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STUDIES ON THE AETIOLOGY OF SWEATING SICKNESS.

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Studies on the aetiology of sweating sickness were given an impetus when it was shown that the bont legged tick *Hyalomma transiens* Schulze is a vector (Neitz, 1954). Prior to that time it was believed that the aetiological agent was a virus but all efforts to transmit the condition experimentally were unsuccessful, using conventional and unconventional methods of transmission with blood and organ emulsions subinoculated by all conceivable routes. Even today the exact nature of the aetiological agent remains obscure but data are being accumulated because it has been possible to breed large numbers of ticks which can be relied upon to transmit infection without fail when fed on susceptible animals.

During the course of these investigations it has been established that all the progeny of a single female, retained the capacity to transmit the infection for at least 5 generations irrespective of whether the adult ticks fed on susceptible or immune calves or upon an insusceptible species, such as the horse.

Further, it has been found that the pig, and in particular the unpigmented Large White, probably is the experimental animal of choice. It is possible to rear pigs under conditions where accidental exposure to tick infestation can be excluded with reasonable certainty. Such pigs can be made available at no great expense in comparatively large numbers. The unpigmented skins make the detection of the characteristic hyperaemia of the skin as an early symptom, in addition to the hyperthermia, a simple matter. The development of pharyngeal and laryngeal lesions can be judged by changes in the tone and pitch of the squeals on handling without resorting to the exceeding painful manipulation of forcing the mouth open.

The object of this report is to record certain interesting observations connected with the transmission of sweating sickness to both cattle and pigs, observations which may throw some light on the possible nature of the aetiological agent, as well as upon the production of immunity to reinfection.

METHODS AND MATERIALS.

The experimental animals had been reared under tick-free conditions so that their susceptibility to sweating sickness was not open to question. The age of the calves varied from five to eleven months, and that of the Large White pigs from three to four months.

Infective adult ticks were fed on the ears of the animals (Tables 1 and 2) according to the method described by Neitz (1937). Each animal, except pig No. 1373 on which 40 ticks engorged, was infested at 8 a.m. with a counted number of from 20 to 30 ticks. At 2 p.m. on the same day all ticks, not attached, were

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removed. Therefore the number of ticks which attached could be determined accurately. At 9 a.m. on the days indicated the attached ticks were removed from the animals in the different groups.

On the controls and on animals which were subjected to an immunity test, ticks were allowed to engorge to repletion for periods of up to 20 days, or until death of the host.

The number of ticks that attached on the susceptible calves varied from 6 to 24, and that on the susceptible pigs from 4 to 40. The number of ticks that fed on animals whose immunity was challenged varied from 2 to 28.

Experimental Observations.

1. *Calves.*

The 14 calves used in the experiment were divided into seven groups according to the length of time the ticks were permitted to engorge. In the first six groups this period varied from one to six days; in the seventh group are included those animals upon which ticks fed for periods of from 8 to 15 days. The immunity of all the survivors except two (7633 and 8065) which had reacted severely was tested by feeding known infective ticks. The results are summarized in Table 1.

Results.

The two calves (7653 and 7702) which comprise groups one and two and upon which ticks fed for 1 and 2 days respectively showed no clinical reaction. When challenged after an interval of 29 days both reacted and died.

In group three, 7 and 12 ticks were allowed to feed respectively on two calves (7810 and 7643) for three days. Neither calf showed any reaction. The one calf (7810) was challenged after an interval of 23 days as a result of which it reacted and died. The other calf (7643) was challenged after an interval of 29 days and was found to be solidly immune. To determine the validity of this immunity test a second batch of 15 ticks was permitted to engorge after a further interval of 48 days. Again no detectable reaction was produced.

In group four, 15, 17 and 24 ticks engorged for four days on three calves (7805, 7642 and 7807) respectively. Two of these calves (7805 and 7642) showed no reaction whatever but the third calf (7807) showed a slight febrile reaction with detectable hyperaemia of the mucous membrane, this mild reaction being classified as +. On immunity test after intervals of 23, 29 and 112 days all those calves were found to be immune. Again the validity of the challenge was confirmed in the case of one calf (7642).

TABLE 1.

Observations on Calves.

No. of Calf.	Ticks fed for days.	No. of Ticks attached.	Nature of reaction.	Result.	IMMUNITY TEST.				
					Interv. in days.	Ticks fed for days.	No. of ticks attached.	Nature of reaction.	Result.
7653.....	1	16	NR.	—	29	11	28	+++++	Died.
7702.....	2	12	NR.	—	29	8	8	+++++	Died.
7810.....	3	7	NR.	—	23	9	8	+++++	Died.
7643.....	3	12	NR.	—	29	11	6	NR.	Immune.
					77	15	5	NR.	Immune.
7805.....	4	15	NR.	—	23	8	8	NR.	Immune.
7642.....	4	17	NR.	—	29	11	7	NR.	Immune.
					77	15	6	NR.	Immune.
7807.....	4	24	+	Recovered	112	10	15	NR.	Immune.
7969.....	5	13	+++	Recovered	112	10	8	NR.	Immune.
7939.....	5	19	+++	Recovered	112	10	10	NR.	Immune.
7971.....	6	14	+++++	Died	—	—	—	—	—
7972.....	8	8	+++++	Died	—	—	—	—	—
7637.....	11	12	+++++	Died	—	—	—	—	—
8065.....	12	6	++++	Recovered	—	—	—	—	—
7633.....	15	6	++++	Recovered	—	—	—	—	—

NR. signifies no reaction.

+ to +++++ degree of severity of reaction from definite but very mild to very severe.

In group five, in which 13 and 19 ticks fed for 5 days on two calves (7969 and 7939) respectively both calves showed a fairly severe reaction, classified as + + +, and on immunity test 112 days later were immune.

In group six, in which ticks were fed for periods of from 8 to 15 days all four calves reacted severely and two died. The immunity of the two survivors was not challenged.

2. *Pigs.*

The salient features of the results that were obtained with calves were investigated in a series of experiments on a larger number of pigs.

Since sweating sickness was not transmitted to calves by ticks that had been attached for only two days, attention was directed to the outcome of feeding ticks for longer periods of time. A total of 24 Large White pigs of both sexes was divided into 5 groups. In the first group of four pigs each, ticks were allowed to remain attached for 3, 4, 5 and 6 days respectively; the number of ticks that attached varied at random from 12 to 28. In the fifth group, ticks were permitted to attach to eight pigs for from 10 to 20 days. The immunity of all survivors except one was challenged.

The results are summarized in Table 2.

Results.

From Table 2 it will be seen that of four pigs, upon which ticks were attached for 3 days, none showed any detectable reaction. On immunity test 19 days later all reacted and one died; of the three survivors two reacted severely but the reaction in one was mild.

Of the four pigs upon which ticks were attached for four days all reacted though the reaction in one (1396) was so mild as to be scarcely detectable; on immunity test 19 days later this pig reacted fairly severely but recovered. The remaining three pigs showed severe reactions and on challenge were immune.

The results in the case of the four pigs in group three, upon which ticks were attached for 5 days, were practically identical with those obtained with the four day attachment period in group 2.

The remaining 12 pigs upon which ticks were attached for a period of 6 days or longer all showed severe reactions and nine died. On immunity test the three survivors were found to be solidly immune.

Discussion.

The febrile reaction together with the easily detectable clinical symptoms of sweating sickness served as reliable criteria for estimating the severity of the reactions in individual animals. Nevertheless, in the case of the cattle it was feared that the pigmentation of the skin might mask a slight cutaneous hyperaemia, and that the prevailing hot weather at the time the experiments were made, might result in confusion between hyperthermia due to climatic factors and a slight febrile reaction. It is for that reason that immunity tests were carried out on all recovered animals except two calves and one pig which had shown unmistakable severe reactions. Since the disease cannot be transmitted by inoculation there was no alternative other than to resort to the method of feeding known infective ticks to repletion.

TABLE 2.

Observations on Pigs.

No. of Pig.	Ticks fed for days.	No. of Ticks attached.	Nature of reaction.	Result.	IMMUNITY TEST.				
					Interv. in days.	Ticks fed for days.	No. of ticks attached.	Nature of reaction.	Result.
1429	3	12	NR.	—	19	20	14	++	Recovered.
1431	3	28	NR.	—	19	20	4	++++	Recovered.
1432	3	20	NR.	—	19	20	7	++++	Recovered.
1430	3	28	NR.	—	19	12	10	+++++	Died.
1396	4	10	+	Recovered	19	20	8	+++	Recovered.
1408	4	20	+++	Recovered	19	20	3	NR.	Immune.
1409	4	21	++++	Recovered	19	20	5	NR.	Immune.
1410	4	27	++++	Recovered	19	20	9	NR.	Immune.
1411	5	17	+	Recovered	63	12	8	++	Recovered.
1412	5	12	++++	Recovered	63	12	2	NR.	Immune.
1419	5	13	++++	Recovered	63	12	3	NR.	Immune.
1413	5	19	+++++	Recovered	63	12	4	NR.	Immune.
1433	6	13	++++	Recovered	96	13	8	NR.	Immune.
1425	6	27	+++++	Died	—	—	—	—	—
1426	6	17	+++++	Died	—	—	—	—	—
1427	6	22	+++++	Died	—	—	—	—	—
1428	10	10	+++++	Died	—	—	—	—	—
1434	10	15	+++++	Died	—	—	—	—	—
1372	10	8	+++++	Died	—	—	—	—	—
1373	10	40	+++++	Died	—	—	—	—	—
1441	15	9	+++++	Died	—	—	—	—	—
1438	20	6	+++++	Died	—	—	—	—	—
1442	20	6	++++	Recovered	77	9	6	NR.	Immune.
1445	20	4	++++	Recovered	—	—	—	—	—

The immunity test was of great value in showing firstly, that a somewhat doubtful clinical reaction such as that in calf 7807 was in fact a sweating sickness reaction, secondly that inapparent reactions followed by solid immunity are by no means uncommon (calves 7643, 7805, 7642) and thirdly that immunity may be partial or quantitative (pigs 1429, 1386, 1411).

It must be borne in mind that there is no known method of determining accurately, say to within a matter of hours, how long each individual tick was attached, nor how long after the mouth parts are inserted into the skin of the host is infection given off. In addition, it is apparent that other unknown factors govern the behaviour of ticks on the host as for instance the fact that although 20 ticks of the same group were placed on three pigs (1408, 1412, and 1419) only 3, 2 and 3 attached on the hosts respectively, whereas on pig 1373 no less than 40 ticks started engorgement. In view of these technical limitations it is all the more remarkable that the results of the experiments on calves so closely paralleled those obtained on pigs.

In comparing the results of the experiments on cattle and pigs it is apparent that the results, though closely parallel were not identical. For instance three calves (7643, 7692, 7805) showed no apparent or detectable reaction to the primary interrupted tick feeding but were found to have developed a solid immunity. Such inapparent infections followed by immunity were not observed in pigs but there was brought to light the phenomenon of partial immunity, which may or may not be quantitative, as exemplified by pigs 1429 and 1411 and to a slightly lesser extent by pig 1396. It is possible that this is due to the ease with which a reaction can be detected in the pigs.

Points on which there is agreement in the experiments on the two classes of animals are, that the severity of the reactions is dependent upon the duration of feeding of the tick and not upon the number of ticks that attached, and that infection is passed to the host from the tick during the early stage of engorgement long before engorgement to repletion is attained. There is a lag period from the time of attachment to the transmission of infection of approximately two days.

Consideration of the somewhat unexpected results from these experiments would appear to leave no doubt that the behaviour of the causal agent of sweating sickness differs materially from that observed with the true viruses. The arthropod transmitted viruses are capable of multiplying within the vertebrate and invertebrate hosts, and artificial transmission by inoculation of emulsions of the vector or of blood and organ emulsions of the vertebrate host occasionally may present difficulties but usually is accomplished with ease. It has been stated, though not recorded and not confirmed, that sweating sickness has been transmitted to calves by injection of emulsions of species of *Hyalomma* but in spite of innumerable attempts over many years artificial transmission from calf to calf has never succeeded. Apparently the causal agent of sweating sickness develops or multiplies, not in the vertebrate but in the invertebrate host, and the timely removal of attached infective ticks is followed by subsidence of the symptoms with recovery and the development of immunity. A similar phenomenon is known to occur in the case of tick paralysis, particularly of sheep, and in that condition it is generally accepted that the cause is a toxin produced by the tick during engorgement. Considerable additional data and information must be collected before the nature of the cause of sweatinng sickness can be determined with certainty though the available evidence points to the fact that it is a toxin generated by the adult stage of the tick during the process of feeding and that, irrespective of the susceptibility of the host, it is transmitted from generation to generation of the tick transovarially.

It is stated above that the results of the experiments were somewhat unexpected. The qualification is deliberate. The experiments were planned from the observation that the incidence of sweating sickness may be controlled by continued regular dipping for the elimination of ticks, together with the knowledge that there is a wide variation in the severity of symptoms and that inapparent infections accompained by immunity production are common in those cases where tick control is practised conscientiously. It is now clear that if a system of tick control is followed whereby *Hyalomma* could be permitted to feed for not less than two days and not longer than four days i.e. by regular five day dipping or spraying, or by seven day treatment using acaricide with a residual effect not shorter than two days the disease, or rather the effects of infection, may be eliminated.

SUMMARY.

1. An account is given of a series of experiments on calves and pigs on which infective *Hyalomma transiens* were allowed to feed for periods of variable duration.

2. It was determined that the causal agent can be transmitted by the vector as early as 72 hours, but usually between 72 and 96 hours after attachment.

3. Tick-feeding periods of three, four or five days are followed by either inapparent infections relatively mild or severe reactions and recovery.

4. Tick-feeding periods of six days and longer are followed by severe or very severe reactions terminating fatally in 75 per cent of cases.

5. The behaviour of the causal agent of sweating sickness does not conform to that observed in arthropod-borne viruses.

6. It is suggested that the causal agent is a "toxin" generated by adult ticks during the process of feeding.

7. Possible prophylactic measures based on control of the infective tick are discussed.

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