

**Comparative Pathology.** — *On the mutual Immunization in Aphthae epizooticae and Vaccine.* (First very concise memoir). By Prof. C. F. VAN OIJEN. (Communicated by Prof. C. EIJKMAN).

(Communicated at the meeting of March 26, 1927).

It has been recorded repeatedly for more than a quarter of a century in the veterinary literature, that animals previously treated with "vaccine", are in a measure immune from Foot-and-mouth disease.

BOULLAND<sup>1)</sup> (1900) reports that in his private practise he observed that cows which had suffered from the genuine cowpox ("variola"), were not taken with foot-and-mouth disease, when this broke out in the same stable.

SEIBERT<sup>2)</sup> (1907) stated that a calf which had served for the preparation of "vaccine" was not affected, when the other cows of the stable in which it was brought afterwards, were seriously afflicted with aphthae. He translated these observations into actions by inoculating calves with 20—25 pocks. After this the calves are said to have been immune against foot-and-mouth disease.

ORY<sup>3)</sup> (1907) inoculated cows with lymph, derived from horses, which had been inoculated with "vaccine", and observed, that several of these animals did not get ill, when they were seriously infested with substances containing aphthae-virus (saliva etc.).

ANKER<sup>4)</sup> (1907) (Oudewater) could not fully confirm ORY's findings. Only a group of young animals (1½ years) being inoculated with pocks and subsequently exposed to infection with aphthae, remained free from this disease.

Neither could UHLENHUTH and BIEBER<sup>5)</sup> establish the immunity in question for all cases, although the critical reader will observe that it did exist in some vaccinated animals.

For a complete survey of the relative experiments we refer to GINS

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1) BOULLAND. Le cow-pox et la fièvre aphteuse. Le répertoire de police sanitaire vétérinaire et d'hygiène publique. Vol. 16 1900. 15 Sept. N<sup>o</sup>. 9. p. 377.

2) SEIBERT. Kuhpocken Impfung als Schützmittel gegen Maul- und Klauenseuche. Wochenschrift für Tierheilkunde und Viehzucht. 1 Oct. 1907 N<sup>o</sup>. 39.

3) ORY. Essai d'un mode prophylactique de la fièvre aphteuse par la vaccination. La Semaine Vétérinaire 1907 p. 279.

4) ANKER. Maul- und Klauenseuche Impfung nach ORY. Berliner Tierärztliche Wochenschrift 1907 p. 882, 883.

5) UHLENHUTH und BIEBER. Untersuchungen zur Frage der wechselseitigen Vakzine- und Maul- und Klauenseuche Immunität bei Rindern und Meerschweinchen. Zeitschrift für Immunitätsforschung. Originale Bnd. 35 1923 Heft 4 p. 10.

and KRAUSE<sup>1)</sup>: "Zur Pathologie der Maul- und Klauenseuche sub. IX Pocken und Maul- und Klauenseuche".

Also the present author was in a position to observe in his private practice that two calves, which had served to prepare "vaccine", did not get ill when housed in the same stable with animals with foot- and -mouth disease.

These observations, based on practice, should not be underrated. Therefore, GINS and KRAUSE and others advocate the urgency of an experimental inquiry into the power of a vaccine-inoculation to protect from foot- and -mouth disease. This is all the more desirable, as in 1926 a report was received from France that very good results were obtained by inoculation of a definite mixture of vaccine and apthae-virus (Belin).<sup>2)</sup>

We purpose to prosecute this inquiry with cows and calves. But these experiments are expensive, while it is very difficult to avoid technical errors. For this reason we also made experiments with infected caviae. The experiments with cows will be published afterwards.

However, the cavia-experiments have reached a stage, at which they can for the present be concluded. A brief account of these experiments follows:

Detailed reports with protocols etc. will soon be published.

The investigation was divided as follows:

- I. Description of the symptoms of foot- and -mouth disease in caviae.
- II. Idem of the symptoms of vaccine ("cowpox") in caviae.
- III. Observations regarding the immunity of caviae from vaccine after inoculation with this virus.
- IV. Observations on the immunity from apthae-virus after inoculation with this infectious matter.
- V. Observations on the immunity of caviae from foot- and -mouth disease after inoculation with vaccine.
- VI. Observations on the immunity of caviae from vaccine after inoculation with apthae virus.

Graphs have been plotted for vaccine- as well as for apthae-infections, in which the succession of the symptoms, their intensity and their duration may be read at a glance. The line *AP* indicates the changes at the hindlegs, *VP* those at the forelegs, *T* at the tongue.

#### I. Description of the *symptoms of foot- and mouth disease* in caviae.

We observed:

1<sup>o</sup>. The body-temperature. After 1 to 2 days' incubation the temperature

<sup>1)</sup> GINS und KRAUSE. Zur Pathologie der Maul- und Klauenseuche Ergebnisse der Allgemeinen Pathologie und Patholog. Anatomie des Menschen und der Tiere 1924 vol. II Abt. II.

<sup>2)</sup> BELIN. Base scientifique d'une méthode de Vaccination antiaphteuse. Recueil de médecine-vétérinaire 1926. Tome 102, N<sup>o</sup>. 14 p. 307.

rises in typical cases and is followed by a fall, occasionally below the normal temperatures. It is soon restored to a slightly higher level. For a long time the temperature remains variable (Fig. 1).

2°. The body-weight. In all the cases there is a heavy loss of body-weight (Fig. 1) from which the animals recover but slowly. Generally the initial weight is not regained before the lesions at the site of inoculation are cured.

3°. The development and healing of the aphthae-blains at the site of inoculation (sole of the foot metatarsus hindlegs). After the incubation blains appear, then their regression, formation of scabs, shedding of these scales, appearance of a skin-lesion, its healing.

4°. Alterations at the soles of the fore-legs. Here we observe redness, swelling, afterwards exfoliation of the skin and ultimate healing.

5°. Changes of the mucous membrane of the mouth. Blains appear in the mouth, especially on the tongue, that bring on a loss of epithelium and often excoriation all over the tongue. Cure, as a rule, proceeds rapidly.

6°. Some other manifestations, so staring that they, so to speak, obtrude themselves to be taken up in the protocols, such as considerable falling off of the hair, hyper secretions from the salivary glands and of intense salivation.

## II. Description of the *symptoms* after inoculation with *vaccine* in *caviae* (Fig. 2).

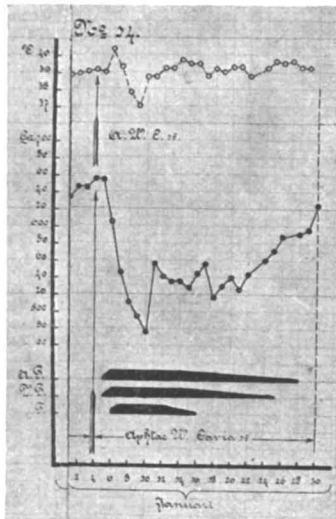


Fig. 1.

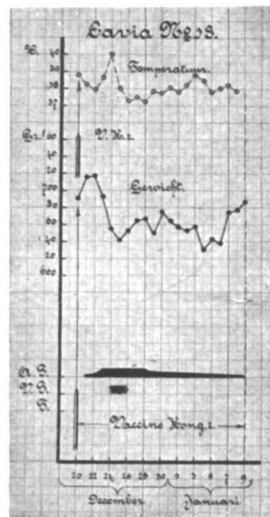


Fig. 2.

We observed:

1°. Changes in the body-temperature. In most cases fever ensues from

3 to 5 days after the inoculation. Gradually a fall succeeds and a varying temperature for some days. A fall below the "normal" temperature was not observed.

2°. Changes in the body-weight. Here also a considerable loss is often seen after the incubation period, truly, not so heavy as with apthae, but sufficient to discern that the inoculation with vaccine has not the effect of a localized inflammation but influences the general condition of the animal. It makes the animal ill.

3°. Growth of the blain and healing of the area of inoculation. A simple formation of blains exists here, that heals under a scab. After the first scales have fallen off there may appear a wound-surface, which heals in the usual way.

4°. Changes at the soles of the fore-legs. Only redness and swelling are observed here. No other symptoms appeared after the ordinary inoculation with vaccine.

III. Observations regarding the *immunity* of *caviae* from *vaccine* after inoculation with *this virus*.

A vaccine-injection imparts to a *cavia* complete immunity against a re-inoculation with this virus, administered immediately after recovery. It does not matter, whether for the re-inoculation the same vaccine-strain is employed or an other. A transit through *cavia* or calf is of no influence.

From the fact that the symptoms mentioned in II, were totally absent, we inferred the existence of this complete immunity. Fig. 3 illustrates this. It will be seen, that in the control-*cavia* N°. 26 the symptoms have been

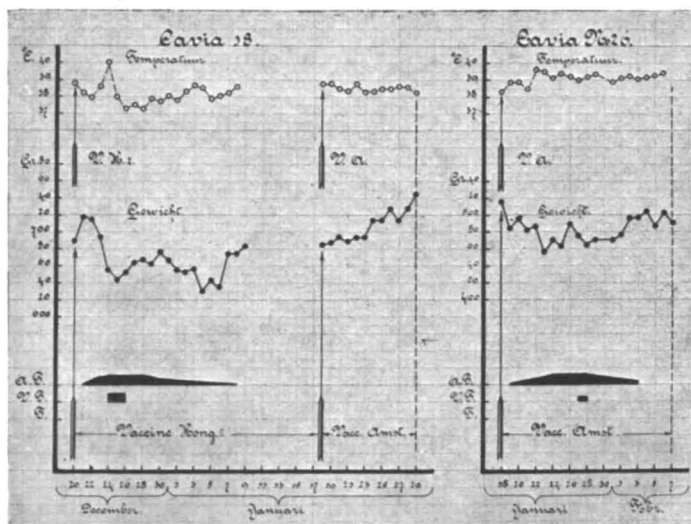


Fig. 3.

fully developed, while in the cavia N<sup>o</sup>. 18 no anomalies could be recognized. This immunity could be established in 5 caviae.

IV. *Immunity* in caviae from *aphthae epizoöticae* after injection of *this virus*.

A single infection with a very virulent aphthae-strain is sufficient to evoke complete immunity against this virus. This is instanced by cavia N<sup>o</sup>. 3 (Fig. 4). The accompanying curve shows distinctly the difference between cavia 3 after re-inoculation and cavia 10 after the first injection with the same infectious matter. The same immunity appears against other strains of equal virulence. Cavia N<sup>o</sup>. 21 (control-cavia 43).

Yet there is a large difference regarding the facts found with vaccine.

When a cavia is inoculated with an aphthae-strain that is only slightly virulent for this animal, the symptoms will be confined to formation of blains at the hindlegs, redness at the fore-legs, loss of weight and an irregular temperature (Fig. 5, cavia N<sup>o</sup>. 7). At a following inoculation

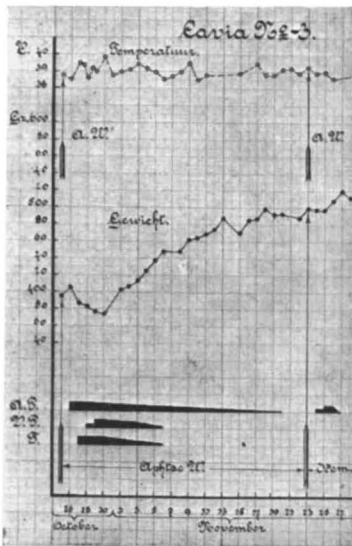


Fig. 4.

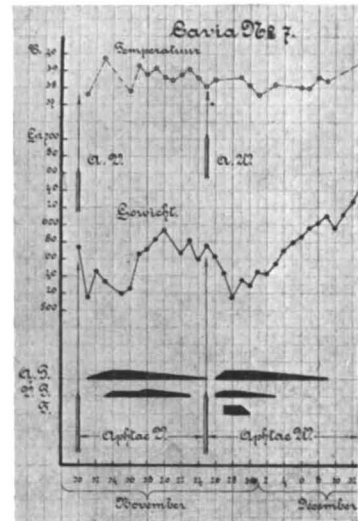
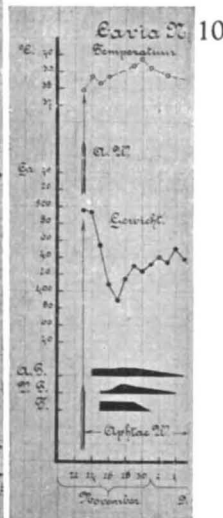


Fig. 5.

with a very virulent strain it appears that no immunity from this virus has been effected. Heavy loss of weight, affections at the hindlegs, forelegs and tongue appear just as with a cavia that has not been treated previously. Only there is a tendency to quicker healing (allergic reaction GINS and WEBER<sup>1)</sup>).

This remarkable "plurality" of the aphthae-strains could be established in three caviae. Here we wish to refer to the observations made by

<sup>1)</sup> GINS und WEBER. Ueber experimentelle Maul- und Klauenseuche. Centralblatt f. Bakteriologie etc. Erste Abt. Originale Bnd. 88, 1922, Heft 3 p. 180.

VALLÉE and CARRÉ <sup>1)</sup>, WALDMANN and TRAUTWEIN <sup>2)</sup> and STOCKMANN and MINETT <sup>3)</sup> in which the same symptoms were recognized.

V. *Immunity against aphtae after inoculation with vaccine.*

In the foregoing we have dwelt on the nature and the scope of the immunity from a specific virus after inoculation with vaccine and aphtae. Now we could pass on to an inquiry into the mutual immunity with cross-inoculation. From this it appeared that *inoculation with vaccine does not induce immunity against aphtae when administered directly after the healing.*

In [fig. 6 we see that a cavia tolerates a vigorous vaccine infection

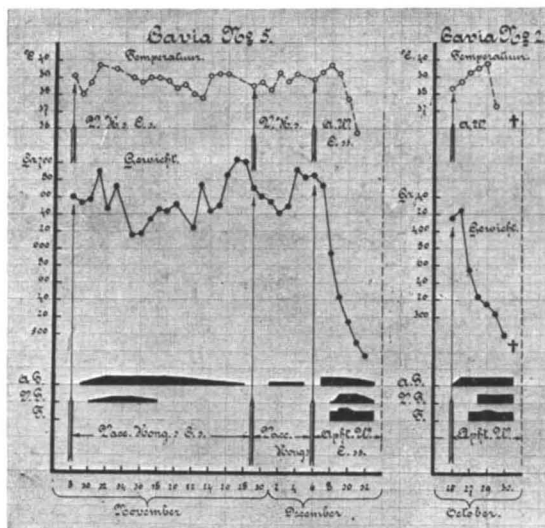


Fig. 6.

with fever, loss of weight, anomalies at the fore-, and hindlegs. Then it appears to be entirely immune against a repeated vaccine-inoculation.

But the subsequent inoculation with aphtae-virus induces death within 6 days. The figure shows that the process is identical with the result obtained with cavia N<sup>o</sup>. 2, which had not been treated beforehand. It was also observed in cavia N<sup>o</sup>. 1 that a previous inoculation with vaccine acted no influence upon the course of the subsequent inoculation with aphtae, though the latter did not induce death.

<sup>1)</sup> VALLÉE H. et CARRÉ H. Sur l'immunité antiaphtheuse *Compt. rend. de l'Acad. des Sciences* 1922, T. 174, p. 207.

<sup>2)</sup> WALDMANN and TRAUTWEIN. Experimentelle Untersuchungen über die Pluralität der Maul- und Klauenseuche Virus (Vorl. Mitteil.) *Berl. Tierarztl. Wochenschr.* Jrg. 42, N<sup>o</sup>. 35.

<sup>3)</sup> ST. STOCKMANN and F. C. MINETT. Experiments on Foot- and Mouth-disease. *The journal of Comp. Path. and Therapeutics*, Vol. 39, Part 3.

These observations stand in harmony with the findings established by UHLENHUTH and BIEBER<sup>1)</sup>

VI. It still remains for us to watch the effect of a preceding inoculation with aphthae upon a vaccine-inoculation following it immediately.

In ten caviae it could be established that *sustaining a serious general attack of aphthae epizoöticae engenders an almost complete immunity against an infection with vaccine succeeding the attack directly.*

Graphs of cavia 10 and cavia 4 go to illustrate this.

It may be seen that a single inoculation with aphthae into cavia 10 (fig. 7) results in almost complete immunity from vaccine. Of all the

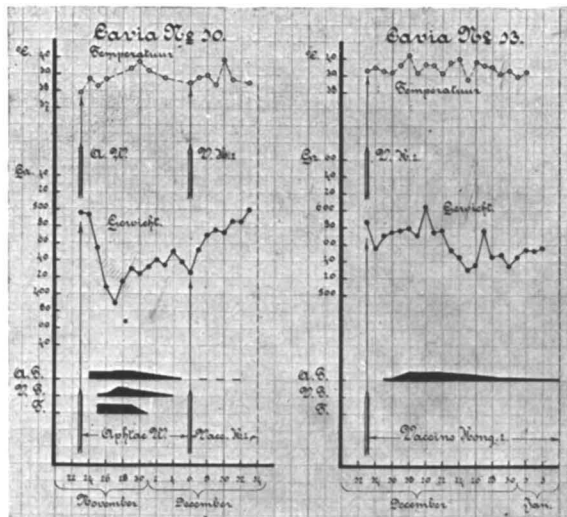


Fig. 7.

symptoms mentioned under II the only ones we notice here, is a rise of the temperature and very insignificant symptoms at the site of inoculation on the 4<sup>th</sup> day after the vaccine-inoculation. The graph of the control-cavia N<sup>o</sup>. 13 shows that the inoculation-matter was sufficiently virulent (Fig. 7).

The same symptoms are distinguished in Cavia 4. This animal had been infected twice with aphthae, the first time with the slightly virulent strain S., the second time with the highly virulent strain W. After inoculation with "vaccine" the animal hardly displays any symptoms: we only detect a very slight reaction at the site of injection, which lasts two days (see fig. 8).

The control-cavia N<sup>o</sup>. 12, however, reveals with the same infectious matter the complete aspect of the disease described in II.

<sup>1)</sup> See note p. 543.

This almost complete immunity could be established for three different vaccine-strains. The results of these experiments are illustrated in the subjoined table I.

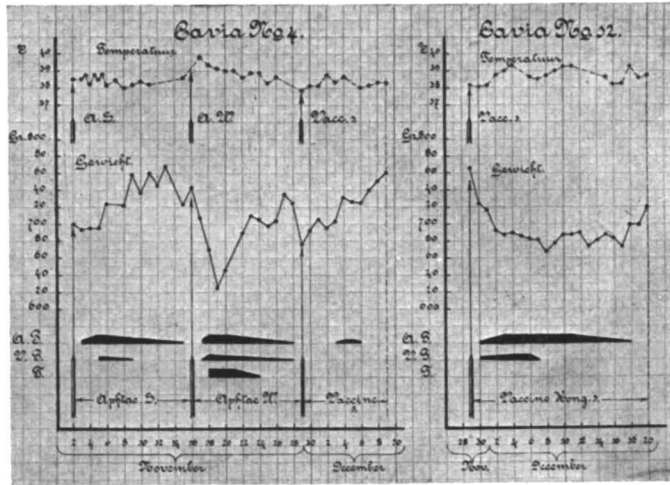


Fig. 8.

In one cavia the immunity appeared to be less complete. Here it should be remembered that this animal:

- 1<sup>o</sup>. could endure only faintly infectious aphthae,
- 2<sup>o</sup>. was already rather old, so that perhaps it had almost lost the capacity of appropriating this immunity.

This experiment, however, cannot on any account be brought forward to detract much from the significance of the other nine observations.

### CONCLUSION.

The above-described results are significant for the following reasons.

The close relation between the aphthae- and the vaccine-virus is proved for the first time by scientific experiments.

The immunity from the latter, after inoculation with the former, points to a relationship between these two viruses.

It matters little that in these experiments vaccine-inoculation does not produce immunity against aphthae, as we could also establish that inoculation with different "aphthae-strains" did not yield immunity against other virulent foot- and -mouth disease-virus. Nevertheless, many facts point to a relationship between the two viruses.

This puts the observations of practitioners in a different light from that in which they were regarded up to the present.

On the basis of the relationship alluded to above, it may very well be possible that an intracutaneous vaccine-injection, properly carried out,



would yield a sufficient immunity against "contact"-infections with "aphthae-virus" to a degree that would make it serviceable for practice.

TABLE N<sup>o</sup>. 1,

N <sup>o</sup> .	Weight	1 <sup>st</sup> Inoculation	2 <sup>d</sup> Inoculation	Vaccine	Résumé
8	860	Apht. W.		Hong. II	Almost complete immunity
9	500	Apht. W.		Hong. II	Almost complete immunity
19	420	Apht. W.		Hong. II	Very high degree of immunity
11	565	Apht. W. cavia 10		Hong. II	Very high degree of immunity
17	620	Apht. W. cavia 15		Amsterdam	Very high degree of immunity
18	900	Apht. W. cavia 17		Amsterdam	High degree of immunity
3	380	Apht. W.	Apht. W.	Hong. I	Almost complete immunity
4	700	Apht. S.	Apht. W.	Hong. I	Almost complete immunity
7	575	Apht. V.	Apht. W.	Hong. II	Almost complete immunity
6	680	Apht. S. cavia 4	Apht. W.	Hong. II	High degree of immunity

In connection with these experiments it is quite expedient that they should be continued in the direction indicated <sup>1)</sup>).

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<sup>1)</sup> In two advisedly arranged experiments it could be established, that two caviae treated beforehand with vaccine and inoculated two, resp. four months afterwards with very virulent aphthae-virus, possessed a much greater resistance against this virus than the animals that had not been treated previously. If this finding should be confirmed in other cases, it will be recorded in a following communication.