TECHNICAL PAPERS

Granulosa Cell Tumors in Female Rats and Rabbits[1]

B. M. PECKHAM, R. R. GREENE, and M. E. JEFFRIES

Departments of Physiology and Obstetrics and Gynecology, Northwestern University Medical School, Chicago

M. S. and G. R. Biskind (*1*) reported that granulosa cell tumors developed in castrated female rats bearing intrasplenic ovarian grafts. Nine rats survived 11 months after implantation. "In 3 of the transplants large tumors were found, apparently of the granulosa cell type, and in 2 others smaller nodules of the same cellular structure were found." They considered that the tumors consisted only of granulosa cell masses and stated that these were "fairly sharply demarcated from the theca cell masses." By this latter (judging from their photomicrographs) they are referring to masses of luteinized cells, presumably of theca cell origin.

Luteomas and "mixed" or luteinized granulosa cell tumors have been produced in the mouse (*3*) by a similar technique. Li and Gardner obtained tumors in 11 out of 33 castrated females with ovaries transplanted to the spleen. The 11 with tumors were examined 153–346 days after implantation; the 22 without, 25–334 days after. Furth and Boone (*2*) have also produced granulosa cell tumors in mice by the same technique. They have given no data, however, as to the number of animals used or the number of tumors produced.

Similar transplants have been made in the guinea pig (*4, 5*) and left *in situ* for as long as 22 months. Atypical changes were noted, but no true tumors. To date, therefore, these tumors have been obtained only in the rat and mouse and not with regularity.

The purposes of this communication are (1) to confirm the fact that granulosa cell tumors may be produced in the rat, (2) to present data demonstrating that granulosa cell tumors are formed in all instances in which an ovarian graft free of adhesions is in the intestinal mesentery of the castrated rat for 265 days or more, (3) to summarize the histologic characteristics of these rat tumors, and (4) to record the production of granulosa cell tumors in still another species.

Female rats and rabbits were used. After castration, a portion of one ovary (approximate diameter of 1.5 mm in the rats and 1–4 mm in the rabbits) was transplanted to a position such that its venous drainage was to the liver via the portal circulation. In such a position destruction by the liver prevents ovarian estrogen from reaching the general circulation. The grafts are therefore exposed to continuous and prolonged hypophyseal gonadotropic stimulation. In 5 rats the transplants were to the spleen. In the remainder, to avoid adhesions, the intestinal mesentery was used. In the rabbits the splenic or intestinal mesentery was used. The rats were 40–50-day-old female albinos of unknown mixed strain. The rabbits, purchased on the open market, were young adults of various breeds, weighing 4.5–8.5 kg when the transplantation was carried out.

Twenty-six rats have been examined to date. Viable transplants were present in all. Vascular adhesions connecting the transplant area to the general circulation existed in 2 animals, excluding them from further consideration. Twelve rats survived 265–399 days postoperatively. A definite tumor was present in each. In 2 rats sacrificed 218 days after implantation, true tumors were not present, but normal ovarian architecture was replaced in some areas by the tissue disorganization characteristic of these tumors. The posttransplantation survival periods of the remaining 10 rats were fairly evenly distributed between 40 and 138 days. No evidence of tumor formation was found in this group.

Three of the rat tumors were cystic with solid nodules embedded in the wall. The cysts varied in size from 1 cm in diameter to 4.5×2.6 cm. The remaining 9 were solid and varied in size from 0.6 to 1.5 cm in diameter.

Grossly, the solid tumors and the nodules in the cysts appeared highly vascular and varied in color from red or orange yellow to dark blue-gray. Microscopically, the tumors resembled those of the theca-granulosa group found in the human and the luteinized granulosa cell tumors described by Li and Gardner. Luteinization was present in each tumor, but to a variable degree. At one extreme were those composed largely of granulosa cells and only a few luteinized cells. At the other was one tumor resembling a very vascular luteoma. However, in this tumor groups of small granulosa-like cells could be seen in some areas.

The description of the tumors in our animals obviously does not coincide with the Biskinds' description of their tumors in the rat (composed exclusively of granulosa cells). It seems very likely, however, that their "theca cell masses" were luteinized elements and also part of the tumor.

Six of 8 rabbits surviving 11–533 days after transplantation had viable implants. The two oldest specimens, 512 and 533 days old, were definite tumors. Both were solid, yellow in color, and measured 0.60 and 0.64 cm in diameter. Microscopically, they were of the granulosa cell type with a rather homogeneous appearance and composed largely, but not exclusively, of luteinized cells.

The hormone production and transplantability of these

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tumors is being studied at the present time and will be reported at a later date.

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History of Crystal Growth Revealed by Fractography[1]

C. A. ZAPFFE, F. K. LANDGRAF, JR., and C. O. WORDEN, JR.

6410 Murray Hill Road, Baltimore, Maryland

During the war there was developed at Battelle Memorial Institute (*8*) and later at the Rustless Iron and Steel Corporation (*6, 7*) a microscope technique for viewing directly the individual granular facets of fractured materials, particularly metals. Under sponsorship of the Office of Naval Research, this technique has been extended to elemental metals (*4*), alloys (*5, 7*), and certain intracrystalline phenomena such as Neumann bands (*2*), as well as dissociation phenomena within inclusions (*3*). The technique is now referred to as "fractography"—the study of fracture facets at high magnification.

Among the numerous informational patterns already observed on fracture facets, those markedly revealing crystal history have not yet been emphasized. Unlike the fracture facets of glass, the patterns of metallic fracture seem always to relate to intrinsic crystal structure, not to superimposed stress pattern—that is, the "hackle structure" typical of glass fractures is generally absent in metal fractures. Fractographs of metals therefore reveal much of the history of original crystal growth.

In Figs. 1–4 are exhibited fractographs, each containing most marked registration of growth characteristics.

A nonmetallic crystal, ammonium dihydrogen phosphate, discloses on its fractured face both extrinsic and intrinsic patterns (Fig. 1). The javelin-shaped markings relate to the pattern of stress at the time of fracture, whereas the dendrite patches obviously refer directly to original imperfection in crystal growth.

A fractograph of molybdenum metal (Fig. 2) reveals an involved pattern which expresses virtually in its entirety the imperfection in structure of the crystal. This metal was melted by an electric arc and cast in vacuum by a process invented at the Climax Molybdenum Corporation's Research Laboratory (*1*). The tortuous path of fracture reveals the great conditions of strain and

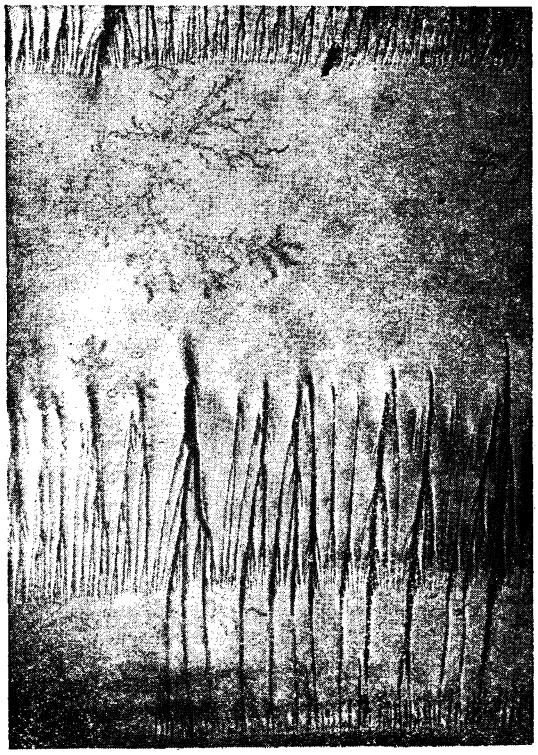

FIG. 1. Ammonium dihydrogen phosphate (140×).

FIG. 2. Molybdenum metal (175×).

[1] From research conducted in the laboratory of the senior author under contract with the Office of Naval Research.