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DEPARTMENT OF THE ARMY
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Authors: J. Vieuchange, M.A. Chabaud, and C. Vialat (with the technical collaboration of Miss E. de Lalun and Mrs. J. Gruest), Pasteur Institute, Paris, France.

Title: Interference between the vaccinal virus and the common rabies virus (interférence entre le virus vaccinal et le virus rabique des rues).

Journal: Comptes Rendus de Société de Biologie (Paris) 160: 2278-2283 (1966).

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In a previous investigation (Chabaud and Vieuchange (1)), we studied the interaction between the vaccinal virus and the virus of yellow fever. An interference action had been observed between the two viruses and the conditions under which this interference was produced had been measured. The phenomenon appears to be reciprocal. For example, previous inoculation of competent cells with vaccinal virus prevents the development of amaril infection. Inversely, one observes an interference between the amaril virus and the vaccinal virus when the inoculation with amaril virus precedesthat with the vaccinal virus.

In a review of the history of the discovery of the phenomenon of interference, one of us (Vieuchange (2)) noted that the production of antagonism between vaccinal virus and the rabies virus was observed in rabbits by Levaditi, Nicolau, and Schoen (3).

In these experiments, the two virus were inoculated by the cutaneous route using the procedure of Calmette-Guerin. When the inoculation of these two viruses took place practically simultaneously, the authors noted a complete protection to the rabies virus. In contrast, when inoculation with the rabies virus preceded inoculation with vaccinal virus by 24 hours or more, the protective effect was not observed.

The authors interpreted the results of their experiments as proof that a "certain antagonism" existed between the two viruses. In our paper in 1965, we emphasized that there was the problem of proving the interference phenomenon and we announced that we intended to examine the data presented by Levaditi and his collaborators.

In an intial series of studies carried out with vaccinal virus and the virus of rabies, we confirmed the existence of this interference and attempted to measure the conditions which govern the phenomenon. We have presented here the results of our tests.

TECHNIQUES

Rabies Virus - Two strains of the rabies virus were employed: one, originating from Cameroun, was isolated at the Pasteur Institute of Cameroun (Dr. A Gamet, Director)**. Since the time of isolation from a local rabbit, it has undergone two passages through rabbit brains; the other strain, originating from Dakar, was isolated from the brain of a dog and has undergone several passages through the brains of mice at the Virus Service of Pasteur Institute (M.P. Lepine)**.

With both strains, rabbits were inoculated intracerebrally at a concentration of 10^{-1} with 0.25 ml of material. In the case of all of the rabbits inoculated, the appearance of paralytic hydrophobia occurred resulting in death by the 10th through 15th day after inoculation with the Cameroun strain and by the 10th through 12th day with the Dakar strain.

When injected intradermally at the same concentration of 10^{-1}, the Cameroun strain resulted in the death of four of the six rabbits inoculated (Assay I); with the Dakar strain, the mortality rate was seven out of seven (Assay II), five out of seven (Assay III), and four out of six (Assay V).

Vaccinal Virus - The vaccinal virus employed was the neurovaccine strain attenuated by passage through rabbit brain.

The intradermal inoculation of 0.25 ml of a 2×10^{-4} dilution in every case during our assays resulted in the appearance of a characteristic vaccinal pustule. The material used for inoculation corresponded to 5×10^{3} infectious units according to titrations on chorioallantoic membranes of chick embryos. In all of the assays, the two viruses were inoculated respectively into one of the two

** We would like to express our thanks to Dr. P. Lepine, Dr. P. Atanasiu, and Dr. A. Gamet who made these strains available to us.

flanks of the rabbit intradermally. In the series of experiments designed to obtain evidence for the interference phenomenon between vaccinal virus and the rabies virus, vaccinal virus was inoculated intradermally into the rabbits at six poins along the edge of a circle. The rabies virus was inoculated at the center. The six inoculation points for the vaccinal virus and the point of inoculation of the rabies virus were equidistant and the distance separating ther from each other w as about 5 cm.

The controls were inoculated chronologically under the same conditions, but received injections with Hanks solution instead of vaccinal virus.

In addition, each assay included two control rabbits inoculated intracerebrally with a suspension of rabies virus.

Controls - The animals inoculated intradermally with rabies virus alone or with the two viruses were observed for a period of time which was never less than three months. When the animals died under these conditions, in order to confirm with certainity the diagnosis of hydrophobia, passages of brain material were carried out.

EXPERIMENTS AND RESULTS

Assay I - Inoculation with rabies virus carried out forty-eight hours after inoculation with vaccinal virus.

(a) Series of animals inoculated with the two viruses: Six rabbits, which had previously received inoculations with the vaccinal virus, were given inoculations with the rabies virus forty-eight hours later. Under these conditions, all of the animals survived (period of observation: four months).

(b) Control series of animals: six rabbits were given inoculations with Hank's solution and forty-eight hours later, an intradermal inoculation of rabies virus was administered to each: four animals developed hydrophobia on

days 23, 25, 45, and 69; two animals survived (period of observation: four months).

Assay II - Inoculation with rabies virus carried out twenty four hours after inoculation with vaccinal virus.

(a) Series of animals inoculated with the two virus: of the seven rabbits inoculated, four survived (period of observation was four months). One died of paralytic hydrophobia on the 28th day and two succumbed to intercurrent infections on the 7th and 21st days.

(b) Control series of animals: seven animals were inoculated intradermally with rabies virus twenty four hours after injection with Hank's medium. They all succumbed to hydrophobia on the 19th through the 26th day.

Assay III - Inoculation with rabies virus carried out one hour after inoculation with vaccinal virus.

(a) Series of animals inoculated with the two viruses: of the seven rabbits inoculated, five died from hydrophobia on the 19th through the 22nd day and two survived (period of observation: three months).

(b) Control series of animals: of the seven rabbits inoculated, five died from hydrophobia on the 18th through the 21st day and two survived (period of observation: three months).

Assay IV- inoculation with rabies virus carried out twenty four hours before inoculation with vaccinal virus.

(a) Series of animals inoculated with the two viruses: of the seven rabbits inoculated, five died from hydrophobia on the 20th through the 34th day and one succumbed to an intercurrent infection on the 14th day. One survived (period of observation: six months).

(b) Control series of animals: of the six animals inoculated, four died from hydrophobia on the 21st through the 22nd day and two survived.

DISCUSSION

We selected the intradermal procedure for inoculation of the vaccinal virus as well as for the rabies virus since this allows one to obtain quantitative data with more preciseness. On the other hand, in order to assure interference between the two virus, this method offers conditions of similar diffusion.

Without doubt, this explains the differences between the results that we observed and those obtained by Levaditi. Actually, scarification of the epidermis represents a more rapid means of diffusion for the vaccinal virus than does intradermal injections. Be that as it may, in the experiments of Levaditi, concomitant inoculation of vaccinal virus and rabies virus at cutaneous scarifications did not give rise to development of rabies interferon. Inversely, in our tests, if the inoculation with vaccinal virus preceded inoculation with rabies virus by only an hour, the animal was not protected against the development of hydrophobia. On the other hand, if the inoculation with vaccinal virus preceded the inoculation with rabies virus by forty-eight hours, protection was complete. Partial protection was achieved if the interval was reduced to twenty-four hours.

Our results agree with those of Lavaditi and his collaborators in the case of inoculation with rabies virus occurring 24 hours before that with vaccinal virus; under these conditions, hydrophobia develops in the same manner as in the control animals.

It is indicated here briefly that parallel investigations with fixed rabies virus have been carried out and that the results will be published soon.

In addition, for the purpose of explaining these data, a study of the mechanism of this interference has been carried out and will be the object of another communication.

CONCLUSIONS

An interference between the vaccinal virus and the virus of rabies has been demonstrated using the rabbit.

The method of inoculation for the vaccinal virus as well as for the rabies virus was the intradermal method and this method allowed the demonstration of interference: the inoculation of vaccinal virus was made along the edges of a circle around the rabies virus inoculation.

This interference is manifested only when the inoculation with vaccinal virus precedes inoculation with rabies virus by a number of hours. ~~In our tests,~~ the protection exerted by the vaccinal virus against the rabies virus became complete when the inoculation with vaccinal virus preceded that with rabies virus by forty-eight hours. The protection was partial when the interval was reduced to twenty-four hours.

One does not observed any protection of animals when the interval is reduced to one hour or if the inoculation with vaccinal virus occurs after that with rabies virus.

The chronological circumstances which afford this protection are suggestive of an interference excerised by the vaccinal virus against the rabies virus.

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