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Experimental Study of the Effects of Thyrodectomy on the Growth of a Spindle-Cell Sarcoma in the Albino Rat

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EXPERIMENTAL STUDY OF THE EFFECTS OF THYRODECTOMY ON THE GROWTH OF A SPINDLE-CELL SARCOMA IN THE ALBINO RAT.

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PURPOSE OF PROBLEM

This experiment was conducted in order to study the effect of thyro-parathyroidectomy on the growth of a spindle-cell sarcoma in the albino rat.

LITERATURE

Published reports on the effect of thyroidectomy on neoplastic growth present divergent opinions. Rohdenburg, Bullock, and Johnson,[16] in a series of twenty-nine thyroidectomized rats, found at forty days after inoculation with Flexner-Jobling carcinoma 52% of "cures" against only 16% of regressions in the control group. Murohara[10] reported that removal of the thyroid restrained the growth of a transplantable rabbit sarcoma, while Matsuaka[9] reported an opposite effect. Murohara[11] observed that a chicken sarcoma, implanted in a chick, was first retarded by thyroidectomy but later accelerated.

Shibata[18] studied the effect of thyroidectomy on epitheliamatous growths, induced on the rabbit

ear by painting with a volatile neutral component of coal tar. The animals were thyroidectomized and tar painting began from 7-10 days later. On the basis of a limited number of animals, Shibata believes that the thyroidectomized rabbits showed resistance to epithelial proliferation after tarring. There was no proliferation of the prickle of basal cell layers in the thyroidectomized rabbits. One scientist observed that thyroidectomy had no effect on those tumors in rabbits produced by tar. Karuicki,(4) on the other hand, concluded that thyroidectomy stimulated tar cancer in the rabbit. He used 35 animals in his experiments.

Bischoff and Maxwell(3) inoculated 13 thyro-para-thyroidectomized rats with rat carcinoma 256 and observed no significant difference in percentage of takes, rate of tumor growth, or final mortality as compared with 16 litter male controls. Levine and Kugel(7) showed the average rate of growth of mouse sarcoma 180 in the thyroidectomized mice was greater than in the controls, while the average size of tumors in the thyroidectomized mice was smaller than in the controls. Reiss and Balent(14) observed that the Jensen rat sarcoma grew poorly, or not at all, in thyroidectomized animals. Yana(19) using 12 rats found that

thyroidectomy inhibited the growth of the Honda rat sarcoma.

Nishida[12], in his recent experiments, found the growth of the Kato rabbit sarcoma was somewhat inhibited when the thyroid was removed seven days before tumor inoculation, on day of inoculation, or ten days after inoculation or when the functional activity of the gland had been diminished by X-Ray irradiation.

METHODS AND MATERIALS

Albino rats of Wistar Institute strain were thyro-parathyroidectomized in the usual manner. Inoculations were made bilaterally into the groin pockets, each litter (or group) being inoculated from the same tumor. The implants were made 1 to 197 days after thyroidectomy. The necks of all animals were examined for possible presence of thyroid gland tissue after completion of the experiment.

Observations and measurements of tumor growth were made bi-weekly beginning the fifth day after inoculation to complete regression of tumors or death of the animal. The measurements were made with a caliper in one direction parallel to the surface of the skin.

The tumor used in this experiment is a spindle-cell sarcoma which arose spontaneously in a rat uterus at the Loyola University School of Medicine. It has been transplanted during the past three years into more than 1000 rats. Successfully inoculated tumors in normal animals did not regress. This indicates that a spontaneous regression of this tumor, if it does so occur, is very uncommon.

RESULTS AND DISCUSSION

In table I where the tabulation is by litters (or groups) the four longest post-thyroidectomy groups (1,2,3,6) show 18 successful takes, 14 of which completely regressed. This high-percentage (17%) of regressions in a group where the shortest post thyroidectomy period was 112 days is in contrast with 30% of regressions in all remaining successfully inoculated rats with shorter post-operative periods.

In both groups it is seen that an initial inoculation may fail and a second one succeed; the same is also true for normal control animals. This failure to take may be due to accidental introduction of bacteria into the pocket.

There is an usual tendency for the second inoc-

ulation tumors to regress in the rats with one unsuccessful inoculation. This may be due to the fact that an average of twenty days has been added to the thyroidectomy inoculation period. A possibility exists that the first inoculation has immunized the animal against the progressive growth of a successful tumor take.

In all, 30 litters (or groups) consisting of 237 rats were used. The thyroidectomized rats had 136 takes with 50 complete regressions. In the 40 controls there were 36 takes and no regressions.

In order to establish the regression of the tumor it was necessary that the inoculated tumor progressively reach a size of 13-15 mm. before starting to shrink. Microscopic sections of biopsy snippings of 30 regressing tumors showed sarcoma without exception. The regressions were almost always completely by the end of the third post-inoculation week and were usually accomplished without ulceration. Those few which adhered to the skin became ulcerated. The operated rats that suffered no regressions and the controls died with large ulcerating tumors.

Great importance has been shown on the regression of well established tumors because this phenomenon appears to represent a condition of maximum resistance

to tumor growth. In the thyro-parathyroidectomized rats that showed no regression there is evidence of retarded tumor growth. Thus on the 21st post-inoculation day the average tumor diameter in these rats was 27.8 mm. as compared with 35 mm. in the control animals. Measurements in the 7th, 14th, 28th and 35th post-inoculation days likewise showed larger tumors in the controls.

Greatest resistance to tumor growth as manifested by complete regressions is seen best when all tissues, including the endocrine system, have been adjusted to the thyroid free state. Judging by the inhibiting effect on tumor growth, the best way to arrive at the thyroid free state is to operate at weaning time. This time element may explain the difference in results obtained by Rohdenburg and co-workers, and by Bischoff and Maxwell.

There is considerable evidence that removal of another endocrine gland, the hypophysis, retards and inhibits tumor growth. Hayashi (4) found that hypophysectomy inhibited the growth of a transplantable rabbit sarcoma. Ball, Samuels and Simpson (2) reported a smaller percentage of takes and a retardation of growth of Walker mammary carcinoma in hypophysectomized rats. Reiss, Druckery, and Aschwald (15) hypophysectomized 250 rats and inoculated each with the Jensen sarcoma. In all the rats, tumors grew for three weeks and underwent regression and

absorption. McEven and Thomson[9] found that hypophysectomy retarded but did not prevent growth of Walker rat tumor. Samuels and Ball[17] confirmed this report and recently[1] using autogenous tumors produced by subcutaneous injections of 1, 2, 5, 6 dibenzanthracine in olive oil showed a markedly slower rate of growth following pituitary removal than tumors in control animals. The majority of these workers believed that the retardation of tumor growth in the hypophysectomized animals is dependent upon the absence of the beneficial direct effect of the pituitary secretion. The experimental data, here compiled, suggests the possibility that the lag in tumor growth in hypophysectomized rats may be a secondary effect resulting from the absence of the thyrotropic substance of pituitary origin.

It is impossible to state at the present time what role the absence of the parathyroids played in the results obtained. A review of the literature reveals very little along this line of research. Park[13] concluded from his experiments that parathyroidectomy gave a slight decrease in the rate of growth of the Flexner Jobling rat carcinoma in the first days but later the effect was the same as in the controls. Inuzuka[5] found that a partial extirpation of the parathyroids increased the rate of tumor growth.

CONCLUSION

In a series of thyro-parathyroidectomized rats inoculated with a spindle-cell sarcoma the tumors completely regressed in 37%. In the controls none regressed. The rate of tumor growth was slower in the thyroidectomized animals than in the controls.

TABLE I

tter grp.	Rats in ea. litter e=thyro-parathyroid c=litter-mate	Age at opera. (days)*	Age at inoc. (days)	No. of takes on 1st inoc.	No. of regress-ions of 1st inoc. tumors.	Result of 2nd inoc. when 1st did not take.
	5e	27	150	5e	5e	
	5e	27	180	5e	5e	
	6e	38 (4L)	150	0	0	4T, 3R
	2e	27	60	0	0	2T, 2R
	9 (4e, 5c)	70	71	7 (2e,5c)	0	0
	6e	60 (3L)	257	3e	0	1T, 1R
	6 (3e,3c)	90	91	2(1e,1c)	0	1eT,1R
	5e	95	96	5e	0	1T, 1R
	10e	100 (3L)	105	6e	0	1T, 1R
	6e	105 (4L)	106	6e	0	
	10e		110	6e	0	0
	4e	33	87	3e	0	0
	21 (17e,4c)	26 (5L)	72	9(5e,4c)	0	9T, 9R
	6e	29	81	2e	0	2T, 1R
	3e	40	97	1e	0	0
	7 (6e,1c)	24 (IL)	74	6(5e,1c)	0	0
	8e	31 (5L)	85	3e	0	4T, 4R
	4 (1e,3c)	30	71	2c	0	0
	15e	27 (6L)	36	11e	4e	0
	8e	27 (4L)	71	4e	1e	1T, 1R
	12 (10e,2c)	25	92	3e	1e	1T, 1R
	7e	26	105	1e	0	0
	6e	25	107	5e	0	0
	11e	100 (5L)	102	11e	2e	
	9e	100 (5L)	104	8e	1e	0
	4e	100	133	2e	0	0
	9e	100	112	2e	0	0
	13e	18 (4L)	98	5e	1e	5T, 5R
	12c	(4L)	24	12c	0	
	8c		Adult	8c	0	

Notes on table:

* Averages but in no group is there more than a 10-day variation in age.
L indicates number of litters represented in the group.
T indicates takes
R indicates regressions
e thyroparathyroidectomized rats
c litter male controls

BIBLIOGRAPHY

(1) Ball, Howard A. Samuels, L.T. ..... The Effect of Hypophysectomy on Antagenous Tumors. Am. J. Cancer 26: 547, 1936

(2) Ball, Howard A. Samuels, L.T., Simpson, W. ..... The Effect of the Hypophysectomy on Transplanted Mammary Carcinoma in the White Rat. Am. J. Cancer 16: 351, 1932.

(3) Bischoff, F., Maxwell, L.C. ..... The Effect of Glandular Extirpation upon the Growth of Transplantable Tumors. J. Pharm. and Exp. Therap. 46: 51, 1932.

(4) Hayashi, T. ..... The Relation between the Hypophysis and the Growth of the Tumor. Trans. Jap. Path. Soc. 20: 661, 1930.

(5) Inuzuka, Atsukata ..... Über den Einfluss der Gl. Parathyreoideal auf die Eutwicklung des malignen Tumors. Trans. Japanese Path. Soc. 23: 680, 1933.

(6) Karuicki, Wadaw. ..... Über den Einfluss der Endokrinen Druisen auf das Entstchen und Verhalten der Experimentellen Krebserkraukungeon. Ztschr. f. Krebsforsch 35: 523, 1932.

7) Levine, M., Kugel, V.H. ..... Disturbance of the Thyroid Mechanism and its Effects on Tumor Growth in Mice. Am. J. Cancer 19: 817, 1933.

8) Matsuaka, H. ..... Relation between the Thyroid Gland and Tumor Growth. Trans. Jap. Path. Soc. 20: 657, 1930

9) McEven, C.S., Thomason, D.L. ..... Effect of Hypophysectomy on the Growth of the Walker Rat Tumor. Brit. J. Exp. Path. 14: 384, 1933.

0) Murohara, Nobuzo ..... The Relation between Thyroid Gland and Tumor Growth. Trans. Jap. Path. Soc. 20: 658, 1930.

1) Murohara, Nobuzo .....Implantation of the Chick Sarcoma in the Chick and the Function of the Thyroid Gland. Trans. Jap. Path. Soc. 21: 780, 1931.

2) Nishida, S. ..... An Experimental Study of the Effect of the Thyroid Function to the Growth of Malignant Tumors. Jap. J. Abst. and Gynec. 18: 195, 1935.

3) Park, J. S. ..... On the Relationship between the parathyroid Hormone and the Growth of Rat Carcinoma. Am. J. Cancer 15: 2756, 1931.

4) Reiss, M., Balent, J. ..... Thyroidektomie und Tumorwachstum. Med. Klin. 30: 706, 1934.

(15) Reiss, M., Druckery, H., Aschwald, A. ..... Tumor und Inkretsystem Klin. Wchnschr. 12: 1049 1933.

(16) Rohdenburg, G. L., Bullock, F. D., Johnson, P. J. ..... Effects of Certain Internal Secretions on Malignant Tumors. Arch. Int. Med. 7: 491, 1911.

(17) Samuels, L. T., Ball, H. A. ..... Hypophysectomy and Tumor Growth. Am. J. Cancer 23: 801, 1935.

(18) Shibata, S. ..... Influence of Thyroidectomy on production of epitheliomatous proliferation in rabbits ear. Acta dermat. 14: 143, 1929.

(19) Yana, Y. ..... Wachstumszustand des transplantablen Sarcomi dei Thyreoidektomierten Ratten. Acta dermat. 23: 67, 1934.