Atypical Hyperlipidemia and Nephropathy Associated With Apolipoprotein E Homozygosity

Demetrius Ellis, Trevor J. Orchard, Susan Lombardozi, Edwardo J. Yunis, Jerry McCauley, Rocco Agostini, and Jonathan R. Diamond

ABSTRACT

Hyperlipidemia has been implicated in the pathogenesis of experimental progressive glomerulosclerosis, but its role in human renal injury is controversial. This report describes a 12-year-old boy presenting with massive proteinuria, hepatomegaly, anemia, severe mixed hyperlipidemia, and progressive renal failure. The initial renal biopsy disclosed large numbers of foam cells that were shown to be monocytes. Evidence is presented suggesting that apoprotein-E2 homozygosity in our patient, together with an 88% reduction in plasma lipoprotein lipase activity associated with severe nephrotic syndrome, is responsible for the atypical clinical features, lipoprotein phenotype III with chylomicronemia, and renal lipidosis. A regimen of dietary lipid restriction, gemfibrozil, and niacin resulted in significant but partial improvement of the dyslipidemia and resolution of the hepatomegaly and ascites. This report stresses the importance of characterizing unique lipid disorders in patients with nephrotic syndrome in order to prescribe effective...
lipid-lowering strategies. Moreover, the striking resemblance of the clinical and nephrohistologic features of this patient to those occurring in experimental models of coexisting glomerular injury and hyperlipidemia led to the speculation that, in this setting, the hyperlipidemia may contribute to the development of progressive glomerulosclerosis.

Key Words: Nephrotic syndrome, hyperlipidemia, glomerulosclerosis

Plasma cholesterol and triglyceride concentrations surpassing the 95th percentile of control values occur invariably in children with nephrotic syndrome (NS) (1) and in most adults as well (2). The pathogenesis, consequences, and treatment of this secondary form of hyperlipidemia have been the subject of recent reviews (3,4). Two paramount concerns arising from such hyperlipidemia include premature coronary atherosclerosis leading to myocardial infarction and accelerated glomerulosclerosis (3,5–7). Experimental studies support the hypothesis that lipids play an important role in the acceleration of glomerulosclerosis and tubulointerstitial nephritis (3,6,7). However, studies supporting an increased susceptibility to these complications in humans are inconclusive because (1) the occurrence of foam cells in renal biopsies of nephrotic patients is rarely reported (8,9); (2) partial or complete correction of the hyperlipidemia by pharmacologic means does not reduce the proteinuria (10); and (3) the influence of hyperlipidemia per se on glomerulosclerosis is difficult to separate from multiple additional contributory factors, including hypertension, dietary protein intake, and circulating vasoactive substances.

Apoprotein-E (apo-E) phenotype 2/2 is associated with impaired clearance and accumulation of cholesterol-rich very low-density lipoprotein (VLDL) remnants, leading to Type III dyslipoproteinemia and an increased risk for atherosclerosis, including lower extremity arterial disease. The expression of this lipoprotein disorder usually requires the presence of a secondary condition, e.g., NS as in this case (11). Herein, we describe a child with massive proteinuria, atypical clinical features including hepatomegaly and mixed hyperlipidemia, and striking alterations in glomeruli and tubulointerstitium with the accumulation of foamy macrophages closely resembling an experimental model of progressive glomerulosclerosis (12). The clinical and nephropathologic implications of characterizing a unique hyperlipidemia due to the combined presence of nephrotic hyperlipidemia and apo-E2 homozygosity are the focus of this report.

CASE REPORT

A previously healthy 12.5-yr-old white boy presented to his local doctor for the evaluation of fatigue and abdominal swelling. Apart from chronic intermittent enuresis, he was previously well and denied recent pharyngitis, fever, or other systemic symptoms including rash or joint pain. He had received no medications or illicit drugs and had no exposure to toxins. Marked hepatomegaly and extreme pallor were noted on examination. Laboratory studies revealed a hemoglobin of 8.0 g/dL with a reticulocyte count of 0.8%; the urine tested large for blood and 4+ for protein. Ultrasound confirmed the presence of enlarged liver, spleen, and kidneys. The normal peripheral blood smear and the initial laboratory studies focused attention to a renal disorder.

Family history revealed that the parents were first cousins and the father had a history of goiter, arthritis, and hepatitis C antigenemia. A 9-yr-old female sibling was healthy. There was no family history of renal disease, malignancy, hyperlipidemia, myocardial infarction, collagen vascular disease, or hematologic disease. Both parents were subsequently found to have the apo-E3/2 phenotype.

Physical examination revealed a pale, well-built, bright normocephalic, preadolescent boy with a blood pressure of 130/98 mm Hg and pulse of 86/min. His abdomen was protuberant with ascites but only minimal eyelid edema and no pretibial edema. Mild digital clubbing was present. Located on the upper trunk were several discrete, round, blanching red macular lesions measuring 2.5 mm across. No xanthomas or lipid deposits were noted on the skin nor in the tendons, although lipemia retinalis was present. There was no lymphadenopathy. The liver was palpable at the right pelvic brim, and the spleen was 3 cm below the left costal margin.

The initial laboratory results are summarized in Table 1. The urinary studies revealed nonselective, severe nephrotic proteinuria as well as small-molecular-weight proteinuria and glucosuria without hyperglycemia, indicative of proximal tubular dysfunction. The liver function tests were not indicative of hepatocellular injury or intrahepatic cholestasis. Coombs test and immunologic studies were all normal. The lipid and lipoprotein studies are highlighted in Table 2. Total fasting cholesterol and triglyceride concentrations were markedly increased, and most of the cholesterol was associated with VLDL and intermediate-density lipoprotein (IDL) fractions. The ultracentrifugation separation at density 1.006 revealed a broad "B" migrating band in the density < 1.006 ("top" or VLDL) fraction and a doubling of the usual cholesterol/triglyceride ratio in VLDL (0.41). These features and the huge increase in total apo-E support the diagnosis of Type III dyslipoproteinemia. In addition, there were chylomicrons. Serum apo-CII concentrations were normal (not shown).

The apo-E phenotype was established by the use of two methods. In the first, a dilipidated, desiccated VLDL sample was subjected to one-dimensional isoelectric focusing electrophoresis with a pH gradient between 4 and 7 (14). The second and more direct approach involved the detection of apo-E2 isoforms with DNA oligonucleotide probes and a Southern blotting technique (15). The patient's postheparin infu-
TABLE 1. Initial laboratory studies

<table>
<thead>
<tr>
<th>Urine</th>
<th>Serum</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urinalysis: 4+ protein, 1 to 2+ blood, intermittent 1+</td>
<td>Creatinine, 1.1 (0.6 to 1.0); BUN, 17 (&lt;20)</td>
</tr>
<tr>
<td>glucose, 15 to 20 red blood cells, 2 to 4 white blood cells, few tubular epithelial cells, many hyaline and coarse granular casts, and many oval fat bodies</td>
<td>Total protein, 4.2 g/dL (6 to 8); albumin, 1.8 (3.8 to 5.4)</td>
</tr>
<tr>
<td>24-h collection: volume, 2,004 mL; creatinine clearance, 73 mL/min per 1.73 m²; protein, 20,321 mg with 50.4% albumin; albumin/β₂-microglobulin, 220; and immunoglobulin G clearance/albumin clearance, 0.55.</td>
<td>Normal glucose, uric acid, calcium, phosphorus, and liver enzymes</td>
</tr>
<tr>
<td></td>
<td>Immunology*</td>
</tr>
<tr>
<td></td>
<td>C₁₇, 224 (83 to 177)</td>
</tr>
<tr>
<td></td>
<td>C₃, 57 (15 to 45)</td>
</tr>
<tr>
<td></td>
<td>Immunoglobulin G, 423 (601 to 1,377)</td>
</tr>
<tr>
<td></td>
<td>Circulating immune complexes were present</td>
</tr>
</tbody>
</table>

*All values are in milligrams per deciliter unless otherwise indicated. Parentheses are reference ranges from healthy age-matched controls.

Initial serum lipoprotein lipase activity (16) was only 12% of normal controls.

The renal histopathologic findings are illustrated in Figure 1. Fifteen glomeruli were available for study. There were abundant aggregates of foam cells in the glomerular tufts and in tubular areas with large focal lymphocytic infiltrates and mild interstitial fibrosis. Two glomeruli showed focal glomerulosclerosis, whereas three others had capsular thickening, dilation of urinary spaces, and shrinkage of the capillary tuft. The foam cells in the glomeruli and interstitium were macrophages as evidenced by intense immunoperoxidase staining with Ham 56 human macrophage antibody, anti-CD68, and antilysozyme staining seen in these locations. Immunofluorescence with immunoglobulin G (1–2+) and C₃ (2+) in granular form was present segmentally in some glomerular capillary loops and paramesangial locations.

Electron microscopy disclosed many glomerular capillary loops, which were distended and filled with foam cells. These foam cells had abundant cell processes and contained lipid vacuoles and lamellated electron-dense material with occasional cholesterol clefts. Lipid vacuoles were also seen in mesangial, endothelial, and tubular lining cells as well as in tubular lumens and blood vessels. Along with increased mesangial matrix, several capillary loops were compressed with occasional subendothelial, intramembranous, or paramesangial electron-dense material in the basement membrane. Extensive foot process fusion was noted.

Neither the location of the foam cells nor the lipid they contained was characteristic of any recognizable storage disease, and the constellation of clinical, laboratory, and biopsy findings did not delineate a specific diagnosis. Focal segmental sclerosis and mesangio proliferative glomerulonephritis were considered.

Once initial laboratory studies were obtained, the patient was begun on dietary restrictions of salt, cholesterol (=300 mg/day), and fat (<20% of total daily calories), as well as lovastatin (10 mg/day) and aspirin (60 mg/day). Enalapril was given at 7.5 mg/day to help reduce the urinary protein loss and to improve the mild hypertension. A trial of 1 g of intravenous cyclophosphamide followed by prednisone (20 mg/day) was given in an attempt to slow the progression of the active renal process.

One month after presentation, the hemoglobin was 11.3 g/dL, the creatinine was 0.7 mg/dL, the total protein was 3.5 g/dL, and the albumin was 1.4 g/dL; total protein excretion fell to 12,054 mg/day. The fasting serum cholesterol was 1,236 mg/dL, and triglycerides were 1,716 mg/dL. At that time, a second cyclophosphamide infusion was given.

After the definition of the lipoprotein disorder, lovastatin was stopped and gemfibrozil was begun with some improvement in the hyperlipidemia. Afterwards, a brief trial of high-dose prednisone ended because of worsening edema. A trial of FK-506 was begun 9

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**TABLE 2. Lipid and lipoprotein abnormalities**

<table>
<thead>
<tr>
<th>Serum (12 to 14 h of fasting)</th>
<th>This Patient</th>
<th>NS Mean</th>
<th>95%</th>
<th>Normal Controls</th>
<th>Mean</th>
<th>95%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Cholesterol</td>
<td>1571</td>
<td>557:958(1)</td>
<td>161:202(13)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Triglycerides</td>
<td>3510</td>
<td>230:443(2)</td>
<td>63:111(13)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>VLDL-Cholesterol</td>
<td>675</td>
<td>47:103(2)</td>
<td>9:9:22(13)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>VLDL C/TG</td>
<td>0.41</td>
<td>0.89(2)</td>
<td>0.20</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LDL-Cholesterol</td>
<td>104</td>
<td>367:735(1)</td>
<td>97:0:132(13)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HDL-Cholesterol</td>
<td>42</td>
<td>31:55(1)</td>
<td>55:74(16)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HDL-C/IDL-C</td>
<td>0.20</td>
<td>0.12:0.89(1)</td>
<td>0.56:0.62(1)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Apo-A1</td>
<td>148</td>
<td>130:200(2)</td>
<td>120:157(2)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Apo-A2</td>
<td>54</td>
<td>30:42(2)</td>
<td>32:47(2)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Apo-B</td>
<td>316</td>
<td>179:268(2)</td>
<td>83:125(2)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>VLDL + IDL Apo-B</td>
<td>273</td>
<td>43</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LDL Apo-B</td>
<td>19</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lp(a)</td>
<td>87:94</td>
<td>50:6:68(2)</td>
<td>19:50:8(2)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Apo-E</td>
<td>58.5</td>
<td>9.0:19(2)</td>
<td>7:14(2)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Genotype</td>
<td>e2/e2</td>
<td>2</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Phenotype</td>
<td>E2/E2</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>III</td>
<td>11a, 11b, IV(2)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*All values are in milligrams per deciliter unless otherwise indicated. Parentheses are reference ranges from healthy age-matched controls.
Figure 1. (A) An obsolescent glomerulus (left) is seen next to one showing some distended capillaries and mesangial prominence on the right. Patches of interstitial fibrosis with round cell infiltration are seen in the adjacent parenchyma with some foam cells (arrows) and vacuolation of tubular lining cells (trichrome stain, x350). (B) Groups of foam cells are seen distending the glomerular capillaries (open arrows). A crystalline structure is also seen (solid arrow) (trichrome stain, x715). (C) Groups of lipid-rich cells are seen within capillary lumens. A lamellar body is seen in the lower right next to a cholesterol cleft (arrow) (trichrome stain, x5,000). (D) An intraluminal lipid-laden macrophage with both lipid droplets and numerous, varying size, electron-dense membranous bodies (trichrome stain, x14,000).

months into the clinical course (serum creatinine, 1.3 mg/dL) as per our center-approved protocol for NS refractory to conventional therapy (17). The combination of gemfibrozil and FK-506 was associated with a reduction of cholesterol and triglyceride levels to 524 and 409 mg/dL, respectively. The hepatosplenomegaly and ascites resolved as did the cutaneous vascular lesions, but neither the proteinuria nor the hypoproteinemia abated. The child developed progressive renal failure and hypertension. At 15 months after the initial presentation, a repeat renal biopsy revealed severe glomerulosclerosis with extensive tubular atrophy and fibrosis. Notably, only rare foam cells were seen.

DISCUSSION

Lipid metabolism is abnormal and complex in individuals with NS (3,4). The overproduction of apo-B leading to both elevated VLDL and LDL appears to be the major cause of the hypercholesterolemia (3,4). With severe albuminuria, lecithin-cholesterol acyltransferase activity may fall and, together with decreased endothelial lipoprotein lipase activity, may lead to the suboptimal catabolism of VLDL and the development of hypertriglyceridemia (3,4). Consequently, the major lipoprotein phenotypes occurring in individuals with NS are independent of the underlying histopathology and include IIa (33%, increased low-density lipoprotein [LDL]), IIb (60%, increased...
LDL and VLDL), and IV (7%, normal LDL but increased VLDL) (2).

As shown in Table 2, our patient is biochemically unique in several respects. First, the serum cholesterol and triglyceride concentrations surpass the 2 SD levels reported in large series of nephrotic children or adults (1,2). Second, the LDL cholesterol concentration was normal; most of the cholesterol was contained in the VLDL fraction, suggesting the presence of elevated VLDL remnants or IDL (Table 2). Indeed, these lipid fractions were confirmed by our special studies and classified our patient into Type III dyslipoproteinemia with additional fasting chylomicronemia. The risk of expressing Type III dyslipidemia in a patient with NS is estimated at 1.5/million based on the relative frequency of the apo-E2 allele of 0.072 (11) and the incidence of NS of 2 in 100,000 in American children (18). In addition, high-density lipoprotein (HDL) cholesterol was reduced, whereas apo-A1, the major lipoprotein in HDL, was normal. Lipoprotein (a) [Lp(a)] concentrations were extremely high. Recent studies have shown a high correlation of Lp(a) with VLDL cholesterol and VLDL triglycerides, suggesting a close link between triglyceride-rich lipoproteins and Lp(a) in nephrosis. This may relate to the severity of proteinuria with a secondary rise in serum triglycerides and increased hepatic synthesis of both VLDL and Lp(a) (19). In the absence of other triggering mechanisms for the expression of Type III dyslipidemia, we infer that, in our patient, this disorder may have been provoked by the NS and accelerated by the hyperlipidemia, which typically characterizes the NS. Although chylomicronemia occasionally occurs in Type III hyperlipidemia, this disorder may be better explained by the massive proteinuria in our patient, leading to a more than the typical 30 to 60% depression of postheparin endothelial lipoprotein lipase activity reported in patients with NS (20). Serum concentrations of apo-CII, the major activator of lipoprotein lipase, were normal and did not explain the reduced activity of the lipoprotein lipase.

The presence of Type III dyslipoproteinemia, chylomicronemia, and high circulating levels of Lp(a) in a patient with NS has several potential important therapeutic and pathogenetic implications, including the risk for premature atherosclerosis coupled with a tendency to thrombosis in patients with NS (21) and lipid-induced progressive renal injury. Although clinical studies are at variance on the issue of atherogenic risk or ischemic heart disease in patients with unremitting NS, our patient was gauged as having a high risk for ischemic heart disease on the basis of several factors: severe and prolonged NS unresponsive to corticosteroids and alkylating agents, extremely high serum cholesterol and triglyceride concentrations, presence of VLDL remnants, which are thought to be atherogenic particularly in association with high serum Lp(a) levels (19), a low HDL/LDL ratio, and marked increases in serum Lp(a) levels. The latter is increasingly recognized as an important independent risk factor for atherothrombosis (22,23), possibly by inhibiting plasminogen activation.

The influence of the severe hyperlipidemia on progressive renal injury is a second major concern. Subacute and chronic phases of a hypercholesterolemic model of nephrosis have been described. This model combines the well-characterized puromycin aminonucleoside–induced nephrosis together with early dietary cholesterol/colic acid supplementation. The latter maneuver converts a transient renal disorder into a lipid-stimulated, monocyte-mediated progressive glomerulosclerosis and tubular fibrosis (12,24). Several lipid-derived chemoattractants including a fatty acid derivative of albumin are likely involved in such cellular recruitment (25,26). Mesangial monocyte accumulation is accompanied by transforming growth factor β1 mRNA synthesis, which has also been implicated in the pathogenesis of both acute and chronic renal disease (12,27,28). Apart from these newer data that may explain tubular dysfunction due to lipid nephrotoxicity, the tubular injury itself may exacerbate the loss of small-molecular-weight apolipoproteins, which modulate the metabolism of lipids and of other apolipoproteins. Furthermore, "protein overload" of the tubular mechanisms that process them may contribute to the development of tubulointerstitial nephritis, as evidenced in proteinuric models of lipid-induced nephropathy (29).

Although hyperlipidemia has been implicated in the pathogenesis of accelerated glomerulosclerosis and tubulointerstitial injury by mechanisms involving monocytes and atherothrombosis (6,7,24), there are only a few clinical instances supporting this hypothesis. Familial lecithin–cholesterol acyltransferase deficiency is one entity wherein a distinct lipoprotein abnormality antedates the development of progressive proteinuria, glomerulosclerosis, and renal insufficiency (30). Second, although foam cells in the kidney may be an incidental finding in several lipid storage or hyperlipidemia disorders with minimal or absent renal manifestations, abundant glomerular foam cells are exceedingly rare (9,31). Only four adults have been reported with good renal function, prolonged NS, and unusually severe hypercholesterolemia and hypertriglyceridemia discovered concurrently with the diagnosis of NS, as in this case (Table 3) (8,9). Although clinical details were lacking and lipoprotein studies were not performed in these previous studies, it is noteworthy that, in two patients whose hyperlipidemia was successfully managed with clofibrate, repeat renal biopsy revealed disappearance of the foam cells (9). The relevance of the foam cells is notably in question because a reduction in serum lipids by dietary and pharmacologic measures in humans may result in their regression without abatement of the proteinuria (9,10). More recent studies suggest that apo-E2 and Lp(a) deposition in the glomeruli is associated with greater mesangial hypercellularity, glomerulosclerosis, and proteinuria (32,33).

Only one other report describes Type III hyperlipid-
TABLE 3. Features of subjects with NS and prominent foam cells in the glomerular tufts

<table>
<thead>
<tr>
<th>Age (yr)</th>
<th>Diagnosis</th>
<th>Protein Excretion (g/24 h)</th>
<th>Serum Albumin (g/dL)</th>
<th>Cholesterol (mg/dL)</th>
<th>Triglycerides (mg/dL)</th>
<th>Ref. No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>35</td>
<td>Diabetic nephropathy?</td>
<td>Moderate</td>
<td>7</td>
<td>852</td>
<td>5477</td>
<td>8</td>
</tr>
<tr>
<td>34</td>
<td>Poststreptococcal glomerulonephritis</td>
<td>9</td>
<td>2.3</td>
<td>768</td>
<td>3800</td>
<td>9</td>
</tr>
<tr>
<td>63</td>
<td>Global glomerulosclerosis</td>
<td>9.4</td>
<td>1.2</td>
<td>634</td>
<td>1800</td>
<td>9</td>
</tr>
<tr>
<td>40</td>
<td>Diabetic nephropathy</td>
<td>6.3</td>
<td>1.9</td>
<td>500</td>
<td>1200</td>
<td>9</td>
</tr>
<tr>
<td>12</td>
<td>This patient</td>
<td>20.3</td>
<td>1.8</td>
<td>1571</td>
<td>3510</td>
<td>9</td>
</tr>
</tbody>
</table>

emia and markedly elevated serum cholesterol and triglyceride levels (34). A 5-yr-old child with apo-E2 homozygosity had proteinuria and intermittent edema since the neonatal period, at which time a renal biopsy was consistent with a "variant of minimal-change disease." At 5 yr of age, the child developed severe edema and marked hyperlipidemia, followed by deterioration in renal function over several months. At that time, apo-E2 expression was believed to have been precipitated by the hyperlipidemia of NS combined with the initiation of diuretics and corticosteroids (34). Although a contemporaneous renal biopsy was not available to evaluate the presence of foam cells, this case suggests that progressive renal injury and renal failure may occur in patients with severe Type III hyperlipidemia in the setting of coexisting glomerular injury and NS. Certainly, several clinical and histopathologic aspects of our case, especially those shared with the cholesterol-supplemented models of nephrosis, led us to speculate that our patient was at high risk for progressive mesangial matrix expansion, progressive glomerulosclerosis, tubulopathy, and interstitial fibrosis in association with local monocyte-induced events.

Several general aspects of the management of hyperlipidemia in our patient deserve emphasis. Control of the hyperlipidemia was needed urgently in order to decrease the possibility of pancreatitis and acute thromboembolic events and to limit the potential contribution of this disorder to ongoing renal injury. Realizing that improvement of the primary renal disease and albuminuria were the key factors, our patient was first begun on cyclophosphamide and only low-dose prednisone because corticosteroids may exacerbate the hyperlipidemia (35). Higher dosages of prednisone were later used once the hyperlipidemia improved but had no benefit. He was also begun on enalapril. The antiproteinuric action of converting enzyme inhibitors was recently demonstrated to lower cholesterol and LDL cholesterol and to decrease Lp(a) levels in adults with nephrotic-range proteinuria and mild renal insufficiency (36). These agents may also reduce glomerular hyperfiltration and retard the development of glomerulosclerosis (36,37). Low-dose aspirin was given to reduce the role of platelets in coronary thrombogenesis in association with NS and atherosclerosis. Subsequently, FK-506 was begun for the treatment of the primary renal disorder (17). It was discontinued when a decrease in creatinine clearance 2 months later was attributed to FK-506 nephrotoxicity exacerbated by the concomitant use of converting enzyme and prostaglandin synthase inhibitors, both of which may reduce RBF and intraglomerular pressure.

Clearly, early lipid-lowering measures including severe dietary restriction of unsaturated fat and cholesterol ("step 2 diet"; Ref. 38) were ineffective in our patient. Moreover, lovastatin, an inhibitor of 3-hydroxy-3-methylglutarylcoenzyme A reductase that may decrease serum cholesterol and triglyceride levels by 30 to 45% in the more characteristic forms of nephrotic hyperlipidemia (10), was equally ineffective. In contrast, gemfibrozil use was associated with a marked reduction in serum cholesterol and triglyceride levels (50 and 80%, respectively). As with clofibrate, used successfully in two other patients with NS and a similar type of hyperlipidemia (9), gemfibrozil stimulates the activity of endothelial lipoprotein lipase and may preferentially enhance the catabolism of VLDL particles. However, it was only after the addition of niacin and the discontinuation of prednisone that serum triglycerides fell to within the normal range, despite the persistent NS.

The role of hyperlipidemia in the progression of renal injury in our patient remains unclear. On the basis of the work of Schlondorff (39) and others (6,7,40), we have constructed a hypothetical schema, shown in Figure 2. This schema emphasizes the importance of the accumulation and oxidative modification of lipoproteins in the extracellular matrix, which is augmented by mesangial matrix expansion and by reactive oxygen species generated by the glomerular disease as well as by the secondary recruitment of lymphocytes (monocytes in particular). Oxidized lipoproteins are not only toxic to mesangial cells but also to endothelial and epithelial cells. The local release of inflammatory, vasoactive, and thrombogenic mediators combine to induce a cycle of cell injury and sclerosis that may be exacerbated by glomerular ischemia. Apart from monocytes, other cells may be elaborating transforming growth factor \( \beta \) and other injurious substances, resulting in fibrosis. Monocytes may be important in the initiation of renal injury but may not be necessary for perpetuating the process.
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We are grateful to Dr. Ira Goldberg and his assistants for measurements of apoprotein lipase activity. Dr. Evan Stein for the apoprotein E phenotyping and lipoprotein analysis, and Dr. Robert Farrell for apoprotein genotyping.

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REFERENCES