Progress report

Treatment of acute alcoholic hepatitis¹

The lesion of acute hepatocyte injury related to alcohol, consisting of swelling and degeneration of liver cells and alcoholic hyaline and polymorphonuclear infiltration, was initially described by Mallory in 1911.¹ Subsequently, it has been referred to by various descriptions, including 'florid cirrhosis', 'acute hepatic insufficiency of the alcoholic', 'steatonecrosis', and 'acute sclerosing hyaline necrosis'. The most up-to-date clinical name for this entity—acute alcoholic hepatitis—was established only 10 years ago by Beckett, Livingstone, and Hill.²

In spite of the high frequency of this clinicopathological disorder, interest in its management as judged by clinical reports has waned remarkably. A review of the literature over the past five years indicates that papers pertaining to therapy of the liver itself (excluding complications of liver failure) have averaged one annually in Anglo-American scientific publications. Treatment has been largely empirical, based upon tradition, conservatism, and the avoidance of iatrogenic problems.

Therapeutic Goals

Three distinct but overlapping aims of treatment may be recognized in the management of alcoholic hepatitis. Reduction of mortality, avoidance of cirrhosis, and removal of hepatic fat are separate yet interrelated criteria by which the efficacy of new agents may be judged. If a consensus is to be sought, clinical trials must be structurally sound in terms of therapeutic intent. For example, when considering immediate survival as an indicator of effect, duration of treatment need not exceed an interval of several weeks. To focus on the evolution of cirrhosis after acute alcoholic hepatitis, however, would require a long-term, multicentre investigation involving large numbers of biopsied patients followed for many months. Additional practical barriers to this approach include the need to achieve sobriety in patients after a period in hospital and the degree of faithfulness to the drug regimen among ambulatory subjects. The third goal—mobilization of hepatic fat—is often easy, but of dubious importance to life or prognosis.

It follows that survival data in evaluating a new therapeutic modality in acute alcoholic hepatitis are the simplest and most decisive.

Conventional Treatment

The general supportive approach to the uncomplicated patient is similar to that outlined by Gabuzda in an excellent recent review³. In the absence of precoma, ascites, and oedema, treatment may begin with a daily frequent feeding regimen containing 25-30 calories per kilogram of body weight,

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including 0.5 g protein per kilogram weight and approximately 2 g sodium. Although these recommendations are sufficient for the majority of patients, the nutritional requirements of critically ill patients with hepatic insufficiency may be greater if negative balances are to be avoided. Certain decompensated patients suddenly fed large quantities of protein may demonstrate impaired urea synthesis, positive nitrogen balance without weight gain, and hyperaminoacidaemia frequently associated with metabolic encephalopathy⁴. Manifestations of encephalopathy or fluid retention would reduce the protein and sodium intakes, respectively. Fat is not restricted in the absence of alcoholic stools or gastrointestinal intolerance. The goal would be gradually to increase the overall caloric intake to approximately 40 calories per kilogram and the protein intake to at least 1 gram per kilogram. Added vitamins would be significant and important, particularly in the patient with malnutrition or specific vitamin deficiencies.

Special Features

Problems arise when the gastrointestinal tract does not permit access to sufficient calories to repair the hepatic injury. In our clinical experience persistent anorexia, and, more frequently, protracted vomiting associated with severe hepatic dysfunction, represent a potentially lethal state and will require all of our ingenuity to achieve recovery. These seriously debilitated individuals pose a great risk with respect to encephalopathy, gastrointestinal bleeding, infection, and renal failure. Nasogastric suction with replacement of the appropriate electrolytes and fluids required may play a temporizing role but will not achieve long-term desired results. Whether forced feeding by nasogastric tube for the persistently anorectic patient or wholly intravenous feeding⁵ for the patient with protracted vomiting have any desirable benefits will remain a task for future clinical investigation. The role of medium-chain triglycerides⁶, parenteral lipid preparations⁷, and elemental diets⁸ (Vivonex, as a current example) remains largely untested. The efficacy of new agents in this disorder may very well be judged by their ability to reverse the severe gastrointestinal dysfunction which is secondary to hepatic insufficiency and often additional lesions—gastritis and pancreatitis—in this severely ill subgroup of patients.

A second area calling for expertise is the occasionally difficult differentiation of intrahepatic cholestasis and extrahepatic obstruction of the biliary tract in these patients. Alcoholic hepatitis may simulate surgical disease⁹ when it presents as fever, right upper quadrant pain, vomiting, and an enlarged liver and leucocytosis. Pathologically, alcoholic hepatitis associated with significant fat deposition is responsible for the cholestatic manifestations; less commonly, obstruction of the common duct due to coexisting pancreatitis may be present¹⁰. Prudent management calls for watchful waiting because of the very high risk of surgery in the presence of a sick liver¹¹. In the majority of such cases the acute manifestations of the hepatic inflammation will subside, confirming the impression of hepatocellular damage. In selected cases liver biopsy may be helpful in ruling out biliary tract sepsis. It should be recognized, however, that if a decision for biopsy is entertained the possibility of immediate surgery must be taken into account so that mortality related to infected bile peritonitis will be minimized. In these circumstances it is best to alert the surgical team so that operative

intervention will be expedited if peritoneal irritation occurs after biopsy.

Thirdly, a low-grade fever may be a significant finding in the patient with alcoholic hepatitis. It is incumbent to search for sources of infection in such patients, but in many instances a so-called 'hepatic fever', possibly related to failure of etiocholanolone degradation, may be present¹². A significant incidence of bacteraemia is present in certain patients related to a defective hepatic reticuloendothelial system and portasystemic shunting of enteric microorganisms¹³.

Finally, it should be recognized that portal hypertension may exist without cirrhosis as a consequence of a sclerosing hyaline necrosis producing sinusoidal hypertension¹⁴. The clinical findings in this syndrome consist of manifestations of portal hypertension, including ascites formation and oesophageal varices, which may occasionally rupture with severe gastrointestinal bleeding.

The Alcohol-malnutrition Controversy

Why do most patients improve in hospital? The concept of good nutrition has its origin with the study of Patek and Ratnoff (1948)¹⁵ which indicated that a high-protein, vitamin B complex-supplemented diet in cirrhosis with ascites improved survival. The control group was maintained on a low-protein, low-fat, unsupplemented intake but was not, unfortunately, contemporaneous with the treated patients. When a nutritious diet was introduced a slow but definite improvement ensued in the surviving patients.

Hartroft, by contrast, has championed the role of dietary deficiency and demonstrated that rats given a cirrhotogenic diet would continue to show histological improvement when adequate nutrients were subsequently administered even if simultaneous alcohol feeding was carried out¹⁶. In man long-term vitamin supplements have not been proved to be beneficial, but, as noted earlier, the patient with an inadequate caloric intake or specific deficiencies in the form of Wernicke's encephalopathy, peripheral neuropathy, or macrocytic anaemia will require appropriate vitamin therapy.

The primary role of alcohol in this form of hepatotoxicity and the importance of abstinence in therapy is manifest by several different lines of evidence:

- 1 The mortality rate due to cirrhosis in the USA sharply diminished with prohibition and subsequently increased following its repeal¹⁷.
- 2 Abstinence has been shown to improve the survival rate in patients with cirrhosis related to alcohol excess¹⁸.
- 3 The morphology of protein-caloric malnutrition (exemplified by kwashiorkor) differs from the inflammatory and necrotic lesions of alcoholic hepatitis.
- 4 Clinical impressions suggest that a good diet is not necessarily protective in the alcoholic. Social drinking in the higher socioeconomic classes can be associated with cirrhosis.
- 5 An unsupplemented diet without vitamins or lipotropic agents consisting of 30 calories per kilogram and 1 g protein per kilogram plus abstinence does not lead to a slower rate of clinical improvement¹⁹.
- 6 The most compelling indication of direct alcohol-induced injury has been obtained by experiments employing non-alcoholic volunteers. In these subjects Rubin and Lieber²⁰ showed that quantities of alcohol insufficient

to produce inebriation (but often consumed by social drinkers) would rapidly lead to increased hepatic triglyceride and alterations in hepatic ultrastructure; the influence of malnutrition was vitiated by providing a surplus of calories, protein, and vitamins.

Attention to host factors is required since a large gap in our comprehension exists in the mechanisms involved between the essentially indiscriminate effect of acute alcohol injury as outlined by Rubin and Lieber and the selective end result—cirrhosis in the chronic alcoholic. We recognize that only man is subject to cirrhosis secondary to alcoholism; there is no experimental model. The importance of unknown metabolic pathways, perhaps genetically determined, is reinforced by the knowledge that only 8-10% of alcoholic patients become cirrhotic.

Pharmacological Therapy

In considering the removal of hepatic fat (which may be variably present in acute alcoholic hepatitis) a substantial number of different dietary formulae and pharmacological agents, including testosterone, growth hormone, and cortisone (25 mg daily), have been shown to be efficacious within six weeks. Norethandrolone, an anabolic steroid, was unique in achieving lipid mobilization within two weeks. Unfortunately, this agent was responsible for damage to biliary canaliculi, thereby precluding its use. A larger series of patients with clinical and histological features of alcoholic hepatitis (and frequently cirrhosis) subsequently proved to be refractory to anabolic agents (testosterone or methenolone enanthate) when subjected to a controlled trial²². Wells²³ in Singapore, however, reported a reduced mortality with large doses of testosterone propionate in cirrhotics but the study group consisted of heterogeneous forms of cirrhosis, the duration of therapy was variable, and only selected data were published. It is apparent that this experience with anabolic agents does not justify their routine use in managing acute liver disease of the alcoholic.

Corticosteroids have periodically enjoyed therapeutic popularity in liver disorders²⁴ although the patient with advanced hepatic disease may be unusually vulnerable to peptic ulceration, infection, electrolyte disturbances, and psychological dysfunction. In Wells's investigation prednisolone-treated subjects with decompensated cirrhosis had a 26% mortality rate as opposed to a 55% mortality rate in the controls, but again, as previously observed, the results in alcoholic patients were not specified, and structural defects in the evaluation raise doubts concerning the conclusions. Subsequently, the experience of the Copenhagen study group for liver disease indicated a significantly higher fatality rate after prednisone treatment (44%) in alcoholic cirrhotics compared with that in controls (25%)²⁵.

Recently, Helman *et al*²⁶ found that prednisolone, 40 mg a day, resulted in the survival of eight of nine seriously ill patients with alcoholic hepatitis and hepatic encephalopathy and the demise of all six comparable patients on placebo treatment ($P < 0.01$). Non-encephalopathic patients with mild or moderate involvement did not benefit in terms of rapidity of healing or incidence of subsequent cirrhosis. Although statistically valid, the small numbers of patients with advanced liver failure in this study preclude total acceptance of the conclusions. Subsequently, in another relatively small series of desperately ill patients with acute alcoholic hepatitis and underlying cirrhosis,

a controlled trial of corticosteroid therapy did not improve survival statistics²⁷. We may ask whether there exists a group of definable patients who may benefit from steroids by virtue of being neither virtually moribund nor sufficiently well to survive without pharmacological treatment²⁸. A wider experience with appropriate controls, including good-risk, biopsied and poor-risk, unbiopsied²⁷ patients, will clearly be required to resolve this clinical dilemma.

Speculation

Advances in the understanding of fibrogenesis following hepatic injury²⁹ may provide an area of fruitful research with significant implications for future treatment. With respect to alcohol-related injury, the occurrence of significant fibrous tissue deposition in the space of Disse has been detected among 50% of chronic alcoholics in the absence of overt clinical-morphological signs of liver damage³⁰. The precise effects of these changes in hepatic nutrition are unknown but reasoning *a priori* suggests that this structural barrier would have functional consequences. In the development of cirrhosis following alcoholic hepatitis, formation of connective tissue septa may be a vital process since anastomoses are created linking portal vein and hepatic artery with efferent veins, thereby impairing parenchymal blood flow. The micro-circulation of the hepatic lobule may also be compromised by intra-lobular inflammation; the abnormal basement membranes which arise around degenerating sinusoidal liver cells contribute further to a self-perpetuating form of injury leading to cirrhosis.

In view of these aspects of pathogenesis, experimental measures to inhibit the activity of hepatic connective tissue require exploration. Several agents—beta-amino propionitrile (the lathyrism factor)³¹, the oestrogenic substance phydroxypropionphenone³², penicillamine³³, and certain peptide compounds³⁴—may alter collagen metabolism by differing modes of action. However, the usefulness of these preparations must await evaluation by carefully controlled clinical trials. Since none of these may selectively affect hepatic fibroblastic activity or collagen maturation, striking therapeutic benefit may not be anticipated until newer compounds with greater specificity of function are found.

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References

- ¹Mallory, F. B. (1911) Cirrhosis of the liver: five different types of lesions from which it may arise. *Bull. Johns Hopk. Hosp.*, **22**, 69-75.
- ²Beckett, A. G., Livingstone, A. V., and Hill, K. R. (1961). Acute alcoholic hepatitis. *Brit. med. J.*, **2**, 1113-1119.
- ³Gabuzda, G. J. (1970). Nutrition and liver disease. *Med. Clin. N. Amer.*, **54**, 1455-1472.
- ⁴Rudman, D., Akgun, S., Galambos, J. T., McKinney, A. S., Cullen, A., Gerton, G., and Howard, C. H. (1970). Observations on the nitrogen metabolism of patients with portal cirrhosis. *Amer. J. clin. Nutr.*, **23**, 1203-1211.
- ⁵Dudrick, S. J., Wilmore, D. W., Vars, H. M., and Rhoads, J. E. (1969). Can intravenous feeding as the sole means of nutrition support growth in the child and restore weight loss in an adult? An affirmative answer. *Ann. Surg.*, **169**, 974-984.
- ⁶Greenberger, N. J., and Skillman, T. G. (1969). Medium-chain triglycerides. *New Engl. J. Med.*, **280**, 1045-1058.

- ⁷Kern F., Jr., Jackson, R. G., Martin, T. E., and Mueller, J. F. (1957). Some effects of multiple intravenous infusions of a cottonseed oil emulsion in patients with Laennec's cirrhosis of the liver. *Metabolism*, 6, 743-757.
- ⁸Stephens, R. V., Thompson, W. R., and Randall, H. T. (1968). The use of a fortified elemental aerospace diet in the management of nutrition following massive small bowel resection. *Surg. Forum*, 19, 381-382.
- ⁹Phillips, G. B., and Davidson, C. S. (1957). Liver disease of the chronic alcoholic simulating extrahepatic biliary obstruction. *Gastroenterology*, 33, 236-244.
- ¹⁰Weinstein, B. R., Korn, R. J., and Zimmerman, H. J. (1963). Obstructive jaundice as a complication of pancreatitis. *Ann. intern. Med.*, 58, 245-258.
- ¹¹Mikkelsen, W. P., Turrill, F. L., and Kern, W. H. (1968). Acute hyaline necrosis of the liver: a surgical trap. *Amer. J. Surg.*, 116, 266-272.
- ¹²Tisdale, W. A., and Klatskin, G. (1960). The fever of Laennec's cirrhosis. *Yale J. biol. Med.*, 33, 94-106.
- ¹³Martin, W. J., Spittel, J. A., Morlock, C. G., and Baggenstoss, A. H. (1956). Severe liver disease complicated by bacteremia due to gram-negative bacilli. *Arch. intern. Med.*, 98, 8-15.
- ¹⁴Reynolds, T. B., Hidemura, R., Michel, H., and Peters, R. (1969). Portal hypertension without cirrhosis in alcoholic liver disease. *Ann. intern. Med.*, 70, 497-506.
- ¹⁵Patek A. J., Jr., Post, J., Ratnoff, O. D., Mankin, H., and Hillman, R. W. (1948). Dietary treatment of cirrhosis of the liver. *J. Amer. med. Ass.*, 138, 543-549.
- ¹⁶Takada, A., Porta, E. A., and Hartroft, W. S. (1967). Regression of dietary cirrhosis in rats fed alcohol and a 'super diet': evidence of the nonhepatotoxic nature of ethanol. *Amer. J. clin. Nutr.*, 20, 213-225.
- ¹⁷Klatskin, G. (1961). Alcohol and its relation to liver damage. *Gastroenterology*, 41, 443-451.
- ¹⁸Powell, W. J., Jr., and Klatskin, G. (1968). Duration of survival in patients with Laennec's cirrhosis. *Amer. J. Med.*, 44, 406-420.
- ¹⁹Klatskin, G., and Yesner, R. (1949). Factors in the treatment of Laennec's cirrhosis. I. Clinical and histological changes observed during a control period of bed-rest, alcohol withdrawal, and a minimal basic diet. *J. clin. Invest.*, 28, 723-735.
- ²⁰Rubin, E., and Lieber, C. S. (1968). Alcohol-induced hepatic injury in nonalcoholic volunteers. *New Engl. J. Med.*, 278, 869-876.
- ²¹Leevy, C. M. (1962). Fatty liver: a study of 270 patients with biopsy proven fatty liver and a review of the literature. *Medicine (Baltimore)*, 41, 249-278.
- ²²Fenster, L. F. (1966). The nonefficacy of short-term anabolic steroid therapy in alcoholic liver disease. *Ann. intern. Med.*, 65, 738-744.
- ²³Wells, R. (1960). Prednisolone and testosterone propionate in cirrhosis of the liver: a controlled trial. *Lancet*, 2, 1416-1419.
- ²⁴Goldgraber, M. B., and Kirsner, J. B. (1959). Corticotropin (ACTH) and adrenal steroids in liver disease. *Arch. intern. Med.*, 104, 469-489.
- ²⁵Copenhagen Study Group for Liver Diseases (1969). Effect of prednisone on the survival of patients with cirrhosis of the liver. *Lancet*, 1, 119-121.
- ²⁶Helman, R. A., Temko, M. H., Nye, S. W., and Fallon, H. J. (1971). Alcoholic hepatitis: natural history and evaluation of prednisolone therapy. *Ann. intern. Med.*, 74, 311-321.
- ²⁷Porter, H. P., Simon, F. R., Pope, C. E., II, Volwiler, W., and Fenster, L. F. (1971). Corticosteroid therapy in severe alcoholic hepatitis. *New Engl. J. Med.*, 284, 1350-1355.
- ²⁸Davidson, C. S. (1971). Alcoholic hepatitis (Editorial). *New Engl. J. Med.*, 284, 1378.
- ²⁹Popper, H., and Udenfriend, S. (1970). Hepatic fibrosis. *Amer. J. Med.*, 49, 707-721.
- ³⁰Edmondson, H. A., Peters, R. L., Frankel, H. H. and Borowsky, S. (1967). The early stage of liver injury in the alcoholic. *Medicine (Baltimore)*, 46, 119-129.
- ³¹Fiume, L. (1962). Inhibition by aminoacetonitrile of early lesions induced in the liver of rats by carbon tetrachloride. *J. Path. Bact.*, 83, 291-293.
- ³²Unakar, N. J. (1960). Effect of *p*-hydroxypropiophenone on fibrosis induced by carbon tetrachloride in mice. *Amer. J. Path.*, 48, 897-919.
- ³³Nimmi, M. E., Gerth, N., and Bavetta, L. A. (1967). Reversibility of a penicillamine induced defect on collagen aggregation. *Nature (Lond.)*, 213, 921-922.
- ³⁴Kivirikko, K. I., Prockop, D. J., Lorenzi, G. P., and Blout, E. R. (1969). Oligopeptides with the sequences. ala-pro-gly and gly-pro-gly as substrates or inhibitors for procollagen proline hydroxylase. *J. biol. Chem.*, 244, 2755-2760.