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Influence of Sex on the Evolution of a Transplantable Mouse Sarcoma.*

LUDWIK GROSS. (Introduced by H. Goldblatt.)

From the Institute for Medical Research, Christ Hospital, Cincinnati, Ohio.

While the relation between sex and the development of certain spontaneous tumors in mice has been established definitely, there is no convincing evidence of the influence of sex on the evolution of implanted tumors. This report concerns observations which show that under certain specific conditions there is a distinct difference in the behavior of a transplantable sarcoma in male and female mice.

The possibility that a transplantable sarcoma behaves differently in male than in female mice was suggested by our recent experiments performed in this laboratory in which small doses of sarcoma S-37 were injected intradermally. In a small series of animals it was observed incidentally that the occurrence of *takes,* as well as the mortality rate due to the tumor growth, was higher in males than in females. More detailed experiments were undertaken to determine whether this observation could be substantiated in systematic studies.

Experimental. Material and Methods. Tumor: The transplantable mouse sarcoma S-37† was used in our experiments. A subcutaneous tumor, 10 to 14 days old, free from necrotic material, was removed aseptically, weighed, and placed in a sterile mortar. The tumor tissue was cut into small pieces with scissors and then ground thoroughly in a mortar, 0.85% solution of sodium chloride being added to obtain suspensions which varied from 1 to 30%. After 5 to 10 minutes of grinding, the suspension was passed through a fine, 56 to 60 mesh screen having wires 0.01 of an inch in diameter.

Inoculation: 0.02 to 0.04 cc, and occasionally more of this cell suspension was injected intradermally into the freshly shaved skin in the middle of the back of the mouse, a tuberculin syringe and 27-gauge needle being used for the injection. A small wheal appeared in the skin following each inoculation. Intradermal inoculations were employed exclusively, because our previous studies with

* Aided by a grant from Mrs. Francis F. Prentiss.

† We are indebted to Dr. H. B. Andervont, National Cancer Institute, Bethesda, Maryland, for this tumor strain.

Besredka[1-4] showed that the resistance of the mouse to tumor implantation can be demonstrated much better following intradermal inoculation than following inoculation by other routes—an observation which has been confirmed by Andervont.[5]

Several successive series of experiments were performed. In each, groups of male and female mice were injected intradermally with equal amounts of the same tumor-cell suspension. Adult, white mice weighing 18 to 24 g, all of the same stock strain, were used.

Results. Incidence of Takes: Within 5 to 15 days, in most cases, however, within the first week following inoculation, small spherical growths (microscopically typical sarcomata) appeared in the skin of the mice. Table I shows that the incidence of *takes* was substantially higher in males than in females, when diluted tumor-cell suspensions were inoculated.

This difference in the resistance of the males and females toward

TABLE I.
Incidence of "Takes" Using Small Doses of Mouse Sarcoma S-37.

Exp. No.	Tumor suspension		Sex	No. of mice	No. of "takes"	% "takes"
	% conc.	cc inject.				
1	1	.03-.04	♂	18	5	28
			♀	20	2	10
2	2.5	.02-.03	♂	20	5	25
			♀	20	1	5
3	5	.03-.04	♂	13	8	61
			♀	15	7	47
4	5	.02-.03	♂	18	11	61
			♀	20	5	25
5	5	.02-.03	♂	17	16	94
			♀	21	12	57
6	5	.03-.04	♂	10	4	40
			♀	9	0	0
7	10	.03-.04	♂	14	14	100
			♀	14	5	36
8	10	.03-.04	♂	13	11	85
			♀	18	10	56
9	10	.02-.03	♂	21	20	95
			♀	18	18	100
10	10	.02-.03	♂	20	12	60
			♀	20	9	45
11	15	.03-.04	♂	18	17	95
			♀	16	13	81
				—	—	—
Total: Exp. 1 to 11			males	182	123	68
			females	191	82	43

1 Besredka, A., and Gross, L., *Compt. rend. Acad. d. sc.*, 1935, **200**, 175.
2 Besredka, A., and Gross, L., *Compt. rend. Acad. d. sc.*, 1935, **200**, 790.
3 Besredka, A., and Gross, L., *Ann. Inst. Pasteur*, 1935, **55**, 402.
4 Besredka, A., and Gross, L., *Ann. Inst. Pasteur*, 1935, **55**, 491.
5 Andervont, H. B., *Pub. Health Rep.*, 1937, **52**, 1885.

TABLE II.
Incidence of "Takes" Using Medium and Large Doses of Mouse Sarcoma S-37.

Exp. No.	Tumor suspension: % conc.	Tumor suspension: cc inject.	Sex	No. of mice	No. of "takes"	% "takes"
12	20	.03-.04	♂	13	13	100
			♀	15	15	100
13	20	.03-.04	♂	11	11	100
			♀	15	13	87
14	20	.03-.04	♂	9	9	100
			♀	9	9	100
15	20	.02-.03	♂	20	20	100
			♀	21	21	100
16a	20	.02-.03	♂	20	20	100
			♀	22	21	96
16b	30	.10	♂	13	13	100
			♀	13	13	100
17	25	.20	♂	18	18	100
			♀	18	18	100
Total: Exp. 12 to 17			males	104	104	100
			females	113	110	98

intradermal implantation of this tumor was discernible only when the more dilute suspensions of tumor cells were inoculated. As is shown in Table II, there was practically no difference in the incidence of *takes* in males and females when the more concentrated suspensions were inoculated.

Incidence of Spontaneous Regression: The cutaneous tumors produced by intradermal inoculation increased rapidly in size. Usually within 10 to 12 days after inoculation they became red and shiny. At that time they measured 6 to 9 mm in diameter, except when massive doses were inoculated, in which instance the tumors were larger.

In some instances these cutaneous tumors continued to increase in size and finally killed their hosts within 28 to 80 days following inoculation. The average survival time of the male animals was shorter than that of the females.

In other instances, as has been observed previously,[1-4] the tumors disappeared spontaneously within 15 to 30 days following inoculation. The incidence of spontaneous disappearance of these tumors was substantially higher in females than in males in all series where either small or medium-sized doses of tumor-cell suspensions were inoculated (Table III). However, this difference in the incidence of tumor regression in males and females was less striking when very large doses of tumor-cell suspensions were inoculated. This is shown in Experiment 17, and especially in Experiment 16, Table III, in which one group of male and female mice received 0.02 to 0.03 cc

of a 20% cell suspension and another group received 0.10 cc of a 30% suspension of the same tumor. In the first group, the incidence of spontaneous tumor regression was 65% in females as compared with 12% in males. In the second group, in which large doses were inoculated, the incidence of regression was 23% and 8% for the females and males, respectively.

Summary. Experiments reported in this paper suggest that female mice are more resistant than males to an intradermal implantation of a small dose of a mouse sarcoma, as evidenced by the smaller incidence of *takes* and greater incidence of regression in the female animals.

TABLE III.
Incidence of Spontaneous Regression.

Exp. No.	Tumor suspension % conc.	Tumor suspension cc inject.	Sex	No. of mice with tumors*	No. of mice tumors regressed	% regression
1	1	.03-.04	♂	5	2	40
			♀	2	1	50
3	5	.03-.04	♂	4	1	25
			♀	6	5	83
4	5	.02-.03	♂	11	1	9
			♀	3	1	33
5	5	.02-.03	♂	16	2	12
			♀	12	7	58
7	10	.03-.04	♂	14	3	21
			♀	5	4	80
8	10	.03-.04	♂	10	3	30
			♀	9	5	55
9	10	.02-.03	♂	20	4	20
			♀	17	9	53
10	10	.02-.03	♂	12	1	8
			♀	9	3	33
11	15	.03-.04	♂	17	3	18
			♀	11	5	45
12	20	.03-.04	♂	11	1	9
			♀	15	6	40
13	20	.03-.04	♂	11	1	9
			♀	13	5	38
14	20	.03-.04	♂	8	2	25
			♀	8	6	75
15	20	.02-.03	♂	20	2	10
			♀	21	11	52
16a	20	.02-.03	♂	17	2	12
			♀	20	13	65
16b	30	.10	♂	13	1	8
			♀	13	3	23
17	25	.20	♂	18	2	11
			♀	18	5	28
Total of all except 16b and 17:			males	176	28	16
			females	151	81	54

*The numbers of mice in some of the experiments in this table are smaller than those reported in the corresponding experiments in Tables I and II, because some of the mice reported in Tables I and II were sacrificed for microscopic studies of the produced tumors and therefore eliminated from further observation.