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THE EFFECT OF ETHANOL ON FAT STORAGE IN HEALTHY SUBJECTS

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Abstract *Background.* Ethanol can account for up to 10 percent of the energy intake of persons who consume moderate amounts of ethanol. Its effect on energy metabolism, however, is not known.

Methods. We studied the effect of ethanol on 24-hour substrate-oxidation rates in eight normal men during two 48-hour sessions in an indirect-calorimetry chamber. In each session, the first 24 hours served as the control period. On the second day of one session, an additional 25 percent of the total energy requirement was added as ethanol (mean [±SD], 96±4 g per day); during the other session, 25 percent of the total energy requirement was replaced by ethanol, which was isocalorically substituted for lipids and carbohydrates.

Results. Both the addition of ethanol and the isocaloric substitution of ethanol for other foods reduced 24-hour lipid oxidation. The respective mean (±SE) decreases were 49.4±6.7 and 44.1±9.3 g per day (i.e., reductions of 36±3 percent and 31±7 percent from the oxidation rate during the control day; $P<0.001$ and $P<0.0025$). This effect occurred only during the daytime period (8:30 a.m. to 11:30 p.m.), when ethanol was consumed and metabolized. Neither the addition of ethanol to the diet nor the isocaloric substitution of ethanol for other foods significantly altered the oxidation of carbohydrate or protein. Both regimens including ethanol produced an increase in 24-hour energy expenditure (7±1 percent with the addition of ethanol, $P<0.001$; 4±1 percent with the substitution of ethanol for other energy sources, $P<0.025$).

Conclusions. Ethanol, either added to the diet or substituted for other foods, increases 24-hour energy expenditure and decreases lipid oxidation. Habitual consumption of ethanol in excess of energy needs probably favors lipid storage and weight gain. (N Engl J Med 1992;326: 983-7.)

ETHANOL accounts for 5.6 percent of the energy in the average American diet.[1] Among consumers of ethanol, ethanol accounts for up to 10 percent of total energy intake, and in alcoholic persons ethanol may supply more than 50 percent of dietary energy.[2-6] Despite the apparent importance of ethanol as a source of energy, whether this energy can be used by the body is less clear. The isocaloric substitution of ethanol for carbohydrates decreases body weight.[7,8] Epidemiologic evidence of a positive correlation between body weight and ethanol intake is inconsistent, however.[9-16] This inconsistency may be due to the difficulty of assessing the ethanol intake of free-living subjects and to the fact that some consumers of ethanol add it to their usual food intake, whereas others replace carbohydrates or lipids with ethanol. One of the metabolic effects of ethanol is the suppression of lipid oxidation, which contributes to pathophysiologic consequences such as hepatic steatosis.[17-22] In view of its effect on fat metabolism, it is possible that ethanol has a crucial role in the body's use of lipids, even in people who consume moderate amounts of ethanol. We studied the effects on substrate oxidation of moderate amounts of ethanol — either given in addition to other foods or substituted for some of the daily food intake — over a period of 24 hours in healthy, nonalcoholic men. Oxidation of substrates was calculated from values obtained by indirect calorimetry; the measured oxygen consumption and carbon dioxide production were corrected for the amount of oxygen consumed and the amount of carbon dioxide produced by the quantity of ethanol metabolized.

METHODS

We studied eight normal men, whose mean age (±SD) was 24±2 years; their mean body weight was 73.8±4.3 kg, their body-mass index (the weight in kilograms divided by the square of the height in meters) was 22.3±0.6, and their relative body-fat mass was 14.7±2.8 percent. None were smokers, and their usual ethanol intake, based on a one-week dietary recall, was 48±44 g per week. All the men had a normal physical examination and history and normal serum aminotransferase, alkaline phosphatase, bilirubin, and albumin concentrations, and none had any serologic evidence of viral hepatitis. The study protocol was reviewed and approved by the ethics committee of the medical faculty of the University of Lausanne, and each man gave written informed consent before entering the study.

The men were studied for two 48-hour periods in a respiration chamber, separated by an interval of five days. They were instructed to pursue their usual diet and physical activities during the study. Their total energy requirements were calculated as 1.5 times the basal metabolic rate. The first day of each two-day session served as a control day, during which no ethanol was ingested. On the second day of one session, 25 percent of the men's estimated total energy requirement was added as ethanol (for a total of 125 percent); on the second day of the other session, 25 percent of the calories were replaced by ethanol (a total of 100 percent); the order of the two sessions was random. The substitution of ethanol for other foods was isocaloric; it replaced dietary lipids (12.5 percent) and carbohydrates (12.5 percent). On the days when ethanol was consumed, 95 percent pure ethanol was given together with meals as a 10 percent solution diluted with tap water and grape juice. The proportion of the nonethanol energy intake that was made up of protein, carbohydrates, and lipids was kept constant at 19 percent, 51 percent, and 30 percent, respectively, on each day and for each meal during the two 48-hour study periods. Only on the day of ethanol substitution was the composition of the diet altered by the substitution procedure (resulting in 26 percent non–ethanol-derived energy from protein, 51 percent from carbohydrates, and 23 percent from lipids). The mean (±SD) quantity of ethanol given to the subjects was 32±1 g per meal; since the subjects ate three meals a day, the total amount of ethanol ingested was 96±4 g per day. On each day of the two study sessions, the same food items were used, and the meals and the ethanol drink were served at 8:30 a.m., 12:30 p.m., and 5:30 p.m. The meals (including ethanol) had to be consumed within 15 minutes. The diet was prepared by a research dietitian, and the men were monitored during eating to ensure that all the food and ethanol were consumed.

For two days before each admission, the men were instructed to avoid intense physical activity and not to consume any ethanol, caffeine-containing foods or beverages, or drugs. On the first day of each session the men were admitted to the institute at 7:00 a.m. after an overnight fast. Body weight and height were measured, and body composition was determined by four skin-fold measurements[23] and by bioimpedance, an indirect measurement of the body's electrical

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resistance.[24] The measurements in the respiration chamber began at 8 a.m., and the men remained there until the following morning at 7 a.m. At 7 a.m. the gas analyzers were recalibrated with standardized gas mixtures and normal air, and the basal metabolic rate of the men was measured by means of a ventilated hood system while they remained in bed.[25] The measurements in the respiration chamber were then restarted at 8 a.m. for the second day (i.e., that on which ethanol was consumed). During each of the four days (including the two control days), the ethanol concentration was measured in expired air at 10-minute intervals from 8 a.m. to 11 p.m. with use of a laptop ethanol breath analyzer (Alcotest 7110, Drägerwerk Aktiengesellschaft, Lübeck, Germany) with an on-line display and printout of calculated blood ethanol values.

Indirect Calorimetry

Each man's 24-hour energy expenditure was measured separately by indirect calorimetry in a climatically controlled respiration chamber kept at 20°C. The respiration chamber was an open-circuit, indirect calorimeter (volume, 30,600 liters) furnished with a bed, desk, toilet, sink, television, and radio.[26] The flow rate of air at the outlet of the chamber was measured by a pneumotachygraph connected to a differential manometer (model 47 303A, digital pneumotachygraph, Hewlett–Packard, Palo Alto, Calif.). A fraction of the extracted air was sampled, and its oxygen and carbon dioxide concentrations were measured with a thermomagnetic oxygen analyzer (Magnos T2, Hartmann and Braun, Frankfurt, Germany) and an infrared carbon dioxide analyzer (Uras 2T, Hartmann and Braun). All the measurements were carried out continuously, and the values for 15-minute periods were averaged. The 24-hour periods were divided into a daytime period (8:30 a.m. to 11:30 p.m.) and a nighttime period (11:30 p.m. to 8:30 a.m.).

Ethanol Measurements and Substrate Oxidation

A fraction of absorbed ethanol can escape unmetabolized into expired air and urine. Consequently, respiratory ethanol losses were measured throughout the study at 10-minute intervals, as described above. The total daily respiratory and urinary losses of ethanol were taken into account in calculating the final amount of ethanol oxidized. This method was validated by measuring ethanol concentrations in blood and breath simultaneously in a separate study involving six of the eight men after they consumed the same quantity of ethanol, but no food, after an overnight fast. Concomitant measurements of ethanol in blood and in the expired air were obtained at 20-minute intervals for 4 hours. The results of the two techniques were strongly correlated ($r = 0.937$, $P<0.001$).

Energy expenditure and substrate oxidation were calculated with indirect-calorimetric formulas[25,27] and the coefficients proposed by Livesey and Elia.[28] By measuring oxygen consumption (VO_2), carbon dioxide production (VCO_2), and urinary nitrogen excretion as an index of protein oxidation, we were able to calculate substrate oxidation. Since ethanol was ingested as a fourth substrate, the nonethanol oxygen consumption ($VO_{2(ne)}$), in liters per minute, and the nonethanol carbon dioxide production ($VCO_{2(ne)}$), also in liters per minute, had to be calculated; that is, the measured oxygen consumption and carbon dioxide production were corrected for the amount of oxygen consumed and the amount of carbon dioxide produced by the quantity of ethanol that was metabolized. We assumed complete oxidation of the ingested ethanol (except for that lost in expired air and urine), as shown by breath and blood ethanol concentrations, which were zero at the end of the days on which ethanol was consumed. This assumption was based on two lines of evidence. First, in a recent study involving indirect calorimetry and measurements of the oxidation of ^{14}C-labeled ethanol, ethanol in amounts similar to those given in our study was completely oxidized to [^{14}C]carbon dioxide within a four-hour period.[21] Furthermore, lipogenesis from ethanol is of importance only when a large amount of ethanol is consumed — a situation different from that in this study.[29,30] According to stoichiometric calculations, the complete oxidation of 1 mol of ethanol requires 67.2 liters of oxygen and produces 44.8 liters of carbon dioxide.

The values for oxygen consumption and carbon dioxide production corrected for ethanol oxidation ($VO_{2(ne)}$ and $VCO_{2(ne)}$) were then used in the final calculations of nonethanol substrate oxidation (i.e., oxidation of carbohydrate, lipid, and protein). The rate of protein oxidation (Pox, expressed in grams per minute) was calculated from the following equation:

$$Pox = 6.25 \times N, \quad (1)$$

where N is the urinary excretion of nitrogen in grams per minute. The rates of carbohydrate oxidation (CHOox) and lipid oxidation (Lox) are obtained by means of the following equations:

$$VO_{2(ne)} = CHOox \times 0.828 + Lox \times 2.015 + Pox \times 1.010 \quad (2)$$

$$VCO_{2(ne)} = CHOox \times 0.828 + Lox \times 1.431 + Pox \times 0.844, \quad (3)$$

where 0.828, 2.015, and 1.010 liters are the amounts of oxygen used to oxidize 1 g of carbohydrate (starch), 1 g of lipid, and 1 g of protein, respectively; 0.828, 1.431, and 0.844 liters are the amounts of carbon dioxide produced when 1 g of carbohydrate (starch), 1 g of lipid, and 1 g of protein, respectively, are oxidized.

Physical Activity

Strenuous exercise was not permitted in the respiration chamber except for two 60-minute periods of walking on a treadmill, one at 3.0 km per hour and 0 percent slope at 10:30 a.m. and another at 3.0 km per hour and 10 percent slope at 2:30 p.m. On the first control day, the men kept a diary of their spontaneous activity at 10-minute intervals, and they were asked to replicate the activity of the first day during the remaining days of the study. Furthermore, the level of activity was inconspicuously monitored by a Doppler radar system.[31]

Biochemical Tests

Complete 24-hour urine collections (divided into daytime and nighttime collections) were obtained during each two-day study. Urinary excretion of catecholamines (epinephrine and norepinephrine) was determined as described by Crout,[32] and total urinary nitrogen excretion was determined for the same time periods by the Kjeldahl method. On the morning of the first admission a venous blood sample was taken for the determination of serum creatinine, electrolyte, liver enzyme, and lipid concentrations and red-cell and white-cell counts. All results were within the normal range. Blood ethanol concentrations were measured on the morning of each admission and on the morning after the days when ethanol was ingested; ethanol was measured in the urine from all daytime and nighttime collections. The blood and urine ethanol determinations were carried out by gas chromatography (model HP 5890 A, Hewlett–Packard) with direct injection of weighed whole blood, urine, and internal standards.[33]

The results from the control days and the days when ethanol was ingested were compared by standard statistical methods, including the paired t-test when applicable. All P values are two-tailed. Except where otherwise specified, the results are presented as means ±SE.

Results

Energy intake, energy expenditure, and substrate oxidation are summarized in Tables 1 and 2. As compared with the corresponding control day, both the addition and the substitution of ethanol caused significant increases (7±1 percent and 4±1 percent, respectively) in 24-hour energy expenditure (Table 2). The addition of ethanol to the diet decreased 24-hour lipid oxidation by 49.4±6.7 g per day (or 36±3 percent of the rate of oxidation on the control day). The isocaloric substitution of ethanol for lipids and carbohydrates resulted in a similar reduction in lipid oxidation (44.1±9.3 g per day, or 31±7 percent of the rate of oxidation on the control day). The rate of fat oxidation did not differ between the day on which ethanol was added to the diet and that on which it was substituted for other foods.

Table 1. Daily Energy and Substrate Intake in Eight Men before and during the Ingestion of Ethanol.*

Day of Study	Energy	Fat	Carbohydrate	Protein	Ethanol
	MJ/24 hr (kcal/24 hr)		*kJ/24 hr (kcal/24 hr)*		
Control	11.4±0.2 (2736±43)	3447±62 (824±15)	5795±84 (1385±20)	2205±37 (527±9)	0
Ethanol added	14.3±0.2 (3418±53)	3447±62 (824±15)	5795±84 (1385±20)	2205±37 (527±9)	2855±43 (682±10)
Control	11.4±0.2 (2736±43)	3447±67 (824±15)	5795±84 (1385±20)	2205±37 (527±9)	0
Ethanol substituted	11.4±0.2 (2736±43)	2009±39 (480±9)	4373±62 (1045±15)	2206±37 (527±9)	2860±45 (683±11)

*Plus–minus values are means ±SE.

As expected, the addition of ethanol to the diet resulted in a positive energy balance as compared with the control day (1688±120 kJ [403±29 kcal] per day vs. −381±166 kJ [−91±40 kcal] per day). The increase in energy expenditure induced by the ingestion of ethanol and the concomitant effects on substrate oxidation occurred only during the daytime, when ethanol was consumed and metabolized (Fig. 1). There were no differences in carbohydrate and fat oxidation during the nighttime. There was a slight increase in the oxidation of protein during the nighttime period of the day on which ethanol was substituted for other foods (70.7±1.5 kJ [17±1 kcal] per hour vs. 61.8±0.9 kJ [15±1 kcal] per hour on the control day; $P<0.05$) (Fig. 1).

The mean respiratory quotients for the two 24-hour control periods were identical (0.84±0.01); the addition of ethanol to the diet significantly lowered the mean 24-hour respiratory quotient to 0.82±0.01, and the substitution of ethanol for other foods lowered it to 0.81±0.01 ($P<0.01$ for both comparisons). There was no significant difference in the respiratory quotient between the two days on which ethanol was ingested. Physical activity, assessed by radar measurements, was similar on the control day and the day when ethanol was added to the diet.

As expected, no ethanol was detected in the blood samples obtained at admission. On the days when ethanol was ingested, the peak blood ethanol concentrations after the meals ranged from 5.86±0.43 to 9.33±0.65 mmol per liter (0.27±0.02 to 0.43±0.03 g per liter). The peak blood ethanol concentration occurred within one hour after ingestion and was similar whether ethanol was substituted for or added to other foods. The urinary excretion of norepinephrine and epinephrine did not change after the ingestion of ethanol, either when the 24-hour periods were compared or when separate daytime and nighttime periods were analyzed.

Discussion

In healthy, nonalcoholic men, both the addition of ethanol to the diet and the substitution of ethanol for 25 percent of energy needs led to a decrease in lipid oxidation. This effect was limited to the daytime, when ethanol was being metabolized (Fig. 1). The magnitude of the suppressive effect on lipid oxidation was similar in both parts of the study (36 percent reduction with the addition of ethanol to the diet and 31 percent reduction with the substitution of ethanol for other foods). Considerable evidence from in vitro and short-term in vivo studies indicates that ethanol decreases lipid oxidation in the liver and other organs.[17-19,21,22,34] Similarly, in a four-hour study, ethanol infusion decreased lipid oxidation in vivo by 70 percent.[21]

Whether ethanol intake and body weight are correlated is controversial.[9-16] The efficiency with which energy from ethanol is used depends on the quantity of ethanol and the frequency of its ingestion. Over the long term, excessive ethanol intake is metabolized predominantly by the microsomal ethanol-oxidizing system, which requires high ethanol concentrations for half-maximal activity and which leads to an increased loss of energy from ethanol as heat.[7,19] In contrast, when intake is light to moderate, ethanol is metabolized primarily by the alcohol dehydrogenase system, with less waste of energy.[13] In our subjects, the ethanol load was probably metabolized mostly by the alcohol dehydrogenase pathway, since their ethanol consumption at admission (corresponding to about 1.6±1.5 oz of spirits per week) would not be expected to lead to metabolism by the microsomal ethanol-oxidizing system.

Table 2. Daily Energy Expenditure and Substrate-Oxidation Rate in Eight Men before and during the Ingestion of Ethanol.*

Day of Study	Energy Expenditure	Oxidation			
		Fat	Carbohydrate	Protein	Ethanol
	MJ/24 hr (kcal/24 hr)	*kJ/24 hr (kcal/24 hr)*			
Control	11.8±0.3 (2827±63)	5439±443 (1300±106)	4308±360 (1030±86)	2081±69 (497±17)	0
Ethanol added	12.6±0.2 (3015±55)	3487±276 (834±66)	4150±261 (992±62)	2134±80 (510±19)	2843±44 (679±11)
Difference	P<0.001	P<0.001	NS	NS	—
Control	11.9±0.2 (2854±50)	5401±321 (1291±77)	4482±201 (1071±48)	2056±48 (491±11)	0
Ethanol substituted	12.4±0.3 (2973±71)	3660±322 (875±77)	3798±191 (908±46)	2136±106 (511±25)	2847±42 (680±10)
Difference	P<0.025	P<0.0025	P<0.05	NS	—

*Plus–minus values are means ±SE. NS denotes not significant.

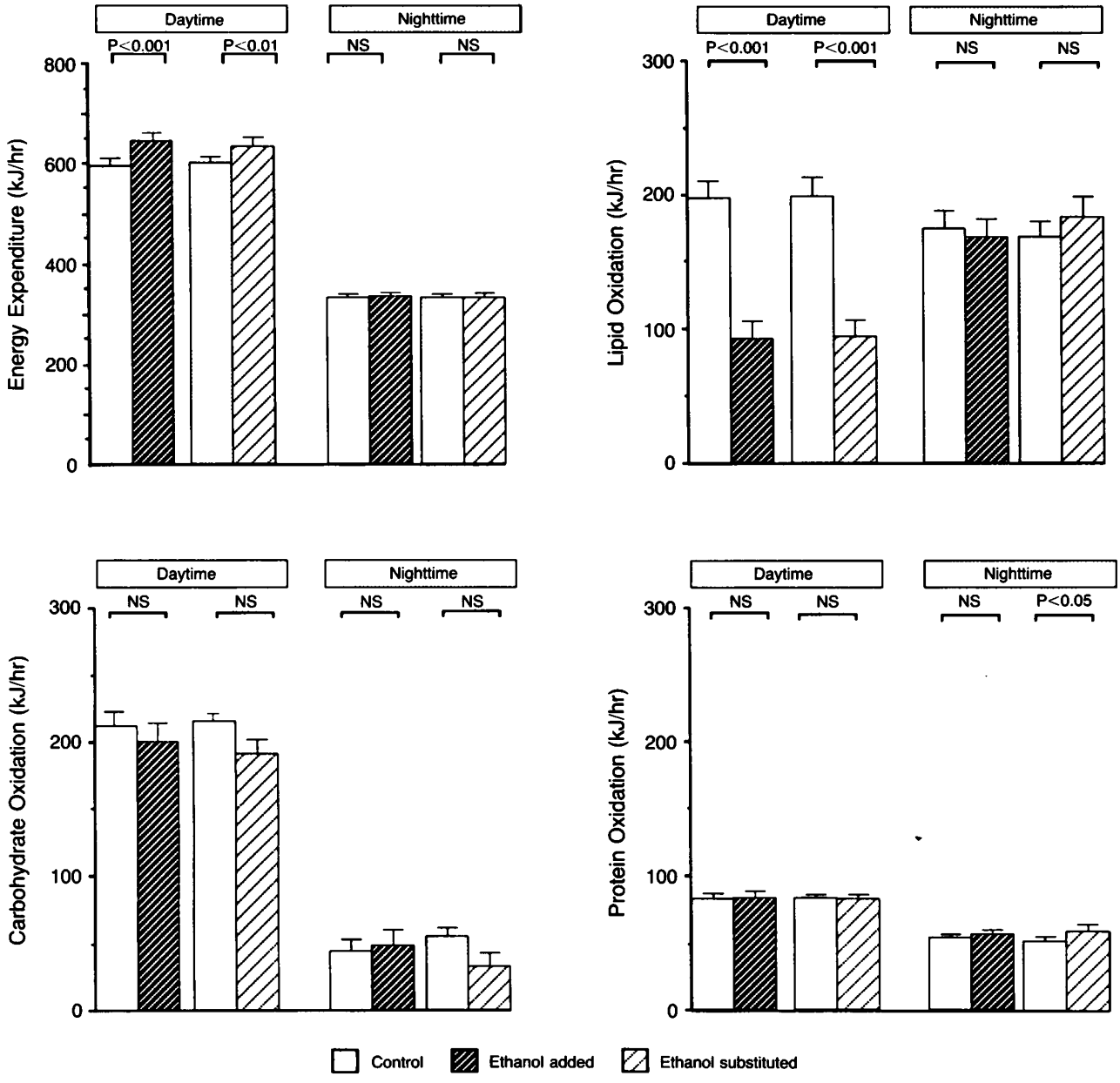

Figure 1. Mean (±SE) Energy Expenditure and Substrate-Oxidation Rates for the Daytime and Nighttime Periods in Eight Men before and during Ethanol Ingestion.

The effects of ethanol were limited to the daytime period (8:30 a.m. to 11:30 p.m.), when ethanol was ingested and metabolized. The T bars indicate the SE. To convert kilojoules into kilocalories, divide by 4.184. The darker hatched bars indicate days on which ethanol was added to the diet, and the lighter hatched bars days on which ethanol was substituted for other foods, providing 25 percent of total energy. The P values shown are for the comparisons between each day on which ethanol was given and its control day; NS denotes not significant.

We found that the ingestion of ethanol reduced whole-body lipid oxidation; ethanol ingestion in excess of energy needs therefore favors fat storage. Several mechanisms might explain these results. First, the oxidation of ethanol causes a shift in the redox state in the liver that decreases lipid oxidation.[19] Second, up to 80 percent of the ethanol metabolized in the liver appears as acetate in the hepatic vein, leading to an increase in the body's acetate pool.[35] Thus, the carbon atoms of ethanol (in the form of acetate) are shuttled for oxidation to the peripheral tissues, where the function of the tricarboxylic acid cycle is not limited by ethanol oxidation. Acetate has been found to suppress the oxidation of lipids in peripheral tissues, and some of the acetate might be used for lipogenesis.[36,37] Lipogenesis might therefore represent one metabolic use of ingested ethanol. With indirect calorimetry, the quantity of ethanol oxidized to carbon dioxide and water and the amount converted to fat cannot be determined separately. Since indirect calorimetry measures net substrate balances — i.e., net fat oxidation or net lipogenesis — it is possible that the two metabolic path-

ways operate simultaneously in different tissues. However, the methods of measuring the net substrate balance remain valid.[25,27,38] A small increase in protein oxidation occurred during the nighttime period of the day on which ethanol replaced other foods; this finding is in agreement with those of earlier studies.[29,39]

In the studies by Pirola and Lieber,[7,8] the isocaloric replacement of carbohydrate by ethanol (50 percent of total calories) resulted in weight loss, and ethanol given as a supplement resulted in less weight gain than supplementation with an equivalent amount of non-ethanol energy. The weight loss resulting from 50 percent ethanol substitution was explained by the increased metabolism of ethanol in the microsomal ethanol-oxidizing system, which resulted in an elevated thermogenic response. In our study, the ingestion of ethanol also increased energy expenditure. This finding explains why the long-term ingestion of alcohol in place of other foods can lead to the loss of body weight. By contrast, the ingestion of ethanol as additional energy above nutritional requirements is a risk factor for obesity, because it decreases lipid oxidation and therefore favors lipid storage. Epidemiologic data support the latter conclusion, since excessive weight gain frequently occurs between the second and fifth decades of life,[16,40-42] a period when a high percentage of energy is often derived from ethanol.[2,16]

Our findings indicate that ethanol can be an important source of energy that is available to the body. Obese patients who follow a weight-reducing diet and subjects who want to maintain a constant body weight without giving up ethanol consumption should therefore decrease their fat intake to allow for the additional energy from ethanol. The habitual consumption of ethanol in excess of energy needs (i.e., the addition of ethanol to the diet) leads, therefore, to a metabolic condition that favors lipid storage and weight gain and can be considered a risk factor for the development of obesity.

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