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TOXICOLOGY OF ETHANOL[1,2]

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Factors Alleged to Accelerate, or Retard, the Disappearance of Ethanol from the Body

The rate of disappearance of ethanol from the entire body is usually expressed as mg/kg per hr, which has been designated B_{60}. For humans the average B_{60} is about 100. It is fairly constant for a given person but varies among individuals, with extremes of about 50 and 200. Essentially the same information may be obtained from the slope of the curve for blood ethanol concentration, which like B_{60}, is a straight line. This is the Widmark β factor. It is now expressed as mg per cent per hr,[2] and designated as β_{60}. For humans the average β_{60} is about 15, with extremes of 10 to 20. To save space, we will use B_{60} and β_{60} in this chapter.

Over the years many chemical or physical factors have been alleged to alter B_{60}, and therefore β_{60}, but most of these claims have not been verified by later investigators (1, 2).

We will now consider certain chemicals which offer promise of really altering B_{60} and β_{60}, and two other procedures of perhaps dubious efficacy.

Fructose.—In 1937 Carpenter & Lee (3) described experiments with human subjects, who ingested 10 to 20 ml of ethanol, alone, or with 30 to 60 g of fructose or glucose. They reported that fructose shortened the ethanol disappearance period to about two-thirds of that of the controls, while glucose caused a slight decrease, if any. Fifteen years later Pletscher, Bernstein & Staub (4) reported that fructose in a dose of 0.9 to 1.8 g/kg caused an increase of 48 to 68 per cent in the β_{60} of human subjects who had ingested ethanol in the amount of 0.9 to 1.0 g/kg. However, this dose of fructose caused severe epigastric pain in subjects receiving ethanol but not in the absence of ethanol. Another paper by this group (5) stated that fructose, 1 to 2 g/kg, increased β_{60} of dogs 80 per cent, while the same dose of glucose caused an increase of only 10 per cent. A still later paper by this group (6) reported that administration of 100 g of fructose to normal humans increased β_{60} by an average of 24 per cent, while patients with hepatitis given the same treatment showed a β_{60} increase of 11 to 25 per cent. Using dogs, Clark & Hulpieu (7) found that fructose increased the ethanol β_{60} by about 50 per cent. Lundquist & Wolthers (8) tested five human sub-

[1] The survey of literature pertaining to this review was concluded in August 1968.

[2] Mg per cent designates mg per 100 ml of a fluid, or per 100 g of a solid material.

jects who ingested ethanol, 0.5 g/kg, and, beginning 2 hr later, ate 22 g of fructose at half-hour intervals. With four of the subjects fructose increased β_{60} 28 to 56 per cent, while the increase was only 2 per cent in the fifth subject. In 1965 Lundquist's Copenhagen group published a study (9) with humans on the mechanism of this action of fructose. They conducted analyses for ethanol, acetate, lactate, pyruvate, and oxygen content on blood from the femoral artery and the hepatic vein. To obtain blood from the hepatic vein without major surgery, they used a Cournand catheter, which was inserted into a small incision in the cubital vein and was passed along the proximal course of this vein until the radio-opaque catheter head traversed the right auricle and entered the hepatic vein. Ethanol, fructose, and ethanol + fructose were given by intravenous infusion, the rates of administration per hour being: ethanol, 6 to 11 g/kg; and fructose, 7.5 to 12 g/kg. On changing the infusion from ethanol alone to ethanol + fructose, the liver blood flow was increased about 30 per cent, and the changes in the liver biochemistry were: 60 per cent increase in oxygen uptake, almost twofold increase in ethanol disappearance and acetate production, 60 per cent decrease in the production of lactate + pyruvate, and 200 per cent increase in the hepatic output of glucose. Compared with fructose alone, ethanol + fructose increased the hepatic uptake of fructose about 20 per cent, and a corresponding amount of a polyol, probably sorbitol, appeared in the hepatic vein blood. With ethanol alone, about 80 per cent of the uptake of oxygen was used for the oxidation of ethanol to acetate; with ethanol + fructose, the per cent of the oxygen uptake required to form acetate from ethanol was less, in spite of the twofold increase in ethanol converted to acetate. As a possible mechanism for the fructose effect on the disappearance of ethanol, the authors suggest that some of the degradation products of fructose serve as hydrogen acceptors in the dehydrogenation of part of the ethanol. They say, "Thereby, a limiting step in the deydrogenation of alcohol to acetaldehyde, namely dissociation of the complex alcohol dehydrogenase and reduced nicotinamide adenine dinucleotide,[3] is circumvented."

Ortho-phenanthroline.—A 1956 paper by Hoch & Vallee (10) described a study of certain factors affecting the activity of yeast ADH, and stated that ortho-phenanthroline (1, 10) markedly inhibits the activity of yeast ADH, as measured by the conversion of NAD to NADH during the incubation of saline containing NAD, ADH and ethanol. In 1963 Lundquist, Svendsen & Petersen (11) reported that *o*-phenanthroline, in a concentration of 5m*M*/L in a homogenate of rat liver containing 51 mg per cent of ethanol, caused total inhibition of the disappearance of ethanol. They ascribed this result to the combination of *o*-phenanthroline with the zinc of liver ADH.

Pyrazoles.—In 1963 Theorell & Yonetani (12) stated that pyrazole inhibits the action of liver ADH, and described the isolation of a crystalline

[3] The modern symbol for this complex is ADH-NADH: formerly it was designated by ADH-DPNH.

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complex formed by the union of pyrazole with ADH and NAD, having the molecular composition, 1 ADH-2 Pyrazole-2 NAD. Two years later Theorell (13) published a further study of certain complexes of ADH, showing that the action of ADH is inhibited by pyrazole and imidazole, and even more by 3-iodopyrazole. In this paper Theorell reported *in vivo* experiments with pyrazole conducted by his colleagues, L. Goldberg & A. Wietlind, showing that a moderate dose of pyrazole inhibited the disappearance of ethanol in dogs and rats. A somewhat larger dose of pyrazole, given to rats, so effectively blocked the action of ADH that some ethanol was still present in the blood one week after the administration of the pyrazole. According to this report, Goldberg & Wietland found that the 3-iodo derivative of pyrazole was even more potent in inhibiting the disappearance of ethanol from the bodies of their animals.

The findings of Goldberg & Wietlind with rats receiving pyrazole and ethanol were subsequently confirmed by Lester et al. (14), who extended the study to include 17 derivatives of pyrazole and nine other compounds. The ethanol dosage was 0.5 or 1.0 g/kg, administered intraperitoneally. The blood ethanol concentration was estimated by injecting 20 to 30 ml of air or nitrogen beneath the skin, and analyzing 2 ml portions of the gas in this bleb at intervals during the experiment. Pyrazole and nine of its 4-alkyl derivatives were listed as inhibitors, since a dose of less than 0.5 mM/kg caused a reduction of at least 25 per cent in the blood ethanol β_{60}. The minimum lethal dose of pyrazole for rats was stated to be about 2 g/kg, whereas 34 mg/kg markedly inhibited β_{60}. This preliminary paper by Lester does not give their complete data.

Exposure to cold.—A 1961 paper by Forbes & Duncan (15) stated that rats on an adequate diet, exposed to a temperature of 2° to 5° C for 3 days and then given ethanol intraperitoneally in a dosage of 3 g/kg, were found to have a blood ethanol β_{60} about 10 per cent higher than that of control animals kept at 26 to 27° C. However, the authors warned, "The increased ethanol utilization by the animals kept at 2° to 5° C . . . may simply be a reflection of a general stimulation of metabolism under this condition."

The question of the effect of environmental temperature on β_{60} of rats was next investigated by Platonow, Coldwell & Dugal (16). Their rats were kept at 20° C, or 5° C for 5 days prior to an intraperitoneal dose of ethanol of either 0.8 or 1.6 g/kg. The ethanol administered was ^{14}C labeled and its disappearance-rate was estimated by measuring the $^{14}CO_2$ exhaled in the breath during various time intervals for 24 hr after the injection of the labeled ethanol. In addition, chemical analyses for ethanol were conducted on the blood and the entire carcass of some of the animals sacrificed at certain time intervals. During the first 4 hr after the ethanol was administered, the fraction of the total ^{14}C injected which appeared in the breath, was much greater with the cold-exposed rats, and the investigators stated, "The differences in the rates of alcohol metabolism of the two groups of animals . . . are clearly evident." However, the average β_{60} values determined by direct blood analyses were 57 for the controls and 65 for the cold-exposed

animals, or an increase of only 14 per cent for the latter. The data from analyses of the entire animal carcass also indicate that β_{60} for the cold-exposed rats was only slightly greater than for that of the controls.

During this 4-hr period, the total CO_2 exhaled by the cold-exposed rats was about double that of the controls, which evidently explains the difference in the rates of exhalation of $^{14}CO_2$. At the end of this period both groups were practically ethanol-free, but the fractions of administered ^{14}C exhaled were 62 per cent for the controls and 75 per cent for the cold-exposed rats.

The curve for the hourly exhalation of $^{14}CO_2$ differed enormously from the β_{60} line, as determined by chemical analysis of the entire carcass of the rats sacrificed at various time intervals. Thus, at 1 hr after the start of the experiment with the control rats, 33 per cent of the administered ethanol had disappeared from their bodies, but the exhaled $^{14}CO_2$ accounted for only 11.7 per cent of the ^{14}C injected.

Prolonged high intake of ethanol.—Mendelson, Stein & Mello (17) have reported a study in which six alcoholics, incarcerated for treatment, were employed to engage in a bout of continuous drinking lasting from 3 to 14 days. The subjects ingested a fixed volume of 86-proof whisky every fourth hour, or oftener in a smaller dose, day and night, during the drinking period. The volume of the whisky consumed per day ranged from 17.4 to 25.5 fluid ounces, and furnished an hourly ethanol intake of 92 to 175 mg/kg. The resulting blood ethanol concentrations ranged from 51 to 175 mg per cent. To determine whether the prolonged drinking bout changed the blood ethanol β_{60}, each subject was given a test of his rate of ethanol metabolism on the day just prior to, and the day just following, the period of prolonged drinking. In these pre and post tests he drank a small amount of whisky to give a blood ethanol concentration of 40 to 80 mg per cent. Thirty minutes later he received intravenously 10 microcuries of ^{14}C ethanol, after which samples of his breath were collected at 20-min intervals for several hours. These breath samples were analyzed for total CO_2 and $^{14}CO_2$. The curves for the hourly pulmonary excretion of $^{14}CO_2$ are similar to those of Platonow, Coldwell & Dugal for rats, but the peaks of the curves for the human subjects of Mendelson, Stein & Mello vary greatly in height. During the first 3 hr after the 10 microcuries of ^{14}C-ethanol was injected, four of the subjects exhaled about twice as much $^{14}CO_2$ during the post test period as in the pre test period. This ratio was reversed in one subject, and the values were about the same for one subject. With one subject only, ethanol levels during his pre and post tests were estimated, using analysis of breath. While the calculated blood ethanol values for the pre period fluctuate considerably above, and below, a straight line, the data indicate very little change in β_{60} between pre and post periods.

In an earlier study by Mendelson & La Dou (18), they conducted similar prolonged drinking experiments with human subjects. With five subjects, who received a daily intake of 30 fluid ounces of 86-proof whisky for 14 days, periodic analysis of their blood by the ADH method did not indi-

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cate any tendency for the ethanol level to fall with continued heavy drinking.

Elsewhere (19), we have reviewed more fully these papers by Platonow, Coldwell & Dugal and by Mendelson, Stein & Mello, and have given reasons for our conviction of the futility of trying to estimate β_{60} from the rate of pulmonary excretion of $^{14}CO_2$ after administration of ^{14}C-ethanol. Our conviction agrees with that of Owens & Marshall in a 1955 paper (106).

Ethanol-Induced Changes in Blood Sugar and Liver Biochemistry

Research on these two interrelated effects of ethanol dates back many years. In a 1941 paper by Tennent (20), dealing with altered levels of blood sugar and liver glycogen caused by ethanol, he included a table summarizing 12 prior papers on this subject, published between 1913 and 1940. In most of these studies, ethanol was found to cause hyperglycemia, but hypoglycemia was reported in a few.

Tennent's 1941 paper reported no change in the blood sugar level of rats fasted for 16 hr and then given one gram of ethanol per kilo intraperitoneally. However, when glucose, in a dose of 6 g/kg, was administered by stomach tube and ethanol was given 4 hr later, the blood sugar rose 150 per cent. The average glycogen content of the livers of the fasted rats was 0.35 per cent, and of the glucose-fed rats 2.40 per cent. Ethanol administration lowered these values to 0.24 per cent and 0.23 per cent, respectively. Tennent found no change in the blood sugar levels of humans from an ethanol dose of 0.6 g/kg, even after they had eaten 250 g of candy 4 hr prior to drinking the whisky.

During the period of 1941–1958, several clinical papers appeared, describing cases of hypoglycemic coma following a bout of heavy drinking (21–27). These clinical reports have been the stimulus for many of the recent scientific investigations regarding the effects of ethanol on glycemia and hepatic biochemistry. We will discuss separately the studies with humans, those with intact lower animals, liver perfusion studies, and incubation of liver slices.

Human studies.—Forsander, Vartia & Krusius (28) reported that an ethanol dose of 0.85 g/kg, given to ten normal subjects, caused a mild hyperglycemia for 1 hr, followed by moderate hypoglycemia during the next 4 hr. A second dose of ethanol, 0.43 g/kg, given 2 hr after the first, abolished the hypoglycemia. Forsander's group (28, 29) also observed generalized hypoglycemia in 58 persons during the hangover following severe ethanol intoxication. Sixteen of the hangover subjects then drank whisky to give an ethanol dose of 0.3 g/kg, and the blood sugar of 11 rose 4 to 24 mg per cent suggesting a possible scientific basis for alleged relief of hangover symptoms by a small "morning after" drink.

In 1962 Lundquist et al. (30) described a study with ten normal individuals, from whom samples of arterial and hepatic vein blood were collected at frequent intervals during a 30-min intravenous infusion of saline, followed by saline plus 3.5 g of ethanol during the next half-hour. A Cournand

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catheter was anchored in the hepatic vein, as described on p. 380. With ethanol, its average concentration in the arterial blood was 15 mg per cent, which decreased to 10 mg per cent in the hepatic vein blood. Acetate, equivalent to about 75 per cent of the ethanol lost, appeared in the hepatic vein blood. Mean oxygen consumption was unchanged by ethanol, but about 74 per cent of the O_2 lost from the arterial blood was used to convert the ethanol to acetate, via acetaldehyde. Ethanol caused an increase of 68 per cent in the β-hydroxybutyrate/acetoacetate ratio, with no change in the sum of the two compounds.

Field et al. (31) administered ethanol, 3 to 4 g/kg, to normal subjects, and to one alcoholic with a history of repeated hypoglycemia. The blood sugar level of the normals was unchanged, but was slightly lowered in the alcoholic. After the normals had fasted for 44 hr, ethanol caused a drop of 13 to 21 mg per cent in the blood sugar level.

During 1963–67, Freinkel and associates published three ethanol-blood sugar studies. The first (32) employed subjects who had been hospitalized during hypoglycemic coma following severe alcoholic intoxication. Administration of 15 g of ethanol per hr for 8 hr caused the blood sugar level of four subjects to fall, reaching a minimum of about 50 mg per cent 4 hr after the ethanol administration ceased. With one subject, ethanol caused no change in the blood sugar level. After a fast of 3 days the blood sugar of all subjects fell below 50 mg per cent within 2 hr after the start of the ethanol administration. Ethanol caused a twofold elevation of the plasma free fatty acids. The second study (33) employed "ketosis-prone" subjects, whose regular insulin medication had been discontinued for some hours, resulting in severe hyperglycemia. Ethanol caused some decrease in the blood sugar levels. In their third study (34) these investigators used normals, hyperthyroid subjects, and obese individuals. With normals fasted 12 hr, ethanol caused no decrease in the blood sugar level; but after a fast of 3 days, ethanol decreased the blood sugar by 30 per cent. About this same fall in blood sugar was produced by ethanol in the hyperthyroid subjects fasted only 12 hr. With the obese subjects fasted for 12 hr, ethanol did not alter the blood sugar level, but did lower the level about 13 per cent when these subjects were fasted for 3 days.

Experiments with intact animals.—Forbes & Duncan (35) reported that ethanol in a dose of 3 g/kg caused no change in the blood sugar level of fed or fasted rats. The livers of rats fasted for 20 hr contained an average of only 0.25 per cent of glycogen, but ethanol decreased it to 0.01 per cent. With fed rats, the mean liver glycogen concentration was 3.8 per cent, and ethanol caused it to fall to 1.7 per cent.

Forsander, Raiha & Soumalainen (36) gave rats ethanol 5 g/kg and, 1 to 4 hr later, under nembutal anesthesia, blood samples were drawn from the portal and hepatic veins. Ethanol caused an increase of acetoacetate in the hepatic vein blood, the resulting levels being 1.9 mg per cent for the fed rats and 4.0 mg per cent for the fasted rats. Acetate levels are not reported. The O_2 content of blood from the portal vein regularly exceeded the content

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of the hepatic vein blood, regardless of whether ethanol was being metabolized. Ethanol caused a drop of about 30 per cent in the NAD/NADH ratio, but no change in the sum of the two compounds.

Klingman & Haag (37) reported that the administration of a lethal dose of ethanol to dogs always resulted in a very marked elevation of blood sugar during the fatal period. However, the three dogs with the longest fatal periods for their respective series had blood sugar levels of 135 to 138 mg per cent near the time of death.

Clark, Wilson & Hulpieu (38) gave fed dogs a daily ethanol dose of 3 g/kg for 34 days, and observed no change in the sugar level of blood drawn 24 hr after the previous dose. On continuing the experiment with the dose increased to 4 g/kg, severe hypoglycemia occurred in about 12 days. When fasted dogs received a daily ethanol dose of 4 g/kg, between the 5th and 9th days the blood sugar level fell to about 35 mg% during the first 8 hr after the ethanol administration, but returned to normal during the next 16 hr. Analyses were made for total lipids and glycogen of the livers of fed and fasted dogs, and of fasted dogs which had received ethanol until the blood sugar level reached 34 to 38 mg%. The values reported are: fed, glycogen 4.9 per cent, lipids 2.6 per cent; fasted only, glycogen 1.9 per cent, lipids 5.3 per cent; fasted + ethanol, glycogen 0.2 per cent, lipids 20.5 per cent.

Raiha & Oura (39) reported that ethanol in a dose of 3 g/kg caused a fall of about 50 per cent in the NAD/NADH ratio of the livers of fed or fasted rats, but no change in the sum of the two.

Field et al. (31) gave rabbits ethanol in a dose of about 5 g/kg, and found a fall in blood sugar which averaged 25 mg per cent.

Bleicher et al. (40) gave saline containing ethanol intravenously to nine fasted dogs, which resulted in blood ethanol concentrations of 143 to 286 mg per cent. These concentrations of ethanol decreased the blood sugar level by 30 per cent in six of the animals, caused no change in two, and increased the blood sugar in one by 40 per cent.

Madison, Lochner & Wulff (41, 42) used dogs to repeat the type of ethanol study conducted with humans by Lundquist et al., described on p. 380, in which a Cournand catheter is anchored in the hepatic vein. In order to isolate the liver metabolism from the remaining splanchnic metabolism, Madison, Lochner & Wulff performed a two-stage operation on their dogs to form a portacaval shunt. This is the classical Eck fistula, which altertion causes the portal vein blood to bypass the liver and enter the inferior vena cava. The dogs were fasted 2 to 3 days prior to the experiments. Ethanol was given intravenously at the rate of 66 mg/kg per hr, or 506 mg/kg per hr, which resulted in blood ethanol concentrations of 10 to 20 mg per cent or 70 to 110 mg per cent, respectively. With the lower levels of blood ethanol the blood sugar of all of the dogs was reduced from a mean of 90 mg per cent to 70 mg per cent. With the higher ethanol dosage, the mean blood sugar level fell from 79 mg per cent to 41 mg per cent. Liver blood flow was measured by a conventional dye method. The values for mean he-

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patic glucose output prior to, and following, ethanol administration were: low dose, 52 mg/min and 29 mg/min; high ethanol dose, 62 mg/min and 37 mg/min. Using the assumption that the extrahepatic "glucose space" represents one-fourth of the body weight, the investigators calculated the peripheral utilization of glucose from the peripheral venous-arterial glucose differential and the blood flow. This calculation indicated that the larger dose of ethanol caused a drop of 0.86 g in peripheral glucose utilization for the 1-hr period of ethanol infusion, and a drop of 0.72 g for the 50-min infusion period with the smaller concentration of blood ethanol. When nonshunted dogs were used to repeat the experiment with the high dose of ethanol, hypoglycemia resulted and the splanchnic output of glucose fell from 45 mg/min to 9.4 mg/min. From their experiments, Madison, Lochner & Wulff concluded that ethanol administration will cause hypoglycemia if the decrease in hepatic glucose output exceeds the drop in the peripheral utilization of glucose. When administered during the ethanol infusion, fructose or methylene blue restored the hepatic output of glucose to normal, or above, but alpha-glutarate or glutamate had no effect.

Bleicher et al. (40) have questioned the use of Eck fistula dogs for testing the effect of ethanol on blood sugar level and hepatic biochemistry, because of possible altered liver metabolism in such animals.

Liver perfusion studies.—During 1960–1965, Forsander and associates published three studies in which the isolated livers of rats were perfused *in situ* with blood containing ethanol or blood alone. Under anesthesia, the abdomen was opened, the portal vein and the inferior caval vein were cannulated, and the latter vein was ligated just above its junction with the renal veins. With the liver remaining in the abdomen, the infusion blood was circulated through it via the two catheters.

The first study (43) employed ^{14}C-ethanol. During ethanol perfusion periods of 1 hr, the ethanol concentration in the perfusion blood decreased 22 to 27 per cent, but the $^{14}CO_2$ formed, when 1-^{14}C-ethanol was used, accounted for only 1.7 per cent of the ^{14}C added to the blood, and the $^{14}CO_2$ accounted for 0.5 per cent when 2-^{14}C-ethanol was used.

The second paper (44) reported that the chief carboxylic acids found in the ethanol-free blood perfused through the rat livers, listed in descending order, were: acetoacetic, acetic, lactic, and β-hydroxybutyric. However, when ethanol was administered to an intact rat, the concentrations of the two "ketone" acids were very much less, because of their oxidation in muscle tissue. Thus, perfusion of an isolated organ may give a distorted picture of the metabolic changes in the intact body.

The third study (45) dealt with the uptake, or output, of certain compounds by the isolated, perfused livers of fed or fasted rats, with or without ethanol (0.2 per cent) in the circulating blood. Ethanol caused no change in the liver uptake of oxygen, but the output of CO_2 almost ceased. The glucose balance results, expressed as μM/g of liver, and designating output as + and intake as −, were: fed, blood only +13; fed blood +

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ethanol, +28; fasted, blood only, +3; and fasted, blood + ethanol, −40. The corresponding results for lactate + pyruvate balance were: fed, blood only, −13; fed, blood + ethanol, −3; fasted, blood only, −18; and fasted, blood + ethanol, +28. Ethanol increased the lactate/pyruvate ratio of the perfusate about sevenfold, and the β-hydroxybutyrate/acetoacetate ratio about eightfold.

Field et al. (31) perfused isolated rat livers with saline alone, or saline containing 0.4 per cent of ethanol. Ethanol caused a 40 per cent decrease in the concentrations of glucose and urea in the perfusion fluid.

Incubation of liver slices.—Forsander (46) incubated slices from fed or fasted rats with saline containing 0.2 per cent of 1^{14}C-ethanol. The chief ^{14}C-metabolite to appear in the incubation fluid was acetate, the concentrations of which were about the same in the experiments with livers from fed and fasted animals.

A 1966 paper by Forsander (47) describes studies in which rat liver slices were incubated with saline only, or saline containing ethanol. In an incubation with saline only, the oxygen uptake per gram of liver tissue was 1.54 μM, and the CO_2 output was 1.21 μM per min. On repeating the experiment with 78 mg per cent ethanol in the saline, the oxygen uptake was 1.63 μM, the CO_2 output was reduced to 0.03 μM, and the ethanol uptake was 1.38 μM. With no ethanol in the saline, the lactate/pyruvate ratio remained practically constant at 12, during the incubation period of 135 min. With saline containing 30 mg per cent of ethanol, the lactate/pyruvate ratio rose rapidly to a peak of about 120 at 60 min, and then declined to its original value of 12 at 120 min, when the ethanol had disappeared from the incubation fluid.

Summary.—Most of the experimental results in this subsection support the following conclusions:

(*a*) Consumption of ethanol can cause either hyper- or hypoglycemia, depending on the liver store of glycogen.

(*b*) Alcoholemia, even of moderate grade, drastically alters certain biochemical processes in the liver: while the O_2 uptake is unchanged, the output of CO_2 practically ceases, and most of the O_2 uptake is used to convert ethanol to acetate, via acetaldehyde; formation of glucose (gluconeogenesis) is inhibited, particularly if the liver store of glycogen is depleted; the dehydrogenation of ethanol causes the concentration of NADH to increase greatly, at the expense of NAD; this increase in the NADH/NAD ratio stimulates the reduction of the redox pairs, lactate/pyruvate and β-hydroxybutyrate/acetoacetate.

(*c*) The acetate formed from ethanol by the liver is oxidized in muscle tissue, supplanting the oxidation of an isocaloric amount of ordinary foods, thus lowering the peripheral consumption of glucose.

(*d*) If the drop in the hepatic output of glucose is greater than the decrease in its peripheral utilization, hypoglycemia will occur.

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TABLE I

COMBINED EFFECTS OF ETHANOL PLUS OTHER DRUGS
(The numbers refer to publications listed in the bibliography. Where the number is in italics, humans were used in the ethanol-drug study; otherwise, the tests were done with laboratory animals.)

Drugs	Result of Combination			
	Hyperadditive	Additive	None	Antagonistic
Barbiturates				
Barbital		57, 60		
Pentobarbital	56, 59	57, 62		104
Amobarbital		64		
Secobarbital		60, 61, 63		
Hexobarbital		55		
Phenobarbital		60, 66		65
Thiopental	*52*, *53*, 54			
Other Hypnotics				
Chloral hydrate		68, 69		
Paraldehyde		70, *71*		
Glutethemide (Doriden)		75		
Tranquilizers				
Promazine		72, 75, 80		
Chlorpromazine	95, 74, 77, 58, 76	72, 78		
Promethazine		72		
Reserpine	*79*, *81*, *83*, 74, 73, 76, 58, 59			
Meprobamate	95, 58, 59, 74, 75, 76, *82*, *85*, *86*, *87*		81, 84	87
Chlordiazepoxide (Librium)	88, 89		*90*, *91*, *92*	
Hydroxyzine (Atarax)	74, 59	72	75	76
Narcotics				
Morphine	76, 93, 94			
Codeine			74, 76	
Stimulants				
Caffeine	96		*105*	
Amphetamine		97	*98*, *100*, *99*	*98*, *99*, *101*
Other Drugs				
Diphenylhydramine (Benzadryl)			103	
Tolbutamide	102			
d-Propoxyphene (Darvon)	76		74	

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Combined Effects of Ethanol and Other Drugs

A monograph on the above subject, written by Forney & Hughes, appeared in 1968 (48). It reviews the chief findings of about 200 studies on this subject.

This section of the present chapter will not be a vest pocket edition of the Forney-Hughes monograph. Instead, we will list some of the less conventional research tools used in these published investigations, and then present a table classifying the findings relative to the degree of potentiation, if any, between ethanol and several of the other drugs studied.

Some of the research procedures used with human subjects were: measurement of nystagmus using an electronic hookup (82); use of a device which simulates the operation of an automobile (49); tests of impairment with a pursuit meter employing a dual beam oscilloscope, which is guided with a steering wheel (103); and use of a delayed auditory feedback (DAF) apparatus, which is essentially a "distraction machine," to produce stress on the subject (50, 51).

In experiments with laboratory animals, one investigator used a wire-mesh screen rectangle, which sloped at an angle of 60° from horizontal. He placed the rats receiving ethanol or drug, or both, on the screen with the heads uphill, and counted the number of animals which lost their grasp on the screen and slid off in a period of 20 min (75). Hughes & Forney employed an enclosure having two shock-avoidance compartments, which is used to test rats for anxiety and discrimination (96).

In the following table we have purposely avoided the use of the term "synergistic," because some of the above mentioned investigators of the matter of ethanol plus drugs have called simple additive effect synergism. Hence, our use of the word "hyperadditive."

In arranging the data in Table I, we have tried to present faithfully the author's interpretation of his findings. However, in some instances the author did not give a clear-cut opinion as to whether the potentiation of ethanol by a given drug, or the drug by ethanol was additive or hyperadditive. In those cases, we have used our best judgment from the author's data.

The results in Table I occasionally show conflicting findings when a given drug was tested by different investigators. The apparent contradictions may well be due to differences in dosage, test methods, or animal species used. Even with these discrepancies, the results agree quite well on certain drugs studied. Thus, the great majority of the studies indicated that the potentiation of ethanol by barbiturates is merely additive, while the effect of most tranquilizers and morphine is hyperadditive. Very few of the drugs were reported to antidote the effects of ethanol.

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LITERATURE CITED

1. Harger, R. N., Hulpieu, H. R. In *Alcoholism,* 152–60 (Thompson, G. N., ed., Thomas, Springfield, Ill., 1956)
2. Lester, D., *Proc., Fourth International Conference on Alcohol and Traffic Safety,* 267–74 (Indiana Univ., Bloomington, Ind., 1965)
3. Carpenter, T. M., Lee, R. C., *J. Pharmacol. Exptl. Therap.,* **60,** 264–85 (1937)
4. Pletscher, A., Bernstein, A., Staub, H., *Experientia,* **8,** 307–08 (1952)
5. Pletscher, A., Bernstein, A., Staub, H., *Helv. Physiol. Acta,* **10,** 74–83 (1952)
6. Bernstein, A., Pletscher, A., Renscheler, H., *Klin. Wochschr.,* **33,** 488–91 (1955)
7. Clark, W. C., Hulpieu, H. R., *Quart. J. Studies Alc.,* **19,** 47–53 (1958)
8. Lundquist, F., Wolthers, H., *Acta Pharmacol. Toxicol.,* **14,** 290–94 (1958)
9. Tygstrup, N., Winkler, K., Lundquist, F., *J. Clin. Invest.,* **44,** 817–30 (1965)
10. Hoch, F. L., Vallee, B. L., *J. Biol. Chem.,* **221,** 491–500 (1956)
11. Lundquist, F., Svendsen, I., Petersen, H., *Biochem. J.,* **86,** 119–24 (1963)
12. Theorell, H., Yonetani, T., *Biochem. Z.,* **338,** 537–53 (1963)
13. Theorell, H., *Experientia,* **21,** 553–616 (1965)
14. Lester, D., Keokosky, W. Z., Felzenberg, F., *Quart. J. Studies Alc.,* **29,** 449–54 (1968)
15. Forbes, J. C., Duncan, G. M., *Quart J. Studies Alc.,* **11,** 373–80 (1950)
16. Platonow, N. Coldwell, B. B., Dugal, L. P., *Quart J. Studies Alc.,* **24,** 385–97 (1963)
17. Mendelson, J. H., Stein, S., Mello, N. K., *Metabolism,* **14,** 1255–66 (1965)
18. Mendelson, J. H., LaDou, J., *Quart. J. Studies Alc., Suppl. 2,* 14–39 (1964)
19. Harger, R. N., Forney, R. B., in *Progress in Chemical Toxicology,* (Stolman, A., Ed., **3,** 20–21, Academic Press, New York, 1967)
20. Tennent, D. M., *Quart. J. Studies Alc.,* **2,** 263–70 (1941)
21. Brown, T. M., Harvey, A. M., *J. Am. Med. Assoc.,* **117,** 12–15 (1941)
22. Tucker, H. S., Jr., Porter, W. B., *Am. J. Med. Sci.,* **204,** 559–66 (1942)
23. Mollerstrom, J., *Arkiv. Kemi Mineral Geol.,* **19A,** 1–26 (1945)
24. Bottura, C., Neves, D. P., Mattar, E., deOliveria, H. L., Ulhoa, C., *Rev. Hosp. Clin. Fac. Med. Univ. Sao Paulo,* **4,** 133–40 (1949)
25. Neves, D. P., Faria, C. V., Fujioka, T., *Rev. Hosp. Clin. Fac. Med. Univ. Sao Paulo,* **5,** 115–20 (1950)
26. Hammack, W. J., *J. Am. Med. Assoc.,* **165,** 24–27 (1957)
27. Gadsden, R. H., Mellette, R. R., Miller, W. C., Jr., *J. Am. Med. Assoc.,* **168,** 1220–24 (1958)
28. Forsander, O., Vartia, K. O., Krusius, F.-E., *Ann. Med. Exptl. Biol. Fenniae, (Helsinki),* **36,** 416–23 (1958)
29. Vartia, K. O., Forsander, O. A., Krusius, F-E., *Quart. J. Studies Alc.,* **21,** 597–604 (1960)
30. Lundquist, F., Tygstrup, N., Winkler, K., Mellemgaard, K., Munck-Petersen, S., *J. Clin. Invest.,* **41,** 955–61 (1962)
31. Field, J. B., Williams, H. E., Mortimore, G. E., Kendig, E., King, E., *J. Clin. Invest.,* **42,** 497–506 (1963)
32. Freinkel, N., Singer, D. L., Arky, R. A., Bleicher, S. J., Anderson, J. B., Silbert, C. K., *J. Clin. Invest.,* **42,** 1112–33 (1963)
33. Arky, R. A., Freinkel, N., *Arch. Internal Med.,* **114,** 501–07 (1964)
34. Arkey, R. A., Freinkel, N., *New Engl. J. Med.,* **274,** 426–33 (1966)
35. Forbes, J. C., Duncan, G. M., *Quart. J. Studies Alc.,* **11,** 373–80 (1950)
36. Forsander, O., Raiha, N., Soumalainen, H., *Z. Physiol. Chem.,* **312,** 243–48 (1958)
37. Klingman, G. I., Haag, H. B., *Quart. J. Studies Alc.,* **19,** 203–26 (1958)
38. Clark, W. C., Wilson, J. E., Hulpieu, H. R., *Quart. J. Studies Alc.,* **22,** 365–73 (1961)
39. Raiha, N. C., Oura, E., *Proc. Soc. Exptl. Biol. Med.,* **109,** 908–10 (1962)
40. Bleicher, S. J., Freinkel, N., Byrne, J. J., Seifert, D., *Proc. Soc. Exptl. Biol. Med.,* **115,** 369–73 (1964)
41. Lochner, A., Wulff, J., Madison, L., *Metabolism,* **16,** 1–18 (1967)
42. Madison, L. L., Lochner, A., Wulff, J., *Diabetes,* **16,** 252–58 (1967)

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43. Forsander, O., Raiha, N., Soumalainen, H., *Z. Physiol. Chem.*, **318,** 1–5 (1960)
44. Forsander, O., Raiha, N. C., *J. Biol. Chem.*, **235,** 34–36 (1960)
45. Forsander, O. A., Raiha, N., Salaspuro, M., Maenpaa, P., *Biochem. J.*, **94,** 259–65 (1964)
46. Forsander, O., *Acta Chem. Scand.*, **17,** 886 (1963)
47. Forsander, O., *Biochem. J.*, **98,** 244–47 (1966)
48. Forney, R. B., Hughes, F. W., *Combined Effects of Alcohol and Other Drugs* (Academic Press, New York, 124 pp., 1968)
49. Loomis, T. A., West, T. C., *Quart. J. Studies Alc.*, **19,** 30–46 (1958)
50. Forney, R. B., Hughes, F. W., *J. Psychol.*, **52,** 185–92 (1961)
51. Hughes, F. W., Forney, R. B., Gates, P. W., *J. Psychol.*, **55,** 25–32 (1963)
52. Smith, J. W., Loomis, T. A., *Proc. Soc. Exptl. Biol. Med.*, **78,** 827–29 (1951)
53. Sandberg, F., *Acta Physiol. Scand.*, **22,** 311–25 (1951)
54. Ramsey, H., Haag, H. B., *J. Pharmacol. Exptl. Therap.*, **88,** 313–22 (1946)
55. Eerola, R., *Ann. Med. Exptl. Biol. Fenniae (Helsinki)*, **39,** *Suppl. 3*, 1–70 (1961)
56. Dille, J. M., Ahlquist, R. P., *J. Pharmacol. Exptl. Therap.*, **61,** 385–92 (1937)
57. Gruber, C. M., Jr., *Arch. Intern. Pharmacol.*, **102,** 17–32 (1955)
58. Kopmann, E., Hughes, F. W., *Arch. Gen. Psychiat.*, **1,** 7–11 (1959)
59. Hughes, F. W., Kopmann, E., *Arch. Intern. Pharmacodyn.*, **126,** 158–70 (1960)
60. Aston, R., Cullumbine, H., *Toxicol. Appl. Pharmacol.*, **1,** 65–72 (1959)
61. Archer, J. D., *Texas Rept. Biol. Med.*, **14,** 1–5 (1956)
62. Graham, J. D. P., *Toxicol. Appl. Pharmacol.*, **2,** 14–22 (1960)
63. Nyiogi, S. K., Lu, F. C., *Can. Soc. Forensic Sci.*, **3,** 110–17 (1964)
64. Fearn, H. J., Hodges, J. R., *J. Pharm. Pharmacol.*, **5,** 1041–44 (1953)
65. Garriere, G., Huriez, C., Willoquet, P., *Compt. Rend. Soc. Biol.*, **116,** 118–90 (1934)
66. Jetter, W. W., McLean, R., *Arch. Pathol.*, **36,** 112–22 (1943)
67. Joyce, C. R. B., Edgecombe, P. C. E., Kennard, D. A., Weatherhall, M., Woods, D. P., *Brit. J. Psychiat.*, **105,** 51–60 (1959)
68. Gessner, P. K., Cabana, B. E., *J. Pharmacol. Exptl. Therap.*, **156,** 602–05 (1967)
69. Kaplan, H. L., Forney, R. B., Hughes, F. W., Richards, A. B., Jain, N., *Toxicol. Appl. Pharmacol.*, **10,** 387 (1967) Abstract
70. Weatherby, J. H., Clements, E. L., *Quart. J. Studies Alc.*, **21,** 394–99 (1960)
71. Kaye, S., Haag, H. B., *Toxicol. Appl. Pharmacol.*, **6,** 316–20 (1964)
72. Erola, R., *Acta. Anesthesiol. Scand.*, **7,** 127–37 (1961)
73. Brodie, B. B., Shore, P. A., Silver, S. L., *Nature*, **175,** 1133–34 (1963)
74. Forney, R. B., Hulpieu, H. R., Hughes, F. W., *Experientia*, **18,** 468–70 (1962)
75. Graham, R. C. B., Lu, F. C., *Federation Proc.*, **16,** 302 (1957)
76. Forney, R. B., Hughes, F. W., Hulpieu, H. R., *Quart. J. Studies Alc.*, **24,** 1–8 (1963)
77. Smith, M. E., Evans, R. L., Newman, E. J., Newman, H. W., *Quart. J. Studies Alc.*, **22,** 241–49 (1961)
78. Sutherland, V. C., Burbridge, T. N., Adams, J. E., Simon, A., *J. Appl. Physiol.*, **15,** 189–96 (1960)
79. Ungerleider, J. T., *J. Nervous Mental Disease*, **127,** 518–27 (1958)
80. Zirkle, G. A., King, P. D., McAtee, O. B., Van Dyke, R., *J. Am. Med. Assoc.*, **171,** 1496–99 (1959)
81. Burger, E., *Hefte Unfallheilk.*, **66,** 99–102 (1961)
82. Goldberg, L., *Quart. J. Studies Alc., Suppl. 1,* 37–56 (1961)
83. Greenhouse, H. R., Pilot, M. L., *Quart. J. Studies Alc.*, **18,** 468–74 (1956)
84. Marquis, D. G., Kelly, E. L., Miller, J. K., Gerard, R. W., Rapoport, A., *Ann. N.Y. Acad. Sci.*, **67,** 701–10 (1957)
85. Zirkle, G. A., McAtee, O. B., King, P. D., Van Dyke, R., *J. Am. Med. Assoc.*, **173,** 1823–25 (1960)
86. Forney, R. B., Hughes, F. W., *J. Psychol.*, **57,** 431–36 (1964)
87. Munkelt, P., Lienert, G. A., Frahm, M., Soehring, K., *Arzneimittel-Forsch.*, **12,** 1059–65 (1962)
88. Madan, B. R., Sharma, J. D., Vyas, D. S., *Ann. Biochem. Exptl. Med.*, **22,** 221–24 (1962)
89. Hughes, F. W., Rountree, C. B., Forney, R. B., *J. Genet. Physiol.*,

103, 139–45 (1963)
90. Miller, A. I., D'Agostino, A., Minskey, R., *Quart. J. Studies Alc.*, **24,** 9–13 (1963)
91. Hughes, F. W., Forney, R. B., Richards, A. B., *Clin. Pharmacol. Therap.*, **6,** 139–45 (1965)
92. Hoffer, A., *Can. Med. Assoc. J.*, **87,** 920–21 (1962)
93. Eerola, R., Venho, I., Vartiainen, O., Venho, E. V., *Ann. Med. Exptl. Biol. Fenniae (Helsinki)*, **33,** 253–61 (1955)
94. Frommel, E., Seydoux, J., Fasel, M., *Experientia*, **19,** 1–2 (1963)
95. Danechmand, L., Casier, H., Hebbelinck, M., De Schaepdryver, A., *Quart. J. Studies Alc.*, **28,** 424–29 (1967)
96. Hughes, F. W., Forney, R. B., *Proc. Soc. Exptl. Biol. Med.*, **108,** 157–59 (1961)
97. Weiss, B., Laties, V. G., *J. Pharmacol. Exptl. Therap.*, **144,** 17–23 (1964)
98. Taylor, J. D., Wilson, L., Nash, C. W., Cameron, D. F., *Proc. Can. Fed. Biol. Soc.*, **7,** 36 (1964)
99. Wilson, L., Taylor, J. D., Nash, C. W., Cameron, D. F., *Can. Med. Assoc. J.*, **94,** 478–84 (1966)
100. Hughes, F. W., Forney, R. B., *Psychopharmacologia*, **6,** 234–38 (1964)
101. Kaplan, H. L., Forney, R. B., Richards, A. B., Hughes, F. W., *Proc., Fourth International Conference on Alcohol and Traffic Safety*, 211–14 (Indiana Univ., Bloomington, Ind., 1965)
102. Kaymakcalan, S., Tugrul, S., *Turk. Ijiyen Tecrubi. Biyol. Dergisi*, **24,** 63–70 (1964)
103. Hughes, F. W., Forney, R. B., *Clin. Pharmacol. Therap.*, **5,** 414–21 (1964)
104. Lind, N., Parker, M. W., *J. Pharm. Pharmacol.*, **19,** 56–57 (1967)
105. Forney, R. B., Hughes, F. W., *Quart. J. Studies Alc.*, **26,** 206–12 (1965)
106. Owens, A. H., Jr., Marshall, E. K., Jr., *J. Pharmacol. Exptl. Therap.*, **115,** 360–70 (1955)

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