Endometrial Carcinoma in BD II/Han Rats: Model of a Spontaneous Hormone-Dependent Tumor [1]

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ABSTRACT—The incidence of endometrial carcinomas as well as the life-spans of 5 groups of female BD II/Han inbred rats were compared. Groups compared were control (CON), ovariectomized (OV), retired breeder (RB), germfree rats (GF), and rats fed a purified diet (PD). Carcinomas, for the most part adenocarcinomas, occurred in 90% of the CON and PD rats and approximately 60% of the RB and GF rats. Carcinomas did not develop in OV rats. The mean life-span of the CON and PD rats was 22 months. The RB and GF rats reached, respectively, 32 and 30 months; and the OV rats, 39 months. An essential influence of ovarian hormones on tumorigenesis was shown. Alimentary carcinogens and phytoestrogens, as well as chronic irritations of the endometrium due to bacteriologic inflammations, could be excluded as tumor initiators. Hormonal dysregulation in the aging BD II/Han rats was discussed as a possible cause of an inappropriate stimulation of the endometrium, promoting a previously transformed tumor cell or initiating an autonomous tumor growth. Such evidence supports the use of the BD II/Han rat as a suitable model for the study of hormonal effects on the tumorigenesis of endometrial carcinomas in women.—JNCI 1987; 78:1245-1251.

Spontaneously developed endometrial carcinomas are common findings in women (*1-2*), laboratory rabbits (*3-5*), and Chinese hamsters (*6-8*) and are thought to be rare in laboratory rats (*9, 10*). In longevity studies, whereby virgin rats were maintained from weaning up to their natural death, we observed endometrial carcinomas in 39.1% of the females in the Han:Wist outbred stock (*11*) and in 62.3% of the DA/Han inbred strain (*12*). A third life-span study using BD II/Han inbred rats kept under the same conditions provides evidence of values exceeding 90% (Kaspareit J, Deerberg F: Unpublished data).

These findings led to the present studies designed to demonstrate influences that promote the development of such tumors, by comparison of the life-span and the incidence of endometrial carcinomas in 5 groups of BDII/Han rats kept under different maintenance conditions. As agents exercising an influence on the pathogenesis of such tumors, we assumed hormonal effects such as those discussed in human endometrial carcinomas, bacteriologic inflammatory reactions generally observed in the tumor tissue, and alimentary carcinogens.

MATERIALS AND METHODS

Five groups of female BD II/Han rats—1 group of CON, 1 group of OV, 1 group of RB, and 1 group of PD, each consisting of 50 animals, as well as 1 group of 36 GF—were maintained until the end of their natural life-span.

All rats belonged to the 65th and 66th inbred generation and originated from a specified pathogen-free breeding colony started in the institute 12 years ago from cesarian-derived animals. CON and PD were submitted to the study after weaning between the 21st and 23d day of life; OV, after ovariectomy at an age of 24-28 days; and RB, after the breeding period between the 7th and 13th month of life. RB had raised at least one litter. GF rats were obtained at an age of 25 days from a small germfree breeding colony established for use in this examination through hysterectomy of rats from the specified pathogen-free breeding colony.

CON, OV, PD, and RB were kept in a barrier-type animal quarter with 22±1°C room temperature, 55±5% relative humidity, 15-mm hyperbaric pressure in relation to external pressure, a 12-hour light-12-hour dark sequence, a light intensity of about 300 lux, and an air change 20 times/hour. The rats were housed in groups of 5 in polycarbonate cages (base area, 1,750 cm^2) bedded with autoclaved softwood granules. Cages and bedding were changed once a week. GF were maintained in a Trexler-type plastic isolator in groups of 3 animals per polycarbonate cage (base area, 900 cm^2). The bedding was again autoclaved softwood granules.

CON, OV, and RB were fed an autoclaved (120°C for 5 min) commercial cereal-based diet supplemented with vitamins and minerals. The metabolizable energy content was 10.3 MJ/kg in 17.7% crude protein, 4.2% crude fat, and 6.8% crude fiber. GF received an identical diet autoclaved at 130°C for 15 minutes. PD were fed an autoclaved (102°C for 5 min) purified diet, composed of carcinogen- and phytoestrogen-free purified casein, soyamin, cornstarch, sugar, soya oil, and a polycarbonate filler. The energy, protein, fat, and crude fiber contents correspond to those of the standard diet. GF received autoclaved tap water. All other groups received pasteurized (95°C for 15 sec) and acidified (pH 2.5) water. Food and water were supplied ad libitum.

ABBREVIATIONS USED: CON = control rats; GF = germfree rats; H & E = hematoxylin and eosin; OV = ovariectomized rats; PAS = periodic acid-Schiff; PD = rats fed purified diet; RB = retired breeder rats.

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All rats were inspected daily, and a complete autopsy was performed on the deceased and moribund animals. Almost all organs and all grossly altered tissues were fixed in 10% Formalin and embedded in Paraplast. Sections 4 μm thick were stained routinely with H & E. Sections from endometrial tumors were also stained with Van Gieson mixture and subjected to the PAS reaction. Selected tumor tissue was embedded in hydroxyethyl-methacrylate. Sections 1 μm thick were subsequently stained with toluidine blue.

Bacteriologic examination of smears taken from the endometrium or uterine carcinomas was completed on all animals showing no or only slight signs of autolysis at the autopsy.

Data were statistically analyzed by the chi-square and Student's *t*-test.

Two rats, 1 from the group of OV and the other from the group of RB, were not considered in the evaluation because of cannibalism and autolysis.

RESULTS

Life-span and Mortality

The age-dependent cumulative mortality of the different groups is shown in text-figure 1. The nearly identical death rates of CON and PD are apparent. All animals had a life-span between 15 and 36 months. The mean life-span was 22.4±4.4 months in CON and 21.9±3.4 months in PD. OV lived extremely longer, all surviving the 1st and 2d year. Of the OV, the youngest died in the 27th and the oldest in the 48th month. Mean survival was 39.1±6.5 months. RB and GF died somewhat earlier, e.g., between the 18th and 42d month; the mean life-span reached 32.1±5.3 and 30.1±4.5 months, respectively.

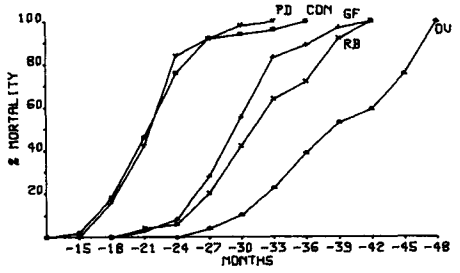
Statistical evaluation revealed significant differences ($P \leq .001$) in the mean life-span of all the groups, except between CON and PD and GF and RB.

Endometrial Carcinomas

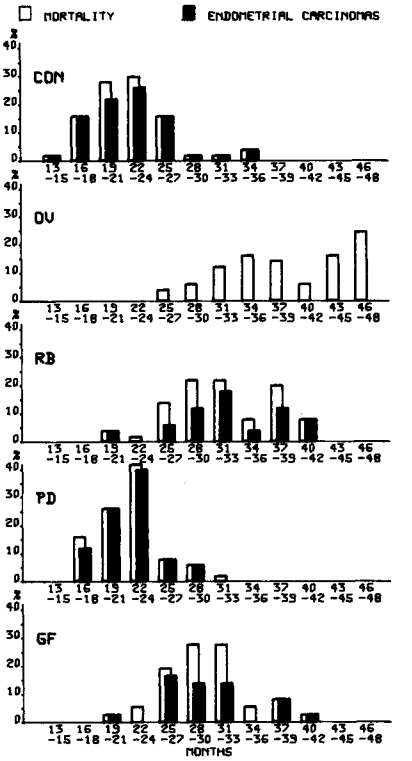
Incidence

With the exception of OV, endometrial carcinomas developed to various frequencies in all investigated groups. Text-figure 2 demonstrates the quarterly mortality together with the percentage of rats showing endometrial carcinomas. As shown in text-figure 3, the highest percentage was observed in CON and PD, 90.0 and 92.0%, respectively. In RB, the tumor incidence reached 65.3%. In GF the percentage of affected animals was 58.3%. In all groups the mean life-span of the tumor-bearing rats was nearly identical with that of the entire group.

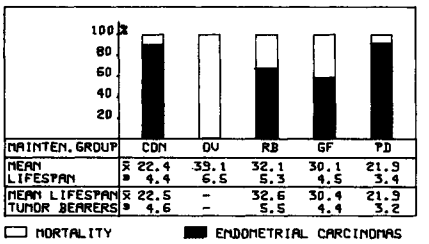
Significant differences ($P \leq .001$) in the tumor incidence and the mean age of the tumor bearers were evident in all groups with only two exceptions: No differences in both parameters could be shown between the groups of CON and PD as well as between GF and RB.



TEXT-FIGURE 1.—Cumulative mortality in female BD II/Han rats of different maintenance groups.



TEXT-FIGURE 2.—Three months' mortality and percentage of animals with endometrial carcinomas in female BD II/Han rats of different maintenance groups.



TEXT-FIGURE 3.—Percentage of females with endometrial carcinomas in female BD II/Han rats of different maintenance (MAINTEN.) groups and mean life-spans of total groups and tumor bearers. $\bar{x}$ = mean; s=SD.

As listed in table 1, most tumors registered were classified as adenocarcinomas. Sporadic cases of adenosquamous, squamous cell, and anaplastic carcinomas were diagnosed. Statistical evaluation revealed no differences in the incidence of the tumor types among the groups. The same holds true for the rate of metastases, except for transcoelomic as well as for extra-abdominal metastases of the lung that were significantly higher ($P \leq .05$) in PD than in CON.

Pathologic Findings

Macroscopically, the tumors arose as small nodular single or multiple processes in one or both of the uterine horns (fig. 1). These areas were, however, often masked by pus that filled the distended uterus. In advanced stages, affected horns were plugged with neoplastic tissue, often enlarged, and filled with blood or exudate cranial to the tumor. In the final stages most of the tumors extended through the uterine wall, causing widespread transcoelomic metastases on the visceral and parietal peritoneum (fig. 2). Extra-abdominal metastases involving the lungs and lymph nodes were, likewise, frequently observed.

The histologic appearance of the adenocarcinomas varied greatly, although no significant differences were evident among the various groups. More confined adenocarcinomas were apparent as glandular projections into the lumen of the endometrial cavity. They consisted of well-differentiated glandular structures lined by one or two layers of uniform columnar cells (fig. 3). The lumina of the neoplastic glands and the spaces between the papillae regularly contained cell detritus with numerous leukocytes due to the inherent inflammation associated with the tumor growth (fig. 4). Although always infiltrating the myometrium, well-differentiated adenocarcinomas showed a greater tendency to spread into the lumina of the uterine horns. More invasive adenocarcinomas, including those invading the abdominal cavity became increasingly undifferentiated. Varying portions of different histologic appearance were apparent. Most prominent were areas with neoplastic glandular elements embedded in an extensive amount of stromal fibrosis (fig. 5) as well as neoplastic cells arranged in solid sheets and nests separated by broad bands of stromal proliferations (fig. 6). On occasional instances, poorly differentiated adenocarcinomas showed areas characterized by an amorphous substance surrounding clusters of tumor cells (fig. 7) or neoplastic cells that were arranged in an irregular trabecular or papillary fashion. This substance was slightly eosinophilic and proved PAS positive.

In our material, most of the adenocarcinomas belonged to the poorly differentiated type, occasionally undergoing squamous metaplasia and often developing transcoelomic and lymphogenic or hematogenic metastases of the lungs and lymph nodes (table 1). Secondary findings included squamous cell carcinomas, histologically identical with squamous cell carcinomas elsewhere; adenosquamous carcinomas with varying portions of squamous; and adenocarcinomatous structures as well as anaplastic carcinomas consisting of irregular formations of highly anaplastic cells (table 1).

Bacteriologic Findings

Bacteriologic examination of smears from the endometrium or endometrial carcinomas in OV and GF were generally negative. Positive findings were observed in 94 from 114 (≈82.5%) tumor bearers and in 11 from 20 (≈55.0%) non-tumor-bearing CON, RB, and PD. The most common infections in neoplastic lesions were with *Escherichia coli* 07 and *E. coli* 04. Both strains were isolated in pure cultures or mixed with *Proteus, Staphylococcus,* or *E. coli* and *Streptococcus* spp. *Proteus* spp. were also isolated from the endometrium of the non-tumor bearers.

DISCUSSION

Endometrial carcinoma is presently the most common cancer of the human female genital tract (*13–15*). Among various laboratory animals the incidence of endometrial cancer has been found to be especially high in rabbits (*3–5*) and Chinese hamsters (*6–8*). In rats, the uterine horns are common sites for neoplasms; however, the frequency of carcinomas is low in most stocks and strains, rarely exceeding 10% (*16*). Results obtained in previous in-house studies indicating endometrial carcinomas in approximately 40% of the virgin females in the Han:Wist stock (*11*) and 60% in the DA/Han^{-} (*12*) and 90% in the BD II/Han inbred strains indicate an uncommonly high incidence of endometrial carcinomas when compared with the existing data. In a further study, it could be shown that the nulliparity of the animals had a promoting effect on the development of endometrial carcinomas (*17*).

More than 90% of the tumors found in this study were adenocarcinomas of different histologic appearance. Single adenocarcinomas from rats of all groups showed areas characterized by an abundant homogeneous eosinophilic PAS-positive ground substance surrounding tumor cell clusters. The histologic pattern of these alterations seems to be identical to the yolk sac carcinoma of the mouse uterus (*18*). However, contrary to the findings described in pure yolk sac carcinoma, the yolk sac-like formations in the tumors of our rats were confined to more or less distinct areas of otherwise poorly differentiated adenocarcinomas; and both the adenocarcinomatous and the yolk sac-like formations were present in the accompanying peritoneal and lung metastases. Identical alterations have also been observed in spontaneous adenocarcinomas of 3 Japanese albino rats (*19*). The intercellular substance was indicated to be an acid-mucopolysaccharide produced by the tumor cells. We cannot exclude that the yolk sac-like formations in the tumors of our rats have a different origin than have the adenocarcinomas. However, since adenocarcinomatous structures are always present and promi-

TABLE 1.—*Endometrial carcinomas in female BD II/Han rats of different maintenance groups: Incidence and classification of tumors, incidence of metastases and squamous metaplasia, and incidence of pituitary gland adenomas in rats with and without endometrial carcinomas*

Maintenance group	No. of rats examined	Rats with endometrial carcinoma										Rats with pituitary gland adenoma			
		Total incidence		Classification	Incidence		Metastases				Squamous metaplasia		With endometrial carcinoma		Without endometrial carcinoma	
							Abdomen		Lung							
		No.	Percent[a]		No.	Percent[b]	No.	Percent[c]	No.	Percent[c]	No.	Percent[c]	No.	Percent[b]	No.	Percent[d]
CON	50	45	90.0	Adenocarcinoma	44	97.8	25	56.8	15	34.1	6	13.6	5	11.1	2	40.0
				Anaplastic carcinoma	1	2.2	1	—	1	—	1	—				
OV	49	0	0		0	0	0	0	0	0	0	0	0	0	0	0
RB	49	32	65.3	Adenocarcinoma	31	96.9	19	61.3	13	41.9	1	3.2	4	12.5	8	47.1
				Adenosquamous carcinoma	1	3.1	1	—	1	—						
PD	50	46	92.0	Adenocarcinoma	41	89.1	32	78.0	26	63.4	2	4.9	1	2.2	2	50.0
				Adenosquamous carcinoma	2	4.4	1	—								
				Squamous cell carcinoma	2	4.4	2	—	1	—						
				Anaplastic carcinoma	1	2.1	1	—	1	—						
GF	36	21	58.3	Adenocarcinoma	20	95.2	13	65.0	10	50.0	2	10.0	0	0	1	6.7
				Adenosquamous carcinoma	1	4.8	1	—								

[a] Related to No. of rats examined.
[b] Related to No. of rats with endometrial carcinoma.
[c] Related to No. of rats with the corresponding tumor type. —=percentage not calculated.
[d] Related to No. of rats without endometrial carcinoma.

nent, we consider this type of tumor as an adenocarcinoma.

Although the etiology of the endometrial carcinomas in BD II/Han rats has not been identified by this study, the results indicate an essential influence of ovarian hormones on the development of the neoplasms. With the exception of 2 leiomyosarcomas, ovariectomized rats showed no signs of uterine cancer or more specifically endometrial cancer. Accordingly, the OV reached an extremely high mean life-span, approximately 18 months more than that of the CON.

The importance of hormones, i.e., estrogens, in the etiology of endometrial carcinomas in women has long been recognized. It is being discussed that a long-term unopposed and uninterrupted estrogenic stimulation of the endometrium, resulting from ovarian hormonal dysfunction or the continued use of exogenous estrogens (*1, 2, 20–22*), leads to a series of histopathologic changes ranging from endometrial hyperplasia through dysplasia to an autonomous cancer growth. Hereby, estrogens could act as either promotors (*23–25*) or initiators of the neoplastic process (*26, 27*). The importance of estrogen in the tumorigenesis is, likewise, evident from animal studies, in which the administration of estrogen to mice and rabbits produced endometrial cancer (*28, 29*).

In animals, correlations of spontaneous endometrial carcinomas with hormonal dysfunctions have not been proved (*30*). Our studies, however, indicate that in animals, at least in BD II/Han rats, ovarian hormones play an essential role in the etiology of endometrial carcinomas. Since specific endocrinologic examinations have not been performed, the results of our study allow only this general statement.

We assume that an endocrine imbalance in the ovarian hormonal metabolism participates in the tumorigenesis of our rats. Such an imbalance appears to occur earlier in virgins than in RB. Furthermore, it appears likely that this endocrine imbalance could be correlated with the cessation of the regular cycling.

Previous studies have shown that virgin rats of different stocks and strains exhibit a constant estrus cycle at about 12 months of age. Hereby, an unopposed level of estrogen causes proliferation and hyperplasia of the endometrial glands (*31*). Furthermore, Pfeiffer (*32*) describes an adenocarcinoma in a female rat with an experimentally induced constant estrus. He indicates that an endocrine imbalance played a definite role in the tumorigenesis. Examination of vaginal smears from BD II/Han rats revealed that irregularities in the normal estrus cycle of a virgin rat begin as early as 9–10 months of age, changing in nearly all rats to a constant estrus for several months. In RB, this alteration of the estrus cycle first appears in the latter stages of life. A significant increase is observed 3 months post breeding. The significantly lower incidence of endometrial carcinomas in RB of the BD II/Han strain as compared with that of the virgin controls may, therefore, be attributed to the delayed occurrence of the endometrial carcinomas in the RB.

Endometrial carcinomas in women have been observed in connection with pituitary gland adenomas (*33*) and granulosa or theca cell tumors of the ovaries (*34, 35*). These have been attributed to a hormonal dysfunction of the endocrinal glands. Pituitary gland adenomas are common findings in aging rats (*36*). Similar findings were not evident in our studies. The incidence of pituitary gland adenomas was higher in non-tumor-bearing than in tumor-bearing rats (table 1). Ovarian tumors were not observed. Furthermore, follicular polycystic degeneration of the ovaries, which results in unopposed levels of serum estrogen, has been suggested to be involved in endometrial carcinogenesis (*37, 38*). Such alterations were occasionally observed in the present study. We believe, however, that histologic evidence seen only at the natural end of life must not be the same as that in the initial stage of the disease.

Assuming ovarian hormones promote the malignant development of previously transformed endometrial cells, we set out in this study to identify exogenous agents that affected our in-house stocks and strains and that possibly were responsible for an initial malignant transformation of endometrial cells. Comparing the tumor incidences in the control rats and rats fed a purified diet free of phytoestrogens and carcinogens, it is evident that an alimentary exogenous agent is not responsible for the endometrial transformations. The same holds true for a chronic irritation of the endometrium by bacteriologic inflammation, a condition regularly observed in the tumor tissue but not to be made responsible for the malignant transformation.

Supporting evidence was the development of endometrial carcinomas in germfree animals, although to a lower degree and later in life than that in the control rats. The germfree status is responsible for the lower tumor incidence; greater age of the tumor-bearing rats, however, excludes inflammatory irritation due to bacterial infection as a tumor-inducing factor. Although the actual effect of the germfree status on the tumorigenesis is not known, its tumor-inhibiting effect has, likewise, been previously observed (*39*). In breast cancer it is suggested that estrogens produced by intestinal bacteria are involved in the causation of cancer (*37*). Such a hypothesis could, likewise, be considered for the alteration of the incidence of endometrial carcinomas in germfree BD II/Han rats. From the definition of "germ-free status"—the absolute absence of bacteria, parasites, and fungi, as well as the partial absence of viruses—we must concede that various viruses not selectively tested for could act as initiators in the etiology of endometrial carcinomas in our rats. Similar reasoning has been discussed for cervical cancer of women (*40*).

Although this study remains to provide a complete explanation of the tumorigenesis of endometrial carcinomas in the rat strain studied, the findings support the use of BD II/Han females as a suitable model for the study of endocrinologic influences on endometrial cancer in women. Hereby, the nulliparity of the rats is of interest because 40% of women with endometrial adenocarcinoma are nulligravid (*41*). As in women, the most frequent cancers are endometrial adenocarcinomas, fol-

lowed by low incidences of adenosquamous and anaplastic carcinomas (*42*). Furthermore, the differing frequencies of tumors in Han:Wist$^-$, DA/Han$^-$, and BD II/Han rats, kept under the same conditions, demonstrate that BD II/Han rats evidently possess a high predisposition for endometrial carcinomas.

REFERENCES

(*1*) DEMOPOULOS RI. Carcinoma of the endometrium. In: Blaustein A, ed. Pathology of the female genital tract. New York, Heidelberg, and Berlin: Springer-Verlag, 1977:278-298.

(*2*) DALLENBACH-HELLWEG G. Histopathology of the endometrium. 3d ed. Berlin, Heidelberg, and New York: Springer-Verlag, 1981:161-199.

(*3*) COTCHIN E. Spontaneous uterine cancer in animals. Br J Cancer 1964; 18:209-227.

(*4*) GREENE HS. Diseases of the rabbit. In: Ribelin WE, McCoy Jr, eds. The pathology of laboratory animals. Springfield, IL: Thomas, 1965:330-350.

(*5*) BABA N, VON HAAM E. Animal model: Spontaneous adenocarcinoma in aged rabbits. Am J Pathol 1972; 68:653-656.

(*6*) WARD BC, MOORE W. Spontaneous lesions in a colony of Chinese hamsters. Lab Anim Care 1969; 19:516-521.

(*7*) BROWNSTEIN DG, BROOKS AL. Spontaneous endomyometrial neoplasms in aging Chinese hamsters. JNCI 1980; 64:1209-1214.

(*8*) FUCHS I. Untersuchungen zur Mortalität und zum Spontantumorspektrum bein Han: CHIN—Hamstern. Veterinarian thesis. Hannover, Federal Republic of Germany: Veterinarian Medical School, 1986:40-47.

(*9*) SQUIRE RA, GOODMAN DG, VALERIO MG, et al. Tumors. In: Benirschke K, Garner FM, Jones TC, eds. Pathology of laboratory animals. Vol 1. New York, Heidelberg, and Berlin: Springer-Verlag, 1978:1190-1191.

(*10*) ALTMAN NH, GOODMAN DG. Neoplastic diseases. In: Baker HJ, Lindsey JR, Weisbroth SH, eds. The laboratory rat. Vol 1. London: Academic Press, 1979:333-376.

(*11*) DEERBERG F, REHM S, PITTERMANN W. Uncommon frequency of adenocarcinomas of the uterus in virgin Han:WIST rats. Vet Pathol 1981; 18:707-713.

(*12*) DEERBERG F, REHM S, RAPP KG. Survival data and age-associated spontaneous diseases in two strains of rats. In: Archibald J, Ditchfield J, Rowsell HC, eds. The contribution of laboratory animal science to the welfare of man and animals. Stuttgart and New York: Fischer-Verlag, 1985:171-179.

(*13*) WEISS NS, SZEKELY DR, AUSTIN DF. Increasing incidence of endometrial cancer in the United States. N Engl J Med 1976; 294:1259-1262.

(*14*) CRISMAN JD, AZOURI RS, BARNES AE, et al. Endometrial carcinoma in women 40 years of age or younger. Obstet Gynecol 1981; 57:699-704.

(*15*) LOVECCHIO JL, AVERETTE HE, LICHTINGER M, et al. Treatment of advanced or recurrent endometrial adenocarcinomas with cyclophosphamide, doxorubicin and megestrol acetate. Obstet Gynecol 1984; 63:557-560.

(*16*) SCHULZE E. Spontantumoren der Schädelhöhle und Genitalorgane bei Sprague Dawley and Bethesda-black-Ratten. Z Krebsforsch 1960; 64:78-82.

(*17*) REHM S, DEERBERG F, RAPP KG. A comparison of life-span and spontaneous tumor incidence of male and female Han:Wist virgin and retired breeder rats. Lab Anim Sci 1984; 34:458-464.

(*18*) STEWART HL, SASS B, DERINGER MK, et al. Pure yolk sac carcinoma of the mouse uterus: Report of 8 cases. JNCI 1984; 73:115-122.

(*19*) KOBAYASHI H, KIKUCHI K, MAKI T, et al. Two transplantable uterine adenocarcinomas in the rat. J Natl Cancer Inst 1965; 34:13-20.

(*20*) SOMMERS SC, MEISSNER WA. Endocrine abnormalities accompanying human endometrial cancer. Cancer 1957; 10:516-520.

(*21*) ZIEL HK. Estrogen's role in endometrial cancer. Obstet Gynecol 1982; 60:509-515.

(*22*) FOX H. Endometrial carcinogenesis and its relation to oestrogens. Pathol Res Pract 1984; 179:13-19.

(*23*) HORWITZ RI, FEINSTEIN AR. Alternative analytic methods of case control studies of estrogens and endometrial cancer. N Engl J Med 1978; 299:1089-1094.

(*24*) LIPSETT MB. Interaction of drugs, hormones and nutrition on the causes of cancer. Cancer 1979; 43:167-181.

(*25*) SIITERI PK, NISKER JA, HAMMOND GL. Hormonal basis of risk factors for breast and endometrial cancer. In: Iacobelli S, Lindner H, King RJ, eds. Hormones and cancer. New York: Raven Press, 1980:499-505.

(*26*) FURTH J. Hormones as etiological agents in neoplasia. In: Becker FF, ed. Cancer. Vol I. New York and London: Plenum Press, 1975:75-120.

(*27*) HENDERSON BE, ROSS RK, PIKE MC, et al. Endogenous hormones as a major factor in human cancer. Cancer Res 1982; 42:3232-3239.

(*28*) MEISSNER WA, SOMMERS SC, SHERMAN BM. Endometrial hyperplasia, endometrial carcinoma, and endometrions produced experimentally by estrogen. Cancer 1957; 10:500-509.

(*29*) PAPADAKI L, BEILBY JO, CHOWANIEC J, et al. Hormone replacement therapy in the menopause: A suitable animal model. J Endocrinol 1979; 83:67-77.

(*30*) MOULTON JE. Tumors in domestic animals. 2d ed. Berkeley, Los Angeles, and London: Univ Calif Press, 1978:339-340.

(*31*) TANG FY, BONFIGLIO TA, TANG LK. Effect of estrogen and progesterone on the development of endometrial hyperplasia with Fischer rat. Biol Reprod 1984; 31:399-413.

(*32*) PFEIFFER AC. Adenocarcinoma in the uterus of an endocrine imbalance female rat. Cancer Res 1949; 9:347-349.

(*33*) BARNES AE, CRISSMAN JD, AZOURY RS, et al. Association of prolactin secreting pituitary microadenoma and endometrial carcinoma. Obstet Gynecol 1981; 58:391-394.

(*34*) DOCKERTY MB, MUSSEY I. Malignant lesions of the uterus associated with estrogen-producing ovarian tumors. Am J Obstet Gynecol 1951; 61:147-153.

(*35*) MANSELL H, HERTIG AT. Granulosa-theca cell tumors and endometrial carcinoma: A study of their relationship and a survey of 80 cases. Obstet Gynecol 1955; 6:385-394.

(*36*) BUREK JD. Pathology of aging rats. Palm Beach: CRC Press, 1978:49-53.

(*37*) LAZEREV NT. Dyshormonal tumors. New York: Consultants Bureau, 1966:54-68.

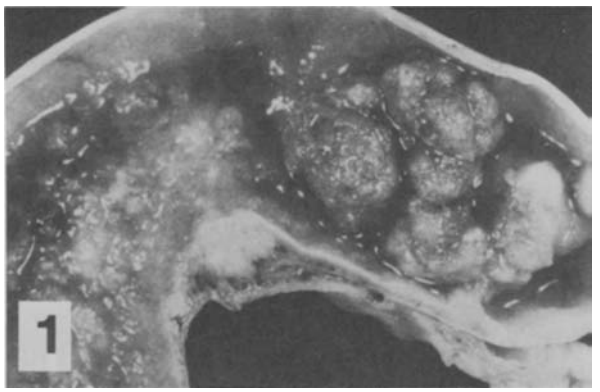
(*38*) FUTTERWEIT W. Polycystic ovarian disease. New York, Berlin, Heidelberg, and Tokyo: Springer-Verlag, 1984:91-92.

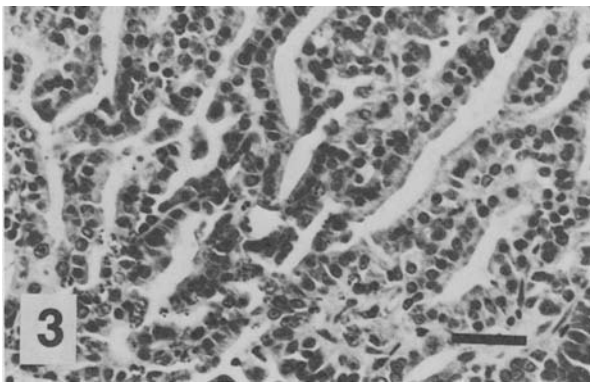
(*39*) DRASAR BS, HILL MJ. Intestinal bacteria and cancer. Am J Clin Nutr 1972; 25:1399-1404.

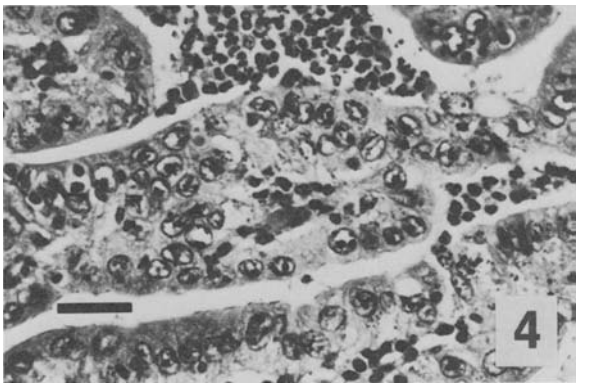
(*40*) NAHAMIAS AJ, NAIB ZM, JOSEY WE. Genital herpes and cervical cancer. In: Biggs PM, De The G, Payne LN, eds. Oncogenesis and herpesviruses. Lyon: IARC, 1972:403-408.

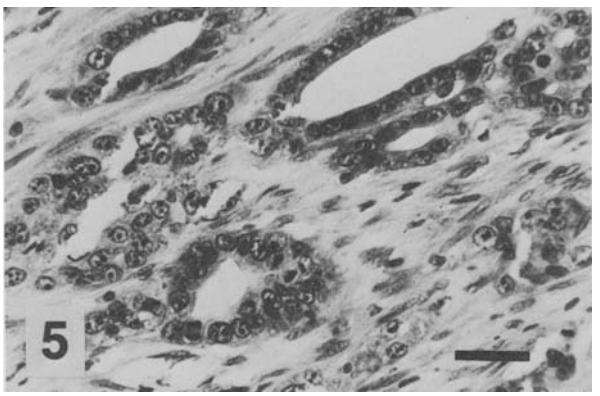
(*41*) DAVIS EW. Carcinoma of the corpus uteri. A study of 525 cases at the New York Hospital (1932-61). Am J Obstet Gynecol 1964; 88:163-170.

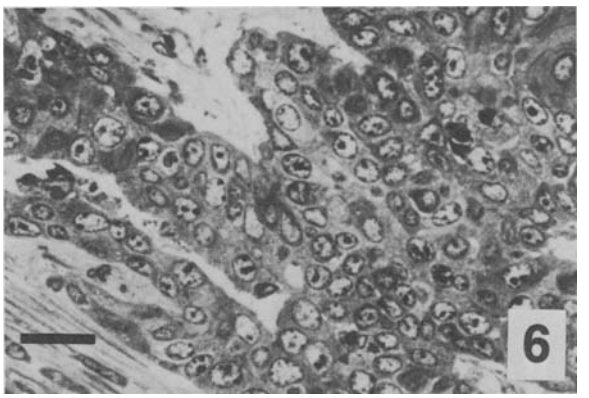
(*42*) SILVERBERG SG, BOLIN MG, DEGEORGI IS. Adenocanthoma and mixed adenosquamous carcinoma of the endometrium. Cancer 1972; 30:1307-1314.











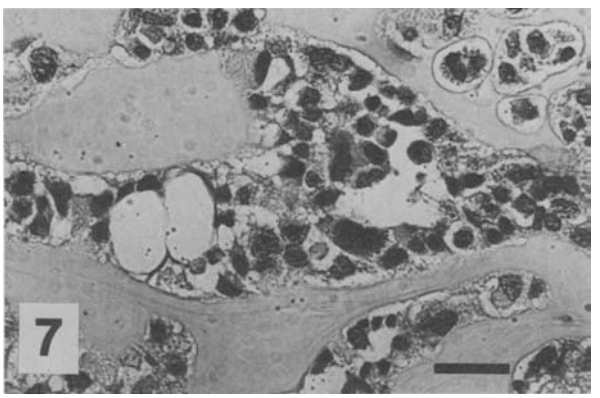


FIGURE 1.—Endometrial carcinoma starting with nodular hyperplasia in a uterine horn. × 4

FIGURE 2.—Endometrial carcinoma with widespread transcoelomic metastases. × 0.8

FIGURE 3.—Glandular structures in a well-differentiated endometrial adenocarcinoma. H & E. *Bar*=42 μm.

FIGURE 4.—Glandular structures of an endometrial adenocarcinoma containing numerous leukocytes. H & E. *Bar*=33 μm.

FIGURE 5.—Neoplastic glandular structures of a poorly differentiated adenocarcinoma embedded in extensive stromal fibrosis. H & E. *Bar*=33 μm.

FIGURE 6.—Cords of closely packed neoplastic cells in a poorly differentiated adenocarcinoma with frequent mitotic figures. Toluidine blue. *Bar*=30 μm.

FIGURE 7.—Clusters of neoplastic cells of a uterine carcinoma embedded in an amorphous eosinophilic ground substance. H & E. *Bar*=33 μm.