Although a number of different drugs or drug combinations are available for the treatment of chloroquine-resistant infections of *P. falciparum*, most of them must be administered for a period of 5 to 14 days. Shorter courses of treatment usually consist of the combination of a dihydrofolate reductase inhibitor, such as pyrimethamine, and a long-acting sulfonamide, such as sulfadoxine or sulfalene. Single-dose treatment with such combinations has been effective, but some patients do not respond adequately to these drug regimens (*1*). A more effective drug or drug combination, administered as a single dose, is clearly needed.

The findings presented here indicate that mefloquine may satisfy the need for a more effective, yet simple, treatment of drug-resistant infections of *P. falciparum*. To confirm the potential value of this drug as an antimalarial agent, further studies are indicated in areas of South America and Southeast Asia where drug resistance is a problem.

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12. Nonimmune individuals had no previous exposure to malaria and were treated with mefloquine during their initial attack of malaria. Partially immune individuals had previously been exposed to malaria, and acute clinical episodes had been suppressed with subcurative doses of other antimalarials. They were frequently asymptomatic at the time of treatment with mefloquine.
13. For patients infected with the Chesson strain of *P. vivax*, a daily dose of 30 mg of primaquine base was given for 14 days together with 1500 mg of chloroquine base administered over a period of 3 days.
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16. We thank the inmate volunteers whose participation made these studies possible. Supported by the U.S. Army Medical Research and Development, under contract DADA17-71-C-1103. This is contribution No. 1331 from the Army Malaria Research Program.

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Alcoholic Hepatomegaly: Accumulation of Protein in the Liver

Abstract. *The hepatomegaly that appears after long-term feeding of ethanol results in accumulation of protein that is quantitatively as important as the increase in lipid. The bulk of protein accumulates in the soluble fraction of the cell. Hepatic albumin and transferrin concentrations increase and colchicine-binding protein decreases, thus suggesting an intrahepatic retention of export proteins.*

Hepatomegaly is a common manifestation of alcoholic liver disease. It is generally attributed to fat accumulation. However, there is no evidence that fat by itself can account for the increase in liver mass. Therefore, we undertook to determine whether there are cell constituents other than fat which contribute to ethanol-induced hepatomegaly. It was discovered that the feeding of ethanol results in deposition of export proteins in the cytosol.

Male rat littermates were pair-fed liquid diets as described (*1*) for 4 to 8 weeks. The diets contained 18 percent of calories as protein, 35 percent as fat, 11 percent as carbohydrate and 36 percent as either ethanol or additional carbohydrate. Ninety minutes after an intragastric administration of the respective diets (6 ml per 100 g of body weight), the rats weighing 180 to 360 g were killed under ether anesthesia by exsanguination from the aorta. The livers were excised and their weights (wet and dry), volume, total lipid, protein, and DNA contents were measured (*2*).

Livers from rats that were fed ethanol increased 30 percent both in volume and in wet weight (4.28 ± 0.13 g per 100 g of body weight compared to 3.34 ± 0.06 in controls; means ± S.E.M. of 24 pairs; $P < .001$ by the paired Student's *t*-test). The specific gravity of the liver was unchanged (1.009 ± 0.010 g/cm^3 compared to 1.016 ± 0.017 in controls) despite the doubling of hepatic lipids in the rats that were fed ethanol (Fig. 1). The increase in liver fat (151 ± 29 mg per 100 g of body weight) accounted for only half of the increase in liver dry weight (304 ± 40 mg per 100 g of body weight). In addition to the increase in liver lipid, there was a concomitant increase in liver protein (Fig. 1). The increase in protein (132 ± 41 mg per 100 g of body weight) accounted for almost all of the other half of the increased hepatic dry weight. Hepatic protein concentration did not change. This similarity in protein concentration indicates that water also increased in proportion to the increase in protein. Liver wet weight/dry weight ratios were similar in both groups of animals.

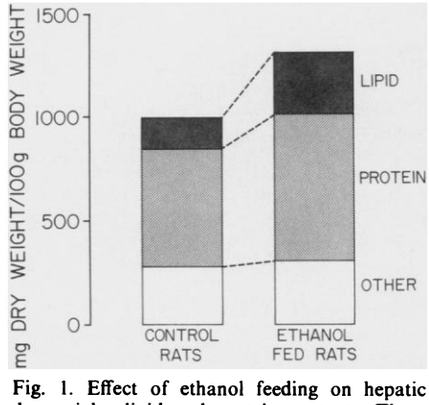

Fig. 1. Effect of ethanol feeding on hepatic dry weight; lipid and protein contents. These three differences are significant ($P < .01$).

In contrast to the increase in protein, DNA content of the liver remained unchanged (10.8 ± 0.5 mg per 100 g of body weight compared to 10.3 ± 0.4 in controls). This dissociation suggested that hepatomegaly was due to an increase in cell size rather than to an increase in cell number. This was verified in histologic sections of the liver. Hepatocytes occupied a significantly larger area (602 ± 43 μm^2 per cell) in livers from rats that were fed ethanol than in those from pair-fed controls (442 ± 36; 8 pairs; $P < .01$), even in zones where there was little visible fat. The 36 percent increase in size of the hepatocytes of rats that were fed ethanol can account for the hepatomegaly, since these cells contribute 87 percent of the liver volume (*3*). The number of mesenchymal cells per area increased by 17 percent in the livers of ethanol-fed rats ($P < .01$). However, because of the small size of the mesenchymal cells, their increased number does not contribute significantly to the hepatomegaly. The increase in hepatocyte size (observed in the

present model), associated with increased intracellular protein and water, may be the basis for the "ballooning" of the hepatocytes that is commonly observed in alcoholic liver disease.

To determine the subcellular distribution of the increase in liver protein, mitochondria, microsomes, and cytosol were prepared. Recovery of each fraction was assessed by appropriate markers (*4*). Protein increased in all three fractions, but the total increase in mitochondrial and microsomal proteins accounted for less than half of the total increase in liver protein (Fig. 2). The major protein increase occurred in the 100,000*g* supernatant, or cytosolic fraction. Thus, in addition to the known increase in organelle protein (*5*), there is an even greater increase in soluble protein.

To determine whether the increase in soluble protein could be due, at least in part, to hepatic accumulation of proteins that are primarily exported from the liver into the plasma, albumin and transferrin where chosen as typical examples of export proteins. The concentration of these proteins was measured in deoxycholate extracts of the liver by immunoprecipitation with specific rabbit antiserums (*6*). The amount of plasma albumin that remained in the liver after perfusion with saline was calculated by tracing extrahepatic albumin with intravenously injected rat albumin labeled with ^{14}C, and dividing the radioactivity in the liver extracts by the specific activity of the plasma albumin. This value was similar in ethanol-fed rats (0.87 ± 0.08 mg per gram of liver) and in controls (0.86 ± 0.08; 8 pairs). The concentration of intrahepatic albumin increased in ethanol-fed rats (2.27 ± 0.24 mg per gram of liver; 10.12 ± 0.95 μg per milligram of liver protein) compared to controls (1.77 ± 0.24 and 7.75 ± 0.70, respectively; $P < .01$). Hepatic transferrin concentration also increased in the ethanol-fed rats (0.40 ± 0.02 mg per gram of liver and 2.15 ± 0.13 μg per milligram of liver protein compared to 0.34 ± 0.01 and 1.91 ± 0.13, respectively, in the controls; $P < .01$). Plasma concentrations of these proteins were similar in both groups of animals. The increases in hepatic albumin and transferrin concentrations indicate that intrahepatic deposition of export proteins could contribute to the increase in soluble protein. By contrast, the concentration of a nonexport protein of the cytosol, ferritin, when measured by radial immunodiffusion (*7*) in a "heat supernatant" of liver homogenate (*8*), showed a significant decrease in the animals treated with ethanol (0.33 ± 0.03 mg per gram of liver and 1.77 ± 0.16 μg per milligram of protein compared to 0.40 ± 0.02 and 2.24 ± 0.11, respectively, in the controls; $P < .02$).

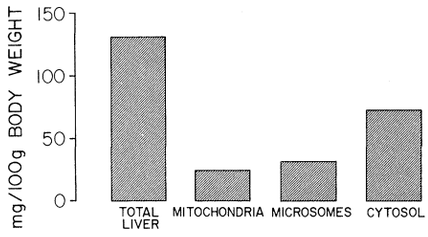

Fig. 2. Distribution among subcellular fractions of the increase in liver protein induced by ethanol feeding. The increase in mitochondrial protein is not significant. All other increases are significant ($P < .01$).

Accumulation of export proteins in the liver could be due either to increased production or to decreased transport into the blood. Albumin and transferrin production decreased after acute administration of ethanol, whereas albumin production was unaffected by long-term feeding of ethanol (*9*). Since it has been postulated that the microtubular system plays a role in the export of proteins by the liver (*10*), colchicine binding, which is a characteristic property of microtubular protein, was measured (*11*). Colchicine binding, which depends on the equilibrium between soluble and insoluble microtubular protein, reflects the functional state of the microtubular system. Cytosolic proteins from the livers of rats that were fed ethanol bound significantly less colchicine (22.23 ± 1.45 nmole per gram of protein; 1.57 ± 0.13 nmole per gram of liver) than those of controls (27.00 ± 1.85 and 2.12 ± 0.14, respectively; 10 pairs; $P < .01$), resulting in an absolute decrease in the hepatic capacity to bind colchicine (18.94 ± 1.98 nmole per total liver compared to 23.30 ± 2.12 in controls; $P < .01$). This suggests a decreased amount or an altered functional state of microtubular protein in the livers of ethanol-fed rats. This finding is consistent with the hypothesis that the feeding of ethanol may decrease the ability of the liver to export proteins. In any event, the alteration of this fundamental hepatic function and the hitherto unrecognized accumulation of proteins in the liver reveal a potentially important new site of the hepatotoxic action of ethanol.

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Exocrine Pancreas: Evidence for Topographic Partition of Secretory Function

Abstract. *The pattern of amylase, lipase, and chymotrypsinogen content found in pancreatic exocrine tissue surrounding the islets of Langerhans (periinsular halos) differs from that of the rest, or teleinsular part, of the pancreas. Such a topographic partition of secretory function may play a role in the regulation of pancreatic juice composition.*

The pancreatic islets of Langerhans were first described more than a century ago (*1*), their endocrine function was established 25 years later (*2*), and their two main hormones, insulin and glucagon, were isolated in 1921 and 1948, respectively (*3*). While much data have accumulated about their structure and function, it is still not clear why the endocrine pancreatic cells are disseminated in discrete clusters within the exocrine gland in most higher vertebrates (*4*).

There is structural and functional evidence that intimates physiological links between the endocrine and exocrine cells of the pancreas, both of which are thought to