The Testis in Adreno-leukodystrophy

JAMES M. POWERS, MD, and
HERBERT H. SCHAUMBURG, MD

From the Department of Pathology (Neuropathology), Medical University of South Carolina, Charleston, South Carolina, and the Departments of Neurology and Pathology (Neuropathology), Albert Einstein College of Medicine, Bronx, New York

Testicular tissue from 7 juvenile and 6 adult patients with adreno-leukodystrophy (ALD) or its adrenomyeloneuropathic (AMN) variant was examined by light and electron microscopy. The seminiferous tubules of the men exhibited hypocellularity, maturation arrest, or Sertoli cells and spermatogonia only. Ultrastructural examination of these specimens revealed vacuolation of Sertoli cell endoplasmic reticulum. Germ cells also demonstrated vacuolation and necrosis, accompanied by slight tubular atrophy and thickening of the tunica propria. Fibrosis or proteinaceous fluid was observed in the interstitium. The tissue of 5 men and 2 boys contained Leydig cells with cytoplasmic striations, which were detectable with the light microscope. A decrease in the number of Leydig cells was noted in some men. All specimens displayed pathognomonic lamellas and lamellar-lipid profiles in mature, immature, or precursor Leydig cells at the ultrastructural level. The Leydig cell demonstrated the primary morphologic defect in the ALD testis; damage to Sertoli cells appeared to be the initial lesion of seminiferous tubules. (Am J Pathol 1981, 102:90-98)

ADRENO-LEUKODYSTROPHY (ALD) is a fatal, sex-linked disease that primarily affects the central nervous system (CNS) and adrenal cortex of boys (5–15 years of age).[1] Cerebral white matter contains inflammatory, demyelinative, and axonolytic lesions, while the adrenal cortex displays primary cytotoxic atrophy without inflammation.[2] ALD is generally held to be a hereditary metabolic disorder, and abnormal cholesterol esters containing very long chain saturated fatty acids have been identified in the brain and adrenal gland.[3,4] The peripheral nervous system (PNS) also may be involved pathologically and clinically.[5-7]

Incidental, yet pathognomonic, lesions of testicular interstitial cells were observed in prepubescent boys and consisted of the same intracytoplasmic lamellas as those in adrenocortical cells, Schwann cells, and PNS or CNS macrophages in ALD.[8,9] Moreover, an adult-onset form of ALD or an adrenomyeloneuropathic variant has been described in which testicular signs or symptoms are conspicuous. Diminished libido, impotence, and infertility have been noted in 5 of 6 men with ALD in the presence of normal secondary sex characteristics.[10] All the men have died of their CNS disease. This report describes the morphologic characteristics and pathogenesis of testicular lesions in ALD.

Materials and Methods

Testicular and adrenal samples were obtained from the following individuals with ALD: 4 juvenile patients (9–12 years) at autopsy, 3 juvenile patients (12–17 years) at biopsy, 5 adult patients, (32–46 years) at autopsy and 1 adult patient (42 years) at biopsy. Their clinical histories have been reported previously.[6,10] The testicular changes of Cases 5 and 6 have been described earlier in part.[7] Clinical data on the 6 adult patients found in Table 1 are listed in the same numerical sequence in a separate communication.[10] Normal control testes were obtained at autopsy from 4 previously healthy young men (24–35 years) and 1 child (12 years) who died sudden, violent, or unexpected deaths. Neurologic control testes were obtained at autopsy from 1 child (12 years) with subacute sclerosing panencephalitis and 4 men (30–54 years) with acute paraplegia (48 days), chronic paraplegia (4 years), amyotrophic lateral sclerosis, or Duchenne's muscular dystrophy. Endocrinologic con-

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Address reprint requests to James M. Powers, MD, Department of Pathology (Neuropathology), Medical University of South Carolina, 171 Ashley Avenue, Charleston, SC 29403.

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Table 1—Adult ALD Testicular Lesions

Case	Diagnosis	Seminiferous tubules (ST)	Interstitium	Leydig cells: Clusters/ ST	Leydig cells: Striations (LM)	Leydig cells: Lamellas (EM)	Adrenal cortex
1 (B)	Adult ALD	Hypocellularity. Mild vacuolation.	Focal fibrosis near hyalinized tubules. Proteinaceous fluid.	0.52* Normal†	+	Few	Marked atrophy with few striated cells.
2 (A)	Adult ALD	Hypocellularity.	Focal fibrosis near hyalinized tubules.	ND Normal	–	ND	Marked atrophy with few striated cells.
3 (A)	Adult ALD	Sertoli cells and spermatogonia (SG). Moderate vacuolation.	WNL	0.72 Normal	+	ND	Many striated cells without atrophy.
4 (A)	Adult ALD	Maturation arrest at 1°. Sertoli cells and SG. Mild vacuolation.	WNL	0.50 Focal decrease	+	Moderate	Moderate number of striated cells with mild atrophy.
5 (A)	AMN	Maturation arrest at 1°. Mild vacuolation.	Proteinaceous fluid.	0.30 Focal decrease	+	Many	Marked atrophy with few striated cells.
6 ($\bar{A}$)	AMN	Sertoli cells and SG. Marked vacuolation.	Diffuse fibrosis.	0.28 Diffuse decrease	+	Many	Marked atrophy with few striated cells.

A = routine autopsy; $\bar{A}$ = perfusion fixation within 30 minutes after death; B = biopsy; LM = light microscopy; EM = electron microscopy; WNL = within normal limits; ND = not determined.

* Semiquantitative estimation. Controls varied from 0.90 to 1.3.

† Visual assessment only.

trol testes were obtained from patients with prior mumps orchitis (53 years) and estrogen treatment for prostatic carcinoma (54 years).

All testes were fixed in neutral buffered formalin, embedded in Paraplast, and stained with hematoxylin and eosin (H & E), Masson's trichrome, Verhoeff-van Gieson, and periodic acid-Schiff with and without diastase. Tissues for ultrastructural examination (all juvenile and adult Cases 1, 4, 5, and 6) were fixed primarily in 4% buffered glutaraldehyde, post-fixed in Dalton's osmium or 2% unbuffered osmium tetroxide, and embedded in Epon 812. Thick sections were stained with 1% toluidine blue; thin sections mounted on copper grids were stained with uranyl acetate-lead citrate. We obtained seminiferous tubule diameters by measuring cross-sections of three tubules with an optical micrometer and calculating their average. The number of Leydig cell clusters per seminiferous tubule was determined with a standard Zeiss calibrated grid and the 25× objective lens.[11]

Results

Juvenile ALD

The seminiferous tubules (ST) were immature or early pubescent, and the interstitium was unremarkable in six. The ST of 1 child (12 years) contained only Sertoli cells with abundant glycogen and a few spermatogonia; the interstitial tissue was diffusely fibrotic, and a few Leydig cells displayed cytoplasmic striations. Leydig cells of 5 juvenile cases were not striated and exhibited variable degrees of maturity. The remaining case (17 years) exhibited many striated Leydig cells without any other abnormality. All juvenile cases displayed, at the electron-microscopic level, Leydig cells (mature, immature, or precursor) with lamellas, lamellar-lipid profiles, or crystalloid clefts. The ease with which cytoplasmic lamellas could be identified varied considerably. Three cases contained many cells with cytoplasmic inclusions, although striations could be perceived with the light microscope in only 2. Striated adrenocortical cells were observed consistently but did not correlate with the number of abnormal Leydig cells. Older children tended to have more lamellas, while the younger tended to have more crystalloid clefts in Leydig cells. Clefts were occasionally detected within canaliculi of rough endoplasmic reticulum. Inflammatory cells were not seen.

Adult ALD and AMN Variant

The seminiferous tubules were abnormal in every

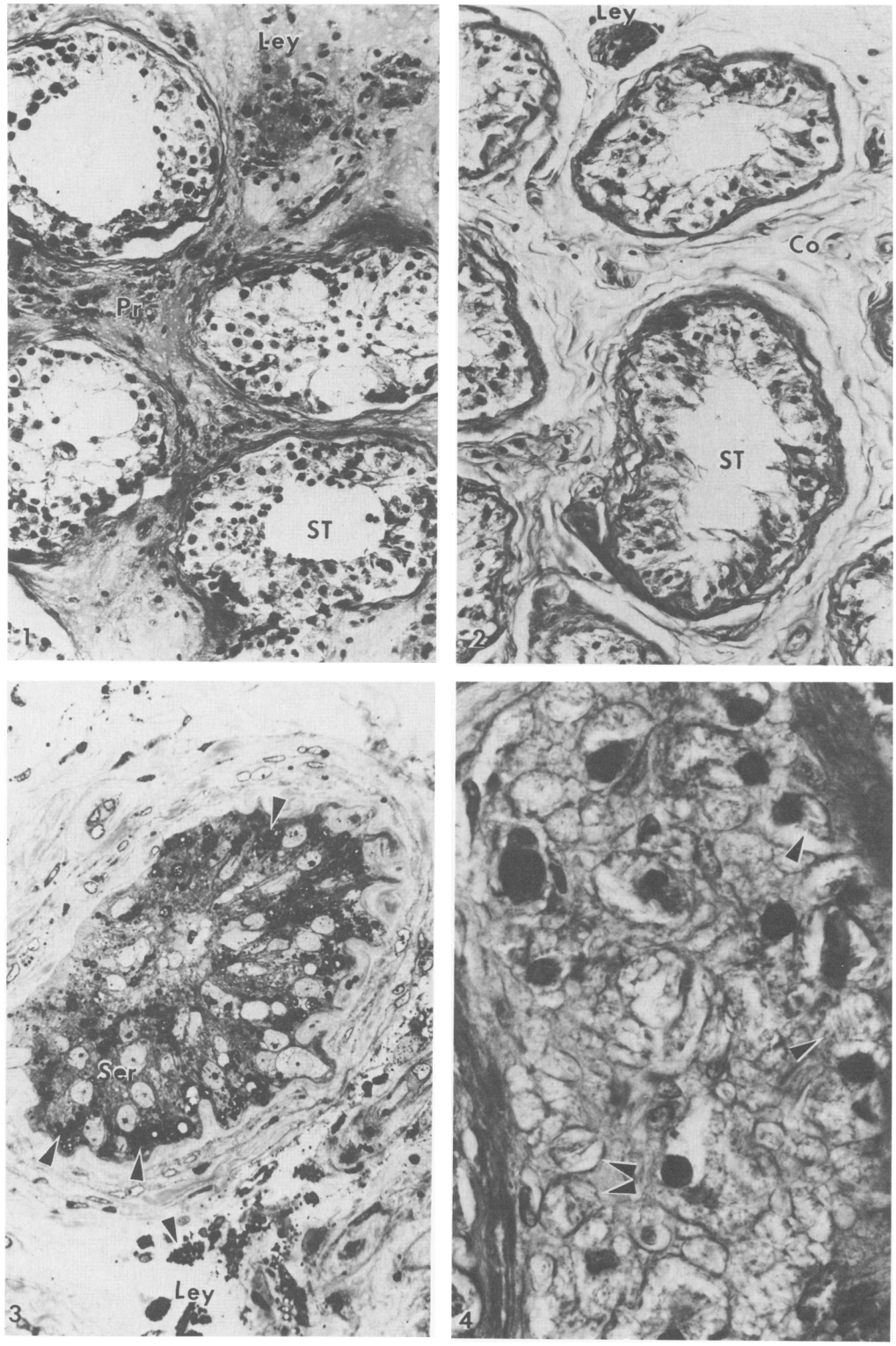

Figure 1—Case 1. Seminiferous tubules (*ST*) are hypocellular with arrested maturation. The interstitium contains a foamy, proteinaceous (*Pr*) fluid and Leydig cell clusters (*Ley*). (Verhoeff-van Gieson, × 200) **Figure 2**—Case 6. Seminiferous tubules (*ST*), containing Sertoli cells and a few spermatogonia, are separated by collagenized (*Co*) interstitial tissue with few Leydig cells (*Ley*). (Masson trichrome, × 300) **Figure 3**—Case 6. Sertoli (*Ser*) and Leydig (*Ley*) cells have large amounts of lipofuscin (*arrowheads*). (Toluidine blue, Epon, × 400) **Figure 4**—Case 5. Striations (*arrowheads*) are discernible in this cluster of Leydig cells. (Verhoeff-van Gieson, × 600)

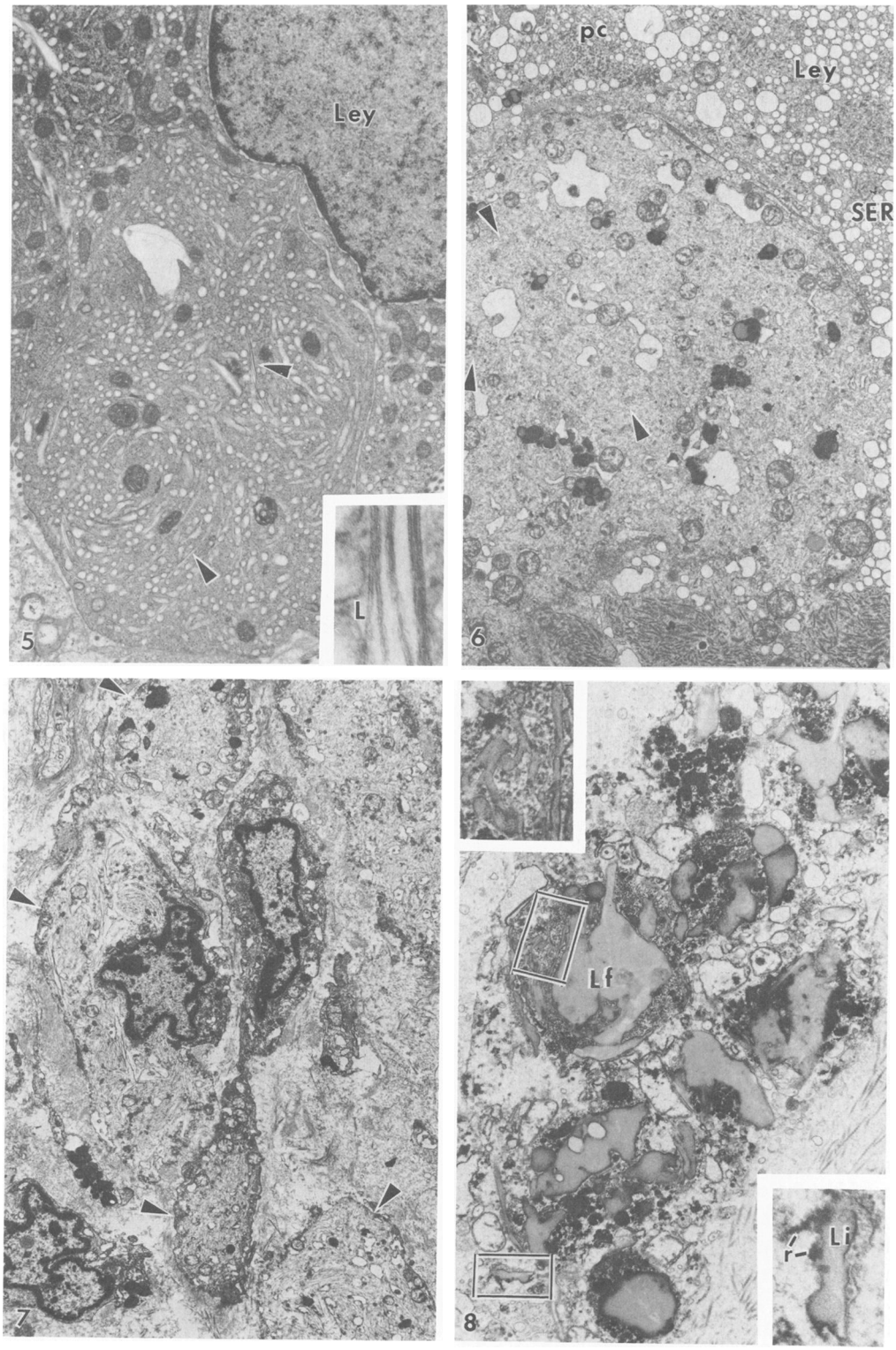

Figure 5—Case 1. Leydig cells display few lamellas and lamellar-lipid profiles (*arrowheads*). **Inset**—The various forms of lamellas (*L*) are appreciated at higher magnification. (UA-Pb Cit, ×10,500; ×105,000) **Figure 6**—Case 6. Normal Leydig cells (*Ley*) with abundant smooth endoplasmic reticulum (*SER*) and paracrystalline arrays (*pc*) are admixed with Leydig cells whose cytoplasm is filled with lamellas and lamellar-lipid profiles (*arrowheads*). (UA-Pb Cit, ×6200) **Figure 7**—Case 5. Almost all Leydig cells in this cluster contain cytoplasmic lamellas (*arrowheads*). (UA-Pb Cit, ×3850) **Figure 8**—Juvenile case. Leydig cell shows bizarre conformations of lipofuscin (*Lf*). The bracketed areas are magnified in the insets. **Upper inset**—A canalicular distribution is suggested. **Bottom inset**—Lipid (*Li*) appears to have precipitated within endoplasmic reticulum lined with ribosomes (*r*). (UA-Pb Cit, ×7125; ×19,950; ×28,500)

case (Table 1). The pathologic lesions, however, varied from hypospermatogenesis or hypocellularity (Figure 1) to almost Sertoli cell only (Figure 2). Vacuolation was noted in 5 cases, tubular atrophy (less than 20% loss) in 4, and mild thickening of the tunica propria due to increased collagen and elastin in 3. Abundant lipofuscin in Sertoli cells was present in the toluidine-blue-stained thick sections of Cases 3 and 6 (Figure 3). Cases 1 and 6 contained abundant glycogen. Spermatids were noted only in Cases 1 and 5. Epithelial sloughing was observed, but this change could not be evaluated because of variability in specimen handling, postmortem interval, and fixation. In contrast to the juvenile cases, striated Leydig cells usually could be appreciated with the light microscope (Figure 4). It should be emphasized, however, that their identification was much more difficult than in the adrenal cortex. One reason for this was their haphazard distribution: they were usually in small clusters. Another reason for the difficulty in visualizing striations was that the Leydig cells generally had less background cytoplasmic staining and were more vacuolated (probably due to lipofuscin) than adrenocortical cells. The trichrome or VVG stain, in concert with through-focusing, aided in the visualization of striations. Reinke crystalloids were observed in all cases but were numerous only in Case 1. Leydig cell clusters were obviously decreased in number in Cases 5 and 6 and probably in Case 4. Inflammatory cells were not identified in any ALD testis. Hypertrophy, or ballooning, of Leydig cells was observed sporadically in ALD and control testes. Leydig cell loss seemed to correlate best with duration of disease (ie, the more chronic nature of the AMN variant). Testicular lesions of adult ALD patients did not depend upon the extent of adrenal involvement. Seminiferous tubular abnormalities did not correlate well with the number of Leydig cell clusters but did seem to parallel the frequency of Leydig cells with lamellas. Similar defects in seminiferous tubules, tunica propria, and interstitial connective tissue were observed in some neurologic or endocrinologic controls, but a diminution of Leydig cell clusters was noted only in the patient with amyotrophic lateral sclerosis. No control subjects demonstrated striated Leydig cells.

Ultrastructural examination was performed in Cases 1, 4, 5, and 6. Fixation was poor in Case 4, adequate in Case 5, and excellent in Cases 1 and 6. Case 1 had mild abnormalities and was ambulatory at the time of biopsy. Ultrastructural examination of the testes of Cases 4 and 5 confirmed the light-microscopic findings and demonstrated lipofuscin and phagocytosed spermatids within Sertoli cells. The interstitial cells of Leydig contained pathognomonic lamellas, being scarce in Case 1 (Figure 5) and abundant in Cases 5 and 6. These abnormal cells were admixed with normal Leydig cells (Figure 6) or found in small clusters (Figure 7). Testicular lamellas were the same dimensions as those in the adrenal, consisting of two parallel electron-dense lines (lamellas) about 2.5 nm thick and an intralamellar clear space that varied from 1.0 to 3.0 nm. Leydig cells also demonstrated variable numbers of Reinke crystalloids, paracrystalline arrays, smooth endoplasmic reticulum, lipid droplets, mitrochondria, and lipofuscin. The latter often contained lamellas, crystalloids, or bizarre conformations (Figure 8). Fragments of cell cytoplasm, predominantly lipofuscin, were occasionally observed lying free in the interstitium. The seminiferous tubules of Case 1 were often ultrastructurally unremarkable except for some abnormal spermatids, usually within Sertoli cell cytoplasm. The earliest abnormality of the seminiferous tubule that could be detected was vacuolation of Sertoli cells (Figure 9) due to irregular and variable-sized dilatations of endoplasmic reticulum. Sertoli cell cytoplasm, containing many particles of beta glycogen, often extended into widened intercellular spaces in the form of blebs (Figure 10). In many areas Sertoli–Sertoli junctions were morphologically intact. Irregularly dilated endoplasmic reticulum was also observed in spermatogonia (dark and light A, and B) and spermatocytes (Figure 11). Cells in the adluminal compartment, presumably of the germ line, occasionally were necrotic (Figure 12). Some of the vacuoles noted with the light microscope were due to large spaces containing debris between Sertoli cells (Figure 13), perhaps the residua of necrotic germ cells. All of these lesions could be found in various combinations in different seminiferous tubules. The most consistent lesion of the seminiferous tubule was the presence of vacuolated Sertoli cells. Other less frequent findings were annulate lamellas in Sertoli cells, increased collagen in lamina propria, and reduplication of basal lamina (Figure 14). Seminiferous tubules which consisted of Sertoli cells and some spermatogonia revealed abundant lipofuscin (which contributed to the vacuolated appearance), basal cytofilaments, and complex infoldings of Sertoli cells (Figure 15).

Discussion

It has been established over the past 10 years that ALD is a uniformly fatal disease of males, predominantly of children (5–15 years). In these patients concomitant, but apparently independent, destruction of the central nervous system (CNS) and adrenal cortex

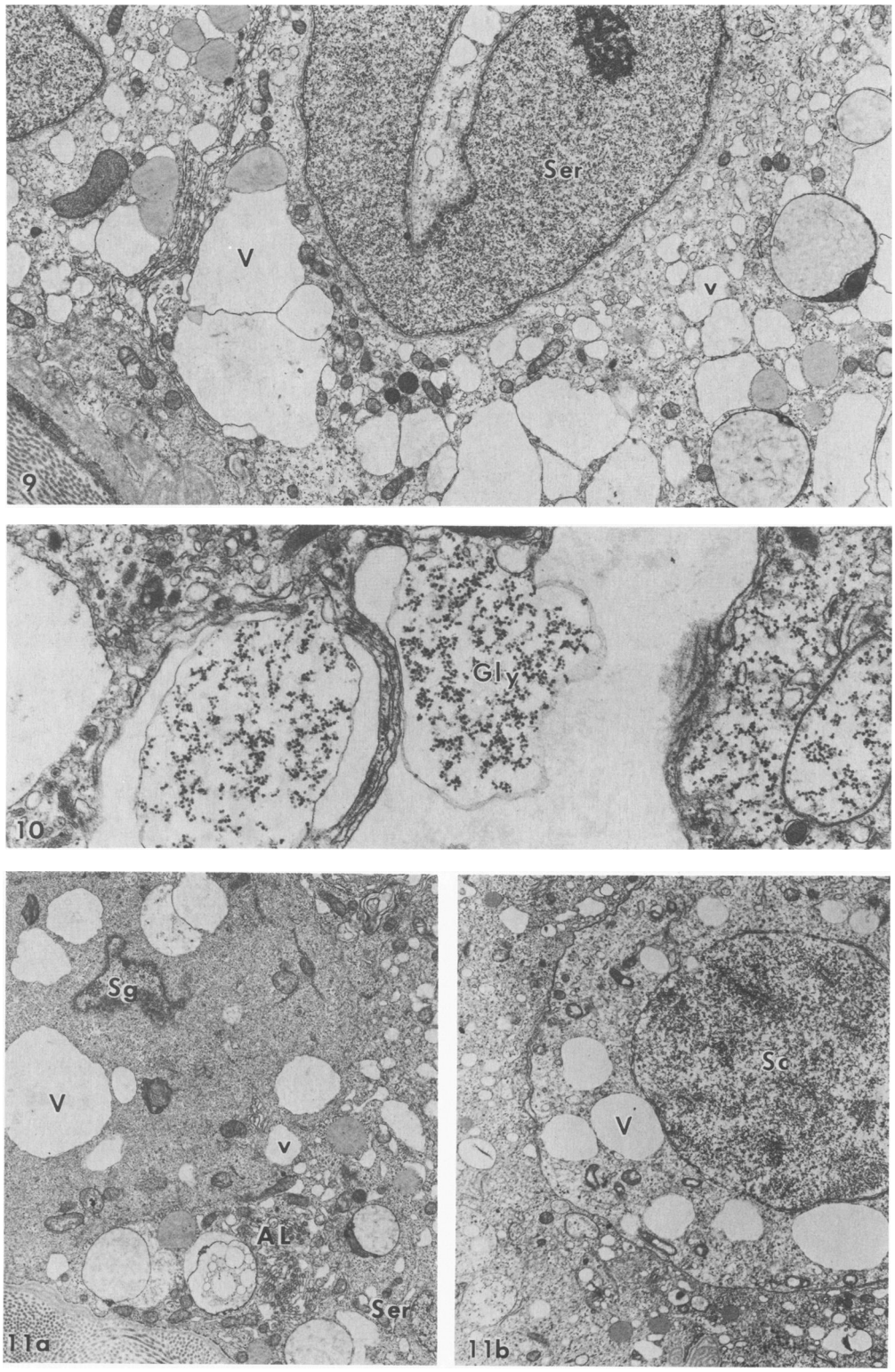

Figure 9—Case 1. Sertoli cells (*Ser*) exhibit abnormal vacuolation of endoplasmic reticulum (*V*). The other organelles appear unremarkable. (UA-Pb Cit, ×6300) **Figure 10**—Case 1. Widened intercellular spaces between Sertoli cells occasionally contain cytoplasmic blebs rich in glycogen (*Gly*). (UA-Pb Cit, ×16,250) **Figure 11**—Case 1. Vacuolation of endoplasmic reticulum (*V*) is observed less frequently in (**A**) spermatogonia (*Sg*) and (**B**) primary spermatocytes (*Sc*). A Sertoli cell (*Ser*) in **A** contains annulate lamellas (*AL*). (UA-Pb Cit, ×5880 and ×3780)

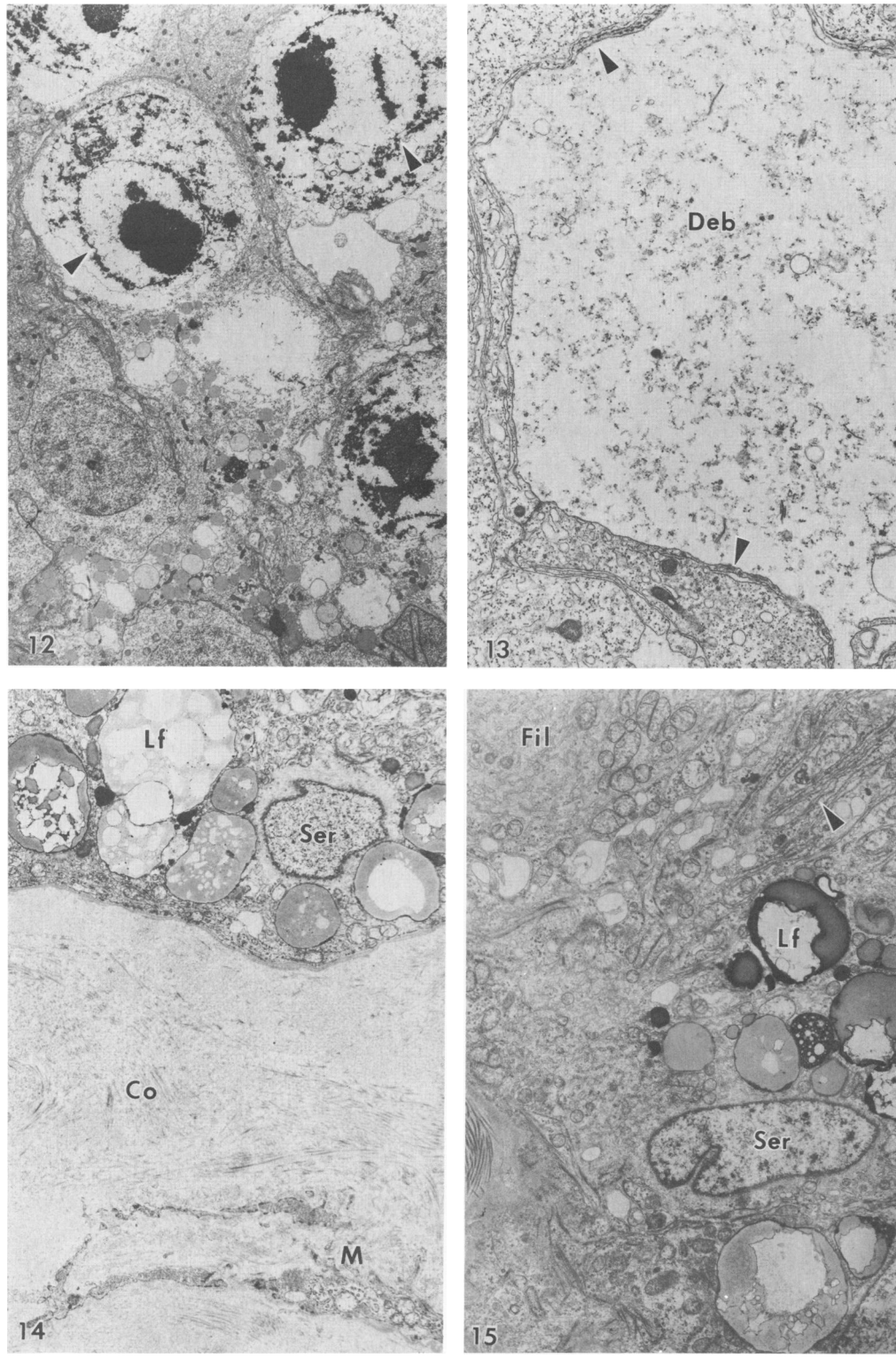

Figure 12—Case 1. Dying cells (*arrowheads*), presumably of the germ line, are present in the adluminal compartment. (UA-Pb Cit, ×5375) **Figure 13**—Case 1. Inter-Sertoli vacuoles contain cellular debris (*Deb*), probably the residua of necrotic cells. The characteristic junctional specializations of Sertoli cells (*arrowheads*) are still present. (UA-Pb Cit, ×7875) **Figure 14**—Case 6. Sertoli cells (*Ser*) with abundant lipofuscin (*Lf*) are separated from the myoid cells (*M*) of the lamina propria by excessive collagen (*Co*). (UA-Pb cit, ×4050) **Figure 15**—Case 6. Sertoli cells (*Ser*) demonstrate increased lipofuscin (*Lf*), cytofilaments (*Fil*), and plasmalemmal infoldings (*arrowhead*). (UA-Pb Cit, ×5250)

develops.[1] The available evidence implicates a sex-linked mode of transmission for this genetic defect. Although a specific enzymatic deficiency has not been identified, abnormal cholesterol esters with very long chain saturated fatty acids have been found in the brain and adrenals of patients with ALD.[3,4] Connatal[12] and adult[6] presentations also occur. Occasionally adults display peripheral nerve and spinal cord lesions, in addition to those of brain and adrenal, and have been designated as the adrenomyeloneuropathic variant (AMN).[7] Testicular signs or lesions have been identified in 2 male adults with AMN and in 5 with adult-onset ALD.[10] Thus the testis appears to be another target organ in ALD, when the CNS disease develops in adults.

Lamellas and lamellar-lipid profiles identified in Leydig cell cytoplasm are identical to those previously described in adrenocortical, Schwann, endoneurial and microglial cells.[8,9] Their demonstration in any of these cells is pathognomonic of ALD, with very rare exceptions.[13] The Leydig cell manifests the initial morphologic defect of the testis in ALD, and it is the only cell that is universally affected—even in immature testes of juvenile ALD patients.[8] The pathogenesis of the Leydig cell abnormality is unknown but is probably similar to that proposed for the adrenocortical cell, where the accumulated very long chain saturated fatty acids eventually destroy their host cells.[13] Pituitary function has generally been normal,[10] and Leydig cell lamellas have not been seen in hypogonadotropic hypogonadism.[14] Serum testosterone has occasionally been low. One individual has demonstrated a blunted response to human chorionic gonadotropin (HCG) stimulation, indicating a primary defect in Leydig cell reserve.[7] It appears that each target organ: brain, peripheral nerve, adrenal cortex, and testis, may undergo a primary loss of function that is independent of the involvement of any other target organ.

The abnormalities observed in seminiferous tubules (ST) in ALD are nonspecific, especially those observed at autopsy. Loss of germ cells, vacuolated Sertoli cells with excessive glycogen, lipofuscin, and cytofilaments, complex interdigitations of plasmalemmae, and thickening of lamina propria have been seen in a variety of testicular disorders.[15-19] The interpretation of these findings in ALD patients is complicated by the fact that most had been bedridden for months to years by their CNS disease. Simple immobilization is capable of causing all of these lesions.[20] Case 1, however, was still ambulatory with minimal CNS disease at the time of his biopsy. This patient also demonstrated a reduction in spermatogenesis and vacuolation of Sertoli cells. The latter appears to represent the initial ST lesion in ALD. Vacuolation of Sertoli (and germ) cells has been reported in other conditions: eg, germinal aplasia,[17] essential fatty acid deficiency,[21] epinephrine stimulation,[22] and estrogen[19] or prostaglandin[23] treatment. The reason for cytoplasmic vacuolation in ALD is unknown. The integrity of Sertoli cells and their junctional specializations for the maintenance of adluminal germ cells and spermatogenesis has been frequently emphasized.[24] Testosterone, derived from Leydig cells, also has been shown to be necessary for spermatogenesis; this effect is thought to be partially mediated through Sertoli cells.[25]

Vacuolated Sertoli cells might be incapable of ful-

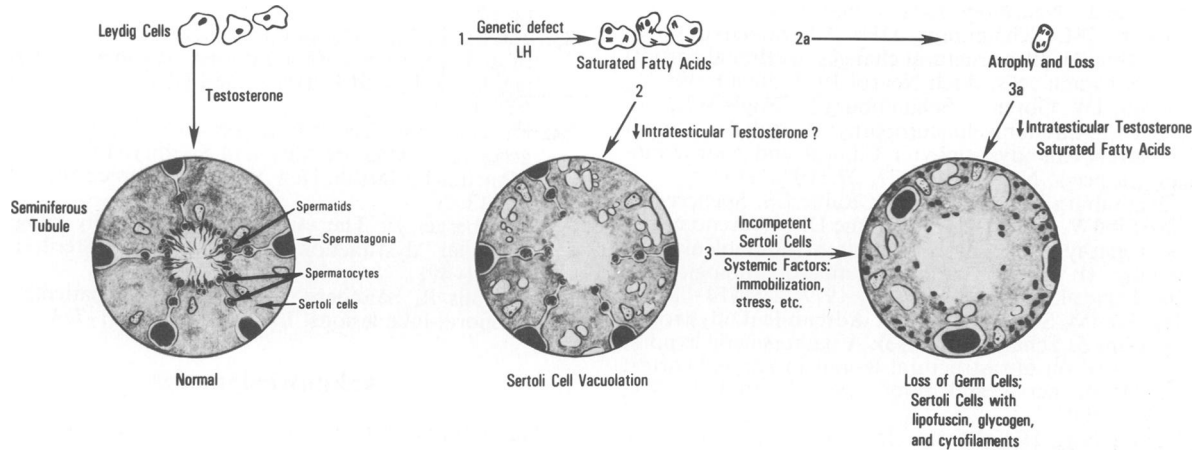

Figure 16—Proposed pathogenesis of testicular lesions in ALD. The original morphologic lesion is the accumulation of lamellas in interstitial cells. The Sertoli cell appears to be the first cell in seminiferous tubules to exhibit vacuolar degeneration. Luteinizing hormone (*LH*) is considered to have a permissive action in the accumulation of lamellas.

filling their normal role of sustaining maturation of spermatocytes and spermatids, resulting in abnormal spermatids and death of differentiating germ cells. This mechanism has been invoked to explain abnormal spermatogenesis in essential fatty acid deficiency.[21] Widened inter-Sertoli cell spaces might indicate such a loss of function leading to a failure of the normal barrier between basal and adluminal compartments. This could expose developing germ cells of the adluminal compartment to toxic factors found in blood or interstitial tissue. Direct damage to spermatogonia in the basal compartment also would adversely affect developing germ cells. The hypothesis that damage to Sertoli cells, and consequently spermatogenesis, is secondary to Leydig cell failure due to accumulation of saturated fatty acids seems to be a reasonable hypothesis for the testicular lesions seen in ALD (Figure 16).

The infertility of some ALD adults is secondary to hypospermatogenesis. Diminished libido and impotency are more difficult to explain and may be due to CNS lesions,[26] Leydig cell failure with a deficiency of testosterone, or a combination of these. Regardless of the precise clinicopathologic correlation and pathogenesis of testicular lesions in ALD, it should be appreciated that ALD represents a rare, and universally fatal, cause of sexual inadequacy in men.

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