not been suitable for use in human therapy.

The preparation of esters of penicillin and the demonstration of their chemotherapeutic activity introduces a group of substances which can be changed from an inactive to an active form by hydrolysis within the animal body. The hydrolysis of these esters with the liberation of active penicillin takes place slowly in the body. A single injection is therefore adequate to give complete protection against hemolytic streptococcal infections in mice.

The ethyl and n-butyl esters of penicillin appear to be stable. In contrast to penicillin, they are not destroyed at the pH of the stomach and are highly active when administered by mouth. Absorption from the stomach is less regular, however, and the therapeutic dose is approximately ten times greater by the oral route than by the subcutaneous.

The toxicity of the ethyl and n-butyl esters of penicillin is 2 to 3 times that of penicillin. However, when the subcutaneous route of administration is used, the toxic range is far above the therapeutic range. When the oral route is used, the therapeutic dose more closely approaches the toxic level. In the case of the n-butyl ester the range is sufficiently wide, however, for satisfactory use of the substance.

Conclusions. Although inactive *in vitro*, ethyl and n-butyl esters of penicillin have been shown to be highly effective chemotherapeutic agents in mice infected with large doses of virulent hemolytic streptococci. These esters are apparently hydrolyzed slowly with the liberation of active penicillin. They are effective when given by the subcutaneous or by the oral route of administration.

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Antigenically Different Strains of Virus from a Localized Influenza Outbreak.

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The purpose of this paper is to present additional evidence that antigenically different, although related, strains of virus may be prevalent during the same outbreak of influenza. It previously has been observed that cases of influenza that occur during the same large epidemic are not all caused by antigenically identical agents.[1] The present data confirm that previous observation, and are of especial interest because they deal with an outbreak of influenza that was a particularly well localized one.

The influenza outbreak with which the investigation was concerned and which consisted of 40 clinically diagnosed cases of epidemic influenza, was observed in the nurses' infirmary of The New York Hospital during January and February, 1941. Throat washings obtained from 11 of the persons were tested for virus, and in 5 instances strains of influenza virus were isolated and adapted to Swiss mice. The 5 strains were compared with each other and with the PR8[2] by means of mouse protection tests in which each strain of virus was tested against the same group of antiserums. The antiserums were obtained from 6 rabbits each of which had been inoculated with a different strain of virus: bleedings were obtained from each rabbit 9 or 10 days and 3 to 4 weeks after a single intraperitoneal injection of a suspension containing 2% infected mouse lung in 0.85% saline. The virus suspensions used in the different protection tests were all comparable in that they contained the same magnitude of lethal doses of virus (from 300 to 600) for mice. The results of the tests are presented in Chart 1.

[1] Magill, T. P., and Francis, T., Jr., *Brit. J. Exp. Path.*, 1938, **19**, 273.

[2] Francis, T., Jr., *Science*, 1934, **80**, 457.

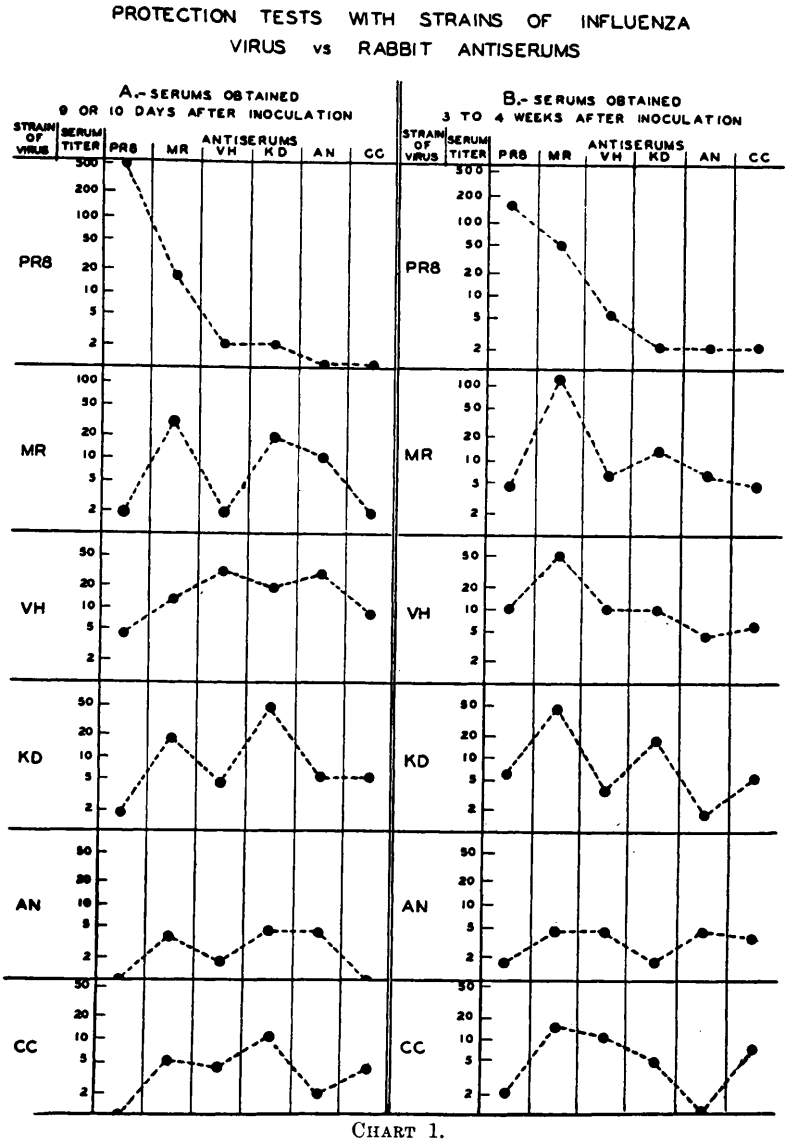

CHART 1.

In Chart 1, the results are summarized in the form of graphs in which the points represent the protective antibody titers of the different serums against the particular strain of virus. The titers are expressed as the initial dilution of serum that would protect 50% of the mice from death.[3] On the basis of the shapes of the graphs it is apparent that all of the 1941 strains (MR, VH, KD, AN, and CC) differ not only from the PR8 but also from each other. For example, in the tests against the 9- or 10-day antiserums, the MR, VH, and KD resemble each other more than they do the PR8, but in each instance the peak of the graph is at a different point; that is, each of those strains was more effectively "neutralized" by the homologous antiserum. The AN and CC strains were poor antigens and produced antiserums that had low protective capacities against even the homologous strain of virus.

As might be expected, the serums obtained 9 or 10 days after inoculation were more

[3] Reed, L. J., and Muench, H., *Am. J. Hyg.*, 1938, **27**, 493.

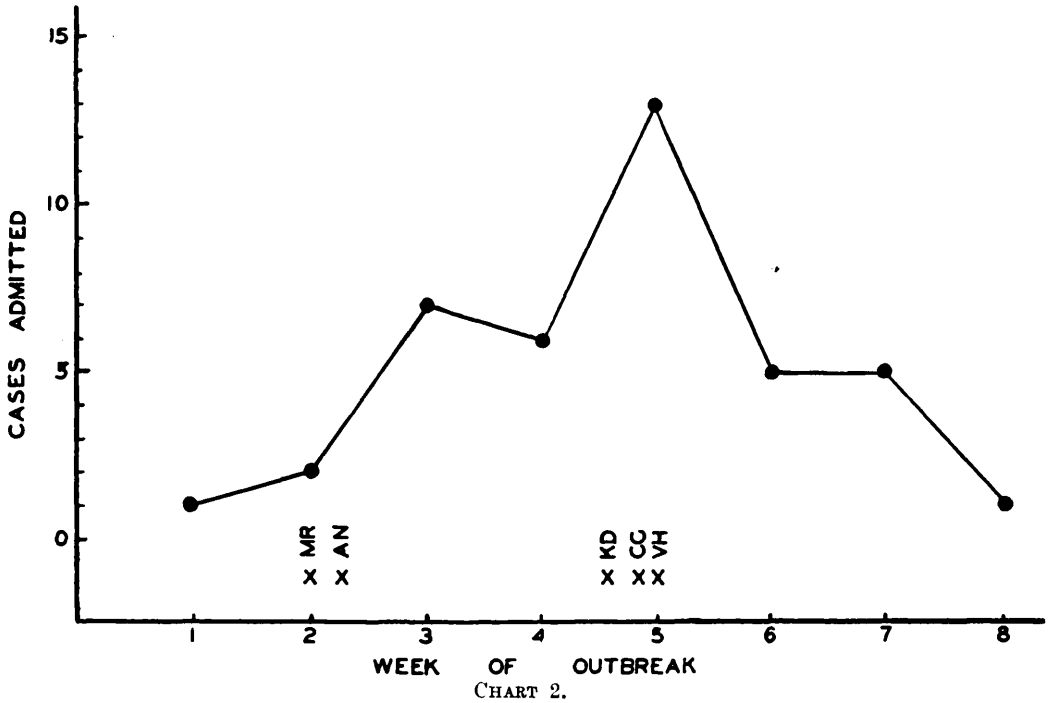

CHART 2.

specific and hence better suited to demonstrate the antigenic differences between the strains than were the serums obtained 3 to 4 weeks after inoculation. In the tests against the latter group of serums the graphs of the MR and VH strains were almost identical. However, the differences between the other 1941 strains were still evident. Furthermore, rather marked differences were still apparent between the 1941 strains as a group, and the PR8.

In view of the nature of the data presented, the relative time during the outbreak at which each of the different strains was isolated seems to be a point of interest. Chart 2 shows the total number of cases admitted to the nurses' infirmary of The New York Hospital during each week of the influenza outbreak, and also the time at which the throat washings were obtained from each person from whom a strain of virus was isolated. The antigenic characteristics seem to be unrelated to the relative time of the outbreak at which the strain was isolated. For example, strains VH and CC which were isolated from persons that were admitted to the infirmary within 24 hours of each other, seem to differ from each other as much as do any other 2 strains; whereas strains MR and VH which were isolated from persons who were ill 3 weeks apart, resemble each other rather closely.

The evidence at present available is insufficient to indicate whether a number of different but stable strains of influenza virus exist, or whether the influenza virus is a relatively unstable agent that may be altered in antigenic characteristics by the peculiar immunologic state of the hosts which it happens to infect. Regardless, however, of the reason for the existence of antigenically different strains, the present data are of interest because they show that even a well localized outbreak of influenza may consist of individual infections some of which are caused by one, some by another of a number of different although antigenically related, strains of influenza virus.