The Pathology of an Epizootic of Acquired Immunodeficiency in Rhesus Macaques

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A syndrome of acquired immunodeficiency within a group of outdoor-housed rhesus macaques (*Macaca mulatta*) with unusually high mortality has been identified at the California Primate Research Center. The cause of death for most of the affected animals included septicemia and/or chronic diarrhea with wasting, often complicated by other problems. In many cases, multiple or unusual infectious agents were isolated or recognized, including cytomegalovirus, *Cryptosporidium* spp., and *Candida albicans*. Septicemias due to usually innocuous agents such as *Staphylococcus epidermidis* and *Alcaligenes faecalis* were seen. Two animals developed cutaneous fibrosarcomas. Affected animals had generalized lymphadenopathy and splenomegaly, with depletion of T-cell populations, initial follicular hyperplasia followed by depletion, and absence of plasma cells. This spontaneous disease syndrome in nonhuman primates has similarities to acquired immune deficiency syndrome (AIDS) in humans, providing an animal model for the study of the complex factors modulating the immune system. (Am J Pathol 1984, 114:94–103)

AN EPIZOOTIC of apparent acquired immunodeficiency syndrome has been identified in rhesus macaques (*Macaca mulatta*) at the California Primate Research Center (CPRC).[1,2] Some features of this syndrome suggest that it may serve as a model for acquired immune deficiency syndrome of man (AIDS).[3–5] The epizootic involves a group of juvenile and young adult animals, housed in a half-acre outdoor corral (NC-1) since September 1981. Unusually high mortality (27.5% versus 5.5% in similar groups) signaled the onset of the outbreak.

The purpose of this paper is to document the lesions that have occurred in this group of animals and to compare these with lesions documented for human beings suffering from AIDS and with immunosuppression syndromes in other species.

Materials and Methods

Clinical records and necropsy reports from all animals housed in NC-1 from 1981 to the present were examined and compared. The group consisted of 56 animals introduced into the enclosure in August 1981 and 8 animals retained from the group previously housed in NC-1, as well as 13 births. Of 6 males in the group, 2 were imported wild animals. The other 4 males and 49 females were colony-born. All 8 animals held over from the previous group were females. Twenty-nine animals from NC-1 have been presented for necropsy since the group was formed.

Animals from NC-1 that have died were examined with the use of standard necropsy procedures. In addition, the most recent deaths (18/29) were subjected to more detailed postmortem examination based on a predetermined protocol. Organ weights were compared with those previously reported.[6] Samples of all organs and tissues and most lymph nodes were fixed in Carson's fixative[7] and processed routinely for paraffin embedding and sectioning at 6 μ for light-microscopic examination. All sections were stained with hematoxylin and eosin (H&E). Selected sections were also stained with Gram's stain, periodic acid–Schiff (PAS), Giemsa stain, Masson's trichrome stain,

Supported by Grant RR-00169 from the Division of Research Resources, National Institutes of Health, Bethesda, Maryland.

Accepted for publication July 28, 1983.

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phosphotungstic acid-hematoxylin (PTAH), Gomori's silver stain (GMS), and Ziehl-Neelsen acid-fast method. Samples of liver, spleen, bone marrow, thymus (when available), and tumors (if present) were also fixed in Karnovsky's fixative[8,9] and in B-5.[10] Tissues for transmission electron microscopy (Karnovsky's-fixed) were postfixed in osmium tetroxide, serially dehydrated for infiltration and embedding in either an Epon-Araldite mixture or methacrylate, and then sectioned at 900 Å. Tissues were stained with lead citrate and uranyl acetate and examined using a Zeiss 10 transmission electron microscope. Tissues for immunoperoxidase staining (B-5 fixed) were embedded in paraffin and sectioned at 2-3 μ. Immunoperoxidase staining for kappa and lambda light chains and for Factor VIII was carried out using an avidin binding method.[11]

Samples of lymph node, thymus (when present), spleen, bone marrow, tumor (if present), liver, kidney, and fat (if present) were snap-frozen in liquid nitrogen and stored at −70 C for possible toxicologic examination or other studies. Similar sets of tissues for virus isolation were collected aseptically and either minced in sterile tissue culture medium and shipped on wet ice or snap-frozen in liquid nitrogen and shipped on dry ice, depending upon the time and day of the necropsy. Viral cultures were performed by either the Southwest Foundation for Research and Education (Dr. R. L. Heberling) or the National Institutes of Health (Drs. J. Sever and D. Madden). Bacterial cultures were performed at the CPRC on all tissues with gross lesions, on intestines, liver, and bone marrow from animals with clinical diarrhea, and on skin, spleen and bone marrow from animals with cutaneous abscesses.

Biopsies from living animals were also examined by methods detailed above. Biopsies have included skin lesions from 1 animal now dead, lymph nodes from 5 animals (three still living), and a subcutaneous nodule from 1 animal that is still alive.

Results

The 29 macaques necropsied in the 16 months since formation of the group include 25 females and 1 male, as well as 3 female infants born in the cage. No stillbirths or abortions have been recognized. Twelve died while hospitalized, and euthanasia was performed on 15 when therapeutic efforts had failed. Euthanasia was performed on 1 animal when ill but not moribund, and 1 died unexpectedly while under anesthesia. Ages at death ranged from 17 to 47 months in introduced animals and 5 to 7 months in the 3 animals born in the corral. Significant lesions and recognized etiologic agents are summarized in Tables 1 and 2.

Table 1 — Significant Lesions

System/lesion	Introduced animals (n = 26)	Corral-born animals (n = 3)
Lymphoid-hemopoietic		
Lymphadenopathy	26	3
Splenomegaly*	15	2
Bone-marrow hyperplasia	25	3
Integument		
Abscesses	9	3
Fibrosarcoma	2	0
Alimentary		
Gastroenterocolitis	21	3
Hepatitis	12	1
Sialoadenitis	6	0
Oral ulceration	5	0
Hepatomegaly†	9	0
Cardiovascular-respiratory		
Pneumonia	8	1
Cardiomyopathy/myocarditis	2	0
Pericarditis	3	1
Nervous		
Meningitis	1	2
Musculoskeletal		
Myopathy/myositis	7	0
Arthropathy/arthritis	3	0
Osteomyelitis	0	1
Urogenital		
Glomerulonephritis	5	1
Interstitial nephritis	14	0
Other		
Weight loss	21	2
Septicemia	10	3

* Out of 20 necropsies with spleen weight recorded.
† Out of 23 necropsies with liver weight recorded.

Gross Pathology

Gross findings in these animals typically included weight loss (11-40% of maximum weight) and evidence of diarrhea. Almost half of the animals had multiple chronically infected skin wounds that appeared to be of traumatic origin (Figure 1). In 1 animal there were several firm cutaneous and subcutaneous nodules 0.3-1.8 cm in diameter located on the trunk and proximal portions of all four limbs (Figure 2). A single subcutaneous nodule 1-cm in diameter was present over the right mandible in another animal. On cut surface, the masses in both animals were pale pink and vaguely lobulated by fine white trabeculas (Figure 3). Pale foci 0.1-0.3 cm in diameter were in some of the nodules in the first animal.

Peripheral and visceral lymph nodes were slightly to moderately enlarged in most animals when compared with age-matched controls from other corrals. The spleens were enlarged two to five times normal weight and had prominent white pulp on cut surface. The thymus was inapparent or smaller than expected

Table 2—Etiologic Agents Recognized

Agent	No. of cases	Organs involved	How recognized
Viral			
CMV	7	Lymph nodes, spleen, liver, skin, kidney	LM, TEM
Rhesus LAHV	2	Spleen, lymph node	Culture*
Bacterial			
Campylobacter fetus subsp. *jejuni*	14	Colon, jejunum, blood	Culture
Shigella flexneri Type IV	6	Colon, jejunum	Culture
Klebsiella spp.	6	Colon, jejunum, spleen, peritoneum	Culture
Staphylococcus aureus	3	Skin abscess, lung, pericardium	Culture
Yersinia pseudotuberculosis	2	Colon, jejunum, blood, lung	Culture
Streptococcus pneumonia	2	Blood, meninges	Culture
Escherichia coli	2	Peritoneum, pleura, meninges	Culture
Coagulase-positive staphylococci	2	Abscess, lung	Culture
Streptococcus viridans	2	Lung	Culture
α-Hemolytic *Streptococcus*	1	Meninges	Culture
Yersinia enterocolitica	1	Lymph nodes, blood, peritoneum	Culture
Staphylococcus epidermidis	1	Bone marrow	Culture
Pseudomonas maltophilia	2	Lung, liver	Culture
Corynebacterium renale	1	Skin abscess, lung abscess	Culture
Acinetobacter spp.	1	Lung	Culture
Alcaligenes faecalis	1	Bone marrow	Culture
Mycotic			
Candida	9	Mouth, esophagus	Culture, LM
Protozoal			
Cryptosporidium	7	Jejunum, ileum, colon, gallbladder	LM
Trichomonas	5	Stomach, jejunum, ileum, colon	LM
Metazoal			
Pneumonyssus simicola	7	Lung	Gross, LM

* Personal communication, R. L. Heberling, Southwest Foundation for Research and Education.
LM, light microscopy; TEM, transmission electron microscopy.

in the three corral-born animals. Dark red bone marrow was present in all medullary cavities.

Hepatomegaly was present in one-third of the animals. Affected livers were often pale, with an enhanced reticular pattern. Oral (lingual and buccal) and esophageal plaques and ulcers were noted in one third of the animals (Figure 4). The stomach and intestines were often unremarkable grossly except for the presence of liquid feces in 24 of the 29 animals. Six animals, however, had multiple foci of mucosal erythema, erosion, or ulceration, which was most severe in the colon. Purulent exudate was in the peritoneal cavities in 2 animals.

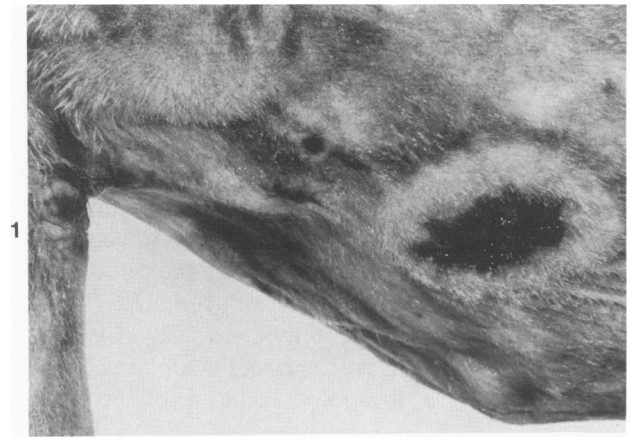
One-third of the animals had grossly visible lung lesions. These varied from irregular foci of hemorrhage to foci of suppuration (in 1 animal). Yellow-gray to red nodules characteristic of lung mite infestation were seen in 6 animals. The pericardium in 3 animals was opaque with fibrinous to fibrous adhesions to the epicardium; suppurative exudate was present in 1 animal. Pleuritis characterized by purulent exudate was seen in 1 animal. Meningeal opacification with suppurative exudate was present in 2 animals.

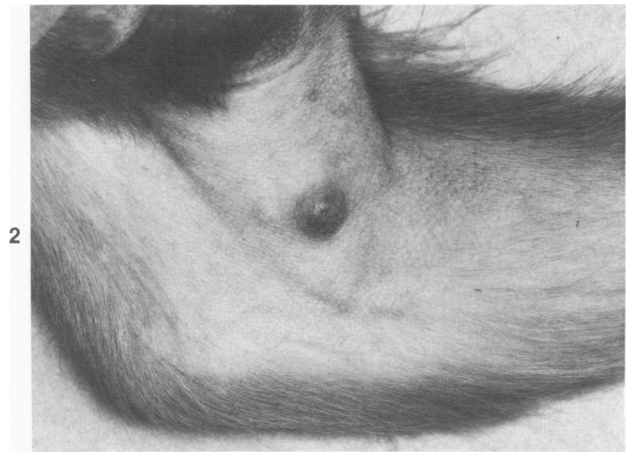
One-fourth of the animals had limited range of motion in at least one joint. The adjacent muscles were irregularly pale and firm. Cutting these muscles allowed the joints to be extended fully. There were no gross lesions in the articular surfaces or synovium of the involved joints. In 1 animal there was a pus-filled focal defect in the cortex of the distal radius associated with a penetrating skin wound.

Living animals from which lymph node biopsies were taken had enlarged nodes. Some of these animals were clinically ill at the time of the biopsy. In an additional living animal, a biopsy was done of a small subcutaneous nodule associated with the underlying muscle.

Histopathology

A variety of changes were seen in lymphoid tissue. Reactive follicular hyperplasia (Figure 5) was present in nodes biopsied from 2 living animals and in the nodes from the animal that died under anesthesia and the animal that was euthanized when ill but not moribund. Secondary follicles with active germinal centers containing large blast cells and mitotic figures





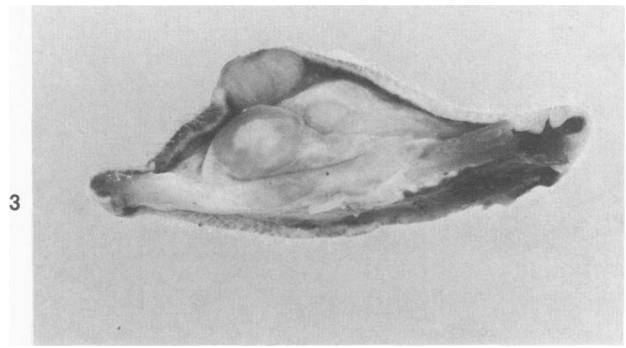


Figure 1 — Multiple ulcerated cutaneous wounds with an indurated border on the chest and arm of a rhesus macaque. The wound was infected and nonresponsive to appropriate therapy. **Figure 2** — Skin nodule on the arm of a rhesus macaque. The lesion was erythematous, with a small central focus of ulceration. **Figure 3** — Cut surface of the same mass as in Figure 2 revealed several tumor nodules on skin and subcutis.

were present in these nodes. A few follicles in medullary areas contained macrophages or pink hyalinized material. Few plasma cells were present in medullary cords. Using immunoperoxidase stains for kappa and lambda light chains, cells positive for each marker could be found in close proximity (polyclonal). The paracortical (T-cell) areas were normally cellular or

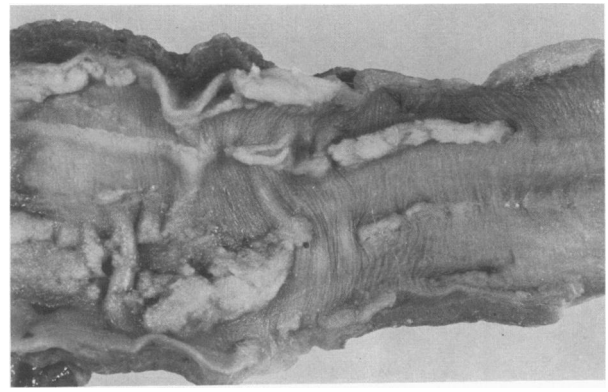


Figure 4 — Multiple white plaques caused by *Candida albicans* in the esophagus of an immune-suppressed rhesus monkey.

slightly hypocellular. Small hyalinized arterioles were in medullary or paracortical areas in 2 of these animals. Sinus histiocytosis was apparent with moderate erythrophagocytosis and hemosiderosis.

In 2 animals that underwent biopsy when ill (2–4 weeks prior to death), and in animals that were found dead or euthanized when moribund, there was mild to severe depletion of follicular lymphocytes. Follicular centers contained histiocytes and amorphous pink hyaline material, which was negative for amyloid by Congo red staining. In some nodes, ill-defined small follicles were present in medullary areas without active germinal centers or central degeneration. Plasma cells were rare or absent. Depletion of paracortical lymphocytes was universal and often the most striking change in these cases (Figure 6). Histiocytes replaced paracortical areas and filled sinusoids. In the 2 animals that underwent biopsy prior to death, neutrophils and eosinophils were scattered in paracortical areas along with hyalinized small arterioles. Lymph node abscesses were seen in 4 animals: in nodes draining suppurative wounds (2 cases) and in mesenteric nodes in 2 cases of intestinal yersiniosis. Cytomegalic cells with intranuclear inclusions were in one of the abscessed peripheral nodes. Erythrophagocytosis and hemosiderosis were present in about half the cases.

The morphologic characteristics of splenic white pulp mirrored changes in the lymph nodes. Hyperplastic follicles with prominent germinal centers and wide periarteriolar lymphoid sheaths were seen in 2 animals that died while relatively healthy clinically. In animals with depleted lymph nodes there was depletion of the periarteriolar sheaths. In other animals depletion and hyalinization of follicular germinal centers were present. Perifollicular amyloidosis was present in 1 animal that also had intestinal amyloidosis. Central arterioles were sometimes hyalinized and

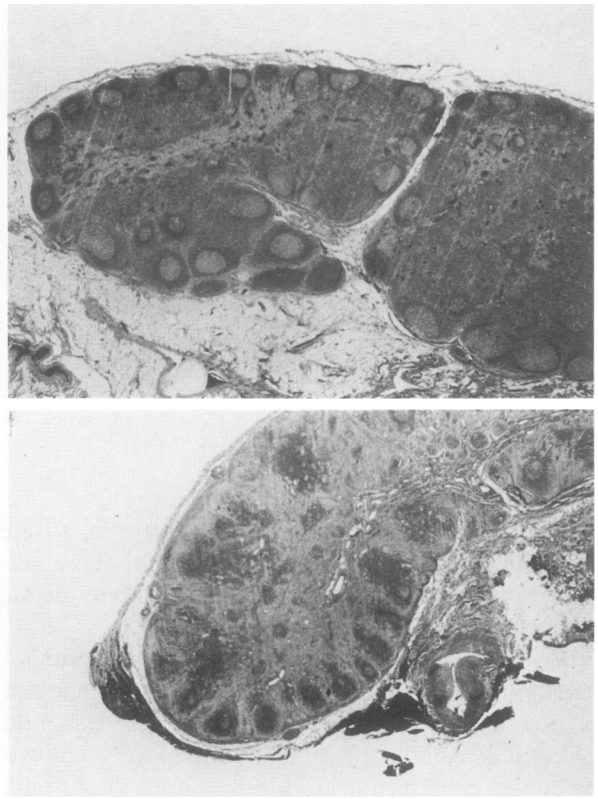


Figure 5 – Reactive jejunal lymph node from a rhesus monkey from NC-1 with lymphadenopathy and hepatosplenomegaly. This animal was otherwise clinically normal. (H&E, ×12) **Figure 6** – Jejunal lymph node from a severely ill rhesus monkey with advanced acquired immune deficiency, in which there is marked paracortical depletion, sinus histiocytosis, and postreactive follicular depletion. (H&E, ×12) (Both with a photographic reduction of 30%)

tortuous. Acute splenitis was present in several animals that were septicemic.

In the three postneonatal infants that died there was marked atrophy of the thymic cortex and slight degeneration of Hassall's corpuscles. Bone marrow from all but the animal that died from anesthesia were hypercellular. All cell lines were well represented, but in a few animals there appeared to be a maturation arrest in the myelocytic series. In 4 animals there were multiple lymphoid follicles with recognizable germinal centers in sections of marrow. These germinal centers were depleted and hyalinized in 1 animal.

Skin lesions consisted of acute and chronic abscesses and cellulitis sometimes extending to involve the underlying muscles or bone. Large cells with Cowdry's type A intranuclear inclusions were in the suppurative exudate of one wound in an animal in which similar cytomegalic cells were present in the abscessed draining lymph node.

The tumors in both animals were multinodular, well vascularized, and composed of interlacing fascicles of spindle cells (Figure 7) with varying amounts of eosinophilic intercellular matrix, which was positive for collagen with the use of Masson's trichrome staining. Multinucleated tumor giant cells were in some lobules in the animal with multiple lesions, and caseation necrosis with neutrophilic infiltrate was present in the center of other lobules. Immunoperoxidase staining of one tumor from this animal for Factor VIII revealed strong positive staining of recognizable capillary endothelium. Some of the tumor cells (about 2%) were also positive for Factor VIII. Tumor cells were characterized ultrastructurally by large nuclei with prominent nucleoli and cytoplasm rich in filaments and free ribosomes. Cisternae of the sparse

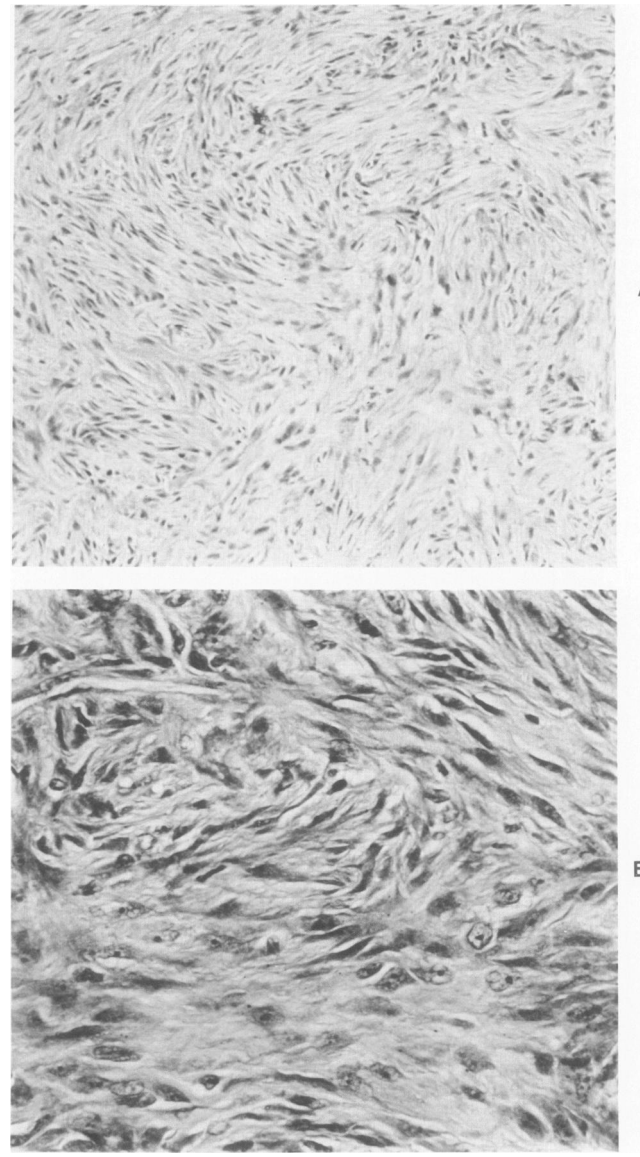


Figure 7 – Interwoven bundles of pleomorphic spindle cells in a cutaneous fibrosarcoma from an immunodeficient rhesus monkey (same animal as Figures 2 and 3). (H&E, **A**, ×50; **B**, ×300)

rough endoplasmic reticulum (RER) were dilated. Golgi complexes were prominent, and there were a few pleomorphic mitochondria. When cells abutted one another, junctional complexes were formed (Figure 8). Vesicular indentations of plasma membranes were prominent. The extracellular matrix was composed of a few mature collagen fibers and greater numbers of smaller (procollagen) fibrils. No viral particles were seen. There were no Weibel-Pallade bodies, characteristic of arteriolar endothelial cells, in any tumor cells examined; nor were residual bodies present. The morphologic characteristics of this tumor were most compatible with a diagnosis of fibrosarcoma.

The single tumor nodule from the second animal had less stainable collagen on light-microscopic examination. By electron microscopy, however, mature collagen fibers were abundant and closely associated with the plasma membranes of the spindle-shaped cells (Figure 9). These cells had fewer cytoplasmic filaments and more smooth endoplasmic reticulum (SER) than cells in the first tumor. The sparse dilated ER, pleomorphic mitochondria, and free ribosomes were similar to those of the other tumors. No junctional complexes were present where cells were in contact. This tumor was also diagnosed as a fibrosarcoma. The subcutaneous nodule from the living animal on which a biopsy was done was reactive granulation tissue.

The morphologic features of gastrointestinal lesions varied considerably. In 1 animal there was amyloidosis of the lamina propria of jejunum and ileum. Lacteals were dilated, sometimes by fibrin thrombi; and numerous cytomegalic cells were often seen associated with microabscesses (Figures 10 and 11). Cryptosporidiae were present on the brush borders of enterocytes in the ileum and colon of this animal and in 6 other animals (Figure 12). In 3 of these animals the cryptosporidiae were throughout the intestine and in the gallbladder as well. Trichomonads were present in large numbers in one-sixth of the animals and in 1 were even present in gastric glands. Inflammation varied, depending upon etiologic agents involved in the gastroenteritis. Animals from which *Shigella* spp. or *Yersinia* spp. were isolated had large numbers of neutrophils in their lesions. In other instances large numbers of macrophages were present. Acid-fast organisms were not seen in any of these cases.

Other lesions in the gastrointestinal tract included large numbers of *Candida* spp. matting together the superficial layers of parakeratotic epithelium in oral and esophageal lesions and multifocal interstitial lymphocytic sialoadenitis in one-fifth of the animals. Hepatitis was present in about half the animals. A

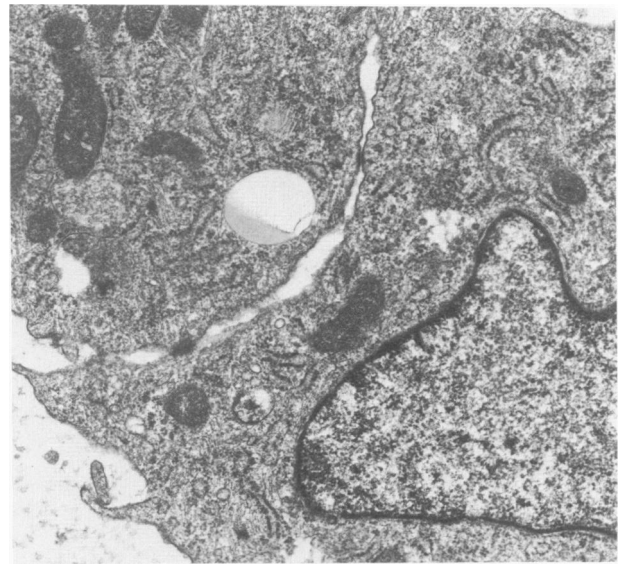


Figure 8 — Ultrastructure of the tumor in Figure 7. Abutting cells with junctional complex formation and many intracytoplasmic filaments and free ribosomes. (Uranyl acetate and lead citrate, × 16,000)

mononuclear infiltrate was in portal areas; and there were multifocal, randomly distributed microabscesses associated with necrosis of individual hepatocytes. Such lesions in 4 of these animals contained cytomegalic cells (Figure 13). In many animals randomly distributed multinucleated hepatocytes were seen.

Light-microscopic examination of lungs confirmed the presence of *Pneumonyssus simicola* infestation in 6 animals. In addition, multifocal fibrinopurulent interstitial bacterial pneumonia was seen in 8 animals. *Pneumocystis carinii* was not recognized in any of these macaques with the use of silver impregnation stains (GMS).

The skeletal muscle lesions consisted of degenerative myopathy with varying amounts of lymphohistiocytic myositis and fibrosis. Although articular cartilage was normal, synovium was sometimes hyperplastic with swollen synovial cells and multifocal mild lymphocytic inflammation without plasma cells or follicle formation.

Within the kidneys, there was mild to moderate lymphocytic interstitial nephritis in several animals. Five animals had proliferative, and 3 had membranoproliferative glomerulonephritis.

Agents recognized by microscopy, culture, or impression smears are presented in Table 2. Cytomegalic cells were present in one or more tissues in 7 animals, often associated with microabscesses. Rhesus leukocyte-associated herpesvirus was isolated from the lymph node biopsy specimen of 1 animal and the spleen specimen of another animal. *Campylobacter fetus* subsp. *jejuni* was cultured from the gastrointes-

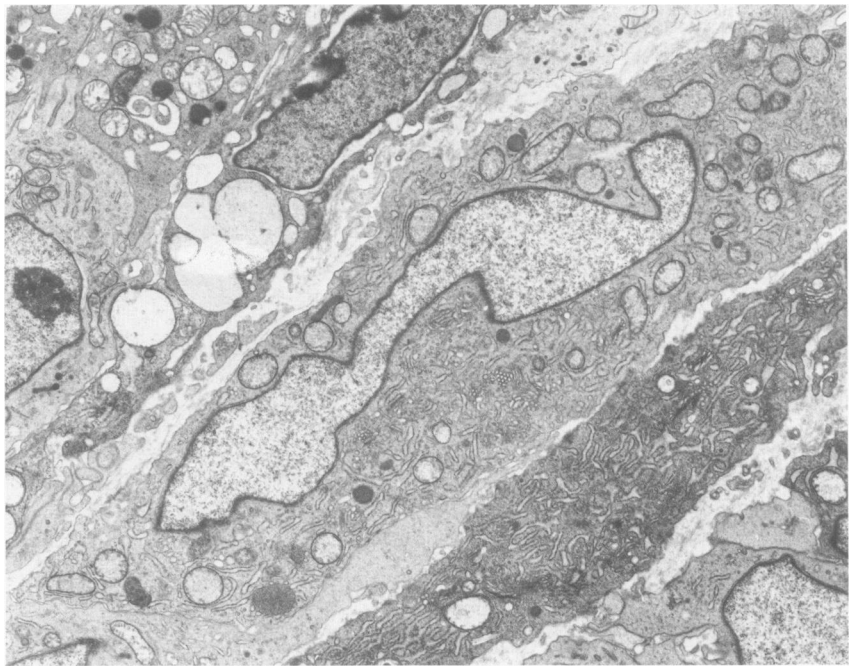


Figure 9—Ultrastructure of tumor from the animal with a solitary mandibular subcutaneous mass, seen at lower power magnification. Collagen fibers are visible between cells. The morphologic characteristics are compatable with a diagnosis of fibrosarcoma. (Uranyl acetate and lead citrate, ×5600)

tinal tract of 16 animals. Nine of these had protozoal infestations as well. Two animals were septicemic, and *Campylobacter* was cultured from blood and other organs. *Shigella flexneri* Type IV was cultured from the intestinal tract in 6 animals; in only 1 of which was it in pure culture. *Klebsiella* spp. was isolated from the gastrointestinal tract of 6 animals, in 2 of which it was in pure culture. *Klebsiella* was also isolated in pure culture from the peritoneal exudate in the animal with peritonitis and from the spleen of another animal.

Yersinia pseudotuberculosis and *Yersinia enterocolitica* were cultured from intestines from 3 animals. In 1 animal, *S flexneri* Type IV was also present in the intestines. *Yersinia* was cultured from or recognized in blood, lymph nodes, lung and/or peritoneum in all 3 animals. Organisms isolated from skin wounds and internal lesions included *Staphylococcus aureus* (3), coagulase-positive *Staphylococcus* spp. (2), and *Cornyebacterium renale* (1). From peritoneum, pleura, or meninges, *Escherichia coli* (2), *Streptococcus pneumoniae* (2), and an α-hemolytic *Streptococcus* spp. were cultured.

Bone marrow cultures yielded several species, often

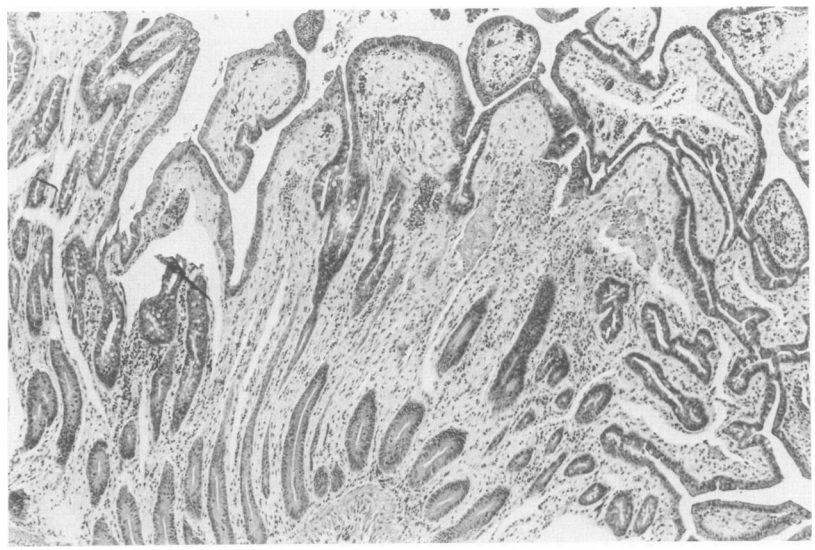


Figure 10—Chronic enteritis with amyloidosis in a rhesus monkey with acquired immune deficiency. Note fibrin thrombi in lacteals in this section of ileum. (H&E, ×50)

more than one per case, including: *Staphylococcus epidermidis, Acinetobacter* spp., and *Alcaligenes faecalis*.

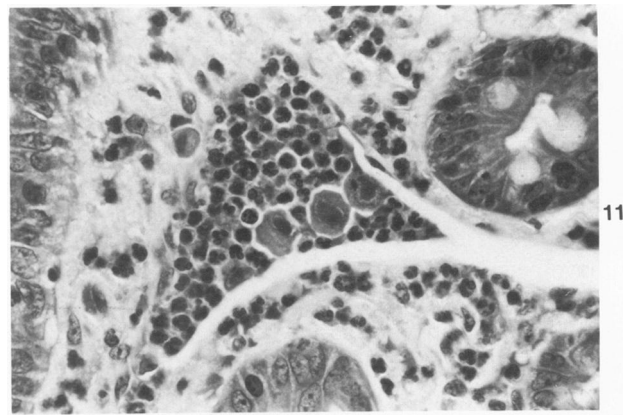
Discussion

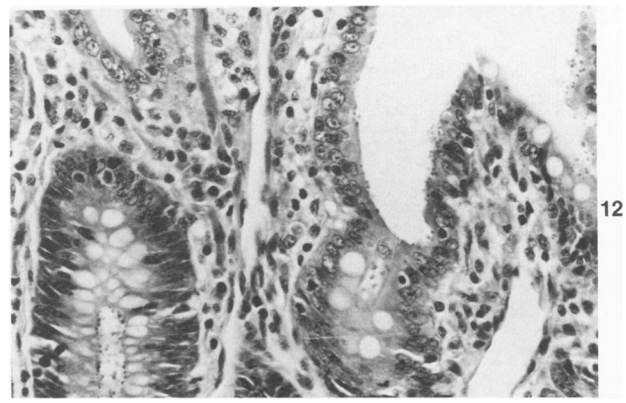
The cause of death or euthanasia for animals from NC-1 was usually septicemia and/or chronic diarrhea with wasting, often complicated by other, less severe problems. In many cases, multiple or unusual infectious agents were isolated or recognized. This pattern and the frequency of death, when compared with morbidity and mortality in otherwise similar animal groups at the California Primate Research Center (CPRC), confirms the possibility of an underlying immune deficiency.

Features frequently present in immunodeficiency in human pediatric patients are reported.[12] The following are considered to be highly suspicious: chronic infection, recurrent infection (more than expected), unusual infecting agents, and incomplete clearing between episodes of infection or incomplete response to treatment. Features that are frequently present and moderately suspicious include: skin rash (eczema, *Candida* infections, etc.), diarrhea (chronic), growth failure, hepatosplenomegaly, recurrent abscesses, recurrent osteomyelitis, and evidence of autoimmunity. A number of these features were present in many of the NC-1 animals. Almost all suffered from chronic and/or recurrent infections, which were poorly responsive to appropriate therapy. Unusual infecting agents included cytomegalovirus (CMV), *Candida albicans*, and *Cryptosporidium* spp. Also unusual was the high rate of septicemia, which included a wide range of organisms not usually considered highly pathogenic such as *Staphylococcus epidermidis* and *A faecalis*.

Features of the lymphoid tissue of these animals also suggest an acquired immune deficiency. Early changes include B-cell (follicular) hyperplasia with prominent germinal centers, and few or no plasma cells. Later changes suggest progressive depletion of both B- and T-cell–associated areas, with the most marked depletion in the T-cell population. Depletion of thymic lymphocytes was also apparent in each of the three infants. The isolation of rhesus leukocyte-associated herpesvirus (LAHV) from two of these animals is consistent with previous reports,[13,14] in which the virus was shown to commonly infect both jungle and laboratory populations of rhesus monkeys without clinical signs. Its pathogenicity is uncertain.

The occurrence of the two fibrosarcomas in the brief period of time in one cage is unprecedented at the CPRC. The tumor type is also unusual in this colony. Two cutaneous fibromas have been diagnosed in older rhesus macaques (15 years and 17 years, 4 months) but were morphologically distinct from the current tumors. A poorly differentiated maxillary sarcoma in a young bonnet monkey (*Macaca radiata*) constitutes the only other fibrous tissue tumor in our files since 1964. A multifocal fibrosarcoma in a woolly monkey (*Lagothrix* spp.) which was associated with





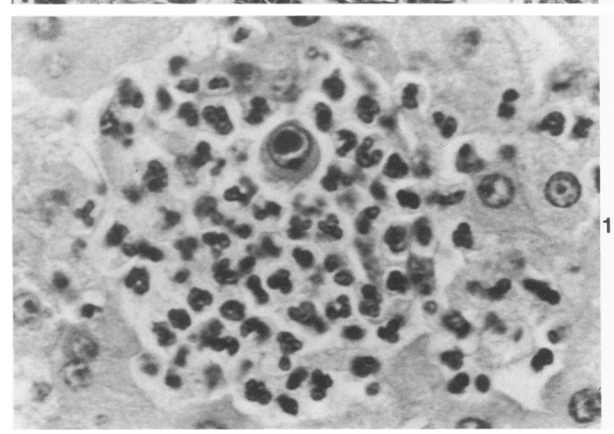


Figure 11 — Cytomegalic cells and suppurative inflammation. Note the distinct intranuclear inclusion bodies. (H&E, ×500) **Figure 12** — Severe cryptosporidiosis in an immune deficient rhesus monkey. (H&E, ×300) **Figure 13** — Cytomegalic cell within a hepatic microabscess in a rhesus monkey with acquired immune deficiency. (H&E, ×750) (All with a photographic reduction of 26%)

C-type virus particles has been reported.[15] Features in common with our cases include the multicentric nature of the tumor and the young age of the animal (3 years). C-type particles were present in woolly monkey tumor tissue examined by transmission electron microscopy; however, this has not been the case in tumors from either of our animals. Attempts to isolate viruses from the tumors from both our animals have been unsuccessful to date.

The syndrome seen in this group of animals includes the following features, at least four of which must be present before we designate the animal as a victim: 1) weight loss (>10%); 2) hepatosplenomegaly; 3) generalized lymphadenopathy; 4) anemia; 5) marrow hyperplasia; 6) persistent diarrhea (enterocolitis), poorly responsive to appropriate therapy; 7) chronic infections (skin, gingiva, or other), poorly responsive to appropriate therapy; 8) opportunistic infections; and 9) tumors (sarcoma or lymphoma).

Several features of this syndrome are comparable to AIDS in humans and to acquired immunodeficiency in other species. The working definition of AIDS in humans given by the Center for Disease Control (CDC) in Atlanta is "a disease moderately predictive of a defect in cell-mediated immunity occurring in a person with no known cause for diminished resistance to that disease."[3] Associated diseases have included Kaposi's sarcoma, *Pneumocystis carinii* pneumonia, and severe opportunistic infections including aspergillosis, candidiasis, cryptococcosis, CMV infection, nocardiosis, strongyloidosis, toxoplasmosis, zygomycosis, atypical mycobacteriosis, cryptosporidiosis, progressive multifocal leukoencephalopathy, and unusual mucocutaneous herpes simplex of long duration.

Lymphoid tissue morphology of AIDS victims varies but generally includes both cortical follicular hyperplasia and paracortical hyperplasia with increased paracortical vascularity and marked plasmacytosis.[16-22] The latter two features are not present in the monkeys seen here. The absence of plasma cells in our monkeys suggest dysfunction of humoral as well as cellular immunity, which may contribute to the incidence of bacterial infections. Similarly, two sources describe advanced changes in the human nodes reflecting abnormalities in B-cell populations as well as T-cell populations, and give a poor prognosis for patients with such changes.[14,20] This has also been our experience with monkeys from NC-1. The presence of Kaposi's sarcoma and some lymphomas in AIDS victims[23-25] and the occurrence of two fibrosarcomas in the monkey group may point to similar defects in immune surveillance systems.

Feline leukemia virus infection (FeLV) is another naturally occurring disease with which immune deficiency and an increased rate of certain tumors have been reported.[26] Histologic examination of lymphoid tissue of experimentally infected kittens generally included marked hypocellularity of paracortical areas, variable germinal center size (small to prominent), and varied medullary cell populations, depending on the presence of intercurrent infections. Marked plasmacytosis was present in a small number of animals. Thymuses in these kittens were strikingly affected, with severe lymphoid depletion and epithelial degeneration.[27] Neoplasia associated with FeLV includes lymphosarcomas and fibrosarcomas. Immunosuppression has been reported in cats chronically infected with FeLV. Anemia, gingivitis, and recurrent infections such as skin abscesses are also seen.

Noninfectious causes for immune dysfunction are known. Experimental zinc deficiency specifically affects T cells. This is reflected by severe thymus atrophy and impaired T-cell helper function in zinc-deficient animals, which maintain intact and functional B-cell populations.[28,29] The monkeys in this report often suffer from chronic diarrhea. They often have microcytic anemia, which may reflect iron deficiency. It seems plausible that zinc levels are also low in these animals, and could compound the already present immune dysfunction.

Environmental toxins are known to modify immune response,[30-32] and have been considered in this epizootic. Preliminary epidemiologic study, however, tends to point to an infectious etiology transmitted through direct animal-to-animal contact.[33] A mechanism involving selection for immune suppressors (T-suppressors or macrophages) or nonspecific suppression of helpers seems more likely than direct cytotoxicity or lymphocyte-toxic autoantibodies. In combination with a probable primary agent, other contributing factors to the ultimate severity of immune suppression in these animals would include malnutrition secondary to chronic enterocolitis and subsequent malabsorption and/or loss of protein and micronutrients such as zinc, as well as septicemias and CMV infection. CMV antibody titers from unaffected animals elsewhere in the colony thus far have all been >1:320, as well as 7 of 12 serum specimens taken from animals before entry into NC-1 that became ill after being placed in the corral.[1]

The syndrome seen in these animals is a naturally occurring acquired immune deficiency that has features similar to those of other naturally acquired immune deficiencies, such as human AIDS and FeLV infection, as well as some features different from the features of these diseases. In spite of the differences, this spontaneous disease provides an excellent oppor-

tunity to study the complex factors modulating the immune system in a species phylogenetically close to man. Search for an etiologic agent and studies to further define the immunopathology, including the roles of neutrophils and macrophages, in this ongoing epizootic are currently under way.

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