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Cardiovascular Effects of Alcohol[1]

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RUBIN, E. *Cardiovascular effects of alcohol.* PHARMAC. BIOCHEM. BEHAV. 13: Suppl. 1, 37–40, 1980.—Epidemiologic studies suggest that moderate consumption of alcohol provides some degree of protection against ischemic heart disease. On the other hand, cerebrovascular accidents and overall mortality are increased at all levels of alcohol intake. Thus, it is inappropriate to advise abstainers to begin to drink alcoholic beverages as a protective measure for coronary artery disease. Acute ingestion of large amounts of alcohol leads to a negative inotropic effect on the myocardium, together with inhibition of a variety of biochemical reactions in subcellular organelles of the heart. Chronic alcoholism is associated with the development of a congestive cardiomyopathy (alcoholic cardiomyopathy), which is independent of vitamin B_1 deficiency or other nutritional deficits.

Alcohol Heart Muscle Coronary arteries

THE preponderance of contemporary evidence suggests a Manichean approach to the effects of alcohol on the heart. On the one hand, chronic alcohol abuse has long been recognized as injurious [6, 8, 23, 47, 55, 64, 71], and resulting damage has been clearly differentiated from beriberi heart disease [15,53]. On the other hand, recent epidemiologic surveys suggest that moderate amounts of alcoholic beverages may protect, to some extent, against coronary artery disease. In this presentation I will review the current understanding of the relation between consumption of alcohol and ischemic heart disease, and damage to the myocardium and conducting system.

ALCOHOL AND CARDIOVASCULAR DISEASE

"Problem drinkers" and chronic alcoholics exhibit a significantly greater mortality from cardiovascular causes than moderate drinkers or abstainers [3, 4, 59], but this finding has not received universal acceptance because the same individuals who abuse alcohol are, for the most part, also smokers. Despite this caveat, the finding is probably valid, in view of the fact that studies of twins, which were controlled for smoking, showed a similar increase in cardiovascular mortality among heavy drinkers [21]. In contrast to the findings in chronic alcoholics, the incidence of fatal coronary artery disease was lower among moderate drinkers in several studies [9, 38, 57, 63, 64]. A corollary study demonstrated an increased risk of myocardial infarction in those who drank no alcoholic beverages, compared to those who did drink [44]. It is difficult to quantitate the amount of alcohol associated with this mild protective effect. In several studies such a protective effect was found in individuals who drank less than two "drinks" a day [27] or fewer than six "drinks" [63]. The difficulty in quantitating the relationship between the amount of alcohol consumed and coronary artery disease is demonstrated by the fact that some studies have not demonstrated statistically significant differences in the risk of ischemic heart disease between drinkers and non-drinkers [22,67]. Cohort studies have generally reported more impressive protective effects of moderate alcohol intake. A lesser risk of ischemic heart disease was found in individuals who drank more than one "drink" a day when the Framingham study [63] was analyzed. Less than three drinks a day provided a negative correlation between ischemic heart disease and alcohol consumption in Honolulu [73], and similar data were obtained in Chicago [13] and Yugoslavia [36].

The reasons for the putative protection against ischemic heart disease afforded by moderate drinking are not known. Alcohol increases the concentration of high density lipoproteins in the blood [5, 11, 29], increases fibrinolytic activity [41] and inhibits the aggregation of platelets [26]. Whether any or all of these factors play a role is not clear at this time.

Before the physician advises a patient to drink moderately in order to protect his heart, he should be aware that overall mortality is not lower, even in moderate drinkers, because of increased mortality from cancer, stroke and accidents. Moreover, some individuals will probably not be able to restrict their drinking pattern to "moderate consumption" and may actually be tempted to drink heavily.

The negative correlation between coronary artery disease and moderate alcohol consumption does not hold true for strokes. The habitual ingestion of large amounts of alcohol seems to increase the risk of cerebrovascular accidents. Such data have been found in the Framingham study [31], Japan, Honolulu and Yugoslavia [36]. It has been suggested that the risk of strokes is increased because acute alcohol intake may temporarily elevate blood pressure [34].

ARRHYTHMOGENIC EFFECTS OF ALCOHOL CONSUMPTION

In man and animals, arrhythmias, principally ventricular,

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have been shown to be associated with chronic alcohol consumption [10, 16, 17, 40]. Electrocardiographic abnormalities have been observed in alcoholic dogs, and a significant incidence of sudden death was noted in these animals [17]. Within one-half hour of infusion of alcohol to dogs, ventricular ectopic beats were produced [49]. Intravenous alcohol injection has been demonstrated to prolong atrioventricular and interventricular conduction times, and to induce second-degree heart block [25]. In experiments using concentrations of alcohol which may be found in human alcoholics, the threshold for ventricular fibrillation in dogs was decreased [20]. The adverse arrhythmogenic events produced by acute administration of alcohol are more severe in animals made chronically alcoholic.

Arrhythmias have been produced in alcoholic volunteers given alcoholic beverages orally [61], and many dysrhythmic episodes have been observed in "spree" drinkers, a condition which has been called the "holiday heart" [18]. Moreover the high incidence of sudden death in alcoholics [14, 37, 65, 69] has been suggested to be due to sudden arrhythmias.

ALCOHOLIC CARDIOMYOPATHY

It is now recognized that a number of alcoholics (the true incidence is not well documented) develop a congestive cardiomyopathy, which is not related to electrolyte disturbances, viral infections, congeners in alcoholic beverages or vitamin B_1 deficiency [15,53]. This syndrome has been well reviewed in recent years [6, 23, 47, 55]. Because alcoholic cardiomyopathy usually occurs only after many years of alcohol consumption, and because a good experimental model for this disorder is not available, it has not been possible to obtain exact data regarding the quantities of alcohol and the duration of alcohol abuse required for the development of this malady. Moreover, while acute and chronic alcohol ingestion have been shown to exert functional effects on the myocardium, it is not clear whether such effects are, in fact, related to the chronic and irreversible myocardial damage found in alcoholic cardiomyopathy.

Both clinically and pathologically, the disease of alcoholic cardiomyopathy is indistinguishable from other forms of congestive cardiomyopathy. The heart is usually enlarged and the chambers dilated. Occasionally the left ventricle exhibits mural thrombi, although these are not as common as thought by earlier pathologists. On pathologic examination the myocardium exhibits varying degrees of hypertrophy of muscle fibers, necrosis, myocytolysis, inflammation and fibrosis. Ultrastructurally, mitochondria are enlarged, the sarcoplasmic reticulum dilated, and increased fat and lipofuscin as well as abnormalities of the intercalated discs may be seen. These clinical and morphologic abnormalities are not specific, and the diagnosis of alcoholic cardiomyopathy is made only on the basis of a clinical history of chronic alcoholism, in the absence of other known causes of heart disease.

ACUTE FUNCTIONAL EFFECTS OF ALCOHOL

There is a general agreement that the ingestion of alcohol results in decreased cardiac contractility [1,50]. Catecholamines may play a role *in vivo*, because blockade of the sympathetic nervous system augments the negative inotropic effect of acute ethanol ingestion [12]. On the other hand, alcohol also reduced contractile force *in vitro* in isolated cardiac tissue from various animal species [19]. Acutely, alcohol shortens the action potential [19,24]. *In vitro*, alcohol, and its primary metabolite, acetaldehyde, inhibit the ATPase activity in isolated cardiac plasma membranes [70], a finding similar to that observed in other tissues [30]. The presence of alcohol *in vitro* also depresses binding and uptake of calcium by the isolated sarcoplasmic reticulum of the heart [66]. The depression of calcium transport is even greater when membranes are phosphorylated by the appropriate protein kinase [52]. Both alcohol and acetaldehyde inhibit the association of actin and myosin *in vitro* [45]. This effect may result from interference with the binding of calcium by troponin, an important constituent of myosin [46]. Perfusion of the heart with ethanol and acetaldehyde has also been shown to reduce total protein synthesis in the heart [60], an effect which might have long-term significance.

CHRONIC EFFECTS OF ALCOHOL ON THE MYOCARDIUM

Chronic alcohol administration to dogs has been shown to produce persistent, though not irreversible, functional effects [43,48]. After 18 months of alcohol administration to dogs, diastolic pressure was higher, and stroke work was reduced, using afterload increments with angiotensin [48]. The ventricular myocardium in these experiments seemed to be "stiffer", a finding which correlated with the accumulation of proteoglycans in the myocardium. These findings were interpreted as comparable to those found in human alcoholics with subclinical cardiac abnormalities. Force-velocity relationships were also decreased in glycerinated heart fibers obtained from chronically alcoholic dogs [58].

In man, asymptomatic cardiac abnormalities are often seen [39,72], including decreased myocardial capacity, as evidenced by increased ventricular filling pressure [35]. Changes in systolic time intervals [72] and mild interstitial fibrosis at autopsy [28] have been described. As noted previously, the symptoms of fully developed alcoholic cardiomyopathy, in which cardiac decompensation occurs, are similar to those seen in other congestive cardiomyopathies. Unlike other forms of cardiomyopathy, improvement is often noted following abstinence from alcoholic beverages [35,50].

Chronic consumption of alcohol affects almost all subcellular structural constituents of the cardiac myocyte. It is associated with altered phospholipid composition of cardiac membranes [51] and other organs [54]. In volunteers fed ethanol for one month, about half showed modest increases in the activity of serum creatine phosphokinase [56,62]. In these volunteers, ultrastructural studies of skeletal muscle showed altered mitochondria and sarcoplasmic reticulum, together with increases in glycogen and fat. In alcoholic cardiomyopathy (and after chronic ingestion of alcohol by experimental animals), mitochondria exhibited conspicuous changes [2, 58, 68]. Chronic alcohol ingestion in animals led to reduced oxidation of fatty acids by cardiac mitochondria [48] and a decreased ability to oxidize other substrates [42]. In dogs fed alcohol chronically, calcium transport by sarcoplasmic reticulum was reduced [58], a finding confirmed in the human volunteers [56]. Chronic alcohol ingestion also affected contractile proteins in man and experimental animals [56]. In such studies, actin and myosin derived from skeletal muscle after long-term alcohol feeding demonstrated a reduced capacity to associate *in vitro*. Moreover, the ATPase activity of myosin, and the sensitivity of this enzyme to calcium, were severely reduced.

In summary, alcohol abuse is associated with the clinical

syndrome of alcoholic cardiomyopathy, a disorder which appears to be a direct toxic effect of ethanol. Acutely and chronically alcohol impairs numerous myocardial functions, but the relationship of these changes to the development of cardiomyopathy remains speculative. Moderate consumption of alcohol may exert a mild protective effect against ischemic heart disease, but does not protect against stroke. Because overall mortality associated with any level of alcohol consumption is increased, it is premature to advise patients who do not drink, to embark upon this habit.

REFERENCES

1. Ahmed, S. S., G. E. Levinson and T. J. Regan. Depression of myocardial contractility with low doses of ethanol in normal man. *Circulation* **48**: 378, 1973.
2. Alexander, C. S., K. K. Sekhri and H. T. Nagasawa. Alcoholic cardiomyopathy in mice: Electron microscopic observations. *J. molec. Cell Cardiol.* **9**: 247, 1977.
3. Ashley, M. J. Alcohol consumption and cardiovascular disease: An epidemiologic perspective. Presented at Workshop on Alcohol Consumption and Cardiovascular Disease: Public Health Implications, Addiction Research Foundation, Toronto, Canada, May, 1980.
4. Ashley, M. J. and J. G. Rankin. Hazardous alcohol consumption and diseases of the circulatory system. *J. Stud. Alcohol*, in press.
5. Barboriak, J. J., A. J. Anderson and R. G. Hoffmann. Interrelationships between coronary artery occlusion, high-density lipoprotein cholesterol, and alcohol intake. *J. Lab. clin. Med.* **94**: 348, 1979.
6. Bing, R. J. and H. Tillmanns. The effects of alcohol on the heart. In: *Metabolic Aspects of Alcoholism*. edited by C. S. Lieber. Baltimore: University Park Press, 1977, p. 117.
7. Blackwelder, W. C., K. Yano, G. G. Rhoads, A. Kagan, T. Gordon and Y. Palesch. Alcohol and mortality. The Honolulu Study. *Am. J. Med.* **68**: 164, 1980.
8. Bollinger, O. Über die Häufigkeit und Ursachen der idiopathischen Herzhypertrophie in München. *Dtsch. Med. Wochenschr.* **10**: 180, 1884.
9. Brummer, P. Coronary mortality and living standard. II. Coffee, tea, cocoa, alcohol and tobacco. *Acta med. scand.* **186**: 61, 1969.
10. Burch, G. E., H. L. Colcolougat, J. M. Harb and C. Y. Tsui. The effects of ingestion of ethyl alcohol, wine and beer on the myocardium of mice. *Am. J. Cardiol.* **27**: 522, 1971.
11. Castelli, W. P., T. Gordon, M. C. Hjortland, A. Kagan, J. T. Doyle, C. G. Harnes, S. B. Hulley and W. J. Zukel. Alcohol and blood lipids. *Lancet* **2**: 153, 1977.
12. Child, J. S., R. B. Kovick, J. A. Levisman and M. L. Pearce. Cardiac effects of acute ethanol ingestion unmasked by autonomic blockade. *Circulation* **59**: 120, 1979.
13. Dyer, A. L., J. Stamler, O. Paul, D. M. Berkson, M. H. Lepper, H. McKean, R. B. Shekelle, H. A. Lindberg and D. Garside. Alcohol consumption, cardiovascular risk factors, and mortality in two Chicago epidemiologic studies. *Circulation* **56**: 1067, 1977.
14. Dyer, A. R., J. Stamler, O. Paul, M. Lepper, R. B. Shekelle, H. McKean and D. Garside. Alcohol consumption and 17-year mortality in the Chicago Western Electric Company study. *Prevent. Med.* **9**: 78, 1980.
15. Eliaser, M., Jr. and F. J. Giansiracusa. The heart and alcohol. *Calif Med* **84**: 234, 1956.
16. Ettinger, P. O., M. I. Khan, H. A. Oldewurter and T. J. Regan. Left ventricular conduction abnormalities in chronic diabetes and alcoholism. *Circulation* **42**: (Suppl. 3): 98, 1970.
17. Ettinger, P. O., M. Lyons, H. A. Oldewurter and T. J. Regan. Cardiac conduction abnormalities produced by chronic alcoholism. *Am. Heart J.* **91**: 66, 1974.
18. Ettinger, P. O., C. F. Wu, C. D. Cruz, A. B. Weisse, S. S. Ahmed and T. J. Regan. Arrhythmias and the "Holiday Heart": Alcohol-associated cardiac rhythm disorders. *Am. Heart J.* **95**: 555, 1978.
19. Fisher, V. J. and F. Kavaler. The action of ethanol upon the contractility of normal ventricular myocardium. In: *Alcohol and Abnormal Protein Biosynthesis*, edited by M. A. Rothschild, M. Oratz and S. S. Schreiber. New York: Pergamon Press, 1975, p. 187.
20. Foerster, J., J. Rasor, P. Gee, V. Zakauddin and D. Mason. Deleterious effects of alcohol upon ventricular fibrillation threshold: Computer controlled determination in the closed chest dog. *Circulation* (abst.) II-85, 1979.
21. Friberg, L., R. Cederlof, U. Lorich, T. Lundman and U. de-Faire.: Mortality in twins in relation to smoking habits and alcohol problems. *Archs envir. Hlth.* **27**: 294, 1973.
22. Friedman, G. D., L. G. Dales and H. K. Ury. Mortality in middle-aged smokers and non-smokers. *New Engl. J. Med.* **300**: 213, 1979.
23. Geller, S. A. and E. Rubin. The effects of alcohol on striated and smooth muscle. In: *Metabolic Aspects of Alcoholism*, edited by C. S. Leiber. Baltimore: University Park Press, 1977, p. 187.
24. Gimeno, A. L., M. F. Gimeno and J. L. Webb. Effects of ethanol on cellular membrane potentials and contractility of isolated rat atrium. *Am. J. Physiol.* **203**: 194, 1962.
25. Goodkind, M. J., N. H. Gerber, J. R. Mellen and J. B. Kostis. Altered intracardial conduction after acute administration of ethanol in the dog. *J. Pharmac. exp. Ther.* **194**: 633, 1975.
26. Haut, M. J. and D. H. Cowan. The effect of ethanol on hemostatic properties of human blood platelets. *Am. J. Med.* **56**: 22, 1974.
27. Hennekens, C. H., B. Rosner and D. S. Cole. Daily alcohol consumption and fatal coronary heart disease. *Am. J. Epidemiol.* **107**: 196, 1978.
28. Hognestad, J. and P. Teisberg. Heart pathology in chronic alcoholism. *Acta path. Microbiol. scand.* **81**: 315, 1973.
29. Hulley, S. B., R. Cohen and G. Widdowson. Plasma high-density lipoprotein and cholesterol level: Influence of risk factor intervention. *J. Am. Med. Ass.* **238**: 2269, 1977.
30. Israel, Y., H. Kalant and A. E. LeBlanc. Effects of lower alcohols on potassium transport and microsomal adenosinetriphosphatase activity of rat cerebral cortex. *Biochem. J.* **100**: 27, 1966.
31. Kannel, W. B., P. A. Wolf and T. R. Dawber. An evaluation of the epidemiology of atherothrombotic brain infarction. *Milbank Meml. Fund Qu. Hlth. Soc.* **Fall**: 405, 1975a.
32. Klatsky, A. L., G. D. Friedman and A. B. Siegelaub. Alcohol consumption before myocardial infarction: Results from the Kaiser-Permanente epidemiologic study of myocardial infarction. *Ann. intern. med.* **81**: 294, 1974.
33. Klatsky, A. L., G. D. Friedman and A. B. Siegelaub. Alcohol use, myocardial infarction, sudden cardiac death, and hypertension. *Alcoholism: clin. exp. Res.* **3**: 33, 1979.
34. Klatsky, A. L., G. D. Friedman, A. B. Siegelaub and M. J. Gerard. Alcohol consumption and blood pressure. Kaiser-Permanente multiphasic health examination data. *New Engl. J. Med.* **296**: 1194, 1977.
35. Koide, T. and K. Ozeki. The incidence of myocardial abnormalities in man related to the level of ethanol consumption. *Jap. Heart J.* **15**: 337, 1974.

36. Kozarevic, D. J., D. McGee, N. Vojvodic, Z. Racic, T. Dawber, T. Gordon and W. Zukel. Frequency of alcohol consumption and morbidity and mortality: The Yugoslavia Cardiovascular Disease Study. *Lancet* **1**: 613, 1980.
37. Kramer, K., L. Kuller and R. Fisher. The increasing mortality attributed to cirrhosis and fatty liver in Baltimore (1957–1966). *Ann. intern. Med.* **69**: 273, 1968.
38. LaPorte, R. E., J. L. Cresanta and L. H. Kuller. The relationship of alcohol consumption to atherosclerotic heart disease. *Prevent. Med.* **9**: 22, 1980.
39. Limas, C. J., N. H. Guiha, O. Lekagul and J. N. Cohn. Impaired left ventricular function in alcoholic cirrhosis with ascites. Ineffectiveness of ouabain. *Circulation* **49**: 755, 1974.
40. Maines, J. E. and E. E. Aldinger. Myocardial depression accompanying chronic consumption of alcohol. *Am. Heart J.* **73**: 55, 1967.
41. Meade, T. W., R. Chakrabarti, A. P. Haines, W. R. S. North and Y. Stirling. Characteristics affecting fibrinolytic activity and plasma fibrinogen concentrations. *Br. Med. J.* **1**: 153, 1979.
42. Pachinger, O., J. Mao, J. M. Fauvel and R. J. Bing. Mitochondrial function and excitation-contraction coupling in the development of alcoholic cardiomyopathy. *Recent Adv. Stud. Cardiac Struct. Metab.* **5**: 423, 1975.
43. Pachinger, O. M., H. Tillmanns, J. C. Mao, J. M. Fauvel and R. J. Bing. The effect of prolonged administration of ethanol on cardiac metabolism and performance in the dog. *J. clin. Invest.* **52**: 2690, 1973.
44. Petitti, D. B., J. Wingerd, F. Pellegrin and S. Ramcharan. Risk of vascular disease in women. Smoking, oral contraception, non-contraceptive estrogens, and other factors. *J. Am. Med. Ass.* **242**: 1150, 1979.
45. Puszkin, S. and E. Rubin. Adenosine diphosphate effect on contractility of human muscle actomyosin: Inhibition by ethanol and acetaldehyde. *Science* **188**: 1319, 1975.
46. Puszkin, S. and E. Rubin. Effects of ADP, ethanol and acetaldehyde on the relaxing complex of human muscle and its adsorption by polystyrene particles. *Archs. Biochem. Biophys.* **177**: 574, 1976.
47. Regan, T. J., P. O. Ettinger, B. Haider, S. S. Ahmed, H. A. Oldewurtel and M. M. Lyons. The role of ethanol in cardiac disease. *A. Rev. Med.* **28**: 393, 1977.
48. Regan, T. J., M. I. Khan, P. O. Ettinger, B. Haider, M. M. Lyons and H. A. Oldewurtel. Myocardial function and lipid metabolism in the chronic alcoholic animal. *J. clin. Invest.* **54**: 740, 1974.
49. Regan, T. J., G. J. Koroxenidis, C. B. Moschos, H. A. Oldewurtel, P. H. Lehan and H. K. Hellems. The acute metabolic and hemodynamic responses of the left ventricle to ethanol. *J. clin. Invest.* **45**: 270, 1966.
50. Regan, T. J., G. E. Levinson, H. A. Oldewurtel, M. J. Frank, A. B. Weisse and C. B. Moschos. Ventricular function in noncardiacs with alcoholic fatty liver: The role of ethanol in the production of cardiomyopathy. *J. clin. Invest.* **48**: 397, 1969.
51. Reitz, R. C., W. Helsabeck and D. P. Mason. Effects of chronic alcohol ingestion on the fatty acid composition of the heart. *Lipids* **8**: 80, 1973.
52. Retig, J. N., M. A. Kirchberger, E. Rubin and A. M. Katz. Effects of ethanol on calcium transport by microsomes phosphorylated by cyclic AMP-dependent protein kinase. *Biochem. Pharmac.* **26**: 393, 1977.
53. Robin, E. and N. Goldschlager. Persistence of low cardiac output after relief of high output by thiamine in a case of alcoholic beriberi and cardiac myopathy. *Am. Heart J.* **80**: 103, 1970.
54. Rottenberg, H., A. Waring, D. E. Robertson and E. Rubin. Effects of chronic ethanol on the physical properties of liver mitochondrial membranes. 5th Biennial International Symposium on Alcoholism, Cardiff, Wales, 1980.
55. Rubin, E. Alcoholic myopathy in heart and skeletal muscle. *New Engl. J. Med.* **301**: 28, 1979.
56. Rubin, E., A. M. Katz, C. S. Lieber, E. P. Stein and S. Puszkin. Muscle damage produced by chronic alcohol consumption. *Am. J. Pathol.* **83**: 499, 1976.
57. St. Leger, A. S., A. L. Cochran and F. Moore. Factors associated with cardiac mortality in developed countries with particular reference to the consumption of wine. *Lancet* **1**: 1017, 1979.
58. Sarma, J. S. M., S. Ikeda, R. Fischer, Y. Maruyama, R. Weishaar and R. J. Bing. Biochemical and contractile properties of heart muscle after prolonged alcohol administration. *J. molec. Cell Cardiol.* **8**: 951, 1976.
59. Schmidt, W. and R. E. Popham. Heavy alcohol consumption and physical health problems: A review of the epidemiological evidence. *Drug Alcohol Depend.* **1**: 27, 1975–76.
60. Schreiber, S. S., K. Briden, M. Oratz and M. A. Rothschild. Ethanol, acetaldehyde and myocardial protein synthesis. *J. clin. Invest.* **51**: 2820, 1973.
61. Singer, K. and W. B. Lundberg. Ventricular arrhythmias associated with the ingestion of alcohol. *Ann. intern. Med.* **77**: 247, 1972.
62. Song, S. K. and E. Rubin. Ethanol produces muscle damage in human volunteers. *Science* **175**: 327, 1972.
63. Stason, W. B., R. K. Neff, O. S. Miettinen and H. Jick. Alcohol consumption and nonfatal myocardial infarction. *Am. J. Epidemiol.* **104**: 603, 1976.
64. Steell, G. Heart-failure as a result of chronic alcoholism. *Med. Chron.* **18**: 1, 1893.
65. Sundby, P. *Alcoholism and Mortality.* Oslo, Norway: University Tsfordaget, Rutgers University Center of Alcohol Studies, 1969.
66. Swartz, M. H., D. I. Repke, A. M. Katz and E. Rubin. Effects of ethanol on calcium binding and calcium uptake by cardiac microsomes. *Biochem. Pharmac.* **23**: 2369, 1974.
67. U.S. Department of Health, Education and Welfare, Public Health Service. Alcohol and Health, Second Special Report to the U.S. Congress, National Institute on Alcohol Abuse and Alcoholism, Rockville, Maryland, June, 1974.
68. Vasdev, S. C., R. N. Chakravarti, D. Subrahmanyam, A. C. Jain and P. L. Wahi. Myocardial lesions induced by prolonged alcohol feeding in rhesus monkeys. *Cardiovasc. Res.* **9**: 134, 1975.
69. Velisheua, L. S., B. G. Goldina and V. I. Boguslavsky. Sudden death in alcohol-induced cardiomyopathy. Proc 1st US-USSR Symp. Sudden Death, Yalta, 1977. NIH Publication 78–1470, 1978.
70. Williams, J. W., M. Tada, A. M. Katz and E. Rubin. Effects of ethanol and acetaldehyde on the $(Na^+ + K^+)$-activated ATPase activity of cardiac plasma membranes. *Biochem. Pharmac.* **24**: 27, 1975.
71. Wood, G. B. *A Treatise on the Practice of Medicine,* Vol. 2. Philadelphia: Lippincott, Gambo and Co., 1847.
72. Wu, C. F., M. Sudhakar, G. Jaferi, S. S. Ahmed and T. J. Regan. Preclinical cardiomyopathy in chronic alcoholics: A sex difference. *Am. Heart J.* **91**: 281, 1976.
73. Yano, K., G. G. Rhoads and A. Kagan. Coffee, alcohol and risk of coronary heart disease among Japanese men living in Hawaii. *New Engl. J. Med.* **297**: 405, 1977.