Chronic Amphotericin Nephropathy: Morphometric, Electron Microscopic, and Functional Studies

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ABSTRACT
The two major hypotheses for the pathogenesis of amphotericin nephrotoxicity are direct interaction with epithelial cell membranes and vasoconstriction. Studies indicating the special vulnerability of the medullary ray and medulla to hypoxia led to a reexamination of amphotericin nephrotoxicity. Twenty-four rats were divided into four groups: amphotericin injection (5 mg/kg daily for 3 wk), amphotericin plus salt depletion, vehicle, and salt depletion and vehicle. The amphotericin group had polyuria ($P < 0.01$) but normal serum creatinine. In contrast, amphotericin plus salt depletion rats exhibited renal failure (creatinine of $1.49 \pm 0.05$ versus amphotericin alone $0.98 \pm 0.01; P < 0.01$). Semiquantitative histologic analysis of cortical and medullary injury correlated with functional impairment. Cortical changes in the amphotericin group were largely restricted to the medullary ray, where focal rupture and calcification of thick ascending limbs were noted. The $S2/S3$ tubules in the medullary rays showed focally diminished cell complexity with histiocytic/lymphocytic infiltration. However, calcification was also seen in the area of the macula densa. Morphometry revealed that the thick ascending limbs in the medulla were hypertrophied ($1,420 \pm 63$ versus $1,195 \pm 48 \mu m^2$ for vehicle; $P < 0.05$). In contrast, in the amphotericin and salt depletion group, the changes in the medullary ray extended to the labyrinth and the thick ascending limbs in the inner stripe showed atrophic changes ($772 \pm 23 \mu m^2; P < 0.01$ versus vehicle). Thus, changes as a result of amphotericin toxicity take place both in areas known to be most vulnerable to hypoxia (medullary ray and medulla), and in areas rich in oxygen (adjacent to glomerulus). Salt depletion potentiates the cortical changes and converts medullary hypertrophy to atrophy. These findings support a dual pathogenesis for amphotericin nephropathy (direct toxicity and vasoconstriction).

Key Words: Hypoxia, thick ascending limb, medullary ray, tubular injury, renal failure, amphotericin B, morphometry, nephrotoxin

Amphotericin B is widely used for severe, life-threatening fungal infections, often in immunocompromised patients (1–3). Its use is limited by a dose-dependent nephrotoxicity, manifested by a reduction in GFR and tubular dysfunction (4). The pathogenesis of amphotericin nephrotoxicity is complex. Direct cellular damage results from its binding to membrane sterols, causing membrane damage and increased permeability to ions and small, uncharged molecules (5). Hypoxic tubular injury may result from profound renal vasoconstriction (6,7). At the same time, increased ion pump activity and oxygen consumption, in response to permeability alterations of plasma membranes (8), may aggravate hypoxic damage to tissues with limited blood supply. The tubules in the outer medulla and medullary ray are particularly prone to hypoxic injury, as a result of low oxygen tension in these zones under physiologic conditions (9,10). In isolated perfused rat kidneys, the addition of amphotericin increases renal vascular resistance and augments medullary thick ascending limb (mTAL) hypoxic injury in the deep inner stripe (11). Inhibition of Na-K-ATPase activity and oxygen consumption with ouabain ameliorates hypoxic mTAL injury and improves renal function without attenuation of renal vasoconstriction (11).

With this perspective, we conducted physiologic and morphologic studies in rats chronically administered amphotericin with or without concomitant salt depletion, a factor that has been shown to poten-
tiate toxicity (12–16). The findings of profound alterations in the outer medulla and medullary rays were reminiscent of those previously noted in experimental chronic cyclosporine (17) and hypercalcemic nephropathy (18). However, other observations suggest a direct tubulotoxic effect as well.

METHODS

Twenty-four male Sprague Dawley rats (215 to 350 g body wt) were randomized to four experimental groups (of six rats each): amphotericin injections (A); salt depletion and amphotericin (SDA); vehicle (dextrose) injection (C); salt depletion and vehicle (SD).

Salt depletion was induced with sodium-deficient diet (*902902; ICN Nutritional Biochemicals, Cleveland, OH), initiated 5 days before the experiment and maintained throughout. Salt depletion was confirmed by the determination of urine sodium content in a 24-h collection at the initiation of the experiment (71 ± 29 versus 1,602 ± 121 μEq/24 h in salt-depleted and nondepleted rats, respectively) (19). Rats were injected 6 days a week ip with amphotericin B (5 mg/kg; Fungizone; Squibb & Sons Inc., Princeton, NJ) for 3 wk. The injection solution was prepared daily, first dissolved in distilled water (5 mg/mL), and further diluted in 5% dextrose solution to a final concentration of 1.25 mg/mL. Control rats were injected with the same volume of 5% dextrose. The injected dose was adjusted to changes in body weight throughout the experiment. All animal experimentation was conducted in accordance with the NIH Guide for the Care and Use of Laboratory Animals.

Functional Studies

The rats were kept in metabolic cages (Nalge Co., Rochester, NY) for 24 h for the determination of urinary sodium excretion before the initiation of the ip injections. At the conclusion of the experiment, another 24-h collection period was performed; determinations of urine volume (milliliters per hour) and osmolality were done. Terminal plasma samples were analyzed for creatinine.

The left kidney was perfused in vivo through the aorta at a pressure of 140 mm Hg, with first a saline rinse of 20 mL and then a solution of 1.25% glutaraldehyde (Eastman Kodak Co., Rochester, NY) in 0.1 M phosphate buffer (pH 7.4). Kidneys were cut in both sagittal (20) and horizontal (parallel to the corticomedullary axis) (17,21) cross-sections for quantitative and image analysis, respectively. The tissue was postfixed in buffered 2% OsO4, dehydrated, embedded in an araldite-Epon 812 mixture, cut at 1-μm sections, and stained with methylene blue.

Semiquantitative analysis of morphologic changes was performed on the sagittal sections by a single person (S. Rosen) in a blinded fashion, as previously described (20). The degrees of tubular atrophy and interstitial fibrosis were ranked as injury scores ranging from 0 to 4+. Injury score was assessed separately for the cortex and the medulla.

Selected blocks of the cortex and inner stripe of the outer medulla were processed for fine structural analysis: 158 blocks were studied with 1-μm sections in preparation for electron microscopy; 30 blocks were selected for electron microscopic studies.

Morphometric Studies

Morphometric evaluation was performed by a single person (I.E. Stillman) who was blinded as to the group identity of the kidneys studied. The inner stripe of the outer medulla was studied in horizontal section (parallel to the corticomedullary axis). The level chosen for image analysis was equivalent to the mid-inner stripe, or level 2 as defined by Bouby et al. (22), where measurements of the percentage of field area occupied with vascular bundles were found to range from 14 to 27% (23). Microscopic images were studied with a Letitz Aristoplan microscope (Wild Leitz USA Inc., Rockleigh, NJ), equipped with a Chromochip II video camera (Javelin Electronics Inc., Torrance, CA), connected to a color video monitor. A SummaSketch Plus digitizing tablet (Summagraphics Corp., Fairfield, CT) was used. Morphometric analysis was done with Bioquant System IV software (version 11/6/89 and version 7/30/91) (R&M Biometrics, Nashville, TN).

The criteria for study were purely technical; only optimally perfusion-fixed and sectioned preparations were morphometrically analyzed (C, N = 4; A, N = 5; SD, N = 4; SDA, N = 3). Sections of inner stripe were examined at a magnification of ×50 (field area 9.9 × 104 μm2), and the areas of most marked damage were identified and evaluated. The cross-sectional area of each mTAL (excluding the lumen) was quantified. Complete ×50 fields were evaluated until a minimum of 200 tubules were evaluated (range, 201 to 218). Nuclei were counted within each mTAL (in one ×50 field) and expressed as the mean nuclei per tubule.

Two ×50 fields were used to measure collecting duct cross-sectional area. All ducts within the fields were quantified (range, 11 to 41).

All available sections of cortex (superficial and deep) were examined at a magnification of ×50. All glomerular tufts sectioned at the vascular pole were quantified (range, 9 to 34).

Statistical Analysis

Values are presented as the mean ± SE, and statistical significance was set at P < 0.05. The results were compared by one-way analysis of variance, followed by the Newman-Keuls multiple sample com-
parision test. Pearson correlation with pairwise deletion was performed between the variables. Multiple regression analysis was carried out to evaluate the contribution of amphotericin and salt depletion to the functional and morphologic changes. Computations were performed by use of the CRUNCH program (version 3) (Crunch Software Corp., Oakland, CA).

RESULTS

Functional Studies

Amphotericin-treated rats (A) and salt-depleted rats injected with vehicle (SD) gained weight to the same degree as control non–salt-depleted rats injected with vehicle (C) (Table 1). A weight loss of 23%, on average, was noted in salt-depleted rats injected with amphotericin (SDA) (P < 0.01 versus other groups).

Plasma creatinine remained normal in the A group rats but was associated with polyuria (3.12 mL/h; P < 0.01 versus other groups) and hyponatremia. The SDA group developed advanced renal failure, with a plasma creatinine of 1.49 ± 0.05 and rising plasma potassium (P < 0.01 versus other groups for all of these values, by analysis of variance).

Morphologic Studies

The most remarkable gross changes occurred in the salt-depleted rats given amphotericin (SDA group). Their kidneys looked smaller and darker and had a rough, granular surface when inspected in vivo; the kidneys of the other animals were generally grossly unremarkable. Microscopically, the most limited cortical changes occurred in the amphotericin without salt depletion group (A). The alterations were largely relegated to the medullary rays, although contiguous structures, such as mTAL macular densa segments, were occasionally involved (Figure 1). The interstitium in these zones appeared widened with fibroblastic proliferation. The thick ascending limbs were commonly affected and showed a characteristic picture (Figure 2). Calcification was noted immediately adjacent to the thick ascending limbs and appeared to be associated with a disruption of the tubular wall. The tubular epithelium frequently surrounded the calcific material and projected into the lumen. Fine structural studies revealed that the epithelium had grown over a necrotic cellular area, because the calcification was at times contained within the basal lamina of the tube (Figure 3). The calcification consisted of large masses of fragmented electron-dense material with a spicular array at its periphery. When the tissue was incubated with EDTA (0.1 M) for 2 h before being processed for electron microscopy, most of the electron-dense material was removed. The spicular array was then seen to be a component of both the perimeter and internal aspect of the calcification; fragments of necrotic epithelium could be recognized as apparently calcified mitochondria. This material was frequently surrounded by fibroblasts. Calcification could also be seen at the base of the mesangium in the zone of the lacs cells with the opposite side of the thick ascending limb intact—i.e., the injury was conspicuously polar in these zones. The S2/S3 proximal tubules did not seem to be involved in this calcification process. Instead, they showed focally diminished cell complexity (loss of brush border, basolateral membranes, and organelles) (Figure 4). Apparent histiocytes/lymphocytes could be noted infiltrating the walls of the proximal tubules. The basal lamina of these tubules was commonly thinned and multilayered and often contained granular cellular debris. Cellular infiltration (as present in proximal tubules) was relatively uncommon in thick ascending limbs. In the SDA group, the cortical changes were diffuse and extended from the medullary ray into the labyrinth (Figure 5). Interestingly, we did not observe vascular alterations in any of the groups, including those animals with severe parenchymal damage.

Except for the SDA group, the medulla showed relatively little change aside from some slight interstitial fibrosis (Figure 6). In that group, there was extensive mTAL atrophy (loss of mitochondria, basolateral membrane array, multilaminar thickening of the basement membrane) and many of the tubules were occluded by casts (homogeneous electron-dense material) (Figure 3). The other three groups showed

<table>
<thead>
<tr>
<th>Group</th>
<th>C</th>
<th>A</th>
<th>SD</th>
<th>SDA</th>
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<tbody>
<tr>
<td>Body Wt (% of Baseline)</td>
<td>145 ± 2</td>
<td>146 ± 6</td>
<td>137 ± 3</td>
<td>77 ± 2*</td>
</tr>
<tr>
<td>Plasma Creatinine (mg/dL)</td>
<td>0.96 ± 0.04</td>
<td>0.98 ± 0.01</td>
<td>0.94 ± 0.05</td>
<td>1.49 ± 0.05*</td>
</tr>
<tr>
<td>Urine Volume (mL/h)</td>
<td>1.15 ± 0.25</td>
<td>3.12 ± 0.17*</td>
<td>1.2 ± 0.26</td>
<td>0.98 ± 0.14</td>
</tr>
<tr>
<td>Urine Osmolality (mosM)</td>
<td>1174 ± 204*</td>
<td>417 ± 15</td>
<td>596 ± 95</td>
<td>381 ± 29</td>
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</tbody>
</table>

* P < 0.01 versus all other groups.
minimal changes. However, alterations were detected by morphometry (see the following section).

Semiquantitative analysis revealed that injury was absent in the C and SD groups, was mild in the A group (injury score of 0.48 ± 0.25 and 0.13 ± 0.1 for cortex and medulla, respectively), and most marked in the SDA group (injury score of 2.2 ± 0.4 and 2.8 ± 0.4 for cortex and medulla, respectively).

The injury score correlated with terminal plasma creatinine, both in the cortex and the outer medulla ($r = 0.77$ and 0.86, respectively; $P < 0.0001$). This correlation remained, even when only those animals treated with amphotericin were included ($r = 0.69, P < 0.02$ and $r = 0.85, P < 0.003$ for cortical and medullary injury, respectively). Both salt depletion and amphotericin independently contributed to medullary and cortical injury indexes, as shown by multiple regression analysis (Table 2).

**Morphometric Analysis**

The mean mTAL cross-sectional area was markedly decreased by salt depletion ($922 ± 45 \mu m^2$ in SD rats versus $1,195 ± 48 \mu m^2$ in C rats; $P < 0.01$)(Figure 7; Table 3). In contrast, the mTAL of the A group was substantially larger ($1,420 ± 63 \mu m^2; P < 0.05$ versus C rats). Interestingly, the SDA group showed a reduction in mean mTAL area beyond that seen in the group treated with salt depletion alone ($772 ± 23 \mu m^2; P < 0.01$ versus C rats).

However, there were other differences in mTAL size between the experimental groups that were not evident by simple comparison of their means—i.e., subpopulations within individual animals and groups. Therefore, we studied frequency distributions for the entire mTAL population of each animal and compared their frequency polygons. A frequency polygon (similar to a histogram) is constructed by plotting the frequency of each class as a dot at the class midpoint and then connecting the dots with a straight line.

Figure 7 depicts the frequency polygons of mTAL size for each kidney of all of the rats studied, graphed by experimental group. A comparison of the trends in each group shows that the curve of the SD group was shifted to the left as compared with that of the C group, but with a slight degree of positive skewness. In contrast, the curve of the A group showed a right-sided shift together with a slight positive skewness. Of most interest is the distribution of the combination group, SDA, which showed a further shift to the left with considerable positive skewness.

A substantial increase in the number of nuclei per tubule was noted in the A and SDA groups, as compared with that in C and SD groups. Multiple regression analysis revealed that the number of nuclei could be predicted significantly by amphotericin treatment.

Both glomeruli and collecting ducts in the SDA group were noted to be significantly smaller than...
Figure 2. Rats injected with amphotericin and fed a normal diet. Areas of calcification are noted immediately adjacent to cortical thick ascending limbs. In panel A, the calcification has occurred in the zone of the macula densa, and epithelium partially surrounds the calcific mass. In panel B, the mass is almost completed circumscribed by the thick ascending limb epithelium. Panel C depicts a medullary ray in sagittal section. In the thick ascending limb on the left, there is a similar pattern of what appears to be necrosis, calcification, and epithelial regeneration. On the right, the thick ascending limb appears to have lost epithelium over much of its length, and the interstitial cells are proliferating through areas of rupture into the lumen. Magnification for all three panels, x475. Bar, 10 μm.

those in the C and A groups. In addition, collecting ducts of the SD group were found to be significantly smaller than those of the C and A groups.

DISCUSSION

The two groups of amphotericin-treated rats were quite distinct. In rats given amphotericin with a normal diet, there was polyuria but a normal creatinine. In these animals, tubulointerstitial injury was largely restricted to the medullary ray, and the inner stripe of the outer medulla showed remarkable thick ascending limb hypertrophy. In contrast, in the amphotericin-treated animals on a salt-deficient diet, chronic tubulointerstitial injury was seen throughout the cortex, and the inner stripe showed extensive atrophy. Interestingly, the mTAL in the salt-depleted animals (without amphotericin) were significantly reduced in size. This finding has been confirmed in subsequent experiments (unpublished data).

The outer medulla is prone to hypoxic damage, because it functions on the verge of hypoxia, even under normal physiologic conditions. Disturbance of the very delicate balance between oxygen supply and demand can easily lead to hypoxic injury in this zone (10). In preliminary studies with Clark-type oxygen microelectrodes, both renal cortical and medullary Po2 values were substantially diminished by the infusion of amphotericin in association with renal vasoconstriction (M. Brezis, unpublished data). It is conceivable that chronic amphotericin administration may alter the delicate balance of medullary ox-
Figure 3. Rats injected with amphotericin and fed a normal diet (A through C) or fed a sodium-deficient diet (D). Fine structural studies confirmed that, in some instances, calcific deposits were surrounded by thick ascending limb epithelium (A). In material processed in the standard way, the calcium was represented as masses of electron-dense material that fragmented when the tissue was cut for electron microscopy. On the other hand, when the tissue was first incubated with 0.1 M EDTA, the calcific material could be sectioned, and it appeared as multiple, curvilinear spicular arrays intermingled with cellular elements (B). When the decalcified material was examined at a higher power (C), calcified mitochondria could be defined; the associated cells are fibroblasts. Except for the sodium-depleted rats given amphotericin (D), the medullary changes were subtle and best assessed by morphometric analysis (see Figure 7). However, Panel D shows a typical mTAL from that treatment group. One can immediately see diminished mitochondria content and loss of the basolateral membrane array. This tubule is markedly reduced in size when compared with those shown in panels A and B. Magnification, ×3,700, ×3,540, ×10,300, ×4,230 for panels A through D, respectively. Panels A, B, and D: bar, 1 μm; panel C: bar, 3 μm.
Figure 4. Rats injected with amphotericin and fed a normal diet (A through C) or fed a salt-deficient diet (D). A fairly intact proximal tubule, taken from the area of a medullary ray, is noted in panel A. The brush border is well maintained, and the cytoplasm contains the typical content of organelles. In the upper right, an infiltrating lymphocyte can be noted, and focally, the basal lamina is thickened (*). In panel B, a proximal tubular segment is noted. On the immediate right, the tubule is fairly normal with a relatively intact brush border. The latter is markedly diminished in the adjacent cells on the left, and thickening of the basal lamina (*) is noted in the cell at the center of the photograph. The basal lamina thickening and cell infiltration can be seen at a higher power in panel C. In panel D, presumably a proximal tubule, the brush border can no longer be recognized, the mitochondrial content is markedly decreased, and the usual basolateral membrane array cannot be identified. Numerous phagolysosomes are present within the cytoplasm. The basal lamina is now highly irregular with a largely clear space between it and the tubule cytoplasm proper. Magnifications, ×3,200, ×3,500, ×5,000, ×4,160 for panels A through D, respectively. Bar, 1 μm.

Oxygenation and cause medullary hypoxia, which in turn may lead to progressive hypoxic tubular damage and interstitial fibrosis.

The pattern and distribution of the tubulointerstitial disease, affecting primarily the medullary rays and the outer medulla, are of particular interest. Similar patterns have been previously described in experimental cyclosporine (17) and hypercalcemic nephropathy (18). Indeed, in a recently published study of cyclosporine nephropathy, a phase of mTAL hypertrophy was noted when medullary damage was limited. With more extensive injury, atrophy became predominant (23).

Our findings are in general agreement with those
of previous studies of amphotericin nephrotoxicity, where damage affecting the distal segments was noted (24–28). In this study, however, we have defined in more detail the specific tubular segments involved. The zonal involvement, in concert with our previous studies, is certainly compatible with the hypothesis that amphotericin toxicity is mediated, at least in part, by oxygen deficiency. On the other hand, the segmental nature of the mTAL injury and, in particular, the involvement of the macula densa, which is located in an oxygen-rich zone, also suggest that direct tubular toxicity is important in amphotericin injury.

The increase in mTAL cell size in the A group may represent a hypertrophic response to augmented workload (22). This change may render the tubules susceptible to hypoxic damage, as happens in the remaining kidney of uninephrectomized rats in vivo and in vitro (20, 29). Nevertheless, despite mTAL hypertrophy, renal function in the A group was generally preserved and the injury score was low. Salt depletion increased injury and renal dysfunction in rats treated with amphotericin. This observation is in concert with other experimental (12–14) and clinical studies (15, 16). Salt depletion and renal hypoperfusion may increase intraluminal concentration of the nephrotoxin and decrease its transit time. Alternatively, the presence of circulating vasopressors might aggravate renal vasoconstriction. In addition, because amphotericin increases intracellular sodium chloride, it has been suggested by some that its combination with salt depletion amplifies tubuloglomerular feedback, leading to diminished GFR (14, 30). However, others have concluded that, on the basis of acute experiments, the amphotericin-associated reduction in GFR is due to vasoconstriction and not to tubuloglomerular feedback activation (31).

The novel finding of reduced tubular cell size in SD rats may represent some kind of disuse atrophy, because most of the filtered sodium chloride has probably been reabsorbed in the proximal tubule. Although they were small in size, the mTAL maintained a normal appearance, and cellular mitochondrial morphology and content seemed to be preserved. Tubular cell size was further diminished in the SDA group, but in contrast, there was a substantial reduction of mitochondrial density and other features of cell atrophy were present.

The number of nuclei identified per tubular cross-section reflects the cellularity of the mTAL and is a function of both cellular size and number. Because nuclear counts in the smaller mTAL of SD rats were identical to those of controls, it follows that a reduction in cellular volume took place. In contrast, both groups treated with amphotericin had increased nuclear counts. In the A group, this was in concert with increased mTAL size; thus, there was both hypertrophy and hyperplasia. The changes in the SDA group (with smaller mTAL) are less straightforward, because the increase in nuclear number might be a function of reduced cellular size alone. Thus, our findings suggest that atrophy and hypertrophy of the
TABLE 2. The effect of salt depletion and amphotericin B: multiple regression analysis

<table>
<thead>
<tr>
<th>Dependent Variable</th>
<th>Predictor Variable</th>
<th>F</th>
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<tr>
<td>Cortical Injury</td>
<td>Salt depletion</td>
<td>9.9</td>
<td>0.0056</td>
</tr>
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<td>Amphotericin</td>
<td>20.7</td>
<td>0.0003</td>
</tr>
<tr>
<td>Medullary Injury</td>
<td>Salt depletion</td>
<td>12</td>
<td>0.0028</td>
</tr>
<tr>
<td></td>
<td>Amphotericin</td>
<td>17</td>
<td>0.0007</td>
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* Values 0 or 1 were used for salt depletion and amphotericin to define their absence or presence, respectively.
Figure 7. Frequency polygons of mTAL cross-sectional area (in square micrometers) for all animals studied, grouped according to treatment. Each curve represents one kidney.

<table>
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<tr>
<th>TABLE 3. Morphometric evaluation of rats chronically treated with amphotericin B, salt depletion, or their combination</th>
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<tr>
<td><strong>Group (No. of Rats)</strong></td>
</tr>
<tr>
<td>mTAL Cross-Sectional Area (μm²)</td>
</tr>
<tr>
<td>Nuclei (No. of mTAL)</td>
</tr>
<tr>
<td>Glomerular Cross-sectional Area (μm²)</td>
</tr>
<tr>
<td>Collecting Duct Cross-Sectional Area (μm²)</td>
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<sup>a</sup> P < 0.01 versus SD and SDA.
<sup>b</sup> P < 0.02 versus C.
<sup>c</sup> P < 0.05 versus SD.
<sup>d</sup> P < 0.05 versus A.
dothelin release in vivo or in cultured endothelial cells (37).

Can any of the physiologic findings in the different treatment groups relate to clinical findings in amphotericin nephrotoxicity (4)? The A group is reminiscent of those patients with amphotericin toxicity that have polyuria and a normal serum creatinine. One may speculate that the maintenance of normal plasma creatinine is related to the injury of the juxtaglomerular apparatus and the loss of autoregulation. Our SDA group parallels those patients in whom amphotericin induces renal failure.

Thus, the chronic administration of amphotericin causes injury largely confined to the medullary ray and the cortex and initiates an mTAL hypertrophic response in the inner stripe. Amphotericin in combination with salt deficiency produces far more widespread cortical damage, together with an atrophic medullary response. The types of tubular injury and the zones they involve suggest pathogenetic roles for both hypoxic injury and direct epithelial toxicity.

ACKNOWLEDGMENTS

This work was supported by grants from the U.S.-Israel Binational Science Foundation, American Heart Association (860719), the National Institutes of Health (DK18078 and DK39249), and the Beth Israel Hospital Pathology Foundation, American Heart Association (880719). The authors are grateful to Lena Eliezen for her excellent technical assistance.

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