Fat Replacement of the Glycogen in the Liver as a Cause of Death

Seventy-five Years Later

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Seventy-five years ago, E. R. LeCount and H. A. Singer published a report in the first issue of the "Archives of Pathology & Laboratory Medicine" entitled "Fat Replacement of the Glycogen in the Liver as a Cause of Death." The report described 11 patients with chronic alcoholism who died suddenly. Markedly enlarged fatty livers were the only abnormality noted at postmortem examination in each of the subjects. Groups in this country and abroad subsequently repeated the authors' observation. The mechanism of sudden death in patients with fatty livers due to chronic alcoholism is currently understood to be an abnormality in the conduction system of the heart, manifested as a prolonged QT interval. The triggering event leading to the conduction defect has been suggested to be hypoglycemia complicated by hypokalemia and hypomagnesemia. In this review we will summarize the changes that have taken place in this field since the initial publication by LeCount and Singer.

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The Archives of Pathology & Laboratory Medicine made its debut in January of 1926 as the official pathology journal of the American Medical Association. The College of American Pathologists has published the journal since 1995, in cooperation with the American Medical Association. Many of the advances in pathology that have occurred in the past three quarters of a century have been published by the Archives, giving the journal an influential role in the practice of anatomic and clinical pathology.

A good example of the changes that have occurred since 1926 are the changes in the field of alcohol and lipid metabolism, which was discussed by E. R. LeCount and H. A. Singer in the first issue of the Archives. They described a group of 11 patients with chronic alcoholism who died suddenly; to the authors' surprise, the only significant postmortem finding was massive hepatic steatosis. All subjects had consumed "inordinate amounts of whiskey or similar liquors (brandy); their death was often sudden or unexpected, not the result of delirium tremens and little else was found within the bodies to explain death." In their discussion, the authors reviewed the scarce literature available at the time on the mechanism of sudden death. One of their references described the pathologic findings in experimental animals, such as rabbits and rats given large doses of alcohol.

Alcoholic-induced fatty liver in humans, which was referred to as fatty degeneration or fatty infiltration, had been common knowledge since the classic writings by 19th century authors. The occurrence of sudden death, however, had been scarcely reported.

LeCount and Singer were able to exclude delirium tremens, acute alcohol poisoning, or bleeding from esophageal varices as a cause of death in their patients. They emphasized the remarkable hepomegaly in their patients, which in their opinion had caused a significant alteration in the ratio of liver to body weight.

To commemorate the 75th anniversary of the ARCHIVES, and also as a tribute to LeCount and Singer, I will summarize the current state of medical knowledge regarding the metabolism of fatty liver and the relationship to alcohol consumption, as well as the mechanism of sudden death in chronic alcoholics with fatty livers, with or without cirrhosis.

PATHOPHYSIOLOGY OF FATTY LIVER

Fatty liver results from the accumulation of lipids in liver cells, where they are stored as triglycerides and phospholipids, causing an increase in excess of 5% of normal liver weight. One of the main functions of the liver is the clearance of lipids, mainly free fatty acids, cholesterol, and triglycerides.

Alcohol-induced liver cell damage causes hepatic steatosis. Hepatic steatosis may also be present in various clinical states, such as diabetes, obesity, drug reactions (tetrazycline, corticosteroids, and amiodarone), exposure to phosphorus, viral infections, inflammatory bowel disease, and pregnancy, and also in childhood diseases, such as Reye syndrome, galactosemia, and abetalipoproteinemia.

Microscopic examination of fatty livers demonstrates the presence of large and small vacuoles within hepatocytes and Kupffer cells (Figure 1). Hepatic steatosis may be complicated by an inflammatory reaction with Mallory bodies encircled by neutrophils (Figure 2). Mallory bodies have been demonstrated to be clumps of denatured cytokeratin filaments, located close to the nucleus in he-
patocytes undergoing hydropic degeneration (Figure 3). Although hyalin bodies were first described in alcoholic liver disease, they are also present in nonalcoholic steatohepatitis,14 Indian childhood cirrhosis, and Wilson’s disease, and in the livers of patients receiving amiodarone therapy. Ubiquitin plays a role in the aggregation of intermediate filaments (Figure 4). Electron microscopic examination has shown the presence of lipid droplets in the endoplasmic reticulum (Figure 5) and the fibrillar nature of Mallory bodies (Figure 6).

HEPATIC STEATOSIS AND SUDDEN DEATH

Regardless of the etiology, hepatic steatosis is the end result of abnormal triglyceride synthesis and secretion. Moderate to heavy doses of alcohol have a direct toxic effect on hepatic triglyceride metabolism. Alcohol also induces lysis of adipose tissue with release of fatty acids, which are then transported to the liver, adding to the lipid pool. In addition, alcohol decreases the oxidation of fatty acids while increasing the synthesis of triglycerides and the release of lipoproteins.

The accumulation of fat in the liver may occur over the course of a few days or weeks in response to excessive alcohol consumption. One third of asymptomatic alcoholic patients accumulate large amounts of fat in the liver; some may also develop a significant inflammation, specifically alcoholic hepatitis. Microscopically, the liver cells are found to contain Mallory bodies surrounded by neutrophils attracted by chemotaxis to the denatured cytokeratin filaments. The clinical manifestations of acute alcoholic hepatitis may include jaundice, peripheral edema, hepatomegaly, and ascites.

There was no evidence of alcohol hepatitis in the patients reported by LeCount and Singer.1 Similar cases, characterized only by fat in the liver, were subsequently reported; interestingly, most of these reports appeared in forensic pathology journals.15–21

One of these reports reviewed the incidence of cirrhosis among young adults in Baltimore during the period between 1957 and 1966.16 The study revealed an increase in mortality in chronic alcoholics with fatty livers, with or without cirrhosis. Of 262 deaths, half were sudden and more than 80% of the deceased were found to have large fatty livers.

A report from Canada in 1970 concluded that alcoholics with fatty livers had a higher death rate than alcoholics who did not have fatty livers. It was suggested that those with fatty livers had a more advanced degree of alcoholism.16 Other investigators examined the blood alcohol levels in postmortem samples; only 7% were found to have levels in excess of 100 mg/dL (21.7 mmol/L). The sudden death of the patients from which the samples were taken was attributed to cardiac arrhythmia.17

Two other reports on chronic alcoholics who died suddenly speculated that death was the result of a combination of factors, including hypoglycemia, hypokalemia, hypomagnesemia, and high serum levels of free fatty acids.18,19

The North Carolina Office of the Chief Medical Examiner20 identified 411 cases of sudden death between 1972 and 1976 in which the deceased were found to have fatty livers. Most of the patients in the study had very low blood alcohol levels, suggesting that the mechanism of death was an acute or hyperacute alcohol withdrawal phenomenon.

A report by the Tokyo Metropolitan Medical Examiner’s Office21 described the findings in 7376 sudden or violent deaths. Ten percent (690) of the deceased were heavy drinkers but only 2.7% had very high blood alcohol levels at the time of death.

The subject of sudden death in alcoholics has continued to interest investigators. The emphasis has shifted toward the cardiovascular status of alcoholics. In one study, a group of alcoholics and a group of nondrinking age- and sex-matched controls were followed for a period of 4 years. The QT interval was longer in alcoholics with and without cirrhosis than in the controls. The conduction defect was attributed to adrenergic hyperactivity, since many of the alcoholics were found to have elevated plasma nor-epinephrine.22,23 Vagal neuropathy also has been found to be prevalent in alcoholic cirrhosis.24

The abnormality identified in the conduction system of the heart in chronic alcoholics, namely a prolongation of the QT interval, may be responsible for their sudden death; it has even been suggested that patients with alcoholic liver disease should avoid drugs known to prolong the QT interval.24

Even though there has been a significant advance in our understanding of sudden death in chronic alcoholics, statistics have not shown a significant reduction in the incidence of sudden death in this population.

There is hope that further research will provide the answer. When that time arrives, it would be only appropriate that the research be published in the Archives of Pathology & Laboratory Medicine, bringing to a closure the question posed by LeCount and Singer 75 years ago.

References