Studies on the Pathogenesis of Neoplasms by Ionizing Radiation

II. Neoplasms of Endocrine Organs*

NECHAMA HARAN-GHERA,† JACOB FURTH,‡ RITA F. BUFFETT, and KENJIRO YOKORO

(Children's Cancer Research Foundation, Children's Medical Center, the Department of Pathology, Harvard Medical School, and Cancer Research Institute of the New England Deaconess Hospital, Boston, Mass.)

In a study on the pathogenesis of pituitary tumor induction by ionizing radiation, data were collected on the development of thyroid, adrenal, ovarian, and mammary gland tumors (adenocarcinomas and sarcomas) in mice exposed to x-rays and neutrons under various experimental conditions.

This communication analyzes these data and compares them with those obtained in the same strain of mice exposed to an atomic detonation (7), to be referred to as Operation Greenhouse (O.G.).

The induction rates of some tumors are described as low, and thousands of animals are required for statistically conclusive findings. Some values are obviously highly significant; others are not. The observations reported here will furnish leads for such studies on the induction of thyroid and adrenal tumors. The statistical evaluation of the data will be the concluding paper of this series. There is no accepted formula to analyze data of the type reported here. Those designed by our two consultants differ and are also subject to criticism. Corrections for mortality from various causes have to be applied, and the tumor incidence has to be assessed in relation to age.

MATERIALS AND METHODS

The experimental set-up, materials, and methods were described in the first paper of this series, which deals with longevity and with the pathogenesis of pituitary tumors (6).

1. Supported by the Atomic Energy Commission and National Institutes of Health.
2. Research Fellow of the Damon Runyon Cancer Research Foundation; present address, Weizmann Institute of Science, Rehovoth, Israel.
3. Present address: Roswell Park Memorial Institute, Buffalo, N.Y.

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Female mice of the LAF1 strain, about 7–9 weeks of age, were irradiated and observed until natural death. The groups, each including slightly over 100 mice, were as follows:

1. Head x-ray irradiation: 475 rad (Xh4.8) and 1235 rad (Xh12).
2. Abdomen x-ray irradiation: 380 rad (Xa3.8) and 712 rad (Xa1.7).
3. Total-body x-ray irradiation: 380 rad (Xt3.8) and 452 rad (Xt4.5).
4. Total-body neutron irradiation: 148 rad (Nt1.5) and 176 rad (Nt1.8).
5. Total-body 380 rad x-ray irradiation and bilateral adrenalectomy 4–8 weeks after irradiation (Xt3.8 adrex 2).
6. Total-body 452 rad x-ray irradiation and unilateral adrenalectomy at about 6 weeks after irradiation (Xt4.5 adrex 1).
7. Bilateral ovariectomy followed by 452 rad total-body x-ray irradiation (Xt4.5g) after an interval of 4 weeks.
8. Fractionation of total-body x-ray irradiation in three equal doses of 150 rad, given in three consecutive weeks (Xt4.5).
9. Control groups, built up parallel with irradiation, consisting of untreated normal (Xo) and bilaterally adrenalectomized mice (Xo adrex 2).

RESULTS AND DISCUSSION

THYROID TUMORS

(Table 1, Chart 1)

One of the novel findings in the present study is the high neutron RBE (relative biological effectiveness in relation to x-rays or γ-rays) for thyroid

1. $r \times 0.95 = \text{rad}$.
2. Concerning care of adrenalectomized animals, see reference 6. Percorten (microcrystals of desoxycorticosterone trimethylacetate) was generously supplied by Drs. Robert Gaunt and A. A. Renzi, of Ciba Pharmaceutical Products, Inc.
tumor induction. No thyroid tumors occurred among the controls and x-radiated mice (single dose) of the present series, and, in contrast, 3.4 and 7.3 per cent of mice exposed to neutrons developed tumors.

Among mice exposed to atomic detonation (228–712 rad of predominantly γ rays), the tumor incidence ranged from 0.0 to 1.0 per cent (7). In a small series of lead-shielded mice of the O.G. series (exposed predominantly to neutrons) the thyroid tumor incidence ranged from 1.8 to 4.4 per cent (7). The combined observations indicate that neutrons have a very high RBE for thyroid tumor induction, the threshold dose being about 140 rad and tumor frequency increasing with the dose.

The group receiving the fractionated dose (3 × 150 rad) had the shortest mean survival time of unoperated groups of mice exposed over the entire body, and therefore any correction for longevity would increase the observed figure (1.7 per cent) for tumor incidence.

Among the partially shielded x-radiated animals a conspicuous increase in tumor frequency (4.2 per cent) occurred only in those exposed to 475 rad over the head and neck regions, including the thyroid, pituitary, and hypothalamus.

In the groups subjected to endocrine stresses, tumors occurred at greatest frequency in the bilaterally adrenalectomized animals, even though their mean survival time was the shortest of all groups. In bilaterally gonadectomized mice, the tumor incidence was 2.5 per cent. It is conceivable that these stresses facilitate thyroid tumor development, but much larger groups are required to test this possibility.

Gross changes associated with thyroid tumors.—No distinct morphological hormonal effects were observed in most mice with thyroid tumors. The pituitaries appeared normal. Ovarian tumors were equally common in the total-body irradiated mice with and without thyroid tumors. In the head-neck irradiated group in which thyroid tumors were frequent, ovarian tumors were very rare. Thus, tumorigenesis in these organs appears to occur independently. The mammary glands and adrenals were similar in mice with and without tumors. In the head-neck irradiated group in which thyroid tumors were frequent, ovarian tumors were very rare. Thus, tumorigenesis in these organs appears to occur independently. The mammary glands and adrenals were similar in mice with and without tumors.

**Histologic characteristics.**—The tumors were small and usually confined to one lobe. Most observed tumors were adenomas, either solid (Fig. 1) or papillary, or mixed (Figs. 2, 4–6). The tumor cells were of small or medium size and fairly normal in appearance. There was little pleomorphism, and mitotic figures were infrequent. The greatest degree of "dedifferentiation" appeared in tumors with papillary struc-

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**TABLE 1**

<table>
<thead>
<tr>
<th>GROUP*</th>
<th>NO. IN GROUP</th>
<th>TUMORS</th>
<th>MEAN SURVIVAL (WEEKS)</th>
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<tr>
<td>X₀</td>
<td>190</td>
<td>0</td>
<td>102.5</td>
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<tr>
<td>Nt₁,5</td>
<td>191</td>
<td>4</td>
<td>3.4</td>
</tr>
<tr>
<td>Nt₁,6</td>
<td>109</td>
<td>8</td>
<td>7.3</td>
</tr>
<tr>
<td>X₁₄,₅</td>
<td>134</td>
<td>0</td>
<td>76</td>
</tr>
<tr>
<td>X₁₄,₆</td>
<td>117</td>
<td>2</td>
<td>1.7</td>
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<tr>
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<td>1.6</td>
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<td>66</td>
</tr>
<tr>
<td>X₅₄,₆</td>
<td>121</td>
<td>5</td>
<td>4.2</td>
</tr>
<tr>
<td>X₆₂</td>
<td>113</td>
<td>1</td>
<td>0.9</td>
</tr>
<tr>
<td>X₀ adrex 2</td>
<td>129</td>
<td>0</td>
<td>85.5</td>
</tr>
<tr>
<td>X₁₄,₅ adrex 2</td>
<td>140</td>
<td>4</td>
<td>2.9</td>
</tr>
<tr>
<td>X₁₄,₅ adrex 1</td>
<td>120</td>
<td>2</td>
<td>1.6</td>
</tr>
<tr>
<td>X₁₄,₅ g</td>
<td>120</td>
<td>3</td>
<td>2.5</td>
</tr>
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* The following abbreviations are used in designating the groups:
  X = x-radiation.
  t = total-body irradiation.
  g = gonadectomy
  a = irradiation over the abdomen, including the ovaries and adrenals
  N = neutron radiation
  adrex 1 = unilateral adrenalectomy
  adrex 2 = bilateral adrenalectomy

Figures following the group designation indicate the dose in rad/100; eg. 4.5 = 450 rad.

† Surviving 6 months.

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**Chart 1.**—Number of thyroid tumors in relation to time (in weeks) after irradiation. One square represents a tumor. The arrows indicate the mean life span for each group. For explanation of symbols, see footnote to Table 1.
tures, some of which may be interpreted as well
differentiated adenocarcinomas (Fig. 3).

ADRENAL TUMORS
(Table 2, Chart 2)

Both cortical and medullary adrenal tumors were observed.

No adrenal tumors were found in the controls of the present series and only 0.9 per cent in the controls of the O.G. series. This difference can perhaps be explained in part by the greater longevity of the O.G. series, in which the first adrenal tumors occurred at 150 weeks of age among the unirradiated control females. This may be caused, in part, by failure to record minute cortical nodules as tumors in the present series. There is no sharp borderline between nodular hyperplasia and adenoma. The histogenesis and character of radiation-induced tumors and the delineation of hyperplasia and adenoma require a special study.

TABLE 2
ADRENAL CORTICAL AND MEDULLARY
ADENOMA INDUCTION

<table>
<thead>
<tr>
<th>GROUP*</th>
<th>NO. IN GROUP</th>
<th>CORTICAL TUMORS</th>
<th>CHROMAFFINE TUMORS</th>
<th>MEAN SURVIVAL (WEEKS)</th>
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<tr>
<td></td>
<td>No.</td>
<td>Per cent</td>
<td>No.</td>
<td>Per cent</td>
</tr>
<tr>
<td>Xo</td>
<td>190</td>
<td>4.3</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>N1.3</td>
<td>121</td>
<td>3.3</td>
<td>4</td>
<td>3.3</td>
</tr>
<tr>
<td>N1.5</td>
<td>124</td>
<td>2.7</td>
<td>4</td>
<td>3.6</td>
</tr>
<tr>
<td>X2.8</td>
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<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>X3.4</td>
<td>117</td>
<td>0.8</td>
<td>2</td>
<td>1.7</td>
</tr>
<tr>
<td>X4.9</td>
<td>127</td>
<td>0.8</td>
<td>1</td>
<td>0.8</td>
</tr>
<tr>
<td>X5.1</td>
<td>118</td>
<td>2.5</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>X6.2</td>
<td>199</td>
<td>5.0</td>
<td>4</td>
<td>3.3</td>
</tr>
</tbody>
</table>

* For definition of abbreviations, see Table 1.

No tumors were observed in the total-body x-radiated mice. In contrast, the adrenal cortical tumor incidence was 3.3 and 2.7 per cent, respectively, in the two groups exposed to total-body neutrons. This is in agreement with the findings of the O.G. series indicating a high RBE value of neutrons. However, in the O.G. series adrenal tumors were also recorded in mice exposed to γ rays. The O.G. series indicates that the threshold of adrenal tumor-inducing dose of neutrons is below 100 rad.

Adrenal tumors occurred in greatest frequency in the ovariectomized total-body irradiated animals. It has now been well established (see 13) that ovariectomy early in life is followed by the development of adrenal tumors. These tumors secrete not corticoid but gonadal hormones (3, 13). Induction of these tumors varies greatly with different strains. In most strains of mice adrenal tumors do not occur if ovariectomy is performed during adult life. In the present series no controls were set up for the effects of ovariectomy without irradiation. However, in a parallel series done with Dr. K. H. Clifton, groups of LAf mice were gonadectomized at neo-natal age. None of the 21 females and thirteen males in this series developed adrenal tumors. Thus, the present findings strongly suggest that gonadectomy greatly enhances the likelihood of adrenal tumor development following irradiation. Both experimental findings and theoretical considerations support this view. Adrenal tumors were also found in mice receiving 712 rad over the abdomen (including the adrenals).

Both medullary and cortical tumors were expansile, replacing each other but not invading distant organs.

Figure 7 shows a small tumor nodule of the adrenal cortex which, on the basis of histologic criteria, might be judged as a carcinoma in situ (Fig. 8). The majority of the tumors were, however, benign-appearing. Figures 9–13 show the various morphologic appearances encountered. Figure 9 resembles granulosa cells, and Figures 10 and 12 luteoma cells. It is not possible, however, to judge on the basis of morphologic appearances whether these tumors secrete gonadal hormones, as described by Woolley et al. (13), or adrenal corticoids, as described by Cohen et al. (3). Most tumors were of the type described by Woolley et al.; that shown in Figure 11 resembles very closely that described by Cohen et al.

The adrenal medullary tumors are illustrated in Figures 14–17. The chromaffinomas were invariably benign-appearing. In those shown in Figures 14 and 15, there were transitional forms between cells that were intensely chromaffine and those...
that were not. Entirely nonchromaffine medullary tumors are illustrated in Figures 16 and 17.

One chromaffine tumor was transplanted in three successive generations and took in all animals. The original tumor was exceedingly toxic to doses of about 40 rad or more will develop these tumors (8). If there is some linearity in response, it “plateaus” at a very low dose.

Spontaneous ovarian tumors are rare. In the literature, the reported incidence among the con-

<table>
<thead>
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<th>TABLE 3</th>
<th>OVARIAN AND MAMMARY GLAND TUMOR INCIDENCE</th>
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<tbody>
<tr>
<td><strong>GROUP</strong>*</td>
<td><strong>NO. IN</strong></td>
</tr>
<tr>
<td><strong>GROUP</strong>*</td>
<td><strong>GROUP</strong></td>
</tr>
<tr>
<td>Xo</td>
<td>190</td>
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<tr>
<td>Xh.5</td>
<td>121</td>
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<td>127</td>
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<td>118</td>
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<td>129</td>
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<tr>
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<td>120</td>
</tr>
<tr>
<td>Xh.5</td>
<td>120</td>
</tr>
</tbody>
</table>

* For definition of abbreviations, see Table 1.

after intramuscular implantation, all animals developing severe respiratory distress and many dying within a few hours. Therefore, the tumor cell suspension was diluted considerably or the tumor fluid (presumably containing adrenalin or nor-adrenalin) was removed. Unfortunately, on subsequent subpassages the tumor became highly malignant and lost affinity for chromation before hormonal assays could be undertaken. In the original passage the tumor became palpable after about 5 months, while in subsequent subpassages the malignant variant developed very large tumors within about 1 month.

**OVARIAN TUMORS**

(Table 3, Chart 3)

Table 3 suggests that ovarian tumors are induced by direct irradiation of the ovary. The abdomen-irradiated animals developed as many ovarian tumors as those irradiated over the entire body. Since the immediate inciters of ovarian tumors are pituitary gonadotropins (see ref. 8), it is noteworthy that shielding of the head and neck, i.e., the pituitary region, failed to alter the ovarian tumor incidence. The tumor incidence in the abdomen-shielded groups approximated that in unirradiated mice.

One remarkable feature of ovarian tumorigenesis is that over 50 per cent of animals exposed...
trols is often high, due to inclusion of hematomas and cysts among the tumors. The latter occur frequently in unirradiated mice. In many ovarian tumors, notably in luteomas, the prominent gross feature is that of hematoma. It appears from earlier studies that over 75 per cent of the irradiated mice living longer than about 1½ years develop ovarian tumors (luteomas, granulosa tumors, and tubular adenomas). In normal mice that were carefully studied, the incidence of similar tumors did not exceed a few per cent.

In order to ascertain the threshold of the modifiers of tumor frequency and the RBE of neutrons and x-rays, much lower doses of irradiation (14-38 rad) should be utilized than those used in this study.

**ADDITIONAL COMMENTS**

**Thyroid tumors** are induced by neutrons. Total-body neutron irradiation (176 rad) produces about 7.5 per cent of thyroid tumors; total-body x-ray irradiations are only slightly effective. Two thyroid tumors were found in the fractionated (1.7 per cent) and none in the single dose x-radiated group.

In the head-irradiated series five mice (4.2 per cent) developed thyroid tumors, much more than in any of the other x-radiated groups. Although this number is small, it does not seem accidental that the frequency of both thyroid and thyrotropic tumors was increased in this group. It seems probable (as suggested by the work of Gorbman and Edelmann [9]) that combined thyroid and pituitary irradiation causes a derangement of thyroid-thyrotrope homeostasis resulting in the development of both thyroid tumors and thyrotropic pituitary tumors. The frequency of these neoplasms is expected to be dependent on the quantity of irradiation received by these two organs, respectively. Complete destruction of the thyroid resulted in the development of thyrotropic pituitary tumors in almost every mouse thus far studied (5).

Thyroid tumors occurred in the irradiated adrenalectomized but not in the unirradiated adrenalectomized mice. The interrelationship between thyroid and adrenals, as well as between thyroid and gonads with respect to tumorigenesis, remains to be explored. Administration of thyroid hormone inhibits both corticosteroid secretion and growth of adrenal tumors, and thyroidectomy stimulates growth of corticoid-secreting adrenal tumors (A.I. Cohen, to be published). Mice bearing thyrotropic pituitary tumors have enlarged adrenals and stimulated gonads (5).

With respect to adrenal tumorigenesis the following leads have been found: (a) a high RBE for neutrons vs. x-rays; (b) the possibility that induction of adrenal tumors by gonadectomy is enhanced by irradiation of the adrenals; and (c)
both medullary and cortical tumors are induced by irradiation.

In following up these observations, localized adrenal irradiation, as well as pituitary irradiation and the modifying effect of various pituitary hormones on adrenal tumorigenesis, should be considered. The adrenal tumors induced in whole-body irradiated animals proved to be gluco-corticoid-secreting (1, 3, 4), while the adrenal tumors arising after gonadectomy appeared to be gonadal hormone-secreting (13). Corticotropins and gonadotropins, respectively, are expected to play a significant role in the pathogenic mechanisms of induction of these tumors. An adrenal tumor arising in the glomerulosa and secreting aldosterone has thus far not been identified in animals. The chief hormone of the adrenal cortex of mice is corticosterone, which has both gluco- and mineralo-corticoid activity, and the individuality of glomerulosa and fasciculata indicated by the studies of Deane and Greep (see 11) calls for renewed investigations.

A novel lead is the induction of chromaffine tumors by ionizing radiation and the high neutron RBE. This presents a new problem, since the chromaffine cells are known not to be under endocrine control. Most puzzling is their occurrence in the X1/4 (fractionated) group. In general, there seems to be a parallelism between induction of cortical and medullary adenomas. Adrenal tumorigenesis requires further investigation. Tumors of the adrenal cortex and medulla are different from the standpoint of both hormonal secretion and pathogenesis. If they are induced by direct radiation effects, tumors might also be expected at other sites of chromaffine cells.

Ovarian tumors.—The prime alteration was at first thought to reside in cells and to be analogous to somatic mutation. Later, through the work of Gardner, Kirschbaum, Kaplan, and their associates (see 8), the importance of stimulation by gonadotropic hormones of the pituitary became evident. Ovarian tumorigenesis by irradiation was likened to that occurring following transplantation of the gonads into the spleen of castrates (see 2, 8). The present series points to both factors: irradiation causes an alteration in the ovary which makes this organ unable to maintain homeostasis with its stimulating pituitary hormone. The primary change is an alteration in the ovary. Transplantation of the ovary into the spleen of castrated animals results in a high gonadotropin level. The tumors so induced are at first fully dependent on gonadal stimulating hormones (10). However, after about 6 months they give rise to autonomous variants. In contrast, all ovarian tumors produced by irradiation proved to be autonomous, though responsive to gonadal stimulating hormones.

**SUMMARY**

In an analysis of the pathogenesis of neoplasms of endocrine organs occurring in mice exposed to an experimental atomic detonation, groups of 109–140 mice were irradiated with fission neutrons or x-rays over the entire body. Some groups were partially shielded; others were subjected to endocrine stresses.

Total-body neutron exposure caused thyroid tumors in 3.4 and 7.3 per cent of mice; none was found in total-body x-rayed mice.

Thyroid tumors were found in irradiated adrenalectomized (1.6 and 2.9 per cent) and gonadectomized (2.5 per cent) mice; none was found in unirradiated, bilaterally adrenalectomized animals.

A high incidence (4.2 per cent) of thyroid tumors occurred in head-neck-irradiated (480 rad) mice.

Both adrenal cortical adenomas and chromaffinomas were induced by total-body neutron irradiation (2.7–3.6 per cent in the various groups), and none was seen in similarly x-rayed mice and unirradiated controls.

The incidence of ovarian tumors in the total-body neutron or x-irradiated groups (67.9–69.5 per cent) was not diminished by shielding the upper half of the body. The ovarian tumor incidence was not appreciably raised by isolated head and neck irradiation.

It is concluded that neutrons have a high rela-
FIG. 3a.--A 6'2-year-old male with mycosis fungoides. Appearance of hands before treatment with epoxypiperazine.

FIG. 3b.--Appearance after treatment.
Fig. 4.—Xh48. Bilateral thyroid tumors; one, cystic papillary, the other adenomatous. X50.

Fig. 5.—Xh48. Bilateral extensive hyperplasia of the thyroid with disseminated microtumors. This lesion is characteristic of thyroid adenomas induced by sustained stimulation with thyrotropic hormone. X50.

Fig. 6.—Xh48. Same tumor as above showing the adenomatous nodules at higher magnification. X145.
FIG. 4.—Xh4s. Bilateral thyroid tumors; one, cystic papillary, the other adenomatous.

FIG. 5.—Xh4s. Bilateral extensive hyperplasia of the thyroid with disseminated microtumors. This lesion is characteristic of thyroid adenomas induced by sustained stimulation with thyrotropic hormone.

FIG. 6.—Xh4s. Same tumor as above showing the adenomatous nodules at higher magnification. X 145.
Fig. 7.—Xt46g. Small adrenal tumor in a distorted cortex with some compression of the medulla. X160.

Fig. 8.—Xt46g. Higher magnification of the tumor nodule in Fig. 7, suggestive of carcinoma in situ, with normal adrenal cortex in left upper quadrant. X600.

Figs. 9 and 10.—Xt46g. Two types of cells in a large adrenal tumor of a gonadectomized irradiated mouse, some resembling granulosa cells (Fig. 9) and others lutein cells (Fig. 10). X200.
Fig. 11.—X160. A large benign-appearing adrenal cortical tumor compressing normal cells of the cortex. The pale-staining cells in the right upper corner are those of the medulla. X160.

Fig. 12.—X200. A benign-appearing cortical adenoma with lutein-like cells. Cells of the medulla are seen at the left upper margin, those of normal cortex at right. X200.

Fig. 13.—X200. A large, degenerating cortical adenoma with disfigured normal cortex. X200.
Fig. 14.—N1.2, Tumor-like hyperplasia or a benign tumor of the adrenal medulla. Well preserved cortical tissue surrounding it. ×145.

Fig. 15.—X2.4.b. High-power view of an adrenal medullary (chromaffin) tumor with adjacent kidney tubules at left upper margin. ×450.
Fig. 16.—X250. Medullary tumor compressing the surrounding adrenal cortex. X145.

Fig. 17.—X400. Adrenal medullary tumor composed of round, spindle-shaped, and polygonal cells. A small part of the disfigured cortex is at the left upper margin. X200.
tive biological effectiveness in relation to x-rays or γ-rays for thyroid and adrenal tumor induction. With respect to ovarian tumorigenesis, it is postulated, on the basis of present data and those of earlier investigators, that the irradiated ovary is unable to respond to homeostatic forces with resultant sustained increase in gonadotropins.

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REFERENCES

Studies on the Pathogenesis of Neoplasms by Ionizing Radiation II. Neoplasms of Endocrine Organs

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