SOME ASPECTS OF THE HUMAN PHARMACOLOGY OF TETRAETHYLTHIURAMDISULPHIDE (ANTABUS) [1]–ALCOHOL REACTIONS [2]

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INTRODUCTION

In 1948, Hald, Jacobsen, Larsen, Asmussen, and Jørgensen working in Denmark published a series of five papers on the effect of tetraethylthiuramdisulphide alone and in combination with ethanol on man and animals (1–5). They reviewed and added to Hanzlik's and Irvine's (6) previous studies on the pharmacology and toxicology of Antabus. In addition these authors described the syndrome occurring during an alcohol-Antabus reaction, emphasizing in particular the cardiovascular and respiratory changes observed. These workers reported marked peripheral vasodilatation (evidenced by increase in skin temperature and flushing), a slightly increased cardiac output, an increase in oxygen consumption, increased ventilation, decreased alveolar carbon dioxide, increased respiratory dead space and increased pulse rate.

These authors next offered considerable evidence to support the theory that the reaction was due to the accumulation of acetaldehyde (assumed to be the first breakdown product of ethanol) in the body. They also postulated that the accumulation was due to increased production of acetaldehyde. Later Hald and Larsen (7) refuted the idea of increased production of acetaldehyde and stated that it was a decrease in the rate of metabolism of this agent that caused its accumulation in Antabus treated subjects.

Later Kjeldgaard (8) showed that Antabus inhibited aldehyde oxidase in concentrations as small as 0.1 microgram per ml. (*in vitro* purified enzyme experiment) thereby preventing the oxidation of aldehydes to acids. This inhibition offered a possible explanation for aldehyde accumulation in the blood of intact animals.

Much of this work was confirmed by Newman (9) in his experiments on dogs. He found that Antabus decreased the ability of the animals to oxidize acetaldehyde and found, as did the Danish workers, that intravenous infusion of acetaldehyde produced a syndrome similar to that occurring with Antabus-alcohol reactions.

Since the use of Antabus as a therapeutic agent for alcoholism has received considerable attention in recent years, this work was undertaken for the purpose of further studying the human pharmacology of Antabus-alcohol reactions.

PROCEDURE

A total of 51 patients was studied of which 41 were out-patients and 10 were hospitalized. These patients were the first 51 in a group of over 100 patients being treated for alcoholism at The Langley Porter Clinic, San Francisco (10). No patient who had any potentially serious organic defect was included in The Langley Porter Clinic study.

Before Antabus therapy was initiated, the status of each patient was evaluated by means of a physical and neurological examination, liver function test, chest x-ray, blood count, urinalysis, and electrocardiogram. In addition, psychiatric and psychologic studies were carried out. All laboratory studies were found to be within normal limits.

Out-patients were started on Antabus five days before their initial test drink and received 1 gram on the first and second days, 0.75 gram on the third and fourth days, and 0.5 gram on the fifth day (at least two hours before the initial test drink of alcohol was given). One-half gram was given as a daily maintenance dose thereafter except in a few cases when it was found necessary to increase or decrease the dosage. The dosage of alcohol used was 0.5 ml. per kg. of a 90 proof beverage. This dosage represents, in an average-sized man, the amount found in one jigger of bar whiskey.

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Each patient had one member of the examining staff remain in attendance with him for at least an hour after the test drink was given to record the data listed below. In addition, one of the authors (E. M.) observed each patient during the entire test period to see that the signs and symptoms in the various patients were rated on an equal basis. An average of four patients was tested a week.

Pulse, respiration, and blood pressure were determined before the test drink was given and every five minutes for a period of an hour after. Blood samples for alcohol and acetaldehyde determinations were drawn in heparinized syringes before and at 10, 20, 30, 45, and 60 minutes after the drink. In subjects showing severe reactions blood samples were also drawn at 80 minutes. Airtight caps were placed on the ends of the syringes which were then immersed in an ice bath. As soon as the test period was over the samples were taken to the laboratory and the alcohol and acetaldehyde determinations made.

Blood alcohols were determined by a modification of the method described by Winnick (11) and blood acetaldehyde by a method developed in this laboratory (12).

An evaluation of the following signs and symptoms was made:

1. Blushing
2. Feeling of heat
3. Itching
4. Conjunctival injection
5. Throbbing (head)
6. Headache
7. Dyspnea
8. Palpitation
9. Dizziness
10. Nausea
11. Vomiting
12. Sweating
13. Cold shivers
14. Abnormal odor (breath)
15. General indisposition
16. Sleepiness
17. Fear
18. Convulsions

These signs and symptoms were listed on a check sheet followed by three spaces. In the first space was noted the time of onset, in the second the time of greatest intensity, and in the third space the observers' rating of the intensity; a mild reaction was rated as 1, a moderate reaction as 2, and a severe reaction as 3.

One week later most patients returned and received the same treatment with the exception that the dose of the alcoholic beverage was one-half of the previous dose.

The hospitalized patients used as a control group for this study were given the same dose of alcohol and the above data recorded prior to as well as after Antabus therapy.

RESULTS

Alcohol determinations

The normal mean alcohol blood level (before the ingestion of alcohol) of the 10 hospitalized patients before treatment with Antabus was 4.9 ± 3.3 mg. per cent.[4] The normal mean level for the 51 Antabus treated patients was 6.0 ± 3.0 mg. per cent. These data subjected to the student "t" test were found not to be significantly different ($p = 0.45$). Therefore we conclude that Antabus does not affect the normal alcohol "blank" value. Neither does Antabus affect the rate of absorption or rate of metabolism of alcohol and this is indicated by the blood levels determined at 10, 20, 30, 45, and 60 minute intervals after small doses of alcohol (see Table I and Figure 1). Curve A, Figure 1 is the "mean curve" for the untreated patients. Curve B is the "mean curve" for the treated patients receiving 0.5 ml. of alcohol per kg. body weight. Curve C is the curve for the treated pa-

[4] This figure includes all volatile oxidizable substances as determined under our experimental conditions and is not intended to represent only ethanol.

TABLE I

Mean increase in alcohol levels for treated and untreated patients after test drink

Time in Minutes	Untreated Patients 0.5 ml./kg.			Treated Patients 0.5 ml./kg.			Treated Patients 0.25 ml./kg.		
	Mean Increase	Stnd. Dev.	Range	Mean Increase	Stnd. Dev.	Range	Mean Increase	Stnd. Dev.	Range
10	7.6	±6.4	2.0-25.0	12.8	±9.9	2.0-40.5	6.7	±4.4	0.0-13.5
20	15.5	±8.6	1.0-23.0	19.2	±8.4	5.5-34.5	7.8	±6.1	0.5-19.0
30	20.7	±7.6	4.0-32.0	17.8	±6.0	10.5-30.5	6.2	±3.3	1.5-14.5
45	15.9	±6.7	2.5-25.5	15.6	±5.8	5.2-28.5	5.6	±3.3	1.0-11.5
60	11.8	±6.9	0.8-23.5	14.2	±5.7	2.0-27.0	3.4	±3.6	0.0-11.0

tients receiving 0.25 ml. per kg. The data in the tables and plotted on the curve represent the increase in alcohol level above normal rather than the absolute level. Note the close proximity of the two curves for the treated and untreated at the high dose. Testing of the mean values at each time interval at which blood was drawn showed no significant difference.

Acetaldehyde levels

The mean normal acetaldehyde level for the 10 untreated patients was 92 ± 38 micrograms per cent. For the 51 treated patients the value was 281 ± 187 micrograms per cent. These two means are significantly different having a p value of 0.006. This difference indicates that Antabus has a definite effect on the normal resting acetaldehyde level in man. This is in contrast to the report of Jacobsen (13) who found that treatment with Antabus alone caused no increase in the resting acetaldehyde value in rabbits.

The increase in blood acetaldehyde following alcohol ingestion is much more marked when the patient is treated with Antabus than when untreated (Table II and Figure 2). This observation confirms the finding that Antabus causes an accumulation of acetaldehyde in the blood. Figure 2, curve A shows the increase in aldehyde over normal plotted against time after 0.5 ml. per kg. of alcoholic beverage in untreated patients. Curve B is the data for the treated patients who received the same dosage. Curve C is the increase in acetaldehyde for Antabus treated patients who received 0.25 ml. per kg. Note that in the treated patients receiving the low

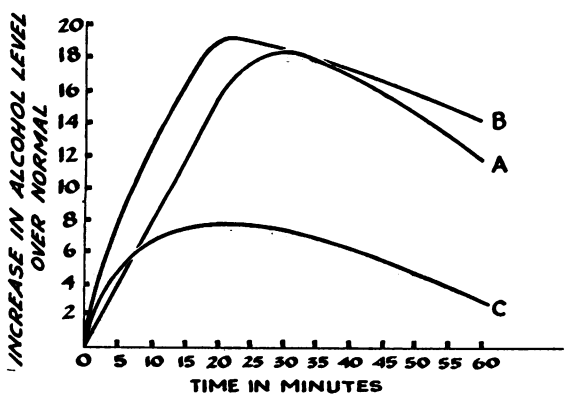

FIG. 1

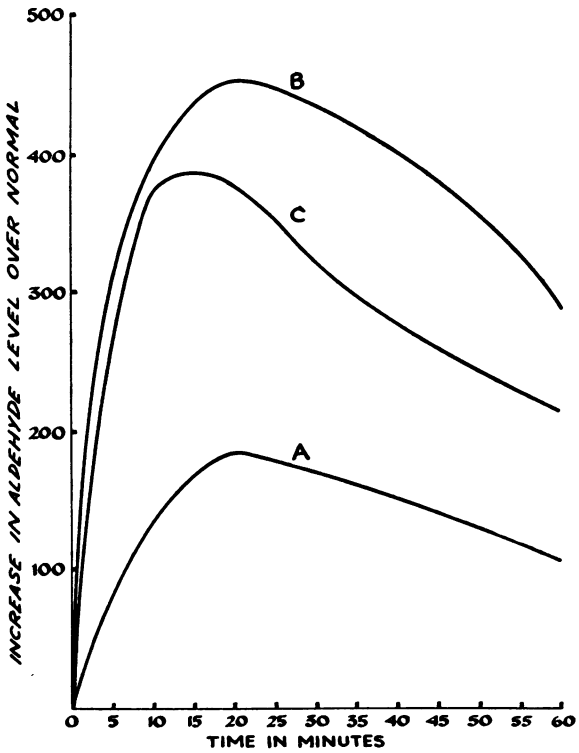

FIG. 2

dose, the increase in acetaldehyde was much greater than one-half that in the patients receiving twice the dose.

While the peak of the mean values represented an increase of 450 micrograms per cent, it is of interest to note that some patients obtained much greater increases. Six patients had an increase in blood acetaldehyde of over 1,000 micrograms per cent; 15 of the 51 patients had an increase of over 600 micrograms per cent at some time during the first hour after the test drink.

Blood pressure

The most striking objective effect of an alcohol-Antabus reaction is the accompanying fall in blood pressure. The maximum fall occurs between 30 and 40 minutes after the ingestion of the alcohol though there is considerable variation. At the high dose the mean blood pressure of 31 patients fell from 132/84 to 107/55 in 40 minutes. This is a highly significant change. "T" testing gives a probability of less than 0.001 for both diastolic and systolic pressures. In some cases the fall in pressure was dramatic. Of a total of 156 blood

TABLE II

Mean increase in acetaldehyde levels of treated and untreated patients after test drink

Time in Minutes	Untreated Patients 0.5 ml./kg.			Treated Patients 0.5 ml./kg.			Treated Patients 0.25 ml./kg.		
	Mean Increase	Stnd. Dev.	Range	Mean Increase	Stnd. Dev.	Range	Mean Increase	Stnd. Dev.	Range
10	136	±66	30-237	399	±318	0-1112	373	±330	0-1325
20	185	±115	25-470	453	±292	22-1338	377	±369	0-1680
30	167	±67	105-326	421	±342	0-1202	319	±220	0-840
45	175	±118	98-373	399	±278	0-1185	262	±171	0-665
60	156	±167	0-320	275	±233	0-937	213	±194	0-660

pressure measurements made on 31 patients receiving the high dosage of alcohol, 24 systolic pressures were below 100 and 11 below 80 some time during the test. Of the same group there were 46 diastolic blood pressure measurements below 60 and 15 below 40. Six patients had blood pressures below 80/40 at some time during the first hour after the test drink.

For the low dose the drop was not significant ($p = 0.45$), the mean maximum drop being from 130/86 to 124/74 in 40 minutes. In addition, of 135 blood pressure determinations made on patients receiving the low dosage only one systolic reading dropped below 100 and five diastolic readings below 60 (Table III).

No significant change was noted in the blood pressure of patients taking alcohol alone and untreated with Antabus.

There was no significant change in pulse pressure at either the high or low dose when the patients were considered as a group. However, eight patients at the high dose, and three at the low dose had a large increase in pulse pressure in the first 10 minutes after the test drink. By 20 minutes

TABLE III

Mean blood pressures for both groups of treated patients at various time intervals

Time In Minutes	Treated Patients 0.5 ml./kg.			Treated Patients 0.25 ml./kg.		
	Mean B. P.	Stnd. Dev.	Range	Mean B. P.	Stnd. Dev.	Range
Before	132/84	±10/±8	166/110-114/70	130/86	±14/±9	175/108-110/70
10	129/74	±10/±12	154/92-114/50	128/82	±16/±12	165/106-106/62
20	117/64	±19/±16	154/88-60/30	126/76	±20/±17	184/108-102/64
30	112/61	±21/±17	150/96-66/22	123/75	±21/±16	180/102-90/50
45	114/65	±17/±13	146/94-68/44	120/76	±11/±11	140/94-96/56
60	108/65	±19/±16	140/94-72/34	125/82	±15/±10	162/108-102/70

TABLE IV

Mean pulse rates for treated patients at both dose levels

Time in Minutes		Treated Patients 0.5 ml./kg.		Treated Patients 0.25 ml./kg.		
	Mean Rate	Stnd. Dev.	Range	Mean Rate	Stnd. Dev.	Range
Before	80	±13	52-112	80	±13	52-112
10	99	±19	54-128	102	±16	82-142
20	106	±17	82-150	104	±13	82-136
30	100	±16	76-142	100	±15	76-130
45	94	±16	66-118	97	±15	80-126
60	94	±13	64-118	89	±13	72-120

the pulse pressures were again in the normal range. All the patients whose pressures fell below 80/40 had a significant narrowing of pulse pressure when compared with the mean normal pressure. This, however, would be expected for a shock-like state.

Pulse rate

An increase in pulse rate was noted in every patient undergoing a clinically detectable alcohol-Antabus reaction. The pulse rate reached a maximum at about 20 minutes and was slow in returning to normal. A rather interesting finding was that in five of the six patients whose blood pressures fell below 80/40, pulse rates were below 95 in spite of the fact that their rates had been higher before the fall in blood pressure was marked. Also unusual was the fact that there was no difference in the mean increase in pulse rate in those patients receiving the high as contrasted to those receiving the low dosage in spite of the fact that the

TABLE V

Mean respiratory rates for both groups of treated patients at various time intervals

Time In Minutes	Treated Patients 0.5 ml./kg.			Treated Patients 0.25 ml./kg.		
	Mean Rate	Stnd. Dev.	Range	Mean Rate	Stnd. Dev.	Range
Before	18	±2	12-24	18	±2	12-24
10	21	±4	10-28	22	±5	16-32
20	22	±4	16-32	23	±4	16-32
30	22	±4	16-36	22	±4	16-34
45	20	±3	12-28	21	±5	16-34
60	20	±3	16-26	19	±3	16-30

overall reactions were more severe in the patients receiving the high dosage. Pulse rates of 120 or more occurred in nine out of 33 patients given the high dose, and five out of 22 patients given the low dose. Five patients (three given the high and two given the low dosage) had a pulse rate in excess of 140 per minute. Table IV gives data on mean pulse rates at various time intervals.

Respiratory rate

In this study the most striking respiratory change was the increase in depth of respiration

TABLE VI

Table of data concerning signs and symptoms

High Dose in 44 Patients

SIGN OR SYMPTOM	MEAN ONSET	STND. DEV.	MEAN PEAK	STND. DEV.	MEAN * RATING	NUMBER FOUND IN	PER-CENT
Conjunctival Injection	10	±5	36	±13	2.2	39	89
Flushing	7	±3	25	±10	2.1	42	95
Feeling of Heat	5	±2	23	±8	1.9	42	95
Throbbing	16	±8	29	±9	2.3	16	36
Dyspnea	12	±7	25	±9	1.9	25	57
Palpitation	13	±6	28	±8	2.1	24	55
Dizziness	18	±10	32	±12	1.8	15	34
Nausea	36	±22	48	±32	2.0	11	25
Vomiting	—	—	—	—	2.2	5	11
Cold Shiver	—	—	—	—	2.1	8	18
Sweating	—	—	—	—	1.8	6	14
Abnormal Odor (Breath)	12	±7	43	±16	2.1	30	68
General Indisposition	31	±15	45	±22	2.2	17	39
Sleepiness	33	±18	56	±24	1.8	25	57

Low Dose in 29 Patients

SIGN OR SYMPTOM	MEAN ONSET	STND. DEV.	MEAN PEAK	STND. DEV.	MEAN * RATING	NUMBER FOUND IN	PER-CENT
Conjunctival Injection	10	±4	31	±12	1.6	26	90
Flushing	7	±6	23	±10	1.8	27	93
Feeling of Heat	6	±3	23	±12	1.6	24	83
Throbbing	11	±4	25	±8	1.5	7	24
Dyspnea	11	±5	22	±6	1.6	14	48
Palpitation	14	±7	25	±9	1.5	16	55
Dizziness	22	±18	34	±19	1.4	8	28
Nausea	—	—	—	—	1.5	4	14
Vomiting	—	—	—	—	—	0	—
Cold Shiver	—	—	—	—	2.0	1	—
Sweating	—	—	—	—	1.7	4	14
Abnormal Odor (Breath)	12	±6	26	±8	1.6	14	48
General Indisposition	19	±11	38	±12	1.7	7	24
Sleepiness	31	±17	41	±18	1.3	16	55

* The mean rating is the mean of the intensity rating with 1 being considered mild, 2 moderate, and 3 severe. These are without a doubt highly subjective data but nonetheless indicate how the investigators felt about the relative influence of the two doses on any particular sign or symptom.

rather than rate. Nonetheless the mean change in the rate from 18 to 23 a minute for the "low dose" group and 18 to 22 for the "high dose" group was highly significant. Upon "t" testing the value for p was less than 0.001. In many cases the patient's subjective complaint of dyspnea was all out of proportion to the change in depth and rate indicating that the phenomenon was more than simple respiratory stimulation.

There were only three patients in the entire group at both dosage levels who had a maximum increase in respiration of more than 12 a minute and only one of those doubled his rate (16 to 34 a minute). Table V illustrates the mean results of respiratory changes in the patients studied.

Signs and symptoms

For the sake of brevity these data will be presented in tabular form with only a few comments here.

The conjunctival injection, blushing, feeling of heat, throbbing, and palpitation (Table VI, all signs and symptoms of cardiovascular origin) have a mean onset between five and 16 minutes and a mean peak between 23 and 36 minutes. If conjunctival injection is excluded, then the mean peak is between 23 and 29 minutes and this is irrespective of dose. This correlates with the onset and peak of pulse rate changes.

Patients frequently complained of dyspnea, tightness of the throat, and of increased expiratory effort. Despite these complaints, the change in respiratory rate was not striking.

Nausea, vomiting, cold shivers, and sweating were so infrequent and the time of onset and peak so variable that mean values were not computed. Further, these four symptoms so frequently have a psychosomatic origin that it is questionable whether their origin is entirely "organic." Vomiting did not occur at all in patients receiving the low dosage.

General indisposition was rated as mild when the patient was unable to walk around, moderate when the reclining position was necessary, and severe when the patient was in a near shock-like state.

Sleepiness became a problem for out-patients. Some of these patients could not stay awake even with effort. Many had to be kept in the hospital from one to four hours after the test period was over before they could be allowed to drive their cars or ride on public transportation.

Several symptoms that were not listed on the check sheet occurred frequently. Six of the patients had tremors that resembled those seen in hypocalcemic tetany. Four patients complained of a pain and tightness in the chest similar to angina pectoris. This symptom was considered serious enough in one patient to warrant cessation of Antabus therapy. Incidentally, this patient had an abnormal EKG when taken during the alcohol-Antabus reaction.

Several patients complained of a metallic taste in the mouth similar to the taste of tarnished silver. This raised the possibility of salivary excretion of Antabus or an Antabus breakdown product. Numerous other complaints occurred but not often enough to accredit them to the alcohol-Antabus reaction.

Itching, expressions of fear, and convulsions did not occur in this group of patients though they were looked for. However, two patients treated with Antabus in a later series but not included in this group had convulsions during a reaction (see Table VI).

DISCUSSION

Antabus apparently has no effect on the rate of disappearance of alcohol. Figure 1 shows the normal and control curves to be very similar. This lack of difference is statistically significant even though only 10 controls are compared with 51 experimental subjects.

An increased alcohol level is necessary for the reaction to take place. In three of the patients studied, no increase in alcohol level was found after the test drink. In none of the three was there any clinical reaction whatever. It is difficult to explain why there was no increase in the blood alcohol level in these patients since they were all presumably in the fasting state. Subsequent tests a week later with double the dose of alcohol in each of these patients produced a definite reaction. The blood alcohol increase was then appreciable.

For the most part, the higher the alcohol level the more severe the reaction (up to 49 mg. per cent, our highest level); however, there were frequent notable exceptions. For example, one patient who on the first test had a 34 mg. per cent increase in blood alcohol showed only a mild reac-

tion. The following week this patient was retested at the lower dose. He had an 11 mg. per cent increase in blood level and a severe reaction. A possible explanation for this discrepancy may be that there was an insufficient quantity of Antabus in the tissues at the time of the first test.

Since the rate of alcohol disappearance is not affected, it is probable that the patient's reaction is due to an accumulation of acetaldehyde in the tissues as a result of inhibition of the acetaldehyde oxidation. Comparison of the three curves in Figure 2 illustrates the effect Antabus has on blood acetaldehyde levels. Note that the difference between the acetaldehyde curves at the low and high alcohol dose is not great and further that the mean values of increase in acetaldehyde level for the low dose is considerably more than half that for the high dose at all time intervals. This suggests that at some alcohol blood levels, in spite of Antabus, the acetaldehyde level will have a maximum increase and that higher alcohol doses will have no further effect. This suggestion is compatible with Kjeldgaard's (8) conclusion that the inhibition of aldehyde oxidase by Antabus is competitive.

The increase in the normal blood acetaldehyde (before alcohol ingestion) in Antabus treated as compared to untreated persons was an unexpected finding in light of Jacobsen's (13) statement that there was no increase in the blood acetaldehyde level in treated rabbits. From this it may be assumed that this response is a species difference.

The observations that the alcohol levels and most of the subjective and objective signs and symptoms reach a peak at the same time as the acetaldehyde levels lend further support to the theory that the acetaldehyde is the toxic agent. In this study only two patients became quite ill early (within 20 minutes) without an appreciable rise in acetaldehyde level. The reaction picture in these patients was somewhat different from that usually observed. Headache, nausea and malaise were outstanding symptoms and occurred early. The cardiovascular complaints occurred after 45 minutes and were accompanied by a delayed rise in acetaldehyde levels. The early complaints in these patients may be evidence of a toxic factor other than acetaldehyde.

Further evidence of the presence of other toxic factors is suggested by the following. Some 15 patients phoned several hours after the completion of the test and complained that they had the worst hangover of their lives. All of these patients' blood alcohol and acetaldehyde levels had returned to normal before they were permitted to leave. All vigorously denied subsequent drinking.

One of the most dangerous effects of the reaction was the fall in blood pressure. Six patients had blood pressure drops to shock levels. One patient not included in this report had an unobtainable pressure for 15 minutes. In addition, five of these six patients had a low pulse rate accompanying the low blood pressure, indicating myocardial dysfunction. This supports Handovsky's (14) finding that acetaldehyde has a direct toxic myocardial action. Such patients responded well to oxygen, rest and intravenous ephedrine. One patient in the series who drank in spite of warning suffered a myocardial infarction (15). This might have been related to the fall in blood pressure and the direct myocardial toxicity of acetaldehyde.

The disproportionately large number of complaints of dyspnea as compared to the small change in rate and amplitude of breathing, suggests that acetaldehyde in addition to the respiratory stimulating effect, adversely affects the respiratory apparatus. It has been the experience of two of the authors (Hine and Burbridge) that acetaldehyde given in large doses to rabbits and rats intravenously will cause an acutely inflamed lung, with small punctate hemorrhages. This would support the idea of direct toxicity of acetaldehyde to the respiratory apparatus.

Cardiac arrhythmias, electrocardiographic evidence of myocardial ischemia and even myocardial infarction may occur during the Antabus-alcohol reaction (15).

Antabus itself is apparently a relatively safe drug, and in this study there has been no indication of damage to any organ due to its chronic ingestion in the dosages used. However, the clinical observations made during this study indicate that the use of Antabus in treating or testing the problem drinker is accompanied by definite risks. The reaction which occurs following the ingestion of alcohol by a patient who is on Antabus therapy is severe and may occasionally lead to severe injury and even death. We strongly recommend the careful observation of the cardiovascular changes which accompany the reaction during a test drink. The physician should be prepared to ad-

minister emergency supportive therapy such as administration of oxygen and placement in the shock position if required. The patient who is chosen for Antabus therapy should be carefully warned concerning the severity of the reaction which may occur if he drinks even small quantities of alcohol.

SUMMARY AND CONCLUSIONS

1. A study was made of 51 problem drinkers following a test drink of alcohol prior to and after Antabus therapy with attention directed to the relationship among the following: blood levels of alcohol and acetaldehyde, clinical symptoms, changes in pulse, respiration and blood pressure.

2. Antabus was not found to alter normal blood alcohol levels. Neither did the compound appear to affect either the rate of absorption or metabolism of the ethanol itself.

3. Antabus significantly increased the normal resting acetaldehyde level in man.

4. There was a very significant increase in blood acetaldehyde in the Antabus treated subject as compared to the untreated patient after the ingestion of alcohol.

5. Evidence is presented to support the view that acetaldehyde is the toxic agent responsible for the most serious consequences of the alcohol-Antabus reaction.

6. Serious decreases in arterial pressure as a result of the alcohol-Antabus reaction are reported.

7. Pulse rate and respiratory rate increased significantly during the alcohol-Antabus reaction.

8. A detailed picture of the clinical symptomatology is presented.

9. In light of the often dangerous cardiovascular effects of Antabus, recommendations for the careful use of the drug were made.

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