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**Resistance of Thyroparathyroidectomized Rats to Growth of a Spindle-Cell Sarcoma.**

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The published reports on the effect of thyroidectomy on neoplastic growth present divergent opinions. Rohdenburg, Bullock and Johnston<sup>1</sup> in a series of 29 thyroidectomized rats found at 40 days after inoculation with Flexner-Jobling carcinoma 52% of "cures" against only 16% of regressions in the control group. Recently Bischoff and Maxwell<sup>2</sup> inoculated 13 thyroparathyroidectomized rats with rat carcinoma 256. Based on a comparison with 16 inoculated litter-mate controls they observed "no significant difference in percentage of takes, rate of tumor growth, or final mortality". Our tumor, a sarcoma, which arose spontaneously in a rat uterus has been transplanted during the past three years into more than 1000 rats. Successfully inoculated tumors in normal rats have not been seen to regress. This is mentioned to indicate that a spontaneous regression of this tumor, if it does occur, is uncommon. The operation consists of complete ablation of thyroid and parathyroid glands. All rats were from our colony of Wistar Institute albino stock. All individuals of the litters, or groups, were inoculated bilaterally into groin pockets from the same tumor and at the same time.

In Table I where the tabulation is by litters the 4 longest post-thyroidectomy ones (1, 2, 3, 4) are placed first. Of the 18 successful takes in this group 14 completely regressed. This high percentage (77%) of regressions in a group where the shortest post-thyroidectomy period was 112 days is in contrast with 25% of regressions in all successfully inoculated remaining rats with shorter post-operative periods. In both groups it is seen that a first inoculation may fail and a second one succeed. This is true also for normal control animals, and sometimes may result from the accidental introduction of bacteria into the pocket. In the rats with relatively short post-thyroidectomy periods there is an usual tendency for the second inoculation tumors to regress. This may be explained in

<sup>1</sup> Rohdenburg, G. L., Bullock, F. D., and Johnston, P. J., *Arch. Int. Med.*, 1911, 7, 491.

<sup>2</sup> Bischoff, F., and Maxwell, L. C., *J. Pharm. and Exp. Therap.*, 1932, 46, 51.

TABLE I.

| Litter<br>or<br>group<br>No. | e = thyro-<br>parathyroid-<br>ectomized<br>rats<br>e =<br>litter-mate<br>controls | Age at<br>oper-<br>ation,<br>days* | Age at<br>inocu-<br>lation,<br>days | No. of takes<br>on 1st<br>inoculation | No. of<br>regressions<br>of 1st<br>inoculation<br>tumors | Result of<br>2nd inocu-<br>lation<br>(when<br>1st did<br>not take) |
|------------------------------|-----------------------------------------------------------------------------------|------------------------------------|-------------------------------------|---------------------------------------|----------------------------------------------------------|--------------------------------------------------------------------|
| 1                            | 5e                                                                                | 27                                 | 150                                 | 5e                                    | 5e                                                       |                                                                    |
| 2                            | 5e                                                                                | 27                                 | 180                                 | 5e                                    | 5e                                                       |                                                                    |
| 3                            | 6e                                                                                | 38 (4L)                            | 150                                 | 0                                     | 0                                                        | 4T, 3R                                                             |
| 4                            | 6e                                                                                | 60 (3L)                            | 257                                 | 3e                                    | 0                                                        | 1T, 1R                                                             |
| 5                            | 4e, 5c                                                                            | 70                                 | 71                                  | 7 (2e, 5c)                            | 0                                                        |                                                                    |
| 6                            | 5e                                                                                | 95                                 | 96                                  | 5e                                    | 0                                                        |                                                                    |
| 7                            | 10e                                                                               | 100 (3L)                           | 105                                 | 6e                                    | 0                                                        | 1T, 1R                                                             |
| 8                            | 6e                                                                                | 105 (4L)                           | 106                                 | 6e                                    | 0                                                        |                                                                    |
| 9                            | 10c                                                                               |                                    | 110                                 | 6c                                    | 0                                                        |                                                                    |
| 10                           | 4e                                                                                | 33 (1L)                            | 87                                  | 3e                                    | 0                                                        |                                                                    |
| 11                           | 17e, 4c                                                                           | 26 (5L)                            | 72                                  | 9 (5e, 4c)                            | 0                                                        | 9eT, 9R                                                            |
| 12                           | 6e, 1c                                                                            | 24 (1L)                            | 74                                  | 6 (5e, 1c)                            | 0                                                        |                                                                    |
| 13                           | 8e                                                                                | 31 (5L)                            | 85                                  | 3e                                    | 0                                                        | 4T, 4R                                                             |
| 14                           | 15e                                                                               | 27 (6L)                            | 36                                  | 11e                                   | 4e                                                       | 0                                                                  |
| 15                           | 8e                                                                                | 27 (4L)                            | 71                                  | 4e                                    | 1e                                                       | 1T, 0R                                                             |
| 16                           | 6e                                                                                | 25 (1L)                            | 107                                 | 5e                                    | 0                                                        |                                                                    |
| 17                           | 11e                                                                               | 100 (5L)                           | 102                                 | 11e                                   | 1e                                                       | 0                                                                  |
| 18                           | 9e                                                                                | 100 (5L)                           | 104                                 | 8e                                    | 0                                                        |                                                                    |
| 19                           | 13e                                                                               | 18 (4L)                            | 98                                  | 5e                                    | 5e                                                       |                                                                    |
| 20                           | 12c                                                                               | (4L)                               | 24                                  | 12c                                   | 0                                                        |                                                                    |
| 21                           | 8c                                                                                |                                    | Adult                               | 8c                                    | 0                                                        |                                                                    |

\*Averages but in no group is there more than a 10-day variation in age.

L indicates number of litters represented in the groups.

T indicates takes.

R indicates regressions.

whole or in part by the fact that an average of 20 days has been added to the thyroidectomy-inoculation period. Altogether 21 litters (or groups) consisting of 184 rats were used. There were 117 takes in the thyroidectomized rats with 39 complete regressions. There were 40 controls with 36 takes and no regressions. Special emphasis has been placed on the regression of well-established tumors because this phenomenon appears to represent a condition of maximum resistance to tumor growth. There is, however, evidence of retarded tumor growth in those thyroparathyroidectomized rats that showed no regression but merely a slowed rate of growth. Thus on the 21st post-inoculation day the average tumor diameter was 27.8 mm. in 13 non-regression thyroidectomized rats against 33 mm. in 9 littermate controls. Measurements on 7, 14, 28 and 35th post-inoculation days likewise showed larger tumors in the controls. To establish that a regression had taken place it was required that the inoculated tumor progressively reach a size of 10-15 mm. before starting to shrink. Biopsy snippings examined microscopically from 30 such tumors in the thyroidectomized rats have shown sarcoma

without exception. The regressions were almost always complete by the end of the third post-inoculation week and were usually accomplished without ulceration, but in a few there was adherence to the skin and ulceration. In the biopsy specimens of regressing tumors the necrosis was often widespread and much greater than that seen in tumors of like size in control animals. The controls have been followed until the animals died or until the tumors became huge ulcerated growths.

Greatest resistance to tumor growth as manifested by complete regression is seen best when all tissues including the endocrine system have been adjusted to the thyroid-free state. Judging by inhibiting effect on tumor growth the best way to arrive at the thyroid-free state is to operate at weaning time. The time element may explain the difference in results obtained by Rohdenburg and co-workers and by Bischoff and Maxwell. There is considerable evidence that hypophysectomy retards tumor growth. Ball and Samuels<sup>3</sup> from observations on the growth of sarcoma produced by 1, 2, 5, 6 dibenzanthracene in hypophysectomized rats believe that the retardation of tumor growth is dependent upon the absence of the beneficial direct effect of pituitary secretion. Our experimental data as now developed suggest the possibility that the lag in tumor growth in rats from which the pituitary has been removed may be a secondary effect resulting from the absence of thyrotropic substance of pituitary origin. After both hypophysectomy and thyroidectomy growth of the animal is retarded and in both instances the question arises as to the effect of a diminished somatic growth on the inoculated tumor. McEwen and Thomson,<sup>4</sup> who disagree with the conclusion of Ball and Samuels found that the retardation of tumor growth was about the same in hypophysectomized rats and in rats on a semistarvation diet. They made the further observation that malnutrition is not a cause of tumor regression. Working with a Walker tumor that rarely regresses they found 1 regression in 23 control rats but none in 23 rats on a semistarvation diet. Bischoff, Maxwell and Ullmann<sup>5</sup> have retarded body growth by starvation and by poisoning with synthalin and heavy metals with no effect on tumor growth. Rous<sup>6</sup> found that the Flexner-Jobling rat carcinoma grew with equal rapidity in hosts emaciated by a restricted diet and in controls. In a series of young rats (not tab-

<sup>3</sup> Ball, H. A., and Samuels, L. T., *Am. J. Cancer*, 1936, **26**, 547.

<sup>4</sup> McEwen, C. S., and Thomson, D. L., *Brit. J. Exp. Path.*, 1933, **14**, 384.

<sup>5</sup> Bischoff, F., Maxwell, L. C., and Ullmann, H. J., *Science*, 1931, **74**, 16.

<sup>6</sup> Rous, P., *J. Exp. Med.*, 1914, **20**, 433.

ulated) in which the body weights have been held constant by heavy feeding with desiccated thyroid we found that our sarcoma in all rats increased in size until the animals died.

In our entire series of thyroparathyroidectomized rats inoculated with a spindle-cell sarcoma the tumors completely regressed in 33.3%. In controls none regressed.

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#### Gonadotropic Excretion in the Male Castrate. Effect of the Male Sex Hormones.

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Our studies on female castrates showed a great increase in gonadotropic hormone excretion in the urine.<sup>1</sup> Two male castrates have now been investigated. In both patients bilateral orchidectomy had been performed for tuberculous epididymitis. In the first patient (L.D.) castration was performed 5 years ago, in the second (L.S.) 8 years ago. In the 1st patient, within 1 week of the operation, severe flushes and sweats occurred and have persisted. The 2nd has suffered from no symptoms.

Gonadotropic hormone urine determinations by the acetone precipitation method<sup>2</sup> were performed on L.D. for a preliminary period of 22 days. Both follicle stimulating and luteinizing factors were found in the urine. The daily output of follicle stimulating factor varied from 4 to 18 rat units per day; of lutein factor from 4 to 7½ rat units per day. In the second patient, 5 random 48-hour urine specimens were examined. The daily output of lutein factor varied from 4 to 8 R.U. The gonadotropic hormone effects produced in the test rats by the urine of these male castrates differed in no way from the effects obtained from the urine of female castrates.

In female castrates the administration of 20,000 to 25,000 R.U. of Progynon B regularly produced prompt disappearance of the

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<sup>1</sup> Frank, R. T., Salmon, U. J., and Friedman, R., *PROC. SOC. EXP. BIOL. AND MED.*, 1935, **32**, 1666.

<sup>2</sup> Frank, R. T., and Salmon, U. J., *PROC. SOC. EXP. BIOL. AND MED.*, 1935, **33**, 311.