Ethanol Produces Muscle Damage in Human Volunteers

Abstract. *Repeated administration of ethanol (42 percent of total calories) for 28 days increased serum creatine phosphokinase activity and produced ultrastructural changes in skeletal muscle of human volunteers. The data suggest that alcoholic myopathy results from ethanol toxicity, rather than from nutritional or other factors.*

A well-defined syndrome of muscle disease associated with chronic use of alcohol was described in 1957 (*1*) and has been increasingly recognized since then (*2–4*). Acute alcoholic myopathy is characterized by muscle pain, tenderness, and edema, and by occasional myoglobulinuria, whereas the chronic form may have an insidious onset of weakness, which is progressive as long as alcohol intake is maintained. By light microscopy, the muscles display varying degrees of necrosis, inflammation, and atrophy. By electron microscopy, intracellular edema, destruction of mitochondria and myofilaments, and mitochondrial inclusions have been observed (*3, 5*). Previous studies were all carried out in chronic alcoholics, for whom reliable histories of dietary habits, amount of alcohol consumed, and drug ingestion are difficult to obtain.

Because dietary deficiencies have been associated with muscle lesions in man (*6*) and experimental animals (*7*), and because drugs have induced myopathy clinically (*8*) and experimentally (*9*), it has not been clear whether alcoholic myopathy is a manifestation of alcohol toxicity or is a result of malnutrition or other factors associated with chronic alcoholism (*4*). We therefore studied the effects of ethanol in man under controlled conditions.

Three white, nonalcoholic men, 21, 27, and 28 years old, were admitted to the Clinical Research Center of Mount Sinai Hospital after the studies had been explained in detail and informed consent had been obtained. All three were occasional consumers of moderate, nonintoxicating amounts of alcoholic beverages but had entirely refrained from alcohol for 1 month prior to admission. On admission, results of physical and laboratory examinations were all within normal limits. After 5 days of the routine patient diet, they were fed a 3900 calorie diet, in which protein accounted for 15 percent, fat 32 percent, and carbohydrate 11 percent of total calories. Ethanol comprised 42 percent of the total calories (225 g of ethanol), and

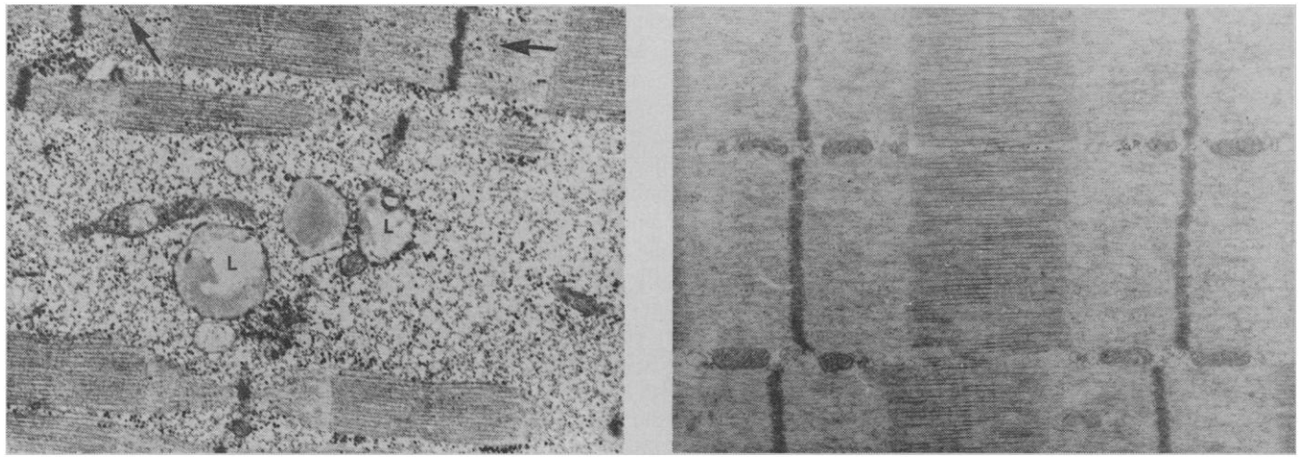

Fig. 1. Electron micrographs of muscle from subject F.B. (× 13,500). (Left) Biopsy specimen after 28 days of ethanol ingestion. The interfibrillar spaces are widened and contain glycogen and lipid droplets (*L*). Excess glycogen is seen between actin filaments in the I band (arrows). (Right) Specimen taken 6 months after cessation of ethanol administration appears normal.

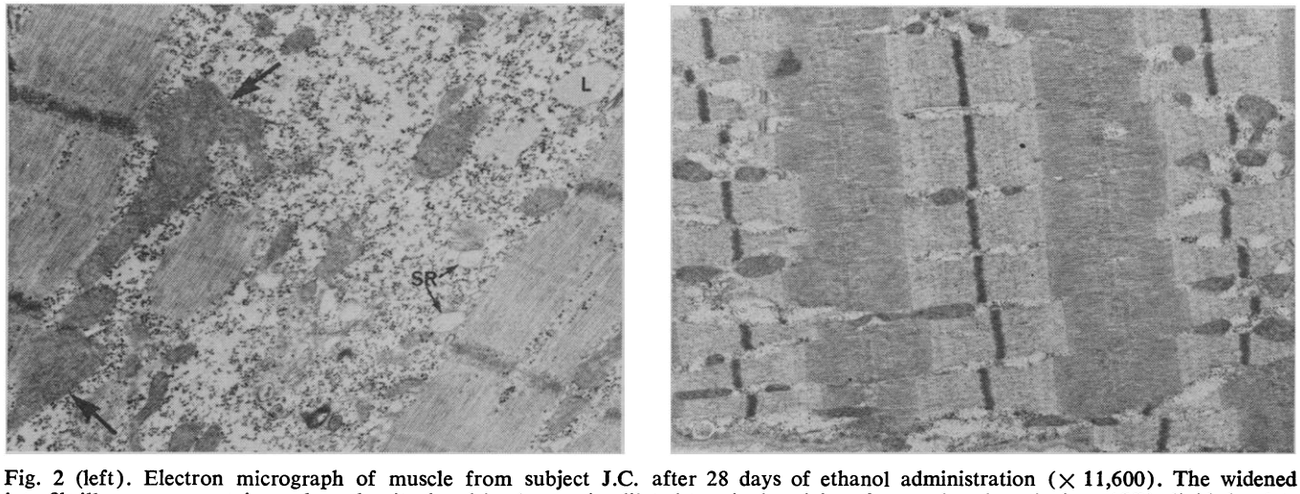

Fig. 2 (left). Electron micrograph of muscle from subject J.C. after 28 days of ethanol administration (× 11,600). The widened interfibrillar space contains enlarged mitochondria (arrows), dilated terminal vesicles of sarcoplasmic reticulum (*SR*), lipid droplets (*L*), and excess glycogen. Fig. 3 (right). Electron micrograph of muscle from subject D.M. after 28 days of ethanol administration (× 8500). Intracellular edema, characterized by widened interfibrillar spaces, is prominent.

Table 1. Activity of serum creatine phosphokinase in three subjects after 1, 2, 3, and 4 weeks of ethanol administration. Normal activity, < 4.5 units.

Subject	Activity				
	Control	1 wk	2 wk	3 wk	4 wk
J.C.	1.5	2.0	2.0	6.8	11.8
F.B.	0.9	1.0	4.6	5.8	5.8
D.M.	1.8	1.9	2.2	5.4	5.6

was given as a 15 percent solution in fruit juices every 3 hours.

This is an amount of ethanol commonly consumed daily by chronic alcoholics. We have previously demonstrated that the fatty liver and increased serum transaminase activity produced by this amount of alcohol is rapidly reversible upon discontinuation of alcohol ingestion. At no time did the subjects display evidence of gross inebriation, such as ataxia or slurred speech. The diet was supplemented with generous amounts of a multivitamin preparation, minerals, and folic acid, as previously described (*10*). The activity of serum creatine phosphokinase was determined weekly by the method of Siegel and Cohen (*11*). Surgical biopsy specimens were obtained at various times from the deltoid muscle in two subjects and from the gastrocnemius muscle in one (Table 1). Ethanol was withheld for 12 to 18 hours prior to the biopsy. The muscle was resected after maintenance of isometric tension in a specially designed double clamp, fixed in 4 percent, cacodylate-buffered formaldehyde, post-fixed in 1 percent OsO_4, and processed for light and electron microscopy (*12*). The ultrastructural features were compared with those of a large number of normal muscle biopsy specimens obtained in other studies.

In all subjects, the activity of serum creatine phosphokinase rose during the period of ethanol administration (Table 1), suggesting that damage to muscle had occurred. The activity of the enzyme had returned to normal in specimens obtained 2 weeks after cessation of ethanol consumption. Light microscopy showed no abnormalities in any of the biopsy specimens. By contrast, striking deviations from normal were observed by electron microscopy in all specimens obtained after 28 days of ethanol ingestion; changes were more severe in subjects J.C. and F.B. (Figs. 1–3). The muscles displayed pronounced intracellular edema. The interfibrillar spaces were widened and contained glycogen, lipid droplets, deranged elements of sarcoplasmic reticulum, and irregular mitochondria, many of which were enlarged. Glycogen was increased in the I band between actin filaments. The sarcoplasmic reticulum was generally dilated and vesicular and often contained small osmiophilic particles. The basic sarcomere architecture was, however, not altered. In subject F.B., the specimen taken 6 months after ethanol intake appeared normal. In subject D. M., the control biopsy specimen, obtained before ethanol administration, appeared normal.

The results of our study indicate that chronic ingestion of ethanol for 28 days, independent of nutritional or other factors, leads to increased serum creatine phosphokinase activity and striking ultrastructural changes in skeletal muscle. The conspicuous separation of intracellular organelles we observed has been noted in rats fed ethanol in drinking water (*4*), and may be the earliest change which occurs. The dilatation of the sarcoplasmic reticulum, mitochondrial enlargement, and increased fat are similar to ultrastructural lesions produced in the liver of rats (*13*) and human volunteers (*10, 14*) by chronic administration of ethanol. Clinical evidence of muscular disease is noted only in a minority of chronic alcoholics. By the same token, the increase in serum creatine phosphokinase activity after controlled ethanol administration appears to be variable, since in another study a number of alcoholic subjects did not display increased activity of this enzyme after 2 to 3 weeks of ethanol consumption (*15*).

Injurious effects of ethanol in an organ such as the liver may be caused by changes induced by the metabolism of ethanol (*16*) or by a direct action of ethanol itself (*17*). In view of the fact that no appreciable metabolism of ethanol occurs in muscle, the muscular damage associated with chronic ethanol intake may be a direct effect of this compound. Alternately, ethanol may injure muscle by interfering with carbohydrate metabolism in that tissue (*4*). Since cardiac muscle shares many characteristics with skeletal muscle, the effects demonstrated in skeletal muscle may also be present in the heart and may play a role in alcoholic cardiomyopathy.

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18. The research protocol of this study was approved by the research committee of the Faculty of Mount Sinai School of Medicine and the research administrative committee of the Mount Sinai Medical Center. Work supported in part by PHS grants MH15558, AM12511, MH20067, RR71, and NBO5041.

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Ethyl Mercury p-Toluene Sulfonanilide: Lethal and Reproductive Effects on Pheasants

Abstract. *Ethyl mercury* p-*toluene sulfonanilide (active ingredient of Ceresan M) at a dietary concentration of 30 parts per million (12.5 parts of mercury per million) was lethal to adult ring-necked pheasants. Egg production and survival of third-week embryos were sharply reduced when breeders were maintained on feed containing 10 parts of this compound per million (4.2 parts of mercury per million).*

The recent discovery of mercury pollution in many American and Canadian ecosystems, as in Sweden and Japan a decade earlier, has precipitated a need to evaluate the potential hazard to wild animals as well as to man. Industrial