

The Influence of Genotype on the Development of Glomerular Lesions in Mink With Aleutian Disease Virus

A Correlated Light, Fluorescent, and Electron Microscopic Study

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In an attempt to document progression rate differences in the development of glomerular lesions in mink infected with Aleutian disease virus (ADV), the glomeruli of Aleutian and non-Aleutian mink experimentally infected with ADV were evaluated by light, fluorescent, and electron microscopy. The animals were also examined for the presence of interstitial infiltrate, neutrophils, and arterial lesions. One hundred percent of the Aleutian mink had glomerular cell proliferation and interstitial infiltrate, while 95% of the Aleutian and 41% of the non-Aleutian mink had neutrophilic infiltrates and arteritis, respectively. Of the non-Aleutian mink, 91, 83, 42, and 12.5% had glomerular cell proliferations, glomerular neutrophils, interstitial infiltrate, and arterial lesions in, that order. All the Aleutian mink had glomerular depositions of γ -globulin (IgG) and complement (C3), whereas 75% of non-Aleutian mink had deposits of IgG and C3. One hundred percent of both genotypes had glomerular deposits of immunoglobulin M (IgM). Ultrastructural glomerular changes consisting primarily of depositions of granular electron-dense material on basement membranes were observed in Aleutian mink 6 weeks after infection and 12 weeks after infection in non-Aleutian mink. These findings document progression rate differences in the development of glomerular lesions in Aleutian disease-affected Aleutian and non-Aleutian mink. Further, they emphasize the need for exploration of pathogenetic mechanisms involved in progression rate differences in lesion development. (*Am J Pathol* 81:321-336, 1975)

ALEUTIAN DISEASE (AD) is a persistent viral infection of mink characterized by systemic proliferation of plasma cells,¹ hypergammaglobulinemia,² hepatitis, arteritis, and progressive glomerulopathy.³⁻⁶ Viremia and hypergammaglobulinemia have been reported to precede the onset of demonstrable glomerular lesions.^{7,8} Henson and co-workers have studied the sequential development of the glomerular lesions in AD and

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demonstrated a proliferative glomerulitis resulting from mesangial cell proliferation subsequent to depositions of abnormal material.^{4,9} Ultrastructurally, the deposits were electron-dense macromolecules that stained positive for host γ -globulin (IgG) and complement (C3) by immunofluorescence.^{5,6} Deposits were also present subendothelially and within basement membranes.^{5,6}

The occurrence of host IgG and C3 within the glomeruli of AD-affected mink was highly suggestive of immunologically mediated lesions. Supportive evidence in the form of antibody directed against viral antigen(s)¹⁰⁻¹² and the occurrence of virus-antibody complexes¹³ has been reported. Porter *et al.*¹² eluted antiviral antibody from kidneys of AD-infected mink. These findings, along with the report of Cheema *et al.*¹⁴ demonstrating the prevention of renal lesions by immunosuppression, offer additional evidence for the immunologic mediation of the glomerular lesions in AD-infected mink.

Mink that are homozygous recessive (*aa*) for the *Aleutian* allele (Aleutian mink) have the Chediak-Higashi syndrome.⁸ Animals having this inherited disease of membrane-bounded organelles of various cell types have increased susceptibility to bacterial infections, develop AD lesions more rapidly, and have a shorter clinical course of Aleutian disease when compared to mink not affected by the Chediak-Higashi syndrome.^{8,14} It is felt that AD in both genotypes of mink reflect similar pathogenetic mechanisms with altered temporal relationships. It is the purpose of this study to compare the development of renal lesions in Aleutian and non-Aleutian mink.

Materials and Methods

Animals

Twenty-four Aleutian (*aa*) and 24 non-Aleutian (*AA* or *Aa*) mink were used in this study. All 48 mink were inoculated intraperitoneally with 0.5 ml of a 10% tissue suspension prepared from the spleen of mink with typical lesions of AD. Three Aleutian and 3 non-Aleutian mink were killed before inoculation and at 3-week intervals for 24 weeks, and their tissues collected. Portions of the kidneys of all animals were prepared for light, electron, and fluorescence microscopy. Serum samples from each mink were collected for determination of γ -globulin and anti-AD antibody levels.

Light Microscopy

Kidneys, mesenteric lymph nodes, spleen, and liver sections were fixed in a 10% buffered formalin solution, embedded in paraffin, sectioned at 5 μ , and stained with hematoxylin and eosin¹⁵ and periodic acid-Schiff (PAS). Criteria for glomerular evaluation consisted of determining the mean number of glomerular nuclei, the morphologic appearance of the glomeruli when stained by hematoxylin and eosin, and the presence and amount of PAS-positive material in the glomeruli. The mean number of glomerular nuclei

in ten glomeruli from each mink was determined. The mean of the 3 Aleutian and 3 non-Aleutian mink killed at the same time were determined from these figures. The glomeruli were evaluated for the presence and amount of PAS-positive material using a scale of 0 to 4+ and for the presence of neutrophils. At 1+ rating was indicative of a slight increase in PAS-positive material using the Day 0 mink as the normals for comparison. A 2+ rating was indicative of a moderate increase in PAS staining, while 3+ and 4+ ratings indicated severe, diffuse increases in PAS-positive material, the difference being the intensity of involvement.

Other indices used for establishing AD renal lesions consisted of finding a proliferative glomerulitis, interstitial infiltration of plasma cells in sections stained with hematoxylin and eosin, and an increase in PAS-positive material in concert. The kidneys were also evaluated for the presence of arterial lesions.

Electron Microscopy

Thin slices of the renal cortices were fixed in 2.5% glutaraldehyde in 0.1 M phosphate buffer (pH 7.4). The specimens were then rinsed in sodium phosphate-buffered 4% sucrose (0.1 M, pH 7.3) and were postfixed in phosphate-buffered 1% osmium tetroxide. Following alcohol dehydration, specimens were embedded in Epon 812.¹⁷ Thin (0.5 μ) and ultrathin (400 to 600 \AA) sections were then cut. Thin sections were stained with toluidine blue for glomerular localization. Ultrathin sections were collected on 200-mesh grids and stained with uranyl acetate and lead citrate.¹⁸ Photomicrographs were taken with a Philips EM-200 electron microscope.

Fluorescent Microscopy

Goat anti-human IgM with cross reactivity to mink IgM was purchased from Hyland Laboratories. Mink γ -globulins were prepared by serial 50% and 40% saturated ammonium sulfate precipitations and dialyzed against phosphate-buffered saline (PBS, pH 7.2). The PBS-suspended γ -globulins were fractionated on DEAE cellulose, and the purity of the eluted IgG was assayed by immunoelectrophoresis against rabbit anti-whole mink serum. They were also tested in gel diffusion against rabbit anti-mink IgG.

Anti-mink C3 was prepared by the method of Mardiney and Müller-Eberhard¹⁹ and Henson's modification.⁸ Purity was assayed in gel diffusion against purified mink IgG and EDTA-treated mink plasma. Antisera to IgG and C3 were prepared in rabbits.

Fluorescent labeling of all antisera was by the method of Clark and Shepard.²⁰ Tissue sections were overlaid with the appropriate conjugate containing 1:10 dilution rhodamine bovine albumin for counterstaining. Patterns of glomerular immunofluorescence were evaluated using a 0 to 4+ scale: zero representing no staining; 1+, staining in any locale of the glomeruli; 2+, staining in at least half of the area of the glomeruli; 3+, staining in three-fourths of the area of the glomeruli; and 4+, staining over the entirety of the glomeruli including mesangial areas and walls of capillaries. Examination and photography were performed using a Zeiss Ultraphot II Microscope with an Osram HBO 200 lamp.

Results

Light Microscopy

Changes observed in the kidneys of Aleutian mink were consistent with those reported by Henson *et al.*^{4,9} in spontaneously and experimentally AD-infected Aleutian mink. The alterations consisted of a mild infiltration of proliferating plasma cells in the interstitium and glomerular changes.

Both lesions were present in the 3 Aleutian mink killed at 3 weeks (Figure 1). The plasma cell infiltrates were focal in distribution and usually were confined to perivascular and periglomerular areas. Glomerular alterations consisted of PAS-positive material in the tufts and occasionally a few neutrophils. The glomerular involvement affected all glomeruli, with the most significant change being an increase in glomerular tuft nuclei. The nuclei count in normal glomeruli sectioned at $5\ \mu$ was 70. The average increase in nuclei present at 8 weeks was 16 (Table 1). The increased number of nuclei appeared to be due to proliferation of native mesangial and endothelial cells. The average increase in nuclei present in glomeruli increased over the preceding two intervals (6- and 9-week intervals), reaching a peak at 12 weeks (Table 1). All 3 animals killed at 12 weeks had kidneys severely involved with the spectrum of renal lesions. The interstitial areas were diffusely infiltrated with plasma cells. The glomeruli were thickened, hypercellular, and contained an abundance of PAS-positive material that occupied the entire tuft (Table 1). These animals also had arterial lesions that consisted of fibrinoid degeneration of the vessel walls with infiltration of a few inflammatory cells (Table 2).

Animals killed at the 12-week interval exhibited varying stages of diffuse involvement of the interstitial areas and glomeruli (Figures 2 and 3). The average number of nuclei present for 3 animals at any given interval was decreased when compared to the average at 12 weeks (Table 1). Many of the glomeruli in the latter animals were undergoing atrophy and sclerosis, while several other glomeruli were obliterated.

Non-Aleutian mink killed at the first three intervals had an average increase of only three to four glomerular nuclei present when compared to the normal glomerular nuclear count of 70 (Figure 4). The amount of increased PAS-positive material was mild (1+), and occasional neutrophils were present (Table 1). Interstitial involvement was also mild and consisted of mild focal accumulations of mononuclear cells usually located around a single vessel. The latter alterations were present in 1 animal at 3 weeks and 2 animals at 6 weeks, while at 9 weeks none had the lesion (Table 2). Two of 3 non-Aleutian mink killed at 12 weeks had no interstitial involvement (Figure 5).

A gradual increase in the number of glomerular nuclei and the occurrence of PAS-positive material were seen in non-Aleutian mink killed at successive intervals (Table 1). The highest average glomerular nuclear count was present at 24 weeks. This average was considerable lower than the highest nuclei count for Aleutian mink which occurred at 12 weeks (Table 1). Only 1 mink at 18-, 21-, and 24-week intervals, respectively, had sufficient lesions to rate as severely affected (Figure 6). Neutrophils

Table 1—Nuclear Counts, Amount of PAS-Positive Material, and Presence of Neutrophils in the Glomeruli of AD-Affected Aleutian and Non-Aleutian Mink

Aleutian mink				Non-Aleutian mink			
Time after inoculation (wks)	Mean No. of nuclei	Neutrophils (No. with change/No. observed)	PAS*	Time after inoculation (wks)	Mean No. of nuclei	Neutrophils (No. with change/No. observed)	PAS*
0	70.00	0/3	0	0	70.00	0/3	0
3	86.70	2/3	++ + ++	3	73.16	0/3	+ + +
6	89.73	3/3	+++ + +	6	73.30	2/3	+ + +
9	110.50	3/3	+ - +++	9	74.43	3/3	++ + -
12	144.83	3/3	+++ ++++ ++++	12	78.33	3/3	++ + +
15	116.83	3/3	+++ ++++ +++	15	76.23	3/3	++ ++ +
18	127.50	3/3	++++ ++++ ++++	18	85.13	3/3	++ +++ +
21	122.40	3/3	++ ++ +++	21	95.03	3/3	++ ++ ++++
24	101.70	1/1†	++++	24	106.30	3/3	+++ ++ +++

* PAS ratings: 1+ = increased staining in any locale of the glomeruli, 2+ = staining in at least one-half of the area, 3+ = staining in three-fourths of the area, and 4+ = staining over the entirety of the glomeruli including mesangial areas and walls of capillaries. The findings in each animal examined at each time interval are given.

† Two Aleutian mink died during the trial, so only 1 animal was alive at 24 weeks after infection

were prominent and abundant in the glomeruli of these 2 animals, and PAS-positive material was also abundant. Glomerular lesions in these severely affected non-Aleutian mink were similar to those reported in the glomeruli of AD-affected Aleutian mink.^{4,9} One animal at 12, 21, and 24 weeks had mild arterial alterations (Table 2). Changes included destruction of the endothelium and mild degenerative changes (myolysis) of the media.

Table 2—Comparison of the Nonglomerular Renal Lesions in Aleutian and Non-Aleutian Mink

Weeks after inoculation	Aleutian mink		Non-Aleutian mink	
	Interstitial infiltrate*	Arteritis*	Interstitial infiltrate*	Arteritis*
0	0/3†	0/3	0/3	0/3
3	3/3	0/3	1/3†	0/3
6	3/3	0/3	2/3†	0/3
9	3/3	0/3	0/3	0/3
12	3/3	3/3	1/3	0/3
15	3/3	1/3	1/3	0/3
18	3/3	3/3	2/3	1/3
21	3/3	1/3	1/3	1/3
24	1/3‡	1/1	2/3	1/3

* Number of animals with change/number of animals examined.

† Infiltrate was focal, surrounding a small vessel.

‡ Two Aleutian mink died during the trial, so only 1 was alive at 24 weeks after infection.

Electron Microscopy

Ultrastructural alterations in the glomeruli of Aleutian and non-Aleutian mink were similar. However, changes were observed at 6 weeks after infection in Aleutian mink, while clearly discernible changes occurred at 12 weeks after infection in non-Aleutian mink. Changes observed at 6 weeks in Aleutian mink consisted of subendothelial depositions of electron-dense granular material. Deposited material with a nodular appearance was also present on the basement membranes. Mild mesangial cell proliferation and mesangial matrix increases were observed.

Capillary basement membranes in non-Aleutian mink glomeruli killed at 6 and 9 weeks were irregular, but no deposits were observed until 12 weeks after infection. These findings were consistent with the presence of γ -globulins and complement by immunofluorescence.

Fluorescent Microscopy

Gamma globulins and C3 were present in glomeruli of all Aleutian mink commencing at the 3-week interval. Maximum intensity of staining was observed at 12 weeks (Figures 7 and 8). Fluorescence in the glomeruli of non-Aleutian mink was present in 1 animal at 9 weeks and 1 at 12 weeks with IgG, but the staining was confined to one part of the glomerulus. Staining involving the entire glomerulus was observed beginning at the 15-week interval (Figure 9). Fluorescence in both genotypes was granular in appearance and was present along capillary walls and mesangial areas, except for the above-mentioned two exceptions (Table 3).

Table 3—Intensity of Glomerular Staining with Anti-C3, Anti-IgG, and Anti-IgM in AD-Affected Aleutian and Non-Aleutian Mink

Weeks after inoculation	Complement (C3)		IgG		IgM	
	Aleutian	Non-Aleutian	Aleutian	Non-Aleutian	Aleutian	Non-Aleutian
0	0	0	0	0	0	0
3	1+, 1+, 1+	0, 0, 0	1+, 1+, 1+	0, 0, 0	1+, 3+, 2+	1+, 1+
6	1+, 2+, 2+	0, 0, 0	1+, 2+, 2+	0, 0, 0	1+, 1+, 2+	1+, 1+, 1+
9	1+, 2+, 2+	0, 0, 0	2+, 3+, 3+	0, 0, 1+	1+, 1+, 2+	1+, 1+, 3+
12	3+, 3+, 3+	0, 0, 1+	4+, 4+, 4+	0, 0, 1+	1+, 2+, 3+	1+, 1+, 1+
15	3+, 4+, 4+	0, 1+, 2+	2+, 2+, 3+	0, 1+, 3+	1+, 2+, 2+	1+, 1+, 1+
18	3+, 4+, 4+	1+, 2+, 4+	2+, 2+, 3+	1+, 2+, 3+	1+, 1+, 2+	1+, 2+, 2+
21	2+, 4+, 4+	1+, 1+, 3+	2+, 2+, 3+	1+, 2+, 3+	1+, 1+, 1+	1+, 2+, 2+
24	4+	3+, 3+, 3+	3+	2+, 2+, 3+	1+	1+, 2+, 2+

The figures given for each time interval represent glomerular staining for each animal examined at that time; 0 = no fluorescence, 1+ = staining in any part of the glomeruli, 2+ = staining in at least half the area of the glomeruli, 3+ = staining in three-fourths of the area of the glomeruli, and 4+ = staining over the entire area of the glomeruli.

Fluorescence with IgM revealed a more granular appearance than either IgG or C3 (Figure 10). Staining was present in the mesangial area of the glomerular tufts and in capillary walls. Staining decreased in capillary walls at the periphery of the tufts. Maximal staining was present earlier than for either IgG or C3. In Aleutian mink, staining reached a maximum at 3 weeks and remained approximately the same from 6 to 18 weeks. At 21 and 24 weeks, however, staining with anti-IgM had almost completely disappeared. In contrast, staining in the glomeruli of non-Aleutian mink reached maximum intensity at 13, 21, and 24 weeks. One mink at 9 weeks had intense staining. Fluorescence with IgG and C3 was similar in appearance to that previously described for AD-affected mink.⁶

Discussion

Aleutian mink appear more susceptible, have a shorter mean death time, and have an accelerated progression rate of lesions when compared to non-Aleutian mink after experimental infection with AD virus.²¹ It appears that the increased susceptibility, earlier deaths, and faster progression of lesions in AD-affected Aleutian mink are a secondary manifestation of genetic homozygosity for the Aleutian allele and resultant undefined biochemical defect(s). Increased susceptibility to infectious diseases in the homology of Chediak-Higashi syndrome in other species is accepted. Gorham *et al.*¹⁵ and Padgett *et al.*⁸ have demonstrated increased susceptibility of Aleutian mink to AD virus.

Aleutian mink in this study had mild lesions (as early as 3 weeks after infection) and severe lesions (one at each of 18, 21, and 24 weeks after infection). *Severe* in this case refers to the occurrence of diffuse proliferation of plasma cells throughout the interstitial areas and a marked proliferative glomerulitis with neutrophils and increase in glomerular PAS-positive material. The histologic appearance of severe renal tissue alterations was strikingly similar in the two genotypes, the only difference being a later development of lesions in non-Aleutian mink. This finding supports an earlier report of Padgett *et al.*²¹

Generally, the severity of renal lesions correlates with increased γ -globulin levels and complement-fixing (CF) antibody titers in both genotypes.^{7,22} McGuire *et al.*¹¹ have reported that CF titers increased concomitantly with γ -globulin levels.

The proliferative glomerulitis observed in severely affected animals of both genotypes appears to result from similar pathogenetic mechanisms. The occurrence of electron-dense macromolecular material that consists in part of host γ -globulin and C3,^{5,6} of circulating virus-antibody com-

plexes,¹⁸ and anti-virus antibody eluted from kidneys of AD-affected mink¹² tend to support this contention. These findings provided the impetus for demonstrating that the glomerular lesions in AD-affected Aleutian mink were immunologically mediated.

Henson *et al.*⁴ have suggested that the earlier deaths in AD-affected Aleutian mink may be due to the inability of Aleutian mink to cope with macromolecular material deposited in the glomeruli or the formation of less of this material in non-Aleutian mink. However, the precise reason for the more rapid development of glomerular disease in Aleutian-type mink and whether this relates to defective host defense mechanisms remain unanswered.

There are several possible mechanisms that could be operative individually or in concert to account for temporal differences in the progression of renal lesions and subsequent deaths in AD-affected Aleutian and non-Aleutian mink. One possibility would relate to the presence of more antigen in the circulation and tissues of Aleutian mink. Present evidence does not completely clarify this possibility. Padgett²³ has reported that whole blood virus titers in AD-infected Aleutian and non-Aleutian mink were practically the same in both types of mink developing typical AD. He also demonstrated, however, that some non-Aleutian mink eliminate infective virus from the circulation. In addition, we have a number of non-Aleutian mink that have failed to develop clinical AD after repeated inoculation with the agent. These studies measured infectious virus, however, and may not relate to the presence and amount of soluble antigen(s) most likely involved in the glomerular alterations.

Secondly, the magnitude and class of anti-virus antibody in the two genotypes could influence the development of lesions. If Aleutian-type mink respond more vigorously or have more antibody of a given class that possess greater potential for the formation of phlogogenic complexes, more rapid glomerular disease could ensue. It has been suggested that both the quantity²⁴ and quality²⁵ of the antibody response affect the development of chronic glomerulonephritis in rabbits. In this connection, glomerulitis of patients with systemic lupus erythematosus have more γG_2 and γG_4 antibody than expected from their serum distribution.²⁶ Five immunoglobulin classes have been identified in mink sera.²⁷ Whether or not AD-affected Aleutian mink have more of one of these classes of antibody that play a role in glomerular lesion progression in contrast to AD-affected non-Aleutian mink is not known.

Genetic differences in the response of antigen stimulation could also account for the slower proliferation of plasma cells in non-Aleutian mink.

The work of Lodmell *et al.*²⁸ does not support this contention, however, but response differences were reported between Aleutian and non-Aleutian mink given booster injections of goat erythrocytes.

Ecklund *et al.*²⁹ have reported that the initial rise in γ -globulin levels in both genotypes following AD virus inoculation occurs at the same time. However, γ -globulin levels in AD-affected Aleutian mink rose more rapidly than those in AD-affected non-Aleutian mink. The work of McGuire *et al.*¹¹ and Cho *et al.*¹⁰ indicate that antibody titer increases to viral antigen(s) are concomitant with increases in γ -globulin levels. Whether spontaneous aggregation of γ -globulin could occur and be deposited remains to be investigated. Ferrets infected with AD virus developed marked hypergammaglobulinemia, however, and do not develop glomerular disease.

Finally, a consideration of cellular function—more specifically, mesangial cell function—may account for glomerular lesion progression rate differences. Marked proliferation of mesangial cells, increases in mesangial matrix, and the occurrence of abnormal material in mesangial areas and basement membranes in Aleutian disease have been reported.^{4,5} It has been suggested that the accumulation of more deposited material and the subsequent, more rapid progression of glomerular lesions in Aleutian mink might reflect a decreased ability of the reticuloendothelial (RE) system of this genotype to catabolize deposited macromolecular material.⁵ Prieur *et al.*³⁰ reported a slowed rate of digestion of horseradish peroxidase by the lysosomes of the proximal convoluted tubule cells of mice with Chediak-Higashi syndrome. This finding led these authors to suggest that a similar defect might occur in all cells of animals with Chediak-Higashi syndrome in which there is lysosomal degradation of protein. Whether a similar mechanism is functional in AD-affected mink remains to be shown and is under investigation.

References

1. Obel A: Studies on a disease in mink with systemic proliferation of plasma cells. *Am J Vet Res* 20:384, 1959
2. Henson JB, Leader RW, Gorham JR: Hypergammaglobulinemia in mink. *Proc Soc Exp Biol Med* 107:919-920, 1961
3. Helmboldt CF, Jungherr EL: The pathology of Aleutian disease in mink. *Am J Vet Res* 19:212-222, 1958
4. Henson JB, Leader RW, Gorham JR, Padgett GA: The sequential development of lesions in spontaneous Aleutian disease of mink. *Pathol Vet (Basel)* 3:289-314, 1966
5. Henson JB, Gorham JR, Tanaka Y: Renal glomerular ultrastructure in mink affected by Aleutian disease. *Lab Invest* 17:123-139, 1967

6. Henson JB, Gorham JR, Padgett GA, Davis WC: Pathogenesis of the glomerular lesions in Aleutian disease of mink: Immunofluorescent studies. *Arch Pathol* 87:21-28, 1969
7. Kenyon AJ, Trautwein JG, Helmboldt CF: Characterization of blood serum proteins from mink with Aleutian disease. *Am J Vet Res* 24:168-173, 1963
8. Padgett GA, Reiquam CW, Gorham JR, Henson JB, O'Mary CC: Comparative studies of the Chediak-Higashi syndrome. *Am J Pathol* 51:553-571, 1967
9. Henson JB: The pathogenesis of the glomerulopathy in Aleutian disease. *Fed Proc* 27:245, 1968 (Abstr)
10. Cho HJ, Ingram DG: Antigen and antibody in Aleutian disease in mink. I. Precipitation reaction by agar-gel electrophoresis. *J Immunol* 108:555-557, 1972
11. McGuire TC, Crawford TB, Henson JB, Gorham JR: Aleutian disease of mink: Detection of large quantities of complement-fixing antibody to viral antigen. *J Immunol* 197:1481-1482, 1972
12. Porter DD, Larsen AE, Porter HG: The pathogenesis of Aleutian disease of mink. I. *In vivo* viral replication and the host antibody response to viral antigen. *J Exp Med* 130:575-594, 1969
13. Porter DD, Laresen AE: Aleutian disease of mink: Infectious virus-antibody complexes in the serum. *Proc Soc Exp Biol Med* 126:680-682, 1967
14. Cheema A, Henson JB, Gorham JR: Aleutian disease of mink: Prevention of lesions by immunosuppression. *Am J Pathol* 66:543-552, 1972
15. Gorham JR, Leader RW, Padgett GA, Burger D, Henson JB: Some observations on the natural occurrence of Aleutian disease. *Slow, Latent, and Temperate Infections*, NINDB Monograph 2. Edited by DC Gadjusek, CJ Gibbs Jr., M Alpers. Washington DC, US Government Printing Office, 1965, pp 273-285
16. Manual of Histologic and Special Staining Techniques. Washington, DC, Armed Forces Institute of Pathology, 1957
17. Luft JH: Improvements in epoxy resin embedding methods. *J Biochem Biophys, Cytol* 9:409-414, 1961
18. Reynolds ES: The use of lead citrate at high pH as an electron-opaque stain in electron microscopy. *J Cell Biol* 17:208-212, 1963
19. Mardiney MR, Müller-Eberhard HJ: Mouse β 1C-globulin: Production of antiserum and characterization in the complement reaction. *J Immunol* 94:877-882, 1965
20. Clark HF, Shepard CC: A dialysis technique for preparing fluorescent antibody. *Virology* 20:642-644, 1963
21. Padgett GA, Reiquam CW, Henson JB, Gorham JR: Comparative studies of susceptibility to infection in the Chediak-Higashi syndrome. *J Pathol Bacteriol* 95:509-522, 1968
22. Porter DD, Larsen AE: Statistical survey of Aleutian disease in ranch mink. *Am J Vet Res* 25:1226-1229, 1964
23. Padgett GA: Aleutian disease virus replication in mink of different genotypes. *Fed Proc* 28:685, 1969 (Abstr)
24. Cochrane CG, Hawkins DJ: Studies on circulating immune complexes. III. Factors governing the ability of circulating complexes to localize in blood vessels. *J Exp Med* 127:137-154, 1968
25. Pincus T, Haberkern R, Christian CL: Experimental chronic glomerulitis. *J Exp Med* 127:819-832, 1968
26. Lewis EJ, Busch GJ, Schur PH: Gamma G globulin subgroup composition of the glomerular deposits in human renal diseases. *J Clin Invest* 49:1103-1113, 1970
27. Tabel H, Ingram DG: Immunoglobulins of mink: Evidence for five immunoglobulin classes of 7S type. *Immunology* 22:933-942, 1972
28. Lodmell DL, Bergman RK, Hadlow WJ, Munoz JJ: Cellular and humoral antibody

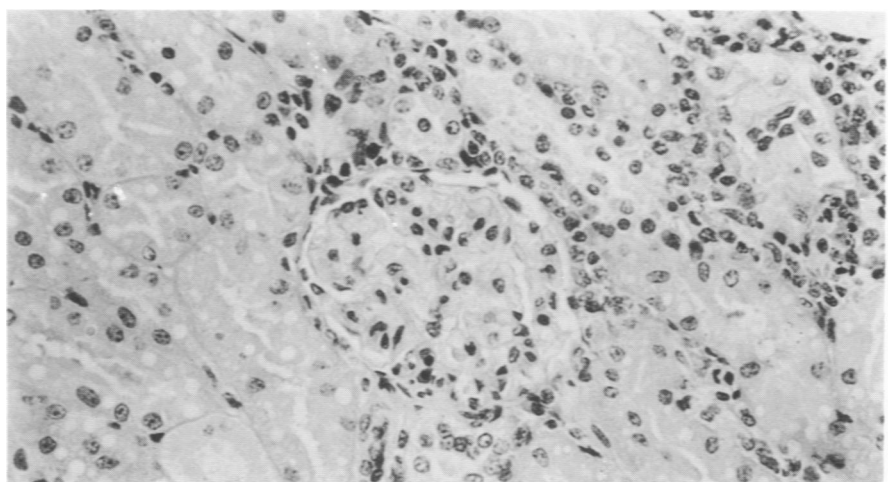
- responses of normal pastel and sapphire mink to goat erythrocytes. *Infect Immunity* 3:221-227, 1971
29. Eklund CM, Hadlow WJ, Kennedy RC, Boyle CC, Jackson TA: Aleutian disease of mink: Properties of the etiologic agent and host responses. *J Infect Dis* 118:510-526, 1968
30. Prieur DJ, Davis WC, Padgett GA: Defective function of renal lysosomes in mice with the Chediak-Higashi syndrome. *Am J Pathol* 67:227-240, 1972

Legends for Figures

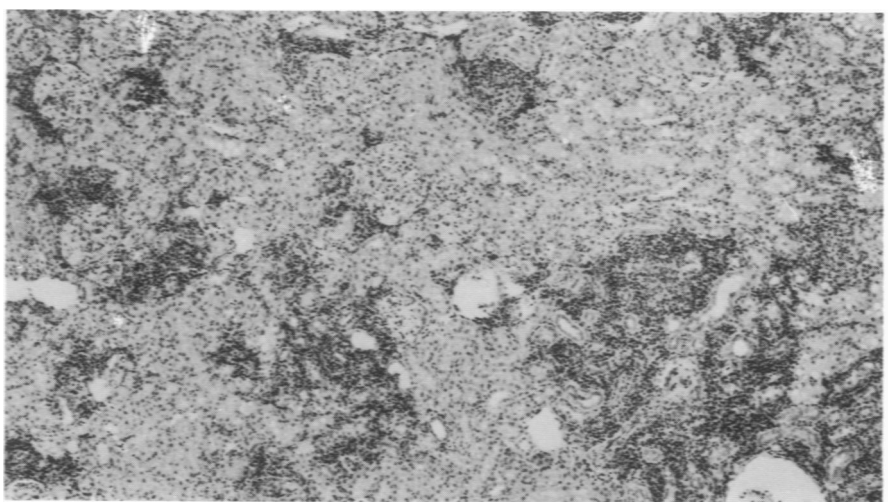
Figure 1—Glomerulus and interstitium from an Aleutian mink 3 weeks after infection. Mild periglomerular and periarterial infiltration of plasma cells are present. ($\times 330$)

Figure 2—Renal cortex of an Aleutian mink 12 weeks after infection. Note the distribution of proliferating plasma cells. ($\times 130$)

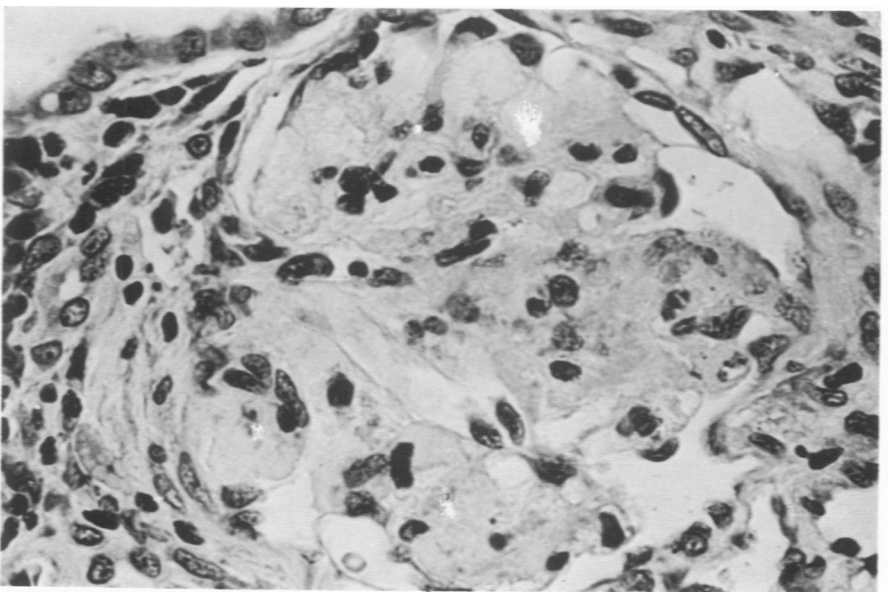
Figure 3—Aleutian mink glomerulus 12 weeks after infection. Dense eosinophilic material is present in mesangial areas. ($\times 1320$)



1



2

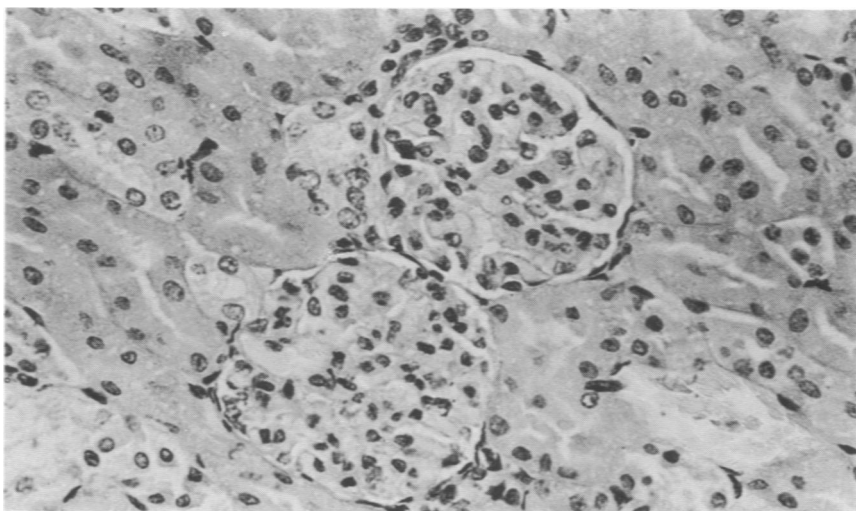


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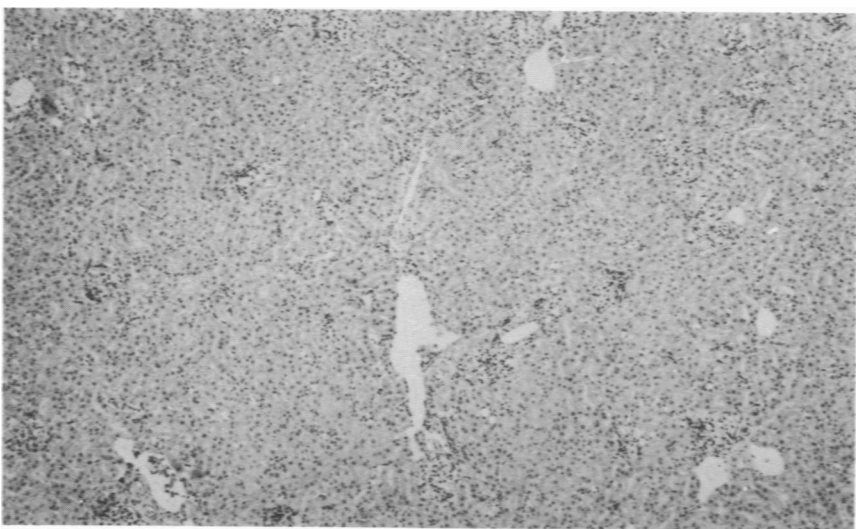
Figure 4—Glomeruli and interstitium from a non-Aleutian mink 12 weeks after infection. A few polymorphonuclear leukocytes are present in glomerular capillaries. (× 330)

Figure 5—Renal cortex of a non-Aleutian mink 12 weeks after infection (×130).

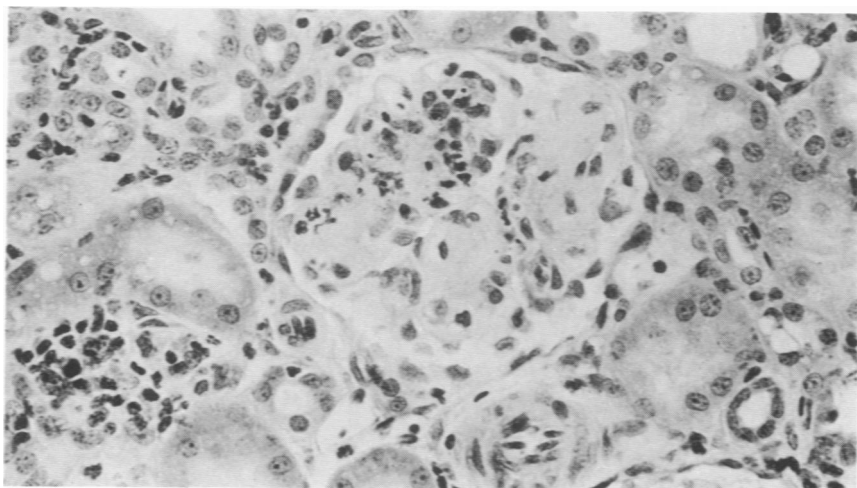
Figure 6—Glomerulus and interstitium from a non-Aleutian mink 18 weeks after infection. The tuft contains polymorphonuclear leukocytes, and mesangial areas are thickened. Plasma cells are present in the interstitium. (× 330)



4



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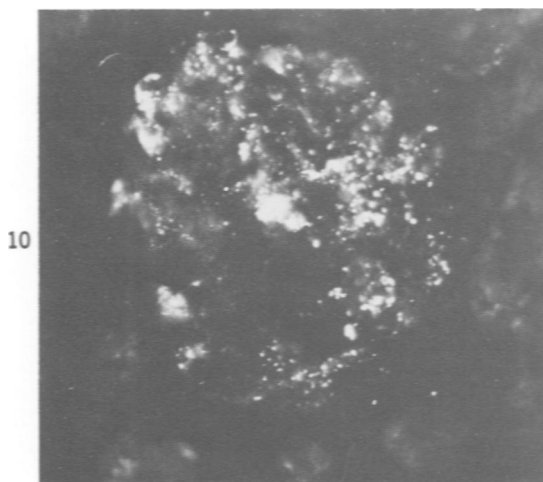
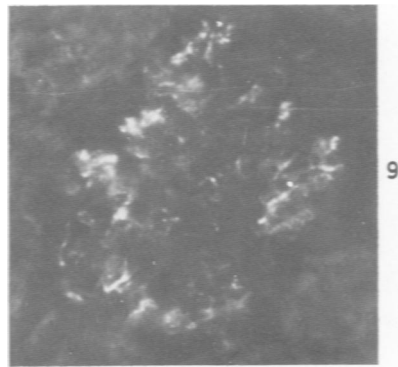
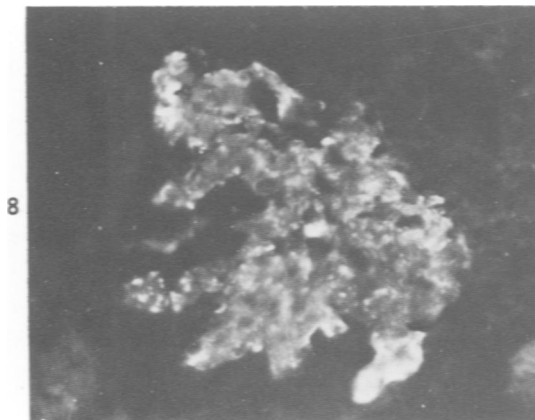
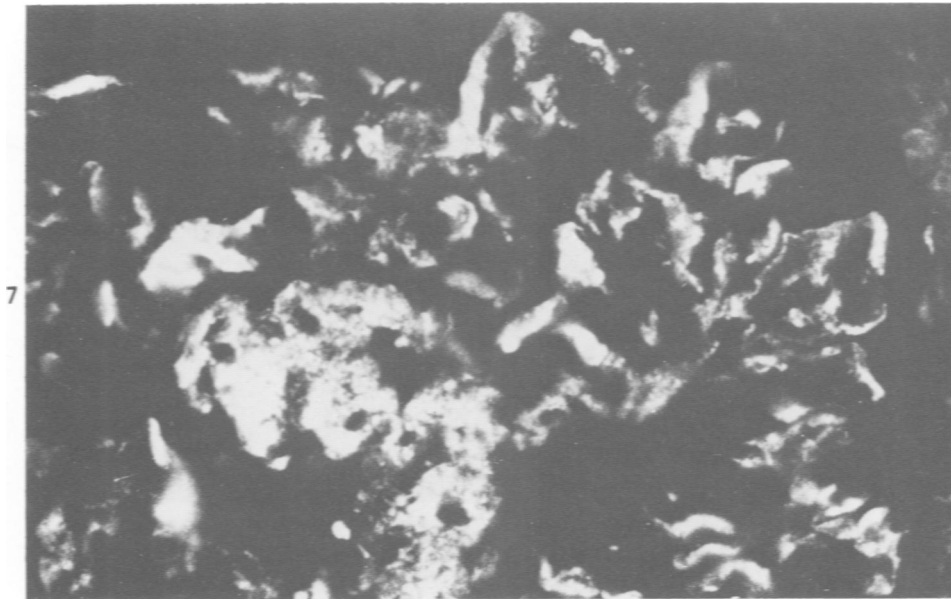


Figure 7—Gamma globulins (IgG) in the glomerulus of an Aleutian mink 12 weeks after infection. Extensive deposits are present in basement membranes and mesangial areas. ($\times 1320$) **Figure 8**—Complement in the glomerulus of an Aleutian mink 12 weeks after infection. Extensive glomerular deposits in capillary basement membranes and mesangial areas. ($\times 530$) **Figure 9**—Gamma globulins (IgG) in the glomerulus of a non-Aleutian mink 15 weeks after infection ($\times 330$). **Figure 10**—Immunoglobulin within the glomerulus of an Aleutian mink 6 weeks after infection. Nodular deposits in basement membranes and mesangial areas. ($\times 530$)