Histopathology of Immunologic Regression of Tumor Metastasis in the Lymph Nodes [1]

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SUMMARY—A transplantable rat tumor (KMT-17) artificially infected with mouse Friend virus and subcutaneously inoculated into the foot of a syngeneic rat grew at first, but ultimately regressed. The tumor cells metastasized to the regional popliteal, lumbar, and inguinal lymph nodes and formed massive metastatic foci in these lymph nodes. These lymph node metastases also regressed spontaneously. Histopathologically, the infiltration and proliferation of lymphoid cells, reticulum cells, and fibrocytes were in the regressing metastatic tumor in lymph nodes as well as in the regressing transplanted tumor in the foot. Lymph node reactions such as temporary disappearance of follicles, intensive sinus histiocytosis, marked increase of large mononuclear cells, and plasmocytosis were apparent when there were metastatic tumor cells in the nodes. Our results, compared with those obtained from control experiments, demonstrate that the regression of the metastatic tumor in the lymph node as well as of the transplanted tumor in the syngeneic rats was due to immunologic reaction by the host.—J Natl Cancer Inst 52: 931-939, 1974.

MANY INVESTIGATORS studied the morphology and biology of experimental tumor metastasis in lymph nodes, especially its occurrence and development (*1–4*). However, no reports dealt with the spontaneous regression of metastatic tumors which occupied almost all of a given lymph node in syngeneic animals. Kobayashi et al. described the difficulties in transplanting tumor lines infected with mouse leukemia virus into susceptible rats and noted that, even when transplantation was successful initially, the tumor cells later regressed spontaneously (*5–7*). Recently, 1 line of rat tumors infected with Friend virus and subcutaneously (sc) inoculated into syngeneic rats showed temporary growth at the inoculation site, metastasizing to draining lymph nodes. The tumor eventually regressed, and lymph node metastasis spontaneously regressed. Our studies evaluate the histopathology of a rat tumor infected with Friend virus sc transplanted and of metastasis to the draining lymph nodes, with special reference to the spontaneous regression of tumor metastasis in the lymph nodes.

MATERIALS AND METHODS

Tumors and rats.—KMT-17 tumor, a fibrosarcoma induced in Wistar-King-Aptekman (WKA)/Mk rats by sc injection of methylcholanthrene, was donated by Dr. Miki Aizawa, Department of Pathology, Hokkaido University School of Medicine, Sapporo. The mean survival after sc transplantation of the tumor was 17 days. The cells were maintained in ascites or solid forms. The histocompatible WKA/Mk rats were the offspring of parents maintained by consecutive brother × sister mating for more than 210 generations in the Animal Laboratory, Hokkaido University. FV-KMT-17 tumor was obtained by infecting KMT-17 tumor with Friend virus. Methods of Friend virus infection of KMT-17 tumor were detailed elsewhere. KMT-17 tumors were serially passaged in WKA/Mk rats 30–50 days after receiving an intraperitoneal injection of Friend virus at birth. These were referred to as Friend-tolerant rats (*7, 8*), since they were in a viremia and tolerant state against Friend virus-induced transplantation antigen.

Procedures.—All rats weighing 120–150 g received a single injection of 5×10^6 living tumor cells sc in the right foot. They were divided into 4 experimental groups. Animals in groups 1 and 2 (45 in each) were normal WKA/Mk rats given injections of KMT-17 tumor in group 1 and of FV-KMT-17 tumor in group 2. At 2–8, 10, 12, and 14 days after injection of the tumors, 4 animals from each group were killed for examination and the 5 remaining were observed until death from tumor growth. Animals in groups 3 and 4, 17 in each, were Friend-tolerant WKA/Mk rats given injections of KMT-17 tumor in group 3 and of FV-KMT-17 in group 4. At 2, 6, 10, and 14 days after injection of tumors, 3 animals from each group were killed and the 5 survivors were observed until death.

The animals were killed under ether anesthesia and autopsied. Tumor size in the right foot and right popliteal, lumbar, and inguinal lymph nodes draining the tumor site were measured and the mean diameter was recorded. Portions of tissues were fixed in 4% formaldehyde solution. Sections of tissues were stained with hematoxylin and eosin and also Azan Mallory's for collagen fibers and Gomori's silver impregnation for reticulum fibers.

RESULTS

Growth of Transplanted Tumors

KMT-17 tumor inoculated into the right foot of normal WKA/Mk rats in group 1 grew, and 5 rats died on approximately the 18th day after inoculation with a maximum tumor size of 25 mm. However, FV-KMT-17 tumor inoculated into normal rats in group 2 showed temporary growth of the tumor (maximum size of 15 mm at the 6th day) followed by regression. At 15 days on the average, all FV-KMT-17 tumors completely regressed. The average growth curve of KMT-17 and FV-KMT-17 tumors is given in text-figure 1.

KMT-17 tumors in group 3 and FV-KMT-17 in group 4 grew well in the right foot of rats given

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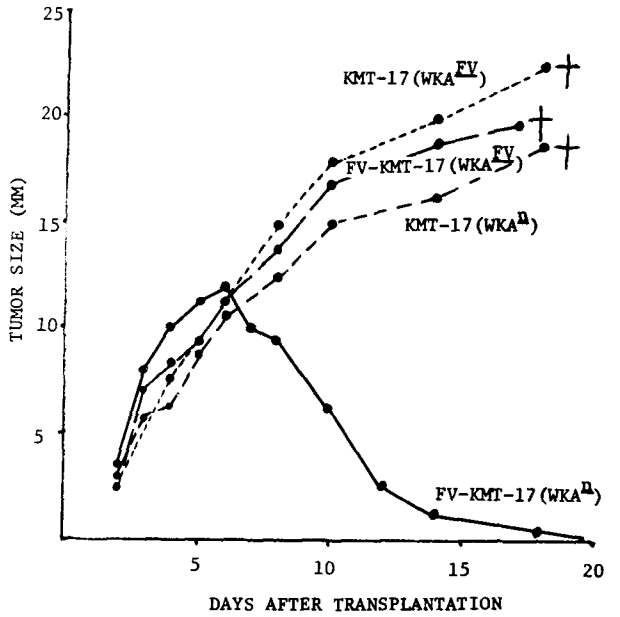
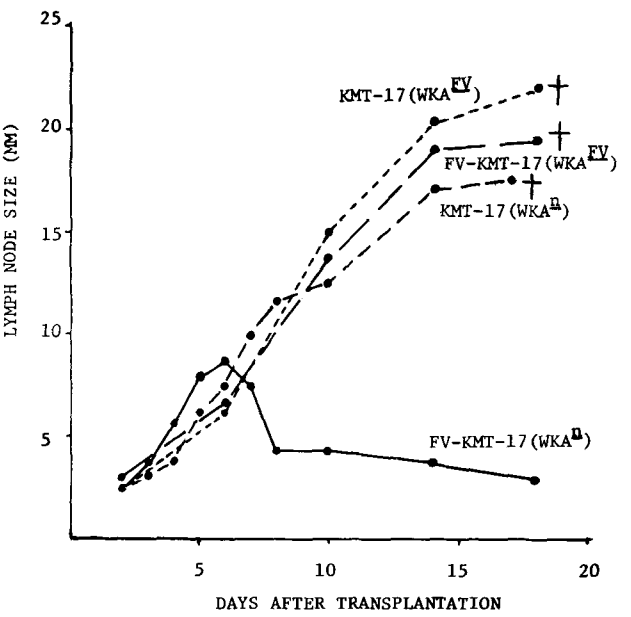


TEXT-FIGURE 1.—Growth curve of KMT-17 or FV-KMT-17 tumor in the right foot of normal and Friend-tolerant WKA rats. WKA^{n}: normal WKA rats. WKA^{FV}: Friend-tolerant WKA rats.



TEXT-FIGURE 2.—Enlargement of right lumbar lymph node after inoculation of KMT-17 and of FV-KMT-17 tumor into right foot of normal and Friend-tolerant WKA rats. WKA^{n}: normal WKA rats. WKA^{FV}: Friend-tolerant WKA rats.

Friend virus at birth (Friend-tolerant), and all 5 rats in each group died from tumor growth after ≈15 days (text-fig. 1). No regressions were seen in rats inoculated with FV-KMT-17 tumor.

Histology of Transplanted Tumors

Histologic examination of KMT-17 tumor grown in the right foot of normal WKA/Mk rats in group 1 showed massive proliferations of homogeneous and uniform tumor cells (fig. 3). When rats died from the tumor growth, focal necrosis of the tumor due to ischemia set in. In group 2, FV-KMT-17 tumors growing in normal rats showed the same findings as for KMT-17 tumors by the 4th day after tumor inoculation (fig. 4). After 5 days, however, abundant lymphocytes, reticulum cells, and fibroblasts appeared within the tumor tissues. Degeneration, necrosis, and elimination of tumor cells gradually occurred (fig. 5). After 10 days, these areas showed residual nests of fibroblasts containing some plasma cells, but no tumor cells (fig. 6).

Both KMT-17 tumor in group 3 and FV-KMT-17 tumor in group 4 inoculated into Friend-tolerant rats showed massive proliferation of tumor cells as did KMT-17 tumor in group 1. When the rats died at 18 days, focal necrosis due to ischemia in the tumor tissue was found.

Enlargement of Lymph Nodes

Right popliteal, lumbar, and inguinal lymph nodes draining the KMT-17 tumor site in normal WKA/Mk rats in group 1 enlarged progressively with tumor growth. When all the rats died from the tumor, lymph nodes were at their maximum size. However, the lymph nodes in normal rats inoculated with FV-KMT-17 tumor in group 2 enlarged temporarily; then they returned to normal size. The average size of the right lumbar lymph node in normal rats after inoculation with KMT-17 and FV-KMT-17 tumors is presented in text-figure 2. The lymph node in rats inoculated with FV-KMT-17 reached a maximum size of 8 mm, 4 times that of the normal control rats, at the 6th day, then returned to normal in ≈15 days (figs. 1, 2). Lymph nodes in Friend-tolerant rats inoculated with KMT-17 in group 3 or FV-KMT-17 tumor in group 4 enlarged progressively with growth of tumor (text-fig. 2). All rats showed a maximal enlargement of lymph nodes at death on approximately the 18th day after inoculation.

Histology of Tumor Metastasis in Lymph Nodes

Lymph node metastasis of KMT-17 tumors in group 1 and FV-KMT-17 tumors in group 2 inoculated into normal WKA/Mk rats first appeared in some animals of each group at day 2. The area of invasion of the tumor cells was from the marginal sinus to the intermediary sinus rather than the cortical pulp (fig. 7). These places were invaded more by tumor cells on days 3 and 4. On day 5, all lymph nodes examined, right popliteal, lumbar, and inguinal, showed tumor metastasis in various grades. In some cases, the lymph nodes were fully occupied by tumor cells without any normal structure (figs. 8–10). The presence and the grade of metastasis in each group are shown in tables 1 and 2. The grade of lymph node metastasis was divided into 3 classes following Kurokawa-Sato's classification as shown in text-figure 3. In normal rats in group 1 inoculated with KMT-17 tumor and killed at day 14, lymph node metastases were observed in the highest degree of frequency and

TABLE 1.—*Grade of lymph node metastasis after inoculation of KMT-17 or FV-KMT-17 tumor into right foot of normal WKA rats**

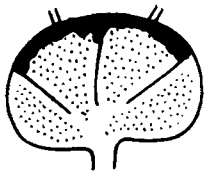
Days after inoculation	KMT-17, lymph nodes			FV-KMT-17, lymph nodes		
	Lumbar	Popliteal	Inguinal	Lumbar	Popliteal	Inguinal
2	0–1	0	0	0–I	0–I	0–I
3	I	0–I	0–I	I–II	0–I	0
4	I–II	I–II	0–I	I–II	0–I	0–I
5	II–III	I–III	I–II	II–III	I–III	I–III
6	II–III	II–III	I–III	I–II	I–II	I–II
7	III	III	II–III	I–II	0–II	0–I
8	III	III	III	I	0	0–I
10	II	III	III	0	0	0
12	III	III	III	0	0	0
14	III	III	III	0	0	0

*4 animals were examined on each day.

TABLE 2.—*Grade of lymph node metastasis after inoculation of KMT-17 or FV-KMT-17 tumor into right foot of Friend-tolerant WKA rats**

Days after inoculation	KMT-17, lymph nodes			FV-KMT-17, lymph nodes		
	Lumbar	Popliteal	Inguinal	Lumbar	Popliteal	Inguinal
2	0	0–I	0–I	0	0–I	0
6	II–III	III	II–III	III	II–III	II–III
10	III	III	III	III	III	III
14	III	III	III	III	III	III

*3 animals were examined on each day.



Grade I.
Tumor cells proliferate in marginal sinus.

Grade II.
Tumor cells proliferate as far as intermediary sinus and invade into parenchyma.

Grade III.
Tumor cells occupy almost all the lymph node.

TEXT-FIGURE 3.—Schematic representation of grade of lymph node metastasis (by Kurokawa, 1970).

grade. However, in metastatic lymph nodes of normal rats inoculated with FV-KMT-17 tumor in group 2, degenerative and necrotic changes of tumor cells accompanied by infiltration of reticulohistiocytes and lymphocytes were recognized at day 6 (figs. 11–13). FV-KMT-17 tumor cells in these lymph nodes rapidly decreased, which indicated sparse metastatic foci. Tumor cells with signs of degeneration occupied only marginal sinuses in some lymph nodes on day 8 (fig. 14). At day 10, no tumor cells were observed in all lymph nodes examined.

Frequencies and grades of lymph node metastasis in Friend-tolerant rats inoculated with KMT-17 tumor in group 3 or FV-KMT-17 tumor in group 4 showed similar progressive increases until death at about 18 days. No regression in lymph node metastasis of tumors in either group occurred.

Histologic changes of elements in lymph nodes with tumor metastasis, such as follicles, sinus histiocytes, large mononuclear cells, and plasma cells, were examined. A summary of the results obtained from findings of lymph nodes at 2 days (early stage), 6 days (middle stage), and 10 and 14 days (late stage) is given in table 3. Marked changes of lymph node elements were observed in normal WKA/Mk rats in group 2 inoculated with FV-KMT-17 in which tumor growth and lymph node metastasis regressed finally. Temporal disappearance of follicles, marked sinus-histiocytosis, and a prominent increase of both large mononuclear cells and plasma cells were seen in these lymph nodes (figs. 15–20). In the lymph nodes of rats in groups 1, 3, and 4, progressive proliferation of metastatic tumor cells, no regression of tumor growth, and weak changes of residual elements in the increase of large mononuclear cells and plasma cells were observed only at the middle stage. After the 10th day of tumor inoculation, almost the entire lymph nodes were occupied with tumor metastasis, and lymph node elements had disappeared.

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TABLE 3.—*Histologic changes in the lumbar lymph nodes after inoculation of KMT-17 or FV-KMT-17 tumors into right foot of normal and Friend-tolerant WKA rats**

Changes	Tumor	Rats	Days			
			2	6	10	14
Follicles	KMT-17	Normal	±	±	−	−
	FV-KMT-17	"	−	−	−	±
	KMT-17	Tolerant	±	±	−	−
	FV-KMT-17	"	±	±	−	−
Sinus histiocytosis	KMT-17	Normal	±	−	−	−
	FV-KMT-17	"	+	+	++	+
	KMT-17	Tolerant	±	−	−	−
	FV-KMT-17	"	±	−	−	−
Large mononuclear cells	KMT-17	Normal	±	+	+	−
	FV-KMT-17	"	±	+++	++	+
	KMT-17	Tolerant	±	−	−	−
	FV-KMT-17	"	±	+	−	−
Plasma cells	KMT-17	Normal	±	+	+	−
	FV-KMT-17	"	±	++	++	+
	KMT-17	Tolerant	±	−	−	−
	FV-KMT-17	"	±	−	−	−

*Grade of changes: −, disappeared; ±, normal; +, slightly increased; ++, moderately increased; +++, markedly increased.

DISCUSSION

Spontaneously developed or chemically induced tumors were difficult to grow in normal syngeneic rats after they were artificially infected with Friend virus; even when they grew initially, the tumors regressed spontaneously (*5*, *6*). Friend virus-injected tumors grew only in Friend-tolerant rats neonatally inoculated with Friend virus at birth or in immunosuppressive rats by irradiation. The same results were obtained with other murine leukemia viruses, Rauscher or Gross virus, and rat tumors (*7*). It was assumed that this phenomenon occurred because the rat tumor infected with murine leukemia virus acquired virus and/or cellular antigens related to the murine leukemia virus, which were recognized as "foreign" by adult rats. Then the tumors were immunologically rejected by the host rats. These findings were referred to as "xenogenization of tumors," which is defined as the immunologic regression of tumors without previous immunization in the host. Studies of xenogenization of tumors have been done by transplantation, immunofluorescence, and cytotoxicity tests (*5–8*).

In the present experiment, Friend virus-infected FV-KMT-17 tumors inoculated into the foot of normal syngeneic rats grew initially, but regressed eventually. In the Friend-tolerant rats, FV-KMT-17 tumor grew well and killed the host. However, noninfected KMT-17 did not regress in either normal or Friend-tolerant rats. These results indicate that FV-KMT-17 tumor regression in normal rats occurred because of immunologic rejection in the host by xenogenization of tumors.

Histologic examination of FV-KMT-17 tumors in normal rats revealed that the tumor tissues were composed of proliferative and infiltrative tumor cells by the 4th day after inoculation. The findings were similar to the histology of FV-KMT-17 tumor in Friend-tolerant rats and also KMT-17 in both normal and Friend-tolerant rats by the same day. Then, after the 5th day, only in FV-KMT-17 tumor tissues in normal rats, degeneration, necrosis, and disappearance of the tumor cells occurred, accompanied by reactive infiltrations of lymphocytes, reticulum cells, histiocytes, and fibrocytes. The tumor cells disappeared completely from the site of inoculation at 10 days. These findings were similar to the histology of homograft rejection with normal skin (*9*), kidney (*10*), and tumors (*11*). In autochthonous tumors of mice induced with murine sarcoma virus, similar findings of tumor regression were also obtained (*12*). Therefore, it is strongly suggested from the histologic characteristics of our study that the regression of FV-KMT-17 tumor in normal rats was due to immunologic reaction by the host.

The most characteristic result emerging from this work was that FV-KMT-17 tumor cells metastasizing to lymph nodes regressed spontaneously in normal rats. In experimental reports on tumor metastasis in lymph nodes, many investigators described the mechanism of formation and development of metastasis (*1–4*). No reports have dealt with the spontaneous regression of the tumor metastasis in the lymph nodes of a syngeneic tumor-bearing host. In our histologic examination of lymph nodes in normal rats inoculated with FV-KMT-17 tumor, 2 phases were observed: 1) lodgment and proliferation of metastatic tumor cells and 2) regression or elimination of metastatic foci. The first phase of lymph node metastasis of FV-KMT-17 in normal rats was similar to that of the same tumor in Friend-tolerant rats. It was also like the metastasis of KMT-17 tumor in normal and Friend-tolerant rats. No more characteristic findings than already reported were found in the lodgment and proliferation of metastatic tumors. In the second phase, after the 5th day of inoculation, degeneration,

necrosis, and elimination of tumor cells were observed only in the metastatic foci of FV-KMT-17 tumors in normal rats, accompanied by reactive infiltration of lymphocytes, reticulum cells, and histiocytes as seen in the FV-KMT-17 tumor tissue regressing in the foot of normal rats. The only histologic difference between regressing FV-KMT-17 tumor tissue in the foot and lymph nodes of normal rats was the weak proliferation of fibrocytes in the lymph node metastasis. Thus regression of FV-KMT-17 tumor metastasis in lymph nodes might have occurred with the immunity of host rats, which was the same mechanism as the tumor regression in the foot.

Morphologic changes in the lymph nodes with FV-KMT-17 tumor metastasis were the disappearance of lymph follicles and the proliferation of large mononuclear cells, plasma cells, and sinus histiocytes. These were noted in the lymph node of the host given intense antigenic stimulation and in the draining lymph nodes of the host in which homograft rejection of skin, kidney, and tumors had occurred (*9–13*). Whether sinus histiocytosis was related to the host defense against cancer and also to the prognosis of the cancer patient was discussed (*14–17*). In our study the most marked sinus histiocytosis was in the lymph nodes where FV-KMT-17 metastasized and then regressed throughout the experiment. Sinus histiocytosis was weakly recognized in the lymph nodes of the experimental rats in which metastasis did not regress.

Zbar et al. (*18*) and Hanna et al. (*19*) reported the regression of intradermally (id) inoculated tumors and prevention of lymph node metastasis after intralesional injection of BCG in tumor-bearing guinea pigs. In their histologic examinations, granulomatous reaction, similar to the delayed-type hypersensitivity of inflammation, lasted several weeks in both the id regressing tumors and the metastatic lymph nodes of BCG-inoculated hosts. In our present study, however, no such lasting granulomatous changes were found, and metastatic tumors completely regressed at 10 days after their inoculation into the host. We considered that the granulomatous reaction in lymph nodes showing regression of metastatic tumors after BCG injection was due to inflammatory changes related to BCG, not to the immunologic response induced by the tumor in the host. Although it has been suggested that lymph node change in human patients with cancer, showing the histologic findings above, indicated an immunologic response of the host, we could not find the specific histologic characteristics related to the immunologic regression of the tumor in both the inoculation site or the metastatic lymph nodes. Further histologic examinations will be made in the hope of discovering the characteristic change in lymph nodes in which the regression of tumor metastasis is shown.

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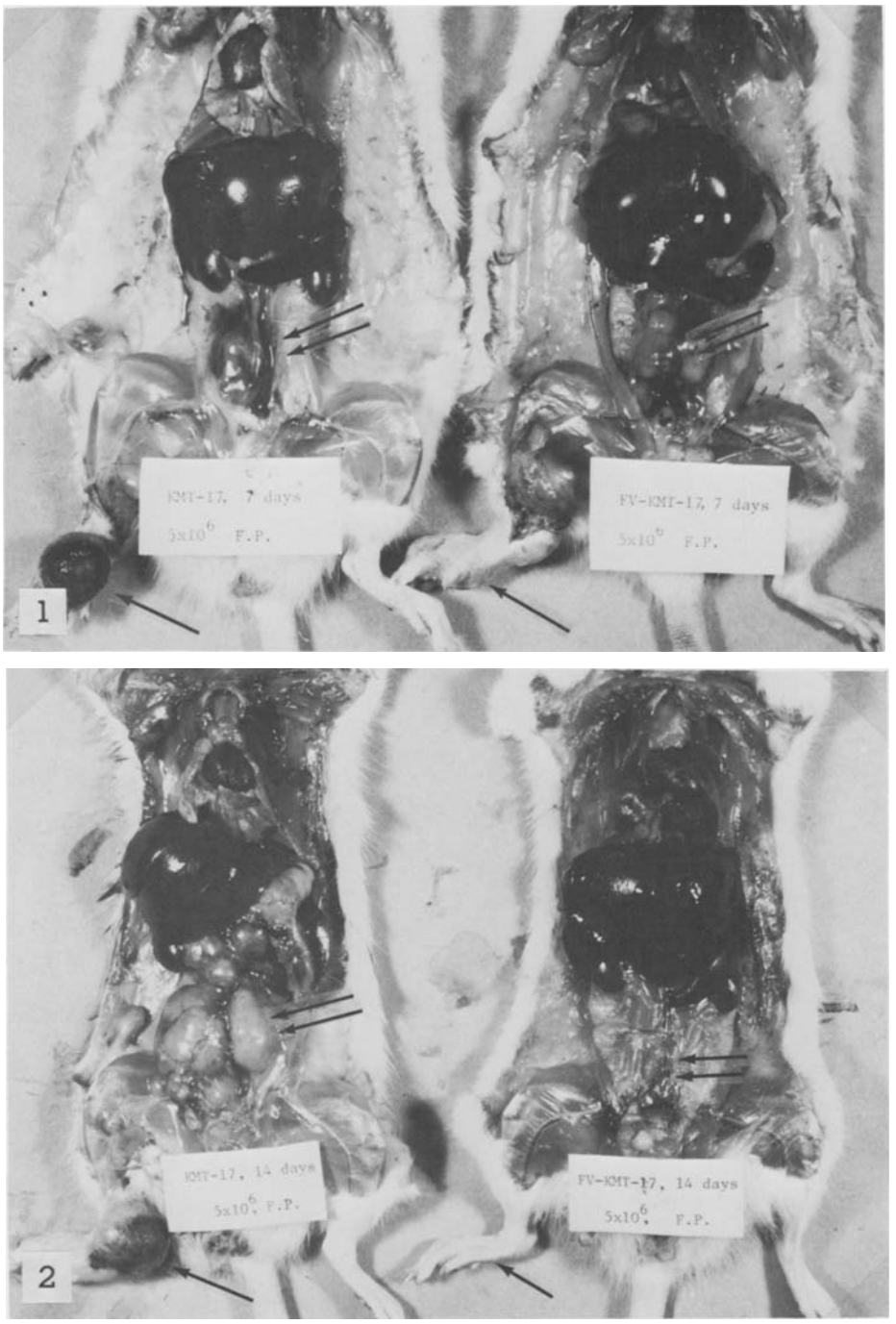


FIGURE 1.—Rats 7 days after inoculation of KMT-17 (*left*) or FV-KMT-17 (*right*) tumor into right foot. *Note* solid tumor grown in right foot of each rat (*arrow*) and enlargement of lumbar lymph node (*arrows*).

FIGURE 2.—Rats 14 days after inoculation of KMT-17 (*left*) or FV-KMT-17 (*right*) into right foot. *Note* solid KMT-17 tumor grown in right foot (*arrow*) as well as enlargements of abdominal lymph nodes (*arrows*) and absence of FV-KMT-17 tumor in right foot (*arrow*) as well as lumbar lymph node in normal size (*arrows*).

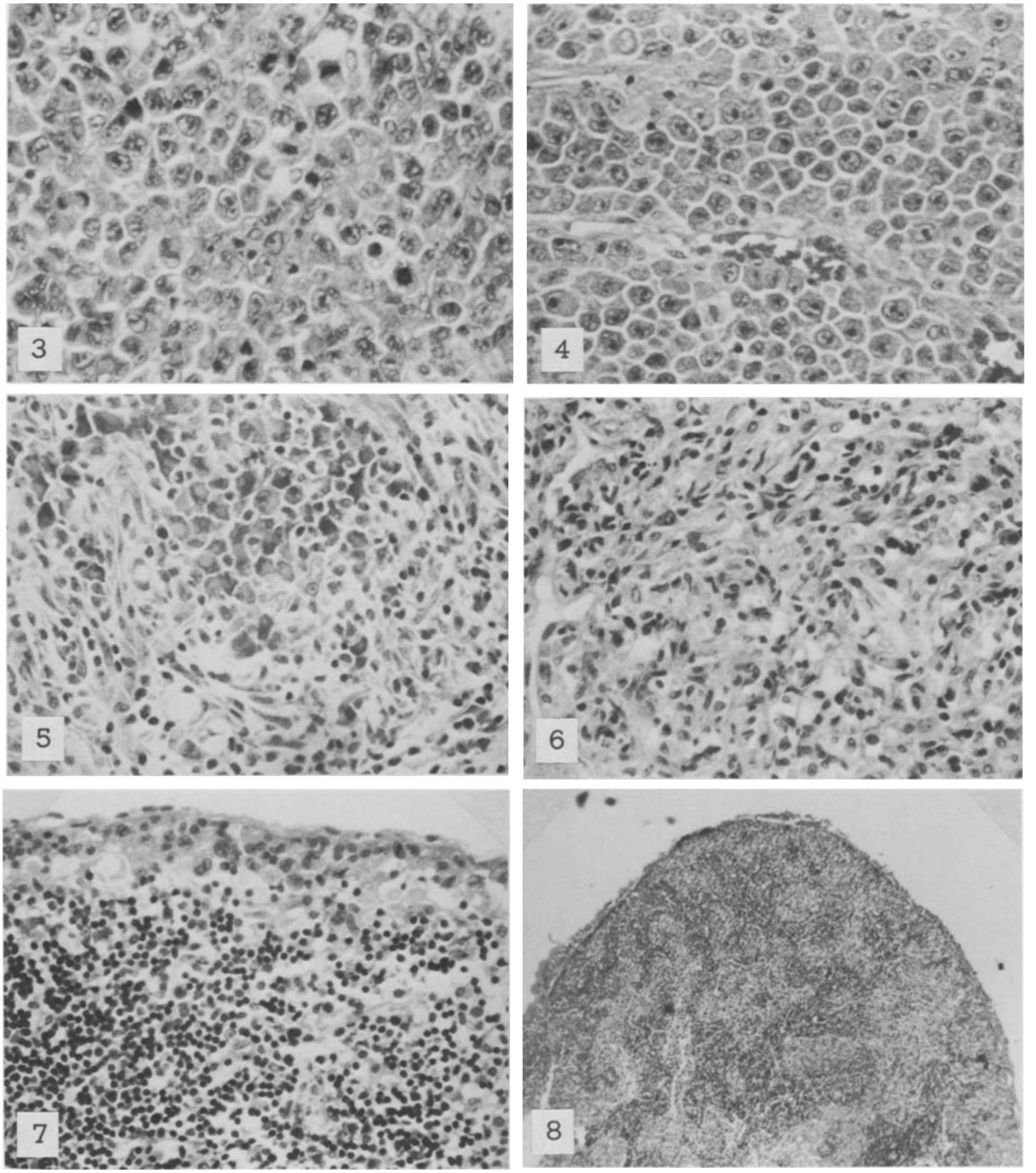


FIGURE 3.—KMT-17 tumor cells in foot 4 days after inoculation. × 300

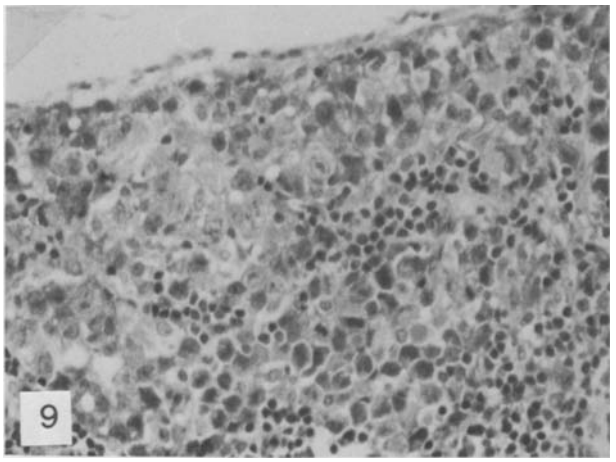
FIGURE 4.—FV-KMT-17 tumor cells in foot 4 days after inoculation. Cells show a regular pattern like KMT-17 tumor cells. × 300

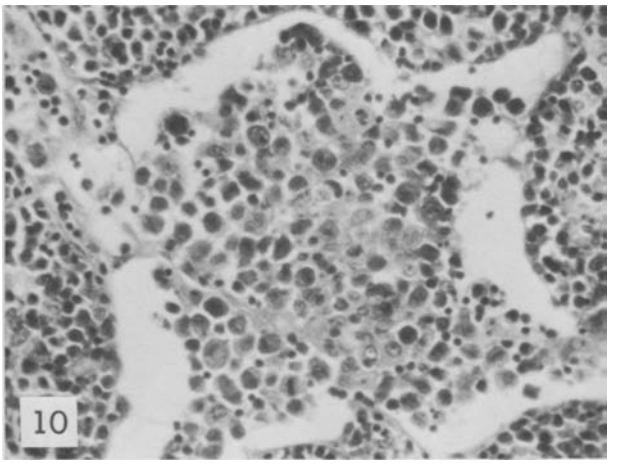
FIGURE 5.—FV-KMT-17 tumor in foot 7 days after inoculation. *Note* degenerative changes of tumor cells and infiltration of fibroblasts accompanied by lymphoid cells. × 250

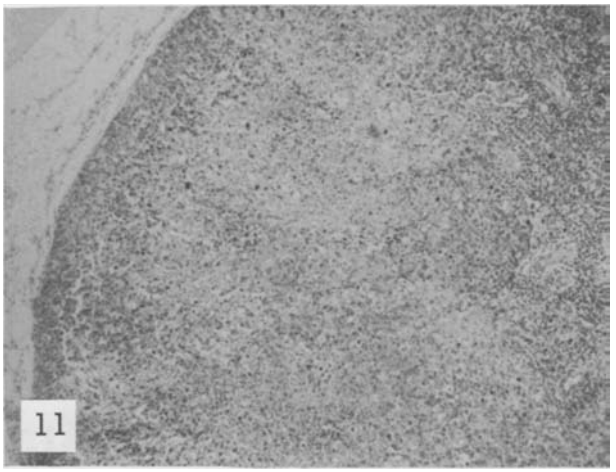
FIGURE 6.—Tissue in foot 10 days after inoculation of FV-KMT-17. No tumor cells were found. × 300

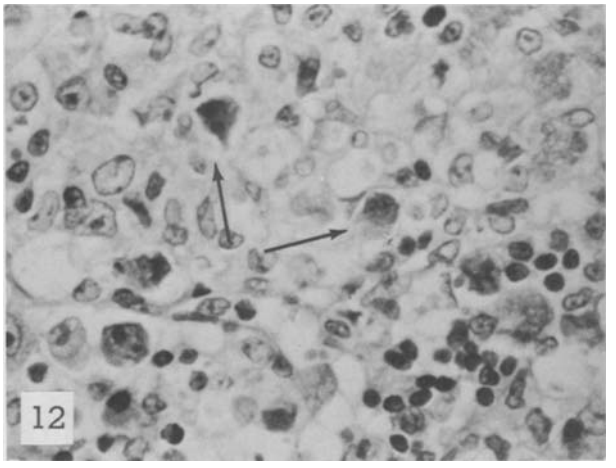
FIGURE 7.—Metastasis of FV-KMT-17 tumor cells in marginal sinus of right lumbar lymph node 2 days after inoculation of tumor cells. × 250

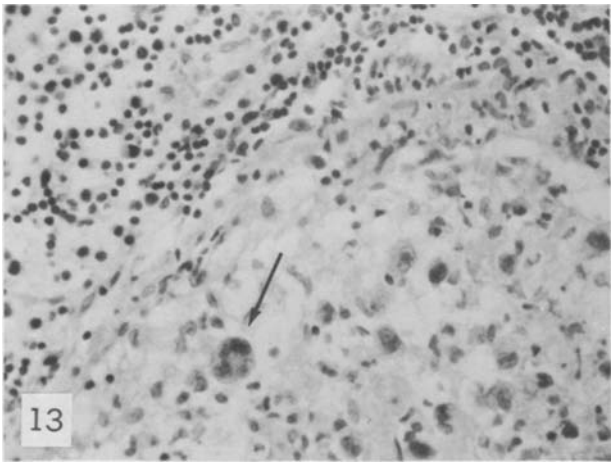
FIGURE 8.—Lymph node metastasis of FV-KMT-17 tumor 4 days after inoculation. Tumor cells deeply infiltrate cortical and medullary areas. × 60











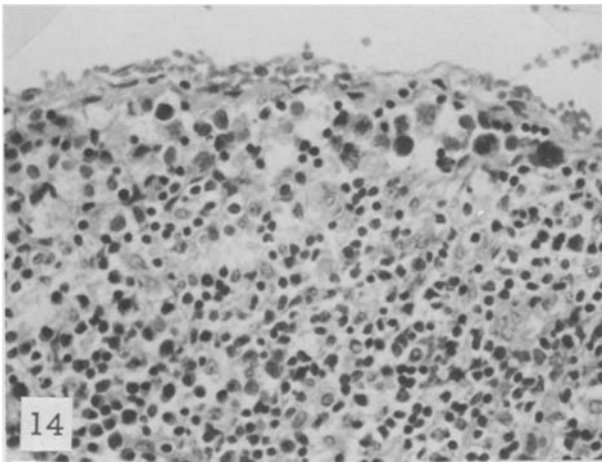


FIGURE 9.—Higher magnification of metastasis of FV-KMT-17 tumor cells which invade cortical pulp 4 days after inoculation. × 250

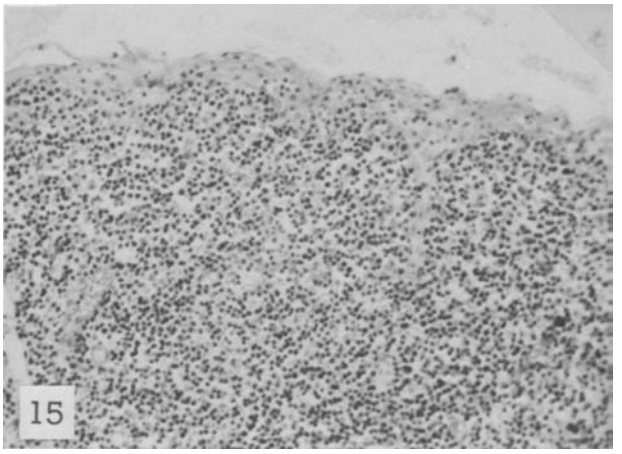
FIGURE 10.—Higher magnification of metastasis of FV-KMT-17 tumor cells which are in embolic state in medullary sinus of lymph node. × 250

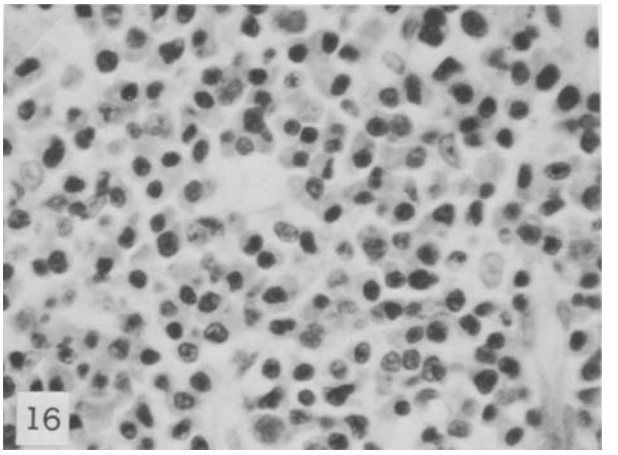
FIGURE 11.—Sparse appearances of metastatic foci of FV-KMT-17 tumor cells in lymph node 6 days after inoculation. × 80

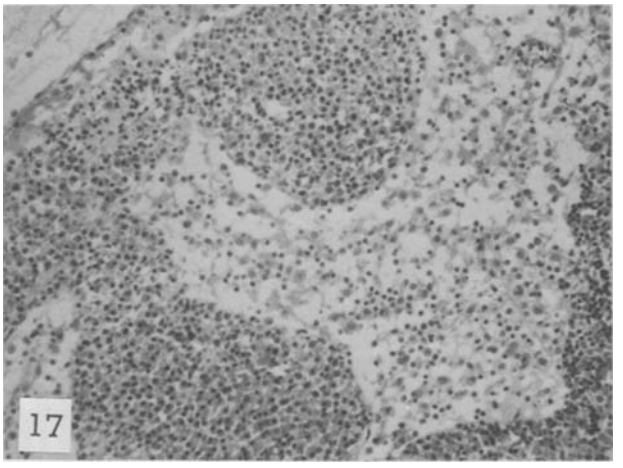
FIGURE 12.—Higher magnification of degenerating FV-KMT-17 tumor cells (*arrows*) in medullary area trapped in reticulohistiocytic reaction centers intermixed with lymphoid cells. Lumbar lymph node 6 days after inoculation. × 300

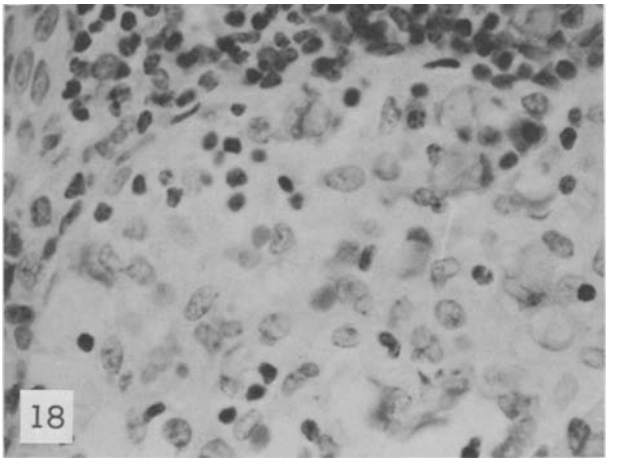
FIGURE 13.—Degenerating FV-KMT-17 tumor cells (*arrow*) in medullary sinus of lymph node 6 days after inoculation. *Note* marked syncytial histiocytosis. × 250

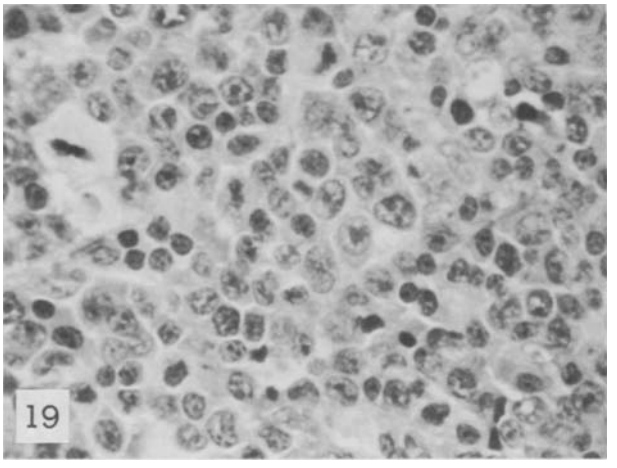
FIGURE 14.—Small number of FV-KMT-17 tumor cells with signs of degeneration in marginal sinus of lumbar lymph node 8 days after inoculation. × 250











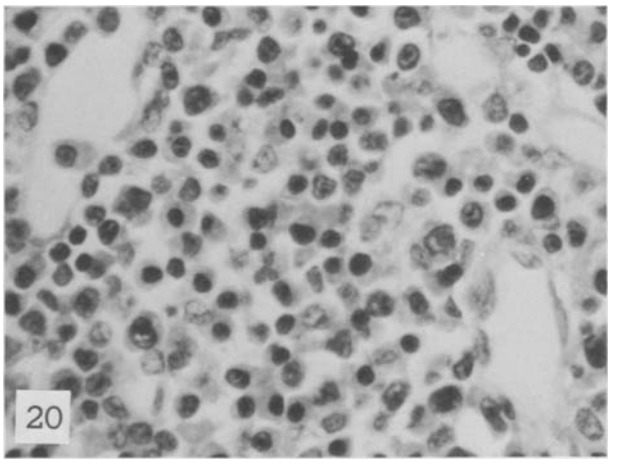


FIGURE 15.—Disappearance of follicles in lumbar lymph node of FV-KMT-17 tumor-inoculated rat at day 2. × 120

FIGURE 16.—Plasmocytosis in cortical pulp of lumbar lymph node of rat inoculated with FV-KMT-17 tumor at day 2. × 400

FIGURE 17.—Syncytial sinus histiocytosis in lumbar lymph node 10 days after inoculation of FV-KMT-17 tumor cells. × 120

FIGURE 18.—Higher magnification of sinus histiocytosis in lymph node 10 days after inoculation of FV-KMT-17 tumor cells. × 400

FIGURE 19.—Proliferation of large mononuclear cells in medullary area of FV-KMT-17 tumor-metastasized lymph node 6 days after inoculation. × 400

FIGURE 20.—Appearance of large mononuclear cells and plasmocytosis in medullary cord of FV-KMT-17 tumor-metastasized lymph node 6 days after inoculation. × 400