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# INTRODUCTION

The problem of chronic alcoholism has been long studied in regard to cause, effect and treatment. Recently, reports in professional and lay literature have called attention to the drug Antabuse in the treatment of the alcohol-intolerant individual.

The etiological factors of chronic alcoholism are most complex but personality structure appears to play a key role. No claims can be made that Antabuse is a cure for alcoholism. When given regularly in sufficient dosage, it will produce an unpleasant reaction when the individual drinks even a small amount of alcohol. In this manner the individual remains sober while he receives the psychotherapy necessary to produce an adjustment which will prevent his return to chronic alcoholism.

## DISCOVERY

The use of tetraethylthiuramdisulfide in connection with alcoholism was discovered by accident in 1948. Erik Jacobson and Jens Hald of Copenhagen were searching for a new antihelmenthic drug and in this connection ingested a quantity of tetraethylthiuramdisulfide with no noticeable effect until both became violently ill after consumption of alcohol a few days later. More than coincidence was suspected and animal experimentation with the drug confirmed its action (6). After further investigation, which showed that alcohol produced symptoms in the Antabuse-treated individual which differed markedly from the expected intoxication, the drug was offered as a possible adjunct to the treatment of alcoholism (9)(24).

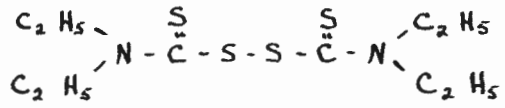
While the early work was carried out and published abroad, chiefly in Denmark, Sweden, Great Britain and Canada, the drug is now being investigated in more than 100 institutions in the United States. Antabuse is still classified as a "new drug" and is not available for prescription use (14).

## CHEMISTRY

Formula and characteristics Antabuse is chemically bis(diethylthiocarbamyl)disulfide, also known as tetraethylthiuramdisulfide. It is yellow crystalline in form and has a melting point of 70° C. The molecular weight is 296.52.

The crystals have a bitter taste and violet-like odor, are water insoluble, slightly soluble in alcohol and ether and soluble in chloroform (17)(21).

The formula is:



The chemical properties are little known except that with cupric salts intense yellow colors are produced (17).

Toxicity Microorganisms are comparatively sensitive to Antabuse. An emulsion in water containing 10% alcohol and giving a concentration of $1:8 \times 10^6$ - $1:16 \times 10^6$ is bacteriostatic for staph. aureus. 0.25 gm. daily for four to six days will free rabbits completely from parasite eggs. The drug has been used as a scabieticide. The high toxicity in lower animals is presumably due to the capacity of Antabuse to form complex compounds with copper. Copper enzymes essential to the metabolism of these animals are thereby blocked.

The compound possesses a very low grade of toxicity for mammals. In puppies and rabbits the fatal oral dose was found to be about 8 gm. per kg. body weight. The fatal symptoms are: gradual depression with ataxia, fall of body temperature, and slowed respiration and pulse. Pre-terminal asphyxial convulsions have been observed. No marked symptoms were seen until the day following the fatal dose.

In man, single doses of up to 6 gm. are tolerated

without symptoms. Smaller doses, 0.25 - 0.75 gm. per day, taken daily, are tolerated excellently. In a series of eighty three patients no harmful effects were observed on the liver, heart, kidneys, or blood forming organs (17)(29). No subjective or objective effects were noted on most individuals (17)(24). However, in some cases there was noted: insomnia, somnolence, diarrhea, constipation, polyphagia, anorexia, palpitation, headache, dizziness, urinary frequency, enuresis, nocturia, and a bad taste in the mouth. In most cases these complaints disappeared within six weeks (5)(13). In a few cases urticaria has been observed (13)(14)(24)(30). Pyribenzamine, 50 mg. three times a day for three to four days while continuing the Antabuse is suggested for these individuals (13).

It is agreed by most authors that Antabuse alone is relatively nontoxic to humans (5)(6)(13)(16)(17).

Absorption and Elimination Antabuse is slowly absorbed from the gastrointestinal tract. The characteristic effect of alcohol is generally first seen about three hours after the oral intake of Antabuse and it seems that six to twelve hours are required for the full effect to occur (17).

About 20% of the amount given orally is recoverable (unabsorbed?) in the unaltered state from the feces during the three days following the intake (6)(16)(17).

The slow elimination of Antabuse is indicated by the

duration of effect after a single dose. Even when alcohol is administered several days after an isolated dose, the characteristic action is seen (17). Fecal excretion can be traced seven to eight days (24). There is no urinary excretion (16)(17).

Action It is known that acetaldehyde is formed in normal human subjects and in animals after ingestion of alcohol (3)(32). In human subjects treated with Antabuse, ingestion of alcohol is followed by formation of acetaldehyde in the blood to a far greater extent than is seen when human subjects not so treated consume the same amount of alcohol (3)(15)(18)(22).

In experiments with isolated organs, it has been shown that the formation of acetaldehyde from alcohol occurs in the liver cells of animals treated with Antabuse (19)(23).

In human subjects, slow intravenous infusion of acetaldehyde results in a marked increase in pulse rate and ventilation with a decrease in alveolar carbon dioxide. Acetaldehyde affects respiration through the chemo-receptors. Oxygen inhalation during infusion of acetaldehyde produces a marked depression of the respiratory effect (2)(3).

Normal blood acetaldehyde concentration has been found to be 0.020 - 0.040 mg.% (32). An increase to 0.2 mg.% will produce marked symptoms. Alcohol concentration of 50 mg.% in blood is accompanied by about 0.1 mg.% increase in acetaldehyde. When alcohol is taken by individuals previously treated with

Antabuse, the formation of acetaldehyde is considerably increased (0.3 - 0.5 mg.%) (20). No difference in the very rapid combustion of acetaldehyde in normal and in Antabuse-treated animals can be seen (19)(20)(28). The increased concentration of acetaldehyde after Antabuse treatment and intake of alcohol must consequently be due to an increased formation of acetaldehyde. The formation of acetaldehyde is limited by the combustion rate of alcohol in the organism, and the rate of alcohol elimination is hardly altered by Antabuse treatment (3)(17).

## EFFECT OF ALCOHOL IN COMBINATION WITH ANTABUSE

When a human subject is sensitized to alcohol with Antabuse, the symptoms after ingestion of alcohol can be described as follows.

Five to fifteen minutes, on the average seven to eight minutes, after the intake of even moderate amounts of alcohol the individual experiences a feeling of heat in the face. A few minutes later facial flushing is evident and reaches a peak at about one half hour. The flushing is most marked on the face but is seen on the upper arms and chest. Vasodilatation is also found in the vessels of the sclerae and the individual shows a "bull-eyed" appearance. A slight edema in the lower lids is also typical(17).

With the flushing, palpitations start and the pulse is strong in the head and neck. A pulsating headache is sometimes experienced. Pulse rate is accelerated to 120-140 while the blood

pressure remains unchanged or drops slightly (5 - 10 mm. Hg).

Most cases complain of a constricted feeling in the neck. Some mention subjective dyspnea but more feel a mild throat irritation resulting in mild coughing (17).

With greater alcohol intake, 40 to 50 gm. or more, and particularly when it is taken with food, nausea is frequent. This follows the cardiovascular symptoms by one half to one hour. With the onset of nausea, the facial flushing passes and may be replaced by pallor. This stage is accompanied by a marked fall in blood pressure, i.e., 65/0 mm. Hg. A fully developed collapse is never seen (17). The nausea leads to vomiting which may be very sudden and surprising to the patient. In addition, a very disagreeable general uneasiness is felt, especially following the higher alcohol dosages.

In a group of 55 patients (13) the subjective complaints were expressed in the following sequence:

1. Warmth
2. Dizziness
3. Blurred Vision
4. Pressure on top of head
5. Pounding headache - particularly in temples of behind the ears
6. Palpitations
7. Difficulty in breathing
8. Tightness in the throat
9. Chest Pain
10. Numbness of hands and feet
11. Nausea
12. Sleepiness

A similarly treated group at Fitzsimons General Hospital

made comparable complaints in much the same order.

The duration and intensity of symptoms depend on the alcohol dosage and individual's temperament. The symptoms follow ingestion of any alcoholic beverage. Symptoms are always seen after the equivalent of 10 gm. of absolute alcohol, while 5 gm. will produce mild symptoms in some individuals. If the alcohol dosage is sufficiently high, the increased pulse rate, respiratory symptoms and general uneasiness are always found but the nausea and vomiting are not always seen. The duration of symptoms varies from one half to one hour in mild cases to several hours in more marked reactions. As the symptoms pass the patient feels fatigued, but after sleep he feels completely well again (17).

In numerous experiments no signs of habituation have been seen. On the contrary, it seems as if the tolerance for alcohol is lowered (17).

The Gelbman and Epstein group (13) and the group treated at Fitzsimons General Hospital showed the following signs, usually in the following order of appearance:

1. Flushing of the head and neck, spreading downwards, later, sometimes, covering most of the body.
2. Vasodilatation of the capillaries of the conjunctivae, later with some conjunctival edema.
3. Sweating.
4. Hyperpnea.
5. Dyspnea.
6. Tachycardia.
7. Decrease in blood pressure.

8. Odor of acetaldehyde on the breath.
9. Somnolence.
10. Sleep.
11. Vomiting - in a majority of patients.

Since the facial flushing is the most manifest symptom of Antabuse-induced hypersensitivity to alcohol, skin temperature measurements may be used as an objective measure of the effect. An increase of 4 to 5 degrees C. was measured within the first 30 minutes with a gradual return to normal (17).

These characteristic symptoms are also seen when alcohol is administered intravenously. The vasodilatation in the face is fully developed when the blood alcohol concentration is as low as 10 - 20 mg.% (17). This same concentration in an untreated individual produces no symptoms at all.

Previous intake of Antabuse does not interfere with the rate of alcohol elimination (17)(26).

## INDICATIONS

Antabuse induced sensitization to alcohol is indicated only for alcoholics who genuinely desire to take the treatment and for whom it is not contraindicated.

## CONTRAINDICATIONS

Until a more complete understanding of the drug and its action is obtained, great care should be exercised in Antabuse treatment of a patient having any of the following conditions (14):

1. Myocardial failure of coronary artery disease. Since the pulse rate increases and the cardiac output may be considerably accelerated, the possible consequences must be weighed before therapy is begun.
2. Hepatic cirrhosis. It is suggested that Antabuse not be given to a patient having less than 85% of normal liver function.
3. Acute or chronic nephritis. Pre-existing albuminuria has been found to increase following initiation of Antabuse therapy.
4. Epilepsy. It is reported that in some cases convulsions have occurred during and after a trial with alcohol (30). Another publication mentions that the hyperventilation resulting from the acetaldehyde of the Antabuse-alcohol reaction is accompanied by a decreased serum bicarbonate level. It is surmised that this is a pseudoacidosis due to hyperventilation and this assumption is confirmed by simultaneous blood pH and serum bicarbonate determinations (33).
5. Goiter. The possibility of goitrogenic activity of Antabuse due to the chemical similarity between thiuracil and tetraethylthiuramdisulfide should be considered.

6. Pregnancy. It is reported that no xanthine oxidase occurs in the livers of newborn rats (33). There is a possibility that this is also the case in humans. Should this be true, there is a possibility that acetaldehyde would rise to a dangerous concentration in the fetal circulation since xanthine oxidase is believed to be one of the enzymes involved in acetaldehyde metabolism.

7. Drug Addiction. The possible increase in use of the more dangerous drugs after alcohol is withdrawn indicates that the treatment should first be directed toward the correction of the drug addiction.

8. Diabetes Mellitus. Two cases of death in diabetic patients treated with Antabuse have been reported. Urine and blood sugar levels are unchanged by Antabuse administration but caution should be exercised when diabetic alcoholics are treated.

9. Asthma. Occasionally asthma is made worse by the Antabuse-alcohol reaction and it is suggested that lower trial doses of alcohol be used.

10. Diseases of the Hematopoietic System. Though no effect has been observed, the similarity of Antabuse to substances which cause disturbances in the blood

forming mechanism should be considered and regular blood examinations made.

It would be extremely dangerous to give Antabuse to an intoxicated person due to the severe reaction which would result. Fatalities have been reported. Patients receiving paraldehyde should not be given Antabuse nor should paraldehyde be given to patients receiving Antabuse.

## ADMINISTRATION

The patient who expresses a real desire for the treatment should bring a friend or relative for consultation in order that the background for his alcoholism may be more clearly determined (13)(14). The individual should be impressed that his use of alcohol is a disease for which he needs treatment. The use of Antabuse in the alcohol-intolerant person may be compared to the diabetic's use of insulin (14)(24). The patient is told how the treatment is administered, how the Antabuse-alcohol will probably affect him and the anticipated result of treatment. The latter, it must be emphasized, is merely to keep him from drinking while the cause for his drinking is removed (8). It is then suggested that the patient return home and consider the matter and discuss it with relatives and friends.

Glud (14) recommends hospitalization for about ten days during the initial administration and first two trials, but

others (1)(13)(24)(29) have described out-patient methods.

Pretreatment When the patient returns, a careful medical and psychiatric history should be taken. It is important to become familiar with the patient's background, drinking habits, and if possible, the cause of his alcoholism. A careful physical and neurological examination is important with particular attention given the cardio-respiratory system. The following laboratory procedures are recommended:

1. Complete blood count.
2. Urinalysis.
3. Electrocardiogram.
4. Liver function test (bromsulfalein).
5. Kidney function test (concentration).
6. Blood sugar.
7. Glucose tolerance test.
8. Blood acetaldehyde - Stolz method (32).
9. Basal metabolic rate.
10. Carbon dioxide combining power.
11. Electroencephalogram (if possible).
12. Rorschach test.

After a careful evaluation of history and objective findings, and the patient found to be reasonably healthy, free from concurrent infection and not psychotic, the patient is put in the best possible physical condition (13). He should be sobered and the use of glucose, insulin and vitamin preparations are valuable in improving his physical condition. He should be given thorough instructions concerning all aspects of alcoholism. After one week of sobriety, if he is then in good physical condition, the administration of Antabuse is begun.

Dosage The drug is furnished as 0.5 gm. oral tablets.

Glud (14) and others (4)(6)(9)(13)(24)(29) recommend the following schedules:

| | | |
|---|---|---|
| 1st day | - | 2 gms. |
| 2nd day | - | 1.5 gms. |
| 3rd day | - | 1 gm. |
| 4th - 8th days | - | .75 gm. |

A maintenance dose of 0.75 is usually satisfactory. It is important that the full dose for the day be given in the morning.

Antabuse should be given for at least three days before the first trial dose of alcohol. The suggested procedure is that 40 - 50 cc. of whisky (or the equivalent amount of any other alcoholic beverage) be given on the fourth day. The patient, if not already hospitalized, should be in a hospital. The patient may choose his own beverage but experience has shown that a slow rate of consumption is advisable (13). On the eighth day a somewhat smaller dose of alcohol is given. Patients are often reluctant to take the second dose, but if possible they should be persuaded to cooperate. A maintenance dose of 0.75 gm. per day is generally adequate but the dose may be adjusted to that amount which, upon the administration of 10 - 20 cc. of whisky, produces a slight flushing, slight increase in pulse rate, and a mild dyspnea. The range of such a dose is 0.125 - 1.0 gm. Within four to six weeks, four or five trials with 10 - 20 cc. of whisky

should be made. The maintenance dose is taken indefinitely.

The patient may be returned to his home after recovery from the effects of the second alcohol trial. With the succeeding trials made with the smaller amount of alcohol, he becomes impressed that a reaction will follow promptly. The earlier trials with the larger dosage of alcohol will be an indication to him of what will occur should he take more. It is thus important that he have severe reactions in the early trials.

During treatment it is suggested that the following tests be done to determine chronic toxicity.

1. Examination of the cellular elements of the blood weekly for the first month and monthly thereafter.
2. Basal metabolic rate monthly.
3. Liver function tests after two or three months of treatment.

Maintenance It is to be reemphasized that Antabuse is no cure for alcoholism but rather a method for keeping alcohol from the alcohol intolerant person (4)(5)(7)(8)(9)(10)(11)(12)(13)(14)(22)(30). The patient must learn to avoid alcohol in his life among normal drinkers (24). The patient must be encouraged to join some group such as Alcoholics Anonymous, since group therapy of this type has been very effective. Frequent interviews with the physician are necessary to discuss the patient's progress, regulate dosage and stimulate the patient to

continue treatment.

Should treatment be stopped for some reason, the maintenance dosage may be resumed (14). However, some believe another alcohol trial should be carried out (29). In some patients alcohol trials every eight to ten weeks are useful.

## COMPLICATIONS

In addition to the toxic manifestations mentioned elsewhere in this paper, there have been noted a few adverse reactions. A few patients are unusually sensitive to the Antabuse-alcohol reaction since deaths have occurred after only small doses of alcohol (25). One death in a Canadian experiment was reported to be due to acute congestive, right sided, cardiac failure (25). A heart attack has been reported in the course of an Antabuse-alcohol reaction (27).

It is stated that, once begun, there is no known method of controlling the Antabuse-alcohol reaction (5). Since this is apparently true and because of the occasional severe reaction, it is suggested that the initial Antabuse alcohol trials be conducted in a hospital (12)(25).

It is obvious that medications containing alcohol must be avoided during Antabuse administration.

## RESULTS OF TREATMENT

In the series reported by Gelbman and Epstein (13),

Jacobsen and Martensen-Larsen (24) and Martensen-Larsen (29), and an unpublished series conducted at Fitzsimons General Hospital there have been comparable results. These groups total 267 cases.

Results termed "promising", "very successful", "controlled", "socially recovered", etc., were reported for 202. In this category are those who remained sober without taking more Antabuse, those who voluntarily continued treatment and remained sober, those who could be encouraged to continue treatment and remained sober.

Seventeen cases were described as "somewhat better" or "improved".

Fifteen patients were so psychoneurotic that the treatment was difficult to follow.

In the remaining 33 cases the treatment failed. Some patients failed to appear for the initial trial, others quit treatment before the second trial and the remainder simply stopped treatment.

It is known that in at least twelve cases, the patients tried drinking but had the typical reactions and continued treatment.

## SUMMARY

Antabuse is a compound nontoxic to humans but when an Antabuse-treated individual ingests ethyl alcohol, a toxic

reaction results. This reaction is evidently due to an increased blood acetaldehyde level. This assumption is based on three facts: (1) Acetaldehyde is a normal product in ethyl alcohol metabolism; (2) The blood acetaldehyde level in the Antabuse-treated individual who ingests alcohol is higher than that produced in a nontreated individual who takes the same amount of alcohol; and (3) intravenous infusion of acetaldehyde produces the same signs and symptoms as those resulting from the Antabuse-alcohol reaction. The manifestations of the Antabuse-alcohol reaction are facial flushing, palpitations, dyspnea, hyperpnea and general uneasiness. Nausea and vomiting mark the more severe reaction.

In the treatment of alcoholism the patient is given Antabuse daily. On several occasions early in treatment he is allowed to drink a small amount of any alcoholic beverage he chooses and then experience the results. During the next few months he is given smaller amounts of alcohol so as to obtain a mild reaction. Thereafter, so long as he continues taking the drug, he will be unable to ingest any ethyl alcohol containing mixture without the reaction. This serves to keep the alcoholic from drinking while an attempt is made to remove the cause of his alcoholism. It is not claimed that Antabuse is a cure for alcoholism but rather is a useful part of its treatment.

Approximately 80% of the reported cases continue to

take the drug regularly and thus remain sober. Treatment in the remainder was unsuccessful due to failure to continue medication.

The author is indebted to Ayerst, McKenna and Harrison, Ltd., for their cooperation in providing Antabuse and reprints of many publications on the drug. Especially helpful were A. E. Miller, Lt. Col. (MC) U. S. A., Acting Chief, Neuropsychiatric Service, Fitzsimons General Hospital, and Charles T. Brown, Major (MC) U. S. A., who directed a research project on Antabuse in which the author was privileged to assist.

## CONCLUSIONS

Antabuse is a nontoxic compound of use in the treatment of alcoholism. When given Antabuse in adequate dosage, the individual will have a toxic reaction after drinking any alcoholic beverage. This reaction is attributed to acetaldehyde, a normal metabolic product in alcohol oxidation, but found in increased amounts after the Antabuse-treated patient ingests alcohol. Antabuse is not a cure for alcoholism but, if taken regularly, will keep the patient from drinking while he receives psychotherapy.

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