

EFFECT OF PREPUBERTY CASTRATION ON SUBSEQUENT CANCER IMPLANTATION.*

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The effect of gonadectomy on the susceptibility of animals to transplanted tumors has remained a disputed subject. Graf¹ could detect no change from the normal rate of growth when a tumor yielding 100 per cent of takes was implanted in castrated males and females; and Rohdenburg, Bullock, and Johnston,² in a similar experiment, noted only a shortening of the latent period. On the other hand, Sweet, Carson-White, and Saxon³ have reported a very considerable increase in susceptibility both as to the number of takes and the growth rate of tumors inoculated into castrated animals. None of these investigators has recorded very completely either the age of the animals or the time between castration and inoculation. Strong,⁴ in an attempt to analyze the time factors involved, noted that mice inoculated 5 to 10 days after castration showed an increased resistance. This persisted but to a diminishing extent until the 16th day. On the other hand, when the inoculation was made during the first 5 days after the operation or later than the 16th day, there was no variation from the normal growth rate of the tumor. Later Strong⁵ noted, incidental to another experiment, that prepuberty castration seemed to result in an increased resistance during the middle age period. This observation,

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¹ Graf, R., *Centr. allg. Path. u. path. Anat.*, 1909, xx, 783.

² Rohdenburg, G. L., Bullock, F. D., and Johnston, P. J., *Arch. Int. Med.*, 1911, vii, 491.

³ Sweet, J. E., Carson-White, E. P., and Saxon, G. J., *J. Biol. Chem.*, 1913, xv, 181.

⁴ Strong, L. C., *J. Exp. Zool.*, 1922, xxxvi, 67.

⁵ Strong, L. C., *J. Exp. Med.*, 1924, xxxix, 447.

however, was based on only nine animals, an insufficient number to be of value, except for the fact that the tumor used for inoculation was one which grows almost without exception in all strains of mice into which it has been inoculated. Leo Loeb⁶ has recorded a similar finding in regard to the development of spontaneous tumors. Utilizing a family of mice which normally gives a very high tumor rate, he observed that animals castrated before 6 months of age had a very much lower cancer incidence than intact animals of the same family, while removal of the gonads at a later period had slight or no effect.

The action of prepuberty castration on a large group of factors, particularly those controlling the development of secondary sex characters, as well as on general metabolism and the interrelation of the glands of internal secretion is perhaps too complex for even an attempted analysis at the present. However, it would seem of importance to gather as much information as possible on the general reactions of the body to such an operation. From this point of view we have undertaken in the following experiments to clear up some of the points as to the effect of castration on the resistance to a transplantable tumor.

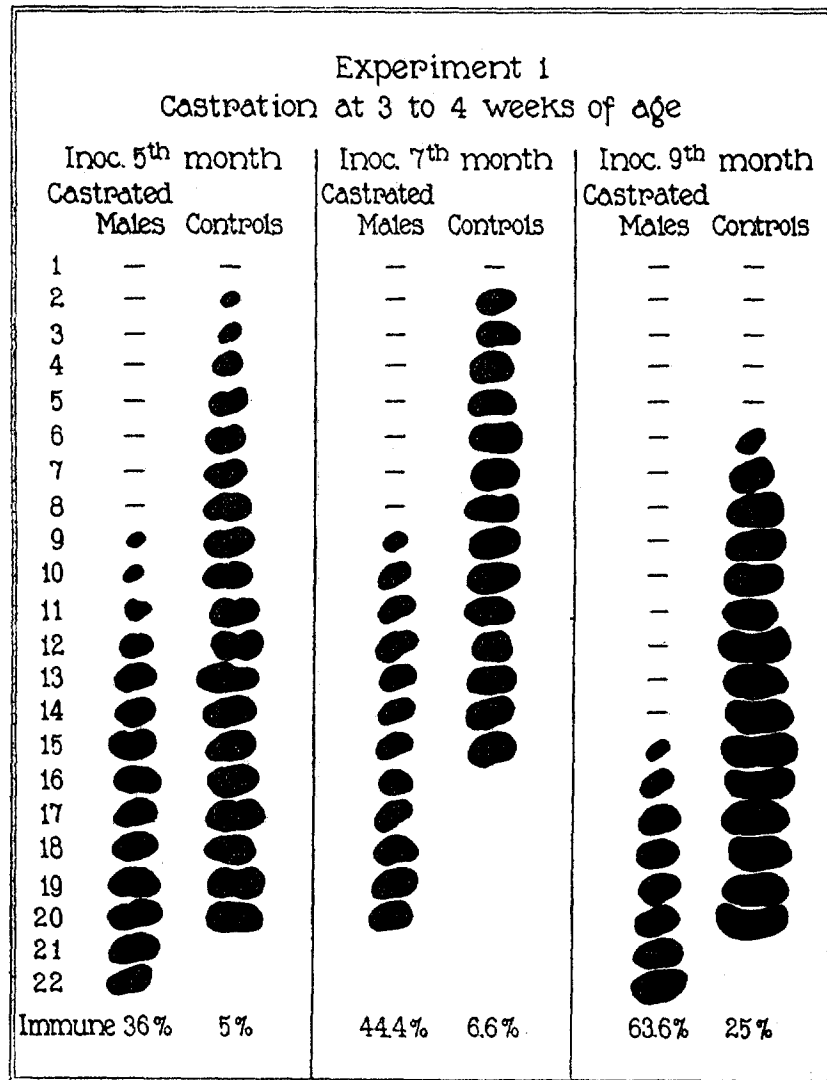
Prepuberty Castration and Resistance to Tumor Transplants.

The first test was designed to determine the effect of castration performed during the first few weeks of life on the resistance to transplantable cancer inoculated at later periods.

Operative Technique.—The animals were etherized, the field of operation shaved in the older animals, and the skin cleansed with alcohol. For castration of the males, an incision was made on either side of the scrotum, the testicle drawn out and a ligature tied so as to include the spermatic cord and blood vessels. The testicle was then severed from its connections and the incision closed with silk sutures and painted over with a thin layer of collodion. For the females a small incision was made in either flank in the ovarian region. The ovary, usually found lying in a bed of fat, was gently pulled through the opening, a ligature tied around the vessels, and then the organ was severed from its connections. There was practically no loss of blood in either of these procedures and only an occasional animal, even among the 3 week old mice, died as the result of the operation.

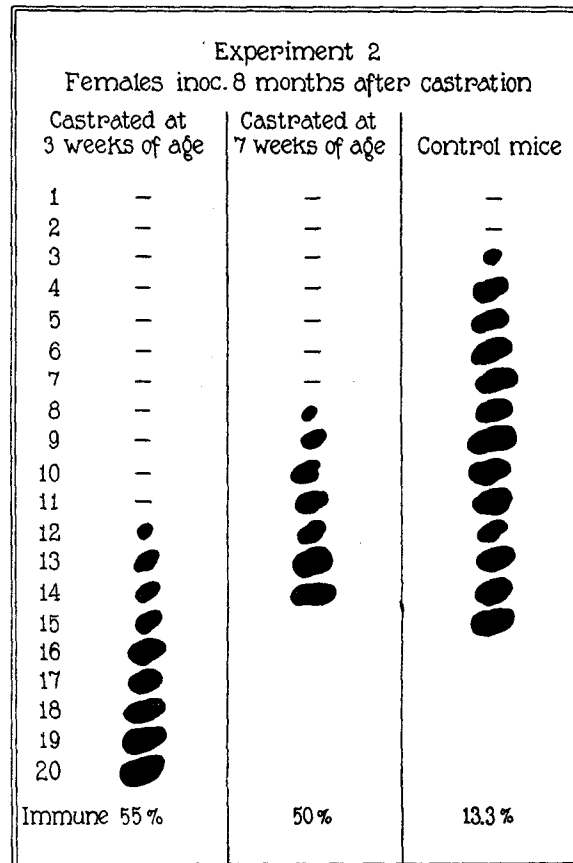
⁶ Loeb, L., *J. Med. Research*, 1919, xl, 477; *J. Cancer Research*, 1924, viii, 274. Lathrop, A. E. C., and Loeb, L., *J. Cancer Research*, 1916, i, 1.

Experiment 1.—This group consisted of 64 male mice castrated at from 3 to 4 weeks of age. These were inoculated with Bashford Tumor No. 63 in groups at 4, 6, and 8 months after the operation. The method employed, as in the experiments which follow, was the usual one of introducing a small bit of the tumor material into the subcutaneous tissue of the groin. In each case a suitable number of controls of about the same age were inoculated with the same tumor. The results are shown in Text-fig. 1.



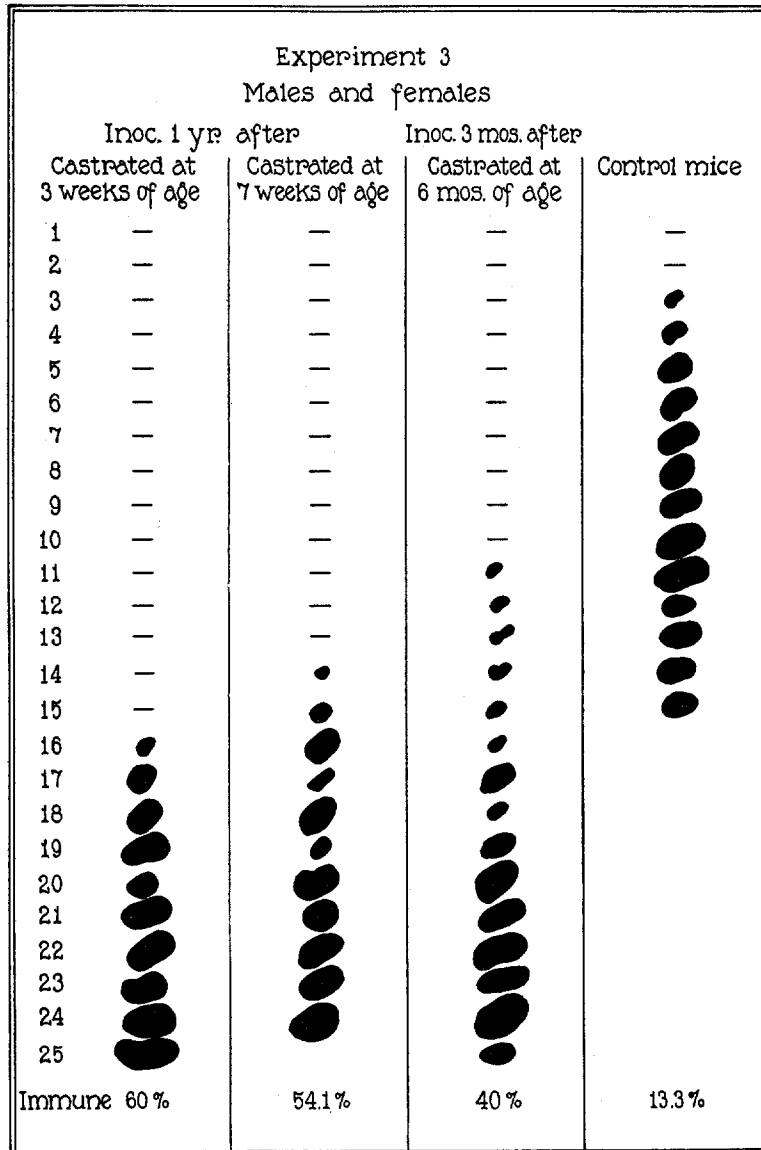
TEXT-FIG. 1.

Experiment 2.—Thirty-four females were castrated between 3 and 7 weeks of age and inoculated 8 months later with the Bashford tumor. For controls fifteen mice of about the same age were inoculated with the same tumor. The results are shown in Text-fig. 2.



TEXT-FIG. 2.

Experiment 3.—In this test there were 49 males and females castrated at 3 and 7 weeks of age and inoculated 1 year later. Another group of twenty-five mice castrated at 6 months of age was inoculated 3 months later. The control group of fifteen mice of about the same age was inoculated with the same tumor. The results are shown in Text-fig. 3.



TEXT-FIG. 3.

Experiment 4.—Eighteen mice, male and female, were castrated at 7 months of age and inoculated with a group of control animals 1 week after the operation. The castrated animals gave 83.4 per cent takes and the controls 88.9 per cent, a difference which would be well within the normal variation of the tumor.

The figures from these four experiments show conclusively that prepuberty castration results in a definite increased resistance of the mice to tumors implanted later in life (Table I). This phenomenon is evident at 3 months after the operation but is more pronounced at the

TABLE I.
Percentage of Immunes.

Ex- per- iment No.	Time of inoculation after castration.....	1 wk.	3 mos.	6 mos.	8 mos.	1 yr.
		<i>per cent</i>	<i>per cent</i>	<i>per cent</i>	<i>per cent</i>	<i>per cent</i>
1	Males castrated at 3-4 wks. of age.....		36.0	44.4	63.6	
	Controls.....		5.0	6.6	25.0	
2	Females castrated at 3 wks. of age.....				55.5	
	“ “ “ 7 “ “ “.....				50.0	
	Controls.....				13.3	
3	Males and females castrated at 3 wks. of age.....					60.0
	“ “ “ “ “ 7 “ “ “.....					54.1
	“ “ “ “ “ 6 mos. “ “.....		40.0			
	Controls.....		13.3			13.3
4	Males and females castrated at 7 mos. of age.....	16.6				
	Controls.....	11.1				

8 and 12 month period. Even the animals castrated at 6 months of age and implanted with tumor 3 months later show a distinct increase over the normal refractiveness but this is not true of castrated adults inoculated 1 week after gonadectomy. There seems to be no difference between the reaction of the females to removal of the ovaries and the males to removal of the testicles.

DISCUSSION.

The susceptibility or resistance of certain physical types of man to disease was at one time much discussed in medical text-books but

with the discovery of bacteria and their relationship to infections this older conception was lost sight of. In recent years the study of the glands of internal secretion has revealed that the various physical types within any given race of man are largely dependent on the interaction of this complex system. Not only this, but the reaction to disease is also influenced. For example, individuals with status thymicolymphaticus are highly susceptible to acute infections and resistant to the development of malignant disease.⁷ Recently Draper⁸ has collected considerable material correlating physical types with susceptibility to certain other disease conditions.

Prepuberty castration has a profound effect on the development of the individual. The variations from the normal are not confined to the more or less superficial secondary sex characters but extend even to the development of the bony structures. It should not be surprising that such altered individuals show variations from the normal in their response to disease processes. Such a variation is evident in the increased resistance to transplanted cancer and the lessened incident of the spontaneous disease exhibited by mice castrated before puberty or in early adult life.

SUMMARY.

Male and female mice castrated during the first 7 weeks of life and implanted with cancer at later periods show a resistance definitely higher than do intact animals of the same age. This increased refractiveness is evident at 3 months after the operation but is more pronounced at 8 months to a year. Even castration in early adult life seems to increase the refractory state to later cancer inoculation. On the other hand, adult mice inoculated within a week after castration show slight if any evidence of increased resistance.

⁷ Bartel, J., Status thymicolymphaticus und Status hypoplasticus, Leipsic and Vienna, 1912.

⁸ Draper, G., Human constitution, Philadelphia, 1924.