THE HOEPPLI PHENOMENON IN SCHISTOSOMIASIS JAPONICA: HISTORICAL FINDINGS AND ADDITIONAL INVESTIGATION IN BOVINES

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Abstract. The present paper deals with a buried knowledge of the early findings of the Hoeppli phenomenon in cattle infected with *Schistosoma japonicum* together with a revised list of bovines and other mammalian species in which this phenomenon has been found. It was noted that the percentage of the mature-egg granulomas with positive Hoeppli phenomena varied with the species of bovines, *ie*, higher positive percentage in the more susceptible cattle than in the less susceptible buffalos. The radiating filaments in fringes of the phenomenon were also stronger in cattle than in buffalos.

INTRODUCTION

The Hoeppli phenomenon is an eosinophilic fringe surrounding schistosome eggs (EFSSE) found in the tissue of infected hosts. It is a picturesque and interesting phenomenon. Although its nature has recently been elicited to be due to interactions of egg antigens and host antibodies in schistosomiasis (Lichtenberg *et al*, 1966; He and Yang, 1979), additional knowledge is still needed for its better understanding.

The present paper deals with a buried knowledge of the early findings of EFSSE in cattle infected with *Schistosoma japonicum* together with a revised list of mammalian species in which this phenomenon has been found. The relationship of the susceptibility of infection and the immune state of the cattle and water buffalo infected with *S. japonicum* with this phenomenon is also dealt with.

A SHORT REVIEW OF THE HISTORICAL EVENTS OF THE EOSINOPHILIC FRINGES SURROUNDING *S. JAPONICUM* EGGS

In 1910, Nakayama discovered EFSSE of *S. japonicum* in histological sections of liver and intestine of cattle in Japan. As the findings were very interesting, 14 pages of descriptions of their characteristics and mechanism of their formation were presented. Because his report was written in Japanese, his findings have, until now, not been quoted in the Western literature.

From 1910 to 1931, more reports of the EFSSE in cattle and other mammalian species appeared in the Japanese literature (Hironaka, 1910; Nakamura, 1911; Akita, 1913; Watanabe, 1913; Fujinami, 1916; Kiyono and Murakami, 1917; Tanaka, 1925). But they met the same fate of not being quoted in the Western literature.

In 1932, Hoeppli reported his finding of EFSSE in the lungs of experimental rabbits which were infected with *S. japonicum*. He was the first to give the description of EFSSE in English. He stated, nevertheless, that this phenomenon has also mentioned in early Japanese literature, for example, by Fujinami (1916). Evidently he did not read Nakayama's paper on this phenomenon.

From 1935 to 1963, a number of papers written in Western languages were published on EFSSE of *S. mansoni*. In 1962, Lichtenberg *et al* designated EFSSE as the "Hoeppli phenomenon". As Nakayama is the discoverer of the EFSSE and Hoeppli is the first author who reported the EFSSE in the Western language, it seems more appropriate to designate it as The "Nakayama-Hoeppli phenomenon" in schistosomiasis, so that both investigators are honored.

MAMMALIAN SPECIES IN WHICH THE HOEPPLI PHENOMENON HAS BEEN REPORTED

In 1966, Lichtenberg *et al* compiled a list of the mammalian species in which the Hoeppli phenomenon has been reported. They listed 3 species for *S. japonicum*, 11 for *S. mansoni*, and 1 for *S. haematobium*. A review of the old Japanese literature and Chinese literature together with new literature in Western languages showed that there are 12 species of mammalian hosts which have been reported positive for this phenomenon (Table 1).

RELATIONSHIP OF THE SUSCEPTIBILITY OF INFECTION WITH *S. JAPONICUM* AND ACQUIRED IMMUNITY AGAINST THIS PARASITE WITH THE PREVALENCE OF HOEPPLI PHENOMENON

Our 1984 field trial of vaccination against *S. japonicum* in China enabled us to have a number of infected livers of cattle and water buffalos in our possession. Histological sections of livers showed that all the animals were positive for the Hoeppli phenomenon.

In our experiments, both the cattle and buffalos were divided into a laboratory and a field trial group. Each group was further divided into a vaccinated and a non-vaccinated subgroups (altogether 8 subgroups). The vaccinated subgroups of the laboratory group were vaccinated 3 times with 38 kR irradiated schistosomula and then challenged with 500 normal cercariae for cattle and with 2,000 cercariae for buffalos. The non-vaccinated subgroups were similarly challenged but without previous vaccination. All the animals of the laboratory group were killed for the worm perfusion on days 54-57 of the infection or the challenge. The perfused liver was fixed in 10%

Table 1

Mammalian species in which the Hoeppli phenomenon has been reported.

Mammalian species	Author (s) and year
Man *(Homo sapiens)*	Hironaka (1910)
	Nakamura (1911)
	Akita (1913)
	Watanabe (1913)
	Fujinami (1916)
	Brachen *et al* (1948)
Japanese monkey *(Macaca fuscata)*	Tanaka (1925)
Rhesus monkey *(Macaca mulatta)*	He and Yang (1962)
Vervet monkey *(Cercopithecus aethiops)*	James *et al* (1977)
Cattle *(Bos taurus)*	Nakayama (1910)
	Nakamura (1911)
	Watanabe (1913)
	Tanaka (1925)
	Kikuchi (1960)
	Present data
Water buffalo *(Bubalus bubalis)*	Present data
Horse *(Equus caballus orientalis)*	Kikuchi (1960)
Dog *(Canis familiaris)*	Nakayama (1910)
	Tanaka (1925)
Cat *(Felis domestica)*	Tanaka (1925)
Rabbit *(Oryctolagus cuniculus)*	Kiyono and Murakami (1917)
	Hoeppli (1932)
	Meleney *et al* (1953)
	Sakurabayashi (1955)
Hamster *(Mesocricetus auratus)*	Hsü *et al* (1973)
Mouse *(Mus musculus)*	Sawada *et al* (1956)
	Hsü *et al* (1972)
	He and Yang (1979)

Table 2

Hoeppli phenomenon-positive mature egg granulomas in *S. japonicum* infected bovines.

Annimal groups and subgroups	No. of animals	No. of mature egg granulomas	Mature egg granulomas with Heoppli phenomenon	
			No.	%
Laboratory animals				
Cattle				
Vaccinated	3	107	80	74.8
Non-vaccinated	3	204	142	69.6
Buffalos				
Vaccinated	3	53	23	43.4
Non-vaccinated	3	32	10	31.3
Field animals				
Cattle				
Vaccinated	9	192	59	30.7
Non-vaccinated	8	223	52	23.3
Buffalos				
Vaccinated	9	114	20	17.5
Non-vaccinated	9	235	30	12.8

Table 3

Comparison of the percentages of Hoeppli phenomenon-positive mature egg granulomas in different host species.

Subgroups, animals (% of Hoeppli phenomenon-positive mature egg granulomas)	X^2	P
Laboratory animals		
Cattle, non-vaccinated (69.6) vs Buffalos, non-vaccinated (31.3)	17.753	0.001
Cattle, vaccinated (74.8) vs Buffalos, vaccinated (43.4)	15.209	0.001
Field animals		
Cattle, non-vaccinated (23.3) vs Buffalos, non-vaccinated (12.8)	5.665	0.003
Cattle, vaccinated (30.7) vs Buffalos, vaccinated (17.5)	6.493	0.011

All proportions are significantly different by chi square test.

formalin. Histological sections of 7 µm were made after the paraffin procedures and were stained with hematoxylin-eosin.

The vaccinated subgroup of the field trial group were similarly vaccinated with irradiated schistosomula and sent to the schistosomiasis japonica endemic area for natural infection. The animals of the non-vaccinated subgroups went together with the vaccinated subgroups in the field. The animals in both subgroups were killed for worm perfusion on day 58-63 in the field. Their livers were fixed in formalin and histological sections were made as for the livers from the laboratory group. (For more detailed information of the experimental procedures, see Hsu *et al*, 1984).

In each of the 8 subgroups of bovines, 32 to 235 granulomas containing single mature miracidium or its degenerated forms obtained from 3 to 9 animals were studied for the Hoeppli phenomenon and the parcentage of Hoeppli phenomenon-positive mature eggs was calculated (Table 2). It was noted that the percentage of granulomas with positive Hoeppli phenomenon varied with (1) the species of bovine, and (2) the presence or absence of previous vaccination. Statistical analysis by chi square test showed that the percentages of the Hoeppli phenomenon-positive egg granulomas were significantly different between cattle and buffalos, *ie* higher positive percentages in cattle than in buffalos (Table 3), whereas those between the non-vaccinated and vaccinated animals were not (Table 4). We noted also that the radiating filaments in fringes of the Hoeppli phenomenon were also stronger in cattle than in buffalos. (Figs 1-5).

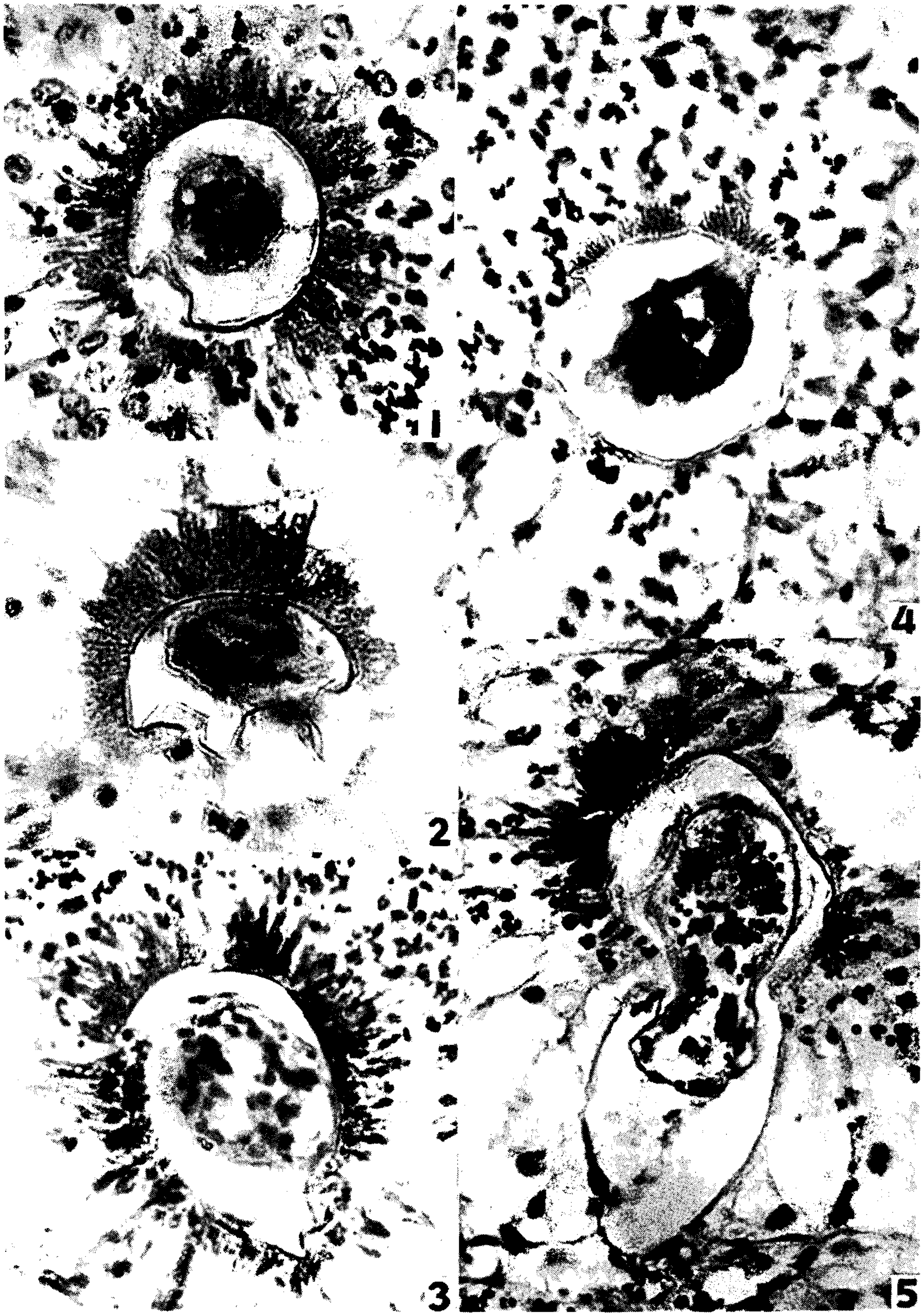
As cattle are known to be more susceptible to *S. japonicum* (Ho, 1963; Hsu *et al*, 1984) than buffalos, the higher percentages and better development of the Hoeppli phenomenon in cattle than in buffalos is evidently related with the susceptibility of the host. It has been demonstrated that the Hoeppli phenomenon is the result of antigen-antibody reaction (Lichtenberg *et al*, 1966; He *et al*, 1979). It may be assumed that the more susceptible animals produce more antibody than the less susceptible hosts, resulting in producing more and stronger Hoeppli phenomena in the former than in the latter. That Hoeppli phenomenon is the result of antigen-antibody reaction may also be used to explain the present finding that the vaccinated cattle and buffalos showed respectively more Hoeppli phenomena than the non-vaccinated

Table 4

Comparison of the percentages of Hoeppli phenomenon-positive mature egg granulomas in non-vaccinated and vaccinated animals.

Subgroups, animals (% of Hoeppli phenomenon-positive mature egg granulomas)	X^2	P
Laboratory animals		
Cattle, non-vaccinated (69.6) vs Cattle, vaccinated (74.8)	0.914	0.339
Buffalos, non-vaccinated (31.3) vs Buffalos, vaccinated (43.4)	1.239	0.266
Field animals		
Cattle, non-vaccinated (23.3) vs Cattle, vaccinated (30.7)	2.892	0.089
Buffalos, non-vaccinated (12.8) vs Buffalos, vaccinated (17.5)	1.428	0.232

No significant differences by chi square test.



Figs 1-3—Liver sections of cattle, showing an intensive Hoeppli phenomenon surrounding mature *S. japonicum* egg × 530.

Figs 4-5—Liver sections of buffalos, showing a less intensive Hoeppli phenomenon surrounding mature *S. japonicum* egg × 530.

animals as the former produces more antibody than the latter. However, the differences were not great enough to be statistically significant.

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