved to be entirely ineffective. It has been possible, however, to prepare vaccines capable of producing active immunity in ferrets against influenza virus. Ferrets which were given these vaccines and subsequently inoculated intranasally with 1,000 infectious doses of heterologous strains of influenza virus showed neither the typical signs of infection nor an increase in neutralizing antibodies, indicating conclusively that no infection by the virus had occurred. Because of the number of variables which are related to the production of an effective vaccine of this kind, much more study will be required to determine the conditions under which an effective immunizing preparation can regularly be reproduced.

This vaccine was also tested on small groups of human volunteers. It was found that a vaccine prepared from the tissues of ferrets suffering from concurrent infections with influenza virus and the strain of distemper virus isolated from spontaneously infected ferrets produced a definite increase in antibodies neutralizing influenza virus in every instance. Another lot of vaccine prepared identically, but using a strain of distemper virus recently isolated from the spleen of an infected dog, failed to stimulate influenza antibody production in human volunteers. Experiments are in progress to determine the duration of the demonstrable immunity in man produced by the complex vaccine.

OBITUARY

MAYNARD MAYO METCALF

MAYNARD MAYO METCALF died on April 19, 1940, at "The Rambles," on Alabama Drive, Winter Park, Florida, where he and Mrs. Metcalf had spent the last two entire years, and the preceding two winters.

Ever since leaving the Johns Hopkins University in 1893, with the doctorate from Professor W. K. Brooks, the *pater noster* of so many distinguished American zoologists, Dr. Metcalf was so prominent a figure, as officer or contributor of papers, at meetings of learned societies, that many readers of this memorial will feel that they already know the man thoroughly well. His cordiality, rare friendliness and quick understanding made him the center of congenial groups, not only of biologists but of economists, sociologists, political scientists and Christian ministers—so broad and active was his interest in all these and other fields.

Of English ancestry fully on record from 1360 to the present, he was born in Elyria, Ohio, on March 12, 1868, of Eliab Wight Metcalf and Eliza (Ely) Metcalf. He was of a family more continuously and significantly represented at Oberlin College than any other, himself receiving the B.A. in 1889 and the honorary Sc.D. in 1914.

On completing graduate study at Johns Hopkins University he relinquished a post-doctorate Bruce fellowship to accept appointment as organizer and chairman of the department of biology at "The Woman's College" (now Goucher), where he remained until 1906, his choice of successor being the late William E. Kellicott—an item which he referred to later as his "best service to the institution." Although his appointment as chairman and reorganizer of the department of zoology at Oberlin began in 1906, laboratory space was not then in readiness; and the next two years were spent in research with Boveri in Wurzburg, in Berlin and at the Naples Biological Station.

He resigned official relation with Oberlin in 1914; but during the preceding eight years gave time, energy and wisdom unsparingly to the development of the department, himself supplying much equipment the college was not in position to afford. His inspiration and ideals have been the major factor in shaping such progress as the Oberlin department has made from his day to the present. Research in his private "Orchard Laboratory," at La Jolla, Calif., Washington, D. C., Baltimore and in South America occupied the years 1914 to 1924. Then for a year he was chairman of