The Pathology of Tumors and Other Lesions Induced in Rodents by Virus Derived from a Rat with Moloney Leukemia

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Summary

The morbid anatomic and histologic changes following inoculation of a sarcoma-inducing virus (derived from a rat with Moloney leukemia) into mice, rats, and hamsters are described. Changes similar to those in Friend disease, with proliferation of reticulum cells and erythroblasts, occurred in mice and rats. In mice, rats, and hamsters, there were also solid sarcomas and angiomatous tumors. There was also ectasia of lymph nodes and lymphatics which was associated with inflammatory, hyperplastic, or neoplastic lesions in the wall of the cysts. Attempts at serial transplantation of some of the solid tumors were successful in syngeneic mice and allogeneic hamsters. Tumors failed to grow in chickens or on the chorioallantoic membrane of embryonated eggs. The histogenesis of the tumors and ectatic lesions is discussed.

Introduction

The origin and some of the biologic properties of a filtrable agent oncogenic for mice, rats, and hamsters have been described by Harvey (19), who first isolated the virus in February, 1964. Other studies on the physical, biologic, and pathologic properties of the virus have been briefly reported by Salaman et al. (31), and Chesterman and Harris (5).

The agent has been termed "Murine Sarcoma Virus" (MSV) (Harvey) for the purpose of current reference, and without prejudice to questions of its nature and relation to other viruses. The following account summarizes results up to the present.

The cell-free plasma of a rat with Moloney virus (MLV) leukemia, when injected into newborn mice, induced multiple tumors and splenomegaly in 4 weeks. Tumors are not seen in Moloney leukemia, which in any case has a longer latent period.

This plasma has since been injected into large numbers of newborn and adult mice, rats, and hamsters. Solid and cystic tumors developed in most mice, rats, and hamsters inoculated when newborn. The plasma of rats inoculated at 6 months was infective between the 4th and 8th days, but non-infective before and afterwards.

Many attempts to detect virus in tumors or plasma of tumor-bearing hamsters inoculated when newborn have all been unsuccessful.

Mouse embryo tissue cultures, infected with MSV, showed no cytopathic changes. Trypsinized cells of MSV-induced sarcomata were cultivated for 2 months: they grew very slowly. The final supernatant fluids were injected into newborn mice, and produced splenomegaly but not tumors; however, the plasma of these mice injected into newborn rats induced both splenomegaly and tumors. A full report of the physical and chemical properties of MSV is in preparation (Mahy et al.), but the following summarizes the major findings. The virus was completely inactivated at 56°C for 30 min, but at 37°C for this period infectivity was unimpaired. No detectable loss of infectivity occurred at —60°C for 18 weeks. The virus was partially inactivated by either at 4°C overnight, and completely by chloroform at 22°C for 10 min. It was sedimented by centrifugation at 200,000 X g for 1 hr. Gradocol filtration indicated a particle size similar to that of Friend virus. Apparent diameter of the particles of MSV in electron micrographs was consistent with the filtration estimates (see Fig. 11).

Significant amounts of MSV were neutralized in vitro by antisera against Friend, Rauscher, and Moloney viruses, but not by an antiserum against Rous (Schmidt-Ruppin strain) virus.2

Ten-day-old mice were as susceptible as newborn when injected with some preparations. In older mice the incidence of splenomegaly remained high, but that of tumors declined, and the latent period of both increased.

Cell-free centrifugates of sarcoma homogenates from mice inoculated when newborn are highly infective, inducing splenomegaly and tumors with very short latent periods (8 days in some cases). Injection of serial dilutions showed that tumor extracts were more highly infective than the corresponding plasmas.

Plasma of tumor-bearing mice inoculated with MSV either when newborn or as adults was also infective, and so was that of rats inoculated when newborn. The plasma of rats inoculated at 6 months was infective between the 4th and 8th days, but non-infective before and afterwards.

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2 Friend Virus/CBI strain was obtained from Dr. Friend in 1959, passed in Swiss or DBA mice at the Chester Beatty Research Institute until 1962, and thereafter in BALB/c mice in the Cancer Research Department of the London Hospital, London. It has been freed of Riley virus by Mahy et al. (21). Anti-Rauscher sera

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Materials and Methods

Virus Preparations

Blood collected under ether anesthesia from several Chester Beatty rats injected with MSV at birth was diluted 1:1 with Hank's saline containing 0.5% lactalbumin hydrolysate and 20 IU of heparin/ml (without preservative). After centrifugation at 3000 rpm for 15 min to remove cells the pooled plasma was further diluted 1:1 with Hank's saline, and passed through a "Sels" porcelain filter, which was tested and found impervious to Escherichia coli. Filtered plasma was stored in sealed glass ampoules in a solid CO₂ chest, until used.

Most of the animals described in the following section were injected with the first large pool of plasma, prepared as described above and designated “MSV Batch 1.” The titer of this pool, as determined by injection into newborn BALB/c mice, is approximately 5000 minimal infectious doses/ml.

Animals

MICE. These were inbred BALB/c strain originally obtained from the National Institute for Medical Research, Mill Hill, and subsequently maintained at the London Hospital Research Laboratories.

RATS. Two strains were used, 1 inbred (CB hooded) and 1 outbred (CB albino). Both were obtained from the Chester Beatty Institute for Cancer Research and bred at the London Hospital Research Laboratories.

HAMSTERS. Two strains were used: Cream hamsters were obtained from the Chester Beatty Institute for Cancer Research. These were descendants of a cream mutant in the golden hamster colony bred from a nucleus purchased from Harrods of Knightsbridge and Parslow's Farm. Syrian golden hamsters were supplied from a closed but not deliberately inbred colony at the Imperial Cancer Research Fund laboratories at Mill Hill. This colony was started 12 years ago from Syrian golden hamsters received from the National Institute for Medical Research at Mill Hill.

All animals were caged in metal boxes containing sawdust or wood shavings. The mice and rats were fed on a standard pellet diet. The hamsters were fed on a pellet diet supplemented with dog biscuit and fresh cabbage. All animals were given water ad libitum.

Method of Inoculation

All animals were inoculated within a few days of birth. The majority were inoculated i.p. through the thigh muscles, and a few s.c. along the back with the needle tip in the subcutaneous tissues of the intersecapular region.

Preparation of Tissues

Animals were killed by ether or coal gas inhalation at various intervals after injection, and selected tissues taken at autopsy were fixed in alcoholic formal acetic mixture. A few tissues were fixed in 10% buffered formal saline. After embedding in paraffin, sections were stained with Ehrlich's hematoxylin and eosin. Other stains used were Van Gieson's connective tissue stain, Mallory's phoshotungstic acid hematoxylin, Perl's Prussian blue, and Ziehl-Neelsen's method for acid-alcohol-fast bacilli. Air-dried smears of peripheral blood, bone marrow, and pleural effusions were stained by the Jenner-Giemsa method.

Fixed mouse tissues containing bone were cut after decalcification in 5% trichloracetic acid. Bony hamster tissues were vacuum embedded after decalcification in Versene. When tumors had been passed to the choroidaallantoic membrane of embryonated eggs, the membranes were fixed in buffered formal saline, "Swiss rolled" (10), and each end of the roll tied with a human hair. Step sections were then cut at intervals of 360 μ.

Tissues for examination by electron microscopy were fixed in Palade's buffered osmic acid, dehydrated in alcohol, and embedded in methacrylate with uranyl nitrate included as a stain. Thin sections were examined in a Siemens Elmiskop I.

Results

Signs of Disease

The first obvious sign of disease in many mice and rats was distension of the abdomen from the grossly enlarged spleen, which was usually readily palpable by the 17th day after the animal had been inoculated. Rupture of the spleen with hemoperitoneum was a common cause of death. In mice subcutaneous solid or cystic tumors were often noticed at about the same time as the splenomegaly. Solid tumors near the site of inoculation of the virus were usually seen earlier in mice than in rats or hamsters.

In rats and mice cystic swellings, varying from 5 to 30 mm in diameter, often appeared in the inguinal or axillary regions at, or a little before, the time that the spleen became palpable. Similar swellings were the first obvious sign of disease in many hamsters. Some of the rats and hamsters were dyspneic, and a few appeared sick with no other outward signs of disease.

AutopsyAppearances

In mice solid and cystic tumors were frequently seen (see Table 1) but, in some rats and hamsters which sickened and had to be killed early, solid tumors were not visible.

The solid tumors presented as soft or firm lobulated pink or greyish white masses varying from 1–2 mm to 25–30 mm in largest diameter. The sites of these tumors depended to some extent on the route of injection of the virus. Following i.p. inoculation of virus through the thigh muscle, solid tumors were seen in the thigh, in the walls of the abdomen or thorax, in the diaphragm (Fig. 1), and on the inner aspect of the lower end of the sternum and the manubrium. Following dorsal s.c. inoculation of virus in hamsters, tumors appeared on the back, axillae, flanks, and sometimes on the limbs.

Other sites where solid tumors were observed in mice included the spleen, the walls of the stomach and urinary bladder, the
TABLE 1
RESULTS OF INOCULATING MURINE SARCOMA VIRUS (MSV) INTO RODENTS

<table>
<thead>
<tr>
<th>Species</th>
<th>Age at inoculation (days)</th>
<th>Site of inoculation</th>
<th>No. of animals injected and surviving more than 7 days</th>
<th>Splenomegaly</th>
<th>Solid tumors</th>
<th>Cystic lesions</th>
<th>Pleural effusions</th>
<th>Latent period to death (days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BALB/c mice</td>
<td>1-7</td>
<td>i.p.</td>
<td>73</td>
<td>73</td>
<td>53</td>
<td>19</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>CB hooded inbred rats</td>
<td>1-3</td>
<td>i.p.</td>
<td>33</td>
<td>31</td>
<td>17</td>
<td>33</td>
<td>15</td>
<td>4</td>
</tr>
<tr>
<td>Cream hamsters</td>
<td>1-3</td>
<td>i.p.</td>
<td>12</td>
<td>0</td>
<td>7</td>
<td>0</td>
<td>0</td>
<td>6</td>
</tr>
<tr>
<td>Golden hamsters</td>
<td>1-4</td>
<td>i.p. s.c.</td>
<td>17</td>
<td>0</td>
<td>6</td>
<td>10</td>
<td>3</td>
<td>3</td>
</tr>
</tbody>
</table>

Microscopic Findings

The major pathologic lesions can be considered in three groups: (a) solid tumors; (b) cystic lesions (this includes inflammatory lesions associated with the tumors or cysts, and proliferative lesions on the borderline of hyperplasia and neoplasia); and (c) lesions in other organs, particularly the spleen and hematopoietic tissues, resembling that seen in Friend or Rauscher disease.

1. Solid Tumors. In mice and rats these were pleomorphic sarcomas (Fig. 3) with some features suggesting a vascular origin. They were composed of elongated spindle-shaped cells orientated in various directions often in bundles or whorls with relatively large amounts of eosinophilic cytoplasm sometimes vacuolated, and centrally placed vesicular nuclei containing 1 or more nucleoli. They infiltrated adjacent tissues, destroying muscle and sometimes bone. Some of the tumors resembled rhabdomyosarcomas but there was no conclusive evidence of origin from muscle in sections stained with phosphotungstic acid hematoxylin. A tumor in the wall of the urinary bladder was eroding the mucosa, causing hemorrhage into the bladder.

Some tumors contained numerous cleft-like spaces, lined by endothelial cells varying in size and shape with hyperchromatic nuclei (Fig. 4). Some of these tumors were considered to be of vascular origin, morphologically similar to hemangioendotheliomas. Other "tumors" appeared even more vascular, containing large spaces filled with blood and lined by 1 or more layers of endothelial cells. The precise origin of these lesions is undetermined.

Some tumors were observed minute red spots in the peritoneal cavity.

Splenomegaly was a frequent finding in both mice and rats. In mice the spleen weight varied between 0.5-3.0 gm. In the spleen, particularly of mice, there were sometimes localized cystic nodules which on section were found to be full of blood. Sometimes these had ruptured into the peritoneal cavity.

Some of the hamsters and rats had straw-colored or pink milky opalescent fluid in both pleural cavities. A pleural effusion of clear straw-colored fluid was seen in 1 rat, which also had blood cysts in the lungs. In mice the pleural fluid was more often bloody than straw colored.
fragments or minces of hamster or mouse tumors induced by MSV.

2. CYSTIC LESIONS. Figs. 7-10 show stages in the development of the ectatic lesions which occur in, and in the region of, lymph nodes. There were inflammatory and degenerative processes together with hyperplastic and neoplastic changes in the tissues comprising these cystic lesions. Clumps of degenerate polymorphs, lymphocytes, foam cells, and cell debris were present in the distended sinusoids (Fig. 10), and there was a destructive effect on lymphoid tissue with loss of normal pattern of the node (Fig. 8). There was edema of the peripheral sinus, and of the hilar and adjacent lymphatics, resulting in the formation of cysts. The lining of the cysts was composed of a layer of endothelium thrown into irregular folds or forming papillary ingrowths into the lumen, with formation of new capillaries. There was thickening of the subendothelial fibrous layer of the cyst wall, together with the appearance in the cyst cavity of cells, irregular in size and shape and with hyperchromatic nuclei (Fig. 9). They apparently derived from lining cells, or possibly from the outer coats, of small blood vessels. In some areas of the cyst walls there were localized sarcomatous nodules consisting of cells similar to those found in the solid sarcomas. Transplantation of cyst wall fragments from a hamster have not given rise to tumors or cystic lesions in the recipients up to a period of 4 months. Survival of cyst fragments, but no progressive growth, was obtained on implantation to the chorioallantoic membrane of embryonated eggs.

In the golden hamster in some of the cyst walls there were collections of giant cells with a sarcoid-like appearance containing eosinophilic cytoplasm and sometimes with intracytoplasmic vacuoles containing "hyaline" material. No acid-alcohol-fast bacilli have been seen in these lesions. These giant cells may represent stages in the formation of those seen in the hamster tumors, as described above. The giant cells in these tumors were similar to those described by Ruffolo and Kirkman (30) in spontaneous giant cell tumors of periarticular connective tissue in hamsters. Some viruses are known to cause polykaryocytosis in vivo and in vitro (27), and giant cells are a conspicuous feature of SV 40-induced hamster tumors (13).

The cystic lesions in the lungs consisted of endothelial-lined cysts located immediately under the pleura and in the substance of the lungs. In addition there was sometimes distension of the perivascular spaces which were filled with serous fluid containing white blood cells. Similar distension of the perivascular spaces has been described in mice with experimentally induced Klebsiella pneumonia (14).

3. LESIONS IN OTHER ORGANS. Blood, spleen, and liver: Changes in the peripheral blood and the spleen of mice and rats were similar to those occurring in Friend disease. In the spleen there was proliferation of reticulum cells with associated erythroidloysis (Fig. 6) replacing the normal follicular pattern. A few of the hematomas were becoming organized as described by Dunn (11) in Rauscher disease. There were also irregular masses of sarcoma cells similar to those of the solid tumors seen elsewhere. In the liver there were focal collections of reticulum cells similar to those seen in the spleen. In 1 case these had ruptured through the capsule and invaded the peritoneum and, in another, similar cells were adherent to the kidney capsule. Occasionally there were areas of liver cell necrosis, fibrosis, or calcification. Electron micrographs showed virus particles in vacuoles of the cytoplasm of megakaryocytes in the spleen of a BALB/c mouse, which also had a diaphragmatic tumor. The morphologic appearance of these particles is shown in Fig. 11: they resemble the type C particles associated with some mouse leukemias (2).

A few similar virus particles were seen in the solid tumors.

Remaining organs: In mice, infiltration of alveolar walls, and peribronchial and perivasculares spaces by reticulum cells were seen in the lungs. In mice and hamsters a pleural or peritoneal serosal reaction was sometimes seen. In 1 mouse the pia-arachnoid surrounding the spinal cord was infiltrated by reticulum cells. Subependymal areas of calcification, which is a common finding in untreated mice, was also observed. In a few mice inoculated with 1 batch of virus, lesions morphologically indistinguishable from those induced by mouse hepatitis virus were present in the liver.

Discussion

The origin of the solid tumors appears to be from mesenchymal connective tissue, blood vessels, and possibly lymphatic vessels. Some of the appearances seen in the cystic lesions were similar to Kaposis sarcoma. Where the chest wall tumors were in contact with the pleura the proliferative serosal lesion appeared to be the reaction to, rather than the origin of, the tumors. The frequency of tumors on the diaphragm, manubrium, and chest wall is of interest. Intrapleural injection of thorotrast in Sprague-Dawley rats shows that the lymphatics of the diaphragm fill first, and the most important pathway from the peritoneal cavity runs via the diaphragmatic and parasternal lymph vessels to mediastinal lymph vessels (24, 32).

Only 1 sarcoma has been seen arising in the diaphragm of our golden hamsters, untreated or treated in other ways, in over 7000 examined during routine autopsies (F. C. Chesterman, unpublished observations). Of 6 tumors induced in 48 newborn hybrid ferrets inoculated with the Mill Hill strain of polyoma virus, 1 tumor, an osteogenic sarcoma, arose in the diaphragm following i.p. inoculation of virus (25).

Some of the cystic lesions produced by MSV are morphologically similar to those produced by the Schmidt-Ruppin strain of RSV (RSV/SH) but the host ranges are different. MSV produces cysts in mice, rats, and golden hamsters whereas RSV/SH produces them only in rats and rabbits. Cysts have also been produced in rats by the B.77 chicken virus, a member of the leukosis group (20). The rat cysts produced by chen-derived viruses are transplantable (5, 20). So far, only attempts to transplant MSV-induced hamster cysts have been made, and these have failed.

Another virus which induces ectatic lesions is polyoma. Rowson et al. (28) have found cysts filled with lymph or blood in the region of the lymph nodes in mice treated with polyoma virus, or with the virus and chemical carcinogens. Polyoma virus also produces ectatic lesions of the liver and lungs, but only in the hamster (6). Proliferation of the cells in the wall of these cysts occurs, giving rise to angiomatosus tumors which are transplantable (9).

Although the roles of destructive, proliferative, mechanical, and other factors in the production of the lymphatic cysts is unknown they appear to be a common response to a variety of
experimental viral infections; they also have been seen in mice following inoculation with sheep pulmonary adenomatosis material (34). Cystic lymph nodes occasionally occur in aged untreated mice (29).

Relation to Friend, Rauscher, and Moloney's Diseases

MSV-induced lesions in the spleen, liver, and peripheral blood in mice and rats are similar to those of Friend and Rauscher diseases (15, 22, 26, 33), but quite different from those of Moloney leukemia (12). The morphologic appearance of local tumors described by Buffet and Furth (3), Friend and Haddad (16), and Dawson et al. (8), in mice following transplantation of spleen or liver from Friend disease does not resemble that of sarcomas induced with MSV. However, it is interesting to note (3) that in several cases a granuloma with giant cells and "reticulum-like cells" marked the site of the cell graft. Reticuloses "on the borderline between inflammatory and tumoral processes" are common in the mouse (7). Perhaps in animals inoculated with MSV an initial granulomatous reaction precedes tumor formation.

There is evidence that unaltered MLV is still present in MSV preparations after several passages. If early death from tumors, or ruptured spleen or cysts, is avoided, lymphatic leukemia eventually appears. Rat plasma taken 8 days after MSV injection, for example, which produced no early tumors or splenomegaly, gave rise later to a generalized lymphatic leukemia typical of MLV. MSV treated with ether, or with anti-FV serum, had a similar effect in some cases.

No procedure so far tried has separated spleen-enlarging from tumor-producing power of MSV preparations. Neither serial dilution, heat, ether, neutralizing antisera, nor passage through tissue cultures, has had a differential action on the two effects.

Moloney virus can be transmitted to hamsters (23) but does not give rise to the cysts and solid tumors we have described following MSV injection. Recently, however, Moloney has reported (Symposium on "Some Recent Developments in Comparative Medicine," WHO and Zoological Society, London, June 1965; also personal communication) the induction of local sarcomas in newborn mice at the site of i.m. injection of a highly concentrated suspension of Moloney virus. There were no tumors at other sites, no cystic lesions, and only minimal changes in the spleen. Sarcomas were induced in newborn thymectomized and cortisoned rats, but not in untreated newborn rats. Newborn hamsters were also resistant. The relation between this agent and MSV, both ostensibly derivatives of MLV, has still to be worked out. Clearly there are differences as well as similarities.

The possibility that an admixture of polyoma virus may be responsible for tumor production by MSV has been tested (19). The evidence, which is strongly against this possibility, may be summarized as follows.

1. Tumor induction by MSV, with a titer of only $10^{-2}$-$10^{-3}$ is faster than preparations of polyoma with much higher titers. It acts as fast in mice as in hamsters, while polyoma tumors in hamsters appear much earlier than in mice; it is effective in mice inoculated as old as 16 weeks, while polyoma is almost entirely ineffective in mice over 14 days old.

2. MSV tumor sites are not characteristic of polyoma i.e., no salivary gland tumors have been seen, and no kidney tumors in hamsters similar to those induced by polyoma virus.

3. Viremia in tumor-bearing mice and rats is the rule in MSV infection, but is often low or absent in polyoma infection.

4. MSV is inactive at $56^\circ$C for 0.5 hr, and is partially ether sensitive. Polyoma resists both procedures.

5. MSV is not cytopathogenic for mouse embryo tissue cultures.

6. MSV does not agglutinate guinea-pig erythrocytes at $+4^\circ$C, and sera of MSV tumor-bearing animals do not inhibit hemagglutination by polyoma virus.

MSV-induced mouse and hamster tumors have failed to give rise to tumors on transplantation to chicks, or to induce Rous sarcoma virus (RSV)-type tumors or pocks on the chorioallantoic membrane of embryonated eggs. This serves to distinguish MSV from RSV.

Electronmicroscopy of the megakaryocytes in the spleen and tumor cells of mice infected with MSV showed virus particles similar to those described by Bernhard (2) as type "C." This type of particle has been associated with the Gross Passage A virus and other viruses which induce murine lymphatic leukemia, e.g., Moloney virus. It must be remembered that Moloney virus is probably present in all preparations of MSV currently available. On the other hand the appearance of the particles suggests a difference from Friend disease, where type "A" particles are found in vacuoles of the cytoplasm of megakaryocytes (18).

The nature and origin of MSV are still undetermined. No mycoplasma have been cultured from mouse plasma containing the virus. No solid tumors or ectatic lesions were found in the leukemic rat whose plasma was the original source of MSV, in any of its inoculated litter mates, or in the Moloney virus-infected mice whose plasma was used to inoculate them. The plasmas of 5 uninoculated litter mates of the leukemic rat, and 5 unrelated rats from the same colony, were each injected into 18 infant BALB/c mice. No tumors have appeared in 6 months.

Whether the lesions in rodents which follow infection with this agent are due to a mutant of Moloney virus, or to the activation of an agent or virus latent in CB hooded rats or BALB/c mice, or to a mixture of such a virus with Moloney virus with consequent additive or potentiated effects, has still to be determined. In this connection it is of interest that the possibility that Friend and Rauscher viruses may consist of mixtures of more than 1 agent is being seriously considered (17; L. Gross, International Conference on Murine Leukemia, Philadelphia, October 1965; E. A. Mirand, Ibid.).

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References

Tumors in Rodents Inoculated with Moloney Leukemia

FIGS. 1-11. All the figures are from animals inoculated with Murine Sarcoma Virus, MSV. All sections except Fig. 11 stained with hematoxylin and eosin.

Fig. 1. BALB/c mouse showing splenomegaly and a tumor in the right axilla and diaphragm. \( \times 1.5 \).

Fig. 2. Hooded rat showing cystic lesions in the regions of the right inguinal and both lumbar nodes and moderate splenomegaly. \( \times 0.8 \).

Fig. 3. Subcutaneous spindle cell sarcoma infiltrating muscle of a BALB/c mouse. \( \times 450 \).

Fig. 4. Angiomatous tumor arising in thoracic wall of an outbred rat. Note clefts lined with endothelium. \( \times 450 \).

Fig. 5. Multinucleate giant cells in a subcutaneous tumor from a golden hamster. \( \times 250 \).

Fig. 6. Spleen of an outbred rat showing areas of erythropoiesis and proliferation of reticulum cells. \( \times 450 \).

Fig. 7. Early ectasia of inguinal lymph node in an outbred rat, showing dilation of marginal sinus. \( \times 14 \).

Fig. 8. Advanced ectasia of inguinal lymph node from a golden hamster. \( \times 21 \).

Fig. 9. Cyst containing free cells irregular in size and shape from an outbred rat. \( \times 250 \).

Fig. 10. Cystic mediastinal lymph node showing clumps of degenerate cells and cell debris from a golden hamster. \( \times 250 \).

Fig. 11. Electronmicrograph of part of the cytoplasm of a megakaryocyte in the spleen of a BALB/c mouse showing type C virus particles. \( \times 50,000 \).
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