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Title	STUDIES ON ECHINOCOCCOSIS XVII : SEX DIFFERENCE IN RESISTANCE TO INFECTION WITH ECHINOCOCCUS MULTILOCULARIS IN UNIFORM STRAINS OF MICE
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STUDIES ON ECHINOCOCCOSIS XVII
SEX DIFFERENCE IN RESISTANCE TO INFECTION
WITH *ECHINOCOCCUS MULTILOCULARIS*
IN UNIFORM STRAINS OF MICE*¹

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YAMASHITA et al. have conducted a series of investigations of echinococcosis, in which the susceptibility to the larval form of *Echinococcus multilocularis* was studied in uniform strains of mice. These investigations demonstrated that there were marked differences in the host parasite relationship in species and strains of mice and other rodents. In one of these experiments, YAMASHITA et al. (1963)²⁾ observed marked resistance to this infection in female mice of the KK strain, the present series of experiments was designed to investigate this phenomenon.

MATERIALS AND METHODS

Two strains of mice, KK and NC, were used (tab. 1). A syringe with a cannula was used to inoculate the mice with approximately 400~500 eggs of the Alaskan strain of *E. multilocularis* in physiological saline. The eggs were obtained from adult tapeworms from an experimentally infected dog. The dog was infected by oral administration of hepatic echinococci obtained from two experimentally infected mice (strains CF#1 & C57 BL/6).

TABLE 1 *Cases examined*

STRAINS	DATE OF BIRTH	DATE OF INOCUL.	AGE AT INOCUL.	DATE OF SACRIFICE	DAYS POST-INOCUL.	SEX	NO. OF CASES EXAM.	NO. OF CASES POSITIVE
			mo.					
KK	12~17/IX '62	16/VII '63	10	29/X '63	105	♂	13	12* ²
						♀	22	10
NC	19~24/IV '63	"	3	"	"	♂	18	17
						♀	20	15

*² No. 11 died 100 days post-inoculation and No. 12, 93 days.

*¹ Dedicated to Dr. S. YAMAGIWA, the President of Obihiro Zootechnical College (1962~), Emeritus Professor in Hokkaido University, former professor in the Department of Comparative Pathology, Faculty of Veterinary Medicine, Hokkaido University

The inoculated mice were sacrificed at 105 days following inoculation with the exception of two of the KK strain which expired. The animals were examined both macro- and microscopically by routine methods to determine distribution of echinococcus foci, worm development, etc.

RESULTS

In all of the cases, the echinococcal foci were limited to the liver.

Strain KK Distribution of the hepatic foci is shown in figures 1, 2, 5 and 6.

FIGURE 1 *Distribution of foci in KK, males*

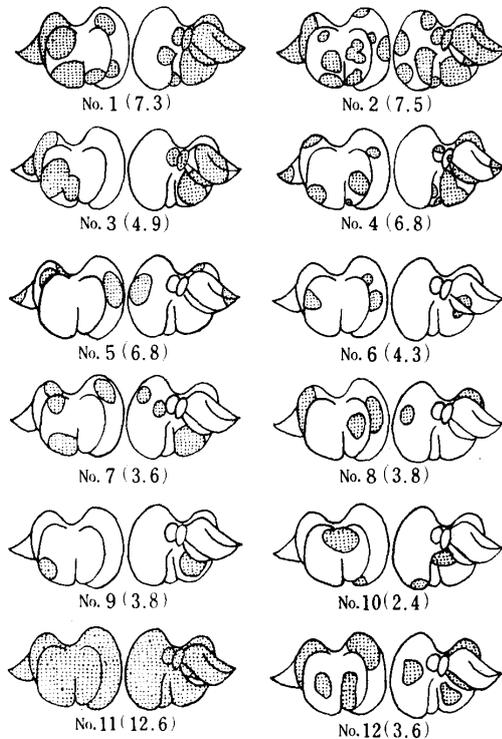
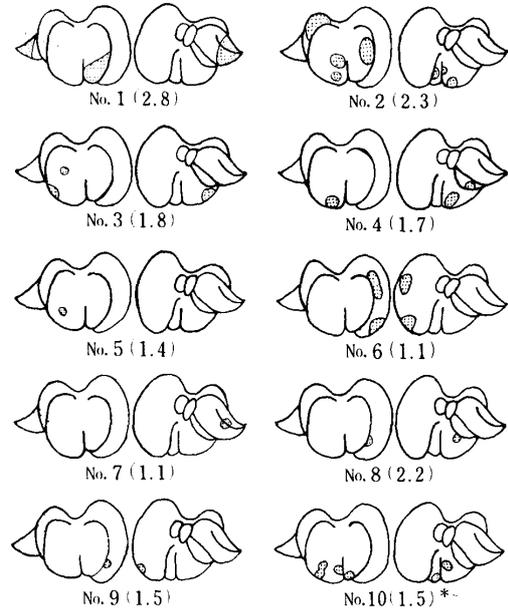


FIGURE 2 *Distribution of foci in KK, females*



* Number in parentheses indicates the weight of the liver in grams.

Males In 13 cases, 12 (92.4%) showed echinococcal foci in the liver. The weight of the livers in these cases ranged from 2.4 to 12.6 g, averaging 5.62 g. Large cysts, from 2 or 3 to several millimeters in diameter, were observed in 11 cases out of 12, or 91.7%. Small-cystic echinococcal foci were only found in one case (No. 10). The echinococci in this group were in the most advanced developmental stage. In 2 cases many brood capsules with immature scolices were detected. In 5 cases immature brood capsules without scolices were found and the remaining 5 cases had no brood capsules (tab. 2). There were few tissue reactions to the echinococci. There was a remarkable increase in the weight of the liver resulting from the active development of the echinococci.

Females In 22 cases inoculated 10 cases (45.4%) were positive for echinococcosis.

TABLE 2 *Development of echinococci in positive cases*
Number of cases (%)

STRAINS	SEX	STAGES OF DEVELOPMENT OF THE ECHINOCOCCUS		
		No brood capsule	Brood capsule formation	
			Without scolex	With scolex
KK	♂	5 (41.7)	5 (41.7)	2 (16.6)
	♀	8 (80.0)	1 (10.0)	1 (10.0)
NC	♂	12 (70.6)	5 (29.4)	—
	♀	13 (86.7)	2 (13.3)	—

The weight of the liver in these positive cases was 1.1~2.8 g, averaging 1.74 g. Compared to the males, this group showed much stronger tissue reactions in the form of granulation tissue. Large cysts were only found in one case (No. 1; 10%) and a large majority of this group showed small-cystic multilocular echinococcal foci. The echinococci were also less well developed than those in the males. In one case immature brood capsules were seen and in another case a small number of scolices were seen (tab. 2). The foci of this group were generally small.

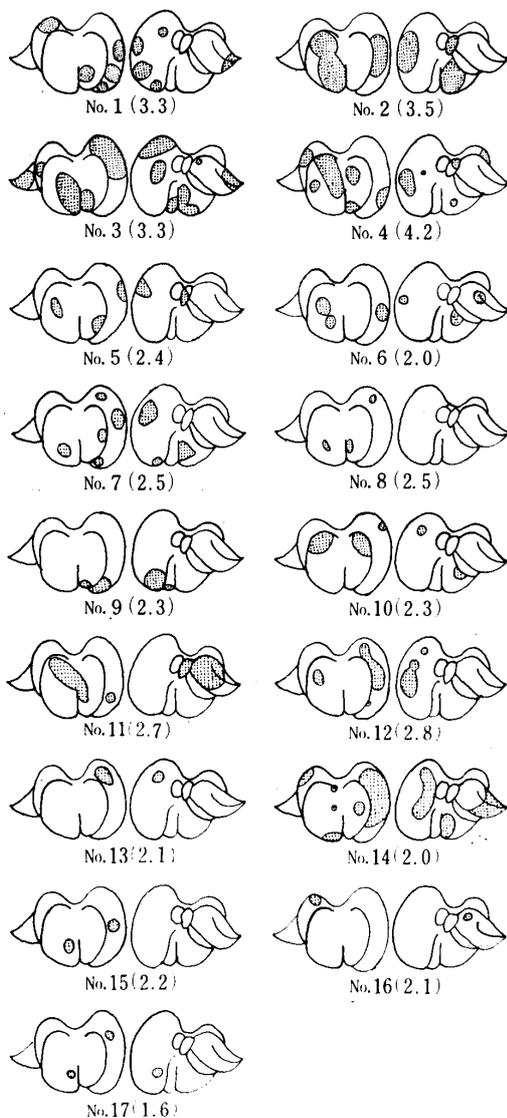
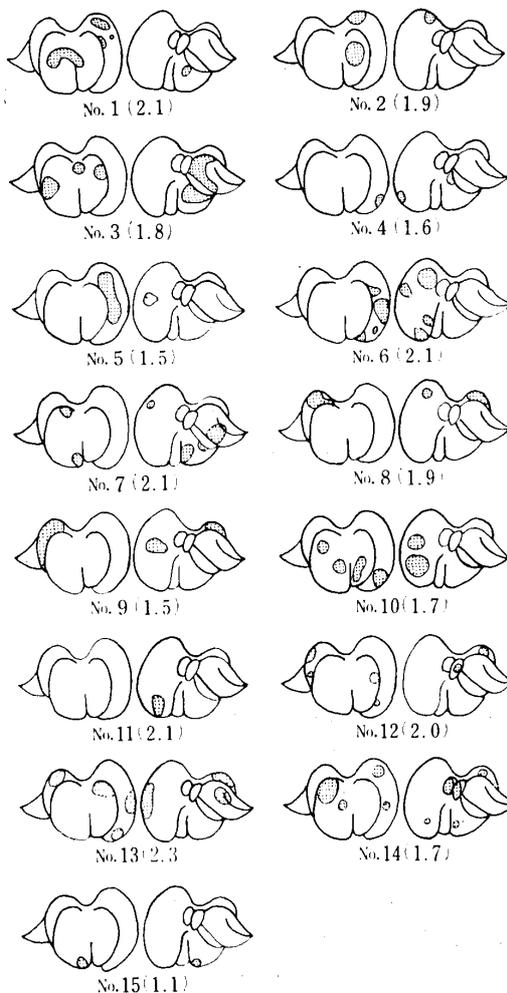
Strain NC The hepatic foci were distributed as shown in figures 3 and 4.

Males In 18 inoculated cases, there were 17 (94.4%) positive cases. The average weight of the livers in the positive cases was 2.57 g, ranging from 1.6 to 4.2 g. There was conspicuous tissue reaction to the echinococci in the form of granulation tissue. In 11 cases (64.7%) there were large cysts. Initial brood capsule formation was observed in 5 cases (29.4%; tab. 2).

Females Echinococcal foci were observed in 15 cases (75%) of the 20 inoculated cases. The foci were generally small. The weight of the livers in the positive cases averaged 1.82 g, ranging from 1.1 to 2.3 g. The majority of the foci had small echinococcal cysts and tissue reactions in the form of granulation tissue. In 7 cases (46.7%), large cysts were detected. The formation of initial brood capsules was only observed in 2 cases (13.3%) and in these cases there were no scolices (tab. 2).

TABLE 3 *Sex differences in resistance*

STRAINS	SEX	SUSCEPTI- BILITIES	AVERAGE WEIGHT OF LIVERS	INCIDENCE OF CASES AMONG POSITIVE IN WHICH FOUND		
				Large cysts	Brood capsules	Scolices
KK	♂	92.4%	5.62 g	91.7%	58.3%	16.6%
	♀	45.4	1.74	10.0	20.0	10.0
NC	♂	94.4	2.57	64.7	29.4	—
	♀	75.0	1.82	46.7	13.3	—

FIGURE 3 *Distribution of foci in NC, males*FIGURE 4 *Distribution of foci in NC, females*

DISCUSSION

The sex differences noted in the foregoing paragraphs are summarized in table 3.

From the results shown in table 3, it is very clear that sex differences do exist in susceptibility, liver enlargement, appearance of large cysts, formation of brood capsules and subsequent formation of scolices. These differences are most marked in the KK strain and less so in the NC strain. The difference in the age

of the two strains when they were inoculated (10 months and 3 months) must, of course, be taken into consideration, but the authors conclude from a series of experiments, that, among many strains, the KK strain exhibits the most marked sex difference in resistance. In his study of the histogenesis of multilocular echinococcosis in experimental animals⁵⁾, one of the authors pointed out that the appearance of large cysts during the progress of multilocular vesiculation is closely related to brood capsule formation. In other words, the appearance of cysts as large as several millimeters in diameter indicates that the echinococci have reached the brood capsule development stage. The authors have also observed that the scolex always develops within the brood capsule. Therefore, echinococci develop in order from large cyst formation to brood capsule and scolex formations. The multilocular echinococci develop much more rapidly in male mice of the KK strain than in female of the same strain. As YAMASHITA et al. (1958) have noted, echinococcosis in experimental animals can be classified into two types. These results agree with those of YAMASHITA et al. (1963)⁷⁾, that type 1 echinococcus develops in males of the KK strain and type 2 in the females. In the beginning of the present experiments, the authors used the NC strain only as controls but sex difference in resistance was observed in this strain as well.

At present, the phenomenon of sex difference in resistance to nematode infection in experimental animals is well-known, but there are few reports of this difference with regard to cestode parasites, with the exception of *Hymenolepis diminuta* and *Cysticercus fasciolaris*. Recently DOW & JARRETT (1960) stated that the sex factor was of minor importance in the resistance to infection in the mice strains studied. The authors were unable to find any reports of sex difference in resistance to multilocular echinococcal infections in experimental animals. The results obtained by the authors are interesting, and the phenomenon must be taken into consideration in future experiments with multilocular echinococcosis.

CONCLUSION

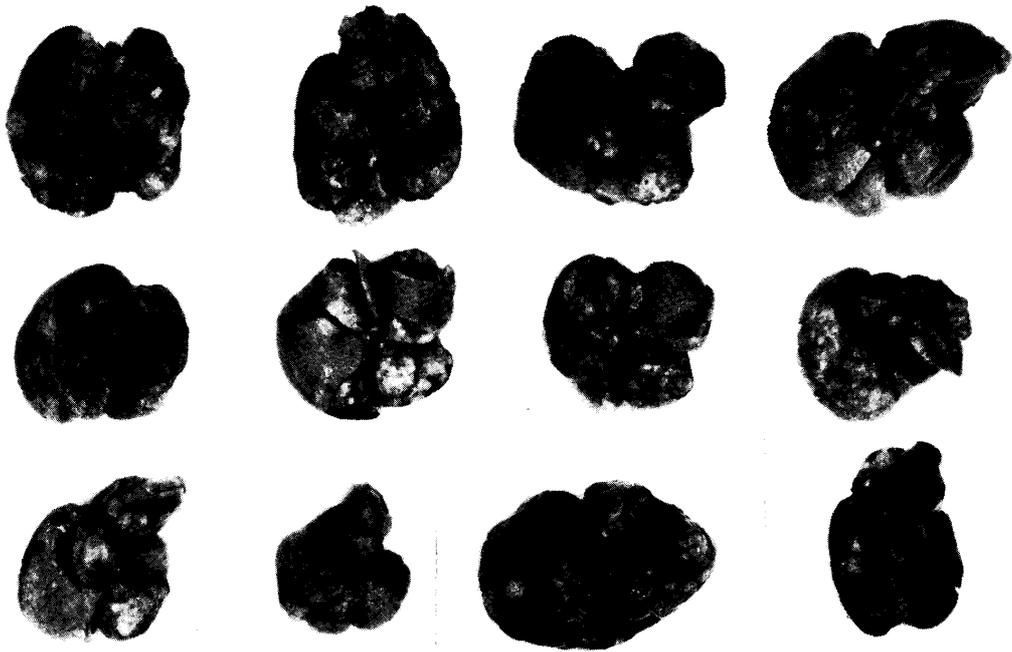
Sex difference in resistance to infection with the larval form of *Echinococcus multilocularis* was investigated in mice of the KK and NC strains. It was demonstrated that females of the KK strain exhibit remarkable resistance to experimental oral infection. The same response, to a lesser degree, was also observed in the NC strain.

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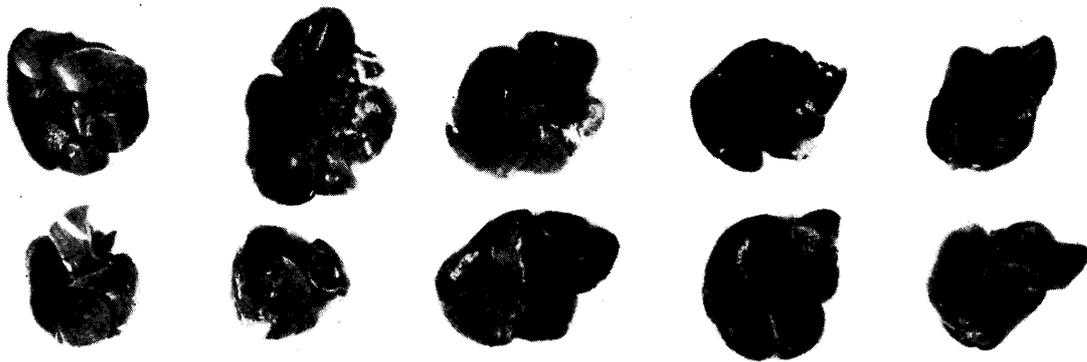
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EXPLANATION OF PLATE

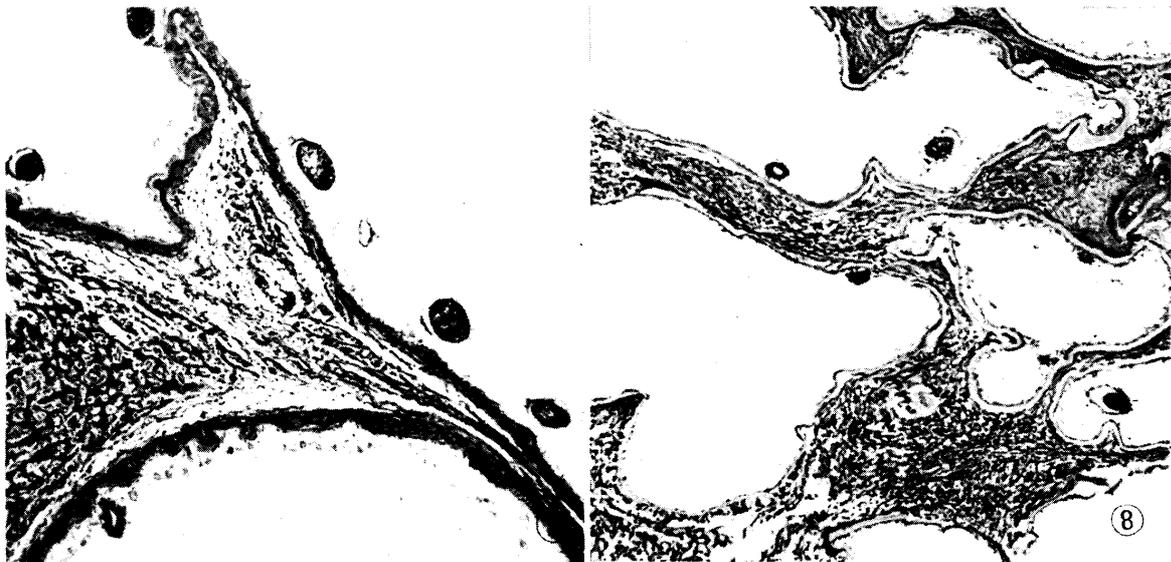
- Fig. 5 Livers from positive males, KK strain × 7/10
- Fig. 6 Livers from positive females, KK strain × 7/10
- Fig. 7 Most advanced male case showing brood capsules and scolices,
KK strain, case No. 2
Hematoxylin-eosin × 90
- Fig. 8 Most advanced female case showing brood capsules and scolices,
KK strain, case No. 8
Hematoxylin-eosin × 90



⑤



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