Biology of Disease

Alcoholism and Aldehydism: New Biomedical Concepts

JEAN-PIERRE VON WARTBURG AND ROLF BÜHLER

Medizinisch-chemisches Institut der Universität Bern, Bern, Switzerland

New results of biomedical research in alcoholism show great interindividual, as well as racial, variability with respect to metabolism of alcohol and its first oxidation product, acetaldehyde. Genetic factors play an important part. The enzymes of alcohol and aldehyde metabolism exhibit a genetically determined heterogeneity (isoenzymes and enzyme polymorphisms). This leads to a large variety of individually different enzyme phenotypes. Thus, the hypothesis is put forward that the individual and racial differences in alcohol metabolism are based on the genetically determined variability of the participating enzymes, alcohol dehydrogenase and aldehyde dehydrogenase.

Alcohol metabolism and alcohol-induced disturbances of the intermediary metabolism are closely interrelated. Hence, genetic codetermination can also be expected in this regard.

As a toxic intermediate of alcohol metabolism, acetaldehyde plays a central role. Three positive ranges of acetaldehyde levels can be defined: (a) the normal range, (b) the "acute aldehyde syndrome" with extremely high levels of acetaldehyde, (c) "chronic aldehydism" with slightly elevated acetaldehyde levels.

In Orientals lacking the mitochondrial low Kₘ, aldehyde dehydrogenase, acetaldehyde accumulates and produces symptoms of intoxication. This acute aldehyde syndrome is highly aversive and, thus, prevents these individuals from drinking. The effect is similar to the consequences of the inhibition of aldehyde dehydrogenase with disulfiram, a commonly employed drug in the treatment of alcoholics.

In alcoholics slightly elevated levels of blood acetaldehyde are observed. There are indications that this chronic aldehydism is not only the consequence of excessive drinking but may reflect a preexisting enzyme pattern that is genetically determined. Therefore, slightly elevated acetaldehyde concentrations could serve as a biologic marker for high risk drinking.

Alcohol dehydrogenase is found in many organs and often in specialized cells within a particular tissue. A specific enzyme pattern in these cells could lead to elevated acetaldehyde concentrations, consequently inducing acetaldehyde-related damage. Such organs could represent direct targets even at low blood acetaldehyde levels.

Medical doctors are confronted daily with the consequences of an uneven distribution of alcohol consumption in our countries (Fig. 1): a small percentage of the population (5 to 10%) drink a third or even up to half of all the consumed alcohol, which in Western industrial countries leads to an average daily consumption of 80 to 120 gm of pure alcohol by these people. On the other hand it is a well-known fact that the majority of the people in an alcohol-consuming society show a lifelong pattern of little or moderate drinking without developing alcohol-related problems. Moreover, genetic studies reveal that not everybody is at equal risk to develop alcohol-related disorders. The importance of genetic factors in alcoholism is being stressed by family, twin, and adoption studies.

Early detection of alcoholics as well as prevention and treatment of alcoholism are hampered by poor knowledge of the biomedical and psychosocial factors that predispose to or protect from the development of alcoholism. Of particular interest are genetically determined factors that could increase the risk of specific target organs to sustain alcohol-induced damage, or genetic factors that could lead to a change in the individual drinking behavior via biochemical mechanisms.

Recent data confirm the fact that the risk of chronic physical damage increases continually with the amount of alcohol consumed and the period of drinking. Hence, no generally valid threshold value for a safe alcohol consumption can be given. On the contrary, great differences in the susceptibility of various target organs in individual consumers as well as different susceptibility between individuals exist. The average dose-effect curve is best established in liver cirrhosis: in male subjects the risk triples upon consumption of 21 to 40 gm of alcohol/day and increases 600-fold with a daily amount of 140 gm of alcohol (58, 59), but even with such large quantities
only a small minority of individuals actually develop liver cirrhosis. In women as little as 20 gm/day can lead to alcoholic cirrhosis. Thus, there is a striking contrast between the relatively high susceptibility of occasional drinkers and the relatively remarkable resistance of some heavy drinkers. These differences in susceptibility might at least partly be due to genetic factors. However, no data are available with respect to the relative importance of genetic and environmental factors that determine the susceptibility of alcohol-induced organ or tissue damage. There is no doubt that both biologic and psychosocial factors play important parts and that the interplay between these factors has been underestimated. In this regard investigations of the alcohol metabolism, notably with respect to the metabolite acetaldehyde and the enzymes by which it is produced and removed and how these are influenced by genetic and environmental factors, have provided interesting indications.

Fate of Ethanol in the Body

The processes that take place in the organism after ingestion of ethanol can be divided into three phases: the absorption phase, the distribution or diffusion phase, and the elimination phase (Fig. 2) (35, 83). During the absorption phase ethanol is absorbed in the upper parts of the gastrointestinal tract purely by diffusion; there is no need of preceding digestion by hydrolytic enzymes as is the case with other food components. However, a partial oxidation of the alcohol by the alcohol dehydrogenase (ADH) in the gastrointestinal mucosa cannot be excluded (40, 84). The absorption rate depends on factors such as the amount of alcohol and concentration and composition (additives) of the alcoholic beverages, as well as on the food intake (dilution, time of passage through the various fast absorbing intestinal parts, blood supply of the mucosa). The average rate of increase of the blood alcohol concentration can vary from about 30 to 270 mg/100 ml in 1 hour (99). Peak alcohol levels occur between 20 and 120 minutes. The absorption phase is usually terminated after 2 hours and overlaps with the diffusion phase.

The most simple pharmacokinetic description of absorption is based on first order kinetics, whereby the rate of absorption at a given time is proportional to the quantity of alcohol still to be absorbed. As the rate of absorption is different for stomach and duodenum, the gastric emptying rate also plays an important part. Therefore, a correspondingly complicated absorption model contains two absorption constants (stomach and intestine) as well as a first order rate constant for gastric emptying (95). Since the absorption kinetics essentially determine the blood alcohol concentration with which the liver is perfused during the absorption phase, they play an eminent role in the elimination kinetics during this phase.

During the diffusion phase the alcohol is distributed in the tissues essentially in proportion to their water content (interstitial and intracellular water plus blood). On the average the total volume of body water is larger in men than in women; therefore, corresponding sex-related differences in blood alcohol concentrations occur even after ingestion of identical amounts. In addition, the total volume of body water is age dependent. During pregnancy alcohol is also distributed within a few minutes into the amniotic fluid and the fetal body water (88). During absorption the arterial blood levels are higher than the concentrations in venous blood because alcohol still diffuses from the intravascular water compartment into extravascular water. During elimination the transcapillary diffusion occurs in the opposite direction, and the venous concentrations are slightly lower. A mathematical model for the ethanol exchange process over the capillary membrane has recently been described (93).

Experiments with 14C-labeled ethanol show that all of the perorally administered alcohol is absorbed and that only a few percent are excreted unmetabolized by the lungs, in urine and sweat (12, 82). Older work has also demonstrated that ethanol is fully absorbed with and without food intake (17, 28, 73). The elimination phase is characterized by a decrease in blood alcohol concentration, whereby approximately 90% of the elimination is accomplished by oxidation of MEOS patterns.
Ethanol is metabolized to carbon dioxide and water, thus representing the main pathway. In the early literature at the beginning of the century there was already a fierce controversy regarding the linearity of the decrease of the blood alcohol curve (for reviews see references 17, 95). At that time little was known about enzyme kinetics according to Michaelis and Menten so that an exponential decrease was assumed with a nonlinear course. The variation in the route of ethanol administration as well as species differences played an important part in the occurrence of so many diverging observations. Finally, however, the dogmatic opinion prevailed that the oxidation of alcohol was independent of the ingested quantity or the given blood alcohol concentration, respectively. These zero-order kinetics found expression in Widmark’s mathematical formulations (94).

By means of numerous determinations using the Widmark method, an elimination rate of 100 mg/kg/hour was established, with a substantial scattering of 70 to 130 (17). At many places these empirical values are still fundamental in practical forensic medicine.

For quite some time observations in animals and humans gave rise to doubts about the exclusive validity of the dogma of dose and concentration independence of alcohol oxidation: repeatedly, dose-dependent kinetics or curvilinear shapes of blood alcohol curves have been described. An important step toward a new interpretation of blood alcohol curves was accomplished by Lundquist and Wolthers (48) in 1958 who essentially suggested a one-compartment open model with Michaelis-Menten elimination kinetics. During the 1970s it was mainly the extensive work done by Wagner and coworkers that led to refinements and extension of the models and finally to the development of pharmacokinetic notions which allowed a mathematical description of the entire blood alcohol curve during the resorption, diffusion, and elimination phases (79, 80, 95). With these models nonlinear least squares regression analysis of experimental blood alcohol curves and the estimation of elimination parameters such as the Michaelis constant ($K_m$) and the maximal velocity ($V_{max}$) are possible. Furthermore, they allow one to carry out computer simulations in order to better understand the interferences of the various pharmacokinetic parameters such as absorption and elimination constants and the area under the curve. Yet, these models are still not able to provide an adequate description of blood alcohol curves observed in drinking experiments under a variety of circumstances.

This is mainly due to the fact that they still neglect such phenomena as the first pass elimination by the liver or the multitude of enzymes involved in alcohol metabolism.

**ETHANOL OXIDATION AND ITS ENZYMES**

Ethanol is almost exclusively eliminated from the body by oxidation. This process takes place primarily in the liver, whereby ethanol is metabolized enzymatically first to acetaldehyde and then to acetate (41, 44, 83). The enzymes which catalyze this two-step oxidation of ethanol to acetate are ADH and aldehyde dehydrogenase (ALDH) (Fig. 3). On the other hand, a small part of the ethanol, 10% or less, can be metabolized by alternative pathways, i.e., the microsomal ethanol-oxidizing system (MEOS) and catalase (44). A mechanism involving hydroxyl radicals has recently been proposed (96). The activity of the MEOS can be induced by various drugs and by chronic alcohol intake. Very little of the consumed ethanol is excreted or exhaled when ethanol concentrations in blood are less than 200 mg/100 ml or 40 mM.

In the older, as well as in the more recent, literature great interindividual differences regarding alcohol elimination rates are reported, whether they be calculated by the now obsolete method of Widmark or by using Michaelis-Menten kinetics. They differ 2- to 3-fold after ingestion of identical amounts of alcohol (3, 17, 65, 79). Such large interindividual differences can be due to a combination of genetic and environmental factors. Newer data indicate that approximately half of the differences in the alcohol elimination rates observed between individuals are genetically determined, whereas the remainder is probably due to environmental factors (38). Several investigations dealing with alcohol metabolism in various racial groups also point to genetic influences. Differences were sought in the absorption, the elimination from the blood, and the oxidation rate between North American Indians, Chinese, Japanese, Europeans, and white Americans. In most studies a statistically significant increase in the alcohol degradation rate was found in Orientals and American Indians as compared with Caucasians (21, 24, 64, 65).

Thus, the question arises whether these individual as well as racial differences in alcohol metabolism are due to genetically determined differences in the respective enzyme patterns. Indeed, several research groups have observed that the activity of human liver ADH shows a considerable interindividual variability (43, 53, 68, 69, 91). Consequently, one can assume that the differences
in alcohol metabolism probably mainly reflect the broad range of the catalytic properties of human ADH, which in turn is due to the large number of multiple molecular forms observed in this enzyme (Table 1).

Many multiple forms can be ascribed to the presence of isoenzymes. They occur by random combination of three different subunits (α, β, γ) to the six possible dimeric forms (41, 68, 71, 72, 87). Further enzyme forms are due to enzyme polymorphisms. At the gene locus coding for γ-polypeptide chains there are allelic genes that lead to γ1- and γ2-subunits. Apparently, several polymorphisms occur at the gene locus that codes for the β-subunits: in addition to the normal β1-subunit the "atypical" β2-subunit (β-Bern) (91, 92) or a β-Indianapolis subunit (discovered there) can occur (5, 42). In addition to these forms other ADHs have been identified. π-ADH is present in all humans, although to a variable extent (43). Finally, forms with a cathodic electrophoretic mobility (χ-enzyme) were also described (57), the structure and gene control of which are still unknown.

The Km for ethanol as substrate for the various forms of human liver ADH varies considerably. The main isoenzyme β1β1, isolated from normal liver homogenates reveals nonlinear kinetics with a lower Km of 0.5 mM and a higher Km of approximately 8 mM and equal contributions to the maximal velocity (6, 9, 15, 80). Hence, the higher value is similar to the one observed for the MEOS enzyme which has been found to be 8 to 10 mM (45). Finally, even higher value of 15 to 30 mM has been reported for the π-enzyme (64, 65), and with the x-enzyme saturation with ethanol could not be reached (57). From these findings the question arises as to what extent the variable affinities of the multiple enzyme forms also affect alcohol elimination in vivo. During the phase of absorption from the gastrointestinal tract the relatively high alcohol concentrations in the portal vein should lead to increasing saturation of the high Km forms of ADH, so that a considerable amount of alcohol could be removed by the first pass elimination during absorption (Fig. 4). Alcohol eliminated by such a mechanism would not appear in the peripheral blood, although it has been absorbed in the gastrointestinal tract. Consequently, an apparently incomplete absorption would result from this phenomenon and the area under the peripheral blood alcohol curve would be diminished in spite of an actually complete absorption.

Obviously, the availability of the coenzyme is a prerequisite for the effectiveness of high Km forms of human liver ADH for a first pass elimination of alcohol during absorption. The activity of ADH in the liver of atypical individuals is considerably elevated. Hence, one might expect that such individuals could eliminate alcohol at a much faster rate than normal. However, a few atypical individuals were found to have only a slightly higher rate during the steady state of alcohol metabolism (16, 92). This fact indicates that in these individuals the reoxidation of NADH becomes the main factor limiting the rate of alcohol oxidation. However, during the initial phase of alcohol metabolism, i.e., immediately after drinking an alcoholic beverage and during the absorption of the alcohol in the gastrointestinal tract, NADH reoxidation would be less limiting until the pool of oxidized NAD+ is depleted and the reoxidation state (NADH to NAD+) has reached equilbrium in the new, more reduced state in the whole organism. Furthermore, an adaptive increase in the rate of ethanol metabolism may occur rapidly after the ingestion of alcohol (swift increase in alcohol metabolism) (76). The phenomenon is based on

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**TABLE 1. POLYMORPHISM OF HUMAN LIVER ALCOHOL DEHYDRogenASE**

| Enzyme class | Gene locus | Alleles | Peptide chains | Km ethanol  
<table>
<thead>
<tr>
<th></th>
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<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>ADH-1</td>
<td></td>
<td>α</td>
<td>α</td>
<td>5</td>
</tr>
<tr>
<td>ADH-2</td>
<td></td>
<td>β1β1</td>
<td>β1β1</td>
<td>0.5</td>
</tr>
<tr>
<td></td>
<td></td>
<td>β2 (βBern, &quot;atypical&quot;)</td>
<td>β2</td>
<td>&lt;5</td>
</tr>
<tr>
<td></td>
<td></td>
<td>βIndianapolis</td>
<td>βIndianapolis</td>
<td></td>
</tr>
<tr>
<td>ADH-3</td>
<td></td>
<td>γ1γ1</td>
<td>γ1γ1</td>
<td>34</td>
</tr>
<tr>
<td></td>
<td></td>
<td>γ2γ2</td>
<td>γ2γ2</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>ππ</td>
<td>ππ</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>χχ</td>
<td>χχ</td>
<td>Very high</td>
</tr>
</tbody>
</table>

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**Fig. 4. Sites of ethanol removal with first pass oxidation in the liver during absorption.**
An increase in the mitochondrial reoxidation of NADH, and catecholamines are probably involved in the mechanism (98). Swift increase in alcohol metabolism seems to occur in humans within one drinking episode but apparently not in all individuals (R. G. Thurman, personal communication). This observation is of great importance because swift increase in alcohol metabolism could allow for enhanced ethanol oxidation during and shortly after absorption in individuals with corresponding isoenzyme patterns of ADH (high Vmax and high Km). The pharmacokinetics of ethanol which determine both the shape and the area under the blood alcohol curve thus depend in a complex way on the enzyme patterns (89). The length of time during which the alcohol remains in the organism, however, is of decisive importance for the immediate toxic effect. Hence, one has to assume that individual pharmacokinetic differences cause disparately strong effects of alcohol, e.g., on the brain membranes. It has been suggested that this membrane-disturbing effect represents a primary mechanism of acute alcohol intoxication. Moreover, it was postulated that physical dependence and tolerance can develop as a result of adaptive changes that counteract the membrane-disturbing effect of alcohol. Therefore, individual differences in pharmacokinetic parameters could directly influence the development of metabolic tolerance (20) or indirectly influence the development of physical dependence and tolerance (51).

Central Role of Acetaldehydes

In addition to the direct effects of alcohol many indirect toxic effects are ascribed to the first oxidative metabolite, acetaldehyde (44, 46, 85). The pharmacokinetics of acetaldehyde are characterized by its rate of formation and degradation, as well as the localization of these processes. The rate of formation is obviously identical with the alcohol elimination rate so that a similarly large individual variation is to be expected. Moreover, isoenzymes and enzyme polymorphisms of the main enzyme responsible for the further degradation of acetaldehyde are known.

Acetaldehyde disposal takes place mainly by oxidation to acetate, whereby ALDH plays the major role. In comparison with human ADH surprisingly little is known about human ALDH and its genetic control. Several multiple molecular forms have been described and characterized. These observations make it likely that ALDH activities show an equally large variability as the ones found for ethanol oxidation (25, 27, 30, 32, 87). In addition, an enzyme polymorphism found in Oriental populations reveals that about 50% of the individuals lack one enzyme form which seems to be the low Km mitochondrial enzyme (1, 22, 23, 26). It has recently been shown by immunochemical methods that the enzyme is indeed present, but that it is inactive (31). A very slow acetaldehyde metabolism would be expected in such individuals, and indeed, extremely high acetaldehyde blood and breath levels have been observed as a consequence of this enzyme polymorphism.

Three different states concerning the range of possible blood acetaldehyde levels in humans can be distinguished: (a) the normal range, (b) the "acute aldehyde syndrome" with extremely high acetaldehyde concentrations, and (c) "chronic aldehyde" with only slightly increased blood acetaldehyde levels.

For many years methodologic difficulties have prevented accurate determinations of acetaldehyde concentrations in blood or tissue samples. Now several methods are available which give the various groups of researchers comparable results, and agreement among has been reached on the actual levels (19, 46, 90). The range of normal acetaldehyde concentrations depends on the alcohol dose. With ethanol ingestions of 0.25 to 0.75 gm/kg of body weight, acetaldehyde levels beyond the limit of detection (ca. 0.5 μM) and up to 2 to 3 μM were found.

In individuals suffering from the acute aldehyde syndrome, acetaldehyde concentrations are dramatically elevated to levels of 10 times normal or more. This phenomenon is observed in Orientals lacking the low Km mitochondrial ALDH (27, 52, 86) or after treatment with ALDH inhibitors such as disulfiram (49). Symptoms such as heavy facial flushing, tachycardia, hypotension, headache, nausea, vomiting, muscle weakness, and sleepiness may occur, and the degree of the symptoms apparently depends on the acetaldehyde levels (67). These symptoms are clearly very aversive and would be expected to prevent individuals from drinking. Factually, only a small percentage of individuals lacking the mitochondrial isoenzyme have been found among Japanese alcoholics as compared with approximately 50% in the whole population (27). This finding is well in keeping with the hypothesis that a genetic hypersensitivity toward the effects of alcohol prevents these individuals from high risk drinking.

In individuals with chronic aldehydism, acetaldehyde concentrations are only slightly elevated to about 2 to 5 times normal (39, 46, 49, 55, 56). Such levels might result from specific isoenzyme patterns of ADH and ALDH and/or the induction of MEOS leading to slightly increased acetaldehyde production combined with a

### Table 2. Distribution of Alcohol Dehydrogenase in Human Organs as Determined by Immunohistochemistry

<table>
<thead>
<tr>
<th>Organ</th>
<th>Cells</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liver</td>
<td>Hepatocytes, mainly pericentral</td>
</tr>
<tr>
<td>Stomach</td>
<td>Mucosa, mainly parietal-, chief-, mucus-producing cells</td>
</tr>
<tr>
<td>Duodenum</td>
<td>Mucosa: villus cells</td>
</tr>
<tr>
<td>Jejunum</td>
<td>Mucosa: surface epithelium</td>
</tr>
<tr>
<td>Ileum</td>
<td>Islet cells, less in exocrine cells</td>
</tr>
<tr>
<td>Colon</td>
<td>Little (calcitonine producing cells)</td>
</tr>
<tr>
<td>Rectum</td>
<td>Epithelium</td>
</tr>
<tr>
<td>Pancreas</td>
<td>Epithelium</td>
</tr>
<tr>
<td>Thyroidia</td>
<td>Seminiferous epithelium, Leydig cells</td>
</tr>
<tr>
<td>Adrenals</td>
<td>Little</td>
</tr>
<tr>
<td>Prostate</td>
<td>Little</td>
</tr>
<tr>
<td>Epididymis</td>
<td>Little</td>
</tr>
<tr>
<td>Testes</td>
<td>Little</td>
</tr>
<tr>
<td>Ovary</td>
<td>Little</td>
</tr>
<tr>
<td>Uterus</td>
<td>Little</td>
</tr>
<tr>
<td>Kidney</td>
<td>Tubuli epithelium</td>
</tr>
<tr>
<td>Heart muscle</td>
<td>Neurons and astrocytes</td>
</tr>
<tr>
<td>Cerebrum</td>
<td>Purkinje cells and astrocytes</td>
</tr>
<tr>
<td>Cerebellum</td>
<td>Neurons</td>
</tr>
<tr>
<td>Hypothalamus</td>
<td>Neurons</td>
</tr>
</tbody>
</table>
slightly slower removal rate. Higher acetaldehyde levels in the tissue could predispose to heavier intracellular cytotoxic effects, thus leading to increased organic damage. In this context it is of interest that high frequencies of atypical ADH have been observed in alcoholic liver disease (36, 66).

In alcoholic liver disease particularly the mitochondria suffer severe damage. Thus, aldehyde oxidation is disturbed, producing an accumulation of acetaldehyde which in a vicious circle leads to further disturbance of the mitochondrial function (4, 10, 29, 37, 50, 74).

Newer data obtained from activity determinations in needle biopsies suggest that a significant fraction of the acetaldehyde oxidation in man—in contrast to the rat—is localized in the cytoplasm and not exclusively in the mitochondria (34, 61, 62). A comparison of cytosolic and mitochondrial ALDHs revealed that both have a similar $K_m$ for acetaldehyde but that the cytosolic enzyme can also use NADP as a cofactor and in addition is more susceptible to inhibition by disulfiram. These results suggest that acetaldehyde toxicity in man is not based on specific damage to the mitochondria as was postulated for rat liver. More important, however, is the fact that the total oxidation of ethanol to acetate in the cytoplasm leads to an increased NADH to NAD$^+$ ratio. This in turn could be the reason for the higher susceptibility to alcohol toxicity of man in contrast to the rat, particularly with respect to the development of fatty liver. In rats the continuous prolonged oxidation of ethanol could be a more important pathogenic factor for alcoholic liver damage than acetaldehyde itself (47).

Cytosolic liver ALDH activity is reduced in patients...
with alcoholic liver disease (33, 54, 55, 75). In these individuals the reduced activity could be the reason for the disturbed acetaldehyde metabolism. Further studies by Peters (61) suggest that the reduced ALDH activity is irreversible, in contrast to reduced ADH activity, suggesting a primary defect. However, this argument is still controversial (78). Acetaldehyde levels were suggested as markers for alcoholism (70). It was shown that a test dose of ethanol led to higher acetaldehyde levels in healthy male relatives of alcoholics. But, as the authors themselves and Eriksson (18) emphasize, the method of blood acetaldehyde determination was not reliable because large amounts of acetaldehyde were produced artificially during sample treatment. It remains questionable whether there is indeed a connection between blood acetaldehyde levels and a predisposition to alcoholism. Preliminary results from analogous acetaldehyde determinations in exhaled air confirm that test persons with

**FIG. 6.** Immunohistochemical staining of ADH in the human gastrointestinal tract: colon ascendens (a and b) and stomach corpus (c and d). Sections were incubated with rabbit antihuman ADH antiserum, diluted 1:100 (a) and 1:10 (c) in phosphate-buffered saline. Control sections were incubated with immunoabsorbed anti-ADH antiserum, diluted 1:100 (b) and 1:10 (d) in phosphate-buffered saline. Sections were counterstained with Meyer's hematoxylin. For more details refer to reference 60. Figure 6 a and b, ×320; c and d, ×100.
alcoholism in their families had higher acetaldehyde levels after a test dose of ethanol than control individuals (M. A. Schuckit and J. P. von Wartburg, unpublished results).

Acetaldehyde is also known to have its own pharmacologic effects (2), some of which are antagonistic to the direct effects of ethanol. For instance, acetaldehyde can liberate biogenic amines such as catecholamine, thereby counteracting some of the sedative effects of ethanol. Therefore, the overall pharmacologic effects of alcohol in an individual might depend on the equilibrium between direct ethanol and antagonistic acetaldehyde effects. People who produce very little acetaldehyde could thus be more affected by the direct effects of ethanol than those with more acetaldehyde who, after ingestion of identical amounts of alcohol, could show fewer signs of drunkenness due to these antagonistic effects. The relationship between acetaldehyde and ethanol effects could, therefore, determine the inherent tolerance of a person toward the intoxicating effects of alcohol.

ARE THERE TARGET ORGANS?

Many organs including endocrine glands are known to be affected by chronic alcohol intoxication. In some instances it has been observed that acetaldehyde is at least as effective as ethanol. As discussed before, variable concentrations of acetaldehyde in the blood could produce different amounts of this toxic compound diffusing into tissues. On the other hand, the presence of ADH and/or MEOS in such organs could lead to intracellular formation of acetaldehyde. Hence, we undertook an immunohistochemical study of the localization of alcohol dehydrogenase in human tissues (7, 8, 60). Antibodies against a mixture of the pyrazole-sensitive human liver ADH were elicited in rabbits. Protein A-peroxidase with dianminobenzidine as substrate was used to detect anti-ADH bound to the enzyme in tissue thin sections. With this method at least some ADH could be detected in all tissues investigated (Table 2). The control sera were always negative. In some organs certain cell types exhibited much stronger staining than others within the same organ, indicating that the enzyme is unevenly distributed in many organs. Such uneven distribution was found in the kidney (Fig. 5), the gastrointestinal tract (Fig. 6), and also in the liver. This is an important observation because it means that high concentrations of ADH may occur in only a few cells of an organ, although the overall activity of ADH in that tissue may appear as no more than just a trace. High concentrations of acetaldehyde at these specific locations might then lead to discrete cell injury.

In brain, for instance, only some neurons exhibited strong staining in sections of cerebral cortex, cerebellum, and hypothalamus. Particularly, some Purkinje cells in the cerebellum stained very strongly (Fig. 7). At this time it is not yet possible to specify the neurons with high
ADH content, but some neurons also stained in the infundibular stalk of the pituitary gland.

The testes have been shown to be affected by alcohol, and the possible involvement of ADH has been suggested (13, 81, 97). We found most of the ADH in the Leydig cells, followed by the seminiferous epithelium, and least ADH in the interstitial cells (Fig. 8). These results are well in keeping with the proposed role of acetaldehyde formation in that organ. Furthermore, ADH was found in the prostate and in the epididymis.

In the ovary and uterus only weak staining was seen. This observation is again in agreement with the conclusion that ADH plays no role in the toxic effects of ethanol on these organs (63).

In the pancreas not only the exocrine functions but also the endocrine part is known to be affected by alcohol. Interestingly, in vitro experiments with rats show that acetaldehyde and acetate have marked effects on insulin and glucagon release (11, 77), and traces of ADH were detected in homogenates of whole pancreatic tissue (14, 69). Although ADH was found in both the exocrine and endocrine parts of the pancreas, much more enzyme was observed in the islets of Langerhans (Fig. 9), suggesting that ADH may be involved in the toxic effects of alcohol on pancreas.

In view of the toxic effects of acetaldehyde on the rat adrenals the possible formation of acetaldehyde from ethanol by ADH would be of special interest. However, the overall staining of the glands was weak, the adrenal cortex showing slightly more ADH than the medulla. Hence, it is more likely that effects of acetaldehyde on the adrenals, such as the release of catecholamines, are mediated by blood acetaldehyde diffusing into the glandular tissue.

In general we may conclude that specialized cells within endocrine organs may contain high amounts of ADH, even though the overall activity of the enzyme in the gland may be quite low. Therefore, many of the organs could be direct targets of acetaldehyde during ethanol intoxication even at low blood acetaldehyde levels.

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Address reprint requests to: Professor Dr. med. J. P. von Wartburg, Medizinisch-chemisches Institut der Universität, Postfach, 3000 Bern 9, Switzerland.

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