Spontaneous Tumors in Long-Term–Vasectomized Mice

Increased Incidence and Association With Antisperm Immunity

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In two independent studies the authors have observed a significantly higher incidence of spontaneous tumors in vasectomized BDF_1 mice over the long term than in age-matched sham-vasectomized control mice. In the first study, necropsies were performed on the animals at 30 months of age (27 months after surgery), and 15 of 24 vasectomized versus 2 of 14 sham-vasectomized mice ($P \leq 0.025$) had detectable tumors in various tissues. In a second study, necropsies were performed on the animals at a younger age (18 months, 15 months after surgery), and liver tumors predominated: 82 of 171 vasectomized versus 33 of 97 controls (48% versus 34%, $P \leq 0.037$) had at least one hepatic tumor, and a significantly higher percentage of vasectomized animals had large (≥ 31 sq mm) hepatic tumor burdens (80% versus 49%; $P \leq 0.002$) and multiple hepatic tumors (19% versus 5%; $P \leq 0.002$). In combined data from both studies, the vasectomy group had a higher incidence of (1) at least one tumor ($P \leq 0.025$), (2) multiple tumors ($P \leq 0.005$), and (3) more than one type of tumor ($P \leq 0.05$). Furthermore, in both studies tumor number and size were significantly associated with antisperm immunity detected by antibody or aspermatogenesis evaluation. It is speculated that sperm degradation products and/or the autoimmune response to sperm that commonly accompanies vasectomy may affect tumor induction or growth directly or indirectly by interfering with immunosurveillance mechanisms. (Am J Pathol 1983, 111:129–139)

VASECTOMY IN PRIMATES and other experimental animals has recently been shown to be associated with several pathologic side effects, most of which can be attributed to the chronic antisperm autoimmune response that frequently accompanies the procedure.[1] The most notable include immune-complex deposition in the testis and reproductive tract,[2,3] patchy orchitis and aspermatogenesis,[4,5] immune complex deposition in the basement membrane of the renal glomerulus,[2,6] arteritis,[7] and exacerbated atherosclerosis.[8,9] We now add to this list evidence that tumor incidence and size are affected by vasectomy in BDF_1 mice. Three years ago we unexpectedly found an unusually high number of spontaneous tumors in a group of vasectomized mice that had been maintained to old age (30 months) for a sperm autoimmunity study. These data prompted us to conduct a larger study ($n > 300$) to confirm this finding and to further investigate the possibility of an association between antisperm immunity and tumor development. In this report we present the tumor incidence and sperm immunity data from both studies.

Materials and Methods

Mice

Male BDF_1 (C57BL/6 × DBA/2) hybrid mice were obtained from the Jackson Laboratory, Bar Harbor, Maine (Study I) and the National Cancer Institute (NCI) (Study II). At 3 months of age they were vasectomized (double ligation with 6-0 proline and resection) or sham-vasectomized under Fluothane (Study I) or Equithesian (Study II) anesthesia. A midventral approach under asceptic conditions was used. In Study I, mice were ear-tagged and housed in mixed groups (3 vasectomized and 3 sham-vasectomized mice per large cage). In Study II, vasec-

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tomized (193) and sham-vasectomized (control) (114) animals were kept in separate cages (5 per cage) in the same room; at necropsy 171 vasectomized and 97 controls remained in the study. Autopsies were not performed on mice that died before necropsy.

Antisperm Antibody Tests

Vasectomized and sham-vasectomized mice were bled at various intervals after surgery by retroorbital puncture, and serum antisperm antibodies were assayed by indirect immunofluorescence or radioimmunoassay. Because only small amounts of serum are obtained from individual mice, at some timepoints there were insufficient quantities of serum for us to perform all antibody assays.

Immunofluorescence on Methanol Fixed Sperm (IF-F)

Smears made from washed epididymal BDF_1 mouse sperm were air-dried, fixed in absolute methanol for 30 minutes, and stored at −70 C until use. Each slide was incubated for 30 minutes at room temperature with twofold serial dilutions of test serum, washed thoroughly in phosphate-buffered saline (PBS), pH 7.2, and then incubated for 30 minutes with fluorescein-conjugated rabbit anti-mouse IgG (Cappel Laboratories, Cochranville, Pa). The slides were washed twice, and then each slide was coverslipped in a mounting medium of buffered glycerol and examined under a Zeiss epifluorescence microscope. Antisperm antibody titers (reciprocal of highest serum dilution giving a positive response) were determined for all animals at necropsy (Studies I and II) and additionally at 6 and 12 months after surgery for animals in Study II.

Immunofluorescence on Viable Sperm (IF-V)

Necropsy serums from a majority of mice in Study II were also tested by immunofluorescence (IF) for antibodies binding to the surface of viable (unfixed) sperm. Test serums were heat-inactivated, cleared by centrifugation at 10,000*g* for 10 minutes, and serially diluted in RPMI medium containing 1% bovine serum albumin (BSA). Twenty microliters of diluted serum was added to 5×10^5 washed BDF_1 epididymal sperm and incubated for 1 hour at 4 C. The sperm were then washed three times by centrifugation in RPMI–BSA and resuspended in 20 μl of fluorescein-conjugated rabbit anti-mouse IgG (diluted 1:20 in RPMI–BSA). After a final 30 minutes incubation at 4 C the sperm were washed three times in RPMI–BSA, mounted in buffered glycerol, and examined immediately by fluorescence microscopy.

Radioimmunoassay (RIA)

BDF_1 mouse epididymal sperm were washed and resuspended at 5×10^6 sperm/ml in RPMI–BSA, and 0.2 ml of the suspension were pipetted into each well of a 96-well microtiter plate. Sperm were pelleted by centrifugation, the supernatants were aspirated, and 50 μl of a 1:4 dilution of mouse serum were added to each well (triplicate wells/serum sample) and incubated at 4 C for 1 hour. The sperm were then washed three times in RPMI–BSA, and 2×10^5 counts per minute (cpm) of ^{125}I-protein A (labeled by chloramine-T method[10]) were added to each well and incubated for an additional hour at 4 C. After five washes in RPMI–BSA, sperm were transferred to tubes and counted in a gamma counter for detection of bound radiolabel.

For better comparison of results obtained on different dates, all RIA data (cpm) were converted to relative response values by the formula:

$$\text{Relative response (RR)} = \frac{\text{cpm test serum} - \text{cpm negative control}}{\text{cpm positive control} - \text{cpm negative control}}$$

Negative control serums were obtained from 3-month-old male BDF_1 mice (pool of 8); positive control serums (pool of 6) were obtained from male BDF_1 mice that had been hyperimmunized with syngeneic epididymal sperm (10^7 sperm, three injections, first injection in complete Freund's adjuvant).

Necropsy

The mice were killed by cervical dislocation at 30 months (Study I) or 18 months (Study II) of age. Blood was collected by cardiac puncture. All major organs were inspected for the presence of tumors or other abnormalities, and the sizes and locations of these lesions were recorded. Affected tissues were removed, fixed in neutral buffered formalin, embedded in glycol methacrylate plastic, and cut at 2 μ with glass knives. Mounted sections, treated with hematoxylin and Lee's stain, were examined by light microscopy.

After inspection of the major organs the vasa deferentia were examined for confirmation of the vasectomy status of each mouse. Until this point, the investigator performing the necropsy did not know the status of the animal under examination.

Criteria for Tumor Types

Hepatoma is a collective term for the various stages of hepatic neoplasia progressing from hyper-

plastic nodules to morphologically and biologically malignant neoplasms. Liver tumors in the mouse, unlike those in man, are biologically dynamic and progressive. Small hepatomas appear grossly as distinct nodules bulging above the capsule. Larger nodes may contain hemorrhagic and necrotic areas occupying an entire lobe. Hepatocellular neoplasms have also been classified as hepatocellular adenomas and well-differentiated, moderately well differentiated, and poorly differentiated hepatocellular carcinomas.[11]

The term *hepatoblastoma* denotes a malignant tumor of the mouse liver comprised of poorly differentiated cells arranged in sheets or rosettes with many vascular channels. Often there is a prevalence of poorly differentiated cells with a high mitotic index.[12] Such tumors are usually found within or in close association with hepatomas.

Hemangiomalike lesion is a term used for derangement of the vascular component of the liver involving dilation of vascular spaces. Here, too, there can be a progression from a peliosislike lesion to a frank hemangioendothelial sarcoma.[12]

Alveologenic carcinomas are lung tumors characterized by closely packed columns of cuboidal and columnar cells supported by a sparse stroma. Few blood vessels are present. Cells are arranged in acini, often with papillary formations. These tumors grow by a combination of expansion, infiltration, and coalescence. As a rule, they are surrounded by compressed pulmonary tissue but are not encapsulated. They can appear solitarily but frequently number two to four per animal.[13]

Evaluation of Aspermatogenesis

One testis was removed from each mouse at autopsy, fixed in neutral buffered 10% formalin, sectioned, and treated with hematoxylin and Lee's stain for histologic evaluation. Testis sections were examined for lymphocytic infiltration and evidence of germ cell maturation within seminiferous tubules. The degree of aspermatogenesis was calculated by the following formula:

$$\%\ \text{aspermatogenesis} = \frac{\text{number of tubules without differentiated germ cells}}{\text{total number of counted tubules}} \times 100$$

Statistical Analysis

Numerical data were analyzed by the nonparametric, distribution-free Mann–Whitney U test (equivalent to the *t* test or analysis of variance with two classes when two samples are compared [ANOVA]). Frequency data were analyzed by chi-square with the Yates' correction for continuity.[14] The Kolmogrov–Smirnov two-sample test was used to determine the optimal cutoff points determining positive antisperm antibody responses in RIA and tumor size differences between vasectomized and control groups.[15]

Results

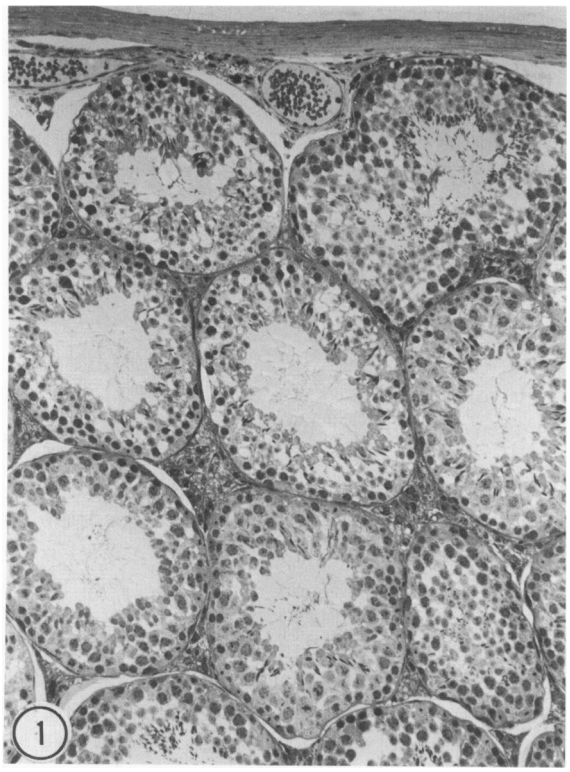
Antisperm Immunity

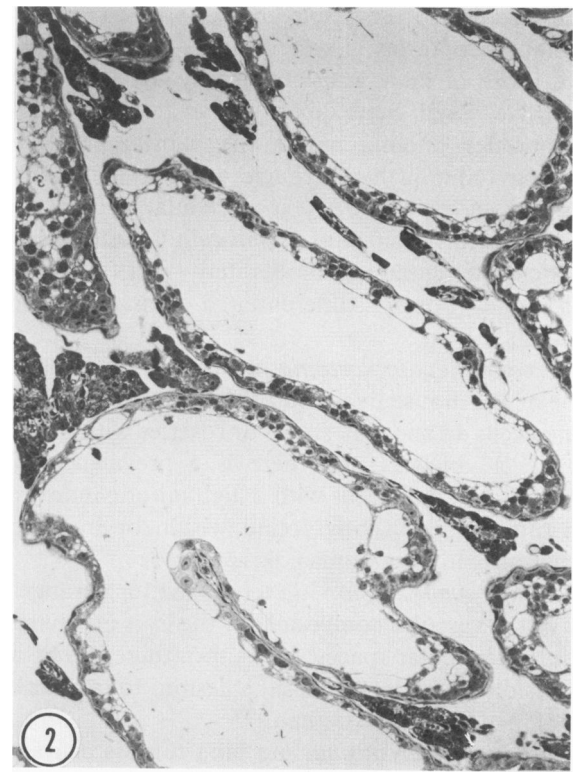
In Study I, 14 of 24 vasectomized and 2 of 14 sham-vasectomized mice had IF-F antisperm antibody titers of ≥ 8 at necropsy (58% versus 14%; $P \leq 0.025$). In Study II, at 6 months after surgery, antisperm antibodies with an IF-F acrosomal binding pattern and a titer ≥ 10 were found in 30 of 181 vasectomized and 2 of 98 sham-vasectomized mice (17% versus 2%; $P \leq 0.0006$); at 12 months after surgery, acrosomal antisperm antibodies were found in serum from 48 of 174 vasectomized and 9 of 100 sham-vasectomized animals (28% versus 9%; $P \leq 0.0005$); at necropsy (15 months after surgery) 19 of 151 vasectomized and 16 of 88 sham-vasectomized mice had acrosomal antisperm antibodies (13% versus 18%). Antisperm antibodies detected by IF-V were associated with vasectomy status (27% versus 5%; $P \geq 0.001$) but were not associated with IF-F data, presumably because the IF-V test detects antibodies binding to a different set of sperm antigens (i.e., only surface antigens). By RIA 77% of the vasectomized, compared with 68% of the control group, had antisperm antibodies at necropsy ($P \leq 0.05$). The RIA cutoff was RR ≥ 0.48, as determined by the Kolmogrov–Smirnov statistical test. The RIA results were positively associated with 12-month IF-F data.

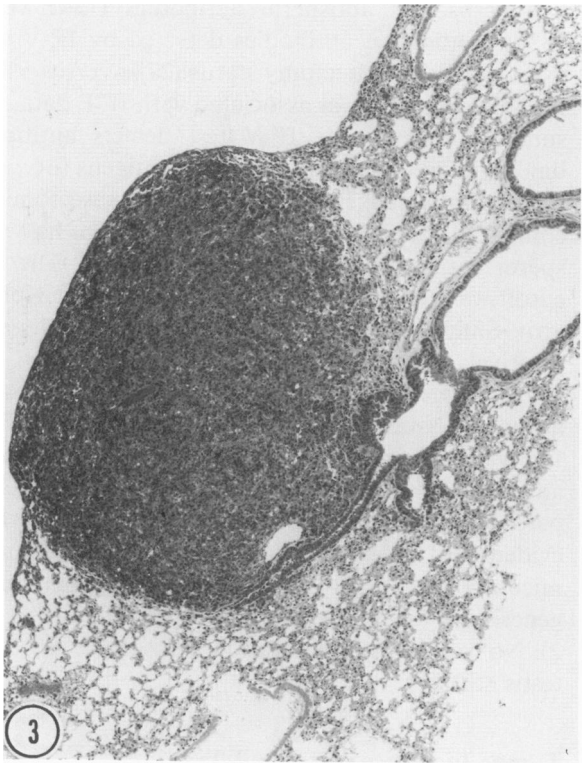
Histologic examination of the testes removed at autopsy from the mice in Study II revealed that 58 of 145 vasectomized and 1 of 97 sham-vasectomized animals (40% versus 1%; $P \leq 0.001$) had at least patchy aspermatogenesis ($\geq 21\%$ of tubules without evidence of spermatogenesis). Eleven vasectomized mice and 1 control had severe ($\geq 81\%$) aspermatogenesis (11% versus 1%; $P \leq 0.046$) (Figures 1 and 2). No lymphocytic infiltration was seen in any of the testis sections.

Tumor Incidence, Size, and Type

In Study I, 15 of 24 vasectomized and 2 of 14 sham-vasectomized mice (30 months old) had grossly detectable tumors at necropsy (63% versus 14%; $P \leq 0.025$). Of these animals, 11 vasectomized animals







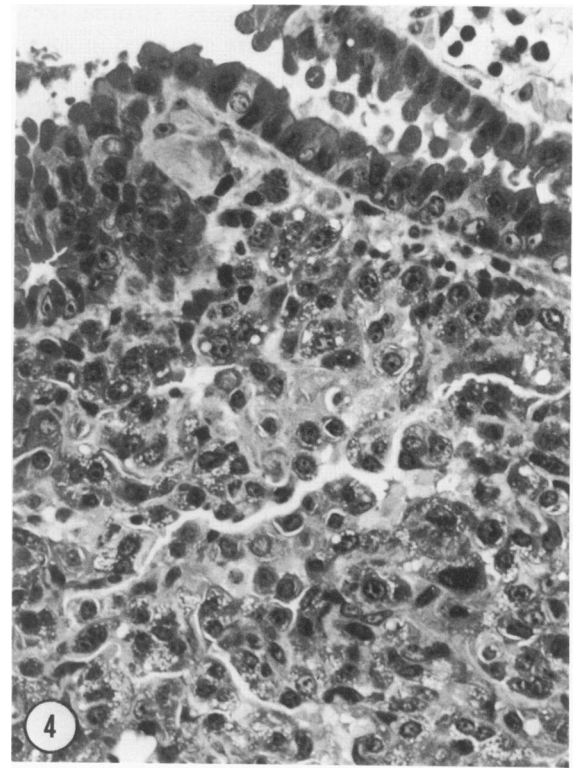
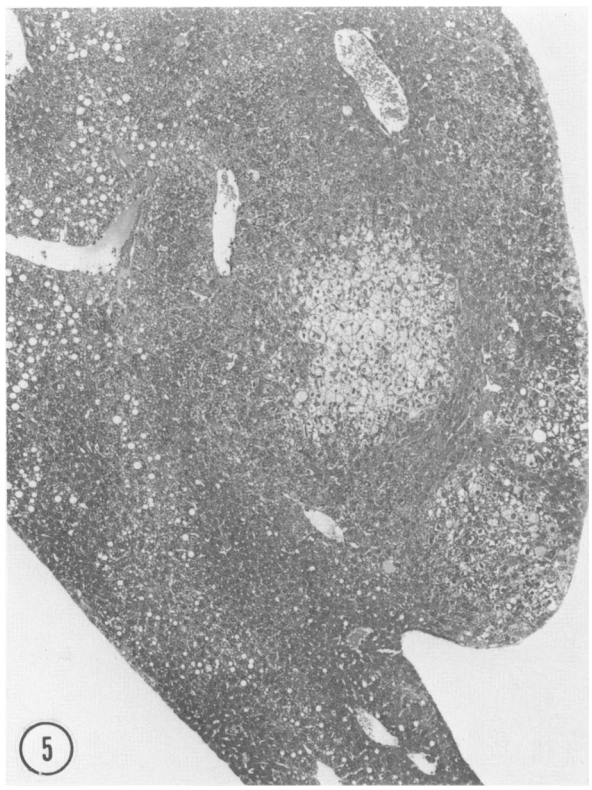
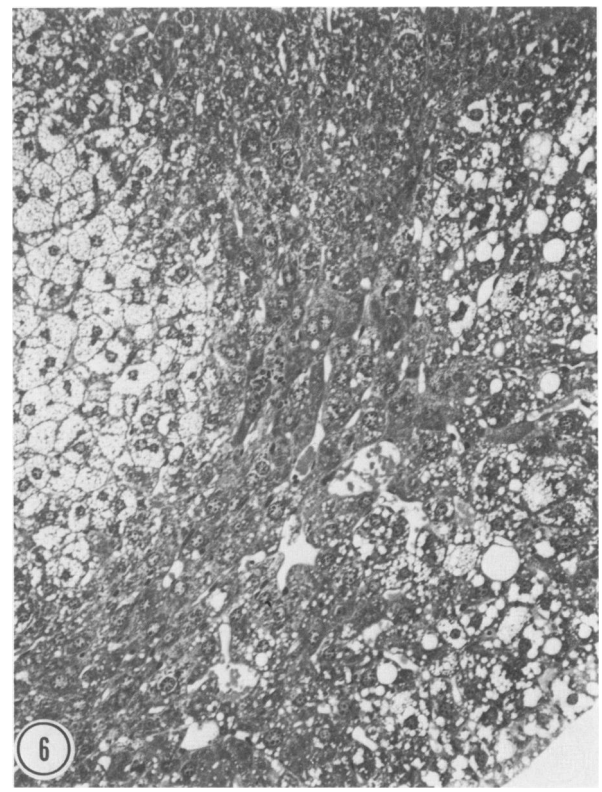
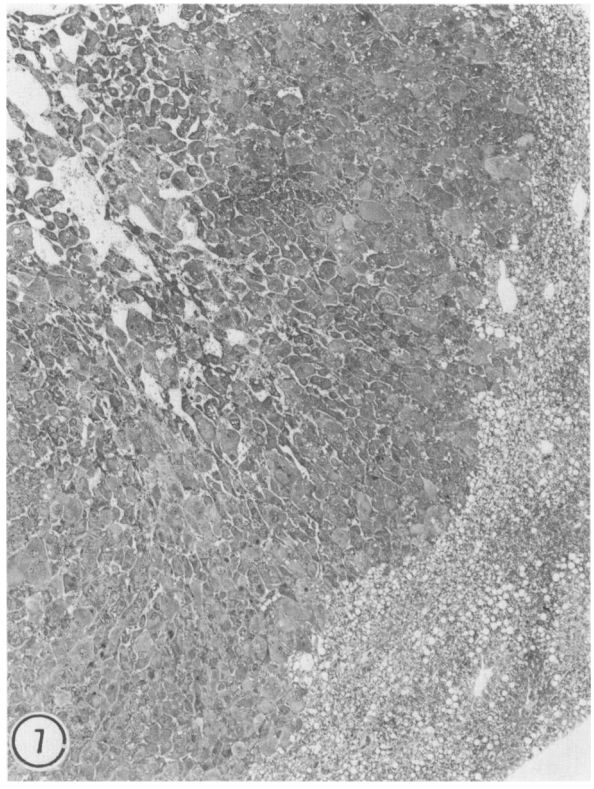


Figure 1—Testis from a sham-vasectomized mouse showing normal architecture with active spermatogenesis. (Hematoxylin and Lee, ×130) **Figure 2**—Testis from a vasectomized mouse showing dilation of tubules, aspermatogenesis, and degenerative changes in the tubular mucosa. (Hematoxylin and Lee, ×130) **Figure 3**—Alveologenic carcinoma. A subpleural solitary nodule projecting above the surface of the lung in close proximity to a bronchiole. (Hematoxylin and Lee, ×40) **Figure 4**—Alveologenic carcinoma with closely packed cuboidal and columnar cells with sparse stroma. (Hematoxylin and Lee, ×340)







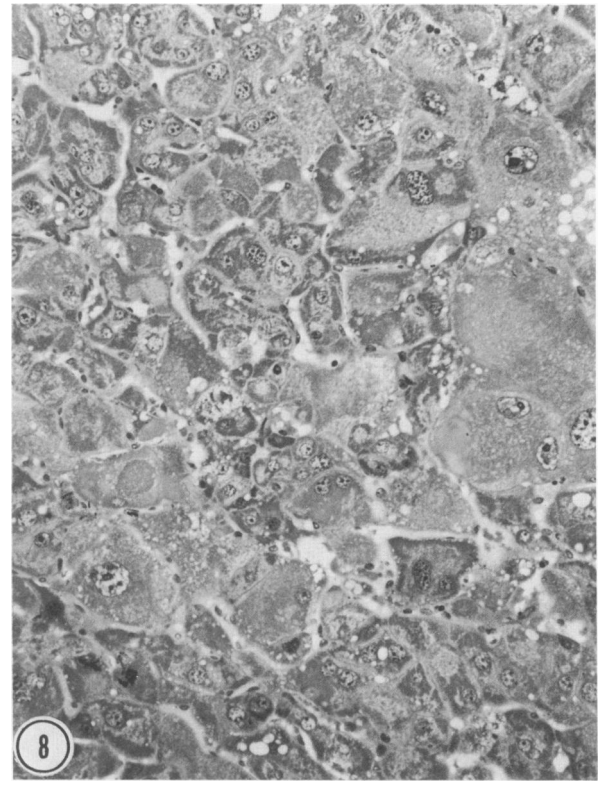
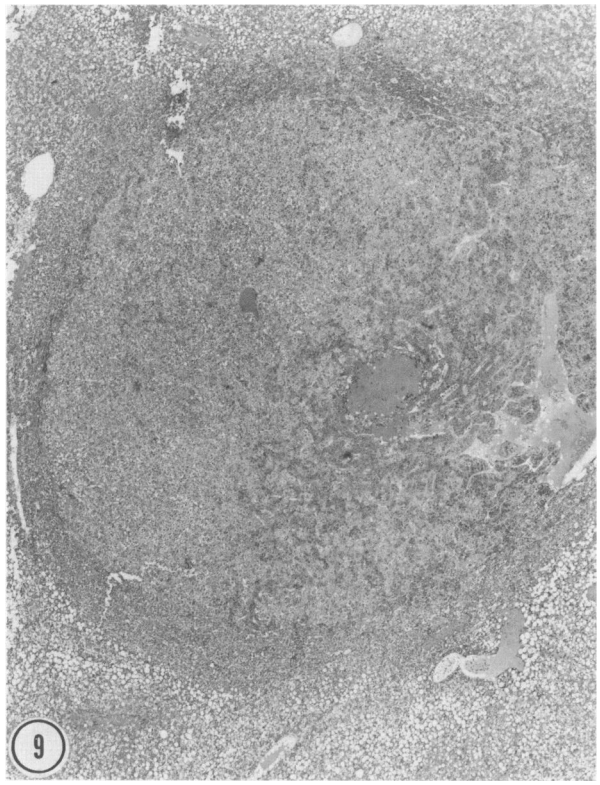
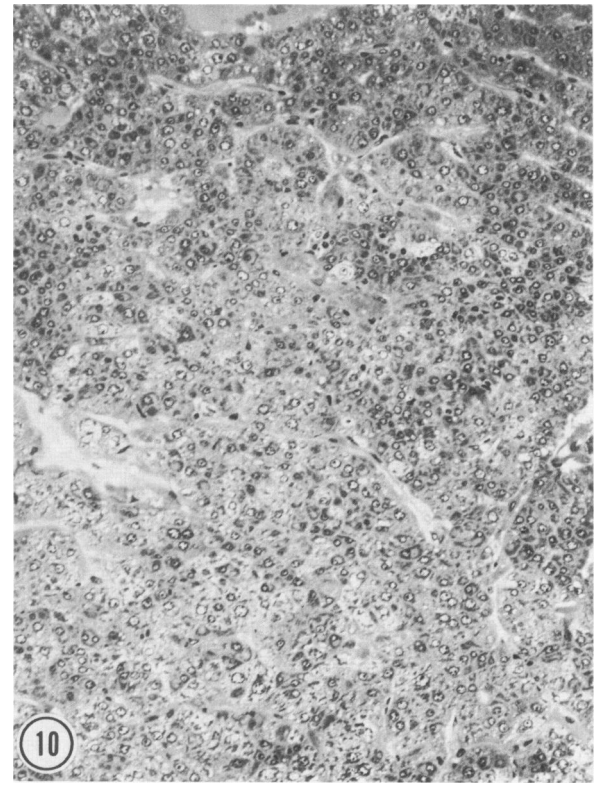
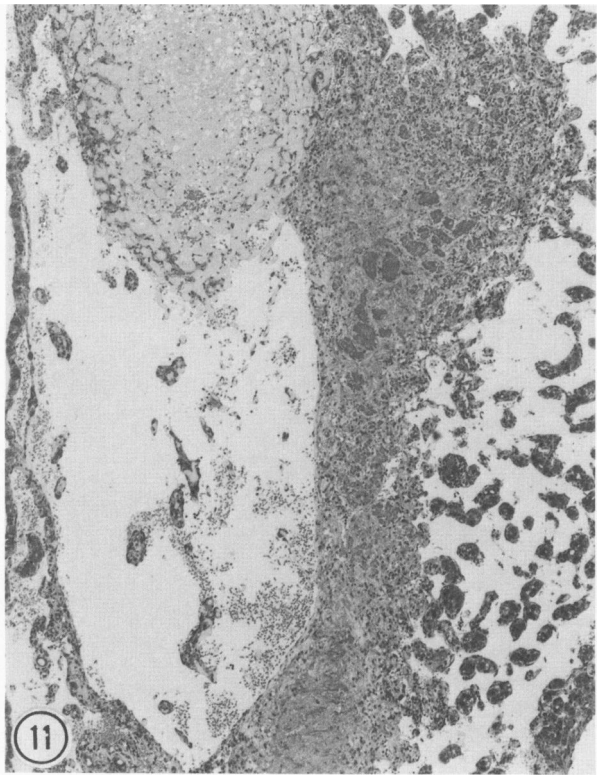


Figure 5—Photomicrograph of liver from a vasectomized mouse with multinodular hepatoma creating bulging of capsular surface. (Hematoxylin and Lee, × 40) **Figure 6**—Higher magnification of hepatoma in Figure 5 showing compression of surrounding cells and prominent cytoplasmic vacuolation. (Hematoxylin and Lee, × 130) **Figure 7**—A poorly differentiated hepatoma with irregular borders and dilated vascular channels appears morphologically malignant. (Hematoxylin and Lee, × 30) **Figure 8**—Higher magnification of Figure 7, showing multiple nuclei, mitotic figures in the *lower left*, and marked variability in nuclear size. (Hematoxylin and Lee, × 130)







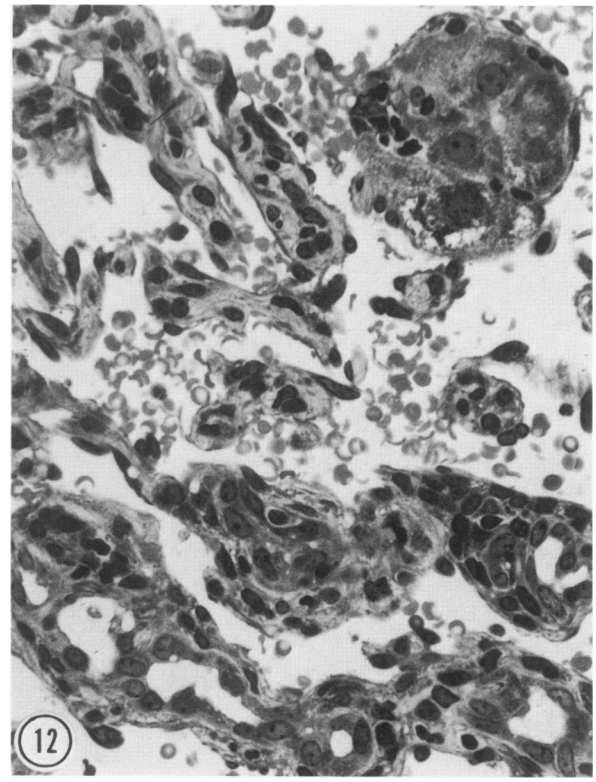


Figure 9—Hepatoblastoma with sheets of poorly differentiated cells demarcated from the surrounding hepatoma. (Hematoxylin and Lee, ×30) **Figure 10**—Higher magnification of Figure 9, showing sheets and cords of cells with vascular channels. (Hematoxylin and Lee, ×130) **Figure 11**—Hemangiomalike lesion with hemangioendotheliomatous character. (Hematoxylin and Lee, ×40) **Figure 12**—Higher magnification of an hemangiomalike lesion showing numerous vascular spaces in the tumor filled with blood. Residual liver cells are covered with endothelium and conglomerates of endothelial cells. (Hematoxylin and Lee, ×340)

and 1 control animal had at least 1 alveologenic carcinoma (46% versus 7%; $P \leq 0.05$) (Figures 3 and 4). Four vasectomized mice and 1 control had hepatic tumors (17% versus 7%), and 3 vasectomized mice and no controls (13% versus 0%) had pancreatic acinar adenocarcinomas or fibrosarcomas.

The mice in Study II were autopsied at a younger age (18 months) than those in Study I to avoid age-related attrition. Of the necropsied vasectomized mice, 48% had at least one liver tumor (hepatoma [Figures 5 to 8], hepatoblastoma [Figures 9 and 10], or hemangiomalike lesion [Figures 11 and 12]), and 19% had multiple liver tumors. In the sham-vasectomized group, 34% had at least one hepatic tumor at autopsy and 5% had multiple hepatic tumors ($P \leq 0.037$ and 0.003, respectively). The mean hepatic tumor burdens (sum of cross-section approximations) were 168 ± 19 sq mm for the vasectomy group and 139 ± 36 sq mm for the sham-vasectomy group. More vasectomized mice than sham-vasectomized controls (79% versus 49%; $P \leq 0.0004$) had large hepatic tumor burdens (sum of cross-sectional areas ≥31 sq mm; cutoff determined by Kolmogrov–Smirnov statistical test).

Of the vasectomized mice in Study II, 14% had at least one lung tumor (alveologenic carcinoma) (Figures 3 and 4), and 5% had more than one lung tumor. In the sham-vasectomized group, 13% had at least one lung tumor, and 2% had multiple lung tumors. The mean lung tumor burdens were 10.9 ± 2.9 sq mm and 6.5 ± 2.7 sq mm for animals in the vasectomy and control groups, respectively.

Of the vasectomy group, 26% had multiple tumors, as compared with 8% of the controls ($P \leq 0.0009$). Five mice from the vasectomy group had less common tumor types: 3 had transitional-cell tumors of the renal pelvis (Figures 13 and 14), 1 had a reticulum-cell sarcoma of the spleen, and 1 had a reticulum-cell sarcoma of a pancreatic lymph node. In contrast, none of the 97 sham-vasectomized mice examined in Study II had tumors in organs other than the liver and the lungs.

The tumor data and ANOVA statistical analysis from Study II are presented in Tables 1 and 2, and the combined data from Study I and Study II are summarized in Figure 15. Overall, hepatic tumors were the most common type and were more prevalent in the vasectomy than in the sham-vasectomy group ($P \leq 0.05$); vasectomized animals also had a higher

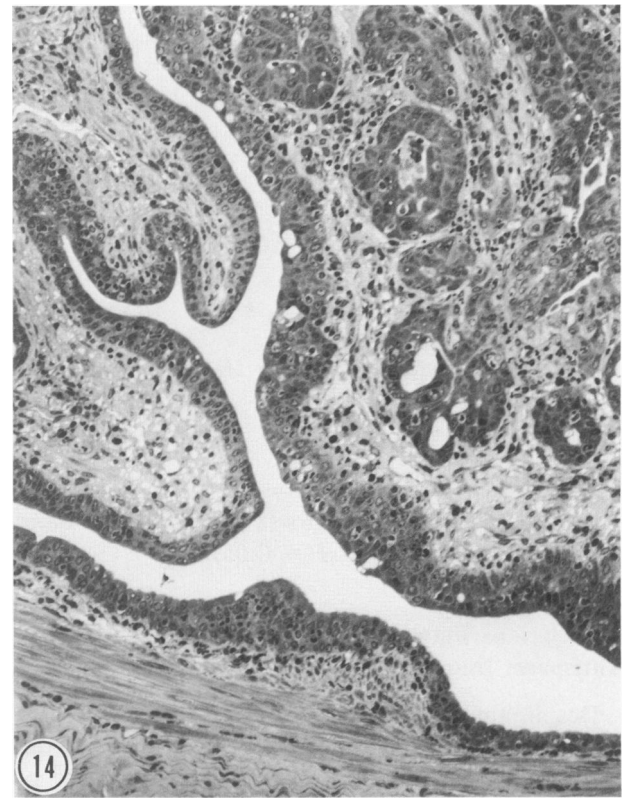


Figure 14—Higher magnification of Figure 13, demonstrating a change from a normal to a neoplastic adenomatous character. (Hematoxylin and Lee, ×130)

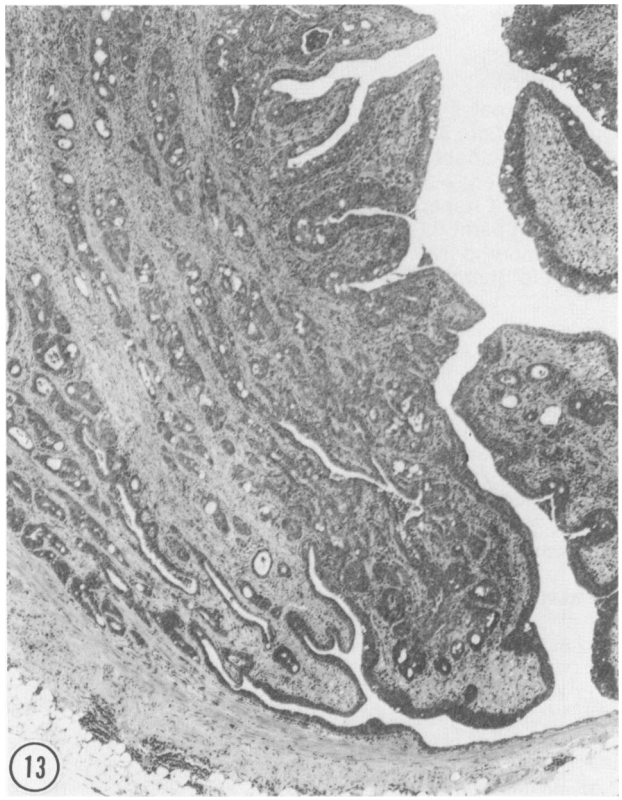


Figure 13—Transitional cell tumor of the renal pelvis causing hydronephrosis. (Hematoxylin and Lee, ×30)

Table 1—Tumors Found in Vasectomized and Age-Matched Sham-Vasectomized Animals in Study II

	Vx (n = 171)	Control (n = 97)
Liver		
Hepatoma	71	31
Hepatoblastoma	3	1
Hemangiomalike	8	1
Reticulum-cell sarcoma	1	0
Lung		
Alveologenic carcinoma	23	13
Other		
Spleen, reticulum-cell sarcoma	1	0
Pancreatic lymph node reticulum-cell sarcoma	1	0
Kidney, transitional-cell tumor	3	0

incidence of multiple tumors ($P \leqslant 0.005$) and more than one type of tumor ($P \leqslant 0.05$).

Associations Between Tumor Status and Antisperm Immunity

Despite the small number of mice in Study I, there was a positive association between necropsy serum IF-F antisperm antibody titers and the presence of tumors. Twelve of the 18 animals (67%) with antisperm antibody titers of ⩾8 had tumors at necropsy, whereas only 4 of the 20 mice (20%) without detectable antisperm antibodies had tumors ($P \leqslant 0.025$).

In Study II, antisperm antibody levels measured in necropsy serums by RIA were positively associated with hepatoma number ($P \leqslant 0.03$) and hepatoma size ($P \leqslant 0.03$) by ANOVA. Aspermatogenesis (probably resulting from cell-mediated antisperm immunity) also was strongly associated with hepatic tumor size and number. The degree of aspermatogenesis (percentage of seminiferous tubules without germ cells) was associated with the hepatoma number ($P \leqslant 0.015$) and hepatoma size ($P \leqslant 0.01$) by ANOVA. Patchy aspermatogenesis (⩾20% of tubules affected) and severe aspermatogenesis (⩾80%/tubules affected) were correlated with hepatic tumor number ($P \leqslant 0.045$ and $P \leqslant 0.033$). Severe aspermatogenesis was associated with hepatic tumor size ($P \leqslant 0.018$) by ANOVA.

Discussion

Spermatogenesis continues after vasectomy, and pressure and distention caused by the accumulation of spermatozoa in the vas deferens and epididymis often cause disruption of the barrier system that normally sequesters germ cells and other reproductive tract products from the rest of the body. Leakage of sperm degradation products from the reproductive tract after vasectomy can elicit autoimmune responses to sperm and testicular antigens. Humoral and cellular antisperm immunity have been detected in a large percentage of vasectomized men and experimental animals by numerous immunologic assays,[16] and patchy to severe autoimmune orchitis and aspermatogenesis have been detected by histologic examination in vasectomized animals[2,4,5] and men.[17] In the experimental models thus far examined, allergic orchitis and ensuing aspermatogenesis result from a cellular anti-germ-cell immune response.[18]

We detected humoral antisperm immunity or evidence for cell-mediated immunity (aspermatogenesis) in a majority of vasectomized mice in these studies. Aspermatogenesis was associated with antisperm antibodies detectable in serum at 12 months after vasectomy, but not every mouse with evidence of aspermatogenesis had such antibodies, indicating that humoral and cellular events may occur separately in mice after vasectomy. As in a previous report[2] we found that antisperm titers plateau or decrease slightly in vasectomized mice 12 months after vasectomy and that antisperm antibody incidence increases to 18% in sham-vasectomized control mice at this time. Antisperm immunity in aged control animals could be a result of 1) testicular damage induced by fighting, 2) cross-reacting antibodies that have

Table 2—Analysis of Variance of Vasectomized and Sham-Operated Mice. Association With Vasectomy for the Following Variables: Hepatoma Incidence, Hepatoma Tumor Burden (⩾ 31 mm²), Lung Tumor Incidence, Incidence of Aspermatogenesis, Immunofluorescence on Fixed Sperm (IF-F) for Acrosome and Tail at 6, 12, and 15 months (Necropsy Serums Were Titered), on Viable Sperm (IF-V), and RIA on Sperm

	Sham-vasectomized (Number positive/total evaluated)	Vasectomized (Number positive/total evaluated)	$P \leqslant$
Hepatoma incidence	33/97	82/171	0.005
Hepatoma tumor burden	16/33	65/82	0.0023
Lung tumor incidence	13/96	81/170	N.S.
Aspermatogenesis	1/97	57/145	0.001
IF-F 6 months, acrosome	2/98	30/181	0.001
IF-F 6 months, tail	0/97	7/181	0.001
IF-F 12 months, acrosome	9/100	48/174	0.001
IF-F 12 months, tail	6/101	26/174	0.001
IF-F 15 months, acrosome	16/88	19/151	NS
IF-F 15 months, tail	3/88	9/151	NS
IF-V	3/64	39/146	0.001
RIA—sperm	31/55	76/103	0.020

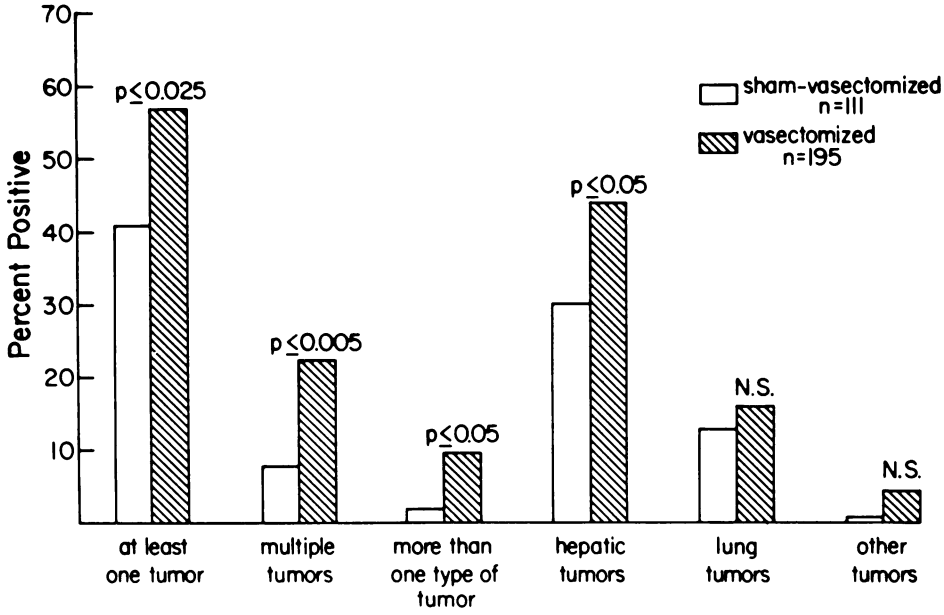


Figure 15—Histogram summary of the combined data from Study I and Study II.

been generated against different antigen sources (ie, bacterial products), or 3) general autoimmune phenomena associated with aging. We examined the testes for orchitis and aspermatogenesis at necropsy only; so we did not record a time course of cellular events associated with testicular pathologic changes. In testes taken from animals 15 months after vasectomy, we saw a high incidence of aspermatogenesis but no lymphocytic infiltration or other signs of inflammation. This finding indicates that the causative events, if cellular, probably occurred earlier.

The incidence of spontaneous tumors varies considerably among different strains of mice. Dr. David Meyers of the Jackson Laboratory found that BDF_1 mice have a moderately high spontaneous tumor incidence; he reported a 20% incidence of hepatic tumors and a 6% incidence of pulmonary tumors in normal male BDF_1 mice at 2 years of age (personal communication). Both vasectomy and control groups in Study II had an abnormally high incidence of hepatic tumors (48% and 34%, respectively). This is possibly due to the different origin of these mice (NCI colony) and exposure to different environmental factors. The incidence of hepatic tumors was significantly higher in the vasectomy group than in the control group in Study II ($P \leqslant 0.037$), and even more striking was the increased hepatic tumor burden (measured as the sum of cross-sectional areas) in the vasectomy group ($P \leqslant 0.006$). The incidence of lung tumors in Study II was not significantly different from that found in the Jackson Laboratory colony and was similar in both vasectomy and control groups (14% versus 13%). A significantly increased number of lung tumors was found in the 30-month-old vasectomized animals in Study I (46% versus 7%) and could reflect a predisposition to tumors of this type in older animals.

Vasectomized mice had larger tumor burdens ($P \leqslant 0.0023$) and a higher incidence of multiple tumors ($P \leqslant 0.005$) and rare tumor types than the age-matched control mice in this study. This suggests that both the initial stages of tumorigenesis and subsequent tumor growth may be affected by conditions associated with the vasectomized state. It is possible that sperm degradation products directly affect tumor initiation and development or have an indirect effect, such as interference with immunosurveillance mechanisms. We propose three hypotheses to explain the association between antisperm immunity and tumor number and size observed in these studies: 1) sperm immunity and tumor status could independently correlate with a third variable (ie, vasectomy), and thus correlate with one another without a causal relationship; 2) sperm immunity (or aspermatogenesis) may be a marker for sustained release of testicular products, some of which may directly exert carcinogenic or tumor-growth-promoting effects, or indirectly affect tumor growth by suppressing immune responses; 3) sperm immunity itself may affect tumor growth by invoking specific immunosuppressive mechanisms such as tolerance or enhancement.

Several reports have appeared that document powerful immunosuppressive products of spermatozoa and reproductive tract secretions.[19-21] Systemic immunosuppression following vasectomy has been reported in rhesus monkeys[22] and guinea pigs[23] but

was not observed in mice.[2] However, Hurtenbach and Shearer[24] recently showed that natural killer (NK) cell activity and the potential to generate cytotoxic T lymphocytes (two important immunosurveillance functions) were drastically reduced in mice after a single intravenous injection of 10^7 syngeneic spermatozoa. They proposed that sperm-induced immunosuppression could account for the abnormally high incidence of multiple viral infections and Kaposi's sarcoma in homosexual men.

It is well established that malignant cells express many embryonic gene products,[25,26] and indeed malignancy resembles the embryonic state (ie, rapid growth and proliferation, invasiveness, and insensitivity to feedback inhibition cues from surrounding tissues). Germ cells express some embryonic differentiation antigens,[27-29] and one group has shown evidence for cross-reacting antigenic structures on sperm or testicular germ cells and malignant cells.[30] Numerous reports have documented immunologic enhancement of tumor growth after immunization with embryonic tissues,[31-33] an effect thought to result from blocking antibodies and/or suppressor cells produced in response to cross-reacting antigens present on both embryonic and tumor tissue. The effect of immunization with germ cells on tumor growth is unknown at this time, but it is possible that a similar enhancing effect would occur; Tung[34] warns that immunologic enhancement of tumor growth could be a major immunopathologic complication of the use of embryonic or sperm antigens in vaccines for contraception. We recently found that leukocytes from vasectomized men with antisperm immunity responded to tumor antigens in vitro and that a majority of patients with certain types of cancer have high titers of antibodies reacting with sperm antigens.[35,36] This provides evidence that immunologically cross-reactive antigens are expressed on human germ cells and tumors, and raises the possibility that tumor immunosurveillance mechanisms may be affected by sperm autoimmunity in vasectomized men.

These studies and the overwhelming evidence that spermatozoa and other reproductive tract secretions contain potent immunosuppressive factors underscore the necessity for epidemiologic studies to determine whether vasectomy has long-term detrimental effects in man. One research group[37] has reported no significant increase in cancer rates in vasectomized men up to 5 years after vasectomy, but it is possible that such an effect will only be seen after a longer period or in older men with a higher tumor incidence.

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