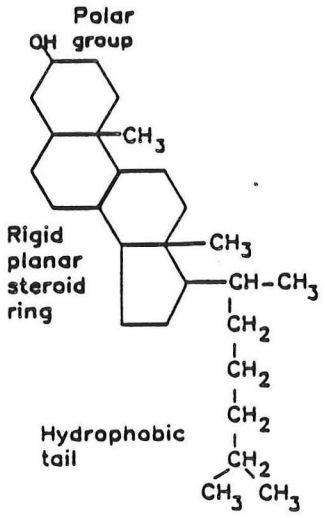
INTERNAL MEDICINE

GRAND ROUNDS

AUGUST 01, 1991

THE ROLE OF

CHOLESTEROL



IN THE PROGRESSION OF RENAL DISEASE

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INTRODUCTION

Some patients who experience a partial loss of kidney function as a result of immunologic or nonimmunologic mechanisms, eventually progress to renal failure, even though the process that caused the partial loss of kidney function is no longer present. It has been proposed that the initial loss of functioning nephrons causes alterations of function and metabolism in remnant nephrons, which per se are self-inflictive, and cause progressive glomerulosclerosis leading to further loss of nephrons. The ultimate outcome of this vicious cycle is the end-stage kidney (Fogo 1991, Hebert 1990, Klahr 1988, Shultz 1991).

In recent years the potential role of various pathophysiologic mechanisms which may result in progressive loss of nephron function have been extensively explored.

TABLE 1

FACTORS WHICH MAY PLAY A ROLE IN THE PROGRESSION OF RENAL INJURY

1) GLOMERULAR HYPERTENSION AND HYPERFILTRATION
2) GLOMERULAR HYPERTROPHY
3) ALTERED LIPID METABOLISM
4) HYPERMETABOLISM
5) CALCIUM-PHOSPHATE DEPOSITION
6) HYPERCOAGULABLE STATE

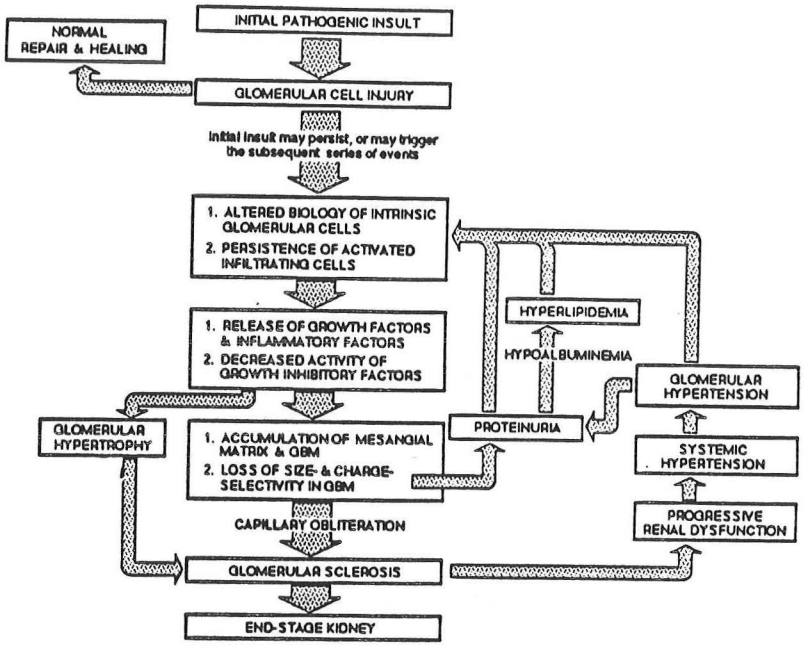

Figure 2. Mechanisms by Which Glomerular Injury May Lead to Glomerulosclerosis. An initial insult may result in glomerular injury, which may heal without functional consequences, or it may lead to altered function in intrinsic glomerular cells or to the persistence of cells invading the renal parenchyma. In turn, these cells may increase the deposition of mesangial matrix and glomerular basement membrane (GBM) through several mechanisms, resulting in the obliteration of capillaries and glomerulosclerosis. Proteinuria, hyperlipidemia, and systemic hypertension may contribute to the development of glomerulosclerosis through the mechanisms depicted here. Note that systemic hypertension is not a prerequisite for the development of glomerular hypertension. Other factors, such as intraglomerular coagulation, have been omitted for the sake of clarity.

Figure 1. From Klahr 1989

In addition to the important roles of glomerular hypertension, hyperfiltration, and glomerular hypertrophy, altered lipid metabolism has also been proposed to play an important role in the progression of renal injury (Diamond 1988, Diamond 1989, Diamond 1990, Diamond 1991, Grönd 1989, Kasiske 1990, Keane 1988, Keane 1989, Keane 1990, Keane 1991, Moorhead 1982, Moorhead 1989, Moorhead 1991, Schmitz 1989).

The evidence for altered lipid metabolism playing a role in the progression of renal disease has been provided by studies which have shown:

1) The presence of glomerular lipid deposits in human and experimental glomerulonephritis, and in patients with inborn error of lipid metabolism, who have glomerular and tubular lipid deposits and progressive decline in renal function,

2) Dietary lipids, especially dietary cholesterol, to induce de novo glomerulosclerosis and proteinuria, or to exarcabate experimentally induced glomerulosclerosis,

3) Analogous pathobiologic mechanisms in glomerulosclerosis and atherosclerosis, including the presence of mesangial receptors for LDL and oxidized LDL, the effect of LDL and oxidized LDL to modulate mesangial proliferation and eicosanoid synthesis, and, an increase in the number and activity of glomerular macrophages in experimental models of glomerulosclerosis,

4) Lipid modulating agents to reduce the glomerulosclerosis and the proteinuria, and to improve renal function in experimental models of glomerulosclerosis.

TABLE 2

EVIDENCE THAT LIPIDS PLAY A ROLE IN THE PROGRESSION OF RENAL DISEASE.

1. PRESENCE OF GLOMERULAR LIPID DEPOSITS IN HUMAN AND EXPERIMENTAL GLOMERULONEPHRITIS WHICH CORRELATE WITH SEVERITY OF GLOMERULOSCLEROSIS AND PROTEINURIA.

2. DIETARY CHOLESTEROL INDUCES DE NOVO GLOMERULOSCLEROSIS OR EXARCABATES PREEXISTING GLOMERULOSCLEROSIS.

3. ANALOGOUS PATHOBIOLOGIC MECHANISMS IN GLOMERULOSCLEROSIS AND ATHEROSCLEROSIS, INCLUDING THE PRESENCE OF MESANGIAL RECEPTORS FOR LDL AND OX-LDL, THE ABILITY OF LDL AND OX-LDL TO MODULATE MESANGIAL PROLIFERATION AND EICOSANOID SYNTHESIS, AND AN INCREASE IN THE NUMBER AND ACTIVITY OF GLOMERULAR MACROPHAGES IN EXPERIMENTAL MODELS OF GLOMERULOSCLEROSIS.

4. LIPID MODULATING AGENTS REDUCE GLOMERULOSCLEROSIS AND PROTEINURIA IN EXPERIMENTAL MODELS OF GLOMERULOSCLEROSIS.

GLOMERULAR LIPID DEPOSITS IN GLOMERULOSCLEROSIS

The first description of the presence of lipid deposits in the kidney was provided by Virchow in 1860 (Virchow 1860). Later, in 1913 Munk drew attention to the lipid abnormalities of the nephrotic syndrome (Munk 1913). Then in 1936, Kimmelstiel and Wilson, in their original description of the lesions of intercapillary glomerulosclerosis in 8 diabetic patients, noted the occasional presence of fat in the involved glomeruli (Kimmelstiel 1936). Subsequently, in 1951 Wilens, Elster, and Baker in 21 cases of intercapillary glomerulosclerosis (19 had history of diabetes) noted that 14% of the glomeruli had marked lipidosis, and 32% had moderate lipidosis (Wilens 1951). Interestingly, these authors proposed that the

lesions of intercapillary glomerulosclerosis may be initiated as intercapillary deposits of fat, and furthermore that a combination of hyperlipidemia and elevated intraglomerular pressure might be responsible for the penetration of lipid-containing materials into the intercapillary substance of the tufts.

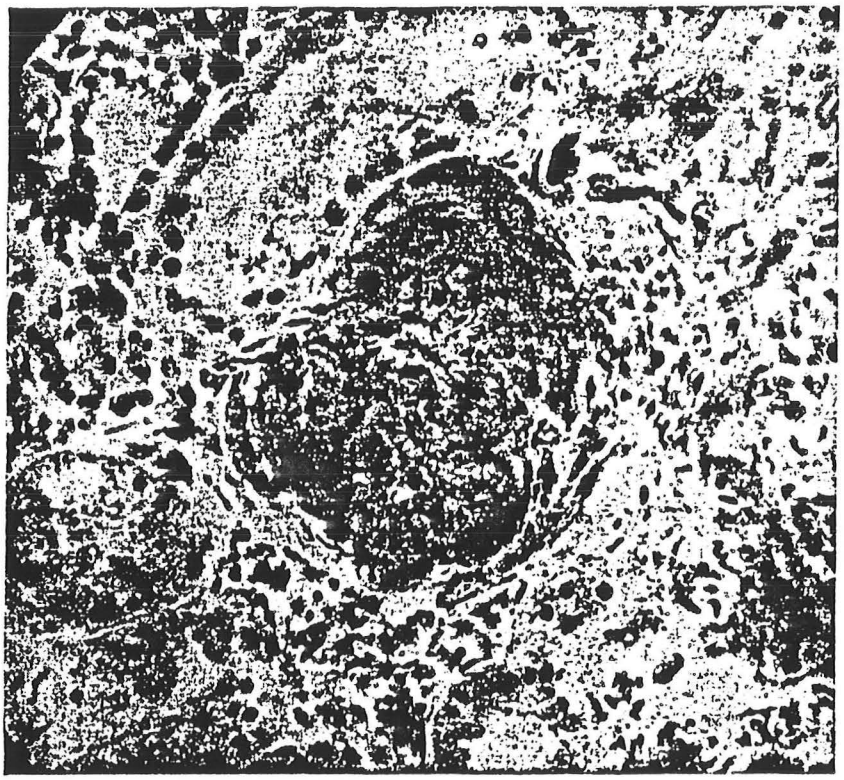

FIG. 2. Glomerulus completely filled with sudanophilic lipid material in intercapillary glomerulosclerosis. Sudan IV stain, × 303.

Figure 2. From Wilens 1951.

In 1955, Hartroft also reported that in 16 diabetic patients with Kimmelstiel-Wilson's lesions (intercapillary glomerulosclerosis), 12 had clear evidence of intraluminal fat within the glomerular capillaries (Hartroft 1955), and suggested that plugging of glomerular capillaries by fat either entrapped as emboli or precipitated in situ initiates a series of events that lead to formation of Kimmelstiel-Wilson lesions in diabetic man.

Glomerular and tubular lipid deposits have also been described in puromycin aminonucleoside induced glomerulonephritis in the rat, an experimental model of glomerulonephritis which bears great similarity to focal and segmental glomerular hyalinosis and sclerosis (FSGHS) in man (Grond 1984, Osawa 1991).

TABLE 3

CORRELATION BETWEEN GLOMERULAR LIPID DEPOSITS AND GLOMERULOSCLEROSIS AND PROTEINURIA IN AMINONUCLEOSIDE GLOMERULONEPHRITIS

	CONTROL	PAN
GLOMERULOSCLEROSIS (%)	0.3	7.8
U prot V (mg/24 hr)	10 ± 3	218 ± 108
GLOMERULAR LIPID DEPOSIT (normal Glomeruli)	0	110 ± 38
GLOMERULAR LIPID DEPOSIT (Glomeruli with FSGHS)	0	1036 ± 361

Adapted from GROND et al, Laboratory Investigation, 1984.

Glomerular and tubular lipid deposits are also seen in nephrotoxic serum nephritis in the rat, where there is a good correlation between tubular lipids and tubular atrophy, and glomerular lipids and glomerular sclerosis (Moorhead 1989).

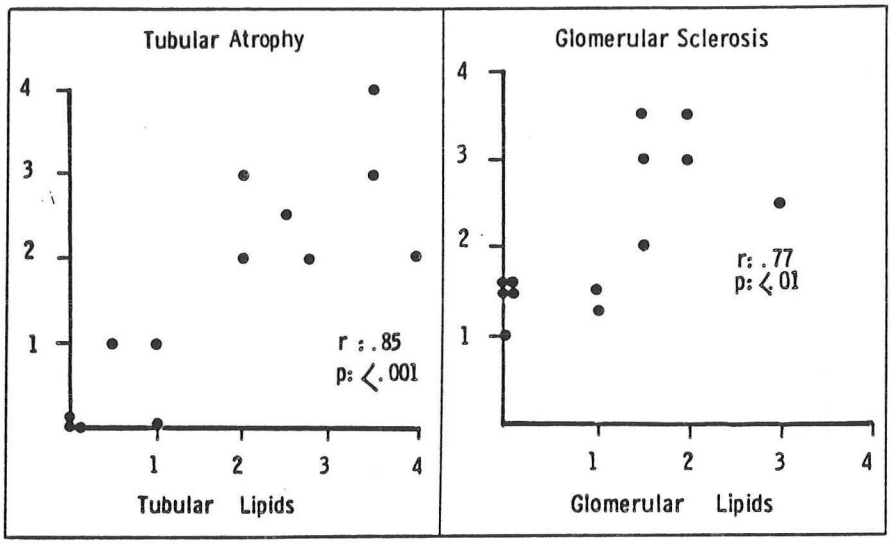

Figure 1. Nephrotoxic serum nephritis in 12 Sprague-Dawley rats. Morphologic damage scored on a scale of 0 to 4 by two independent observers who were unaware of the identity of the rats. **Left,** tubular atrophy and tubular lipids. **Right,** glomerular sclerosis and glomerular lipids.

Figure 3. From Moorhead 1989.

Glomerular and tubular deposits lipids also occurs in a number of diseases of inborn error of metabolism. Each of these diseases are characterized by lack of a specific enzyme which regulates lipid metabolism, resulting in the overaccumulation of the substrate and related lipids, for example sphingomyelin in Nieman-Pick disease.

TABLE 4

DISEASES OF INBORN ERROR OF METABOLISM ASSOCIATED WITH RENAL LIPIDOSES

1. FABRY DISEASE
   (ANGIOKERATOMA CORPORIS DIFFUSUM)
2. NIEMAN-PICK DISEASE
3. GAUCHER DISEASE
4. KRABBE DISEASE
   (GLOBOID CELL LEUKODYSTROPHY)
5. METACHROMATIC LEUKODYSTROPHY
6. MUCOLIPIDOSES
7. GANGLIOSIDOSES

8. FARBER DISEASE
(LIPOGRANULOMATOSIS)

9. WOLMAN DISEASE

10. BATTEN DISEASE
(NEURONAL CEROID LIPOFUSCINOSIS)

11. REFSUM SYNDROME

12. HYPERLIPOPROTEINEMIAS

13. LECITHIN-CHOLESTEROL ACYL
TRANSFERASE DEFICIENCY

LECITHIN-CHOLESTEROL ACYLTRANSFERASE DEFICIENCY: LCAT catalyzes the esterification of plasma cholesterol, whereby a fatty acid is transferred from the 2-position of lecithin (phosphatidylcholine) to the 3-hydroxyl position of free cholesterol. A familial disease, LCAT deficiency has been reported most often in people of Scandinavian origin. It is apparently inherited as an autosomal recessive trait. It occurs in both sexes, beginning generally in the second decade of life and progresses slowly. The absence or very low levels of LCAT leads to elevation of serum levels of free cholesterol, triglycerides, and phospholipids, and almost total lack of esterified cholesterol. An abnormal lipoprotein (large molecular weight LDL: LP-X) is often present. Patients have mild hemolytic anemia and corneal opacities (Gjone 1974, Gjone 1981, Magh 1982, Myhre 1977, Ohta 1986). Renal symptoms begin as proteinuria and microscopic hematuria, and sometimes end in renal failure after a prolonged course. Histologically, there is accumulation of foam cells in the glomeruli, as well as collections of dark irregular particles in the subendothelial spaces and mesangium. In some cases, serpiginous deposits are found under the endothelium. In other instances lipid is deposited in the glomerular basement membrane under the epithelium in a manner reminiscent of membranous glomerulonephritis. Such patients have massive proteinuria and even nephrotic syndrome. There is progressive expansion of the mesangium with accumulation of matrix and eventual sclerosis of the glomeruli.

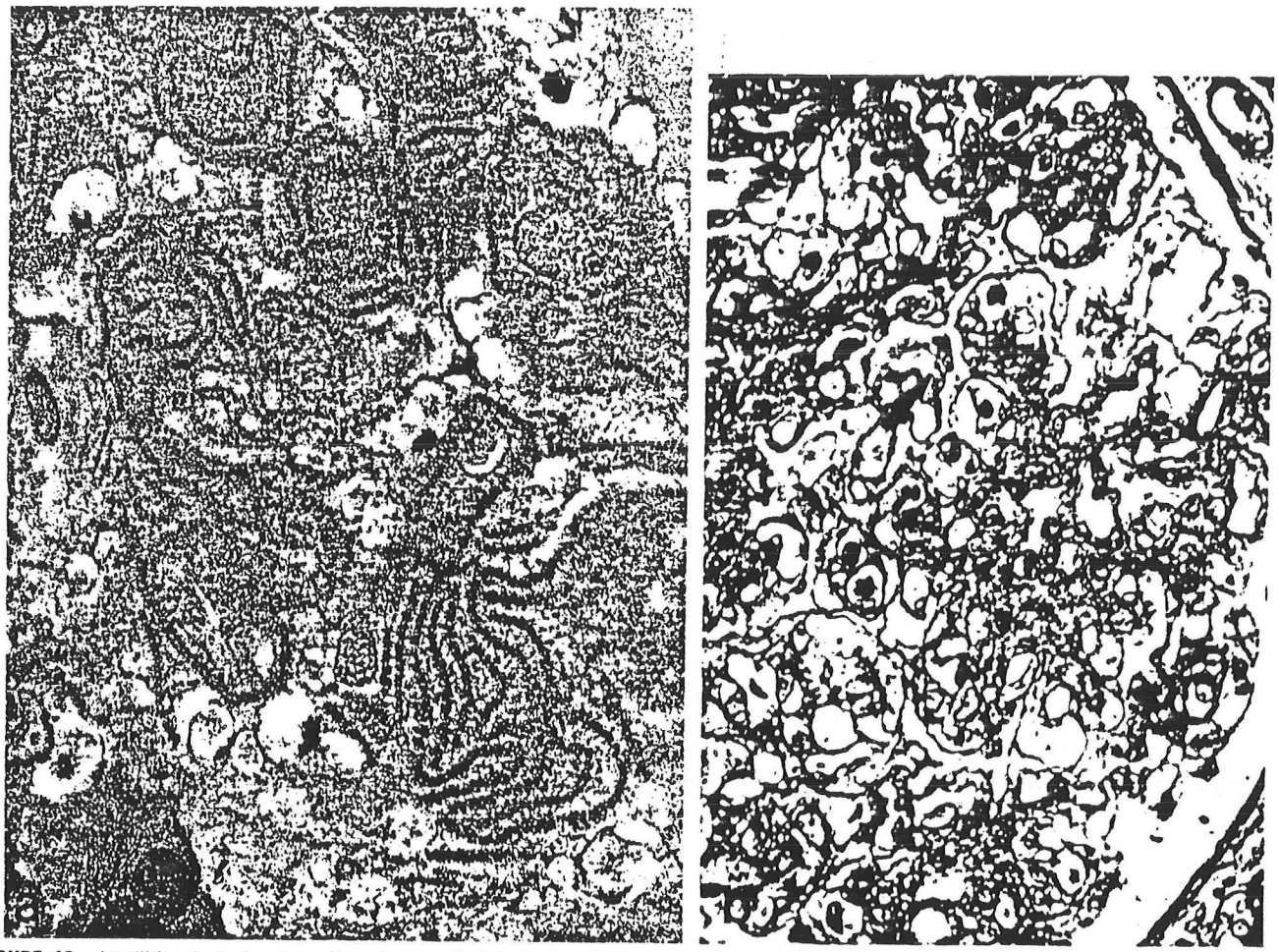

FIGURE 10. Lecithin-cholesterol acyltransferase deficiency. **a,** Electron micrograph illustrating an additional feature of the glomerular deposits of complex lipids. Note the serpiginous pattern of the lamellar structures. (Original magnification, ×38,000.) **b,** Histologic aspect of a glomerulus in late-stage disease. Note the expanded mesangial areas and thickened capillary walls, due to accumulation of lipids in the subendothelial areas. (Original magnification, ×640.)

Figure 4. From Faraggiana 1987.

HYPERLIPOPROTEINEMIAS: Familial hypercholesterolemia is a common inborn disorder of lipid metabolism. The kidneys frequently have been reported as sites of lipid storage in patients with this disorder, including homozygous fetuses. Lipid droplets have been described in glomerular, tubular, and interstitial cells. Histochemically, the lipid droplets mostly behave as cholesterol esters; they are stained by routine Sudan dyes and the Schultz reaction and are bifringent. Renal involvement has also been noted in type III hyperlipoproteinemia. In a case report of a 64 year od black woman with severe atherosclerosis, histopathological examination of the kidneys revealed mesangial foam cells which stained positively with oil red 0 (Amatruda 1974). Similar occurrence of mesangial foam cells has also been described in 4 other patients with elevated triglyceride levels (McKenzie 1969). In recent case reports of hyperlipoproteinemia, originating from Japan, severe capillary ballooning (aneurysmal formation) with mesangiolysis and deposition of lipoprotein-like substance in the capillary lumen has been described. Special staining with Sudan III, direct immunofluorescent microscopy for human ß-lipoprotein and indirect immunofluorescence for human apolipoproteins B and

E revealed positive staining of the substance in the capillary lumen. Some of these patients have a progressive increase in proteinuria and decline of renal function (Faraggiana 1987, Saito 1989, Watanabe 1989).

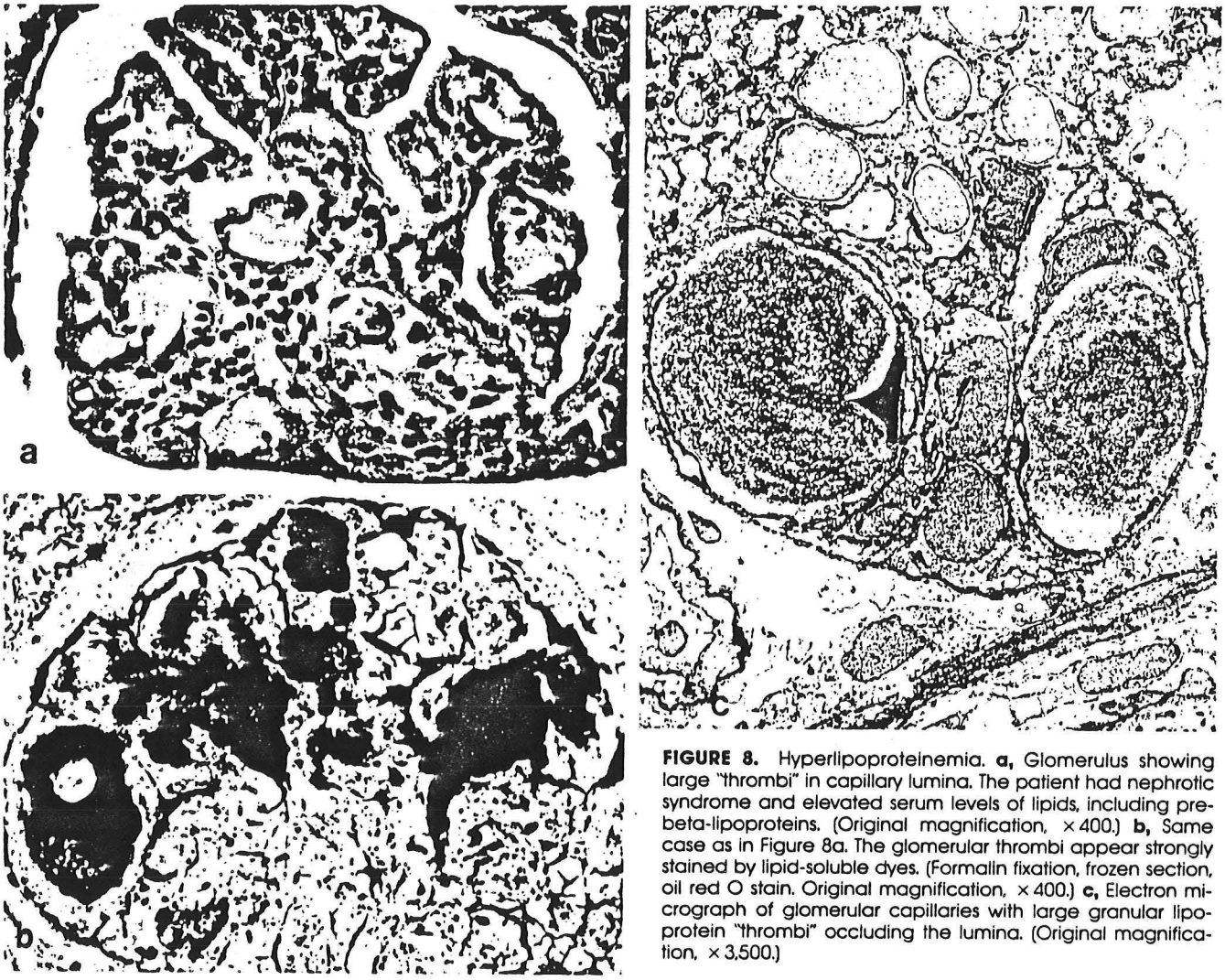

FIGURE 8. Hyperlipoproteinemia. **a,** Glomerulus showing large "thrombi" in capillary lumina. The patient had nephrotic syndrome and elevated serum levels of lipids, including pre-beta-lipoproteins. (Original magnification, ×400.) **b,** Same case as in Figure 8a. The glomerular thrombi appear strongly stained by lipid-soluble dyes. (Formalin fixation, frozen section, oil red O stain. Original magnification, ×400.) **c,** Electron micrograph of glomerular capillaries with large granular lipoprotein "thrombi" occluding the lumina. (Original magnification, ×3,500.)

Figure 5. From Farraggiana 1987.

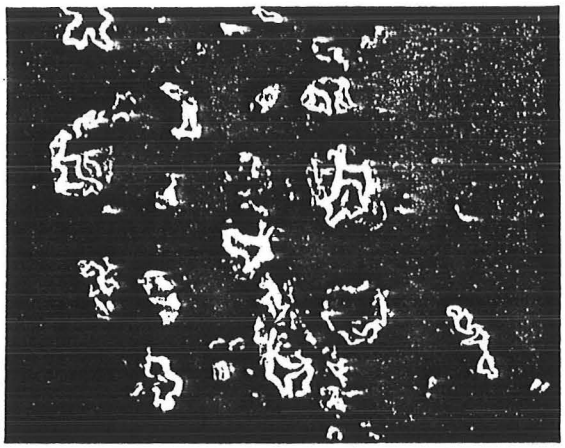

Fig. 7. IF staining with antihuman β-lipoprotein antiserum. Flower leaf pattern staining is shown. × 58.

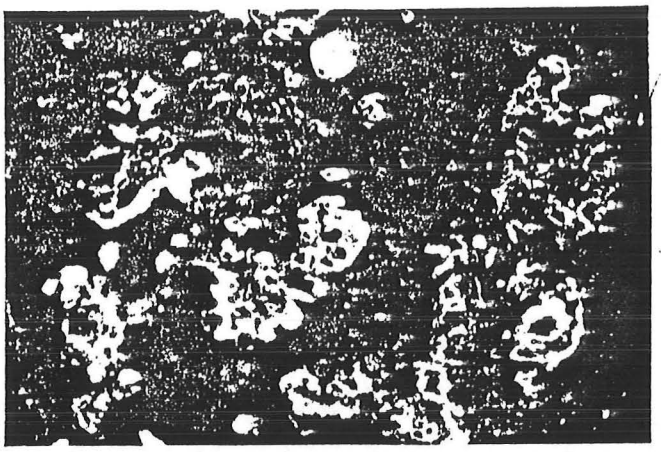

Fig. 8. Indirect immunofluorescence with antihuman apoprotein E. The positive staining is shown around the deposits circumferentially. × 58.

Figures 6 and 7. From Watanabe 1989.

DIETARY INDUCED GLOMERULOSCLEROSIS

Diets enriched in cholesterol have been shown to cause glomerulosclerosis and proteinuria in a number of experimental animals including the guinea pig (Al-Shebeb 1988, French 1967), rabbit (Welmann 1971), and the rat (Gröne 1989).

In the guinea pig the observed glomerular changes include a) increased mesangial matrix, b) increased mesangial and endocapillary cellularity, c) oil red 0 positive droplets predominantly in glomeruli but also focally in tubular and arteriolar walls, d) increased number of nonspecific esterase (NSE, a marker of monocytes) positive intraglomerular cells, and e) focal fusion of foot processes. These glomerular histopathological changes are paralleled by a significant increase in urinary protein excretion.

The effects of a high cholesterol diet on glomerular histopathology and the proteinuria are further accentuated by the combination of a high cholesterol and a high protein diet (Al-Shebeb 1988).

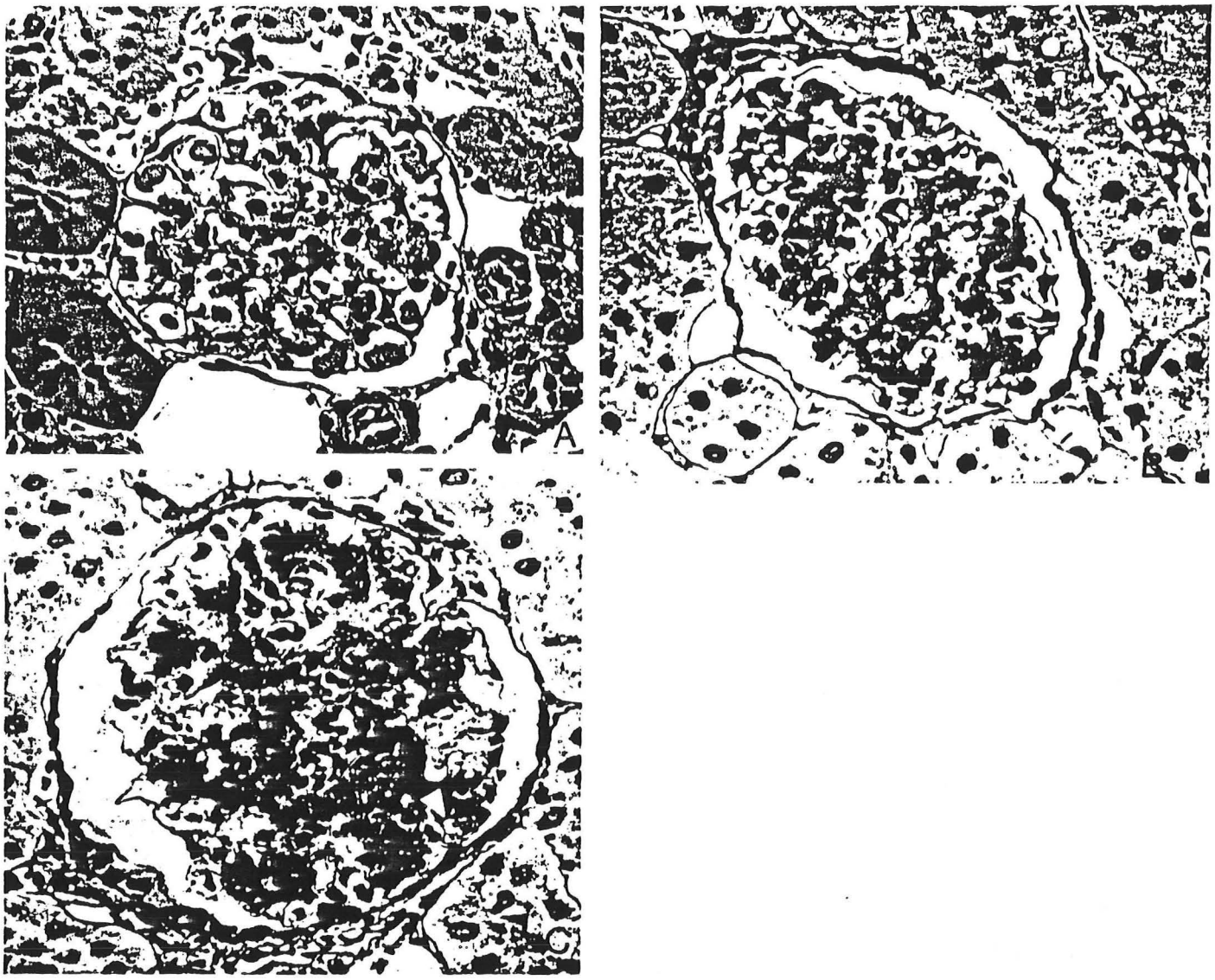

Fig. 1. *Glomerular histology at day 70 of control (C), high cholesterol (HC) and high cholesterol-high protein (HCHP) guinea pigs.* (A) C guinea pig. The glomerulus shows normal cellularity and mesangium (Hematoxylin and Eosin × 400); (B) HC guinea pig. The glomerulus is hypercellular and the mesangium is expanded (grade 2+). Some cells within the tuft contain large, clear cytoplasmic vacuoles (arrowheads). (PASM × 400); (C) HCHP guinea pig. There is considerable mesangial expansion (grade 3+). (PASM × 400).

Figure 8. From Al-Shebeb 1988.

TABLE 5

THE RENAL EFFECTS OF DIETARY CHOLESTEROL AND DIETARY PROTEIN IN THE GUINEA PIG

	C	HC	HP	HCHP
CORTICAL TOTAL CHOLESTEROL (μg/mg protein)	3.0 ± 0.5	5.4 ± 1.9	4.0 ± 1.1	7.0 ± 2.0
U prot V (mg/24 hr)	6.4 ± 2.3	22.1 ± 7.2	13.7 ± 6.3	57.9 ± 10.3
MEAN MESANGIAL SCORE	14.5 ± 8.2	70.1 ± 30.6	20.5 ± 12.5	101.3 ± 18.3
NSE POSITIVE CELLS PER GLOMERULUS	0.2 ± 0.1	1.3 ± 0.8	0.4 ± 0.1	1.9 ± 0.6

C = control diet, HC = high cholesterol diet, HP = high protein diet, HCHP = high cholesterol, high protein diet.

Adapted from Al-Shebeb et al, Kidney International, 1988.

Dietary cholesterol and fat supplementation has also been shown to exarcabate the glomerulosclerosis and proteinuria in rats with unilateral nephrectomy and rats with two-kidney, one-clip (2-K, 1-C) hypertension (Gröne 1989).

TABLE 6

THE RENAL EFFECTS OF A HIGH CHOLESTEROL, HIGH FAT DIET IN THE RAT

	ME	GS	U prot V
2 KIDNEYS			
CON	9.5 ± 1.5	1.8 ± 0.6	14 ± 4
HC/HF	20.6 ± 2.2	13.2 ± 4.1	39 ± 11
UNINEPHRECTOMY			
CON	10.6 ± 2.1	8.7 ± 3.0	46 ± 10
HC/HF	25.1 ± 6.3	38.2 ± 9.5	70 ± 12
2K,1C UNCLIPPED KIDNEY			
CON	19.2 ± 2.0	12.2 ± 2.6	-
HC/HF	32.9 ± 3.1	31.0 ± 4.0	-
2K,1C CLIPPED KIDNEY			
CON	5.2 ± 1.0	0	-
HC/HF	19.4 ± 2.0	0	-

ME = mesangial expansion index, GS = % glomeruli with glomerulosclerosis, U prot V = urinary protein excretion, mg/24 hrs, CON = control diet, HC/HF = high cholesterol, high fat diet, 2K,1C = 2 kidney, 1 clip hypertension model.

Adapted from Gröne et al, Laboratory Investigation, 1989

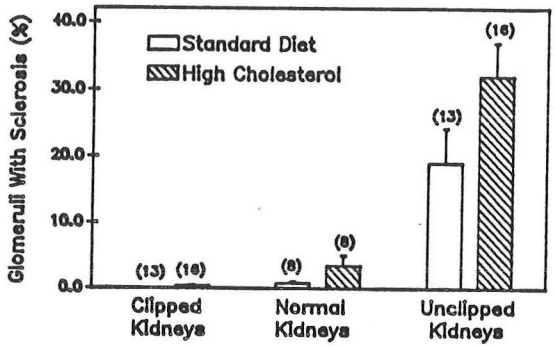

FIGURE 2. *Bar graph showing relation between reduced, normal, or elevated perfusion pressure and glomerulosclerosis in rats fed a standard diet (open bars) or high cholesterol (hatched bars). Clipped kidneys of Goldblatt hypertensive rats with low renal perfusion pressure are compared with kidneys from rats with normal renal perfusion pressure[56] and unclipped kidneys that have glomeruli exposed to systemic hypertension.*

Figure 9. From Kasiske 1990.

In the 2 kidney, 1 clip hypertension model the exarcabation of glomerulosclerosis by dietary cholesterol and fat in the unclipped kidney which is exposed to the systemic and glomerular hypertension, and the protection of the clipped kidney, which is protected from systemic hypertension suggest that glomerular hemodynamic factors play an important pathogenic role in the induction of glomerular sclerosis by a lipid rich diet. In this regard, two recent studies have shown that a high cholesterol diet per se causes an increase in glomerular capillary pressure (P_{GC}) (Kaplan 1990, Kasiske 1990). Thus, dietary cholesterol may induce glomerulosclerosis, at least in part, by causing or exarcabating glomerular hypertension.

Dietary cholesterol supplementation has also been shown to exarcabate chronic puromycin aminonucleoside glomerulosclerosis (Diamond 1987).

TABLE 7

EFFECT OF A HIGH CHOLESTEROL DIET ON CHRONIC PUROMYCIN AMINONUCLEOSIDE NEPHROSIS (PA) IN THE RAT

	PA/SD	PA/HCD
GFR ml/min	1.54 ± 0.12	1.13 ± 0.14
U prot V mg/24 hr	119.7 ± 17.7	449.5 ± 96.7
% GLOMERULI WITH FOAM CELLS	16.6 ± 2.4	62.4 ± 5.9
% GLOMERULI WITH SEGMENTAL MESANGIAL PROLIFERATIVE AREAS	44.2 ± 5.7	59.9 ± 3.4
% GLOMERULI WITH GLOMERULOSCLEROSIS	18.0 ± 3.2	28.9 ± 2.1

PA/SD = standard diet, PA/HCD = high cholesterol diet

Adapted from Diamond et al, Kidney International, 1987.

Glomerular hemodynamic studies in the recovery and chronic phase of puromycin aminonucleoside glomerulonephritis has shown an increase in glomerular capillary pressure, P_{GC}, which indicates the presence of glomerular hypertension which may mediate the eventual glomerulosclerosis (Anderson 1988). Indeed chronic angiotensin converting enzyme inhibition with enalapril has been shown to normalize P_{GC}, the glomerulosclerosis, and the proteinuria, and to ameliorate the tubulointerstitial damage associate with chronic aminonucleoside nephrosis (Anderson 1988, Diamond 1990). The effects of a high cholesterol diet to exarcabate chronic aminonucleoside nephrosis may therefore be mediated, at least in part, by the exarcabation of the glomerular hypertension (Anderson 1989).

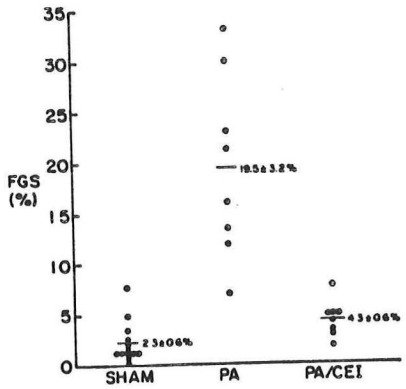

Figure 6. Percentage of glomeruli exhibiting focal and segmental glomerular sclerosis (FGS) in individual rats at 70 wk. Sham rats demonstrated mild degrees of FGS, due to normal aging. Striking FGS was evident in PA rats, whereas values for FGS in PA/CEI rats were comparable to those in sham rats. Values are means±SEM.

Figure 10. From Diamond 1990

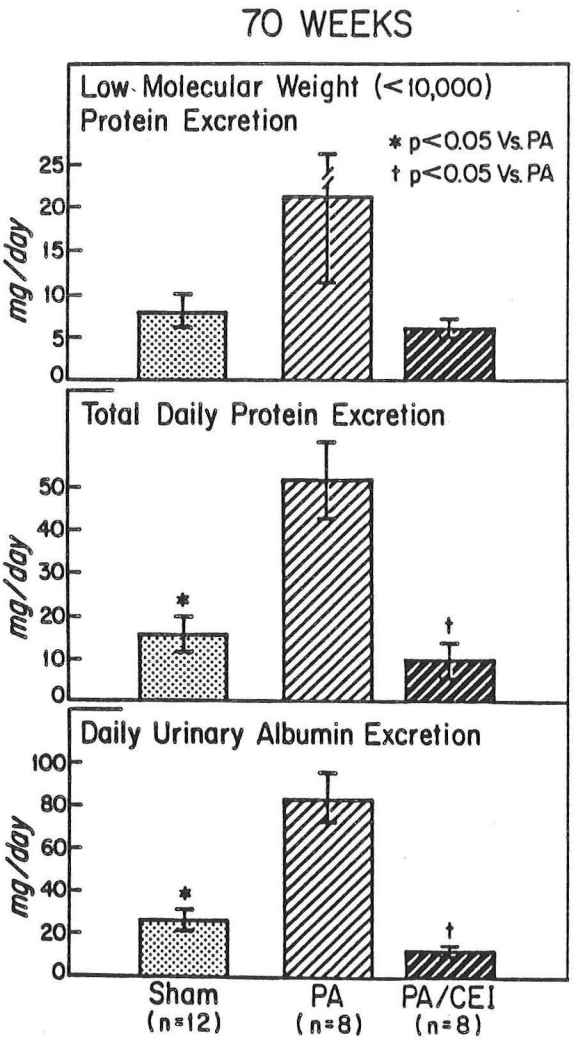

Figure 4. *Patterns of urinary protein excretion 70 weeks after PA administration, at the conclusion of the study. Note that there are still statistically significant differences in daily total protein and urinary albumin excretion in Sham* vs. *PA and PA/CEI* vs. *PA. Although low molecular weight protein excretion was numerically higher in PA rats as compared to PA/CEI and Sham rats, these differences did not reach statistical significance.* * P < 0.05, *sham* vs. *PA;* ‡ P < 0.05, *PA* vs. *PA/CEI. Values are means* ± *SEM.*

Figure 11. From Diamond

Table 1. *Tubulointerstitial Abnormalities in Chronic Aminonucleoside Nephrosis 70 Weeks After PA Administration*

	Intratubular casts	Interstitial fibrosis	Tubular dilatation
PA (n = 8)	2.81 ± 0.13	2.88 ± 0.12	2.38 ± 0.31
PA/CEI (n = 7)	1.43 ± 0.41‡	0.57 ± 0.07†	1.00 ± 0.15†
SHAM (n = 11)	0.73 ± 0.12*	0.82 ± 0.15*	0.77 ± 0.17*

* $P < 0.001$ vs. PA.
† $P < 0.001$ vs. PA.
‡ $P < 0.01$ vs. PA.

Table 8. From Reference

ANALOGOUS PATHOBIOLOGIC MECHANISMS IN GLOMERULOSCLEROSIS AND ATHEROSCLEROSIS

There are several histological similarities between the evolving fatty streak, which is characteristic of atherosclerosis, and glomerulosclerosis (Diamond 1991).

TABLE 9

HISTOLOGIC SIMILARITIES BETWEEN ATHEROSCLEROSIS AND GLOMERULOSCLEROSIS

1. Influx of monocytes following nonimmune injury into vessel wall and glomerulus, respectively
2. Lipid-rich macrophages ("foam" cells)
3. Histochemical presence of cholesterol and cholesteryl ester
4. Proliferating contractile cells, either vascular smooth muscle or glomerular mesangial cells
5. Collagenous and noncollagenous extracellular matrix expansion culminating in fibrosis

Similarly, there are also certain similarities between contractile mesangial cells and the vascular smooth muscle cells (Diamond 1991).

TABLE 10

SIMILARITIES BETWEEN MESANGIAL CELLS AND VASCULAR SMOOTH MUSCLE CELLS

1. Mesodermal origin
2. Histochemical localization of myosin
3. Cytoskeletal components: myosin, actin
4. Express angiotensin II receptors
5. Contractile response to angiotensin II, arginine vasopressin, and norepinephrine

6. Proliferative response to interleukin-1 and other growth factors

7. Inhibition of growth by both anticoagulant and non-anticoagulant heparin compounds

The mesangium has been shown to contain at least two functionally distinct subgroups of cell types. One cell type is smooth muscle-like and is probably derived from the paraglomerular mesoderm. The second cell type is derived from the bone marrow and constitutes approximately 3% to 5% of the total cells in the mesangium and is a macrophage. The macrophage-like mesangial cells have been shown to bear Ia and common leukocyte antigens, which are both indicative of a hematopoietic derivation. It should be noted that in the studies discussed in the preceding section, in dietary cholesterol induced glomerulosclerosis and in chronic aminonuceoside nephrosis, utilizing a mouse monoconal antibody, ED1, which is directed against rat monocyte/macrophage cytoplasmic antigens, the majority of mesangial foam cells have been shown to be macrophages (Diamond 1991).

Recent studies have demonstrated the importance of the monocyte/macrophage in the pathobiology of the atherosclerotic process (Steinberg 1989). Goldstein and Brown in 1979 were the first to describe a modified form of LDL that could be taken up rapidly enough by macrophages to convert them into foam cells (Goldstein 1979). They found that chemical acetylation converted LDL to a form recognized specifically by the monocyte/macrophage and taken up at a rate many times that of native LDL, resulting in a massive cholesterol deposition. This uptake was attributed to a new, specific receptor, designated either the "acetyl LDL receptor" or the "scavenger receptor" which is distinct from the LDL receptor as it does not interact with native LDL.

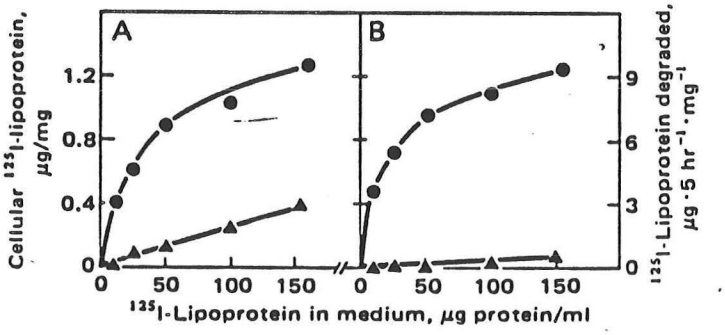

FIG. 1. Accumulation and degradation of ^{125}I-LDL (▲) and ^{125}I-acetyl-LDL (●) by mouse peritoneal macrophages. Each dish received 1 ml of medium B containing the indicated concentration of either ^{125}I-LDL (57,000 cpm/μg of protein) or ^{125}I-acetyl-LDL (50,000 cpm/μg of protein). After incubation for 5 hr at 37°C, the amount of ^{125}I-lipoprotein in the cells (*A*) and the amount of ^{125}I-labeled acid-soluble material in the medium (*B*) were determined in duplicate dishes.

Figure 12. From Goldstein 1979

Table 2. Stimulation of cholesteryl ester formation in mouse peritoneal macrophages incubated with acetyl-LDL

Addition to medium	Incorporation of [^{14}C]oleate into cholesteryl [^{14}C]oleate, nmol/mg protein
None	0.62
LDL, 25 μg/ml	0.83
LDL, 250 μg/ml	0.92
Acetyl-LDL, 25 μg/ml	70.0
Acetyl-LDL, 25 μg/ml + maleyl-albumin, 250 μg/ml	10.6
Acetyl-LDL, 25 μg/ml + fucoidin, 50 μg/ml	2.2

Cell monolayers were prepared by the standard procedure except that 2 ml of medium A containing 5×10^6 peritoneal cells was dispensed into 60 × 15-mm plastic petri dishes. After the adherence step (2 hr, 37°C) and the subsequent washes, each dish received 1.5 ml of medium containing 10% fetal calf serum, 0.1 mM [^{14}C]oleate-albumin (9600 cpm/nmol), and the indicated addition. After incubation at 37°C for 24 hr, the monolayers were washed by the standard procedure (13), the cells were scraped from the dish in 1 ml of phosphate-buffered saline, and the cellular content of cholesteryl [^{14}C]oleate was determined. Each value is the mean of duplicate incubations.

Table II. From Goldstein 1979.

In 1981 Steinberg and coworkers demonstrated that when LDL was incubated with cultured endothelial cells for 12 to 18 hours, it underwent a series of physical and chemical changes, and the modified LDL was then taken up by cultured macrophages more rapidly than native LDL (Henriksen 1981, Henrisken 1983). It has then been shown that smooth-muscle cells, monocytes and macrophages are also able to effect a similar modification of LDL (Cathcart 1985, Henriksen 1983, Hiramatsu 1987, Parthasarathy 1986). It was subsequently shown that modification of LDL by all the 3 cell types involves lipid peroxidation and degradation of LDL phospholipids (Morel 1984, Steinbrecher 1984), and that the modification of LDL by cells is totally inhibited by antioxidants, such as butylated hydroxytoluene, vitamin E, or probucol (Carew 1987).

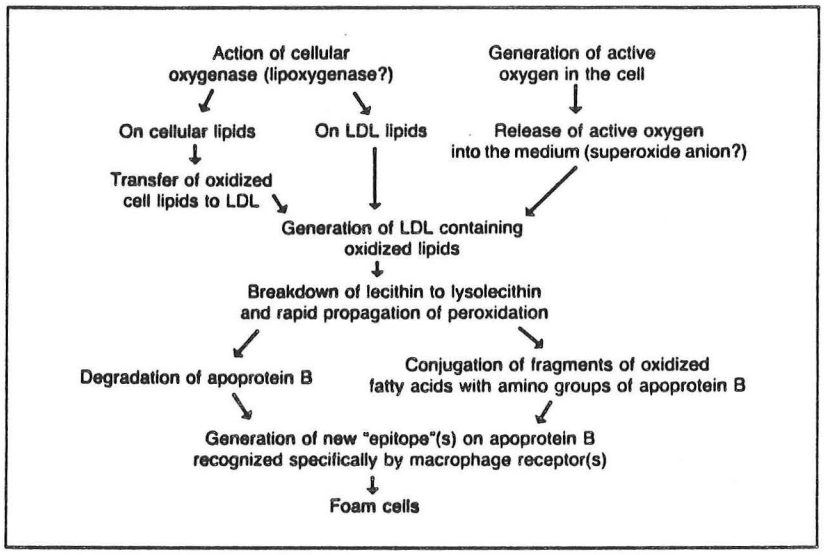

Figure 1. Mechanisms Thought to Lead to the Oxidative Modification of LDL by Cells.

Figure 13. From Steinberg 1989.

Table 1. Properties of Oxidatively Modified LDL, as Compared with Those of Native LDL.*

Increased rate of uptake and degradation through the acetyl LDL or "scavenger" receptor, leading to foam-cell formation
Reduced rate of uptake through the LDL receptor
Increased negative charge
Increased density (to as high as 1.07 or 1.08)
Increased lysolecithin content
Decreased content of polyunsaturated fatty acids because of oxidation
Increased content of oxidized forms of cholesterol
Fragmentation of apoprotein B_{100}; decreased histidine, lysine, and proline content
Chemotactic activity for circulating human monocytes
Cytotoxicity (in the absence of serum)

*Oxidative modification was effected by incubation with endothelial cells at 10 to 100 μg of LDL protein per milliliter in protein-free Ham's F-10 medium for 20 to 24 hours at 37°C. Comparable changes can be obtained by incubating with cultured smooth-muscle cells or mouse peritoneal macrophages, or by incubating for several hours with 5 μM copper ion in the absence of cells.

Table 12. From Steinberg 1989.

Cell-modified or oxidized LDL (Ox-LDL) was shown to be taken up by macrophages, at least in part by the same receptor that recognizes acetylated LDL. More recent studies suggest, however, that a portion of the uptake and degradation of cell-modified LDL also occurs by way of an alternative high-affinity receptor (Sparrow 1989).

Based on the recently discovered properties of Ox-LDL, Steinberg and co-workers have proposed a hypothesis regarding the development of the fatty-streak lesion that is based solely on the presence of elevated plasma LDL levels plus the oxidative modification of LDL within the artery wall. This hypothesis is constructed on four potentially atherogenic effects of oxidized LDL (Steinberg 1989).

TABLE 13

ATHEROGENIC EFFECTS OF OXIDIZED LDL

1. THE RECRUITMENT OF CIRCULATING MONOCYTES BY MEANS OF THE CHEMOTACTIC FACTOR PRESENT IN OXIDIZED LDL, BUT ABSENT IN NATIVE LDL
2. INHIBITION BY OXIDIZED LDL OF THE MOTILITY OF RESIDENT MACROPHAGES AND THEREFORE THEIR ABILITY TO LEAVE THE INTIMA
3. ENHANCED RATE OF UPTAKE OF OXIDIZED LDL BY RESIDENT MACROPHAGES, LEADING TO THE GENERATION OF FOAM CELLS
4. CYTOTOXICITY OF OXIDIZED LDL, LEADING TO LOSS OF ENDOTHELIAL INTEGRITY

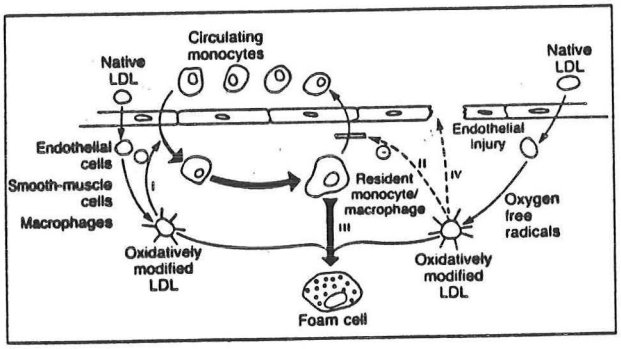

Figure 2. Four Mechanisms by Which the Oxidation of LDL (Catalyzed by Endothelial Cells, Smooth-Muscle Cells, or Macrophages) May Contribute to Atherogenesis.

Mechanisms are the recruitment of circulating monocytes by means of the chemotactic factor present in oxidized LDL, but absent in native LDL (I); inhibition by oxidized LDL of the motility of resident macrophages and therefore of their ability to leave the intima (II); enhanced rate of uptake of oxidized LDL by resident macrophages, leading to the generation of foam cells (III); cytotoxicity of oxidized LDL, leading to loss of endothelial integrity (IV). Reproduced from Quinn et al.[55] with the permission of the publisher.

Figure 14. From Steinberg 1989.

Recent studies indicate that mesangial cells have LDL receptors, and that LDL has a biphasic effect on mesangial cell proliferation; LDL at 10 μg/mL enhances thymidine incorporation, whereas a progressive and marked inhibition of thymidine incorporation occurs at LDL concentrations from 100 to 500 μg/mL (Wasserman 1989, Wheeler 1990). Similar to the macrophages, mesangial cells in culture and glomerular cells in vivo also bind and internalize Ox-LDL much more avidly than native LDL (Coritsidis 1991).

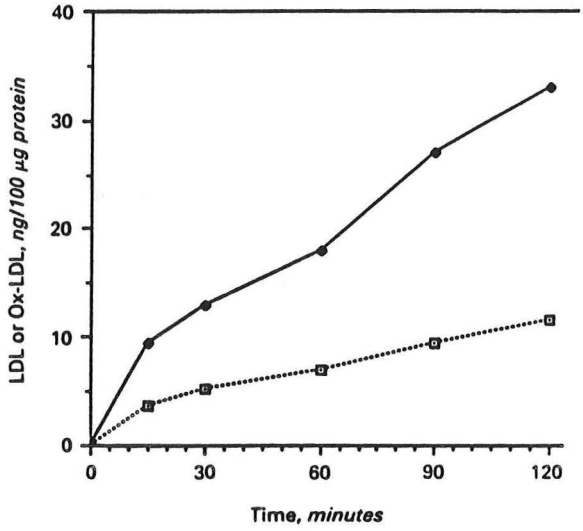

Fig. 4. *Time course of binding and internalization of ^{125}I LDL (--⊡--) and ^{125}I Ox-LDL (◆-) by mesangial cells at 37°C.* Mesangial cells were incubated at 37°C with ^{125}I LDL (1 μg/ml) or ^{125}IOx-LDL (1 μg/ml) for the indicated times and uptake was evaluated as described in Methods. Each value represents the mean of 2 experiments, each carried out in duplicate.

Figure 15. From Coritsidis 1991.

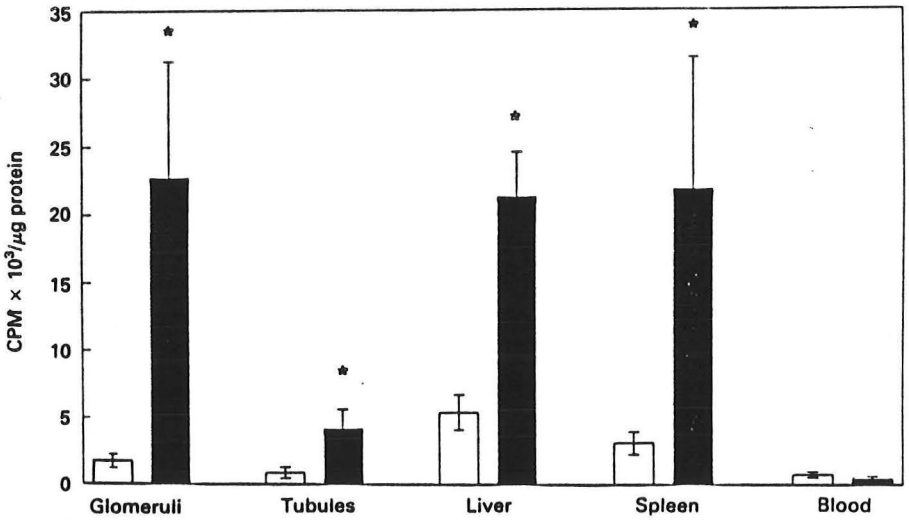

Fig. 9. *Uptake of LDL compared to Ox-LDL in normal rats in vivo.* ^{125}I labeled LDL or Ox-LDL were infused into the aorta above the renal artery for 10 minutes as described in Methods. Organs and glomeruli were then isolated and tissue content of ^{125}I labeled LDL or Ox-LDL was determined and expressed as cpm per microgram of tissue protein. Results represent the means ± SEM of 8 animals for LDL and 6 for Ox-LDL. Asterisks indicate $P < 0.05$ or better comparing content of ^{125}I LDL versus ^{125}I Ox-LDL.

Figure 16. From Coritsidis 1991.

The preferential binding and uptake of Ox-LDL by the mesangial cells results in enhanced cholesterol esterification (as indicated by enhanced incorporation of (^{14}C) oleate into mesangial cell cholesteryl esters), in enhanced synthesis of PGE_2, and in more marked inhibition of mesangial cell thymidine uptake and cell number (Coritsidis 1991).

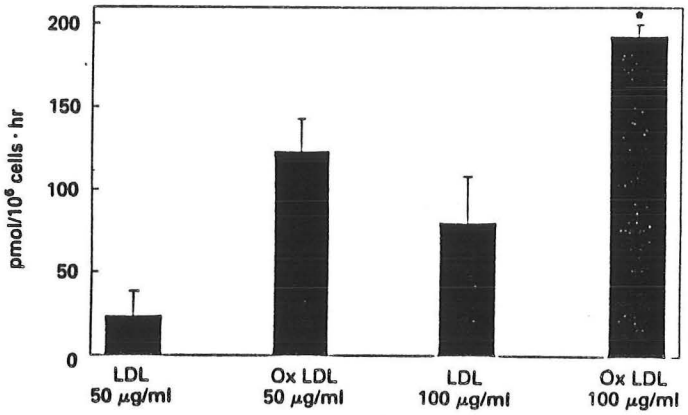

Fig. 5. ***Incorporation of [^{14}C] oleate into mesangial cell cholesteryl esters.*** Mesangial cells were incubated with [^{14}C] oleate plus the indicated concentrations of LDL or Ox-LDL for 2 hours prior to extraction of cellular lipids and their analysis as described in Methods. Values for [^{14}C] oleate incorporation into cellular cholesteryl esters in the absence of lipoproteins were subtracted for each experiment. Results are means ± SEM of 3 series of experiments at 50, μg/ml of lipoproteins and of 2 series at 100 μg/ml and are expressed as pmol oleate incorporated into cholesteryl esters of 10^6 cells per hour.

Figure 17. From Coritsidis 1991.

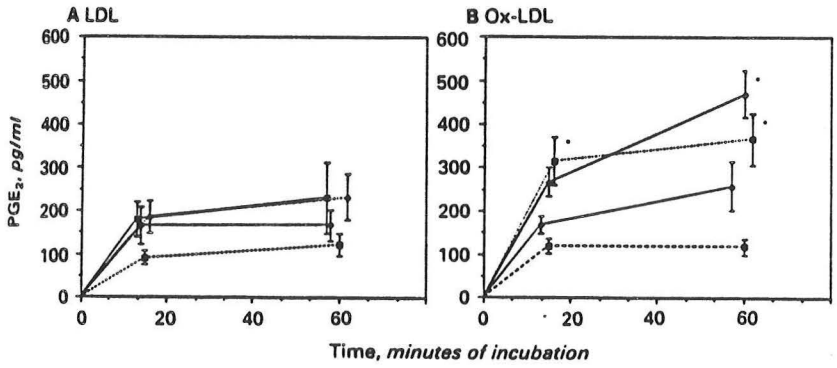

Fig. 8. *Time course for PGE_2 synthesis following MC incubation with variable concentrations of LDL (A) or Ox-LDL (B).* MC in 24 well culture plates were incubated with medium only (⊡, control), medium plus LDL or medium plus Ox-LDL at the concentrations given: (--◆--) 10 μg/ml; (--■--) 20 μg/ml; (—◇—) 50 μg/ml. Aliquots of media were taken at the indicated time points and PGE_2 contents were determined as described in Methods. Results are means ± SEM of four series of experiments. Asterisks indicate $P < 0.05$ or better as compared to the respective control values.

Figure 18. From Coritsidis 1991.

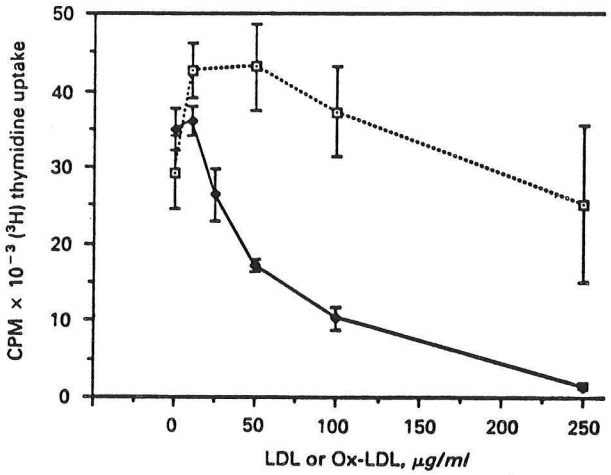

Fig. 6. *Effect of Ox-LDL (-◆-) or LDL (--⊡--) on [³H] thymidine incorporation by mesangial cells.* Thymidine incorporation into mesangial cells was determined in the presence of increasing concentrations of LDL or Ox-LDL during 24 hours of culture. Results represent [³H] thymidine incorporated per well on 96 well plates and are means ± SEM of 8 experiments for Ox-LDL and 7 experiments for LDL, each carried out in triplicate or quadruplicate.

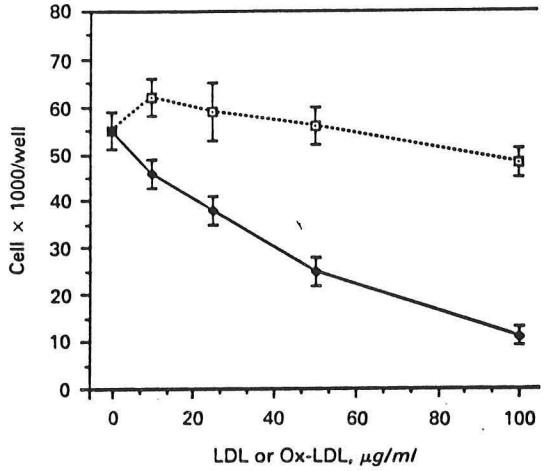

Fig. 7. *Effect of LDL (--⊡--) or Ox-LDL (-◆-) on mesangial cell number as measured by the methylene blue uptake assay.* Methylene blue uptake by viable mesangial cells was determined in the presence of increasing concentrations of LDL or Ox-LDL after a 72 hour incubation. The results are means ± SEM of 4 experiments, each carried out in quadruplicate.

Figure 19 and 20. From Coritsidis 1991.

These findings in renal mesangial cells are in agreement with the previously noted effects of Ox-LDL on endothelial cells and peritoneal macrophages (Yokode 1988), and provide further evidence in support of the analogy between the pathogenesis of atherosderosis and glomerulosclerosis as a complication of hyperlipidemia in renal disease. Due to the fenestrated endothelium of the glomerulus, LDL may have relatively easy access to the mesangium (Mene 1989, Schlondorff 1987). LDL may then be trapped in the mesangial matrix, where it can be exposed to reactive oxygen species, whose production is increased in various experimental glomerular disease (Shah 1989). Oxidation of LDL would then follow, leading to its cytotoxicity and internalization by mesangial cells and macrophages.

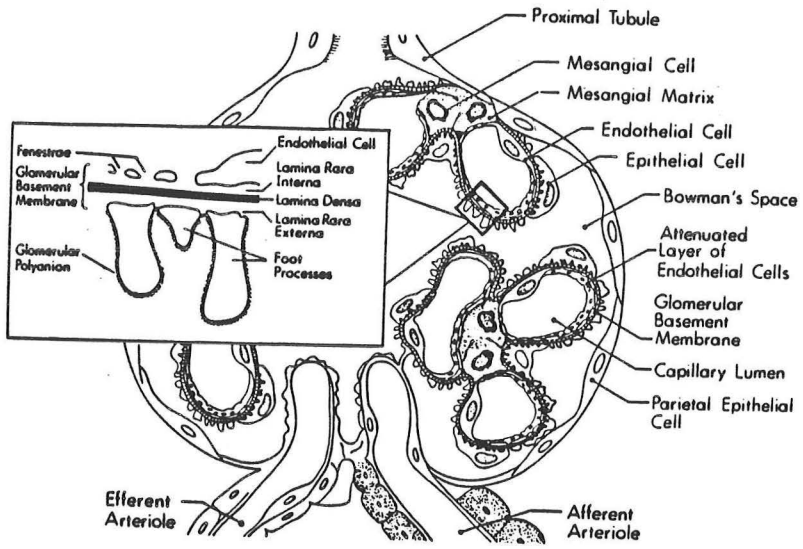

Figure 1. Diagram of the Glomerulus, Illustrating Three of the Glomerular Cell Types (Epithelial, Endothelial, and Mesangial).

The glomerular basement membrane is absent between the mesangium and the capillary lumen. The inset shows in greater detail the components of the glomerular capillary wall. For additional information, see the text.

Figure 21. From Klahr 1989.

Studies in the puromycin aminonucleoside (PA) induced nephrotic syndrome in the rat strongly suggest that macrophages play an important role in the pathogenesis of glomerulosclerosis. During the peak phase of PA nephrosis there were increases in the number of glomerular macrophage number, in peritoneal macrophage thomboxane production. Dietary cholesterol per se also caused similar changes, and the combination PA and dietary cholesterol caused a further increase in these parameters (Diamond 1989).

TABLE 14

Table 1. *Effect of Diet and Nephrotic State on Fasting Serum Lipid Values*

Group	FTC (mg/dl)	FTG (mg/dl)
Normal/standard chow (N = 6)	56 ± 7	41 ± 6
PA/standard chow (N = 6)	266 ± 22*†	466 ± 28*‡
Normal/HICHOL (N = 6)	279 ± 39*	81 ± 5*
PA/HICHOL (N = 6)	1548 ± 227*‡	611 ± 171*‡

* $P < 0.001$ *vs.* Normal/standard chow; † $P < 0.001$ *vs.* PA/HICHOL; ‡ $P < 0.001$ *vs.* normal/HICHOL.

Standard chow, standard rodent laboratory diet; PA, puromycin aminonucleoside; HICHOL, 4% cholesterol/1% cholic acid dietary supplement; FTC, fasting total cholesterol; FTG, fasting triglycerides.

TABLE 15

Table 2. *Urine Protein Excretion and GMϕ Number in Response to Hyperlipidemia*

Group	UVprot (mg/dl)	GMϕ number
Normal/Standard chow (N = 5)	6 ± 2	1.6 ± 0.1
PA/standard chow (N = 14)	153 ± 22*	2.6 ± 0.2†‡
Normal/HICHOL (N = 6)	4 ± 1	3.7 ± 0.6†‡
PA/HICHOL (N = 6)	106 ± 15*	6.8 ± 0.6†

* $P < 0.001$ *vs.* normal/standard chow and normal/HICHOL; † $P < 0.02$ *vs.* normal/standard chow; ‡ $P < 0.01$ *vs.* PA/HICHOL.

GMϕ, glomerular macrophage; UVprot, urine protein excretion; standard chow, standard rodent laboratory diet; PA, puromycin aminonucleoside; HICHOL, 4% cholesterol/1% cholic acid dietary supplement.

TABLE 16

Table 3. *Peritoneal Mϕ Phagocytosis in Response to Hyperlipidemia*

Group	Cells ingesting three or more latex beads (%)
Normal/standard chow (N = 5)	24.8 ± 6.7
PA/Standard chow (N = 5)	59.2 ± 7.0*†
Normal/HICHOL (N = 5)	72.1 ± 1.9*†
PA/HICHOL (N = 5)	88.4 ± 2.4*

* $P < 0.010$ *vs.* normal/standard chow; † $P < 0.010$ *vs.* PA/HICHOL.

Mϕ, macrophage; standard chow, standard rodent laboratory diet; PA, puromycin aminonucleoside; HICHOL, 4% cholesterol/1% cholic acid dietary supplement.

TABLE 17

Table 4. *Peritoneal Mϕ Basal TXB_2 and PGE_2 Produced in Response to Hyperlipidemia*

Group	TXB_2 produced (pmol/mg cellular protein)	PGE_2 produced (pmol/mg cellular protein)
Normal/standard chow (N = 7)	46 ± 15	5.4 ± 1.5
PA/standard chow (N = 5)	71 ± 31*	4.2 ± 0.9
Normal/HICHOL (N = 6)	91 ± 30†	8.6 ± 3.3
PA/HICHOL (N = 5)	199 ± 46‡	7.9 ± 3.2

* $P < 0.02$ *vs.* PA/HICHOL; † $P < 0.05$ *vs.* PA/HICHOL; ‡ $P < 0.02$ *vs.* normal/standard chow.

Mϕ, macrophage; TXB_2, thromboxane B_2; PGE_2, prostaglandin E_2; standard chow, standard rodent laboratory diet; PA, puromycin aminonucleoside; HICHOL, 4% cholesterol/1% cholic acid dietary supplement.

The role of glomerular macrophages in the subsequent glomerulosclerosis in PA nephrosis is further substantiated in studies which has examined the effects of an essential fatty acid defient diet. Essential fatty acid deficiency had previously been shown to deplete rat glomeruli of resident macrophages and to inhibit angiotensin II-induced eicosanoid synthesis (Lefkowith 1987). In the PA nephrosis rats essential fatty acid deficiency resulted in a significant decreases in the number of glomerular macrophages, in urine albumin excretion, and in the percentage of glomeruli exhibiting focal and segmental glomerulosclerosis (FGS) (Diamond 1989).

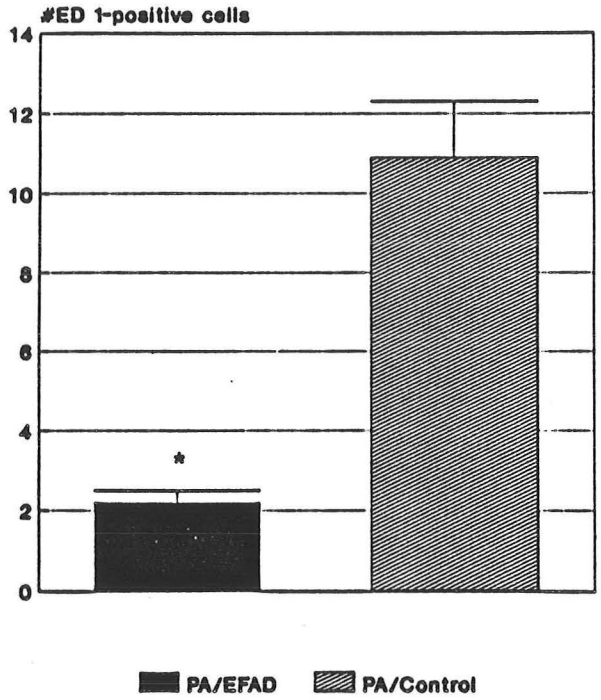

FIG. 1. Glomerular macrophage number as determined by the number of ED 1-positive cells within glomerular mesangium, 2 wk after PA injection. Values are expressed as means ± SE. * Significant difference between PA/EFAD group ($n = 6$) and PA/control animals ($n = 6$) with a P value <0.001. Glomerular macrophage number for age-matched normal rats on EFAD ($n = 4$) and control ($n = 4$) diets was 1.6 ± 0.1 and 2.4 ± 0.1, respectively ($P < 0.01$). There was no significant differences in the glomerular macrophage number in nephrotic and normal age-matched rats on the EFAD diet; however, this value was significantly greater in PA/control rats when compared with their normal dietary controls ($P < 0.01$). See text for definitions of abbreviations.

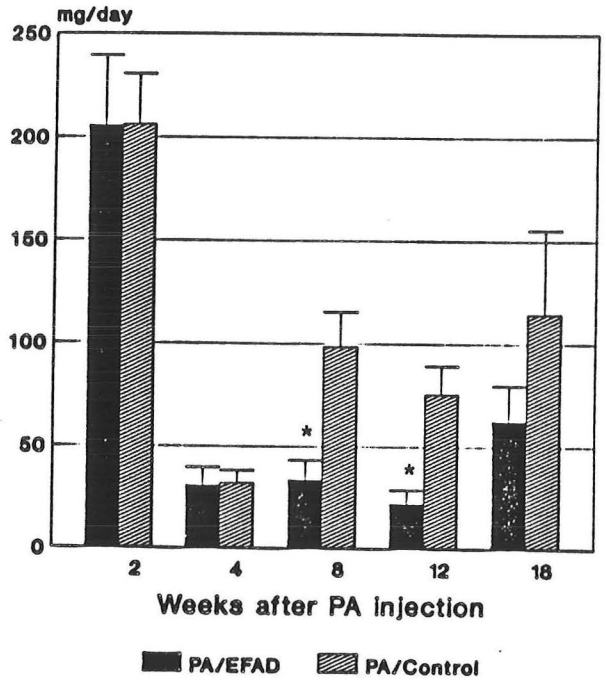

FIG. 2. Urine albumin excretion in PA/EFAD ($n = 15$) and PA/control ($n = 13$) rats followed for 18 wk after PA injection. At 2 wk after PA injection, which constitutes peak albumin excretion, values for urine albumin excretion rate were comparably elevated in PA/EFAD and PA/control rats. At 8 and 12 wk, which corresponds to a phase of recurrent proteinuria without further PA injections, urine albumin excretion was significantly lower in PA/EFAD group. * $P <$ 0.01 vs. PA/control group. Normal age-matched rats on EFAD and control diets during 4 wk after PA injection excreted <3 mg/day of albumin. Thereafter, normal age-matched rats on standard laboratory diet also excreted <3 mg/day of albumin until termination of study. See text for definition of abbreviations.

Figure 21 and 22. From Diamond 1989.

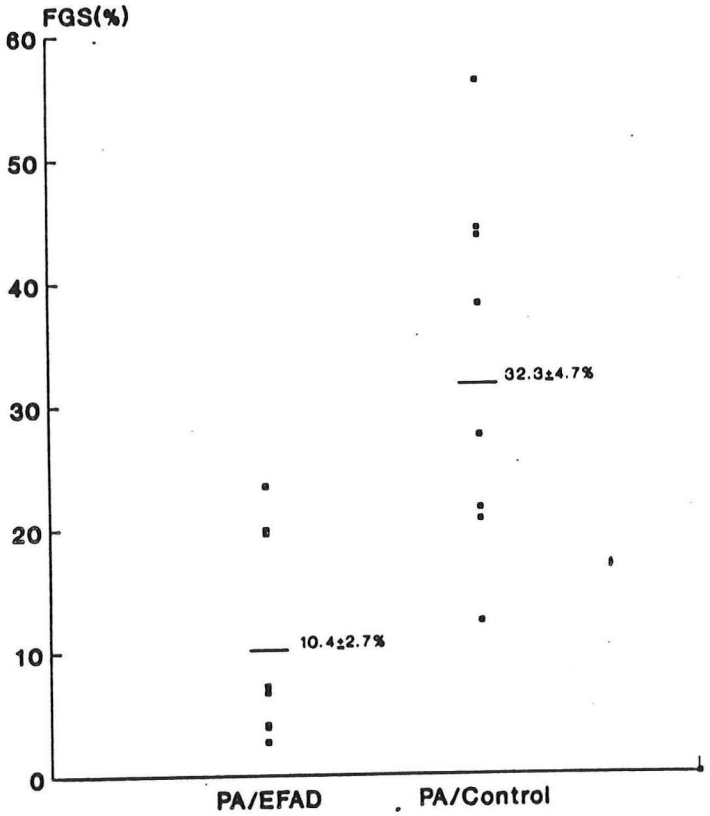

FIG. 4. Percentage of glomeruli exhibiting focal and segmental glomerulosclerosis (FGS) in individual rats in PA/EFAD ($n = 9$) and PA/control ($n = 9$) groups at 18 wk after PA injection. Normal age-matched rats ($n = 4$) demonstrated mild degrees of FGS, due to normal aging, 1.5 ± 0.4%. Striking FGS was evident in PA/control rats, whereas values for FGS were significantly lower ($P < 0.001$). Although numerically greater, the difference between PA/EFAD and normal age-matched rats did not reach statistical significance. Values are means ± SE.

Figure 23. From Diamond 1989.

It is of interest that essential fatty acid deficiency has also been shown to prevent glomerulonephritis and prolong survival in New Zealand Black/White F_1 hybrid mice, which spontaneously develop an autoimmune disease that is similar to systemic lupus erythematosus (Hurd 1981).

More recently, PA rats fed an essential fatty acid deficient diet were shown to have significant reductions in the number of tumor necrosis factor (TNF)-positive glomerular cells and interleukin-1 (1L-1)-positive glomerular cells in contrast to nephrotic control rats. Thus, alterations in macrophage-derived peptide growth factors may play an important role in the eventual glomerulosclerosis in the PA nephrosis model (Diamond 1991).

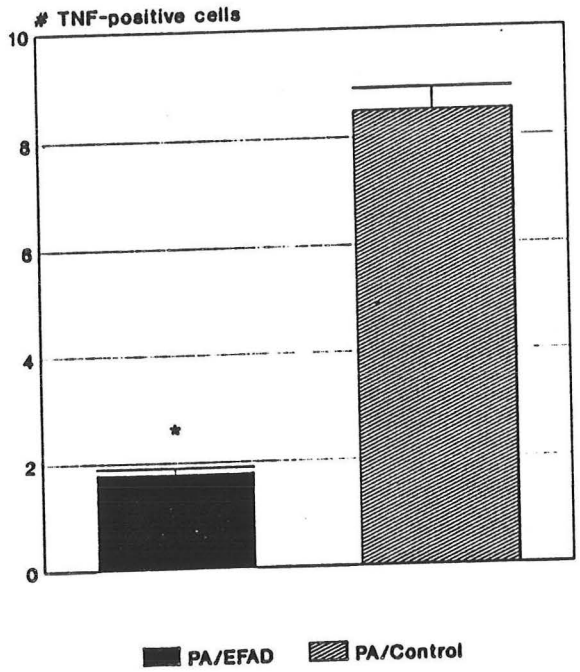

FIG. 1. Number of TNF-positive cells within the mesangium of 100 randomly scored glomeruli using an avidin-biotinylated horseradish peroxidase method with rabbit antimurine TNF as the primary antibody. Values are expressed as mean ± SE. • denotes significant difference between PA/EFAD group ($n = 6$) and PA/control rats ($n = 6$) with $p < .001$.

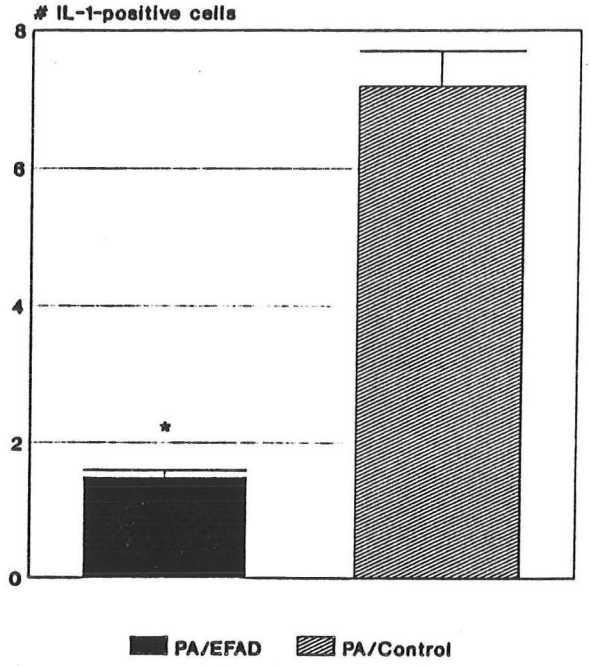

FIG. 2. Number of IL-1-positive cells within the mesangium of 100 randomly scored glomeruli using an avidin-biotinylated horseradish peroxidase method with rabbit antimurine IL-1-α as the primary antibody. Values are expressed as mean ± SE. • denotes significant difference between PA/EFAD group ($n = 6$) and PA/control rats ($n = 6$) with $p < .001$.

Figures 24 and 25. From Diamond 1991.

A further role for macrophages in the pathogenesis of glomerulosclerosis in the PA model is suggested by recent studies which have shown that whole body X-irradiation depletes glomerular and intestitial macrophage number, and prevents the late renal injury as indicated by decreases in urine albumin excretion and percentage of glomeruli exhibiting focal and segmental glomerulosclerosis (FGS) (Diamond 1991, Harris 1990).

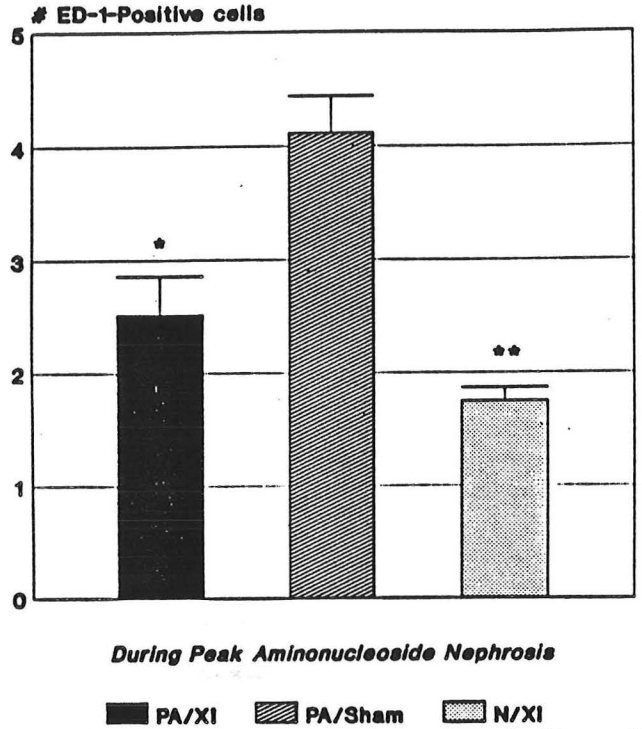

FIG. 1. Glomerular macrophage number as determined by number of ED-1-positive cells within glomerular mesangium, 11 days after puromycin aminonucleoside (PA) injection. Values are means ± SE. * Significant difference between PA/XI and PA/Sham ($n = 6$ rats for each group, $P < 0.010$). **Significant difference between N/XI and PA/Sham ($n = 4$ and 6 rats, respectively, $P < 0.001$). There was no statistically significant difference between PA/XI and N/XI groups. See text for definitions of abbreviations.

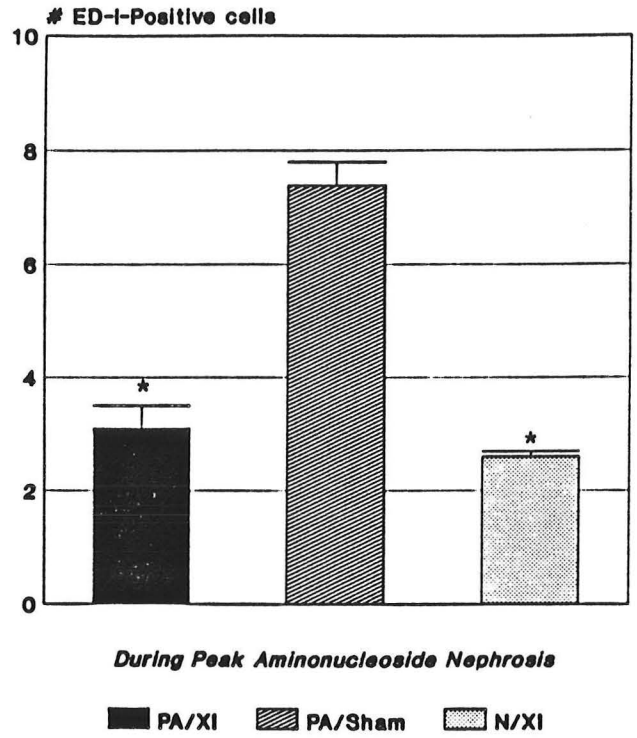

FIG. 3. Interstitial macrophage number as determined by number of ED-1-positive cells within randomly scored cortical tubulointerstitial areas, 11 days after PA injection. Values are means ± SE. *Significant differences between both PA/XI ($n = 6$) and N/XI ($n = 4$) groups as contrasted to PA/Sham ($n = 6$) rats with ($P < 0.001$). See text for definitions of abbreviations.

Figure 26 and 27. From Diamond 1991.

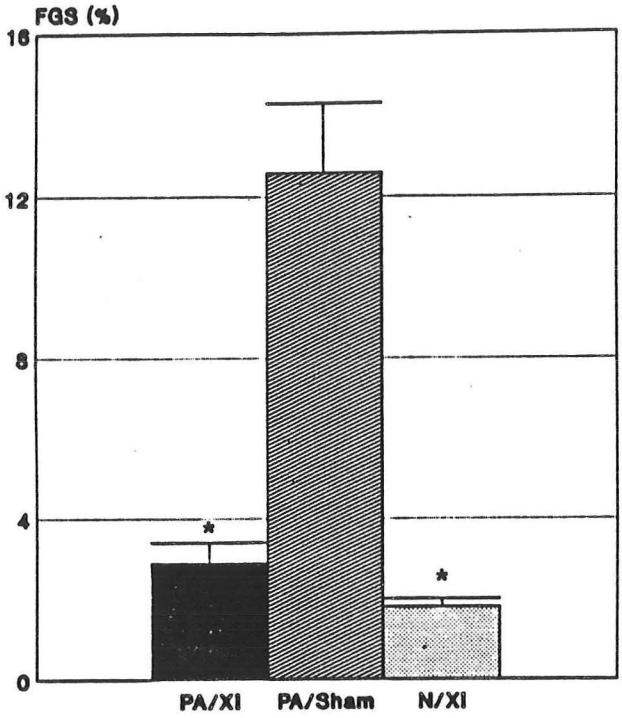

FIG. 5. Percentage of glomeruli exhibiting focal and segmental glomerulosclerosis (%FGS) lesions in PA/XI ($n = 7$), PA/Sham ($n = 7$), and N/XI ($n = 5$) rats at 18 wk after PA injection. N/XI and PA/XI rats demonstrated mild degrees of FGS (1.8 ± 0.2% and 2.9 ± 0.5%, respectively) in contrast to PA/Sham animals, which manifested a significantly higher percentage of glomeruli with FGS lesions (12.6 ± 1.7%). Difference between PA/XI and N/XI rats was insignificant. * Significant difference between PA/Sham and either PA/XI or N/XI groups ($P < 0.001$).

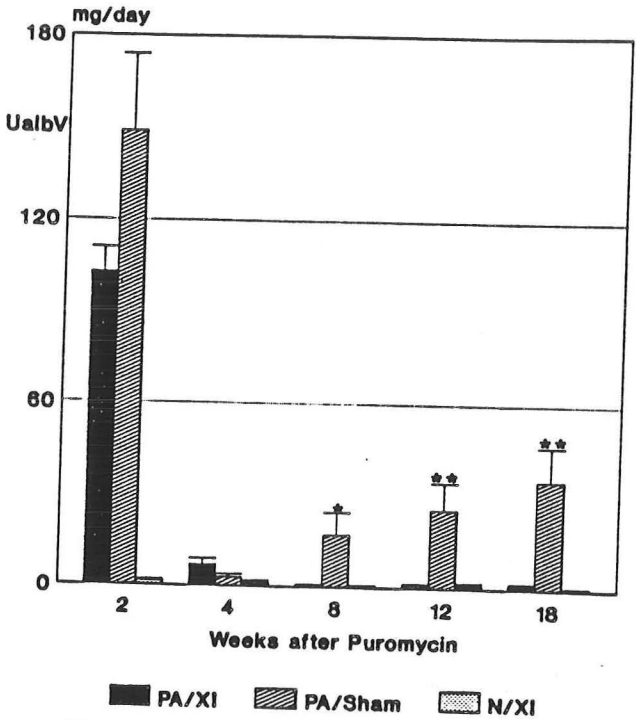

FIG. 4. Urine albumin excretion ($U_{alb}\dot{V}$) in PA/XI ($n = 13$), PA/Sham ($n = 12$), and N/XI ($n = 6$) rats followed for 18 wk after PA injection. At 2 wk after PA injection, which constitutes peak albumin excretion in this model, values for urine albumin excretion were comparably elevated in both PA/XI and PA/Sham groups. Despite a similar magnitude in severity of nephrotic state in these 2 groups, there was no recurrence of albuminuria in PA/XI group, whereas beginning at 8 wk PA/Sham rats exhibited a steadily progressive increase in albuminuria that was significantly greater than normal albumin excretion rates seen in either PA/XI or N/XI groups at 8, 12, and 18 wk after PA. * Significant differences between PA/XI and PA/Sham ($P < 0.05$). ** Significant differences between PA/XI and PA/Sham with ($P < 0.01$). Values in N/XI group were significantly ($P < 0.05$) lower than PA/Sham rats at 8, 12, and 18 wk after PA delivery. See text for definitions of abbreviations.

Figure 28 and 29. From Diamond 1991.

The following slide illustrates the proposed schema for the glomerular macrophage (GM0) propagating initial glomerular injury to glomerulosclerosis (Diamond 1991).

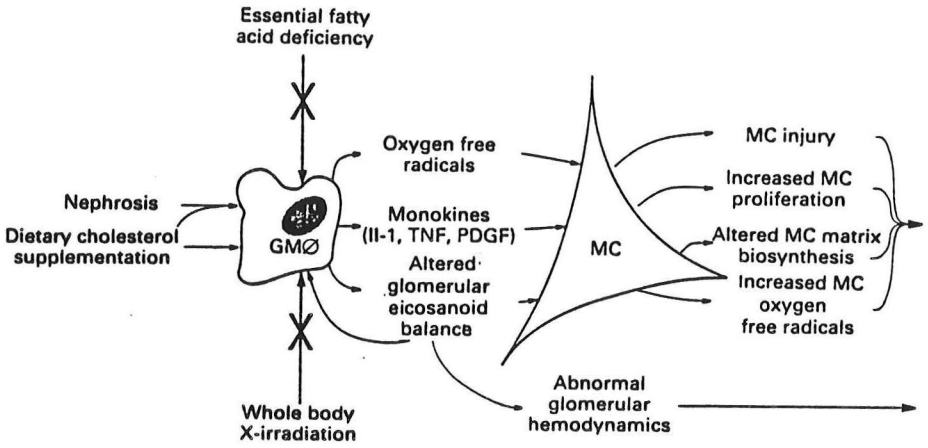

Fig. 3. *Proposed schema for the glomerular macrophage (GMø) propagating initial glomerular injury to glomerulosclerosis (GS).* In this paradigm, both nephrosis and cholesterol feeding are capable of increasing the glomerular macrophage number and perhaps, activity. Either an essential fatty acid deficient state or whole body X-irradiation can significantly reduce this augmentation in the glomerular macrophage number. When the glomerular macrophage number is increased, macrophage-derived substances (e.g., oxygen free radicals, cytokines, eicosanoids) can directly perturb glomerular mesangial cell (MC) function as to effect further MC injury, increased MC proliferation, altered MC matrix production, and augmented MC oxygen free radical generation. The altered glomerular eicosanoid balance produced by the increased glomerular macrophage number accompanying acute nephrosis or produced by cholesterol feeding could also perturb the glomerular microcirculatory determinants of ultrafiltration which may contribute to the progression of initial glomerular injury to GS.

Figure 30. From Diamond 1991.

THE EFFECTS OF MEASURES WHICH LOWER LIPIDS OR ALTER LIPID METABOLISM ON GLOMERULOSCEROSIS

The final evidence that lipids play a role in glomerulosclerosis and the progression of renal disease is provided by several studies, most of them in experimental animals, which have shown that pharmacological measures which lower lipids or alter lipid metabolism result in attenuation in the progression of renal disease.

In rats fed a high cholesterol diet, as discussed earlier, there are significant alterations in renal hemodynamics, including decreases in renal blood flow and glomerular filtration rate, and increases in renovascular resistance and glomerular capillary pressure. Treatment of these rats with PROBUCOL, which prevents oxidation of LDL, normalizes these renal hemodynamic parameters (Kaplan 1990).

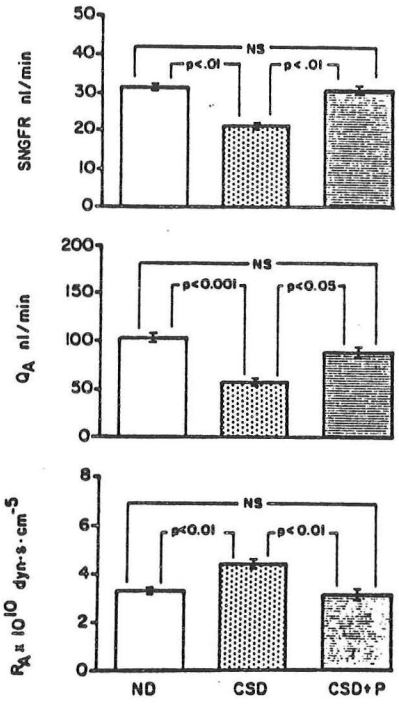

Figure 1. SNGFR, Q_A, and R_A in rats on a normal diet (*ND*), cholesterol-supplemented diet (*CSD*), and CSD plus probucol (*CSD + P*). Data analyzed by ANOVA.

Figure 31. From Kaplan 1990.

These hemodynamic effects of probucol may be mediated, in part, through reduction in glomerular thromboxane generation, as probucol causes a significant decrease in thromboxane concentration in early proximal tubule fluid, and furthermore acute infusion of a thromboxane receptor antagonist SK and F 96148 also causes normalization of the renal blood flow, glomerular filtration rate, and renal vascular resistance (Kaplan 1990).

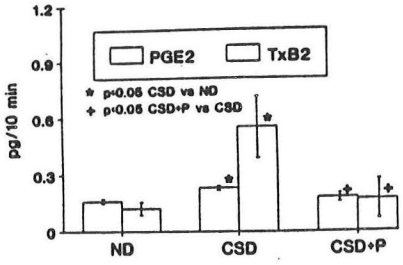

Figure 2. PGE_2 and TXB_2 in fluid collected from early proximal tubule segments. Data expressed as picograms excreted in 10 min.

Table IV. Urinary PGE_2 and TXB_2

Group		PGE_2	TXB_2
		pg/h	*pg/h*
ND	5	859±86	130±19
CSD	6	2,645±275*	481±50*
CSD + P	6	1,596±176‡	131±22‡

* $P < 0.01$ vs. ND; ‡ $P < 0.01$ vs. CSD.

Figure 32. From Kaplan

Table 18. From Kaplan 1990

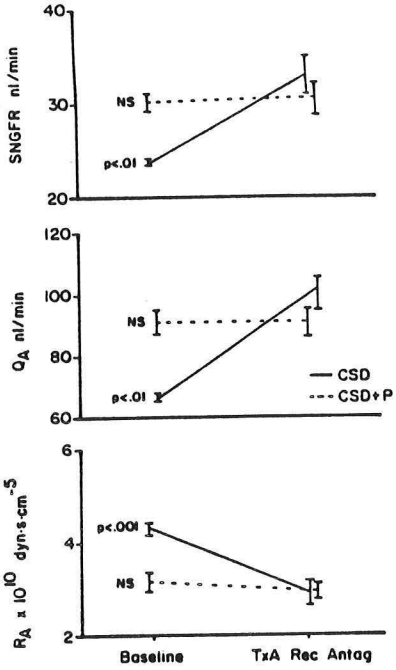

Figure 3. Effect of aortic infusion of TXA_2 receptor antagonist on SNGFR, Q_A, and R_A in CSD and CSD + P rats. *P* values compare data before and during receptor antagonist infusion by paired *t* test.

Figure 33. From Kaplan 1990.

In the puromycin aminonucleoside nephrosis model chronic treatment with CHOLESTYRAMINE resin, a bile-acid-sequestrant antilipidemic agent, results in significant amelioration of the proteinuria and the glomerulosclerosis (Diamond 1990).

TABLE 19

THE EFFECT OF CHOLESTYRAMINE ON PROTEINURIA AND GLOMERULOSCLEROSIS IN AMINONUCLEOSIDE NEPHROSIS

	U prot V	FSGS
PA/RESIN	9.9 ± 1.5	3.1 ± 0.2
PA/CELLULOSE	18.5 ± 2.5	9.6 ± 0.8
CONTROL	2.6 ± 0.4	2.1 ± 0.4

In a similar model of glomerulosclerosis, in uninephrectomized rats injected with puromycin and protamine sulfate, treatment with LOVASTATIN was also shown to ameliorate the development of glomerulosclerosis and uremia (Harris 1990).

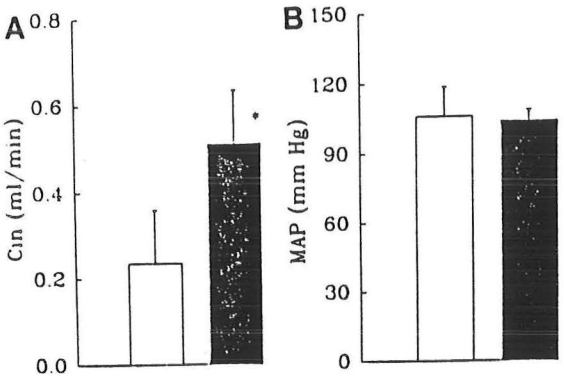

Fig 4. The values for (A) inulin clearance (Cin) and (B) mean arterial BP (MAP) 60 days following the induction of the nephrotic syndrome. □, Gp I (vehicle-treated); ■, Gp II (lovastatin-treated). *$P < 0.05$ compared with vehicle-treated group for inulin clearance. There was no difference in the mean arterial BP between the two groups.

Table 3. Histological Analysis of Kidneys 60 Days After Induction of the Nephrotic Syndrome in Gp I (Vehicle-Treated Rats, n = 9) and Gp II (Lovastatin-Treated Rats, n = 8)

Glomerular Histology Grading*	Percent of Glomeruli Examined	
	Gp I	Gp II
1	8.33 ± 3.33	26.50 ± 5.70†
2	4.44 ± 2.02	15.25 ± 3.52†
3	45.56 ± 8.65	38.75 ± 3.85
4	43.89 ± 10.07	18.25 ± 6.96‡

*1, Normal or the presence of minimal mesangial hypercellularity; 2, the presence of focal areas of sclerosis and loop collapse in the glomerulus with or without mesangial thickening; 3, segmental sclerosis with loop collapse; 4, global sclerosis, hyalinosis, and fibrosis.

†$P < 0.02$ compared with Gp I.

‡$P < 0.05$ compared with Gp I.

Figure 34. From Harris 1990

Table 20. From Harris 1990

In the 5/6 nephrectomy model of chronic renal failure, treatment of the hyperlipidemia (which is characterized by increases in serum cholesterol, 94 ± 7 vs 43 ± 3 mg/d in control, and serum triglycerides, 71 ± 6 vs 52 ± 12 mg/dl in control) with either CLOFIBRIC ACID or MEVINOLIN (LOVASTATIN) results in significant decreases in the albuminuria and the focal glomerulosclerosis (Kasiske 1988).

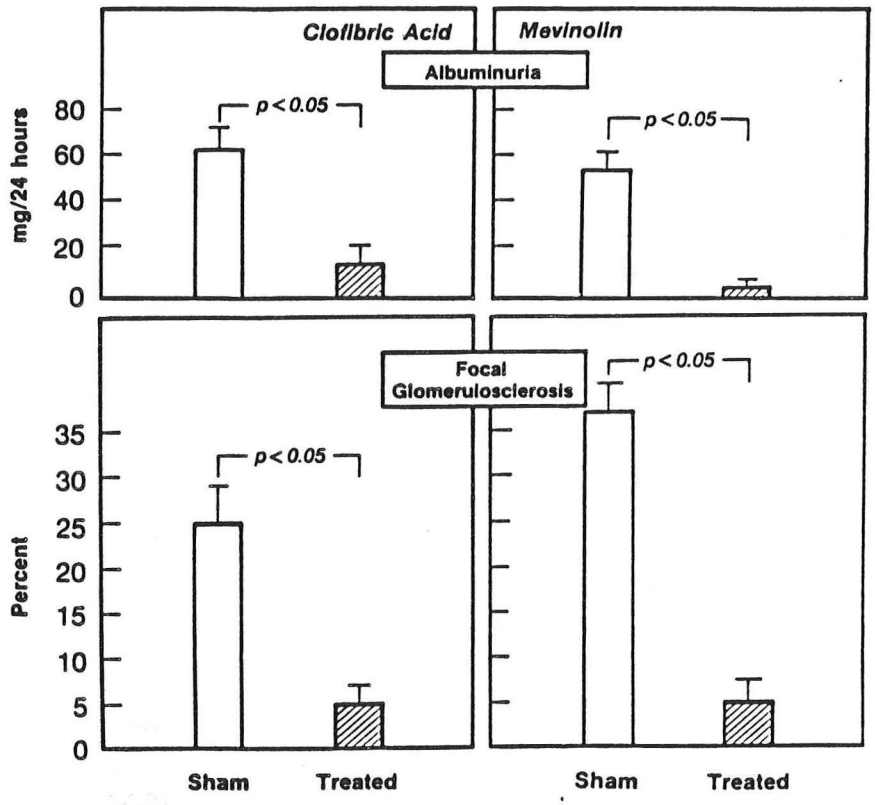

Fig 3. The effect of the lipid-lowering agents, clofibrate, and mevinolin (lovastatin), on albuminuria and focal glomerulosclerosis in rats with 5/6 nephrectomy after approximately 12 weeks of treatment.

Figure 35. From Kasiske 1988.

Similar protective effects of CLOFIBRIC ACID and MEVINOLIN has also been noted in the obese Zucker fatty rat. Of interest, these rats have many of the characteristic features of noninsulin-dependent diabetes mellitus, such as insulin resistance in muscle and adipose tissue, mild glucose intolerance, pancreatic ß-cell hypertrophy, obesity, and hyperlipidemia characterized by increases in both serum cholesterol and serum triglycerides (Kasiske 1988).

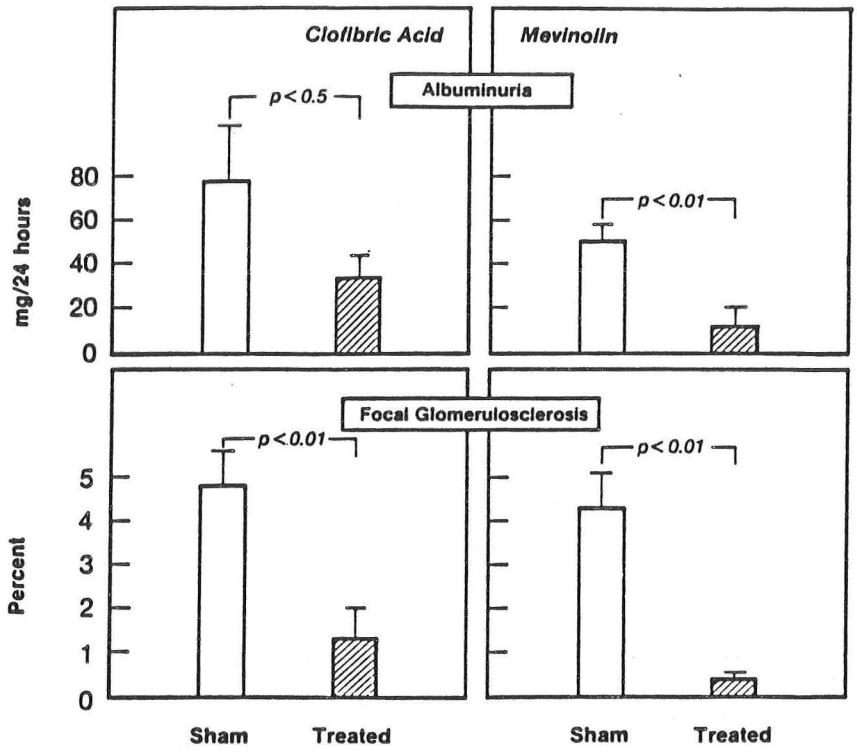

Fig 2. The effect of the lipid-lowering agents, clofibrate and mevinolin (lovastatin), on albuminuria and focal glomerulosclerosis in obese Zucker rats treated for approximately 6 months.

Figure 36. From Kasiske 1988.

In patients with primary (Familial Homozygous Hypercholesterolemia) and secondary (Nephrotic syndrome) hypercholesterolemia who either do not respond or only partially respond to customary measures which lower cholesterol, including diet, exercise, and hypolipidemic drug therapy, plasma LDL cholesterol has been successfully lowered by LDL apheresis (Homma 1986, Lupien 1976, Parker 1986, Pokrovsky 1987, Saal 1986, Stoffel 1981).

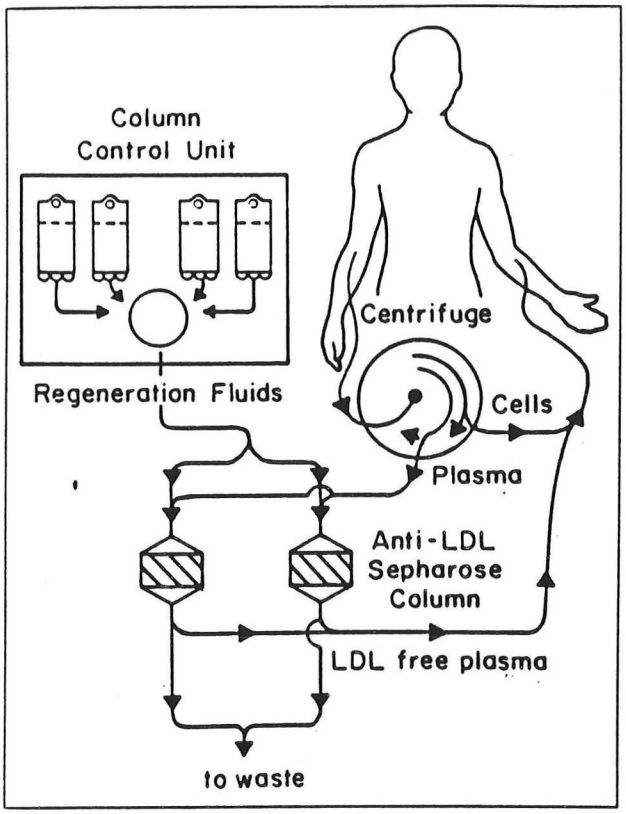

Figure 1. Schematic of the immunoadsorption and regeneration systems for LDL-pheresis. The cell-free stream exiting the centrifuge is directed through one of two columns containing sheep anti-LDL IgG immobilized on Sepharose CL-4B. The LDL-free plasma stream exiting the column is mixed with the cell-rich stream from the cell-separating centrifuge and pumped back to the patient through the return line. The column control unit isolates the column saturated with LDL so that it can be regenerated, while allowing LDL-rich plasma to flow through the other column. (Reproduced with permission from Saal *et al* [43].)

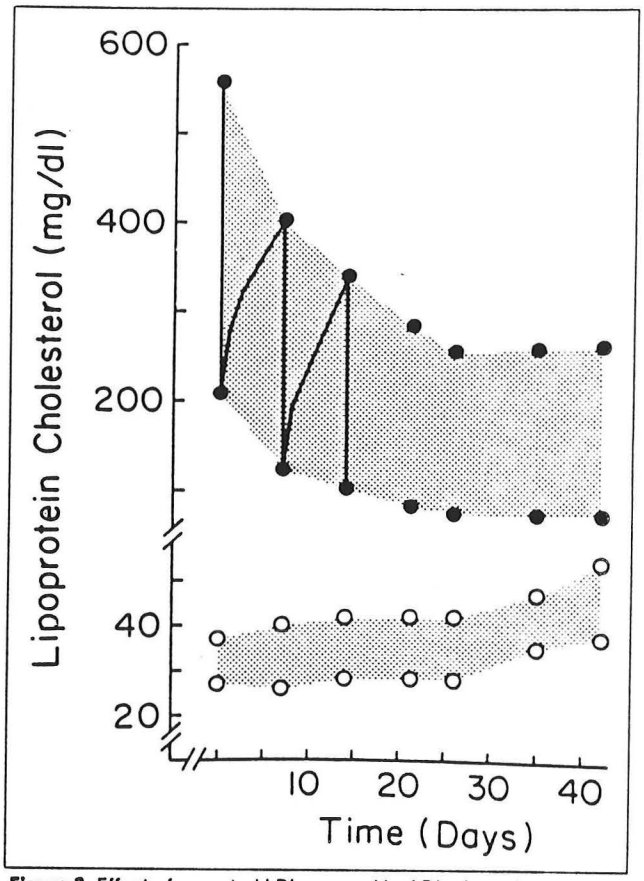

Figure 3. Effect of repeated LDL removal by LDL-pheresis on plasma LDL and HDL concentrations in a patient with homozygous familial hyercholesterolemia. The pre- and post-treatment LDL (•) and HDL (O) concentrations are shown for a series of seven treatments carried out at intervals of seven, seven, seven, five, nine, and seven days. (Reproduced from Parker *et al* [10].)

Figure 37. From Saal 1989

Figure 38. From Saal

Recently the technique of LDL apheresis in conjunction with double filtration plasmapheresis has been applied to 5 patients with drug-resistant nephrotic syndrome secondary to focal glomerular sclerosis, who had marked elevations in serum cholesterol and triglycerides. LDL apheresis was performed by using the specific sorbent of apoprotein B- containing lipoprotein, Liposorber LA40. Polyanionic dextran sulfate was used as the ligand, which has a homologous sequence to human LDL receptor. Following 6 to 8 treatments in each patient, in addition to the lowering of the plasma lipids, incomplete remission of proteinuria was also achieved in 4 of the 5 patients, which lasted for at least 1 year (Tojo 1990). Although the long-term efficacy of this procedure remains to be established, this preliminary study provides further support to the thesis that alterations in lipoprotein metabolism in the nephrotic syndrome play an important role in the process of the propagation of glomerulosclerosis and proteinuria.

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