

Effect of Tetracycline on Spontaneous Aortic Lesions in Weanling Rabbits (35939)

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Experimental studies in our laboratory suggest a possible role for a milk-related infectious agent in the etiology of medial aortic lesions in rabbits. The "spontaneous," non-lipid, medial lesions found in rabbit aortas have been described previously (1). Fragmentation and disruption of the elastic lamina with accumulation of acid mucopolysaccharide is observed confined to the inner one-half to one-third of the media. Frequently the fragmented portions of the elastic fibers are calcified. The relatively high incidence of these lesions in a large sample of rabbits of different breeds, sexes, ages and geographical sources has also been described (2). The results of that study suggested the need for a more extensive analysis of familial factors in the etiology of these lesions. The establishment of families that are either "resistant" or "nonresistant" to the lesions, based on incidence at 8 weeks of age, was achieved through a careful selection program.

Rabbits from these families were then used to demonstrate the existence of a milk factor related to the incidence of the medial lesion (3). Newborn pups were exchanged, between mothers of unrelated familial lines, for foster nursing. Aortas were examined for lesions when the babies were 8 weeks old. Lesions were found in the aortas of rabbits that had been left with their own mothers of the non-resistant families and also in aortas of rabbits foster-nursed by these does. No lesions were found in aortas of rabbits nursed by resistant does regardless of whether the pups were their own or had been born to does of the nonresistant families. The study reported here was undertaken to test the hypothesis that an infectious agent is related to the incidence of this lesion. Tetracycline was selected as the test drug because of its effec-

tiveness against a broad spectrum of microbial organisms.

Methods. Does of nonresistant familial strains were bred to bucks of their own strain. All does used had previously delivered at least two litters. Tetracycline (66 mg/kg of body wt) was administered orally to the does from approximately 5 days prepartum until 5 days postpartum. A portion of each litter was also treated with the drug at the same dose level for the first 5 days postpartum. Aortas were examined for incidence and severity of medial aortic lesions when the pups were 8 weeks of age. The appearance of a single, grossly visible, lesion was sufficient to categorize an aorta as being involved. The severity of the lesion was based on the area of the arch and ascending aorta involved with the lesion. The only procedural change made for the second phase of this study was the elimination of the treatment of the does. As a control, two resistant does were also tested. One litter from each doe was used in the first phase and only one litter was used in the second phase. No lesions were found in any of these 14 rabbits.

Results and Discussion. The results of this study are outlined in Table I. Previous controls represent 132 pups born, under normal conditions, to the same does used in this study. Almost 76% of these rabbits had lesions with an average severity of 19%. Another control group was developed in the second phase of this study. This is the group in which neither mother nor pup was treated. Of the 23 rabbits in this group 78% had lesions with an approximate average severity of 21%. The lesion frequencies of these control groups were compared by chi-square analysis (Table II) and found to be independent (4). A comparison of the severity of the lesions

TABLE I. Number of Animals With and Without Aortic Lesions and Average Severity of Lesions in Rabbits Treated With Oral Tetracycline.

Treatment	Lesions absent	Lesions present	% with lesions	Av severity (%) $\pm$ SD
Previous controls (PC)	32	100	75.8	18.8 $\pm$ 16.64
First phase-mothers treated (MT)				
Babies not treated (BN)	9	9	50.0	5.3 $\pm$ 6.10
Babies treated (BT)	23	15	39.5	8.4 $\pm$ 7.56
Second phase-mothers not treated (MN)				
Babies not treated (BN)	5	18	78.3	21.4 $\pm$ 22.32
Babies treated (BT)	27	18	40.0	13.1 $\pm$ 12.23
Total controls (PC + MNBN = TC)	37	118	76.1	19.2 $\pm$ 17.57

found in these groups was made by *t* test (4), and no significant difference was found. Since the severity of lesions is most likely a continuous process, we felt that this parametric measure was appropriate, even though our subjective method of measuring the area of involvement seems to give greater stress to the lower values than to the higher ones. On the basis of these results we combined the control groups for further statistical analysis. Chi-square analysis of the four groups: total control (TC), mothers treated with babies not treated (MTBN) and babies treated (MTBT), and mothers not treated with babies treated (MNBT), showed that lesion frequency was highly dependent on tetracycline treatment (99.5 percentile). A comparison of the 76.1% incidence of the total con-

trols with 50.0% for the group in which only the mothers were treated (MTBN) indicates a difference in lesion frequency due to treatment differences at a level between the 95 and 97.5 percentiles. Similar comparisons between controls and each of the two groups in which the babies were treated (MTBT and MNBT), both with frequencies of 40% showed significance at greater than 99.5 percentile. When the babies only treatment group (MNBT) was compared with the group of littermate controls (MNBN) the level of significance was between the 99 and 99.5 percentiles. Comparisons between the three treated groups show no differences. These results indicate a dramatic reduction in the incidence of medial aortic lesions when tetracycline is administered orally to mother, baby, or both. In this respect, treatment of the babies seems to be more effective but not significantly.

However, when we consider the average severity of the lesions (only rabbits with lesions were used in this computation), treatment of the mothers seems to be more effective than treatment of the babies. The mother treated groups, MTBN (av severity 5.3%) and MTBT (8.4%), were both significantly different from the total controls (19.2%) at the 5% level of significance (*t* test). The group in which only the babies were treated (MNBT, 13.1%) was not significantly different from either the total control group or the littermate control (MNBN, 21.4%). The differences between the three treated groups also were not significant.

We can conclude from this study that tet-

TABLE II. Chi-Square Analysis of Lesion Frequencies Shown in Table I.

Groups compared ^a	Chi-square ^b	df ^c
PC, MNBN	0.28	1
TC, MTBN, MTBT, MNBT	31.84	3
TC, MTBN	4.38	1
TC, MTBT	17.47	1
TC, MNBT	19.29	1
MNBN, MNBT	7.72	1
MTBN, MTBT	0.21	1
MTBN, MNBT	0.20	1
MTBT, MNBT	0.03	1

^a See Table I for definition of abbreviations.

^b Chi-square values for 1 degree of freedom for the following percentiles: 3.84, 95; 5.02, 97.5; 6.63, 99; 7.88, 99.5; for 3 degrees of freedom: 12.84, 99.5.

^c Degree of freedom.

racycline does have an effect in reducing incidence and severity of medial aortic lesions in young rabbits. The effect due to treatment of the does is not permanent. Most of the does used in the second phase of this study were also used in the first phase. The earlier tetracycline treatment had no effect on subsequent litters as shown by the evidence that the littermate control group was not different from the previous control group.

The results of this study support the hypothesis that the milk factor reported on previously (3) is probably an infectious agent. Even though only partial effectiveness was achieved in this study, using a dose level on the low side of normal, an important point has been made. Other drugs can now be tested to narrow the spectrum of possible infectious agents; and then higher dose levels can be tested to achieve complete prevention of the aortic lesions.

Summary. Tetracycline was orally adminis-

tered to pregnant does and/or their newborn pups. This treatment was effective in reducing both the incidence and severity of nonlipid, medial aortic lesions in rabbits belonging to families normally highly susceptible to these lesions.

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