

the same sex (in most cases littermates) were chosen. One circular wound of 20 mm diameter was produced on the back, the skin being excised down to the superficial fascia.

The technic of producing wounds was that described in the previous paper. The method of treatment consisted in intraperitoneal injections of 1 cc sterile 33% saline extract of adult chicken heart, on every second day. The control animal remained untreated. The wounds of both animals, treated and untreated, were covered with lanolin and sterile gauze, the dressing being changed daily. The experimental and control wounds were measured at intervals of 48 hours. The injections were begun on the day of operation and continued until the wounds were completely healed. The criterion of healing was based on the complete closure of the wounded area.

The results of the present investigations are given in Table I.

These data indicate that in rats treated with intraperitoneal injections of saline extract of adult chicken heart the closure time of the wounds is on the average 21.8% shorter than

in the untreated controls. These results are in agreement with earlier experiments of Roulet,³ Lorin-Epstein,⁴ Amorosi,⁵ and Sandelin and Björkesten,⁶ who observed stimulation of wound healing following injections of extracts of embryonic tissues.

Summary. Rats with experimental skin wounds received intraperitoneal injections of saline extract of adult chicken heart. The course of wound healing in animals treated in this way was compared with the healing process in wounds of equal size in untreated rats. The experiments showed that treatment with cell growth-promoting extracts of adult hearts caused a significant reduction (21.8%) in the mean time required for healing, as compared with the controls.

³ Roulet, F., *C. R. Soc. de biol.*, 1926, **95**, 390; *Ann. d'anat. path.*, 1927, **4**, 337.

⁴ Lorin-Epstein, M. J., *Arch. f. klin. Chir.*, 1927, **144**, 632.

⁵ Amorosi, O., *Riv. di pat. sper.*, 1931, **6**, 33.

⁶ Sandelin, M., and Björkesten af G., *Finska läk.-sällsk. handl.*, 1932, **74**, 826.

14862 P

Liver Changes Associated with a Transplantable Granulosa Cell Carcinoma in Mice.*

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Earlier experiments^{1,2} have indicated that irradiation of the entire body of mice results in the development of granulosa cell tumors of the ovary in many of the X-rayed animals. Although many tumors attained a large size,

none of the induced ovarian growths of our first series³ has metastasized to distant organs, and for this reason the neoplastic character of these tumors was questioned.

In the present series, granulosa cell tumors were induced by a single dose of 175 or 350 r. Many of these animals are still alive, and a final analysis of the incidence of ovarian tumors cannot be presented. In one com-

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¹ Furth, J., and Furth, O. B., *Am. J. Cancer*, 1936, **28**, 54.

² Geist, S. H., Gaines, J. H., and Pollack, A. D., *Am. J. Obs. and Gyn.*, 1939, **38**, 786.

³ Furth, J., and Butterworth, J. S., *Am. J. Cancer*, 1936, **28**, 66.

⁴ Traut, H. F., and Butterworth, J. S., *Am. J. Obs. and Gyn.*, 1937, **34**, 987.

⁵ Butterworth, J. S., *Am. J. Cancer*, 1937, **31**, 85.

pleted series of 78 mice receiving 175 r at 4 to 7 weeks of age and living until 10 months of age or longer, ovarian tumors appeared in 49 mice. Many other mice had a proliferative change^{4, 5} that precedes the development of tumors.

Four of the induced granulosa cell tumors metastasized to distant organs. Transplantation was attempted with 2 of these growths by grafting pieces of the tumor into the subcutaneous tissue or peritoneal cavity of related mice. Both attempts were successful. A fifth granulosa cell tumor that measured 25 mm. in greatest diameter but had no gross metastases also proved transplantable.

Microscopically, cells of the granulosa cell tumor 1 deviate but little from those of normal granulosa cells, though mitoses are abundant. Occasionally they show the characteristic follicular arrangement resembling normal ovarian follicles. In the neoplastic follicles are noted spaces with pale-stained, homogeneous, precipitated material resembling closely the formation of ovarian follicular fluid. The microscopic appearance of the tumors produced by cellular grafts is indistinguishable from that of the induced tumor. These grafts grow slowly in the subcutaneous

tissue, but eventually attain a large size. The tumor was induced by X-rays in an F₁ hybrid mouse, and thus far transfers have been successful in 62 of 172 genetically identical F₁ hybrids receiving subcutaneous grafts of tumor cells, and in only 1 of 20 mice of the parental stocks.

There is a peculiar liver change in most, if not all, of the mice that have carried the transplanted growth for several weeks. This has not been observed in other mice of our colony, either in normals or in those carrying different transmissible tumors or leukemic grafts, but it was noted in some mice with induced granulosa cell tumors of the ovary. A study of 15 livers of mice with transplanted granulosa cell carcinoma 1 shows the following changes:

Branches of the portal vein and liver sinusoids are tremendously dilated, so that the width of the sinusoids is double or triple that of the liver cords (Fig. 1). If the changes are mild, they tend to be focal. When they are advanced, they involve almost the entire organ, and cords of liver cells undergo atrophy. In scattered areas thrombosis occurs, with occlusion of sinusoids leading to necrosis of liver tissue; this may heal with

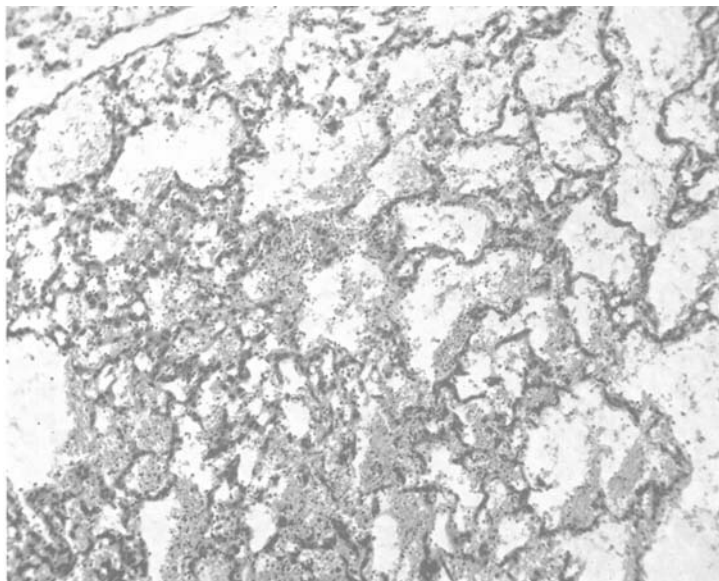


FIG. 1.
Cavernous dilatation of liver sinusoids in a mouse with transplanted granulosa cell carcinoma 1. $\times 50$.

scar formation. The scars are usually focal and disseminated. The massive hyperemia with cavernous dilatation of the sinusoids is usually unaccompanied by any inflammatory reaction; occasionally small lymphoid cells accumulate about cavernous sinusoids. Kupffer cells and large epithelioid cells of undetermined character filled with yellow-brown pigment giving a diffuse yellowish hue to their cytoplasm are present in variable numbers about cavernous sinusoids. There appears to be an increase in the number of Kupffer cells and endothelial cells about many sinusoids. The presence of scattered small hemopoietic foci seen about sinusoids of these mice has also been noted in normal animals at comparable ages.

The character and pathogenesis of this liver damage remain to be determined. The possibility that it is due to a virus carried by and only accidentally associated with granulosa cell carcinoma is unlikely, since in the earlier stage of this liver damage, inflammatory reactions or other changes known to be produced by viruses are absent. It is more probable that it is due to substances derived from the tumor cells. Similar changes have not been described in mice receiving estrogens over a long period of time (*cf.* ⁶) or in mice with

transplanted granulosa cell carcinoma originating in a non-irradiated mouse.⁷ The liver is known to receive and inactivate estrogens, and may undergo swelling with hyperemia during menstruation, and is sometimes profoundly damaged in the course of pregnancy (*cf.* ⁸). Thus it can be postulated that a substance of hormonal nature reaches the liver in small quantities under physiological conditions, and that this substance is produced or initiated by granulosa cell carcinoma of the ovary and is discharged in large quantities in animals carrying transmitted granulosa cell growth thereby leading to liver damage. It is also possible that this hypothetical substance is related to, but is not identical with, normal steroid hormones.

Summary. Three granulosa cell tumors of the ovary induced in mice by X-rays have been successfully grafted to related mice, indicating the neoplastic character of this growth.

Associated with the transplantable granulosa cell carcinoma No. 1 is a cavernous dilatation of liver sinusoids, which leads to thrombosis and scar formation. The relation of sex hormones to liver changes is discussed.

⁷ Strong, L. C., Gardner, W. U., and Hill, R. T., *Endocrinology*, 1937, **21**, 268.

⁸ Eckelt, K., in Halban-Seitz, *Biol. u. Path. d. Weibes*, 1927, **3**, 483.

⁶ Gardner, W. U., *Arch. Path.*, 1939, **27**, 138; Allen, E., *Endocrinology*, 1942, **30**, 942.

14863 P

Hypothalamic Facilitation of the Motor Cortex.

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Observations in this laboratory upon a monkey paralyzed from experimental poliomyelitis suggested that emotional states accompanied by hypothalamic activity may elicit cortically induced movements not otherwise operative. It was therefore decided to study the effect of direct stimulation of hypothalamic and adjacent forebrain nuclei upon skeletal

muscular responses evoked by electrical stimulation of the cortical motor areas in the experimental animal, in the hope of further clarifying cortico-hypothalamic relations.¹⁻⁴

¹ Morison, R. S., Dempsey, E. W., and Morison, B. R., *Am. J. Physiol.*, 1941, **131**, 732.

² Morison, R. S., Finley, K. H., and Lothrop, G. N., *J. Neurophysiol.*, 1943, **6**, 243.

³ Obrador, S., *J. Neurophysiol.*, 1943, **6**, 81.

⁴ Kennard, M. A., *J. Neurophysiol.*, 1943, **6**, 405.

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