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Current concepts in the treatment of alcoholism

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CURRENT CONCEPTS IN THE TREATMENT OF ALCOHOLISM

by

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INTRODUCTION

The World Health Association defines alcoholism as follows: "Alcoholics are those excessive drinkers whose dependence on alcohol has attained such a degree that it shows a noticeable mental disturbance or interference with their bodily and mental health, their interpersonal relationships, and their smooth social and economic functioning; or who show the prodromal signs of such development. They, therefore, require treatment."[53] 14.3 per cent of the new admissions to public mental hospitals in 1958 were for alcoholism;[52] it accounted for 14.7 per cent of the admissions in 1959.[16] Still a larger portion of the alcoholics are treated in "dry out" rest homes, general hospitals, and hotel rooms. Alcoholism is a major cause of absenteeism in industry, a contributor to highway accidents, and a complicating factor in many marriages. The magnitude of this growing problem in our society cannot be underestimated.

With a disease of this severity it can be seen why the medical treatment of alcoholism is rapidly becoming more important in accomplishing recovery. The practicing physician should become well equipped with knowledge of the medical treatment of this illness, not only because encountering such patients is common, but because this is the first step toward reaching the goal of treatment; the cure of the alcoholic. The fear and threat that so

many alcoholics feel about any treatment makes a medical approach seem much more acceptable. With a general feeling of physical well being, any further type of therapy becomes less of a threat and the cooperation of the patient becomes much more possible. Once treatment of the acute state has produced the desired effects, other types of therapy may be employed as indicated. The following outline of treatment is intended as a general medical approach to the problem of treatment of the acute alcoholic withdrawal state.

While it is not completely necessary to treat the patient with acute alcohol withdrawal in the hospital, there are no doubts as to the advantages of doing such. Here the necessary laboratory procedures may be performed quickly and accurately. Intravenous therapy is at your disposal. All the necessary emergency equipment is readily available. Also the attitude toward the acutely ill alcoholic that he is sick and welcome for treatment makes these patients more cooperative than many other hospital patients, contrary to the general belief of some of the personnel.

There are other advantages to hospitalization of the acute alcoholic. All too frequently, the family is in an emotional turmoil concerning his state; they don't know how to cope with the situation and how to handle his behavior. They may continue to give alcohol to the alcoholic, or in an attempt to stop his drinking get into trouble with the patient suffering the emotional reactions resulting from abstinence. In other cases, the environment may have contributed to the cause of his drinking and a return to this environment would only aggravate his condition. Finally from the point of view of the hospital, especially the teaching hospital, it gives the house staff and nurses the opportunity to deal with these patients and learn the various ways in which they react. It prepares the resident staff for treating

such patients after they leave their hospital training.

It has been found that beyond routine hospitalization a special area for the treatment of alcoholism is advantageous, since alcoholism must be treated with both the acute and the long-range aspects of the disease in mind. Such a unit can be part of the general medical service, or part of the psychiatric facility. In the case of the latter it should be sufficiently isolated as to avoid the alcoholic's reluctance to associate his problem with anything "mental". Initially, in most, the idea that his problem has anything to do with neurosis is impossible for the alcoholic, because such a concept leads to the unbearable feeling of inadequacy and inferiority which are basic factors in his use of alcohol for escape from anxiety. The alcoholic treated in this atmosphere feels he is in the hands of therapists especially skilled in the treatment of his disease. This makes it easier for the therapist to establish a rapport with the patient that may be carried on to lay a foundation for his long term treatment.

With such a unit even a small group the alcoholic gains a sense of security, and is relieved of his feelings of loneliness and being a cast out.

The last advantage is the very substantial gain from developed nursing skills. This is vital in many aspects, where signs of possible relapse are present,

threatening convulsions, rate of early safe ambulating, and other details of ward management are gained with long term exposure to this type of patient.

EVALUATION OF THE PATIENTS CONDITION

As with the treatment of any disease the first step in the treatment is physical and laboratory examination and the evaluation of the patient's condition.

Alcohol withdrawal, appearing within eight to twelve hours after the last intake is characterized by psychomotor agitation, which if untreated may progress to hallucinosis and finally delirium which may be complicated by seizures. Associated symtoms and signs include muscle cramps of the muscles of locomotion, peculiar abdominal quivering which may be confined to the epigastrium (referred to as butterflies by the patient), nausea, vomiting, insomnia; are varying degrees of sweating, tachycardia, and diastolic hypertension.

The alcohol withdrawal syndromes may be classified by the criteria of Schultz[34] and Johnson:[47]

(1) Delirium tremens- Those toxic states associated with withdrawal of alcohol, manifested by confusion, clouding of sensorium, psychomotor agitation, hallucinations, and delirium.

Delirium tremens is rare in the person under thirty years of age, or after less than three to four years of

chronic alcoholism.[43] The prodrome is usually manifested in an oversion to food, restlessness, and irritability, and disturbed sleep. Occasional hallucinations and illusions become followed by more frequent ones, usually of a fleeting and terrifying nature. Olfactory hallucinations my occur, while visual hallucinations are more frequent.

Consciousness becomes clouded, and the patient may be greatly confused with disorientation for time and place. Speech becomes incoherent. Attention is fleeting and impressions are retained only a moment.

On physical examination, the conjunctivae and face are usually congested. The pupils are dilated and react slowly. A coarse tremor is constantly present. The tongue and facial muscles are tremulous in well developed cases. The pulse is rapid, but usually irregular and weak. The temperature is elevated. The tendon reflexes are usually increased, although they may be absent in cases of neuropathy. Epileptiform seizures may occur.

In the laboratory the physiological disturbances may be varied and consist of one or more of the following syndromes: (a) dehydration; (b) low serum magnesium; (c) low salt syndrome (Decreased serum sodium and chloride).[37]

(2) Acute hallucinosis-Presence of auditory hallucinations and a relatively clear sensorium in

association with the withdrawal of alcohol.

As in the case of delirium tremens acute hallucinosis developes only after prolonged drinking and excessive use of alcohol. This reaction presents as auditory hallucinosis occuring in a clear sensorium accompanied effectively by a marked fear. In most of the cases the hallucinations are accusatory or threatening or both. Olfactory hallucinations are not infrequently associated. Illusions of sight are not uncommon. Visual hallucinations may be intermingled to a slight extent but are rarely present in a typical case.

The patient's idealationnal content and his behavior are determines by his acceptance of the hallucinations as reality. Ideas of reference and misinterpretation are common. A delusional system is rapidly acquired. In contrast to delirium tremens consciousness remains clear and the patient remains oriented. Also in contrast to delirium tremens, after recovery there is no amnesia.

(3) Tremulous states- This is the toxic states associated with withdrawal from alcohol, manefested by psychomotor agitation, confusion, and clouding of sensorium (disorientation), without demonstratable auditory or visual hallucinations.

FLUID AND ELECTROLYTES REPLACEMENT

One of the most consistent and serious findings in the chronic alcoholic is dehydration. Marked individual

variation in the amount of alcohol consumed and the duration of the bout accounts for the variation in the degree of dehydration. Alcohol acts like a diuretic causing a dehydration without the loss of electrolytes. This is similar to the diuresis caused by the consuming of large amounts of water. The alcohol acts to inhibit the effects of ADH on tubular reabsorbtion of water. The effects of alcohol last up to six hours, and it is a moderately potent diuretic.

In Krystal's[37] series, forty percent of his patients developed the symtoms of gastritis before admission and had a food intake limited to alcohol, and water, for two to three weeks. Typically the patient lost his appetite, and for a variable period of time before admission suffered vomiting and other symtoms of gastritis. This contributes to the loss of water as well as the loss of electrolytes. The vasodilation manefest in congestion and facial flushing, and accompanying profuse sweating further contributing to water and electrolyte loss.

Electrolyte losses consist of Na Cl and Mg. With gastritis, vomiting, and poor food intake, sodium deficiency is marked particularly in hot weather. Flink[20, 21] and Suter and Kingman (11)[48] showed that in alcoholics with delirium tremens, there is a very high incidence of magnesium deficiency. Krystal attributes

this to gastritis in the chronic alcoholic.[37]

It must be stressed that the alcoholic who comes in sobered up is in acute starvation. There has been little nourishment other than alcohol for several weeks. The rather slow weight loss is not apparent to the examiner unless his former weight was known and the patient was re-weighed on admission. Binge drinkers lose a remarkable amount of weight in one week. The appetite has usually been poor, and he has suffered various digestive complaints: diarrhea, gastritis, and stools may show undigested food.

During and immediately after a drinking bout, the ability of the body to use stored and endogenous food is curtailed.[46] This suggests that alcohol suppressed the rate of synthesis of ATP. Fasting decreases the synthesis of ATP, but fasting plus alcohol was found to decrease the ATP even further.

It cannot be stressed greatly enough the importance of immediate administration of fluid, electrolytes, glucose, and vitamins to the acute alcoholic patient. Hydration and glucose administration in itself when administered rapidly, partially relieves the symtoms of withdrawal.[23]

With the advent of the tranquilizers, it has become quite feasible to use the oral route for hydration.

Only one patient in a hundred cases studied by Schultz[37] required intravenous fluids. Generally the patient should receive large amounts of dextrose. This may be given in the form of frequent large amounts of orange juice or as intravenous administration of 100 ml. of 50% glucose repeated, if necessary, every three hours. Unless the patient is suffering from cardiac failure or there is some other medical contraindication, the patient should receive 3000-4000 ml. of fluids a day. Orange juice is by far the most desirable form of liquid, since it controls acidity, supplies certain minerals and Vitamin C, and perhaps helps to prevent or overcome infection.

The administration of Na Cl is advisable both to combat loss from sweat, vomiting, etc. and to increase the alkalai reserve. Capsules containing sodium chloride should be administered every four hours.

Along with encouragement of fluids and solids if tolerated, Berocca C 500 in a dose of 4 cc. daily, for four days is given parenterally. This is advisable to prevent complication of Vitamin B deficiency such as: Wernicke's syndrome, Korsakoff's psychosis, or encephalopathy of nicotinic acid deficiency. If solids are tolerated, they should be rich in carbohydrates and contain 3000 to 4000 Calories a day.

Finally we must consider the use of magnesium therapeutically. As was stated in the foregoing this ion deficiency is frequently associated with alcoholism. The similarity between the syndrome of magnesium deficiency and that of delirium tremens would probably justify the use of magnesium in therapy in most cases of delirium tremens.[49] In addition, benefit may be derived from its pharmocologic properties providing sedation and anti-convulsive activity. When used to replace a deficiency, Flink has suggested using eight mgm. magnesium sulfate intramuscularly daily in divided doses for the first three days, then continuing 4 gms. daily for two to four days in severe cases.[48]

THE USE OF TRANQUILIZING DRUGS

In treating symtoms such as excitability, restlessness, nausea, vomiting, and hyperactivity measures are necessary to control the patient and enable the above treatment to continue. It is of great importance that care must be taken to conserve the strength of a patient suffering from withdrawal symtoms. The patient should be placed in bed immediately and should constantly be supervised. Many a patient has died from exhaustion while struggling under mechanical restraint or from the depressive effects of the sedative drugs. Restraint should therefore

never be employed. If restraints are necessary, the medication dosage is not aggressive enough! This is the keynote to treating the alcoholic. Now the various types of tranquilizers and sedatives will be considered separately:

Chlordiazepoxide. Librium (chlordiazepoxide hydrochloride) is one of the more widely used medicants in the treatment of tension and anxiety caused by a variety of conditions. In the treatment of alcoholic withdrawal it has won its widest acceptance. Extensive studies suggest it exerts its influence on the limbic system of the brain. Animal studies of the drug have shown a "taming" active with elimination of aggressive and fearful responses. These responses are produced without excessive sedation. Several authors [1,4,5,10,14] report effective reduction of the agitation common to alcohol withdrawal states. Parenteral chlordiazepoxide is usually begun at a dose of 80-100 mgm. and followed by repeated oral dosages up to 300 mgm. per day. When the agitation becomes reduced, a maintenance dose of 25 to 50 mg. three times a day may be used.

D'Agostino and Schultz[14] reported on the use of chlordiazepoxide in three hundred patients with agitated alcoholic states. They found that in acute

alcohol intoxication there was significant alleviation of aggression and agitation and a calming action leading to light sleep. They reported the complete clearing of hallucinations in acute alcoholic hallucinosis within five minutes of the administration of 100 mgm. of the drug. It was also found that an additional 500 mgm. of the drug was necessary to eliminate the gross, generalized tremors when they were present as the sole manifestation of alcoholic withdrawal. A repeated 100 mgm. dosage was necessary to control convulsions. Chlordiazepoxide produces more muscle relaxant effect than these other preparations, as well as less hypotension and less drowsiness.[38]

The physician should avoid using Librium in combination with potentiating compounds such as MAO inhibitors and the phenothiazine group; in elderly people minimal doses are best used for maintenance, and other drug combinations - noted later- should be used. Precaution should be used in any patient with suicidal tendencies.

Although the evidence of toxic effects is limited,[4] syncope, drowsiness, atoxia, and confusion have been reported.[6] Skin eruptions, idiopathic jaundice, and extrapyramidal symtoms and nausea are

associated with the use of Librium. It is advisable to procure liver function tests and blood tests when chlordiazepoxide is used as a medication for a prolonged period of time. Most of the adverse effects can be controlled by reducing the dosages or elimination of the drug.

Propyldimethylamino subroup of phenothiazines. For this group we shall use chlorpromazine as an example, although promazine (Sparine) is a comparative drug. The chlorpromazine group of drugs affected some revolutionary care for the alcoholic. They provided for the chronically hospitalized mental patient. The ability of Thorazine to relieve tension and anxiety without causing mental fogging or drowsiness is well known.[4, 7, 12, 41, 45] This calming or tranquilizing effect led to a host of derivatives commonly labeled "tranquilizers", but chlorpromazine remains the most effective, and the most toxic. The sense of comfort that permits sleep in the acutely intoxicated patient is enhanced by the lessening of nausea and the ability to eat much earlier. Anxiety is allayed, psychomotor agitation is lessened, and a more easily managable patient is usual.

Chlorpromazine may be administered in varying

doses dependent on the severity of presenting symtoms, the state of alcoholic withdrawal, and the complicating factors. It can be administered intramusclarly or orally in dosages ranging from 25 mg. to 100 mg. every three hours, while other clinicians use 100 mgm. to 200 mgm. dosage by mouth every three hours until agitation or confusion is eliminated or until the patient passes into sleep. For those patients who may be disoriented, confused, combative, or suffering severe alcoholic gastritis, 50 mg. (I.M.) every three hours may be indicated.

Side effects of the phenothiazine group are well known; hypotensive responses, jaundice, dermatitis, agranulocytosis, dryness of the mouth, constipation, and extrapyramidal symtoms. The appearance of jaundice and agranulocytosis calls for the immediate cessation of the use of the drug. Again with the use of prolonged and high dosages the patients should be followed by liver function tests and blood counts. Dermatologic manefestations can usually be counter-acted by the administration of an anti-histaminic drug such as Benedryl, 50 mg. three times a day. Extrapyramidal symtoms can be controlled by reducing the dosage and adding anti-Parkinsonian medication such as benztropine methanesulfonate, 2 mg. to 6 mgm. daily,

without impairment of theraputic efficacy. Reduction of dosage and bed rest will usually control the hypotensive and other side effects of chlorpromazine. Here again the potentation of depression must be born in the mind.

The potentiating pharmocological action of chlorpromazine has led to the extensive use of this medication along with paraldehyde. Paraldehyde, in dosage of 12 ml. for the first dose, gradually reduced by 4 ml. every six hours may be employed in combination with 25-50 mg. of chlorpromazine ever four hours. The combination results in a synergistic action of great benefit to the patient. Sleep and calming effect is introduced and easily with less need for protracted hospital stay. Because of the reduced dosages of each, the tendency to overmedicate is avoided and the best of both pharmacological worlds results. Side effects are negligible and the potential for habituation reduced with delineated medication schedule set early.[9]

Evaluation of the results of chlorpromazine have been for the most part favorable. The trend now is to test more recent drugs and their effectiveness in the treatment of alcohol withdrawal

against chlorpromazine. One such study by Ban and his group[4] compared chlorpromazine with chlordiazepoxide in their relative effectiveness in preventing and treating alcohol withdrawal. While both drugs were beneficial, it was concluded that chlorpromazine is "more rapid and less erratic than that of chlordiazepoxide."

Paraldehyde

Another drug that enjoyed wide popularity for years is paraldehyde. It has long been a treatment for acute alcoholism. Doses vary from 5-25 cc. orally or 10 to 15 cc. intramuscularly depending on the size of the patient. When giving this drug intramuscularly, great care must be taken that the drug is administered deeply into the muscle, since superficial deposits of the drug will result in necrosis of the tissue.

The drug is largely metabolized in the body; probably to acetaldehyde, then to acetic acid, a path way that resembles that taken by alcohol.[26] Thus for years clinciions have probably been giving the equivilent of alcohol for treatment. Also the withdrawal symtoms for paraldehyde closely resemble delirium tremens.

The toxicity of paraldenhyde is extremely variable and liver damage may be responsible for the fatalities that have occurred after rectal administration of 12 to 24 ml. of the drug.

The main disabilities of the drug are the similarity of its metabolism to that of alcohol, the disagreeable oder, the increased susceptability of the patients to liver disease. Due to its metabolism the drug should not be used in a patient who is using disulfram (antabuse).

Even though alcohol is potentially effective in therapy, there are arguments against its use.[28] Alcohol's duration of action is relatively short, and the margin of safety between the toxic cumulative does on the one hand and doses sufficient for maintaining a steady blood level on the other hand, appears to be quite narrow. This drug produces calories devoid of nutrition and may even enhance fatty metamorphosis in the liver.[38] These factors tend to make its use in the treatment of withdrawal difficult and rather hazardous. In addition, the necessity for its use is lessened with the other preferred drugs mentioned above that are available.

Barbiturates too have been employed, but here too

there appears to be a partial equivalence with alcohol.[33] With barbiturates there is also a chance of becoming an addict, so that their use is discouraged. The habituating properties of these drugs often lead the addictive alcoholic to switch to barbiturates for relief. The habit forming property will sometimes render the alcoholic a much more complex problem than he was before the beginning of such drugs.

Where sleep is essential and the desired hypnosis not produced by the above drugs slutethamide in doses of .5 gm. or 1 gm. will often produce the desired effect. These are supposedly less habit forming and have no drug "hang over", and few toxic effects. Ethchlovynal, (Placidyl), and methyprylon, (Nodular) produce similar effects.

Chloral hydrate is another old favorite. It has a good sedative and hypnotic effect, but also may be habituating. The advantage of this drug is that it renders the patient sleepy and drowsy.

Until recently the literature contained no studies which evaluates the comparative efficacy of paraldehyde with chloral hydrate, chlordiazepoxide, the phenothiazines, and alcohol in the treatment of withdrawal symtoms, and because of this there has been much confusion as to which

is the drug of choice. In a study by Goldbert[25] these drugs were compared. With each of the drugs, the dosage was taken to the maximum necessary to releave the symtom, ie: agitation, insominia, confusion, etc. Alcohol is given to a maximum dosage of equivalent to 600 cc. of 100% alcohol and when improvement occurred, the alcohol is gradually withdrawn during not less than five days. Chlordiazepoxide is given to the maximum total dose of 3.2 gm. in 24 hours. Promazine is given to a maximum dose of 3.6 gm. in 24 hours. With combined paraldehyde and chloral hydrate the dose of paraldehyde is increased to a maximum of 10 cc. every two hours and one gram of chloral hydrate every four hours until restraints could be removed. They condluded that paraldehyde and chloral hydrate in combination were therapeutically more effective and better tolerated than any of the other drugs studied in the treatment of all three of the classic withdrawal syndromes. Promazine was ineffective and showed serious complications. Chlordiazepoxide showed equally poor results. Alcohol neither prevented or cured alcohol withdrawal syndromes. Promazine failures

in the study were effectively reversed by paraldehyde and chloral hydrate."

ALCOHOL INDUCED HYPOGLYCEMIA

Prior to 1964 there were over 100 cases of alcohol induced hypoglycemia in the literature.[30] With more widespread recognition of alcohol induced hypoglycemia as an entity, this may emerge as one of the most common types of hypoglycemia in man.

Many attempts have been made to study the mechanism in this process.[19,22,39] In the fasting state glucose inhibits release of glucose from the liver by inhibiting glycogenesis and gluconeogenesis. It vitro studies show that glucose in concentrations comparable to those in a man moderately intoxicated inhibit formation of glucose from pyruvate and alanine by the liver. The incorporation of fructose into glycogen is also impaired. Studies also imply that alcohol interferes with the hexose monophosphate shunt and the production of urea from amino acids. Thus it appears that alcohol inhibits enzymes in the liver concerned with glycogenesis, gluconeogenesis, and deamination of urea, the conversion of galactose to glucose, hexose, monophosphate shunt.

It has been suggested that all the metabolic effects of alcohol stem from excessive production of NADH by the catalytic oxidation of alcohol by alcohol dehydrogenase which is present in high concentration in the liver but

not in other tissues NAD serves as a coenzyme in conversion of UDP galactose to UDP glucose. NADH inhibits this reaction explaining the inhibition of galactose metabolism by alcohol.[31]

Experimental work in man[19,39] has shown that 50-100 gm. of alcohol regularly produces hypoglycemia in healthy volunteers fasted 3 days. This is not the case in well fed humans indicating that preformed hepatic glucose is available for release into the blood. In contrast of seven patients with alcohol induced hypoglycemia developed hypoglycemia spontaneously after an overnight fast.

Clinically the patient is usually comatose when first seen and the diagnosis of hypoglycemia must be made by physical and laboratory findings. The patient does not have to be a chronic alcoholic. The hypoglycemia usually developes six to thirty-six hours after the ingestion of alcohol in moderately to large amounts. The blood glucose is generally below 30 mgm. percent and the blood alcohol concentration usually under 100 mgm. percent. In acute intoxication the concentration may be much higher.

The skin is usually diaphoretic, the pulse rapid, and the temperature subnormal. Signs of liver damage are only occasionally present, and the liver function test may reveal only a moderate elevation of the serum glutamic oxaloacetate transaminase in the chronic

alcoholic.

Differentiation from other types of hypoglycemia may be difficult or impossible. If the patient with alcohol induced hypoglycemia has fasted for 72 hours, even weeks after an acute episode, the blood glucose may go below 40 mgm. percent.[22] This is a greater fall than in normal age matched subjects. Some degree of hypoglycemic unresponsiveness during an intravenous tolerance is common. Induction of hypoglycemia and associated symtoms by moderate doses alcohol after an overnight fast is almost pathognomomic, but does not occur in every subject.

Treatment is by restoring the blood glucose levels to normal by intravenous glucose as rapidly as possible. If this fails to produce immediate response, it is justifiable to employ intravenous hydrocortisone and constant glucose infusion until a response is obtained. Recovery may be delayed many hours or many days.[40] Despite vigorous treatment death may occur.[13,42]

The case at which hypoglycemia can be provoked in these patients[22] would suggest that the patients should completely abstain from any alcohol ingestion.

GLANDULAR AND HORMONAL PRODUCTS

The alcoholic patients is often found to have a degree of thyroid dysfunction. Wheresuch a condition is suspected it is recommended that the radioactive uptake be performed.[24] Whether the thyroid dysfunction is caused by excessive alcohol consumption, or primary thyroid dysfunction contributed to the alcoholism has not yet been proven by study. Goldberg undertook such a study to determine which was the etiology and concluded only that there was a high incidence of hypothydoidism amoung true chronic alcoholics and this deserves attention in their overall treatment. Treatment serves to correct a debilitative complication, but should not be expected to correct his underlying disease state: his abnormal craving for alcohol.

It has also been postulated that of triiodothyronine might be used in the treatment of acute and chronic alcoholism as a means of sobering us acutely intoxicated patients rapidly with the minimum of withdrawal symtoms. Kalant,[35] in a double blind study has shown this to be a fallacy and no observable effect of treatment with

tri-iodothyronine could be detected.

The use of adrenal corticoids has also been suggested in the treatment of alcohol withdrawal. That belief that corticotrophin is of benefit has been supported by Smith[47] who postulated pituitary adrenal insufficiency in these syndromes. This is based on the resemblance of alcohol withdrawal to an Addisonian crisis. No adequate studies have been performed to bear out the efficacy of using corticoids or corticotrophin in alcoholism. In the delirious patient, the plasma or hydroxycorticoid levels are characteristically increased,[36] thus it seems very unlikely that there is total adrenal insufficiency. In alcoholics with primary liver disease, there is a decrease in the urinary 17 hydroxycorticoids, probably due to impaired conjugating ability. But their plasma steroid levels are nornal in the resting state and in response to ACTH stimulation.[8, 47]

Nevertheless patients who undergo post-mortem for death due to delirium tremens show lipid depletion of the adrenals. Clinically they appear to have undergone an extreme stress, and in many

cases have become hypotensive prior to their death.[50] Since lab studies were done on only those patients surviving the crisis, one might wonder whether they had undergone an absolute or a relative adrenal insufficiency in the fatal cause. Also steroid administration might exert a non-specific effect on their toxicity. Hyperthermia in the absence of infection in these patients shows a particularly high mortality.[50] Here in this limited situation the empirical use of adrenal cortical steroids might be suggested.

OTHER MEDICATIONS

Diphenylhydantoin (Dilantin) alone or combined with phenobarbital should be employed prophylactically where there is a history of epilepsy and "alcolepsy" (the term used by Chambers[11] for the grand mal seizures seen in alcohol withdrawal). Dilantin is in an initial dose of 250 mgm. intramuscularly, followed by 100 mgm. four times a day, orally, on the first day together with, 32 mg. of phenobarbital four times a day.[11] These doses are gradually decreased as the patient recovers from his toxic state. During a convulsion if necessary thiopental sodium or mephenesin may be given intravenously. Before discontinuing the medications it would be of value to have an electro-

encephotogram taken in an attempt to differentiate "alcolepsy" from true epilepsy which would require further treatment.

DETERRENT DRUGS

No discussion of alcohol withdrawal and preparation of the patient for complete rehabilitation is complete without a discussion of drugs to deter drinking. Much hope has been raised by their presence for those who wish to find a simple answer to the complex problem of alcoholism. To these people the results of their use has been disappointing. When they are placed in their proper perspective they become a valuable adjunct to the total treatment program.

Disulfiram. In 1948 the Danish workers Hald, Jacobsen, and Larsen,[28] in the course of their work noted an intolerance to alcoholic beverages after the ingestion of the drug tetraethyl-thiuram, disulfide-which is the best known in this country by its trade name, Antabuse, but preferably referred to as disulfiram. This substance is relatively inert in the body under ordinary circumstances, but when alcohol is ingested it interferes with its metabolism. It would appear disulfiram interferes with

the second stage of alcohol through inhibitions of oxidative enzymes.[27] The acetaldehyde accumulates and reaches levels possibly five to ten times levels with the normal metabolism of alcohol. There is also evidence that Antabuse alters the pattern of vascular reaction to acetaldehyde.[18,43]

Moments after the ingestion of alcohol the patient who has taken disulfiram undergoes a toxic reaction. A rapidly deepening, ever-spreading lobster red color develops from the head downwards. The intense redness is accompanied by a sensation of heat and a gradually increasing pounding headache. The headache is accompanied by feelings of constriction in the neck and an irritation in the throat, trachea, resulting in spasms of coughing. All of these unpleasant happenings are accompanied by a steep rise in the blood pressure for about thirty minutes to a point of maximum intensity. Then there is a rapid fall in the blood pressure, the onset of nausea, and the replacement of the redness with pallor. If enough alcohol has been taken, the nausea turns into vomiting. Breathing is difficult and gasping, precordial pain simulating a coronary attack is present; a sense of uneasiness and fear of dying

develops. After the severe discomfort has gone on two to four hours, the patient falls asleep, ending the discomfort that was caused by the reaction. Other symtoms that have been reported are: dizziness, head pressure, blurred vision, air hunger, palpitations, numbness of the hands and feet, and insomnia.

When the drug first was introduced, it was thought a single "reaction" from the drug would certainly "cure" the alcoholic of his desire to drink. Patient after patient was hospitalized, begun on disulfiram and given a half ounce of whiskey. In time and after several deaths[32] from cardiac and respiratory failure, it was deemed unnecessary and cruel to the patients. Consequently now the physician only explains the consequences to the patient imbibing alcohol. It has also been suggested that the patient have a thorough physical examination and electrocardiogram before being placed on the drug due to the dire consequences of severe reaction.

When a patient has accidently or purposefully undergone a "reaction", treatment should be instituted by placing the patient in the shock position and providing generous amount of ascorbic

acid introvenously. To the unconscious patient, intramuscular caffeine and sodium benzoate will be beneficial. Dextrose and saline should be infused to maintain electrolyte balance. Oxygen and plasma may be used where necessary. The most useful drug in an uncomplicated reaction is chlorpromazine in a dose of 50 to 100 mgm. intramuscularly. The calming restful sleep which it induces produced a refreshed patient on awakening.[9]

Side effects of disulfiram alone have been miminal. Some complain of fatigue or a mild impotence. Others may develop a mild dermatitis, malaise, headache, or gastric distress, and a few have a characteristic "garlic odor" on the breath.

Some therapists caution against the patient with incipient psychosis, severe cornorary disorder, cirrhosis of the liver, kidney disease, diabetes, pregnancy, asthma, and epilepsy, although most practitioners are confident that the drug can be used in these patients with caution.[9]

The administration of disulfiram is relatively easy. One 500 mgm. daily upon rising for five days,

twenty four hours after the first drink, and then half a tablet (250 mgm.) daily is used for a maintenance dose. Some therapists may maintain the patient on 125 mgm., one-fourth tablet. Patients who discontinue their disulfiram should be advised to wait at least four days and preferrably a week before resuming their alcohol.

Calcium carbimide: With the deterrent effects of disulfiram in mind it was pertinent to seek out other drugs with comparable effects, but more acceptable to the patient and more reliable in its action. Ferguson[17] explored some of the other substances known to demonstrate a similar reaction, interfering with alcohol metabolism. Among these are the carbimides, which had been used safely for a year in industry with few toxic effects other than those from combination with alcohol. Another advantage was the fact that it did not leave a bad odor on the breath, as did disulfiram.

The syndrome caused by the consumption of alcohol after taking carbimide was called "mal rouge". It is characterized by intense flushing of the face and neck and often the whole body, accompanied by a rapid pulse,a pounding heart, a rapid respiration.

At this stage acetaldehyde can usually be tasted by the patient. Nausea and vomiting sometimes follows and in more severe reactions a precipitous fall in blood pressure may occur, particularly if the patient attempts to sit up or stand. The severity of the reaction depends on the amount of carbimide in the system and the amount of alcohol taken. The "reactions" usually subside within a few hours and the patient feels none the worse in twenty four hours. The action of the drug is thought to be similar to disulfiram; ie. interfering with the second stage of alcohol metabolism.[6, 2]

Citrated calcium-carbimide was found to be the most suitable form of the drug. Its slow release form was found to show few of the side effects from rapid absorption experiences with other preparations.[3] Each tablet contains 50 mgm. of calcium carbimide one was marketed under the name Temposil. A single dose of 50-100 mgm. of carbimide was sufficient to sensitize a patient with a few hours. The action lasted one day and at the most two days after the last dose had been taken. Side effects are practically nil.[15]

Comparing the use of the two drugs the following observations were made:[3]

(1) "Reactions" occur with CCC after a few hours while seven to ten days is necessary for disulfiram to act.

(2) Similarly CCC sensitivity is lost more rapidly compared to disulfiram. Therefore the danger of delayed reaction after discontinuance of the drug is less.

(3) There appears to be a general impression that CCC reactions are less severe, and a somewhat larger percentage have no reactions than with disulfiram.

(4) The side effects, particularly drowsiness, is less with CCC.

Metramidazole. The mass media has raised recent hope about metramidazole (Flagyl) as a drug to keep the alcoholic patient from alcohol. Its proponents say that it produces a mild disulfiram like reaction with alcohol, but its main effect is to produce a rapid aversion to alcohol, a decreased tolerance effect, and a reduced compulsion to ingest alcohol. The pharmacologic basis of these effects is unknown. All information

in writing at this time is based upon uncontrolled observations of clinical findings.[50] No serious toxic effects have been reported to date and even its enthusiastic proponents stress that "the degree of motivation present or induced by the therapist in continuing to take medication as prescribed is, of course, a major factor in the success or failure of management of the alcoholic." To date the use of this drug is only in the investigative stage.

Again it must be emphasized that these drugs do not operate through their specific pharmcological function, but rather have value because of the patient's awareness of the nature of the pharmatological action. Hence, the usefulness of the drugs in controling alcoholic illness lies within the patient's grasp at any time. He can continue the drug and remove its protection at any time. There must be motivation on the part of the patient to take the drug. The general usefulness of deterrents are not as a "cure" but as a valuable ancillary to the total program of rehabilitation.

SUMMARY

This paper has been undertaken to outline a general program of medical treatment of the acute withdrawal symdromes of alcohol and with recovery fromthe acute stage the use of deterrents in the preparation of the patient for rehabilitation. In treating the alcoholic, the cooperation of the patient is perhaps the single greatest factor in addition to the understanding and patience of the attending physician, and proper medical treatment is a strong initial step in gaining this cooperation. Initial rapport gained through concern with the patient's physical ills is the valuable asset which may be carried on into his further treatment and attempted rehabilitation.

With the advent of tranquilizers the treatment of the acute phase has been greatly simplified. With the use of deterrents the patient can remain without alcohol sufficiently long enough for an interested physician to help him gain further insight into his problems. Helping to give the alcoholic a healthy body will in itself make him feel better and more able to face his problems induced by his illness.

BIBLIOGRAPHY

1. Armour, P. S.: Management of acute alcoholic and barbiturate withdrawal states, West. Med. 4: 369. 1963.

2. Armstrong, J.D. and Kerr, H.T. Canad., Med: A.J. 74: 795, 1956.

3. Armstrong, J.D.: The protective drugs in the treatment of alcoholism, Canad., Med: A.J. 77: 228, 1957.

4. Ban, T.A. et al.: Comparative study of chlorpromazine and chlordiazepoxide in the preventionand treatment of alcoholic withdrawal symtoms, Clinic, Med. 72: 59, 1965.

5. Barvody, et al.: Management of alcoholic withdrawal, J. South Car., Med. 58: 439, 1962.

6. Bell, R. G.: Canad. M.A.J., 74: 797, 1956.

7. Block, M.A.: Medical treatment of alcoholism, New York State M.J., 58: 2813, 1958.

8. Brown, H.: Corticosteroid metabolism in liver disease, A.M.A. Arch. Int., Med: 107: 773, 1961.

9. Chafetz. M: Drugs in the treatment of alcoholism., Med: Cl. N.A. 51, No. 5: 1249, 1967.

10. Chambers, J. F., and J. D. Schultz: Double blind study of three drugs in the treatment of acute alcoholic states, Quart. J. Stud. Alcohol, 26: 10, 1965.

11. Chambers, J.F. et al.: Comprehensive care of the acute alcoholic in a municipal hospital, Canad. Med: Ass. J. 86: 1112, 1962.

12. Cummings, J. F., et al.: Use of chlorpromaxine in alcoholics, Amer. J.M. Sc., 227: 561, 1954.

13. Cummins, L.H.: Hypoglycemia and convulsions in children following alcoholic ingestion, J. Pediat. 58, 23, 1961.

14. D'Agostina, A. and J.D. Schultz: Clinical experience with chlordiazepoxide in acute alcoholism, Psychosomatic 2: 1, 1961.

15. Di Palma, J.R.: Drills pharmocology in medicine, 3 ed. New York, McGraw Hill Co., 1965, p. 225.

16. Fact Sheet 17 of the American Phychiatric Association and the National Association of Mental Health, April, 1962.

17. Ferguson, J.K.: Canad. M.A. J. 74: 793, 1956.

18. Ferguson, J.K.; et al: J. Pharmacol. et., Exper. Therap. 113: 20, 1955.

19. Field, J. P.,Williams H.E.,& Mortimore, G.E.: Studies on the mechanism of ethanol-induced hypoglycemia, J. Clin. Invest. 42, 497, 1963.

20. Flink, E. B.: J.A.M.A. 160: 1407, 1956.

21. Flink, E.B., et al.: Journal of Lab. & clin. Med. 43: 169, 1954.

22. Freinkel, N., Singer, D.L., arky, R.A., Bleicher, S.J., Anderson, J.B., and Silbert, C.K.: Alcohol hypoglycemia I. Carbohydrate metabolism of patients with clinical alcohol hypoglycemia and the experimental production of the syndrome with pure alcohol, J. Clin. Invest., 42, 1112, 1963.

23. Godfrey, Lincoln, et al: Treatment of acute alcoholic withdrawal syndrome, Quart. J. St. Alcohol, 19: 118, 1958.

24. Goldberg, M: Thyroid impairment of chronic alcoholism, Amer. Journ. of Psych. 119, No. 3: 255.

25. Goldbert, T.M.: Treatments of alcohol withdrawal syndromes, J.A.M.A. 201, No. 2: 99, 1967.

26. Goodman, L.S., et. al.: The pharmacological basis of therapeutics, Ed. 2, New York, The MacMillan Co., 1956.

27. Graham, W.D.: J. Pharm. & Pharmacol. 3: 160, 1951.

28. Hold, D., et.al.: Act. Pharm. et Tox. 4: 228, 1948.

29. Isbell, H., et al: An experimental study of the etiology of "Rum fits" and delirium tremens, Q.J. St. Alcohol 16: 1, 1955.

30. Isselbacher, K.J. and Greenberger, N. J.: Metabolic effects of alcohol on the liver, New Engl. J. Med. 270: 351 and 402, 1964.

31. Isselbacher, K.J. and Krane, S.M.: Studies on mechanism of inhibition of galactose oxidation by ethanol. J. Biol. Chem. 236: 2394, 1962.

32. Jacobsen, E.: Quart. J. Stud. Alcohol 13: 16, 1952.

33. Jelliffe, S. E.: Diseases of the nervous system, Philadelphia, Leo & Febiger, 1935, P. 1067.

34. Johnson, R. B.: The alcohol withdrawal syndromes, Quart. Journ. St. Alcohol, 22(Suppl.): 85, 1961.

35. Kalant, H.: Evaluation of the tri-iodolhyronine in the treatment of acute alcoholic intoxication, New Eng. J. obed. 267: 1, 1962

36. Kissin, B.et al.: Adrenal cortical function and liver disease in alcoholics, Amer. J. Med Sci. 238-344, 1959.

37. Krystal, H.: The physiological basis of the treatment of delirium tremens, Amer. Journal of Psych., 116: 137, 1959.

38. Lieber, C.S., et al.: Stimulation of hepatic fatty acid synthesis by enthanol in vitro and in vivo, J. Clin. Invest. 39: 1007, 1960.

39. Lochner, A. & Madison, L.: Quantitative role of liver and peripheral tissues in ethanol-induced hypoglycemia, Clin. Res. 11: 40, 1963.

40. Marks, V. and Med, W.E.: Alcohol-induced hypoglycaemia, Brit. J. Psychiat., 110: 228, 1964.

41. Mitchell, E.H.: Chlorpromazine in the treatment of acute alcoholism, Am. J. M. Sc., 229: 363, 1955.

42. Neame, P.B. & Joubert, S.M.: Post alcoholic hypoglycaemia and toxic hepatitis, Lancet ii: 893, 1961.

43. Noyes & Kolb: Modern Clinical Psychiatry, Saunders Co. 185, 1963.

44. Raby, K.: Quart. J. Stud. Alcohol 15: 21, 1954.

45. Sainz, A.A.: The treatment of drug and alcoholic withdrawal effects with Thorazine, Psych. Q. 3: 375, 1957.

46. Schiff, L.: Diseases of the liver, A Symposium, Lippincott, Phil., 1956, pg. 89.

47. Smith, J.J.: The treatment of acute alcoholic states with ACTH and adrenocortical hormones, Quart. J. Stud. Alcohol 11: 190, 1950.

48. Suter and Kingman, W.O.: Neurol., 5: 691, 1955.

49. Tavel, M.E.: A new look at an old snydrome: delirium tremens, Arch. of Int. Med., 109, No. 2: 129, 1962.

50. Tavel, M.E. et al: A critical analysis of mortality associated with delirium tremens, Amer. J. Med. Sc. 242: 18, 1961.

51. Tayor, J. A.: Metronidazole-a new agent in combined somatic and psychic therapy of alcoholism, Bull. Los Angeles Neurol. Soc. 29: 158, 1964.

52. What are the facts about mental illness? National Committee Against Mental Illness Inc., Washington, 1961.

53. World Health Organizations, Report on expert committee on mental health, subcommittee alcoholism. World Health Organization Tech. Report., Ser. No. 48, 1952.