

# Concentrations and Residues of Gentamicin in the Milk of Dairy Cows After Intramammary Infusion

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## Introduction

Gentamicin is one of the more recent antibiotics introduced into large animal practice (2). It is a broad-spectrum aminoglycoside that is *in vitro* effective against many gram-positive and gram-negative pathogens, including *Pseudomonas aeruginosa*. In a recent report on the *in vitro* antibiotic resistance patterns of bovine mastitis pathogens conducted in the U.S. (3), less than 1% of *Staphylococcus aureus* and *Escherichia coli* strains, and approximately 3% of *klebsiella* strains of udder origin were considered resistant to the drug. Intramammary gentamicin therapy was regarded by several investigators to be of value in the therapy of acute toxic mastitis (5). Intramammary infusion of 100 mg of gentamicin twice a day and intramuscular administration at 4.4 mg/kg twice a day, along with supportive therapy for endotoxemia, was suggested for severe cases of colimastitis (1, 6). Other practitioners (4) regard intramammary treatment alone to be of value.

**Gentamicin is not approved for therapeutic purposes in food animals in the U.S. and a search through the relevant literature has failed to find references on the concentrations and residues of the drug after intramammary treatment. The present report deals with milk gentamicin concentrations after intramammary treatment of variable doses of the drug in normal and inflamed udders.**

## Materials and Methods

Studies were conducted on 23 Israeli-Friesian dairy cows (Group A) and 6 Holstein cows (Group B) located in commercial farms. Cows were toward the end of their lactation period, and their daily milk production ranged between 10 and 16 liters. Cows were milked twice daily at approximately 10 and 14 hours intervals. The udders of all cows secreted macroscopically normal milk. Slight fibrosis was found in one or two quarters of the udders of 4 cows in Group A and 2 cows in Group B. Non-agalactiae streptococci were isolated from quarter milk samples examined bacteriologically which were collected from the slightly fibrotic quarters and from 3 quarters of two other cows, but other types of major udder pathogens were not isolated. With the exception of the infected quarters, which

produced milk containing 700,000 to 1,200,000 somatic cells/ml, the cell count in quarter milk samples collected before the studies started were less than 400,000/ml.

Throughout the studies, the same produce<sup>a</sup> was used for intramammary infusion; it contained 50 mg gentamicin base/ml of a sterile aqueous solution for parenteral injection. The left front (LF) and the right rear (RR) quarters of the udder of Group A cows were infused with 50 mg, 100mg, and 250 mg gentamicin; infusions were given at 3 weeks intervals. The LF and RR quarters of Group B cows were first infused with 500 mg gentamicin. Three weeks later, these quarters were infused with 1 mg of crude *E. coli* endotoxin<sup>b</sup> dissolved in 2 ml of sterile saline solution. Twelve hours and thirty six hours after endotoxin infusion these quarters were treated each time with 500 mg gentamicin.

Quarter milk samples were collected at the end of each milking; they were examined macroscopically for evidence of flakes and clots, and were placed at -20 C° pending antibiotic assay. The udders were palpated by hand and any clinical abnormalities were recorded. Concentration of gentamicin in milk was determined by microbiological assay, using an agar diffusion method (7) which has a sensitivity limit of 0.04 µg gentamicin/ml milk.

## Results

Infusion of gentamicin into the normal quarters did not result in any macroscopical changes in the milk. Slight swelling at the base of the teat which lasted 2 to 3 days was observed upon hand palpation in 3 out of the 6 cows treated once with the 500 mg dose of the drug/quarter.

Concentrations of gentamicin in milk from the treated quarters of the udders of Group A cows after single intramammary infusions of 50 mg, 100 mg, and 250 mg gentamicin/quarter are presented in Table 1, Table 2, and

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(a) *Gentocin, Gentamicin sulfate, Schering Corp. Animal Health Division, Kenilworth, N.J.*

(b) *E. coli-Lipopolysaccharide 026:B6, Difco Lab. Detroit, Mich.*

TABLE 1. Concentration of gentamicin in milk from the left front and rear quarters of 7 cows with normal udders after a single intramammary infusion of an aqueous solution of gentamicin sulfate equivalent to 50 mg gentamicin base/quarter.

Cow	Quarter	Milking after treatment						
		1	2	3	4	5	6	7
concentration, ug/ml								
011	LF	13.0	2.5	0.30	0.10	0.05	—	—
	RR	5.6	1.8	0.17	0.05	—	—	—
1211	LF	6.0	1.9	0.56	0.17	0.10	—	—
	RR	13.0	1.0	0.42	0.18	0.13	—	—
1326	LF	15.0	5.0	4.2	0.17	0.10	—	—
	RR	13.0	2.5	0.22	0.10	0.05	—	—
408	LF	10.8	2.4	0.98	0.12	0.07	—	—
	RR	6.8	2.0	0.62	0.16	0.05	—	—
465	LF	11.0	1.8	0.65	0.12	0.05	—	—
	RR	9.2	1.2	0.38	0.10	0.05	—	—
1213	LF	7.6	1.8	0.70	0.21	0.10	—	—
	RR	8.8	1.4	0.52	0.18	0.08	—	—
1111	LF	12.6	2.4	0.42	0.16	0.05	—	—
	RR	17.0	2.2	0.30	0.12	0.05	—	—
Mean		10.7	2.1	0.75	0.14	0.07	—	—
S.D.		3.47	0.95	1.02	0.04	0.03		

TABLE 2. Concentration of gentamicin in milk from the left front and right rear quarters of 8 cows with normal udders after a single intramammary infusion of an aqueous solution of gentamicin sulfate equivalent to 100 mg gentamicin base/quarter.

Cow	Quarter	Milking after treatment								
		1	2	3	4	5	6	7	8	9
concentration, ug/ml										
1316	LF	15.0	9.6	3.2	0.85	0.12	0.08	0.05	—	—
	RR	4.4	4.0	1.8	0.32	0.10	0.06	—	—	—
280	LF	23.0	2.8	2.0	1.0	0.26	0.12	0.05	—	—
	RR	3.2	2.0	0.62	0.12	0.10	0.06	—	—	—
1154	LF	5.6	2.3	1.2	1.0	0.26	0.12	0.05	—	—
	RR	4.8	1.8	0.46	0.28	0.10	—	—	—	—
1264	LF	7.2	2.7	2.7	0.26	0.12	0.10	—	—	—
	RR	36.0	2.9	2.0	0.38	0.17	0.10	0.06	—	—
1000	LF	12.4	3.0	1.8	0.52	0.14	0.08	0.05	—	—
	RR	13.7	2.8	1.0	0.40	0.10	—	—	—	—
915	LF	18.8	5.5	2.6	1.0	0.06	—	—	—	—
	RR	24.3	4.0	2.7	0.68	0.23	0.12	0.05	—	—
1010	LF	13.8	2.5	1.4	0.96	0.31	0.16	0.08	—	—
	RR	23.6	4.8	2.8	1.0	0.26	0.12	0.08	—	—
15	LF	19.6	2.0	1.0	0.70	0.26	0.10	0.05	—	—
	RR	21.4	6.3	3.6	0.68	0.28	0.12	0.07	—	—
Mean		15.4	3.7	1.9	0.63	0.18	0.09	0.06	—	—
S.D.		9.14	2.05	0.94	0.31	0.08	0.04	0.03		

Table 3, respectively, and the mean values are depicted in fig. 1. Gentamicin was depleted from milk by a single exponential rate which appeared to be dose-independent. Milk drug levels, however, were dose-dependent. Gentamicin residues were not found in any milk sample collected at the end of the 6th milking following the 50 mg dose, the 8th milking after the 100 mg dose, and the 9th milking after treatment with the 250 mg dose.

Drug concentrations in the milk after two intramammary infusions, at 24 hour intervals, of 500 mg gentamicin are given in Table 4. Milk samples collected at the end of the 9th milking after the second treatment contained drug residues which were close to the sensitivity limits of the assay method, and the drug was not detected in any milk sample collected at the 10th milking after the second treatment.

Twelve hours after endotoxin treatment, the infused quarters were hard, swollen, and secreted macroscopically abnormal milk, which contained clots and flakes. Table 5 presents drug levels in milk from the inflamed quarter after two intramammary infusions of 500 mg gentamicin. Drug concentrations were slightly lower than those found in the same quarters after an equal dose was administered prior to endotoxin infusion. The drug was not detected in milk from the inflamed quarters at the 9th milking after the second treatment. Mean data for the 500 mg/quarter dose are given in Fig. 2.

The drug was not detected in milk from the non-treated quarters after treatment with 50 mg, 100 mg, 250 mg, and 500 mg into the normal quarters. Gentamicin residues were detected in milk from the non-treated quarter of all the cows during 3 to 5 milkings after the 500 mg dose was infused into the inflamed quarters, the highest concentrations (0.45 µg/ml) were seen on the first two milkings after the second treatment with gentamicin.

### Discussion

Gentamicin concentrations  $\geq 2.0$  µg/ml were maintained in the milk during the first 3 to 4 milkings after intramammary infusion of 100, 250, and 500 mg gentamicin/quarter. These concentrations are considered to be equal to or higher than the minimal inhibitory concentrations (MIC) of the drug for the majority of gram-negative udder pathogens, including *Pseudomonas aeruginosa* (8). It should be realized, however, that after intramammary antibiotic treatment high milk drug concentrations do not necessarily indicate high udder tissue drug levels and, in effect, the opposite relationship may exist (9). Like other aminoglycoside antibiotics, gentamicin was shown to be slowly absorbed by the udder into the general blood circulation. The distribution throughout the udder of dihydrostreptomycin, which is physicochemically closely

TABLE 3. Concentration of gentamicin in milk from the left front and right rear quarters of 8 cows with normal udders after a single intramammary infusion of an aqueous solution of gentamicin sulfate equivalent to 250 mg gentamicin base/quarter.

Cow	Quarter	Milkings after treatment								
		1	2	3	4	5	6	7	8	9
concentration, ug/ml										
1316	LF	80.0	21.0	8.0	1.7	0.23	0.23	0.13	0.11	—
	RR	6.0	5.2	4.8	0.80	0.18	0.07	0.05	—	—
280	LF	80.0	5.8	4.0	1.9	0.55	0.36	0.17	0.05	—
	RR	5.9	2.7	0.95	0.27	0.19	0.17	0.11	0.10	—
1154	LF	6.3	4.4	3.0	1.9	0.38	0.22	0.10	0.08	—
	RR	5.8	2.5	0.60	0.38	0.06	—	—	—	—
1264	LF	8.9	5.2	5.1	0.60	0.23	0.08	0.07	0.05	—
	RR	50.0	5.7	4.8	0.80	0.09	0.07	—	—	—
1000	LF	30.4	6.6	3.9	1.0	0.24	0.16	0.09	0.06	—
	RR	34.1	6.0	2.4	0.68	0.16	0.11	0.05	—	—
915	LF	42.7	11.0	5.2	0.7	0.36	0.20	0.18	0.06	—
	RR	55.0	9.2	4.7	1.4	0.27	0.15	0.10	0.07	—
1010	LF	27.5	4.8	3.1	1.8	0.33	0.22	0.13	0.08	—
	RR	42.0	9.0	5.2	2.0	0.46	0.20	0.12	0.06	—
15	LF	28.8	4.2	2.2	1.5	0.38	0.17	0.08	0.05	—
	RR	48.5	13.7	7.2	2.0	1.1	0.26	0.10	0.07	—
Mean		35.1	7.3	4.1	1.3	0.33	0.17	0.10	0.05	
S.D.		25.0	4.7	2.0	0.6	0.24	0.08	0.04	0.03	





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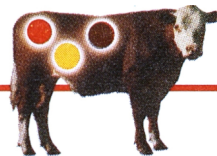
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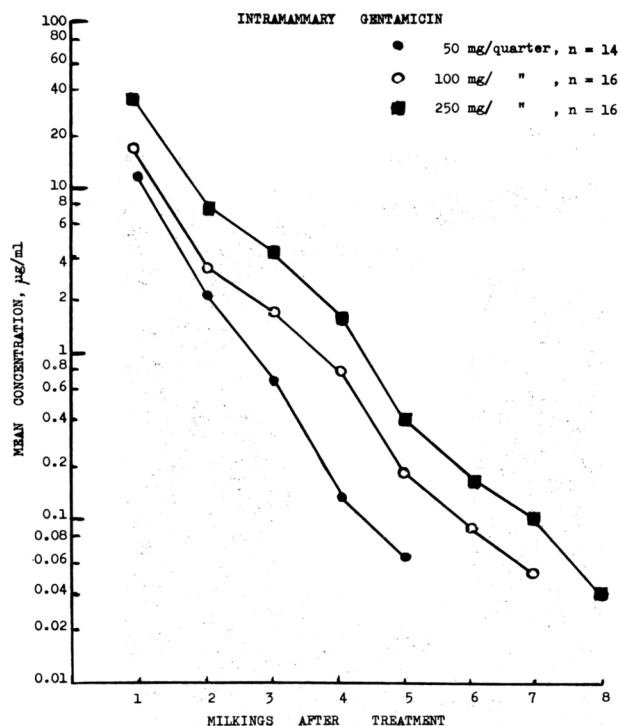


Fig. 1 Mean concentrations of gentamicin in quarter milk samples of cows with normal udders after single intramammary infusion of 50, 100, and 250 mg gentamicin/quarter.

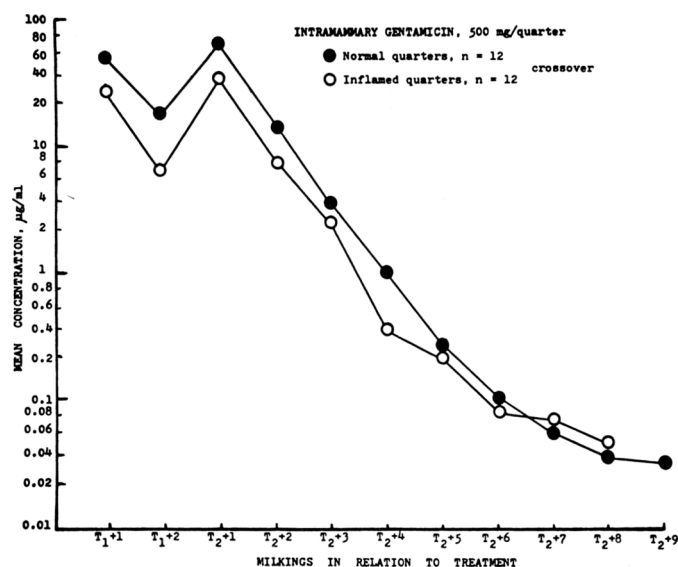


Fig. 2 Mean concentration of gentamicin in milk from normal and experimentally inflamed quarters after 500 mg of the drug were infused twice, at 24 hour interval.

TABLE 4. Concentration of gentamicin in milk from the left front and right rear quarters of 6 cows with normal udders after two intramammary infusions, at 24 hours interval, of an aqueous solution of gentamicin sulfate equivalent to 500 mg gentamicin base/quarter.

Milking in relation to treatment	COW NUMBER														Mean	S.D.
	6583		2622		6437		6689		6881		6672		concentration, µg/ml			
	LF	RR	LF	RR	LF	RR	LF	RR	LF	RR	LF	RR				
T <sub>1</sub> + 1	95.2	87.6	75.6	62.8	19.6	67.6	84.3	48.6	18.5	27.5	32.8	46.0	55.5	26.0		
T <sub>1</sub> + 2	24.3	12.8	38.7	17.6	15.8	11.6	21.8	13.3	7.2	9.6	4.8	24.6	16.8	9.0		
T <sub>2</sub> + 1	102.8	84.7	62.6	43.0	29.0	98.5	121.8	52.0	16.8	37.3	42.0	81.6	64.4	31.8		
T <sub>2</sub> + 2	6.8	9.6	27.6	15.0	9.2	11.5	24.6	14.8	5.6	14.7	8.2	19.3	13.9	6.7		
T <sub>2</sub> + 3	1.3	2.0	8.2	3.8	2.3	5.0	4.3	7.2	2.9	2.0	3.0	6.1	4.0	2.1		
T <sub>2</sub> + 4	0.28	0.56	2.0	2.1	1.4	1.8	0.96	0.82	0.34	0.28	0.23	0.48	0.94	0.68		
T <sub>2</sub> + 5	0.18	0.26	0.92	0.50	0.32	0.28	0.12	0.21	0.10	0.12	0.20	0.10	0.28	0.22		
T <sub>2</sub> + 6	0.12	0.08	0.23	0.08	0.10	0.12	0.05	0.10	0.08	0.08	0.10	0.05	0.10	0.04		
T <sub>2</sub> + 7	0.08	0.06	0.12	0.05	0.08	0.08	0.05	0.05	0.05	0.06	0.08	—	0.07	0.02		
T <sub>2</sub> + 8	0.06	0.05	0.08	0.05	0.05	0.06	0.05	—	—	0.05	0.05	—	0.08	0.01		
T <sub>2</sub> + 9	0.05	—	0.05	—	0.05	0.05	—	—	—	0.05	—	—	0.05	0.00		
T <sub>2</sub> + 10	—	—	—	—	—	—	—	—	—	—	—	—	—	—		

TABLE 5. Concentration of gentamicin in milk from the left front and right rear quarters of 6 cows with experimentally inflamed udders after two intramammary infusions, at 24 hours interval, of an aqueous solution of gentamicin sulfate equivalent to 500 mg gentamicin base/quarter.

Milkings in relation to treatment	COW NUMBER												Mean	S.D.
	6583		2622		6437		6689		6881		6672			
	LF	RR	LF	RR	LF	RR	LF	RR	LF	RR	LF	RR		
	concentration, ug/ml													
T <sub>1</sub> + 1	73.6	38.7	52.3	38.2	9.2	58.6	62.8	22.0	9.8	19.8	21.3	37.5	37.00	20.40
T <sub>1</sub> + 2	11.2	5.2	21.3	6.5	3.6	2.5	11.0	5.8	1.8	4.3	3.6	10.0	7.46	5.08
T <sub>2</sub> + 1	78.0	43.0	44.6	27.4	14.5	78.0	95.0	25.0	6.3	25.0	27.5	48.0	42.7	26.60
T <sub>2</sub> + 2	4.6	4.5	25.0	4.8	4.8	4.5	13.05	6.3	2.2	6.3	4.8	13.6	7.90	6.17
T <sub>2</sub> + 3	0.98	0.80	4.5	1.6	1.8	2.8	2.8	4.6	1.6	1.6	1.2	3.8	2.34	1.28
T <sub>2</sub> + 4	0.15	0.21	1.3	0.80	0.52	0.80	0.37	0.38	0.10	0.15	0.14	0.36	0.44	0.35
T <sub>2</sub> + 5	0.10	0.10	0.14	0.14	0.16	0.26	0.16	0.10	0.05	0.14	0.12	0.15	0.28	0.29
T <sub>2</sub> + 6	0.05	0.05	0.05	0.12	0.13	0.15	0.08	0.05	—	0.08	0.10	0.10	0.09	0.03
T <sub>2</sub> + 7	—	—	—	0.10	0.10	0.12	.05	—	—	—	0.05	0.08	0.07	0.02
T <sub>2</sub> + 8	—	—	—	0.05	0.10	0.05	—	—	—	—	0.05	0.05	0.055	0.001
T <sub>2</sub> + 9	—	—	—	—	—	—	—	—	—	—	—	—	—	—
T <sub>2</sub> + 10	—	—	—	—	—	—	—	—	—	—	—	—	—	—

related to gentamicin, was shown, by contact autoradiographic methods, to be poor and uneven (9). Furthermore, the failure to detect gentamicin in milk from the non-treated quarters after the drug was infused into normal quarters at doses as high as 250 and 500 mg can perhaps be viewed as indirect evidence for the limited distribution of gentamicin throughout the udder.

Distribution of gentamicin in the inflamed udder may be better than throughout the normal parenchyma and a greater proportion of the dose may have been absorbed from the inflamed quarters. This assumption is based on the present findings which indicated that lower milk gentamicin concentrations were found in milk from the inflamed quarters, the drug was depleted from these quarters sooner, and that the drug was detected in milk from the non-treated quarters after the inflamed quarters were infused.

### Summary

The concentrations of gentamicin in milk from normal and experimentally inflamed quarters of the udders of dairy cows were determined after intramammary infusion at dosages ranging between 50 mg and 500 mg gentamicin base/quarter. Gentamicin milk concentrations  $\geq 2.0 \mu\text{g/ml}$  were maintained during 3 to 4 milkings after infusion of 100, 250, and 500 mg gentamicin/quarter. There were indications that the drug was better distributed throughout the inflamed gland than throughout the normal gland. The drug was

detected in milk during 9 milkings after treatment with 500 mg, and during 8 milkings after 250 mg gentamicin were infused.

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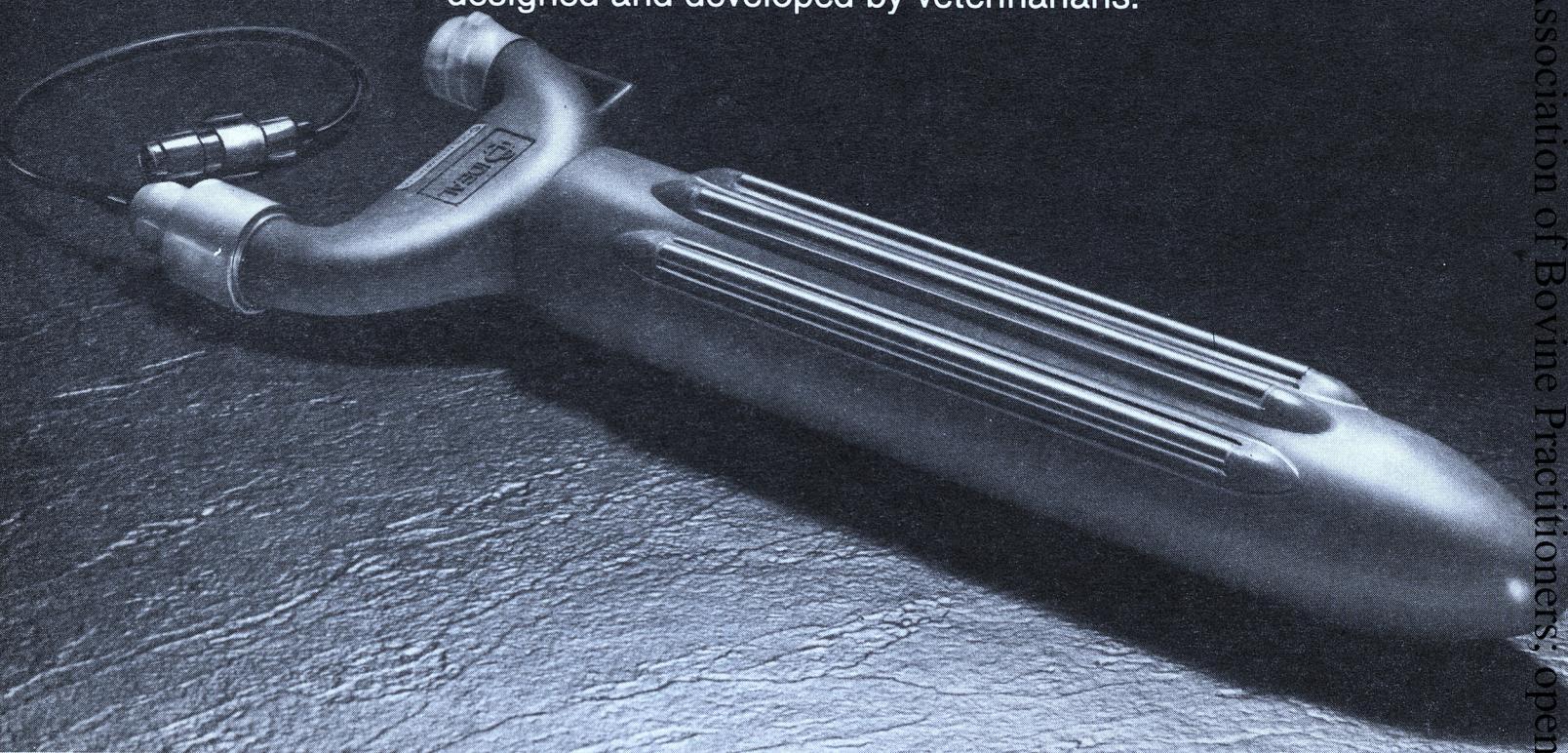
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