FACTORS INFLUENCING THE METABOLISM AND DISAPPEARANCE OF ALCOHOL

by

DR. DAVID LESTER*

I should like to say, first off, that this review of various factors and agents influencing the metabolism of alcohol is looked at from the point of view of forensic science, that is, from the point of view of what influence such agents may have on the blood values or the breath values reported for legal purposes.

It is hardly possible in this short time to discuss the host of factors which investigators have seen fit to test for their effect on the metabolism of alcohol without devoting initially some time to data which, by and large involve only the presence of alcohol and where no other agent has been used. For forensic purposes, it would appear germane to view these data about the effect of various agents in the context of the usual variations expected in the rate of disappearance of alcohol.

The first three lines of the slide (Table I) indicate the results that have been obtained by three groups of investigators on a range of human subjects: some subjects under experimental conditions and others arrested for various reasons, but usually drunk driving.

Now you will note that where no agent other than alcohol was present, the rate of disappearance of alcohol ranges from 8 to 26 milligrams of alcohol per 100 milliliters of blood per hour. This is thus the value for β60. These values, I believe, are well within the experience of most of us.

I have chosen these particular data because a large number (165,568,922) of subjects were used and because the analytical methods seemed exemplary. They do illustrate well the fact of biological variation. It should be added that other investigators have found differences in the rate of oxidation as between alcoholics and non-alcoholics to be non-existent. The range of values in Table I are, therefore, in all probability applicable to the population as a whole, even if these data are weighted toward non-naive drinkers.

Again in Table I, diurnal variations are of the order of ±25%, and, according to Wilson, Newman and Newman (63), the rate of disappearance is proportional to body temperature. But you will note further that neither sleep (2) nor unconsciousness (11) is reported to have an effect upon the rate of disappearance of alcohol, and, in these two instances (sleep or unconsciousness), a decrease in body temperature would be expected. The findings are thus somewhat contradictory except as may be noted that the diurnal variability of ±25% is well within the range of normal variability.

The slight increase which has been reported in the rate of disappearance of alcohol as a result of heavy muscular work (21) arises in all probability from an increased loss of alcohol in respiration and sweat; an increased expenditure of energy per se, it seems fair to say, has no effect upon the rate of oxidation of alcohol.

Table I

<table>
<thead>
<tr>
<th>Rate of Disappearance of Alcohol</th>
<th>(Man)</th>
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<tbody>
<tr>
<td>17 ± 9 mg/100 ml/hr (1,655)*</td>
<td>Ponsold and Heite (48)</td>
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<tr>
<td>13 ± 5 mg/100 ml/hr (68)*</td>
<td>Coldwell and Smith (8)</td>
</tr>
<tr>
<td>18 ± 4 mg/100 ml/hr (922)*</td>
<td>Abele (1)</td>
</tr>
<tr>
<td>Diurnal variation: ± 25%</td>
<td>Wilson, Newman, and Newman (63)</td>
</tr>
<tr>
<td>Sleep: no effect</td>
<td>Apel (2)</td>
</tr>
<tr>
<td>Unconsciousness: no effect</td>
<td>Forster (13)</td>
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</table>

*Number of subjects used.
Increased losses in respiration and perspiration are also probably the cause of the reported (40) greater rate of disappearance of alcohol in eight subjects exposed to an environmental temperature of 37°C as compared to the rate when these subjects were at 20°C. A quite opposite effect was reported by Platonow, Coldwell and Dugal (46), mentioned by Dr. Clark in the first paper of this session. These investigators (46) exposed rats for four days at 2°C and found an increase in the rate of oxidation of alcohol of 50%, an effect, however, which was especially marked in the first 30 minutes. Since other groups (12, 20, 39) have reported in mice and in rats at ordinary room temperature similar high initial rates of oxidation, at least part of the effect at 2°C may be ascribed to this high initial rate rather than to the effect of stress or some other explanation not yet advanced.

Two other factors, fasting and feeding, have also been investigated. Before going over the literature, I was under the impression that fasting caused decreased rates of oxidation and feeding increased rates. As a result of a more judicious look at the literature, I would say that the effects are variable as between investigators and variable even with the same investigator at different times. Hegsted, Vitale and Giorgio (17) were the first to report that fasting of rats for 120 hours decreased the rate of oxidation 35%. A somewhat longer period of time, 144 hours, produced no such differences in dogs (29), nor was this in-vivo difference in rats evident when rat liver suspensions from starved animals were compared to those from fed animals; but in this instance, sufficient NAD was added to secure a maximum rate of oxidation (34). When this was done, it was found that the maximum rate of oxidation of a liver suspension from a fasted rat was equivalent to the in-vivo rate from a fed rat. Perhaps starvation affects NAD availability more in the rat than in the dog. In weanling male rats, however, on a niacin-deficient diet, there appeared to be no difference between fed and fasted rats; moreover, pair-fed niacin-deficient rats metabolized alcohol 20% faster than controls—and for this no explanation was advanced (41). As between fasting and feeding, at least in animals, the results are quite variable (55, 59).

Human Experiment

There is only one reported experiment in humans on the effects of feeding and fasting. Abele (1) found the rate of disappearance of alcohol to be non-significantly less in fed than in fasted human subjects! This investigator, in his 922 subjects, found no correlation between the rate of oxidation and time of day, sleep, age, weight, or body type.

In the second slide (Table II), you will note that a large variety of agents have been tested in five animal species. I daresay that this listing may not exhaust the compounds which have been tested and which, for one or another reason, are not listed.

Turning for a moment from the slide, I have already noted that niacin deficiency increases alcohol oxidation by 20%, whereas 500 mg/kg of niacin, when given to a normal rat or to a nondeficient mouse had no effect on the rate (54). The effect was only in the deficient mice. The results on mice and rats hardly illuminate the sobering effects of DPN, which have been reported by O'Hollaren (45).

Pyridoxine is also found to have no effect on alcohol oxidation in dogs (43).

With 10% alcohol as sole drinking fluid to rats for 185 days, no effect on the in-vivo rate of oxidation was found (60); yet if the liver is removed and liver slices tested for their rate of alcohol oxidation, liver slices from treated rats oxidize alcohol 35% faster than liver slices from rats which were not subjected to alcohol ingestion for this period of time.

In addition to the compounds listed, pyruvate of course has been extensively investigated, especially in dogs (62). It is not surprising that the results have been highly variable. At best, there is probably a non-significant increase in the rate of oxidation as a result of pyruvate intake; Westerfeld (61) comments that such increases occur only when the dog is metabolizing alcohol initially at a low rate. Only under these conditions do dogs show an increased rate of oxidation when pyruvate is given.

Why dogs or humans should exhibit such variability, apart from whether pyruvate or other materials are given, seems an equally important matter for investigation.

Also, in addition to the compounds listed are the early experiments with glucose and combinations of glucose and insulin, going back some 25 years. In animals, with the exception of a report by Newman, Smith, and Newman (44), who found an increase in oxidation as a result of giving glucose and insulin (which they say was not related to the original rate of metabolism), a number of other investigators have found no effect of glucose or of the combination (7, 27, 33). Understandably, when such contradictions exist, the magnitude of any effects that have
Table II

<table>
<thead>
<tr>
<th>Compound</th>
<th>Effect of Various Agents on Rate of Oxidation in Animals</th>
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<tbody>
<tr>
<td>3-Amino-1,2,4-triazole</td>
<td>Dinitrophenol (c) (21)</td>
</tr>
<tr>
<td>Reserpine (d) (54)</td>
<td>Dinitrocresol (c) (21)</td>
</tr>
<tr>
<td>Phenobarbital (d) (57)</td>
<td>Hydroxylamine (b) (26)</td>
</tr>
<tr>
<td>Disulfiram (c,d) (21, 33)</td>
<td>Diphenhydramine (d) (25)</td>
</tr>
<tr>
<td>Cyanamide (c,d) (21)</td>
<td>Meprobamate (d) (25)</td>
</tr>
<tr>
<td>Triiodothyronine (c) (28,43,53)</td>
<td>Chlorpromazine (d) (25)</td>
</tr>
<tr>
<td>Amphenone (a) (11)</td>
<td>Diphenhydantoin (d) (25)</td>
</tr>
<tr>
<td>Chlorpromazine (a,c) (51,52)</td>
<td>Benactyzine (d) (25)</td>
</tr>
<tr>
<td>Chlor-Trimeton (d) (50)</td>
<td>Pilocarpine (d) (25)</td>
</tr>
<tr>
<td>Dormison (d) (50)</td>
<td>Tetraethylammonium Br (d) (25)</td>
</tr>
<tr>
<td>Probanthine (d) (50)</td>
<td>Priscoline (d) (25)</td>
</tr>
<tr>
<td>Oxygen (c) (23,30)</td>
<td>Phenacetin (d) (25)</td>
</tr>
<tr>
<td>Oxygen-CO² (c) (30)</td>
<td>Phenylbutazone (d) (25)</td>
</tr>
</tbody>
</table>

been observed are not particularly substantial.

Only fructose, among all the compounds investigated, increases the rate of oxidation in dogs consistently (7), but more of this in relation to the effects of fructose in man.

To return to the slide (Table II), neither the increases nor the decreases noted here are of any substantial moment; to my mind, they represent for the most part a shotgun approach and not necessarily well conducted in all instances. With the exception of the first four compounds in the increase column, the compounds all below hexobarbital were done by one investigator. He also finds the last two compounds in the third column, adrenalin and reserpine, to decrease the rate of oxidation. Surprisingly, in all of the compounds tested, he found none that had no effect.

In any event, by the usual standards and considering normal variability, one is forced to conclude that none of the compounds listed, at doses that are reasonably compatible with life, influence the oxidation of alcohol in other than a trivial fashion.

The next slide (Table III), which lists some of the compounds that have been tested in human beings, is concerned, not unexpectedly, with far fewer compounds. Neither pyridoxine nor ascorbic acid has an effect. Pyridoxine, given intravenously, is reported to decrease the subjective feeling of intoxication, an experiment that merits repetition. O’Hollaren (45) reported that DPN increased the rate of alcohol oxidation substantially in two non-alcoholics and two alcoholics, and in two alcoholics also eliminated delirium tremens. This experiment has been repeated, as you will note from the no-effect column, by a group of German workers (56) who used it in 36 subjects and could find no effect.

I believe that we may take this as a prototype of well-touted therapies—that others like this will arise again, in one or another guise, to be contradicted by one or another group.

Fructose Effect

Triiodothyronine, insulin, glucose, Promill-Ex, Bavarin 404, Contra, and Stop, all are essentially in the same category. Of all the compounds, only fructose has an effect that is both significant and substantial. Only two of the earliest investigators (18, 22) who worked with fructose were unable to find an effect of fructose on the rate of oxidation. In both of these cases, small numbers of subjects were used, and, more importantly, probably insufficient fructose. Later many different groups of investigators found from 30 to 70% increases in the rate of alcohol oxidation when fructose is given at the rate of 50 grams or more per hour. In most cases, the joint administration, or presence of both alcohol and fructose, is accompanied by nausea and severe gastric pain, and these symptoms are absent, of course, if either alcohol or fructose is given alone.

Pletscher, Bernstein, and Staub (47) suggest that these symptoms arise from the increase of acetaldehyde consequent upon the increase of oxidation of alcohol. This explanation appears unlikely because this symptomatology does not occur after disulfiram in which increased levels of acetaldehyde are certainly noted. Perhaps these symptoms arise from the increased liver metabolism and local increase in liver tem-
perature, but neither liver temperature nor acetaldehyde level has been measured in any of these fructose experiments.

The reason for this real increase of alcohol oxidation is ascribed by Lundquist and Wolthers (35) to the more rapid reoxidation of DPNH to DPN by way of the reduction of glyceraldehyde to glycerol, a scheme originally suggested by Holzer and Schneider (20) on the basis of in-vitro experiments. In a paper this year, however, Tygstrup, Winkler, and Lundquist (58) also suggest, with experimental support, that the reduction of fructose to sorbitol is important in increasing the ratio of DPN to DPNH and by this means increasing the rate of alcohol oxidation. These workers present values of sorbitol levels after fructose as evidence to support their case.

Although the rate of oxidation is indeed increased by fructose in large amounts, it would be better economy, especially for dieters, to reduce alcohol consumption rather than to increase caloric intake by a ratio of 8:1 via fructose. It hardly seems necessary to decrease the pleasurable effects of alcohol by a simultaneous bellyache. Seriously, fructose does not appear to offer any significant advantage in overcoming the effects of alcohol.

One last word—the only compound reported in a scientific journal to have exemplary influence in both increasing alcohol oxidation (by a resounding and non-defeatist 100%) and also inducing fabulous clinical improvement is triiodothyronine. Unfortunately, careful and controlled study indicated that the original report was wholly in error.

Except for fructose, therefore, both the popular nostrums and the scientifically acceptable treatments are seen to influence the oxidation of alcohol so much less than the agent-less variability (Table I) as to indicate the worthlessness of their use—and even for fructose the disadvantages are both great and real.

I would conclude that no agent known to us today plays an effective and practical role in any of the calculations that are used in the forensic aspects of alcohol ingestion and especially in what is called back calculation.

References


*CAAAL—Classified Abstract Archive of the Alcohol Literature, available at many depositories throughout the world.

Table III

Factors Influencing Rate of Oxidation (Man)

<table>
<thead>
<tr>
<th>NO EFFECT</th>
<th>INCREASE</th>
<th>DECREASE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heavy muscular work (21)</td>
<td>Increased body temp (40)</td>
<td>Decreased body temp (63)</td>
</tr>
<tr>
<td>Sleep (2)</td>
<td>DPN (45)</td>
<td></td>
</tr>
<tr>
<td>Unconsciousness (13)</td>
<td>Insulin-glucose (21)</td>
<td></td>
</tr>
<tr>
<td>Pyridoxine (1, 23, 43)</td>
<td>Fructose (3, 5, 35, 47, 56, 58)</td>
<td></td>
</tr>
<tr>
<td>Ascorbic acid (56)</td>
<td>Triiodothyronine (14)</td>
<td></td>
</tr>
<tr>
<td>Lactoflavin (56)</td>
<td></td>
<td></td>
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<tr>
<td>Cytochrome (56)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>DPN (56)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ATP (56)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Phosphoglyceric acid (56)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Carbutamide (9)</td>
<td></td>
<td></td>
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<tr>
<td>Pyruvate (56)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insulin (37)</td>
<td></td>
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<tr>
<td>Glucose (21, 35)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fructose (18, 22)</td>
<td></td>
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<tr>
<td>Galactose (4)</td>
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<tr>
<td>Promill-Ex (38)</td>
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<tr>
<td>Bavarian 404 (6)</td>
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<tr>
<td>Contra (16)</td>
<td></td>
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<tr>
<td>Stop (16)</td>
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<tr>
<td>Triiodothyronine (24)</td>
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<td></td>
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<tr>
<td>Adrenalin (15)</td>
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<tr>
<td>Prednisolone (31)</td>
<td></td>
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<tr>
<td>Cortisone (31)</td>
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</tr>
</tbody>
</table>


DISCUSSION

Dr. Clark: This is not a question, I simply want to back up Dr. Lester’s observations. We have tried similar experiments, but we don’t report negative results. I would say I have to agree with him about pyridoxine and triiodothyronine. In our hand both proved to be inactive in accelerating a significant amount of alcohol metabolism. Fructose did accelerate, as we reported. The glucocorticoids are the only things that I have seen that do a real good job. They are within this 25% that he speaks of, but from my data this morning, I showed that this was taking this variation in due consideration. We still get about a 20% increase in the rate of disappearance. I have, as I have mentioned to Dr. Lester this morning, some evidence indicating that fructose will take carbon-14 label from carbon 2-labeled ethanol and make fat of it in the liver. This is to be reported in the very near future. I have done quite a few studies in this area. It has been reported that alanine accelerates it, and alanine does the same sort of thing as fructose, as far as putting fat in the liver is concerned. Now I haven’t measured the rate of disappearance of alcohol from these rats, but it looks, as far as the fat is concerned, that it is doing the same thing as fructose does.

Dr. Lester: Just restricting ourselves to the effect of glucocorticoids, I would point out that the last two compounds actually tested in humans were cortisone and prednisolone, and, in their use with human beings, they had no effect at all upon the rate of oxidation of alcohol. Now I don’t question the fact that this was so in dogs, but I think that, practically speaking for forensic purposes, we can say that these materials have no effect in human beings.

Dr. Smith: I agree that, as far as forensic use is concerned, probably there has been very little, if any, significance to it, because it is not enough to be really important over a couple of hours or something like that. I don’t think that it would make any real difference.

Dr. Redetzki: I should like to make a point on this fructose acceleration of alcohol metabolism. I have been quite interested in these claims, and I also have done experiments in this line. We are not greatly impressed by the fructose acceleration. I want to offer a little different explanation for it. My assumption is that probably the rate of alcohol oxidation by the enzymes has shown us that a bottleneck is the disassociation of the used DPN from the enzymatic site and that this is really the slowest reaction. If we think of fructose as an accelerator, it is possible that alcohol acts as a transhydrogenase, that is, it accepts the glucocorticoids as a hydrogen, as a substrate, and it can very well produce glucocorticoids. It does not need a dissociation of the reduced DPN from the enzyme. This DPN can remain at the active site, but by reaction with another homologous aldehyde it can give its hydrogenase reaction. I can show this with the measurement of the reduction or oxidation of DPN and in the presence of these substrate per cents. This is certainly possible, and we have to assume that alcohol hydrogenase acts as transhydrogenase. Whether this is a true mechanism, I cannot tell, but at least in the experiments it is possible to show that this can take place.

Dr. Lester: Are you really showing that there is no change at all in the NADH ratio? For this transhydrogenation to take place without any breaking of DPN, you have got to show that there is no change in the ratio and that you still have an increased rate of oxidation of alcohol in the presence of this aldehyde or fructose to sorbito.

Dr. Redetzki: Not quite. I don’t think so. In such a setup, the concentration of DPN becomes very unimportant, since DPN now becomes a true enzyme in a true sense when it really is not. When you just oxidize alcohol, then it is a substrate, because it goes per mole. But if you have a recycling system in which this DPN is a true coenzyme in which its concentration is rather irregular. I can show that this takes place at the physiological pH 7.3 in contrast to the alcohol oxidation which is much better at an alkoline pH.

Dr. Lester: Except alcohol oxidation occurs at 7.3, too, not at 9.5. If you run the ADH analysis you are running at an accelerated pH, but this is hardly the pH at which the actual oxidation occurs in vivo. So I am not convinced that because you can find a certain thing going on in a rat liver suspension or in a rat liver slice, this is hardly the state of organization at which it is actually taking place in the liver organism.

Dr. Redetzki: This is done only in vivo. The enzyme is crystallized. This is a matter of the kinetic study, not a matter of in vivo. This is just a theory, as I indicated.

Mr. Bernstein: I noticed the slide showing the effect on animals. You had disulfiram which had no effect. I am just wondering about human subjects. I realize that this would be a kind of a hazard to a human subject, with the effect of alcohol in giving
him disulfiram. Would you care to say what you think disulfiram does to alcohol levels?

**Dr. Lester:** I don't think it has any influence at all. Obviously we are both aware of the dangers there, and you don't see levels much above .03%. This is 30 milligrams per 100 milliliters with the human that is treated with disulfiram and then given alcohol. But I can't ever say that I have done the calculations. I have data, and I have published stuff on it, but I have never really looked at the rate at which alcohol is disappearing in these human subjects. But I certainly think I would have been struck by large disparities between patients who were not getting disulfiram and ones who were. I am unaware of anyone who has actually done or reported on this. I don't think there is any difference.

**Question:** I was just wondering whether this would tend to increase acetaldehyde concentrations indicated in papers this morning, using pyridoxine, that is, in relation to ethanol.

**Dr. Smith:** I believe in the Hal Jackson group somebody brought up the fact that alcohol was metabolized or disappeared at the same rate under reserpine.

**Dr. Lester:** Probably they did, and probably everyone else has done so and didn't think it worth commenting on because nothing happened.