COMPARATIVE STUDIES OF THE CHEDIAK-HIGASHI SYNDROME

PATHOLOGY

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The Chediak-Higashi syndrome (C-HS) is an inherited disease of the membrane-bound organelles of various cell types. It has been reported in man,[1] mink,[2,3] and cattle.[4] Since the syndrome has recently been reviewed,[5] the clinical aspects and general characteristics of the condition will not be considered here. There are several reports in the literature which describe gross and histologic changes in children with the C-HS.[6-12] Death was caused by massive hemorrhage, pneumonia, or infections which usually had been repeated problems clinically. An infiltrate composed of lymphocytes, reticulocytes, and histiocytes has been present in various tissues of most of the affected children. In 5 affected children this cellular accumulation led to a diagnosis of malignant lymphoma.[7,10,13-15]

The purpose of this paper is to compare the lesions of C-HS-affected children, mink, and cattle. In addition, the morphologic alterations in the 3 species will be discussed with regard to the possible diagnosis of the secondary diseases that affect individuals with C-HS.

THE LESIONS IN THE CHEDIAK-HIGASHI SYNDROME

Studies in Children

Three of 6 children in a single family were affected with the C-HS and these cases have not been previously reported. There were 2 boys and a girl, and they were 16, 78, and 31 months old when they died. Growth and development were not remarkable; all had hepatosplenomegaly, partial albinism, and repeated infections. Skin hemorrhage complicated the course in 2 patients; all displayed some jaundice terminally.

Gross Anatomic Examination. When examined at necropsy, all 3

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children had enlarged liver and lymph nodes. Two of them had an enlarged spleen; the spleen of the third child had been removed surgically. One had a perforating ulcerative colitis with peritonitis and bilateral pulmonary abscesses. The others had multiple abscesses and areas of focal necrosis in various organs. All had petechial or ecchymotic hemorrhages scattered through numerous tissues and organs.

Histologic Examination. In nearly all the tissues examined, there was a mononuclear infiltrate with a general perivascular distribution. The infiltrate consisted primarily of large mononuclear cells with a copious amount of cytoplasm and small to medium-sized lymphocytes. Occasional plasma cells and neutrophils were also present and mitotic figures were rare. The large mononuclear cells frequently contained large amounts of cytoplasmic PAS-positive material. Germinal centers in the spleen were scanty and the normal architectural pattern was deranged. The sinusoids frequently contained macrophages, although the spleens appeared generally to be depleted of cells rather than infiltrated with them. Some of the lymph nodes were similar in appearance to the spleen while in others a relatively normal architectural pattern was present.

There were scattered areas of necrosis with bacterial colonies present in the lesion in various tissues and organs. In 1 instance there were scattered bilateral mycotic abscesses in the lung. The histologic appearance of the fungi was suggestive of *Asperigillus fumigatus*. The tissue reaction and cellular infiltrate present in these lesions was essentially the same as one would expect to find in a similar lesion in an individual without C-HS.

In renal tubular epithelial cells and reticuloendothelial cells of all 3 children there were large amounts of material showing positive results with the periodic acid-Schiff (PAS) reaction, Sudan black B stain, and reactions for acid phosphatase. These cytoplasmic accumulations were also autofluorescent with near ultraviolet light. This material was present in the neurons throughout the central nervous system, but was most readily observed in the Purkinje cells, the large neurons of the cerebellar peduncles, and ventral horns of the spinal cord. The material was present both in the Kupffer cells of the liver and in the large mononuclear cells of the generalized infiltrate. It is probably the same type of lipid-staining material which has been previously described in a C-HS child by Kritzler *et al.*[12]

The final gross and histologic diagnoses in the 3 children were as follows.

First Child. Male, 78 months old at death
Generalized lymphocytic and mononuclear infiltration of the organs: epicardium, myocardium, liver, lungs, spleen, brain (meninges and cerebral perivascular tissue), kidneys, wall of gastrointestinal tract, marrow
Lymphoid tissue atrophy

Hypocellular bone marrow with erythrophagocytosis
Hemorrhage in submucosa of gastrointestinal tract, lungs, skin of extremities (primarily legs)
Ulcerative colitis with perforation of ascending colon
Peritonitis, generalized (*Pseudomonas*)
Abscesses, mycotic, in lungs
Infarction of spleen
Necrosis, subcapsular, in liver
Septicemia (*Pseudomonas*)
Abscesses in psoas muscle

Second child. Male, 16 months old at death
Generalized lymphocytic and mononuclear infiltration of the organs: epicardium, myocardium, pericardium, liver, lungs, brain (meninges and perivascular tissue), kidneys, wall of gastrointestinal tract, marrow
Splenectomy during course of disease
Lymphoid tissue atrophy
Hypocellular marrow with erythrophagocytosis
Hemorrhage in gastrointestinal tract (focal petechiae), skin of extremities (primarily legs)
Hepatitis
Septicemia (*Staphylococcus*)
Abscesses in lungs, skeletal muscle, scalp, subepicardium (left ventricle)
Encephalomalacia with microscopic perivascular calcifications

Third Child. Female, 31 months old at death
Generalized lymphocytic and mononuclear infiltration of the organs: myocardium, lungs, liver, spleen, brain (meninges and perivascular tissue), kidneys, marrow
Lymphoid tissue infiltrated with mononuclear cells
Hypocellular marrow with erythrophagocytosis
Hemorrhage in rectal mucosa, pericardium, lungs, abdominal and mediastinal connective tissue, skin of extremities (primarily legs)
Hepatitis
Septicemia (*Aerobacter*)
Necrosis with bacterial aggregates in psoas muscle and in cerebral vascular channels
Glial nodules (cerebrum)

Studies in Cattle

Of 15 C-HS cattle that have been necropsied, only 7 will be discussed since the lesions observed in the other 8 cattle were consistent with those presented here. The cattle were 9, 1, 15, 36, 2, 2, and 24 months old at time of death; 5 were females and 2 males. The average age at time of death of all 15 animals was 12.4 months. All were partial albinos, with decreased coat pigment and gray irises instead of the normal dark brown to black. Several had had a hemorrhagic tendency.[16]

Gross Anatomic Examination. The spleen and liver were of normal size in all the C-HS cattle. The lymph nodes were of normal size unless they were in sites draining inflammatory areas. Severe peritonitis and ascites with specific sites of infection were present in 3 of the 7 cattle. Petechial or ecchymotic hemorrhages were present in various tissues and organs. A mild pleuritis was observed in 2. One animal had calf diphtheria (necrotic laryngitis and pharyngitis) which was present clinically in 7 other calves on which necropsy was not performed. All 7 of the cattle included in this report had pulmonary abscesses or broncho-

pneumonia. One calf had roughening and depression of the kidney surface with fibrous streaks in the cortex and medulla, but the renal pelvis was not involved. All of the cattle had single or multiple abscesses (0.5–15 cm. in diameter) scattered randomly through the hepatic parenchyma. Less often, subcutaneous and intramuscular abscesses occurred. The primary and secondary sex organs were normal except for 1 calf in which there was focal chronic necrotic orchitis and epididymitis. One calf had a purulent pericarditis and another had severe nutritional mopathy (Vitamin E and selenium deficiency) that has also been observed clinically in 4 others. The animals had experienced repeated subcutaneous and intramuscular abscesses and oral and lingual ulcerations. One calf had a suppurative arthritis in the right hock joint (tarsal-metatarsal) and another had a serofibrinous polyarthritis. All other organs were grossly normal.

Histopathologic Examination. The peculiar infiltrate of lymphocytes and histiocytes which has been a consistent lesion of the C-HS children was not observed in any of the cattle.

The histologic appearances of the lesions in the C-HS cattle were similar to those of the same etiology encountered in cattle without C-HS.* Furthermore, the appearance of the lesions in general fit the textbook descriptions as given by Smith and Jones[17] or Jubb and Kennedy,[18] whether the lesion was of a bacterial or vitamin-deficiency origin. Unfortunately, no well-documented viral diseases have been observed in the C-HS cattle.

Melanin granules were scant in the skin even in the areas which are normally heavily pigmented in non-C-HS animals. Sections of the eye revealed depletion but not absence of pigment in the normally pigmented areas. Where melanin was present, the granules varied tremendously in size, with some as large as 15 μ in diameter. The difference in the amount and size of melanin granules in the ciliary processes of C-HS and non-C-HS cattle is shown in Fig. 1 and 2.

The final gross and histologic diagnoses of the 7 C-HS cattle were as follows.

64-2144 PA Hereford Angus Cross. Female, brown, 9 months old
Chronic bronchopneumonia
Multiple pulmonary abscesses
Chronic suppurative arthritis
Chronic interstitial nephritis
Focal necrotic enteritis
Chronic peritonitis
Multiple hepatic abscesses

64-132 PA Hereford Angus Cross. Female, white, 1 month old
Necrotic laryngitis and pharyngitis

* For the sake of brevity, the children, cattle, and mink without C-HS will hereafter be referred to as "non-C-HS."

Torsion and incarceration of small intestine
Multiple glossal ulcerations
Mild focal interstitial nephritis
Diffuse nonsuppurative hepatitis
Diffuse nonsuppurative epi- and endocarditis
Steatitis
Diffuse nonsuppurative interstitial pneumonia
Focal suppurative bronchopneumonia
Peritonitis

64-2262 PA Hereford. Female, white, 15 months old
Acute rumenal tympanites (bloat)
Multiple hepatic abscesses
Acute interstitial pneumonia
Pulmonary edema and emphysema
Mild chronic interstitial nephritis
Lymphadenitis
Mild glossal ulceration
Serofibrinous polyarthritis

65-147 PA Hereford. Male, white, 2½ months old
Severe bronchopneumonia involving all lobes of the lung with multiple large areas of abscess
Multiple hepatic abscesses
Mild interstitial nephritis

64-1009 PA Hereford. Female, white, 3 years old
Traumatic reticulitis and hepatitis
Ascites
Multiple hepatic abscesses
Lymphadenitis
Severe interstitial nephritis
Peritonitis
Severe interstitial pneumonia
Pulmonary edema and emphysema

63-755 PA Hereford. Male, white, 2 years old
Chronic rumenal tympanites (bloat)
Multiple hepatic abscesses
Chronic hepatic cirrhosis
Sperm granuloma

65-944 PA Hereford. Female, white, 2 months old
Severe white muscle disease (Vitamin E and selenium deficiency)
Multiple hepatic abscesses
Multiple pulmonary abscesses
Mild interstitial nephritis

Material with the same staining characteristics and distribution as that described in the C-HS children was present in the neurons of the CNS, renal tubular epithelium, and cells of the reticuloendothelial system. The inclusions present in the tubular epithelium of the kidney of C-HS mink, cattle, and children are shown in Fig. 5–7. The numbers of C-HS and non-C-HS mink and cattle with this material present in the various cell types are shown in Table I.

Studies in Mink

Mink homozygous recessive for the Aleutian allele *a* have the characteristics of the C-HS. There are several color phases (phenotypes) of mink with this particular genotype, the first of which was named Aleu-

TABLE I

THE DISTRIBUTION OF PAS-POSITIVE, SUDAN BLACK B-POSITIVE, ACID PHOSPHATASE-POSITIVE, AND AUTOFLUORESCENT ACCUMULATIONS IN MAN AND ANIMALS WITH AND WITHOUT THE C-HS

	No.	*Neurons*	*Renal tubular epithelium*	*Kupffer cells (liver)*	*Macrophages & other RE cells*
C-HS Children	3	3/3 *	3/3 *	3/3 *	3/3 *
C-HS Cattle	8	7/8	8/8	8/8	8/8
Known heterozygous cattle (non-C-HS)	5	0/5	0/5	5/5	5/5
Known homozygous dominant cattle (non-C-HS)	20	1/20	0/20	20/20	20/20
C-HS mink (*aa*) with Aleutian disease	12	12/12	7/12	12/12	12/12
C-HS mink (*aa*) without Aleutian disease	11	11/11	8/11	11/11	11/11
Dark mink (*Aa* or *AA*) with Aleutian disease (non-C-HS)	11	0/11	0/11	11/11	11/11
Dark mink (*Aa* or *AA*) without Aleutian disease (non-C-HS)	10	1/10	0/10	10/10	10/10

* Numerator, number of animals with lipid present; denominator, total number of animals examined.

tian or gunmetal. They are collectively termed Aleutian, blue, or mutation mink. Due to the unfortunate coincidence in names, "Aleutian" as a type of mink (those with the C-HS) is often confused with Aleutian disease (AD) of mink. Mink with the *aa* genotype always have the abnormal leukocytes and other characteristics of the C-HS, independent of AD. Moreover, mink of the *Aa* or *AA* genotypes never have the C-HS, regardless of whether they had AD. The C-HS in mink is the result of a genetic abnormality, and AD is a viral disease which can affect all mink.

Several hundred C-HS and non-C-HS mink have been examined clinically and at necropsy and are grossly normal unless affected by a secondary agent.

Gross and Histopathologic Examinations. In the rapidly fatal viral diseases or intoxications such as distemper, mink virus enteritis, and botulism, no difference in the course of the disease or in the gross and microscopic lesions was observed when C-HS and non-C-HS mink were compared. When bacterial diseases or a chronic viral disease (Aleutian disease) were studied in C-HS and non-C-HS mink, differences were observed. The number of C-HS mink contracting infections under natural conditions was greater and the clinical course was usually more rapid under both experimental and natural conditions.[19] We have necropsied C-HS and non-C-HS mink which succumbed to purulent pleuritis, avian tuberculosis, tularemia, pasteurellosis, peritonitis, *Sphaerophorus*

necrophorus infection, pneumonia, and Aleutian disease, and mink with cutaneous abscesses or phlegmons in various parts of the body. The gross and histologic appearances of the lesions were essentially the same in C-HS and non-C-HS animals.

C-HS mink are similar to cattle in that the characteristic cellular infiltrate observed in children was not seen. Neither have neoplastic processes been observed to occur in a greater proportion of C-HS mink when compared to non-C-HS mink.

All of the C-HS mink examined had less melanin present in the normally pigmented structures than did wild type mink. The size of the melanin granules in the C-HS mink varied considerably, with many being 4–5 times normal size. The amount and difference in size of the melanin granules in C-HS mink can be seen in Fig. 3 and 4.

Twenty-three C-HS and 22 non-C-HS mink with and without AD were examined for the presence of PAS-positive material in neurons of the CNS, renal tubular epithelium, and reticuloendothelial cells. The results are presented in Table I. All the C-HS mink had deposits in the neurons, and 15 of the 23 C-HS mink had deposits in the renal tubular epithelium. The deposits were not associated with AD. Similar material was observed in one 3-year-old non-C-HS female mink. Cells of the reticuloendothelial system throughout the body of C-HS mink contained the pigment, but it was also present in similar cell types in non-C-HS animals.

Experimental Aleutian Disease

Aleutian disease is one of the conditions in which a marked difference in susceptibility of C-HS and non-C-HS individuals has been demonstrated in both epidemiologic and experimental studies.[19,20] Mink with the C-HS contract the disease more readily under natural conditions and die more rapidly under experimental conditions than non-C-HS mink. As a matter of fact, the condition was named Aleutian disease because Aleutian type mink are more susceptible and at one time were thought to be the only mink which were affected. Despite the difference in susceptibility when the lesions of mink which had died of AD were examined histologically, C-HS and non-C-HS mink could not be differentiated on the basis of severity or type of lesion present. In essence, the amount of tissue damage necessary to cause death in C-HS and non-C-HS mink was similar, but the progression to the terminal changes was apparently more rapid in the C-HS mink.

To study the progression of lesions in AD, 28 C-HS and 28 non-C-HS mink were inoculated intraperitoneally with 1 cc. of a crude suspension of spleen, liver, and kidney containing approximately 10^4 ID_{50} of AD virus. An equal number of noninoculated controls were maintained. Four

C-HS and 4 non-C-HS mink in both control and inoculated groups were killed 1, 2, 3, 4, 6, 8, and 10 weeks post inoculation. Tissues were fixed in neutral buffered formalin and Bouin's fluid, sectioned at 6 μ, stained with hematoxylin and eosin, and observed for microscopic lesions. No lesions were observed in any of the control mink.

The microscopic lesions in the inoculated mink were graded according to the following criteria: (1) minimal—occasional plasma cells, lymphocytes, and histiocytes in the portal areas of the liver; (2) mild—5–20 mononuclear cells per portal area and involving at least 5 portal areas per low power field; (3) moderate—heavy mononuclear cellular infiltrate involving nearly all of the portal areas in the section; (4) severe —the same as moderate liver lesions but with perivascular infiltrates and glomerular lesions in the kidney; and (5) very severe—the same as severe, but with bile duct proliferation in the liver.

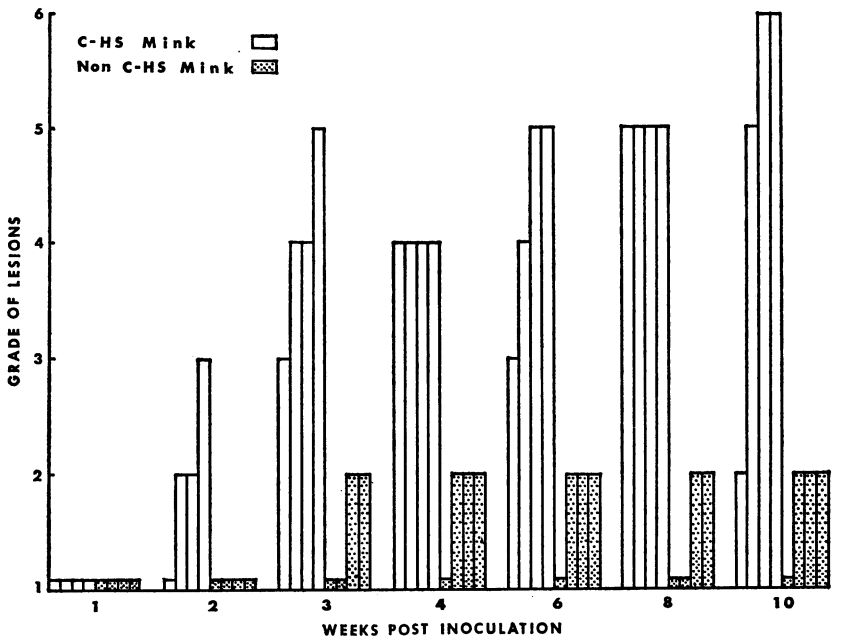
At the end of the first week post inoculation no lesions were observed in either the C-HS or non-C-HS mink. The first microscopic lesions of the disease were minimal-to-mild plasma cell and lymphocytic infiltrates in the portal areas of the liver, which occurred in 3 of the 4 C-HS mink at the end of the second week post inoculation. None of the non-C-HS mink killed in the second week had lesions of AD. With one exception, in the third week and thereafter, all of the C-HS mink could be readily distinguished from the non-C-HS mink on the basis of the severity of AD lesions.

Seventeen of the 20 inoculated C-HS mink killed in the third week and thereafter had moderate-to-severe liver lesions. Ten of the 20 C-HS animals had lesions in the kidney which began with perivascular plasma cells and lymphocytic infiltrates in the arcuate area and progressed to heavy infiltrates with derangement of the basement membranes of the tubules and mild glomerular lesions. In 2 of the C-HS mink killed the tenth week post inoculation there was bile duct proliferation. There was no difference in the cell types present in the infiltrate in C-HS and non-C-HS mink.

None of the inoculated non-C-HS mink had lesions which could be graded as more than minimal. During the course of the experiment, 13 of the 20 non-C-HS mink killed the third week post inoculation and thereafter had minimal lesions. The remaining 7 animals were histologically normal. The results are presented in Text-fig. 1. As might be expected, there were variations in response within a given group (i.e., 1 C-HS mink or 1 non-C-HS mink may have more severe lesions than another sacrificed at the same time).

Inflammatory Response. In order to study cellular infiltrates after inoculation with bacteria, 2 C-HS and 2 non-C-HS mink were anesthe-

tized with pentobarbitol and silk suture material which had been soaked for 2 hr. in a 24-hr. culture of *Staphylococcus aureus* was stitched through the skin into the subcutaneous musculature of the back at ap-



TEXT-FIG. 1. Differences in rate of progression and severity of lesions in liver and kidney, due to Aleutian disease virus in mink with (C-HS) and without (non-C-HS mink) Chediak-Higashi syndrome. Mink were experimentally inoculated intraperitoneally with 1 cc. of 10% suspension of infected mink spleen and kidney containing 10^4 ID_{50} of virus. Grades of lesions are indicated on left axis: 1, normal; 2, minimal; 3, mild; 4, moderate; 5, severe; and 6, very severe.

proximately 1-in. intervals. The stitches were made at hourly intervals for 10 hrs. At the end of the tenth hour the mink were killed, and the skin and musculature at each site was excised and fixed in neutral buffered formalin. The tissues were embedded in paraffin, sectioned, and stained with hematoxylin and eosin and with Giemsa. The thread marked the center of the lesion.

No difference was found in the type of cellular infiltrate or in the rapidity with which the infiltrate occurred when the C-HS and non-C-HS animals were compared. The infiltrate during the first 8 hr. in both types of mink was composed almost entirely of neutrophils. In the ninth and tenth hours macrophages and lymphocytes were observed, but the infiltrate was still primarily composed of neutrophils. Since the infiltrate tended to spread along the planes between the muscle bundles and into the looser tissue the amount of infiltrate present could not be quantitated.

Discussion

Reports of a high prevalence (5 of 47 cases) of neoplasms (probably malignant lymphoma) in C-HS children has aroused considerable interest. This diagnosis was made by 2 groups of investigators and was based on clinical and pathologic features which were similar in many respects to those observed in malignant lymphoma.[7,10,13,14] They stressed the hepatosplenomegaly, lymphadenopathy, and cellular infiltrate which was present not only in these 5 cases but in nearly every case of the C-HS in children in which a necropsy was performed. In addition, virus-like particles which resemble the Bernhard Type C virus have been observed in 2 C-HS children, and spleen cells from 1 child were maintained in tissue culture for 152 days.[13,14,21]

The infiltrate present in the 3 children included in this report more closely resembles a reactive rather than a neoplastic response. Several other investigators have ruled out neoplasm as a cause of the infiltrate observed in the C-HS children they examined.[6,8,9,11,22–25] In 2 reports it was suggested that the lesions present may have been due to infectious mononucleosis,[1,11] but in another study this diagnosis was ruled out, on the basis of the severity of the clinical course.[8] The descriptions of the infiltrates present in C-HS cases which were not diagnosed as malignant lymphoma were similar to those present in cases in which such a diagnosis was made.

Other lesions present in the children and animals with the C-HS may be of some help in resolving the question. In every instance—whether an experimental or a natural disease, and regardless of the etiologic agent —the lesions, as judged by histologic appearance, were typical of those which would be expected in non-C-HS individuals. If these observations also apply to neoplasms, one would expect a lymphoma in a C-HS child to look like a lymphoma in a non-C-HS child. Indeed, this is not the case. The infiltrate in C-HS children has been described as being due to a "peculiar" or "atypical" lymphoma.[10,21]

The only disease observed in C-HS animals which had a generalized tissue infiltrate was AD of mink. Two investigators have suggested that AD may be a plasma cell myeloma.[26,27] On the other hand, several have stated that it is more likely to be due to a reactive response to a virus.[28–31] No investigator has reported that the appearance of the lesions in C-HS mink was different from that found in non-C-HS mink.

While not providing definitive evidence, the following information should be considered in a discussion concerning lymphoma and the C-HS. Lymphoma is more prevalent in cattle than it is in people (18/100,000 in cattle[32] compared to 6.7/100,000 in people[33]). It has been diagnosed in

the non-C-HS herd at Washington State University, and contact between these animals and the C-HS herd occurred. In addition, lymphomas from various sources and serum from a C-HS child, which had the infiltrate, were injected into C-HS mink and cattle and no neoplasms have resulted.

If the infiltrate observed in the C-HS children is not due to lymphoma, then what is the cause? The clinical and pathologic features in many respects resemble those of infectious mononucleosis. There have been spontaneous recoveries in the children and recoveries following treatment with cortisone and/or antibiotics, with full remission of signs and of the hepatosplenomegaly and lymphadenopathy. Many of the children were not treated with cancer therapeutic drugs. The appearance of the infiltrate in the 3 children reported herein suggested infectious mononucleosis more than it did lymphoma. A comparison of the histologic findings in lymphosarcoma, infectious mononucleosis, and the C-HS is presented in Table II. If this is mononucleosis, then the clinical course in the children is suggestive of the clinical course of AD in mink—that is, it is much more severe and rapid in C-HS than in non-C-HS individuals. On the other hand, the heterophil antibody test has been positive in only 2 of the children in which the test was reported.[1,11] In 5 children it was high normal and in 2 it was negative. In 1 of the 3 children included in this report the test was positive at 5 months and again at 1 year of age. In addition, the titer 1:112 remained the same after guinea-pig absorbtion. If there is a single agent causing the tissue infiltrate which has been morphologically very characteristic in the C-HS children, the evidence concerning its identity is at best inconclusive.

The PAS-positive inclusions in the neurons, renal tubular epithelium, and reticuloendothelial (RE) cells are of interest. Similar material is present in the RE cells of non-C-HS mink and cattle (Table I) and C-HS and non-C-HS animals cannot be differentiated on this basis. There are several diseases such as the lipidoses in which similarly staining material is present in the neurons. In addition, the staining characteristics of the material are similar to those of lipofuscin, the so-called aging pigment. One non-C-HS cow (11 years old) and 1 non-C-HS mink (3 years old) had similar material present in the neurons (Table I). When tissue sections from C-HS and aged non-C-HS animals of various species (mink, cattle, horses, cats, dogs) were stained with PAS and examined as unknowns, the C-HS animals could not be differentiated, on the basis of the neuronal inclusions, from the aged animals of any of the species examined. In C-HS animals the neuronal deposits have been present at less than 1 week of age.

We have never observed inclusions in the renal tubular epithelium of

TABLE II

COMPARATIVE PATHOLOGY OF LYMPHOSARCOMA, INFECTIOUS MONONUCLEOSIS, AND CHEDIAK-HIGASHI SYNDROME IN HUMAN BEINGS

Lymphosarcoma	*Infectious mononucleosis*	*Chediak-Higashi syndrome*
	LYMPH NODES	
Replacement of architecture by sheets of lymphocytes or -blasts. Peripheral sinuses obliterated, pericapsular fat infiltrated; capsule intact.	Architecture intact, usually, or distorted with sheets of lymphocytes (normal and atypical) obscuring germinal centers. Lymphocytes (typical and atypical) in capsule, trabeculae, in lymphatics of blood vessel walls, in dilated sinuses and pulp. Mitotic figures may be abundant (but are not abnormal).	Architecture generally retained. Follicles become smaller and sparse as disease progresses. Medullary cords composed of adult and immature lymphocytes. Mitotic figures are scattered. Sinusoids become compressed but contain mature and immature lymphocytes and mononuclear cells. Erythrophagocytosis is present. Terminally, there is depletion of lymphoid structures with loss of architectural pattern and fibrosis.
	SPLEEN	
Architecture replaced by sheets of lymphocytes obscuring white and red pulp. Lymphatics in trabeculae clogged with lymphocytes and -blasts.	Architecture generally intact. Dilated sinuses with mature and atypical lymphocytes. Lymphocytes abundant in red pulp, trabeculae, capsule, and lymphatics of vessel walls.	Architecture generally intact; follicles may be reduced, may have peripheral laminations of typical and atypical lymphocytes. Lymphocytes in sinusoids, trabeculae capsule. Prominent sinusoids lined by hyperplastic reticuloendothelial cells. Sites of erythropoiesis with megakaryocytes.
	LIVER	
Marked portal lymphocytic infiltration. Lymphatics (perivascular) and—usually—sinusoids clogged with lymphocytes and -blasts.	Abundant lymphocytes in portal areas. Aggregates may extend into adjacent parenchyma where there may be liver cell replacement and bile duct proliferation. Sinusoids packed with normal and atypical lymphocytes. Kupffer cell hyperplasia.	General architecture preserved with some focal parenchymal necrosis. Periportal lymphocyte and mononuclear cell infiltrate. Extension of this into adjarcent parenchyma with hepatic atrophy and fibrosis.
	MARROW	
Replacement of myeloid tissue by lymphocytes and -blasts.	Normal or hyperplastic with hyperplasia limited to granulocytic series.	Granulopoiesis, erythropoiesis, and megakaryocytes may be depressed by prominence of lymphocytes and monocytes. Late in the course, mononuclear cells and macrophages with red cell phagocytosis leave only islands of normal marrow.

non-C-HS mink or cattle. However, similar inclusions have been experimentally induced in the renal tubular epithelium of other species.[34]

Whether the material present in the 3 cell types discussed above is a primary cell defect and is produced specifically by the cell or is the result of another as yet unrecognized defect in the C-HS is unknown. This material could well represent either faulty digestion or excretion of material removed from the blood.

Why C-HS individuals are more susceptible to infection is still unanswered. Padgett[35] has been unable to show a difference in killing capacity of neutrophils obtained from C-HS and non-C-HS mink and cattle. In addition, he found essentially no difference in the respiratory rate or motility and in the phagocytin, histone, lysozyme, acid phosphatase, cathepsin, and β-glucuronidase content when neutrophils from C-HS and and non-C-HS animals were compared. No one has reported a difference in the immune response of C-HS and non-C-HS individuals of the three species.

As Page *et al.*[10] have pointed out, using the Rebuck skin window technique with C-HS children, and as was observed by stitching suture material into the skin and musculature of mink, the type of inflammatory response and the rapidity of the occurrence of the response was similar in C-HS and non-C-HS individuals. Unfortunately, neither of these techniques, as used, was of value in quantitating the degree of response.

Levine, Padgett, and Leader[36] found no difference in the tissue reaction present or in time of onset of symptoms with experimental allergic encephalitis when C-HS and non-C-HS mink were compared. Their findings indicated that the immunologic mechanism of C-HS mink was normal in a delayed hypersensitivity situation.

The interaction of AD of mink and the C-HS in mink presents an intriguing problem. All types of mink can and do become infected with the virus of AD, but the course of the disease in C-HS mink is shorter and more severe. The cellular infiltrate which is characteristic of AD in mink occurs much more rapidly in C-HS than in non-C-HS mink. Although it is not always the case, one generally associates cellular infiltrates with protection of the host from the deleterious effects of invading organisms. In the case of AD-infected C-HS mink, however, the rapid tissue reaction apparently augurs early death. Gorham *et al.*[20] and Padgett *et al.*[19] have clearly shown a greater susceptibility of C-HS mink to the AD virus. This increased susceptibility is expressed in the present report by the more rapid progression of lesions which would eventually have led to a shorter mean death time, had we not intervened by killing the animals.

Aleutian disease is grouped with the so-called chronic or latent virus infections such as scrapie and visna of sheep, and mink encephalopathy.

One should consider hypothetical generalizations with care, especially when the evidence available is only suggestive. However, it would appear with AD, at least, that the chronicity of the disease is host-, not virus-dependent since by altering host characteristics and maintaining the same agent, the course of the disease is considerably shortened.

The greater susceptibility of C-HS individuals—or greater resistance of non-C-HS individuals, depending on how you view the situation—is quite different from the genetic mechanisms involving susceptibility or resistance which have been described in rabbits,[37] mice,[38] and chickens.[39] In these reports, resistance or susceptibility to a given agent was generally independent of resistance or susceptibility to an unrelated agent, whereas C-HS individuals are susceptible to a wide variety of agents, including bacteria and a virus, suggesting that the defect which is present may be of basic importance in understanding resistance to disease. In addition, the greater susceptibility of C-HS individuals to a variety of agents is apparently controlled by a single gene.

It appears that C-HS individuals can and do respond to infections in much the same way that a normal individual does. Yet for some unknown reason the response is ineffective.

Summary

The histologic appearance of the inflammatory response observed in C-HS mink, children, and cattle was similar to that evoked by the same agent in non-C-HS individuals. Malignant lymphoma was not present in C-HS individuals of all 3 species examined. The lesions of Aleutian disease occurred more rapidly in C-HS than in non-C-HS mink, but their histologic appearances were similar.

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LEGENDS FOR FIGURES

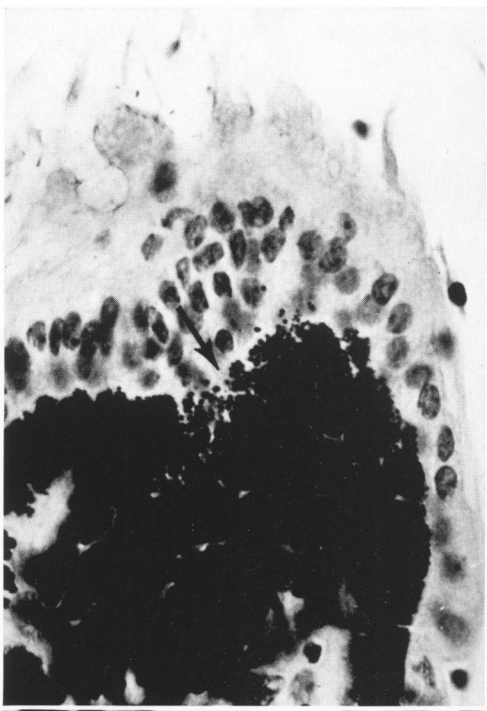
Photomicrographs were prepared from sections stained with hematoxylin and eosin.

FIG. 1. Ciliary process of normal Hereford. Note small size of melanin granules (arrows) and amount of pigment present. Iris in normal animal appears very dark brown or black. × 300.

FIG. 2. Ciliary process of Hereford with Chediak-Higashi syndrome. Note large size of many melanin granules (arrows), but some melanin granules present are approximately normal in size. Iris of C-HS animal appears gray. × 300.

FIG. 3. Ciliary process of standard dark mink. Note small size of melanin granules (arrows) and amount of pigment present. Iris of normal animal appears black. × 300.

FIG. 4. Ciliary process of Hope color phase mink with Chediak-Higashi syndrome. Note large size of melanin granules (arrows); a few granules of approximately normal size are also present. Iris of C-HS mink appears light pink or red. × 300.



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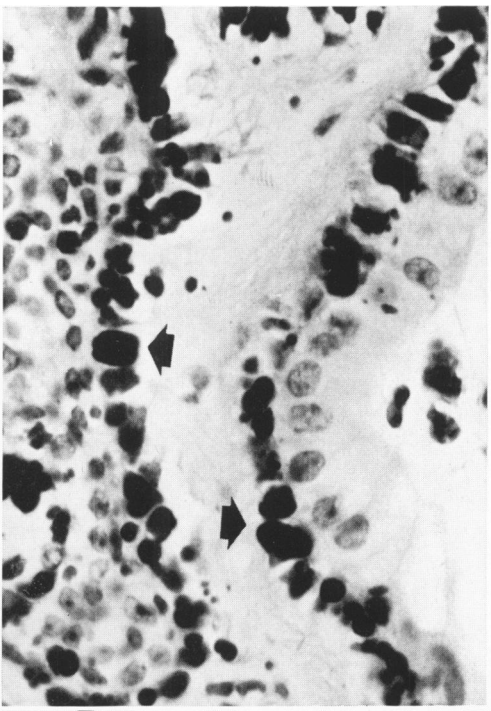

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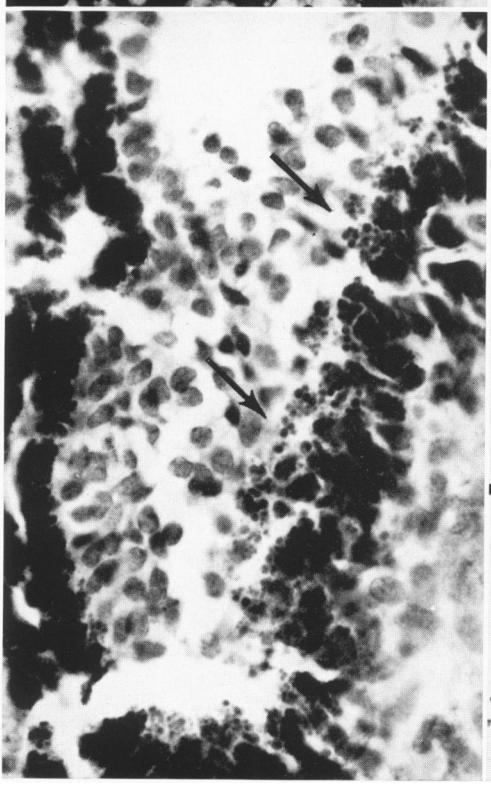

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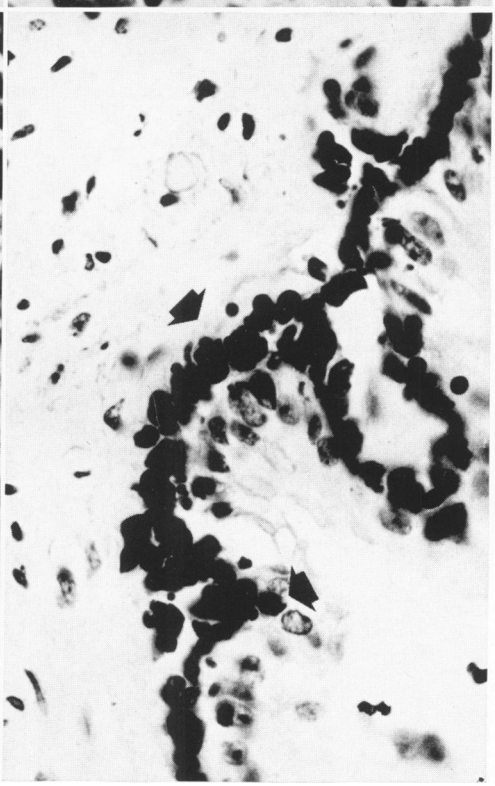

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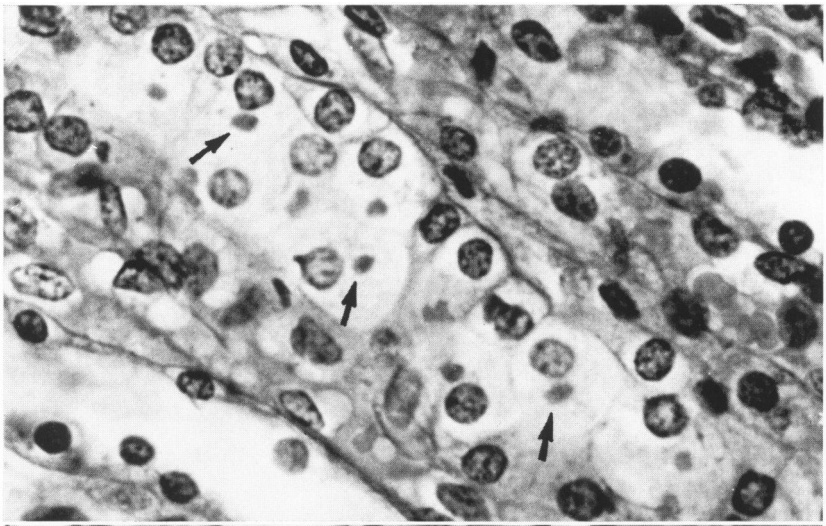
Photomicrographs were prepared from sections stained with periodic acid-Schiff method.

FIG. 5. Renal tubules of mink with Chediak-Higashi syndrome, showing deposits of PAS-positive material in cytoplasm (arrows). In mink the material is most readily observed in collecting tubules. × 400.

FIG. 6. Renal tubules of Hereford calf with Chediak-Higashi syndrome, showing deposits of PAS-positive material in cytoplasm (arrows). × 400.

FIG. 7. Renal tubules of child with Chediak-Higashi syndrome, showing deposits of PAS-positive material in cytoplasm (arrows). × 400.



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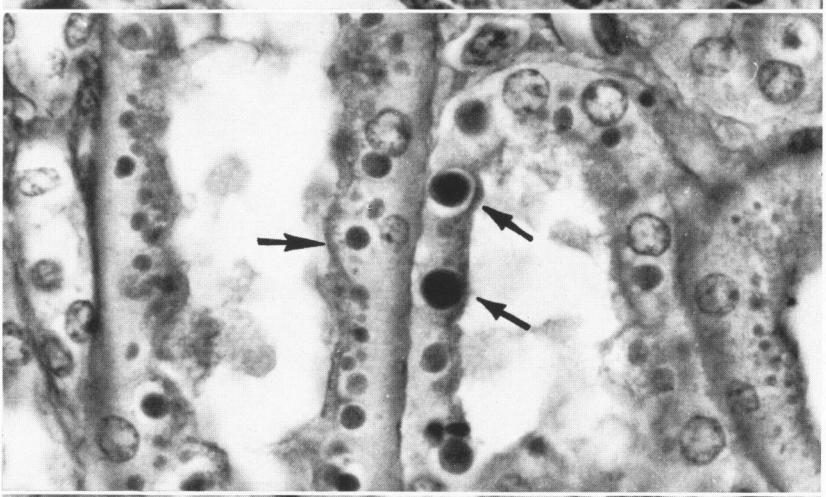

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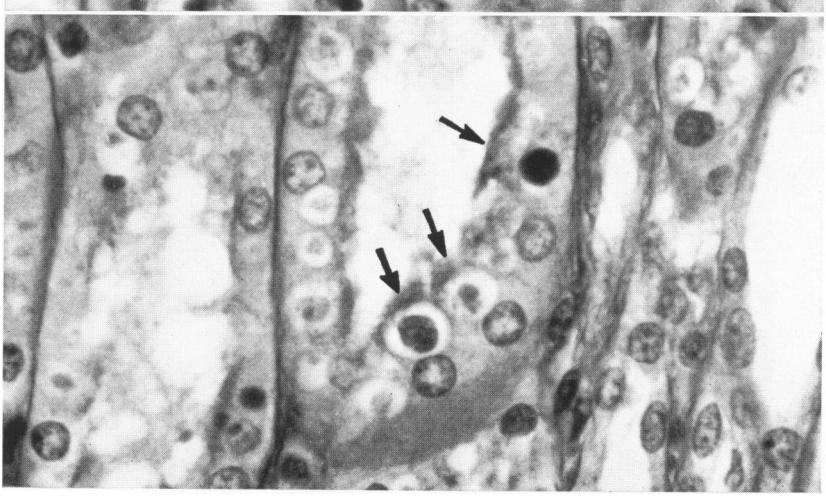

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