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Antabuse in alcoholism

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ANTABUSE IN ALCOHOLISM

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TABLE OF CONTENTS

TABLE OF CONTENTS (Cont'd)

TABLE OF CHARTS

INTRODUCTION

Alcoholism is concerned with the specific need of the individual to use alcohol as a means of adjustment to his environment. Obviously alcoholics differ from each other in their reasons for use of alcohol and in their mode of drinking although the end result eventually is similar. Many people use alcohol to obtain homeostasis, and to achieve relief from tension, anxiety, and the problems of interpersonal relationships. Although alcohol often is used deliberately as a means of combatting stress, more often there is no awareness of discomfort, and the drinking is used to achieve a state of emotional and physical harmony that usually can be obtained in no other way. Beyond a certain stage in this use of alcohol, the individual begins to develop dependency complications. The alcohol becomes an integral part of the defensive mechanism, and any attempt at the removal of this defensive unit in the personality structure creates a new stress situation unless substitute forms of relief are furnished (1).

To cope with this situation, special therapeutic techniques have evolved in recent decades, including the utilization of Tetraethylthiuram disulfide (also known as Antabuse, Disulfiram, TETD). This paper will attempt to relate the effectiveness of the drug in the

treatment of alcoholism. It must be stressed from the onset that for most alcoholics, Antabuse is not therapy in itself but rather a valuable gateway to more fundamental treatment. Antabuse is an effective means of preparing the patient for psychotherapeutic procedures, particularly during the period of otherwise temporary abstinence. However, the first essential for success in utilizing this form of therapy is a sincere desire for help on the part of the patient, who must completely recognize his inability to control drinking and who exhibits a willingness to take the drug with consistency. As long as the patient's basic difficulties are not resolved, the desire for alcohol will persist and together with it a desire to stop the medication (2,3,4).

TETD is an old chemical that has been used for many years in the rubber industry as one of the substitutes for inorganic sulphur in the curing of rubber. Workers exposed to these industrial processes noted that contact with even small amounts of alcohol produced a highly unpleasant reaction. Recently this chemical was found to have fungicidal properties, and on this basis the Danish scientists, Dr. Erik Jacobsen and Dr. Jens Hald, investigated the compound for its anthelminthic properties. The drug was effective in rabbits but prior to release, investigation was necessary from the standpoint of toxicity in

humans. Since these animals exhibited no signs of chronic poisoning, the two men were encouraged to take oral doses of the chemical themselves (5). No after effects were noted. However, a few days later each experienced a puzzling uneasiness with intense flushing and palpitations upon drinking alcohol at a party. The drug was soon suspected to be the possible cause of the reactions. This was subsequently confirmed by animal experimentation as well as by clinical trials. Thus a new mode of treatment for alcoholism was discovered.

Following extensive and successful application in Scandinavian countries including administration to over 22,000 patients in Sweden, the drug was introduced to North America in January 1949, for further controlled investigations as to pharmacology and clinical application. As of December, 1952, it has been used in over 12,000 patients in the United States and Canada. The results and conclusions of these studies will be presented in the following paper.

CLINICAL APPLICATION OF ANTABUSE

I - Effects of Alcohol on the Patient Treated with Antabuse

Antabuse provides a new means of breaking the drinking cycle and affords the patient a new approach to social and physical rehabilitation. The rationale for administration of TETD is thus: an alcohol intake that

normally would elicit little or no symptomatic response has been found to produce the following characteristic unpleasant effects in a patient sensitized with at least 1.5 gms. of Antabuse. If such an individual drinks 15-20 cc. of ethyl alcohol at least three hours after the intake of Antabuse, he will experience a sensation of heat in the face in five-fifteen minutes, followed by an intense vasodilitation observed in the face and neck making the whole area a purplish red. This flushing spreads downward, sometimes covering most of the body. A characteristic vasodilitation of the sclera also occurs accompanied by a slight edema in the loose connective tissue under the lower eyelids (63). The pulse rate is increased to 120-140 although at this stage the blood pressure is either unaltered or slightly depressed. The cardiac output is increased 50% in resting persons and only slightly (5-15%) in persons doing moderate work. The ventilation is increased with a corresponding decrease in alveolar C02 (42).

After 40-50 cc. of alcohol or more, the intense flushing disappears and is replaced by facial pallor and signs of incipient shock. Copious vomiting may occur. Higher doses of alcohol in some patients result in dizziness and syncope for as much as thirty minutes (72).

These objective symptoms are accompanied by an intense feeling of discomfort to the patient who experiences a pulsating headache, palpitations, and subjective dyspnea. In most cases the individual notes a constrictive feeling in the neck as though his collar was too tight. This feeling of a "premature hangover" is so intense that once experienced, it prevents an overwhelming majority of patients from further attempts to take alcohol as long as they are influenced by TETD (63).

Child (26) has attempted to quantify the alcohol-antabuse syndrome. Erythema was the earliest sign manifesting itself eight minutes (average) after taking the alcohol and generally persisted for two hours. The tachypnea, dyspnea, tachycardia, and hypotension reached their maxima at approximately the same time, which was also the time that most of the patients felt the greatest effect subjectively. The mean duration of the syndrome based on the overall picture and in particular upon the return of the blood pressure and cardiac rate to normal was forty minutes. Using the skin temperature of the face as the most sensitive sign, it was found that the sensitivity to alcohol produced by a single dose of 0.5 gm. of TETD lasted three-four days; sensitivity produced by 1.5 gms. of the drug lasted seven-eight days (65).

II - Treatment Program

The treatment program presented below follows the recommendations of Glud (79) and Bennett (66). As soon as possible the patient is hospitalized and a responsible relative interviewed in order to evaluate probable extent of family co-operation and to attain a medical and psychiatric history. During the first two days in the hospital the patient is given complete physical and neurological examinations. A complete blood count with emphasis on the while count, serology and urine are routine. An EKG is done if deemed necessary. A high protein, high carbohydrate, and low fat diet is administered supplemented by B complex vitamins. After two days, a glucose tolerance and BSP tests are done. If the patient has no more than 15% retention of the dye in thirty minutes, the other findings are negative, and the patient's co-operation is assured, Antabuse is administered. An initial dose of two grams is followed by 1.5 grams on the second morning and 1.0 gram on the third. On the fourth day an experience session is held where each patient is allowed to drink 2-6 ounces of 100 proof liquor (67).

It is well to remember that occasionally the Antabuse-alcohol reaction may be so violent that a state

approaching surgical shock may occur; furthermore there seems to be no way of determining in advance how severely each patient will react. Consequently means of resuscitation must be at hand including oxygen, intravenous fluids, (5% dextrose in isotonic NaCl), ascorbic acid, stimulants (caffeine, coramine, and benzedrene), and vasoconstrictors (epinephrine, ephedrine). Blankets for warmth and means of elevating the foot of the bed are helpful (14).

After recovery from the Antabuse-alcohol reaction, the patient is discharged from the hospital and given supply of tablets (0.5 gms. to be taken/day), and a card to carry stating name, medication patient is taking, and whom to notify. The individual is told to return for a second test on the eighth day at which 30-40 cc. of alcohol are again administered. Following the second test reaction, an appointment is given for a psychiatric interview. Maintenance dosages are adjusted individually from 0.25 to 1.0 gms./day, according to the severity of the reaction and the side effects. An attempt is made to adjust the dosage so that upon drinking 10-20 cc. of whisky, the patient experiences a slight flushing about the head, a slight increase in pulse rate, and a mild dyspnea lasting fifteen-twenty

minutes (66). Thimann (68) suggests that the dosages recommended by Glud are too great and should be reduced to the following: on the first day 1.0-1.5 grams of Antabuse, on each of the two following days 1.0 gram, and 0.5 grams on the fourth day. Frequent checks must be made of the dosage taken by the patient especially during the first three months of treatment during which time the effects of the drug may vary (69). It should be emphasized that patients under treatment with TETD must be on guard against intake of alcohol in any form lest they experience severe reactions.

III - Antidotes

Antidotes to the Disulfiram-alcohol reaction deserve prominent mention in this discussion. Jokivartio (38) studied the ability of i.v. iron and ascorbic acid to abort a reaction. Injections of an aromatic compound containing these substances into twenty sensitized alcoholic patients indicate that i.v. iron in doses as small as 13 mg. has a distinct curative effect on the toxicosis produced by alcohol in a sensitized patient. Injections given immediately after the intake of alcohol in thirteen cases aborted the toxicosis almost instantly. If iron was administered before the intake of alcohol, the appearance of the toxic symptoms was not prevented

but their development is slower than in the usual Antabuse-alcohol state.

Further investigation as to the efficacy of ascorbic acid as an antidote was conducted by Niblo (39) and Lester (36). During carefully controlled experiments with thirteen patients, they discovered that i.v. ascorbic acid or ferrous chloride had no effect on the increased acetaldehyde concentration noted during the reaction, nor on the symptons believed to be related to it including blood pressure and pulse rate. It did seem, however, to have a favorable effect on the subjective symptoms of the reaction, such as headache, palpitations, apprehension, and weakness. Niblo concluded that there are two types of symptoms in the TETD-alcohol reaction; those due to the effects of increased acetaldehyde and those due to inhibitory effects of Disulfiram upon cellular respiration. Corroborating this latter contention is the work of Nowinske (40). He noted that the inhibition of respiration caused by TETD could be completely overcome by the addition of 20 mg. of ascorbic acid per Warburg vessel. Smaller amounts of ascorbic acid restored lesser amounts of respiration.

Arruda (41) reports that magnesium thiosulfate can counteract and prevent an unduly severe Antabuse reaction.

IV - Symptoms Due to Antabuse Per Se'

In daily doses greater than one gram some undesirable clinical manifestations were evident in many patients (26). These included gastro-intestinal disturbances (tenesmus and mild diarrhea), fatigue, somnolence, visual disturbances, decreased mental acuity and changes in sexual potency. These effects were reduced or eliminated entirely with a decrease in the daily dose to 0.5 gram. Martensen-O'Larsen have tabulated the frequency of these complaints in 600 patients (43). Fatigue was noted in 36%, drowsiness (11%), indigestion (12%), headache in 8.5%, vertigo (8.7%), and decreased potency in 9.7%.

V - Correlation with Psychotherapy

The role of Disulfiram merely as an aid to psychotherapeutic procedures is emphasized throughout this paper, but unfortunately many alcoholics are not amenable to psychriatric treatment. Herein lies the limiting factor to this new mode of attack. For if the patient's inability to adjust is not resolved, and hope placed upon Antabuse per se' as the final treatment, the conflict over whether or not 'I should drink' may well be replaced by 'whether or not I should take the pill.' To complicate matters, the ability of the patient to

accept and respond to help is not necessarily based on conscious mechanisms. Thus many who initially appeared eager for a solution to their problems have been prominent failures.

TETD seems best indicated from a psychiatric standpoint in those individuals who exhibit a capacity to develop sustained interpersonal relationships and some utilizable dependency traits. The best results were obtained in relatively stable middle-aged men who had drifted into addiction from heavy social drinking, usually precipitated by some personal and environmental problem.

To some alcoholics, Antabuse and the implications of sobriety and therapy can represent a stress which forces them to utilize 'a last ditch' defense measure, the psychotic or near psychotic reaction (18). Several cases of frank psychosis subsequent to therapy have been reported (1,11,13). All these patients responded to mild sedation and withdrawal of the drug. Such patients who have become disorganized subsequent to therapy include the projectile hostile patient who feels threatened by help. An indication of incipient psychosis, a history of psychotic episodes, or a diagnosis of borderline schizophrenia contraindicates treatment with TETD (1).

Character neurotics do poorly. Such patients usually embrace the idea of therapy with enthusiasm but their unstable character fails to provide the necessary perseverance to continue. Periodic drinkers who were basically cyclothymic were not particularly good subjects (37,54).

Guild (74) describes the onset of a psychotic episode following the administration of Antabuse. The personality changes gradually increase in severity and are heralded by somnolence. This symptom usually is followed by complaints of marked tiredness, sometimes dizziness and headache, then by forgetfulness, memory loss, and mild incoordination. Orientation becomes impaired. These changes in sensorium are paraleled by an ataxic gait and a decrease in activity which may approach catatonia. Elements of agitation or hypomania may be present also.

VI - Contraindications

Concluding the discussion on the clinical application of Antabuse, a review of contraindications would be in order. These are presented as listed in the main by Glud (17).

1 - Cardiovascular disease - especially coronary insufficiency and myocardial failure since Asmussen (42)

showed that during the Antabuse-alcohol reaction, the cardiac rate and output may be considerably accelerated. Furthermore, coronary flow may be significantly reduced because of the sustained fall in diastolic blood pressure.

2 - Liver pathology - the possible effect of TETD on the liver was studied in six patients with reversible liver disease as determined by biopsies done before treatment and at various intervals over a three-six month period. Medication was started with 0.2 gram on the first day and continued with 0.5 gram daily. Since all these patients exhibited improvement in their hepatic state both clinically and on biopsy, it was concluded that TETD administered to such patients over several months had no adverse effects on the rate and completeness of recovery as estimated by clinical observations, liver profile tests and the disappearance of fat from liver biopsy fragments (30). Since it is not feasible to perform liver biopsies on a general scale to determine the extent of liver damage, we may follow the suggestions of Glud who recommends that TETD is contraindicated in patients with less than 85% of liver function. Voegtlin (33) in comparing 17 liver function tests found that the BSP test best indicates liver damage associated with chronic alcoholism.

3 - Acute or chronic nephritis - although TETD as such is not excreted in too great quantities, both Glud (17) and Pfeiffer (5) report that nephritic patients with slight albuminuria will develop an increase coincident to Antabuse therapy.

4 - Epilepsy contraindicates treatment since EEG studies indicate that TETD aggravates abnormal patterns. It has been reported that in a few cases convulsions have occurred during and after a trial with alcohol (58).

5 - Thyroid disease - simultaneous therapy with thiouracil derivatives for thyroid disease is contraindicated since a chemical similarity exists between thiouracil and TETD (5).

6 - Diabetes may be considered a relative contraindication since two deaths are reported in diabetics treated with Antabuse (17). Investigations on fifteen well regulated hospitalized diabetic patients given the usual therapeutic dose of Antabuse revealed no influence on the course of the diabetes. Examination of 800 patients indicated that TETD in the usual therapeutic dose is without diabetogenic effect on non diabetics (50).

7 - Drug addiction - TETD should not be utilized in a drug addict since the withdrawal from alcohol may result in an increased use of the drug (4).

8 - Antabuse should be administered to asthmatics with caution because occasionally asthma is made more severe by the Antabuse-alcohol reaction.

9 - Paraldehyde cannot be tolerated with TETD since the former is a triomer of acetaldehyde.

10 - Any retinal vascular lesions should definitely contraindicate treatment with TETD. Observation of the eye grounds during an alcohol reaction in patients treated with TETD reveals that the macular arterioles have become exsanguinated and that the diastolic pressure particularly, drops severely (35).

CHEMISTRY

Antabuse consists of colorless or slightly yellow crystals with the following formula:

$$(C_2H_5)_2N\cdot\overset{\overset{S}{\|}}{C}-S\cdot S-\overset{\overset{S}{\|}}{C}N(C_2H_5)_2$$

The substance melts at 70-72 degrees centigrade, and has a peculiar but weak aromatic odor resembling violets. The taste is slightly bitter. It is insoluble in water but dissolves readily in ethyl ether or chloroform. Complex compounds of an intense yellow color are formed with cupric salts (6).

EXPERIMENTAL STUDIES

I - Mechanism of Antabuse Action

A - Disruption of alcohol metabolism with subsequent increased blood acetaldehyde levels.

Acetaldehyde production is one of the normal intermediary steps in the oxidation of ethanol, and evidence has been presented that Antabuse interferes with the further metabolism of acetaldehyde, thereby allowing the latter to accumulate (63). It is this increased blood acetaldehyde that is in part responsible for the clinical symptoms observed during an Antabuse-alcohol reaction. Asmussen (31) administered i.v. acetaldehyde into normal human subjects and elicited many of the circulatory and respiratory manifestations present after administration of 40 cc. of absolute alcohol twelve hours following 1.5 gms. of Antabuse. (32). The blood acetaldehyde levels were compatible in the two instances ranging from 0.2 to 0.7 mgs.% during the intravenous infusion of acetaldehyde and 0.57 mgs.% subsequent to the alcohol-Antabuse administration.

1 - Rate of acetaldehyde metabolism in animals treated with Antabuse.

Hald (9) infused acetaldehyde into rabbits and found a maximum constant rate of metabolism for this substance which could not be exceeded no matter how much was infused. However, in animals sensitized with TETD,

the blood concentration of acetaldehyde had to rise much higher than in the controls to effect this same maximum rate.

2 - Relationship between dose of Antabuse, concentration of alcohol, and blood acetaldehyde levels.

Experiments were conducted in rabbits to show the relationship between the dose of Antabuse and the level of acetaldehyde in blood (the concentration of alcohol remaining constant). Hald (8) found that increased doses of Antabuse, up to 1.0 gms., resulted in proportional increases in the amount of blood acetaldehyde. When more than 1.0 gms. of Antabuse was absorbed, it had no further effect on the acetaldehyde level. One must conclude from these observations that the effect of Antabuse on acetaldehyde formation depends only to a limited extent on the dose of Antabuse. The organism apparently can be saturated with Antabuse so that an increase beyond this dose gives no further effect.

3 - Site of formation of acetaldehyde.

The site of formation of acetaldehyde was determined in the following manner (12). In this experiment livers from normal and Antabuse treated animals were perfused with blood to which alcohol had been added.

When livers from normal untreated animals were used, no acetaldehyde was observed in the perfused blood. A marked increase of acetaldehyde in the perfused blood was noted when perfusion was made through Antabuse treated livers. Therefore, it is obvious that the formation of acetaldehyde from alcohol occurs in the liver cells. Perfusion through the isolated hind limbs of a rabbit treated with Antabuse showed no alcohol combustion or acetaldehyde formation. However, it certainly cannot be concluded from this experiment that acetaldehyde formation cannot occur in <u>other</u> organs although any such formation must be of minor degree.

4 - Reasons for acetaldehyde accumulation (interference with alcohol oxidizing enzymes).

Having established partially the mechanism of TETD action by interference with normal oxidation of alcohol and subsequent accumulation of Antabuse, we will now consider more specifically the reasons for acetaldehyde accumulation. It has been shown that Antabuse inhibits two of the three liver enzymes capable of acting upon acetaldehyde, namely xanthine oxidase and aldehyde oxidase.

Studies were conducted on xanthine oxidase by Richert (15). This investigator found that the 'in vitro' addition of Antabuse to a normal rat liver homogenate inhibited its xanthine oxidase activity in proportion to the amount of Antabuse added and the original activity of the liver. 0.2 and 0.4 mg. of Antabuse per cc. of homogenate gave an average 58% and 71% inhibition respectively. (Evidence indicated that xanthine oxidase occurred in rat liver as two independent enzymatic activities. Antabuse inhibits only the oxidase activity which is responsible for the reoxidation of the reduced enzyme by atmospheric oxygen. The dehydrogenase activity of the enzyme was not affected.) Methylene blue added to the liver homogenate in the aerobic test system as well as heating the homogenate to 56 degrees for five minutes overcame the inhibition of xanthine oxidase (16).

The effect of Antabuse on aldehyde oxidase, the other enzyme system capable of using acetaldehyde as a substrate was studied by Kjeldaard, (18). He found that the oxidation of acetaldehyde by this liver enzyme is markedly inhibited by Antabuse in concentrations as little as 0.10 microgms./ml. of liver homogenate. Reduced Disulfiram, however, was found to have no

inhibitory effect in concentrations as high as 0.25 mg./ml. This indicates that it is the -S-S linkage in TETD which constitutes the inhibitory part of the molecule. The work of Kok (19) substantiated this finding.

Thus we have seen that Antabuse inhibits two of the three liver enzymes capable of acting upon acetaldehyde. Work done by Graham (20) upon another of the liver enzymes, aldehyde dehydrogenase, indicates that it is also strongly inhibited by low concentrations of TETD. This inhibition appeared to be of the competitive type with the diphosphopyridinenucleotide competing with TETD for the active centers of the enzyme. Diphosphopyridinenucleotide is a coenzyme necessary for maximum activity of liver aldehyde dehydrogenase. The affinity of the enzyme for TETD is forty-six times greater than that for diphosphopyridinenucleotide. The high degree of affinity of this enzyme for its inhibitor is rather a rare occurrence. This investigator further reported that reduced glutathione at a very low concentration was able to reverse the effect of TETD on the aldehyde dehydrogenase. To restore the enzyme to 50% activity, a molar ratio of reduce glutathione to TETD of only 3:1 was required.

B - Interference with cellular respiration

Although the Danish investigators have postulated that the observed toxic effects following TETD-alcohol ingestion are due to an increased concentration of acetaldehyde, evidence has been presented that many of the symptoms elicited during the reaction result from a generalized anoxia secondary to interference with cellular respiration. Edwards (21) showed that Antabuse inhibits 85% of cellular respiration. The average figure obtained for oxygen uptake of rat liver homogenate plus Antabuse was 10.54 cu. mm./hr. The average figure obtained for the oxygen uptake of the homogenate without Antabuse was 70.94 cu. mm./hr. This investigation helps explain the toxic manifestations found after the TETD-alcohol combination which do not occur after i.v. infusion of acetaldehyde, for example, sweating, dyspnea, dizziness, nausea and vomiting. In addition, one now is able to explain the acute reactions encountered in some patients many hours after all the acetaldehyde presumably has been excreted or metabolized.

II - Metabolism of Antabuse

A - Absorption and elimination

Absorption from the gastrointestinal tract of rabbits is not complete and elimination is slow (7). In

experiments conducted with rabbits, only 12.8% of the given dose was recovered from the feces over a period of three days following administration. The corresponding figure in similar experiments with dogs was as high as 56-77%, and 18.5-21% in man (6)

In an attempt to discern the rate and quantity of Antabuse eliminated, Eldjarn (24) administered 1 mg. of TETD (labelled with 0.4 microcuries of S35) to rats both orally and parenterally. Urine and feces were collected for five-fifteen days and analyzed for TETD and the reduced form of TETD, diethyldithiocarbamic acid (henceforth referred to in this paper as DDC). About 20% of the ingested drug was found to be excreted in the feces while the rest is absorbed from the g.i. tract. Of this ingested portion about 60% is excreted in urine as free or esterified radioactive sulfate, almost all of it in the first few days. In similar experiments with man 45% of the absorbed radioactive sulphur was excreted in the urine (48). In both instances only traces of TETD as such was recovered although 2-5% of the ingested amount was detectable in its reduced form in man (22). Domar (25) was unable to recover any DDC in human urine since he disregarded the pH, and in acid urine, DDC disintegrates into carbon disulfide and diethlyamin.

B - Rate of metabolism

Although absorption is not complete, Antabuse is metabolized rather rapidly in the mammalian body (see Table I), and the danger of intoxication due to an accumulation of Antabuse per se' in the tissues is rather remote (10).

Table I*

Mean Blood Levels (microgms./ml.) of Antabuse in Rabbits (weighing 3±0.2 kg.) at Varying Intervals after the Single Administration

Time in Minutes after administration	Dosage of TETD Administered Intragastrically		
	0.75 gms./kilo	0.50 gms./kilo	0.25/gms./kilo
30	10.2	5.7	4.1
60	4.4	3.2	1.0
120	0.0	0.0	0.0
140	0.0	0.0	0.0

* taken from Divatia (10).

As will be noted by referring to Table I, at each dose level the highest blood concentration was obtained at the thirty minute interval. Similar results were also obtained in experiments on humans (10). In no case was there any indication of an accumulation in the tissues

as reflected by blood analysis.

C - Conversion to reduced form

In an attempt to explain the fact that while TETD is absorbed rapidly it is slow in action, Eldjarn (48) suggests that the active agent is not TETD itself but rather its reduced form, DDC, since determinations indicate that the reduced form can be found to an appreciable extent in the blood and tissues after TETD is no longer present. Some controversy has arisen concerning exactly which portion of blood contains DDC. Linderholm (22) found approximately a 10-20 mgs.% concentration in corpuscles but none in plasma, while Eldjarn (22) reports levels of 1.6-4.0 mgs.% in plasma (either as TETD or as DDC). Since different methods were used for the determination of the DDC in protein rich solutions by the two investigators, the findings are not necessarily incompatible.

D - Site of detoxification

Boyd (23) demonstrated that Antabuse most probably is detoxified in the liver. TETD was administered by stomach tube thirty-six hours after operation, in doses of 4-6 gms./kilo (LD50 is 4 gms./kilo of body weight) to some 60 subtotally hepatectomized albino rats and to sixty suitably laparotomized but not hepatec-

tomized controls. The mortality rates ranged from 76-95% in the subtotally hepatectomized rats and from 50-70% in the laparatomized controls receiving Antabuse, the P value of the difference being 0.05 or less. (This difference is statistically significant.) The mean number of days survival after Antabuse ranged from 2.0-4.4 in the hepatectomized rats and from 6.6-9.3 in the laparatomized controls, the P value of the mean differences being less than 0.01.

III - Toxicity Studies

I shall conclude this section on experimental studies by a discussion of toxicity. Single doses of Antabuse were given to dogs, rabbits, and rats by stomach tube (26). The results (see Table II) indicate a low degree of toxicity. Signs of toxicity include: nausea and vomiting, bloody stools, diarrhea, loss of up to 34% of control weight, lethargy, and ascending paralysis with transient periods of remission (27). A lethal dose produced death by respiratory arrest. This ascending paralysis was not alleviated by prostygmine, a sign suggestive of spinal cord interneuron blocking (29).

Table II

Acute Toxicity of Antabuse Given Orally in a Single Dose

Animal	Vehicle	Toxic Dose	Gms./kgm
Rat	Water, divided doses	LD_{50}	2.5±0.38
Rat	Aqueous, single dose	LD_{50}	8.6±0.37
Rat	Cottonseed oil	LD_{50}	1.3±0.35
Rabbit	Aqueous	LD_{50}	1.8±0.13
Dog	Aqueous	LD_{50}	3.5

The species difference in the toxicity of TETD was not unusually great. The low oral toxicity of TETD given in water in a single dose to rats appeared to have been due in part to the slow movement of the drug from the rat stomach. It will be noted that when fat solvents were used as vehicles for oral administration of Disulfiram to rats, the signs of toxicity occurred at smaller doses and were more severe than when the aqueous suspension was used. This greater toxicity of TETD in fat solvents may be of some significance when TETD is used therapeutically on human subjects (28).

In chronic toxicity studies, 20% of the respective lethal dose was given orally to dogs, rabbits, and rats. The same signs of toxicity were obtained after a number of weeks. Upon discontinuing the drug, the animal recovered completely (26). Doses far smaller than the

lethal dose may be administered for months with no apparent ill effects. Rats were given 1.0 mg. daily doses and rabbits 60 mg./day for ten months without any influence on growth, body weight, appearance, or blood picture (30).

The histopathology of the sacrificed animals is shown in Table III. Of particular interest were the kidney lesions which resembled a lower nephron nephrosis, and the patchy demyelinization of the brain which resembled lesions seen in multiple sclerosis. The cardiac edema was very slight and not found in all animals (26).

Table III

Major Pathological Lesions Found in Animals Given Toxic Doses of Antabuse

Organ	Pathology
Spleen	toxic necrosis; focal hemorrhage; pigmentation
Kidney	degeneration of proximal and distal convoluted tubules
Lungs	congestion
Liver	focal necrosis; fatty infiltration; passive congestion
Brain	demyelinization, patchy in medulla, cerebellum, and spinal cord
Stomach	gastritis; edematous, distended, and contained free blood; ulcerations
Adrenal	congestion
Heart	edema

The pathologic changes in the tissues with which TETD came into direct contact were largely inflammatory and could be attributed to its local irritant action. However, it would be difficult to explain the demyelinating effect of TETD as due to its irritant properties. It should be emphasized that the amount of TETD required to produce these therapeutic changes was far beyond the amount required therapeutically to produce the alcohol sensitization in man.

PHYSIOLOGIC CHANGES

I - Respiratory

Since the respiratory and circulatory manifestations are most prominent they will be listed first. Four healthy men, aged 23-45, received 1.5 gms. of TETD and twelve hours later drank 60 mls. of gin. The findings are tabulated in Table IV. The increased ventilation leads to alkalosis which may cause hypocalcemia. Oxygen abolishes the hyperventilation, indicating that it is due to irritation of the chemoreceptors in the carotid body (43).

Table IV*

Effect of Alcohol in Normal People with and without Previous Treatment with 1.5 Grams Antabuse

	Before intake of Alcohol	½ hr. after intake of 60 ml. gin	
		Not treated with Antabuse	Treated with Antabuse
Respiratory dead space (ml.)	121.	138.	154.
Ventilation in liters/min.	19.1	19.1	23.1
Alveolar CO2 (percent)	5.35	5.40	4.42
O2 consumption (ml/min.)	264.	270.	324.
Cardiac output (per min.)	6.02	5.76	8.64
Pulse rate (per min.)	65.	64.	90.

*taken from Hald (73)

II - Circulatory

The circulatory manifestations predominate during the reaction and include an increased pulse rate, and a slightly increased cardiac output (44). A short rise in blood pressure is followed by a sharp and prolonged drop. The systolic pressure often drops to between 60-80 mm. Hg. and the diastolic pressure to

0 mm. Hg. (45). The reasons for this profound drop in blood pressure have been explained by Christensen (34). TETD seems to increase the sensitivity of the sympathomimetic receptors to acetaldehyde thus prolonging vasodilitation in the blood vessels with a subsequent sustained fall in blood pressure.

III - Electrocardiographic Changes

Macklin (46) conducted EKG studies on fifty-two problem drinkers during a test reaction with routine doses of TETD and alcohol. All of these patients had undergone prior extensive examination with particular emphasis on the cardiovascular system to eliminate the possibility of physical disease. In all fifty-two patients, flattening of the T waves was noted at the height of the TETD-alcohol reaction. Two patients exhibited EKG changes suggesting myocardial ischemia including S-T depressions in Leads I and V5, inversion of the T waves in Lead II and increased depth of the T waves in Leads III and V_6. Similar changes were reported by Raby (45) and Norman (47). Many of the non-specific EKG changes could be attributed for the most part to the tachycardia. Raby (49) offers the following explanation for those electrocardiographic changes not attributable to the increased cardiac rate.

He demonstrated a fall in serum potassium during the Antabuse-alcohol reaction. The intensity of the clinical reaction followed in the main the fall in serum potassium and the increase in blood acetaldehyde. The more pronounced EKG changes (flattening of the T waves and depression of the S-T intervals in Leads I and II) were seen in the subjects with an intense reaction and coincided with the greatest changes in serum potassium.

Table V*

Alcohol-Antabuse Syndrome in Human Subjects

EKG Changes in Fifty Patients

Depressed T waves	38
Depressed QRS complex	13
Rate over 100	40
Q2 Q3	7
Axis shift	5
Ectopic beats	2
Elevated S-T	2
Sagging S-T	1

*taken from Child (26)

IV - Central Nervous System Changes

The effect of Disulfiram on the electroencephalogram was conducted by Busse (51). In a series of

thirty patients who had been placed on Antabuse therapy, the degree of change in the EEG was influenced by the stability of the cortex prior to TETD medication. Those patients with normal brain waves pre-antabuse had normal records while on therapy in 12 out of 15 cases (80%), and what disturbances did appear were not severe. Patients whose EEG's were classified as being questionably normal prior to Antabuse had records which became distinctly dysrhythmic in all cases after a period of Antabuse therapy, while records that were clearly disturbed before Disulfiram invariably showed the greatest proportional increase in abnormalities while on the drug.

Therefore, Antabuse, when employed in therapeutic doses, produces definite toxic symptoms and in addition exerts a toxic influence on the brain as demonstrated by EEG alterations. These findings support the belief that Antabuse may produce a histotoxic anoxia secondary to interference with respiratory enzyme activity in the cortical cells. The electrical changes seen in the cortex resulting from Antabuse are usually seen as an increase in the amplitude and a slowing of the cortical rhythm. Consequently, the drug should be used with caution in patients suspected of organic brain disease

and particularly in patients with a history of a convulsive disorder (51).

V - Skin

The use of TETD has produced an acneform eruption in a few instances, undoubtedly on a sensitivity basis. Barefoot (52) reports such a case subsequent to the ingestion of TETD. Two other references are cited in the literature, (67,53) in which skin eruptions occurred during a test reaction. Since no eruptions were noted if either substance were given alone, the sensitivities encountered probably resulted from the increased blood acetaldehyde levels.

VI - Miscellaneous

Child (26) performed the following laboratory tests at intervals on thirty patients who had been receiving Antabuse six-nine months in an attempt to ascertain the effect of Antabuse on vital body functions:

1 - Blood - CBC; CO2 combining power; TSP; a/g ratio;

2 - Liver - thymol turbidity; cephalin flocculation; serum alkaline phosphatase; biliribin; cholesterol and esters; BSP;

3 - Kidney - urinalysis; PSP; Mosenthal concentration; NPN;

4 - Miscellaneous - glucose tolerance; BMR; EKG; EEG;

With the exception of two cases in which there was a slight increase in thymol turbidity and cephalin flocculation values, the results of all these tests were negative. The 17 ketosteroid excretion was determined in six patients who complained of decreased sexual potency. The excretion was normal. Two patients developed a transient leucopenia with no change in differential.

VII - Deaths

Concluding this section on physiologic manifestations, I shall review those few deaths reported during administration of Antabuse. In no instance did any death result from use of the drug alone. As of December, 1952, 17 fatal cases have been reported out of approximately 11,000 treated patients in Denmark (64). Of these 17 fatal cases, in 12 the causes of death was incidental to the utilization of the drug and not directly attributable to it. In the five remaining cases no cause of death could be attributed to the effect of Disulfiram per se'. All these unexplained deaths occurred among patients who drank some alcohol while under the influence of Antabuse. The cause of

death was sudden respiratory or circulatory collapse. In view of these facts it is inadvisable to ever institute treatment before detoxification has occurred. Jacobsen (63) cites a death in a patient who was given Antabuse during a heavy drinking period. Twenty hours after he had stopped drinking his blood alcohol level was still 140 mgs.% with a blood acetaldehyde reading of 1.3 mgs.% and eight hours later his blood alcohol was 40 mgs.% (blood acetaldehyde 0.3 mgs.%). The next day he died.

Jones (71) and Steckler (70) each report a death which occurred several hours after the test reaction. The physical examination prior to treatment in each case was negative. The acetaldehyde concentration at the height of the reaction was 0.86 mgs.% and 0.74 mgs.% respectively. Post mortem examination of Jones' patient revealed an acute congestive right sided cardiac failure but gave little indication as to why this cardiac failure should have occurred. Jones raises the question that the high acetaldehyde levels may have been responsible for the cardiac failure. A search of the literature revealed no information regarding the toxicity of acetaldehyde. Furthermore, nothing has been found in either case to explain the high concentrations

either in terms of the amount of alcohol administered or any hindered excretion.

One more death was reported in a forty-nine year old hypertensive who died four and one half hours after the test reaction. Autopsy disclosed arteriosclerotic heart disease but again gave no clue as to the immediate cause of death (60).

REVIEW OF CONTROLLED STUDIES

Although Antabuse has been administered to over 34,000 patients at the time of this writing, a review of controlled studies, nevertheless, is exceedingly difficult for the following reasons: first, there is no correlation among the different investigators as to what constitutes successful treatment; obviously an individual who abstains completely subsequent to therapy, and one who still retains an occasional compulsion to drink but who does not endanger his status by doing so, should both be considered as successes yet a decided difference exists in the degree of improvement between the two. Secondly, great variation exists as to the length of administration of the drug and regularity with which it is taken. Finally some therapists administer Disulfiram as an adjunct to therapy, some without. I have chosen a random sampling of approxi-

mately 1,000 patients who received treatment from three-twenty-eight months. The results are tabulated in Table VI. In attempting to classify the degree of social recovery, I have used the categories proposed by Martensen-Larsen (57).

1 - Socially recovered - abstinence; regained ability to stop drinking before control is lost so that social drinking causes no loss of working time or disruption in family life; regained status in community.

2 - Much better - occasional compulsion to drink with brief periodic bouts which does not endanger patients status or job but does involve sporadic loss of working time; acceptable adjustment in family and community life.

3 - Somewhat better - frequent periodic drinking bouts with job endangered; familial disharmony less than previously with an indefinite social status.

4 - Unchanged - drinking practices the same as before treatment.

5 - Unknown - patient has terminated contact with the clinic.

Table VI

Results of Treatment

Investigators (by no.)	Treatment Time (mo.)	Socially Recovered (no. of pts.)	Much Better	Somewhat Better	Unchanged	Unknown	Total
55	3	16	2	2	2	8	30
56		11			17	16	44
26		17	1		7		
55	6	10	1	2	7	2	22
56		38		16			54
1		144		48	31	15	238
59*		8			35		43
60*		15		4	5		24
63		52	19	12	16		99
55	9	5	2	1	5	4	17
26		74			46		120
55	12	5		1	3	4	13
61		64	16	13	19		112
55	15	11	6	5	10	11	43
26		9	3		13		25
54	28	36	23		12		71
							981

*No psychotherapy accompanies treatment

These 981 patients represent a heterogeneous group from

all walks of life presenting a wide variety of psychiatric disorders.

Wallace (62) compares results obtained in twenty-six patients treated with TETD with those in another twenty-six patients who were treated by the usual methods. All the patients were treated on a voluntary basis. (The usual treatment program consisted of rapid withdrawal of alcohol, sedation, hi-caloric diet, vitamins, hydrotherapy and psychotherapy.) The procedure of Glud was followed for therapy.

Twelve patients of the TETD group have been abstinent for six-eighteen months. (Only four of those who relapsed resumed treatment.) In the control group seventeen out of twenty-six relapsed within two months and all relapsed within six months.

SUMMARY

Antabuse is a drug which produces highly unpleasant reactions when taken prior to ingestion of a moderate amount of alcohol. These symptoms include flushing, sweating, palpitations, dyspnea, hyperventilation, accelerated pulse rate, fall in systolic and diastolic blood pressure, nausea and ultimate vomiting; these are clinical manifestations of the following physiologic changes which may be divided into two main categories: Antabuse produces a generalized histotoxic anoxia secondary to cellular enzymatic respiratory inhibition; secondly, Antabuse interferes with the normal metabolic degradation of alcohol via enzymatic inhibition, consequently allowing an accumulation of blood acetaldehyde to occur.

The successful utilization of Antabuse in the management of chronic alcoholism necessitates a sincere desire for help on the part of the patient coupled with the application of psychotherapeutic measures by the therapist. It must be emphasized repeatedly that Disulfiram alone cannot be expected to remove the underlying maladjustments; hospitalization including both psychiatric care, and attention to complicating disease is essential if the patient is to achieve emancipation from alcohol.

Antabuse serves primarily as a sobering crutch on which the alcoholic may lean during the initial uncertain period of sobriety.

Disulfiram has little toxicity when used in the recommended dosage, and no deaths have been reported which are attributable to the drug alone. Extreme caution is mandatory, however, when it is utilized in patients with renal, cardiac, or advanced hepatic disease because of the circulatory and respiratory manifestations evident during an Antabuse-alcohol reaction. Continuous medical supervision is necessary in all treated patients because unduly severe and alarming reactions occur as a result of excessive trial doses of alcohol or surreptitious drinking during the initial stages of treatment. Recommended procedures to lessen the severity of the alarming reactions include intravenous administration of ascorbic acid and ferrous chloride, inhalation of oxygen, cerebral stimulants, and parenteral ephedrine sulphate.

Patients unwilling to cooperate should not be placed on therapy with Disulfiram. Administration of the drug under such circumstances provides small chance for a cure. Only with the realization that the drug merely serves as a means of correcting underlying maladjustments, does Antabuse become a useful adjunct in the management of care-

fully selected and adequately supervised cases of chronic alcoholism.

CONCLUSIONS

1 - Antabuse introduces a new method of treating chronic alcoholism. It is excellent as an adjunct to psychotherapeutic procedures, but offers only limited usefulness per se'.

2 - Alcohol administered to persons previously treated with TETD produces a series of disagreeable severe symptoms resulting from an inhibition of cellular respiration and an increased concentration of acetaldehyde.

3 - In a random sampling of 981 patients treated from three-twenty-eight months, 459 are socially recovered, while 99 may be considered as "somewhat better." 193 are unchanged.

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