Subcapsular Steatonecrosis in Response to Peritoneal Insulin Delivery: A Clue to the Pathogenesis of Steatonecrosis in Obesity

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Hepatic steatosis and steatonecrosis occur in nonalcoholic individuals, usually in a setting of obesity, type II diabetes mellitus, and after jejunoileal bypass. We propose an hypothesis for the pathogenesis of these hepatic lesions based on an observation in peritoneal dialysis patients.

Hepatic histology was examined at autopsy in 11 patients with type I diabetes mellitus and renal failure who had received i.p. insulin in conjunction with continuous ambulatory peritoneal dialysis (CAPD). Steatosis in a unique subcapsular distribution occurred in 10 of 11 patients treated with i.p. insulin and in 0 of 9 controls receiving CAPD without insulin. Three of the 11 had steatonecrosis, 2 of whom had Mallory bodies.

We suggest that insulin has an important role in the pathogenesis of steatosis and steatonecrosis. In CAPD patients the lesions occurred only under the capsule where concentrations of insulin are high secondary to its i.p. administration. In obese patients the lesions occur throughout the liver where insulin concentrations are high because of elevated levels in the portal vein. Free fatty acids (FFA) are oxidized in the liver by a pathway that is blocked by insulin. In the presence of insulin, FFA are preferentially esterified into triglycerides which accumulate in large quantities leading to steatosis; small amounts of FFA escaping local control may lead to membrane injury and steatonecrosis. Steatosis and/or steatonecrosis will occur when there is insulin secretion sufficient to block FFA oxidation but not sufficient to block FFA mobilization from adipose tissue. This situation occurs in obesity associated with type II diabetes where adipose tissues are resistant to insulin, and in obesity after jejunoileal bypass where continued eating and insulin secretion occur in the face of marked weight loss.

Key words: Obesity, Liver, Steatonecrosis of liver, Mallory bodies, Insulin, Peritoneal dialysis, Jejunoileal bypass.

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Steatosis and steatonecrosis occur in nonalcoholic individuals, usually in a setting of obesity, type II diabetes mellitus, and especially after jejunoileal bypass surgery (1, 13, 18, 20, 23, 26, 30). The pathogenesis of these hepatic lesions is unknown (2, 8, 32).

We have observed steatosis or steatonecrosis in patients having type I diabetes mellitus with end-stage renal disease treated by continuous ambulatory peritoneal dialysis. These tissue reactions were seen only in those patients receiving insulin in the peritoneal dialysis fluid and were confined to the subcapsular region of the liver, *i.e.*, that part of the liver in close contact with the dialysis fluid.

These observations lead us to propose a mechanism for the diffuse steatonecrosis occurring in obesity and type II diabetes mellitus. This theory explains the exacerbation of liver disease occurring in postjejunoileal bypass patients and may explain, in part, the mechanism of steatosis occurring in kwashiorkor. It also helps to define the mechanism of Mallory body formation.

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MATERIALS AND METHODS

Twenty consecutive autopsied patients who had received continuous ambulatory peritoneal dialysis (CAPD) at Toronto Western Hospital for at least 3 mo and continuing into the last month of life were studied. The patients were autopsied between 1978 and 1988. The hospital and outpatient clinical records were reviewed for the following parameters: diabetes; alcohol abuse; peritonitis; insulin dose and route of delivery; steroid therapy; height; triglyceride and cholesterol concentrations; and, for the last week of life, fasting serum glucose, liver tests, insulin and glucose concentrations in dialysis solutions; and ideal (dry) body weight. On the CAPD protocol, 1.5 or 2 liters of 1.5 to 4.25% glucose (Dianeal; Baxter) were infused into the peritoneal cavity, held for 6 h, drained, and replaced (4 cycles per 24 h). Insulin-dependent diabetics received insulin that was added to the bag prior to infusion.

Autopsy liver slides were examined for the presence of large droplet fatty change (steatosis), necrosis, Mallory bodies, inflammation, and fibrosis. Subcapsular steatosis (SCS) was graded 1 to 3+ according to the number of hepatocytes containing fat. The thickness of the SCS was measured from the deep margin of

the capsule to the deepest clusters of fatty hepatocytes using an eyepiece graticule. The degree of obesity was estimated as the percentage above optimal body weight as calculated according to Hamwi (17).

RESULTS

Twelve of the 20 patients had insulin-dependent diabetes mellitus (all but one were type I). Eleven of the 12 diabetics received most or all of their insulin requirement in the peritoneal cavity. All but one of these 11 had SCS (Table 1). Patients not receiving i.p. insulin did not have SCS, despite receiving similar concentrations of glucose in the peritoneal fluid. Although the severity of SCS could not be accurately predicted by any single parameter examined, there was a tendency to more severe SCS in those patients with longer duration of CAPD, higher insulin dose, greater obesity, and higher serum triglycerides. The SCS was present in 4 patients who had discontinued both CAPD and i.p. insulin therapy 6 to 14 days before death. The SCS was very mild in 3 of these 4 patients. None of those with SCS was believed to abuse alcohol.

The SCS was noted on visual inspection of the liver in the 5 cases with Grade 2 or 3 SCS (Fig. 1). Histologically, SCS consisted of a discontinuous subcapsular rim from 0.05 to 12 mm in thickness involving 5 to 80% of the surface area (Fig. 2). The mildest lesions were composed of a layer of fatty hepatocytes as little as 4 cells thick. The deep

Table 1. Patients Receiving Continuous Ambulatory Peritoneal Dialysis

Case	Age, gender	Diabetes mellitus	i.p. insulin (units/liter)	Subcapsular steatosis (grade)	Days off CAPD terminally	mo on CAPD	Hypertonic dialysate (% of bags)	Fasting blood sugar (mmol/liter)	Triglycerides (mmol/liter) ($n < 1.8$)	Cholesterol (mmol/liter) ($n < 6.2$)	Overweight (%)	Peritonitis[a]	Steroids[b]
1	73 M	−	0	Absent	5	39	0	5.6	3.0	4.7	−11	MT	
2	59 F	−	0	Absent	0	55	0	4.8	2.8	3.8	1	5T	
3	66 M	−	0	Absent	0	27	60	5.6	1.5	5.1	0	2	
4	60 M	−	0	Absent	0	49	99	6.6	3.7	6.1	50	0	
5	74 M	−	0	Absent	0	10	29	10.0	4.5	5.6	−6	0	
6	57 M	−	0	Absent	0	15	29	3.3	2.3	3.6	40	3	
7	79 M	−	0	Absent	0	7	50	5.7	1.7	6.0	−33	0	
8	64 M	−	0	Absent	0	30	0	5.3	1.7	8.0	−19	0	
9	67 M	+	0	Absent	16	15	0	5.2	3.7	3.1	0	3T	
10	32 M	+	7	Absent	0	3	36	34.9	1.2	7.9	−25	1	
11	28 M	+	4	1	7	4	20	10.4	1.1	1.8	−29	1T	Low dose CS
12	65 M	+	5	1	0	18	50	12.8	0.6	4.7	0	2T	
13	36 M	+	6	1	0	30	33	14.9	2.5	6.7	−30	2	
14	26 F	+	8	1	14	18	80	16.0	2.9	1.6	12	2T	
15	51 M	+	38	1	7	25	0				35	MT	High dose CS
16	42 M	+	8	2	6	25	73	22.2	3.7	5.2	29	0	High dose CS
17	44 M	+	10	2	0	52	44	21.8	1.5	6.4	1	1T	Testosterone
18	73 M	+	63	2[c]	0	67	33	10.4	6.2	4.4	18	2	
19	46 M	+	7	3	0	14	27	14.4	4.8	8.0	6	0	
20	73 F	+	25	3	0	7	25	8.7	3.5	7.6	33	1T	

[a] Number of episodes; M, multiple; T, terminal episode.
[b] CS, corticosteroids, prednisone and/or solumedrol, in the last month of life.
[c] Steatonecrosis with Mallory bodies was present in the subcapsular liver tissue.

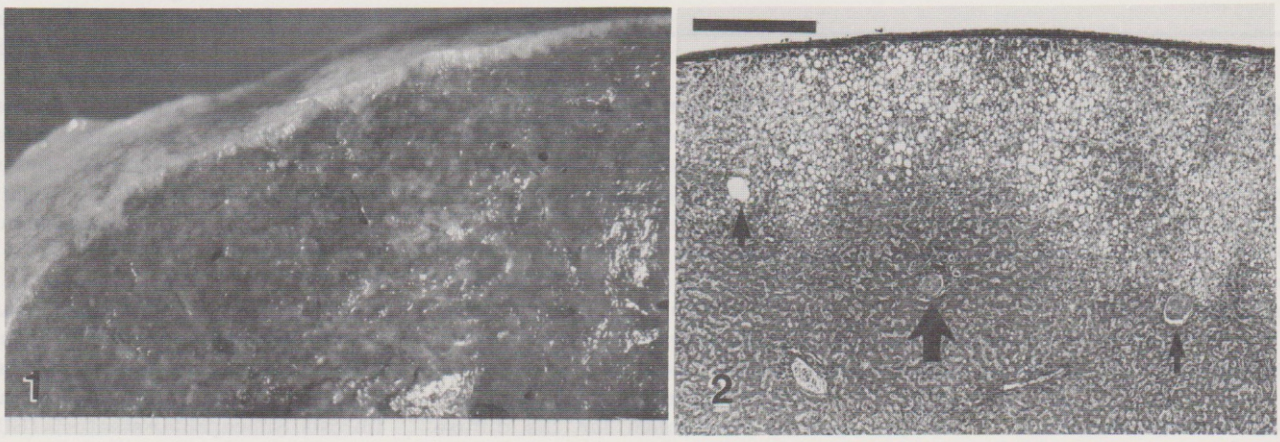

Figure 1. Cut surface of liver (Case 17) showing 1-mm-thick pale region beneath the capsule (metric scale).
Figure 2. Photomicrograph of liver (Case 18) showing the scalloped deep margin of the fatty change. The appearance suggests that the causative factor(s) was rendered inactive by dilution with blood flowing from portal triads. Portal triad (*large arrow*), terminal hepatic venules (*small arrows*). Masson's trichrome; *bar*, 5 mm.

margin of the SCS was usually scalloped with a definite topographical relation to the microvasculature (Fig. 2). Steatosis was also seen deep in the liver tissue in the patient with type II diabetes (Case 20) and in 4 of 8 nondiabetics. In Case 20 the steatosis in deep tissue involved approximately 20% of hepatocytes compared to 100% in the subcapsular region.

Three patients with SCS also had ballooning necrosis of subcapsular hepatocytes. In one of these patients, Case 18, several dozen Mallory bodies were found and in another patient, Case 14, a single Mallory body was found (Fig. 3). There were neutrophilic inflammation and fibrosis only in Case 18. This patient had normal serum bilirubin and aspartate aminotransferase, but the serum alkaline phosphatase was 223 units/liter (n<100) in the last week of life; serum triglycerides had been 18.8 and 13.7 mmol/liter (normal, <1.8) 4 and 3 yr antemortem and 6.2 mmol/liter 1 mo antemortem.

DISCUSSION

This study demonstrates that chronic i.p. insulin therapy is associated with the presence of steatosis, with or without necrosis, in subcapsular liver tissue. The importance of this phenomenon is that these lesions are qualitatively identical to lesions found more diffusely in the liver of obese and alcoholic individuals. In our patients the subcapsular hepatocytes are exposed to high concentrations of insulin and glucose in the dialysate bathing the liver surface. It follows that high insulin, and possibly glucose, concentrations may also be important in the pathogenesis of hepatic steatosis and steatonecrosis generally. We cannot exclude a role for the type I diabetic state itself in the production of this lesion, but this is unlikely since hepatic steatosis is rare in type I diabetes (34).

The expected concentrations of glucose and insulin in CAPD patients with type I diabetes are shown in Table 2. Insulin has been shown to diffuse through the hepatic capsule (38). The high concentrations of insulin and glucose would be expected to decrease rapidly approximately 1 mm into the liver tissue where blood from terminal portal triads is available to dilute these substances and prevent their diffusion into deeper tissue. In all but two cases the SCS was confined to the tissue less than one acinus diameter from the surface. One of the exceptions was a patient (No. 20) with type II diabetes who presumably had considerable insulin levels in the portal vein.

There is evidence in the literature that insulin is important in the pathogenesis of hepatic steatosis. Steatosis is frequent in obesity and in

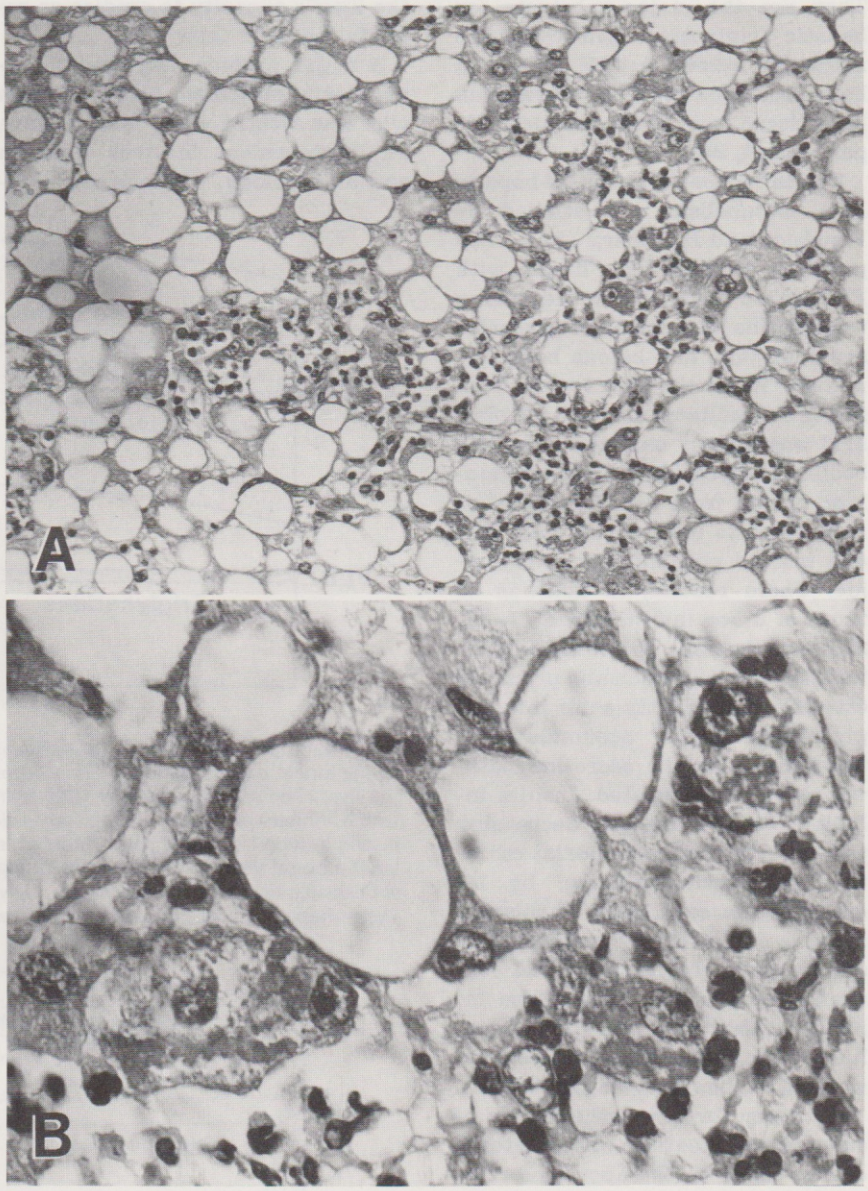

Figure 3. Photomicrographs of liver (Case 18). *a*, marked steatosis and neutrophilic inflammation. Hematoxylin-phloxine-saffron, × 310. *b*, three hepatocytes containing Mallory bodies. There is prominent inflammation and steatosis. HPS, × 1040.

Table 2. Approximate Insulin and Glucose Concentrations and Gradients during Peritoneal Dialysis in Patients with Diabetes Mellitus Type II

	Glucose (mg/dl)	Insulin (μU/ml)
Peritoneal fluid	1,500–4,500	4,000–63,000
Plasma	150	10
Gradient	10–30 fold	400–6,300 fold

type II diabetes where peripheral and portal vein insulin levels are high (3, 9, 22, 28, 31–33), but not in type I diabetes (34) where insulin blood levels are low.

In addition to insulin, free fatty acids (FFA) may have a role in hepatic steatosis and steatonecrosis. They are the major substrate for hepatic triglyceride synthesis, are markedly cytotoxic (15, 35), and have been reported to be elevated in liver tissue from obese and alcoholic patients (4, 24).

The influence of insulin on hepatic FFA metabolism was studied by Woodside and Heimberg (37). They perfused isolated rat livers with FFA (oleic acid), while measuring triglyceride secretion, triglyceride accumulation, and ketone body formation. When the livers were from fasted or insulinopenic rats, the oleic acid was largely oxidized to ketone bodies; triglyceride did not accumulate. Livers from fed (high-insulin) rats failed to oxidize the oleic acid and instead accumulated triglyceride. These results, in addition to those of other investigators (7, 19, 22), demonstrate that insulin inhibits fatty acid oxidation and promotes esterification of fatty acids into triglycerides which accumulate in hepatocytes as the secretion pathway becomes saturated. Insulin inhibits FFA oxidation by decreasing the activity of mitochondrial carnitine palmitoyltransferase, by increasing the sensitivity of this enzyme to inhibition by malonyl-CoA, and by increasing malonyl-CoA concentration (7, 25). Insulin also inhibits synthesis and secretion of apolipoprotein B and triglycerides from isolated rat hepatocytes (11, 29, 33).

A theory for the pathogenesis of subcapsular steatosis and steatonecrosis, based on the above information, is shown schematically in Fig. 4. The importance of this schema is that it suggests a parallel mechanism by which histologically identical lesions occur diffusely in the livers of obese type II diabetics (Fig. 5). These patients have insulin resistance with secondary elevations of plasma insulin and glucose. The highest concentrations of both insulin and glucose occur in portal vein blood, so that all hepatocytes, not just subcapsular cells, are exposed to high concentrations of these substances. During fasting, plasma FFA rise to higher levels in obese individuals compared to lean individuals (27). The exacerbation of steatosis and steatonecrosis seen in obese patients after jejunoileal bypass surgery may be related to massive mobilization of FFA from adipose tissue to the liver (5, 23), overwhelming the liver's capacity to oxidize or esterify the toxic fatty acids.

A major problem has been to explain why massively obese patients who lose weight while fasting have an improvement in liver function and morphology, whereas obese patients losing a comparable amount of weight after jejunoileal bypass have worsening of liver function and morphology (10, 32). The present hypothesis explains this differential response. Fasting patients have a marked fall in pancreatic insulin secretion. This should protect the liver from the ensuing flux of FFA by allowing disposal of FFA by their oxidation to ketone bodies. Jejunoileal bypass patients have a similar flux of FFA while losing weight but continue to eat, absorb nutrients, and release insulin, thereby blocking

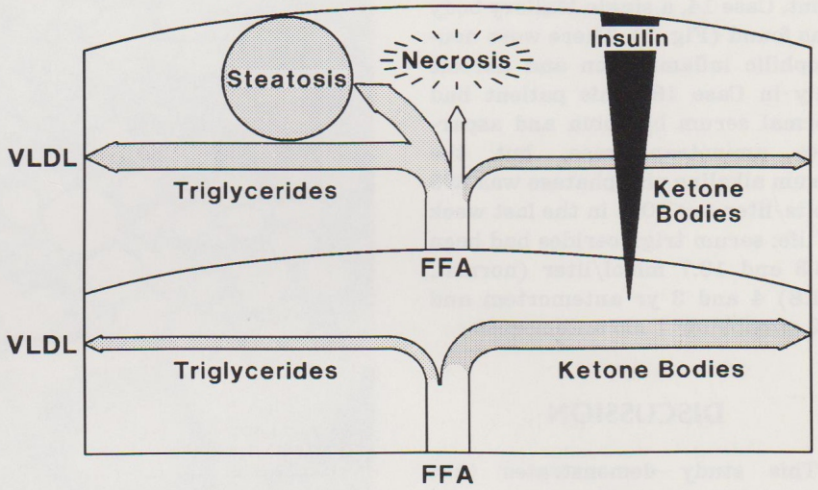

Figure 4. Proposed schema for the pathogenesis of subcapsular steatosis and steatonecrosis in peritoneal dialysis patients. The diagram depicts two metabolically distinct regions of the liver. The subcapsular liver (*top*) is influenced by a high local insulin concentration which inhibits oxidation of free fatty acids (FFA). Deeper liver (*bottom*) is depleted of insulin in type I diabetes and is more able to oxidize FFA which arrive in the liver largely via the portal vein. In the presence of high insulin concentrations in the peritoneal fluid, subcapsular liver tends to synthesize triglycerides, some of which is stored as fat droplets. Excess hepatocellular FFA not removed by synthetic or excretory pathways cause necrosis.

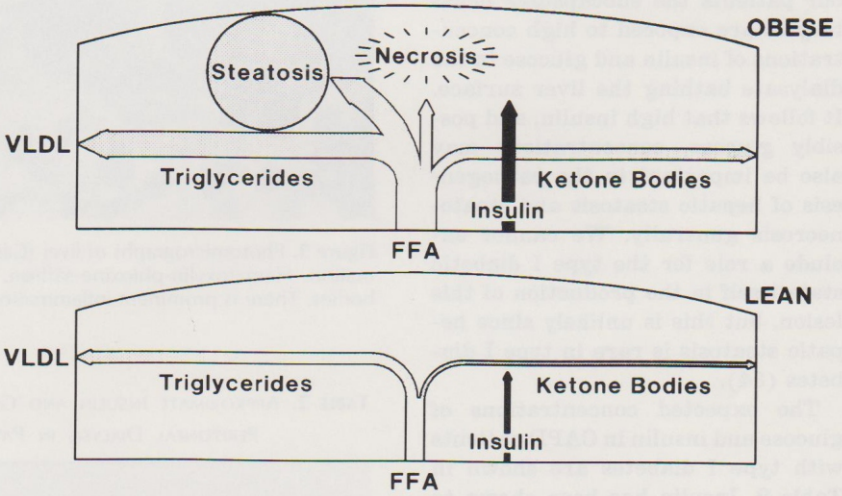

Figure 5. Proposed schema for the pathogenesis of diffuse steatosis and steatonecrosis in obesity. Lean individuals seldom have sufficient flux of FFA to overload the metabolic pathways. The obese have increased flux of FFA as well as sufficient insulin to inhibit the oxidation and secretion pathways, leading to steatosis and occasionally necrosis. The combination of high FFA and high insulin is more likely to occur in obese individuals after jejunoileal bypass.

the major pathways for disposal of FFA.

This differential response is also seen in protein-energy malnutrition. Steatosis occurs in patients with kwashiorkor, who are deprived of protein but eat relatively large amounts of carbohydrate, but not in patients with marasmus who are deprived of all classes of nutrients. Plasma insulin is likely to be higher in kwashiorkor than in marasmus because of continued carbohydrate intake in the former. Elevated fasting plasma insulin has been reported in the early phase of kwashiorkor (16, 21); plasma insulin was higher in Uganda where kwashiorkor was common, compared to Gambia where marasmus was more common (36). High insulin levels would explain the absence of ketonemia in kwashiorkor. Impaired hepatic lipoprotein synthesis likely impairs secretion of triglyceride, thereby contributing to the development of steatosis in kwashiorkor.

This theory has implications for the therapy of steatonecrosis in the obese diabetic. Treatments likely to minimize stress on the liver are those leading to decreased delivery of insulin and FFA to the liver. A low calorie diet has been shown to improve liver histology (10, 12, 32). This indicates that an uninhibited FFA oxidation pathway is able to handle the increased flux of FFA during weight loss. If insulin is required to control hyperglycemia, then giving insulin i.v. or s.c. should result in a beneficial decrease in the ratio of portal vein to peripheral vein insulin concentrations. Sulfonylurea therapy would not be advisable since this class of drugs inhibits FFA oxidation (6).

This study may also have implications for the pathogenesis of Mallory bodies. The Mallory bodies developed in subcapsular tissue which differed from deeper tissue mainly in the insulin and glucose concentration. The theory proposed above would predict that FFA are increased in the subcapsular tissue; it has been suggested that FFA may be the common toxic principle in the liver disease of alcoholism and obesity (24). Mallory bodies are aggregated intermediate cytokeratin filaments, usually associated with ballooning of the cytoplasm (14). Free fatty acids might lyse the membrane attachments of cytokeratin filaments by detergent-like action, allowing filament aggregation during necrosis of the cell. Similar lytic action may be produced by hepatocellular bile acids in severe cholestasis, explaining the presence of Mallory bodies in late primary biliary cirrhosis and other cholestatic states (14).

The peritoneal dialysis model provides a system which may be easily reproduced in animals. The advantage of this model is that the subcapsular and deep liver tissues share a common nutritional and hormonal milieu, thus providing internal control.

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