LITHIUM AVERSION TREATMENTS WITH ALCOHOLICS

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by

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ABSTRACT

An extensive literature shows that animals can be trained to avoid a flavored substance if sickness follows consumption. These experiments question the use of electrical aversion treatment for alcoholics and offer a strong rationale for the less popular chemical aversion treatment. These studies also suggested the following possible improvements to the design of chemical aversion treatment: (a) Lithium may be the preferred drug with which to produce sickness. (b) The strength of the alcohol-sickness association would be increased by minimizing competing associations between alcohol flavors and eliminating interference from non-alcohol flavors. (c) The sickness should be induced after the patient begins to drink even if this results in a considerable delay between drinking and the peak of sickness. (d) Intoxication may be avoided by having patients consume a small quantity of alcohol but allowed exposure mainly through smell and taste.

In this study a treatment design incorporating the above main features received preliminary testing with 15 detoxified male alcoholics. The patients received an average of six alcohol-sickness pairings spaced at least two days apart. Clinical results indicated that single oral dosages of 1500 and 1800 mg. of lithium carbonate were necessary to produce effective aversive reactions. No signs of lithium toxicity developed and serum lithium levels showed

these dosages to be conservatively safe. Clear aversions to alcohol developed in 11 of 15 patients even though the alcohol was introduced a considerable time before sickness started. This was supported by reports of nausea and vomiting by relapsed patients and by patients who were inadvertently exposed to alcohol during treatment. The pattern of onset and duration of sickness developed by patients over treatment sessions was also indicative of conditioned sickness. The four patients who did not develop strong aversions to alcohol proved resistant to lithium sickness. A correlation of -.68 between degree of reaction to lithium and rate of excretion indicated a possibility of selecting out these poor reactors. A matched retrospective control group was drawn from 200 previous admissions and a one year follow-up will be reported separately.

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The animal study (Appendix A) completed as preliminary work towards this thesis has been published in Animal Learning and Behavior, 1973, Vol. 1, 3-4.

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INTRODUCTION

One behaviourally oriented treatment approach to alcoholism has grown directly out of the animal work of Pavlov (1927) on the conditioned reflex. The drinking of alcohol (CS) is paired with an aversion agent (UCS) in an attempt to have the patient develop a conditioned response to the alcohol similar to his unconditioned response to the aversive stimulus. It is hoped that the resultant conditioned aversion to alcohol will free the alcoholic from active craving for the drug and allow him time to adjust to life without it.

Choice of Aversive Agent

Two main aversion treatment methods can be differentiated on the basis of the agent used as the UCS or punishing stimulus.

1) Chemical Aversion: Drinking is punished by a nauseous gastrointestinal sickness induced independently by means of a drug.

2) Electrical Aversion: Drinking is punished by peripheral pain produced by electric shock.

Although many therapists in the last decade have utilized electric shock in aversion treatments for alcoholism (Blake, 1967; MacCulloch, Feldman, Orford, and MacCulloch, 1966; McCance and McCance, 1969; Volger, Lunde, and Martin, 1971) clinical reviews of aversion treatments (Rachman, 1965; Rachman and Teasdale, 1969) have shown that chemical

aversion treatments produced superior results (Lemere and Voegtlin, 1950; Thimann, 1949). Despite this, psychologists have directed little research or interest in further understanding or improving chemical aversion treatment. In fact, there appears to be a theoretical bias in favour of electric shock (Franks, 1967, 1969). According to Revusky (1973) this bias stems from the belief that close temporal contiguity between the CS and UCS was the essential component of conditioning whether electric shock or chemical sickness was used as the UCS. Since precise control over temporal parameters was not possible with chemical sickness, psychologists committed to this belief rightly concluded that electric shock, which offered control over onset, duration, and intensity, was the best agent for creating aversions to alcohol (Franks, 1967, 1969). A strong body of experimental animal studies existed which supported this rationale for the use of electric shock. These studies all utilized non-sickness unconditional stimuli and showed that CS-UCS intervals longer than a few seconds made learning impossible (Solomon and Brush, 1956). It has only been in the last ten years that strong experimental justification developed for the clinically more successful chemical aversion treatment.

The Experimental Rationale for Sickness

Animals fed a flavoured substance and made sick afterwards by means of drugs or X-irradiation will avoid that

substance on future occasions (for reviews, see Revusky and Garcia, 1970; Rozin and Kalat, 1971). This phenomenon, referred to as the "Garcia Effect", is generally produced in a single flavour-sickness pairing. A variety of flavours and odours, including alcohol, (Peacock and Watson, 1964) have been used as conditioned stimuli. Emetine (Revusky and Gorry, 1973) and apomorphine, (Garcia, Ervin, and Koelling, 1966) the drugs commonly used in aversion treatment, have been used to induce sickness.

Long Delay Learning: Flavour aversions (McLaurin, 1964; Revusky, 1968; Smith and Roll, 1967) and odour aversions (Taukulis, 1974) have been produced in animals with CS-UCS delays of up to several hours. These studies are of significance to the use of chemical sickness in that they indicate that precise control over temporal parameters is relatively unimportant for the formation of flavour aversions. Of course, in the clinical situation, a much greater degree of temporal proximity between the CS and UCS is possible. When made sick under these conditions, animals show extremely pronounced aversions with slow extinction (Garcia, Kimeldorf and Koelling, 1955).

Relevance of Sickness to Flavour Cues: In a study with direct bearing on the choice of aversive agent to be used with alcohol Garcia and Koelling (1966, 1967) pitted X-rays and drug induced sickness against electric shock. They arranged a combination stimulus referred to as "bright

noisy saccharin-tasting water" such that each time the rat licked at a tube containing saccharin flavoured water it would set off a bright light and a noisy click from a drinkometer apparatus. This allowed the audio-visual part of the stimulus cue to take on the same function as the flavour or gustatory part. In one group of rats consumption of "bright noisy saccharin-tasting water" was punished by peripheral pain produced by electric shock to the feet. In another group consumption was punished by sickness produced by exposure to X-irradiation or drug. After a number of sessions the animals were tested in a discrimination learning paradigm for acquired aversions to the separate elements of the compound stimulus cue. They found that the combination of flavour and sickness led to the subsequent formation of a strong aversion to the saccharin-flavoured water, whereas punishment of bright noisy water by sickness was ineffective. On the other hand, the combination of bright noisy water and shock led to a subsequent decrease in consumption of bright noisy water, but punishment of saccharin-flavoured water by shock was ineffective.

To account for such findings, the authors argue that natural selection would favour an "innate tendency" to associate flavours with the after-effects of ingestion and that animals would be unlikely to associate sickness with the many external stimuli to which they are continually exposed. This association tendency is usually referred to

as "relevance" (Capretta, 1961) but has also been referred to as "preparedness" (Seligman, 1970) and "belongingness" (Rozin and Kalat, 1971). Further support for the finding comes from Braveman and Capretta (1965), Dietz and Capretta (1967), Domjan and Wilson (1972,a.) and Garcia, McGown, Ervin, and Koelling (1968). The significance of this study for the choice of aversive agents to be used in the treatment of alcoholism has been pointed out by Wilson and Davidson (1969) and Revusky (1973). The relevance of chemically induced sickness to the gustatory cues of alcohol would be more important than the temporal contiguity possible with electric shock.

Generalization of Flavour Aversions: Garcia, Kovner, and Green, (1970) showed that even when rats learned to avoid a flavoured substance in the experimental chamber when drinking was punished by electric shock, the avoidance did not transfer to the home cage. On the other hand, an aversion to the flavoured substance conditioned by subsequent sickness readily transferred to other situations. Generalizing to the clinical situation this suggests that aversions to alcohol produced by subsequent sickness would not be bound to the situational stimuli in which they were produced. Because of this no special setting, such as a simulated bar, need be used to increase generalization. On the other hand, changes in situational stimuli, such as leaving the hospital setting, would be detrimental to an avoidance of alcohol

conditioned with electric shock.

Not only have animal experiments supplied a theoretical rationale for chemical aversion treatment, but their findings also suggest specific improvements as to aversive agent and procedure.

An Improved Aversive Agent: Lithium Carbonate

In the animal literature lithium is recognized as the most efficient drug for producing flavour aversions (Nachman, 1970; Nachman and Ashe, 1973). Revusky and Gorry (1973) have suggested its use in chemical aversion treatment.

Lithium in Humans: At present lithium is used in the treatment of mania and there are over a hundred published reports concerning its use and safety (for reviews see Gatozzi, 1970; Gershon, 1970; Prien, Chaffey, and Klett, 1971; Schou, 1968; Tupin, 1970).

Of primary interest in its use in aversion treatment, are the characteristic early side effects which occur shortly after lithium is ingested. These have been described by Australian investigators who themselves ingested lithium at single high doses. They established that a syndrome consisting of nausea, vomiting, vertigo, muscular weakness, and dazed feeling occurred whenever lithium levels in the blood climbed over 1.3 to 1.5 Meq/L (Trautner, Morris, Noack, and Gershon, 1955). The sickness usually ended about two hours after ingestion just as the blood level turned down from its peak. In mania these side effects are experienced regularly for the first two weeks of treat-

ment and then disappear. In his National Institute of Mental Health publication Gatozzi concludes:

> "The transient lithium-peak side effects are considered to be harmless upsets, rather than warning signs of impending toxicity. Nevertheless, the syndrome consists of some particularly bilious feelings, something like a cross between a seasickness and a hangover (Gatozzi, 1970, p. 73)."

In the treatment of mania these side effects are reduced by having a patient take his daily prescription in divided doses. In aversion treatment these side effects would be accentuated by having the patient take his daily prescription all at once as did the Australian investigators.

Effectiveness of Lithium: Revusky and Gorry (1973) compared lithium with emetine and apomorphine, the drugs used in aversion treatment. In rats, at equivalent doses, lithium produced the strongest aversions, apomorphine the weakest, and emetine was in between. These basic results were also confirmed by the authors with squirrel monkeys.

Safety of Lithium: Just as important as its superiority in producing aversions is the fact that lithium appears to be a much safer drug than emetine or apomorphine. Apomorphine is a morphine derivative, and in the U.S.A. is characterized legally as a dangerous drug. Because of its poor conditioning properties, and the severe shock reactions sometimes encountered, the Shadel Clinic switched from apomorphine to emetine (Lemere and Voegtlin, 1950). This of course is in agreement with the findings of Revusky and

Gorry. However emetine too, is a dangerous drug that has not found wide acceptance among physicians. Its long half life in the human body limits the number of treatments that can be given without exposing the patient to cumulative hepato-toxic and cardio-toxic effects (Grollman and Grollman, 1970). Although emetine has been used with success at the Shadel clinic, lithium seems to offer an even better promise of effectiveness and safety.

Though lithium has been widely used and reviewed there is no evidence to show that a patient ever died from a single acute dose of lithium. Instead, the evidence indicates that the few deaths reported were due to the chronic administration of the drug, usually without proper monitoring. For example, there were a few deaths in the forties when lithium was used unrestrictedly as a taste substitute for salt by people on low sodium diets (Gatozzi, 1970). This was before lithium was seriously studied or used medically. Platman and Fieve (1968) later showed that more lithium will be retained if sodium intake is low and that this can lead to toxic buildup. Given normal salt intake there is no interaction. Lithium is further contra-indicated for patients with kidney or cardiovascular diseases, and for pregnant women because it may affect the fetus (Gatozzi, 1970).

The dosage used in the present treatment was within the therapeutic range (1800 mg.) suggested by Schou and

Baastrup, (1967), the only change being that it was taken all at once rather than in divided dosage. In mania, lithium is given every day, but in the present aversion treatment trials it was given every second or third day. Considering that lithium has a biological half life of approximately 24 hours this should contribute towards preventing any toxic buildup (Gershon, 1968) and allow for safe and accurate monitoring of serum lithium levels. Under these conditions there is no question that lithium ought to be safer than emetine or apomorphine.

Clinical Determination of Dosage: Animal research has shown that in a single trial the higher the dosage of lithium used the stronger the resultant aversion (Revusky and Gorry, 1973). Furthermore, available information on humans (Trautner et. al., 1955) suggested that a minimum dosage of 1200 mg. to 1500 mg. would be necessary to produce a satisfactory aversive reaction. However, in view of the fact that little was known of the administration of acute doses of lithium on repeated occasions, medical safety dictated that the dosage, especially the starting dosage, should be determined by clinical experience. Thus, patients were started at either 900 mg., 1200 mg., or 1500 mg. of lithium and raised by 300 mg. steps to the limit of 1800 mg. as treatment progressed.

Improvements to Procedure

According to concurrent interference (Revusky, 1971)

there can be competition between a number of different flavours consumed prior to sickness. The more strongly any one flavour becomes associated with the sickness (as evidenced by aversion to the flavour) the more it will tend to prevent other flavours from becoming associated. Thus, in order to insure that a maximally strong alcohol-sickness association will form, other sources of interference must be ruled out or minimized.

Interference Between Alcohol Flavours: Rozin (1969) has shown with animals that flavour aversions are specific to the flavour consumed prior to sickness. This parallels the unsuccessful clinical technique of producing an aversion only to the patient's favourite alcoholic beverage (Quinn and Henbest, 1967). However the alternative of exposing the patient to every conceivable alcoholic beverage (Lemere and Voegtlin, 1950) poses a problem with interference. For example, it would be a mistake to give a patient who habitually drank only beer and wine, a novel strong tasting whiskey along with these prior to sickness . Although interference would not be complete (Kalat and Rozin, 1971), the strong aversion formed to the novel tasting whiskey would greatly attenuate the more important aversion to the beer and wine.

In the present treatment, to allow sampling of as many beverages as possible while still minimizing interference, the beverages were arranged in a manner which would facili-

tate an overall aversion. The patient's past preferences for different liquors were arranged along a continuum of novelty (least preferred) - familiarity (most preferred). Revusky (1971) has shown that the more novel the flavour, the stronger the resultant aversion. Thus, the more novel end of the continuum was introduced during the early conditioning sessions. With the patient's distaste for liquor mounting the more familiar end of the continuum was then introduced. Should the patient have finished his last drinking binge before entering hospital on a highly familiar beer, this arrangement would take advantage of McLaurin, Farley, and Scarborough's (1963) findings. They showed that the weakening of an aversion through familiarity of the flavour could be partially reversed if the familiar substance had not been consumed by the animals for a number of days. For the final two sessions of treatment the patients were exposed to the whole continuum of flavours. By this time all flavours were aversive to some degree and Garcia, Ervin, and Koelling (1966) have shown that an aversion is strengthened with each additional flavour-sickness pairing. Finally, Tapper and Halpern (1968) have found that there was less interference between similar flavours than between dissimilar flavours. This finding was utilized in any given treatment session by including somewhat similar tasting liquors together (eg. blended whiskeys and bourbons).

Interference From Non-alcohol Substances: Flavour aversion may develop to substances consumed hours before sickness is induced. Such flavoured substances as mouth-wash, toothpaste, fruit juices, and carbonated beverages inadvertently ingested or tasted within this conditioning interval may compete with the alcohol-sickness association and reduce the strength of the alcohol aversion. With animals, this conditioning interval for lithium is up to at least four hours. To be on the safe side with the present treatment, interference from these sources was avoided by administering the aversion treatment to fasting patients before breakfast.

There is one other non-alcohol source of interference worth mentioning. Clinicians have sometimes administered emetine and apomorphine in oral solutions (Williams, 1947). Others have given a sharp tasting oil-sugar of mint solution to accentuate the sickness (Stojiljkovic, 1969). This route of administration allows these non-alcohol flavours to compete with the alcohol for association with the sickness. Animal (Garcia, Mcgowan, and Green, 1972) and clinical (Voegtlin, Lemere, and Broz, 1940)evidence indicate that injection would circumvent these problems. However, although intravenous injections of lithium iodide have been tried (Rimon and Rakkolainen, 1968) it is probably not feasable to inject lithium at the dosage needed for an aversion treatment. The dosage of lithium to be injected would

require over 100 cc. of solution even if injected at a molarity three times greater than that of body fluids. In the present treatment the lithium was given in fast-dissolving gelatin capsules, whose weak flavour, it turned out, could be effectively masked by the alcohol used to wash them down.

Temporal Factors in Alcohol-Sickness Pairings: Because of the stress on temporal contiguity some therapists (Hammersley, 1957) have introduced the patients to alcohol after the start of sickness in an attempt to pair it with the vomiting, or peak of sickness. Boland, (1973, see Appendix A) has shown that this procedure would greatly attenuate an aversion to the alcohol. He found that rats who drank saccharin solution 30 min. before intubation of lithium exhibited far stronger aversions than rats who drank 30 min. after, even though for the former group there was a considerable delay between drinking and sickness. It may be estimated from a study by Robinson and Tripoli (1972) that the lithium sickness started for the rats about 20 min. after intubation. This means that the 30 min. backward conditioning group started to consume their saccharin solution about 10 min. after the start of sickness. Furthermore, since these rats had only 10 min. of access to the saccharin solution it can be inferred that they finished drinking before the peak of sickness. This indicates that giving alcohol after the start of sickness will lead to in-

ferior conditioning, even if it is withdrawn before the peak of sickness.

A final danger of pairing the alcohol with the vomiting or peak of sickness is that the alcohol might associate with alleviation of the sickness and become even more highly preferred. Green and Garcia (1971) demonstrated such an effect with rats who consumed food near the peak of sickness produced by apomorphine injection. In these animals the preference for the flavoured food increased. Clinical findings that indicate such an increase in preference can occur have been supplied by Rachman and Teasdale (1969, p. 22).

In the present treatment trials the exact moment when lithium sickness starts is relatively unimportant. The subjects will be exposed to alcohol from just before the lithium is ingested to approximately 15 min. after the noticeable start of sickness. This procedure retains any advantage of temporal contiguity with the start of sickness, and insures that no alcohol will be consumed too near its peak.

The Problem of Intoxication: Although intoxication does not prevent a flavour aversion from forming in animals (Peacock and Watson, 1964) many clinicians feel that it reduces the efficiency of conditioning (Kant, 1944). For example, with the Shadel procedure four or five ounces of alcohol were given during a treatment session and the stomach

emptied if signs of intoxication developed (Voegtlin, et. al., 1940). However, generalizations from animal studies indicate that such a procedure is unnecessary. Domjan and Wilson (1972, b.) flushed saccharin solution through the mouths of rats without allowing them to drink and then induced sickness. Although these rats still exhibited aversions, they were not as strong as aversions produced in rats who had consumed the saccharin solution. However, if the non-drinking rats consumed even a small amount of the saccharin solution they exhibited much stronger aversions.

In line with these findings, the patients in the present procedure were allowed to drink slightly more alcohol than it takes to wash down the lithium capsules (limited to about one ounce absolute alcohol). The subsequent exposure to alcohol consisted of taking a mouthful, swirling it around for a few seconds, and then spitting it out.

METHOD

Subjects

Aversion Treatment Group: The criteria for admission into this group were as follows: The patients were to be male alcohol addicts between the ages of 25-55. They were to show psycho-physiological dependence upon alcohol, defined as having exhibited a history of increased tolerance and craving for alcohol with one or more of the following symptoms: tremors, epileptic fits, or delirium tremens. After recovery from the acute withdrawal stage they were to show no evidence of brain damage or psychosis. In addition they were to be normal by the following investigations advised for manic patients starting lithium treatment: Serum creatinine, Serum electrolytes, Chest X-ray, Urine analysis, and E.K.G. Finally all subjects had to agree to the following additional conditions: (a) That they were alcohol addicts and that abstinence was a major goal of treatment. (b) That they be off medication at the time of conditioning. (c) That the technique of aversion conditioning and the experimental use of lithium for this purpose had been explained to their satisfaction. (d) That they sign statements of volunteerism with the understanding that they may withdraw at any time. (e) That they have relatives, friends, or personal physicians participate in follow-up procedures.

The subjects were 15 consecutive admissions to St. Clare's Mercy Hospital Psychiatric Unit over a six month period who

fulfilled all these criteria. Two patients fulfilled all medical criteria for inclusion but refused to agree to this method of treatment and thus were not used.

Retrospective Control Group: This study was not intended to be a full scale investigation of the effectiveness of lithium aversion treatment but rather a preliminary trial to determine if lithium could produce safe, strong aversions to alcohol in alcoholics. However, since there was considerable anecdotal evidence regarding the relatively poor results of treatment prior to this study, it was felt that some form of comparison would be useful. A double blind control was not feasable because the staff would certainly realize which patients were sick and so would the patients. Without the double blind, factors such as the novelty of treatment, the addition to ward personnel (FJB), and the additional physical investigations performed because of the use of lithium, could be expected to influence the results by contributing towards a Placebo effect. Thus, at this preliminary stage of investigation, and with limited treatment facilities available, it was felt that a matched retrospective control group, would offer a reasonable comparison.

Fifteen retrospective controls were selected from a list of 102 alcoholics admitted to the psychiatric unit over the previous two years by an independent observer who knew nothing of treatment outcome. Each was matched as close as possible with an aversion treatment subject on the basis of

age, period of drinking, years of education completed, and the Straus-Bacon Index of Social Stability (Straus and Bacon, 1951). Both groups had been hospitalized for approximately the same period of time and with the exception of aversion therapy received the following treatment: (a) Psychotherapy directed towards understanding the nature of their dependence upon alcohol and the development of less harmful modes of dealing with anxiety. (b) Information concerning Alcoholics Anonymous was supplied and patients were encouraged to join that organization.

Table 1 shows comparison data on the result of the match between the two groups. The match was generally good, however, the controls were better educated and scored generally higher on social stability. These factors are usually associated with a favourable treatment outcome.

Apparatus

Treatment was conducted in any one or two bed unit of the 24 bed psychiatric ward which happened to be available at the time. Pans for spitting out tasted liquor and adequate toilet facilities for vomiting were provided. A supply of lithium carbonate in 300 mg. gelatin capsules (Lithane) and an assortment of alcoholic beverages was kept on hand.

Procedure

Aversion Treatment: The aversion treatment was superimposed on the already existing treatment routine of the psychiatric unit. Throughout the entire treatment an effort was made to have patients understand the nature of the con-

TABLE 1

Summary Data on Aversion Treatment Sample And Matched Retrospective Controls by Age, Years of Drinking, Years of Education Completed, and the Straus-Bacon Index of Social Stability

Item	Aversion	Control
Number of subjects	15	15
Mean age	35.5	35.9
Range of ages	25-48	25-46
Mean years of drinking	18.2	18.2
Range of years drinking	9-33	9-31
Mean years of education completed	7.66	9.87
Range of years of education completed	2-10	7-11
The percentage of subjects in each category of the Straus-Bacon Index:		
1. Steady job for three preceding years	27%	33%
2. Residential immobility for two preceding years	33%	66%
3. Lives in own home or with relative or friend	87%	87%
4. Married and living with spouse	53%	87%

ditioning process and questions to this end were always answered frankly (see Appendix B). Approximately six sessions generally spaced two days apart comprised a completed treatment. The author or a male nursing assistant presided over the conditioning session. Sessions were conducted with either one, two but never more than three patients at any given time. Except for changes in lithium dosage and liquor brands as treatment progressed, each session was run as follows.

Basic Technique: The patients were seated and the necessary liquors conveniently displayed in front of them. Small drinks were administered to each patient and he was directed to take a mouthful, swirl it around, and spit it out in 30 seconds. The lithium capsules were then given and the patient used the remainder of his drink to wash them down. Fresh drinks were then administered from each of the liquors designated for that session and the patients were directed to taste, smell and occasionally drink small amounts. Exposure to alcohol was terminated approximately 15 minutes after the patient reported the start of sickness or sooner if vomiting seemed imminent. The amount of spirited alcohol actually consumed was limited to about one ounce absolute alcohol. If beer or wine was used in a particular session, there was a proportionate allowable increase in the amount consumed. The patients were directed to stay in the treatment room until all symptoms of sickness dissipated and to refrain from other beverages or foods for a further 1 hr. period.

Clinical Determination of Dosage: To insure safety, no commitment to an a priori pattern of dosage could be made. Instead dosage administration proceeded by clinical observation and judgement. The first patient initiated treatment at 900 mg. and the next eight patients started at 1200 mg. of lithium carbonate. These starting dosages did not elicit satisfactory aversive reactions and so the final six patients were started at 1500 mg. of lithium carbonate. This dosage generally provided satisfactory sickness responses.

The dosage of patients who started at 900 mg. and 1200 mg. was raised in 300 mg. steps to 1500 mg. of lithium carbonate in consecutive sessions. For these patients, as well as those who started at 1500 mg., further increases in dosage to the a priori limit of 1800 mg. of lithium carbonate were dictated by two considerations: (a) The literature on mania suggested that some habituation could be expected with dosage held constant. Thus, patients were raised to 1800 mg. of lithium carbonate if they showed a decline in intensity of reaction at the 1500 mg. level. This was usually evident by the fourth session. (b) In anticipation of this habituation effect and realizing that stronger reactions were produced at higher dosages, the last few patients treated were routinely raised to 1800 mg. of lithium carbonate at the third session.

For those patients who started treatment at the higher dosage of 1500 mg. of lithium carbonate, a further precaution was taken to identify non-excretors of lithium.

These patients were given a non-aversive test dosage of 600 mg. of lithium carbonate two days before actual treatment began and their lithium excretion was monitored.

Serum Lithium Monitoring: Blood samples were taken from patients approximately 90 minutes after ingestion of lithium as well as 24 hours later. The former coincided approximately with the serum lithium peaks in the blood. The latter offered a further safety check of the patients' capacity to excrete lithium normally, as the serum lithium levels should fall by approximately 50% in 24 hours.

Urine Lithium Excretion Tests: It was apparent from the first four patients treated that some reacted better to lithium than others. In an effort to find out why this was so, urine samples were collected from the remaining 11 patients for a period of four hours after each ingestion of lithium. This gave a measure of the rate of lithium excretion during the treatment interval.

Further Data Collected: Since this was the first time lithium had been used to produce flavour aversions in humans, data were collected on the onset and duration of symptoms of sickness experienced during treatment in an effort to further elucidate the formation of an aversion to alcohol.

Follow-up Procedure: Information was gathered by personal contact, phone, or letter from the patients themselves, from relatives, friends and personal physician. Follow-up procedures were initiated about once every month and are still in progress. Follow-up will be reported

separately from this thesis.

RESULTS

Safety of Lithium Levels

Table 2 shows the means and standard deviations in terms of milliequivalents of lithium per liter of blood (Meq/L) of the 90 min. and 24 hr. serum lithium samples for each of the dosages used during treatment. Data for the 900 mg. dosage were not included because this dosage was used only once. The mean 24 hr. serum lithium levels showed an approximately 50% drop in serum lithium levels since the peak 90 min. readings. On those occasions when three days were allowed to lapse between treatment sessions, the 48 hr. readings (not shown in Table 2) showed a similar 50% drop over the 24 hr. levels. Thus the biological half-life of lithium in this study was in the vicinity of 24 hours.

At no time during this study were signs of lithium toxicity observed. This observation is supported by a comparison of the present serum lithium levels with those generally considered safe for the treatment of mood disorders. According to Amdisen (1967), serum lithium levels can be used to monitor safe dosage provided the patients have not consumed lithium for about 14 hr. prior to serum lithium determination. At this time, the therapeutic and prophylactic serum lithium levels in patients treated for mood disorders ought to be in the vicinity of 0.6 to 1.6 Meq/L, while levels of 2.0 Meq/L are considered dangerous and to be avoided. Amdisen noted that serum lithium readings taken

TABLE 2

The Mean 90 Minute and 24 Hour Serum Lithium Levels Expressed in Terms of Milliequivalents of Lithium per Liter of Blood (Meq/L) For Each of the Dosages Used During Treatment

	90 Min. Readings			24 Hr. Readings		
Dosage	N.	Mean(Meq/L)	S.D.	N.	Mean(Meq/L)	S.D.
1200 mg.	10	0.74	0.14	9	0.21	0.10
1500 mg.	36	0.85	0.40	31	0.44	0.15
1800 mg.	48	1.05	0.38	32	0.45	0.16

two hours after ingestion peaked 3-5 times higher than the 14 hour readings, which seems greater than those in Table 2, however he felt that these peak levels were unimportant for the monitoring of safe dosage. If Amdisen's guidelines apply to the treatment of alcoholics, the dosages used in the present study were conservative. The highest 24 hour serum lithium level recorded from any patient during treatment was 0.79 Meq/L, less than 40% of the 2.0 Meq/L level considered dangerous at 14 hours by Amdisen. Indeed, even the highest recorded 90 min. level of 1.85 Meq/L fell short of this danger level. Furthermore, Table 2 shows that the average 24 hour lithium levels did not even reach the minimum 0.6 Meq/L level recommended for the treatment of mood disorders. Finally, patients in the present study had at least 48 hours to excrete lithium before a second dose was administered. Taken together, these considerations show that the dosages of lithium used in the present study were unquestionably safe. In fact, the present procedure of administering 1500-1800 mg. of lithium carbonate with at least two days between treatment sessions, seems equivalent in conservatism to giving acute manics or depressives 750-900 mg. of lithium daily for a period of a week.

Reactions to Lithium Carbonate

The patients described their reactions to lithium as being very much like the withdrawal symptoms of a hangover. They reported varying intensities of nausea, gas, and general discomfort. Often the reactions culminated in vomiting and

all patients experienced mild diarrhea at some point during treatment. Table 3 shows the scale which was used to gauge the intensity of sickness reported by patients. Reports of diarrhea were not included in this scale because diarrhea generally occured after the conditioning session.

In Figure 1 the mean intensity of reaction for a particular dosage-session combination is represented by vertical bar graphs along the intensity scale shown in Table 3. The number of patients on which a particular average intensity of reaction was based is shown above each bar graph and gives some indication of the pattern of dosage followed throughout treatment. Not all patients completed six sessions. One patient withdrew from treatment after completing four sessions. Another patient developed such a pronounced aversion after five sessions that a further session was thought unnecessary. Finally, six patients were given a seventh session in an effort to increase the strength of an aversion to a particular beverage, usually beer.

A comparison of initial first session reaction as a function of dosage showed a significant increase in intensity of reaction with increases in dosage ($F = 14.29$, df 2, 12, $p < .001$). A similar increase in the severity of aversive reaction with increasing dosage of lithium was obtained in rats by Nachman and Ashe (1973) and by Revusky and Gorry (1973).

TABLE 3

Intensity of Reaction Scale

Observation	Rating
No subjective feelings of discomfort and no observed distress.....	(0).
Moderate feelings of discomfort usually described as 'gas'. Occasional mild distress observed.....	(1).
Complaints of severe discomfort, marked nausea, gaseous upper abdominal cramps, heaving as if to vomit, mild headaches, and occasional mild tremors.....	(2).
As in a rating of (2) but culminating in vomiting.....	(3).

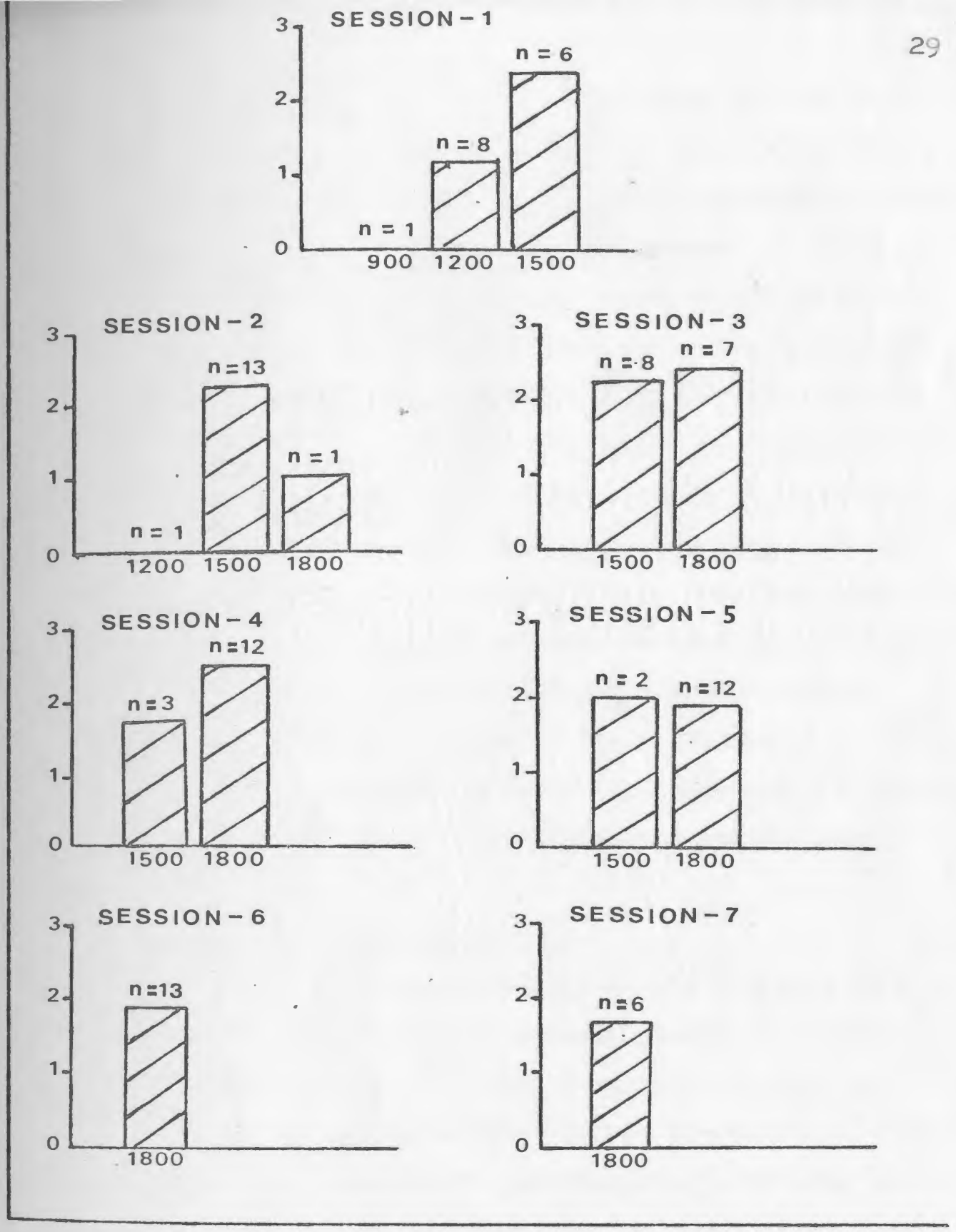

Figure 1. The average intensity of reaction as a function of Lithium Carbonate dosage (mg) is shown as vertical bar graphs for each treatment session. The number of subjects contributing to a particular average reaction is shown above each bar graph.

It was expected on the basis of reports from studies on the use of lithium in the treatment of mood disorders (Gatozzi, 1970) that the intensity of the aversive reaction would decline for a given dosage as the number of lithium treatments increased. Unfortunately we were not able to replicate this habituation effect statistically here because the treatment was partly designed to overcome the habituation effect. This resulted in increases in dosage for different patients at different times during the course of treatment. However, on an observational level, there was some evidence that this habituation effect was operative. After a number of successive sessions at 1500 mg. of lithium carbonate, the intensity of reaction typically became attenuated and then was reinstated by an increase in dosage to 1800 mg. With additional sessions at 1800 mg. of lithium carbonate, the intensity of reaction again showed some decline.

Effective and Ineffective Reactions

Figure 2 shows the distribution of the ratings of reactions by the intensity scale shown in Table 3. These results are pooled over all lithium administrations at all dosages. For the purpose of further breakdowns, ratings of (0) and (1) were considered ineffective reactions and ratings of (2) and (3) were considered effective reactions; our clinical impression was that the distinction between ratings of (1) and (2) was more meaningful than the distinctions between other points on the scale. Thus, there

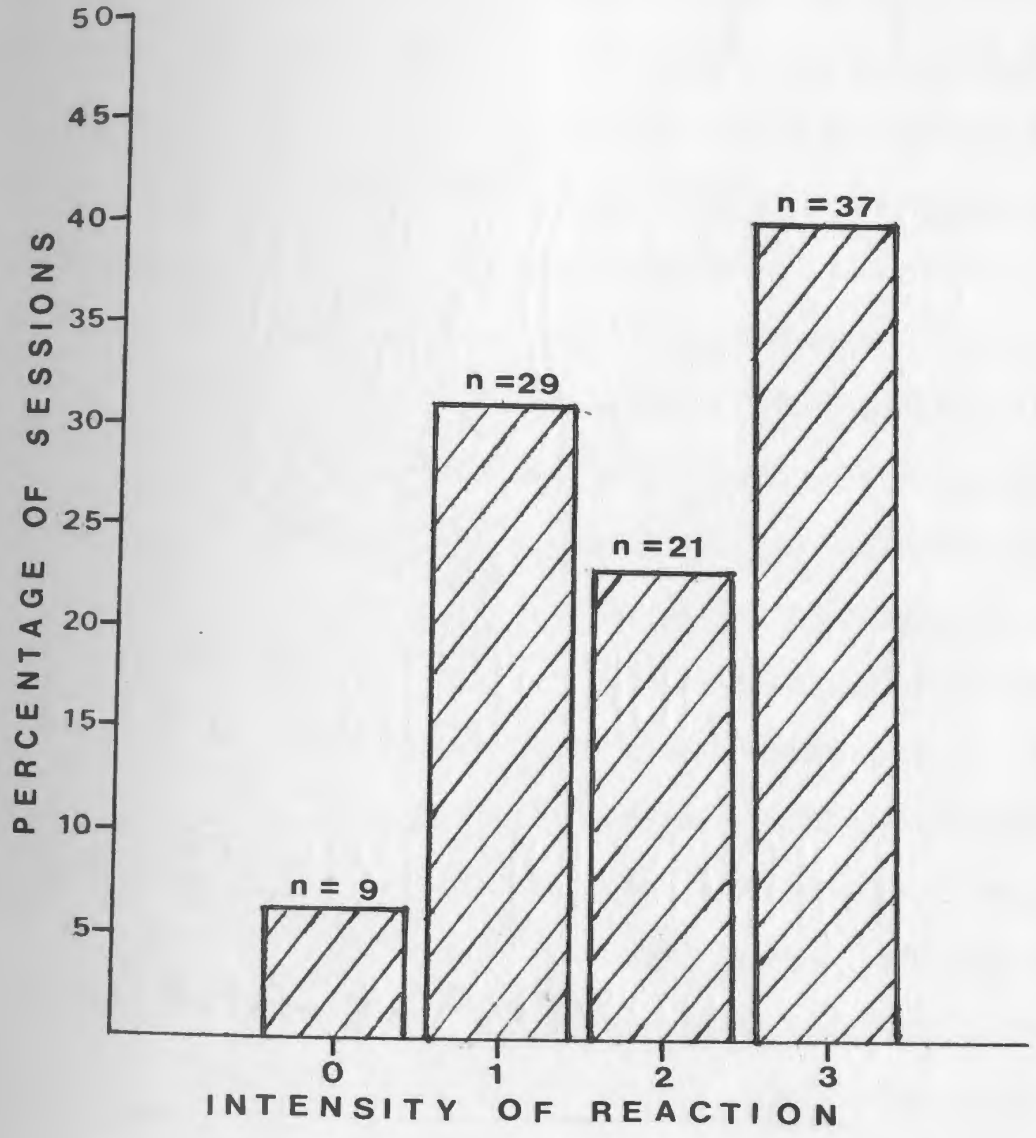

Figure 2. The percentage of sessions in which subjects reacted at a given intensity rating (Table 3).

was a total of 58 (62.4%) effective reactions and a total of 35 (37.6%) ineffective reactions. The 35 ineffective reactions can be accounted for as follows: (a) Dosages of 900 mg. and 1200 mg. were ineffective. Of ten such dosages there was only one effective reaction. (b) Four of the 15 patients seemed highly resistant to lithium sickness yielding only four effective reactions in 24 sessions. (c) The six remaining ineffective reactions not attributable to low dosage or high resistance to lithium sickness were probably a result of habituation; in each such case the ineffective dosage or a lower dosage had been effective before.

Of the 15 patients, 11 were subjected to 4 hr. urine lithium excretion tests; three of the four patients who proved resistant to lithium sickness were included. The average amount of lithium excreted in the four hours following ingestion, expressed as a percentage of the administered dose, was 9.4% for the patients resistant to lithium sickness and 5.3% for the other patients. It so happened that each of the three sickness-resistant patients excreted a higher percentage than any one of the other eight patients ($p<.01$, U-test). This finding that lithium sickness was inversely related to amount excreted was further confirmed by a rank order correlation of -0.68 between amount of lithium excreted and the mean sickness of the patient as judged by the rating scale in Table 2. This suggests that the patients resistant to lithium sickness were actually subjected to less of the toxic effect of lithium than the

other patients.

Aversions to Alcohol

Since the goal of treatment was total abstinence, it would possibly have been counter-productive for the treatment to test for conditioned sickness to alcoholic beverages by administering such beverages outside the conditioning situation. However, there was indirect evidence for conditioned sickness, even among two patients considered resistant to lithium sickness.

Observations During Treatment: After the fourth alcohol-sickness pairing, three patients were inadvertently exposed to the smell of alcohol either from an inebriated visitor or from a patient recently admitted for drying out. These patients reported nausea a few minutes after exposure and two of the three vomited within ten minutes of exposure. Several other patients reported nausea on entering a treatment room in which the smell of alcohol still lingered from a treatment administered hours earlier. A final patient reported nausea while watching a T.V. commercial for alcoholic beverages.

Reports From Known Relapses: Six patients who relapsed within five months of discharge reported repeated nausea and vomiting when drinking was initiated. One of the six reported that it took him three days of dogged drinking to break down the aversion. This group of six included two poor reactors both of whom reported nauseous aversions to spirits and wines but not to beer. Three of the six

reported that this initial reaction to drinking removed any enjoyment and to an extent motivated them in a short time to stop drinking again. Typically, the patients who relapsed began their relapses by drinking beer, which we observed to be more difficult to condition strongly.

The Pattern of Onset and Duration of Sickness: The average time from administration of lithium to the onset of symptoms was 50.7 minutes and the average duration of the symptoms was 50.2 minutes. Figure 3 gives a further breakdown of the average onset (solid line) and average duration (dotted line) of symptoms as a function of treatment sessions. It is evident that a major change occured after the fourth session; the onset of sickness occured more quickly and the duration of sickness showed a corresponding increase. However, this pattern was opposite to what would be expected from observations made on the habituation of lithium's side effects in the treatment of mood disorders and seems to be evidence that conditioned sickness developed during treatment. The rationale is as follows: Gattozzi(1970) reports that in the treatment of mood disorders the aversive side effects experienced after lithium is ingested gradually disappear within two weeks of the start of treatment. Since sickness is experienced with greatest intensity at the serum lithium peaks about 90 minutes after ingestion (Trautner, et. al., 1955) one would expect that the gradually disappearing side effects would occur in increasing proximity to these peaks.

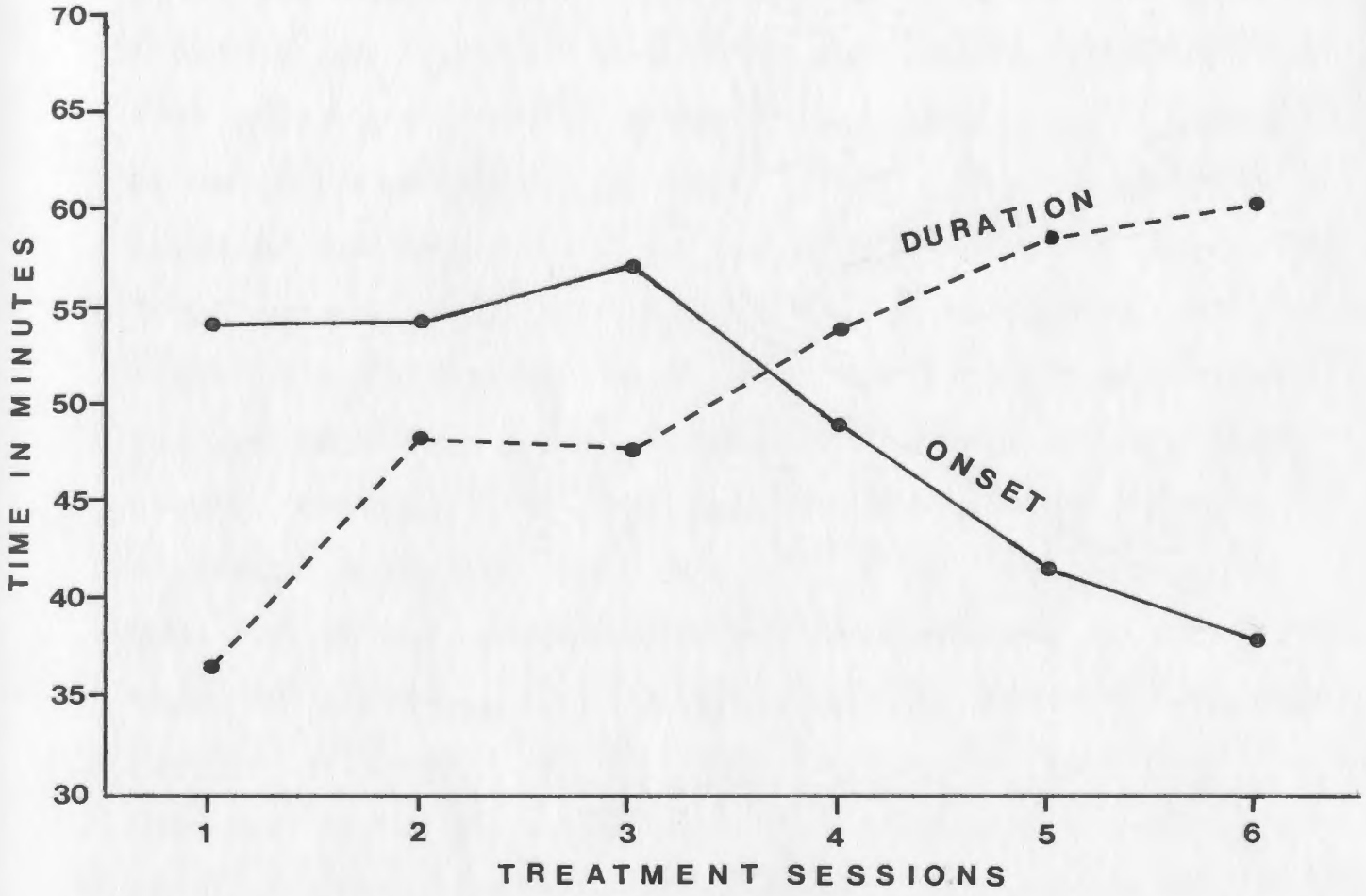

Figure 3. The average onset (solid line) and average duration (broken line) of symptoms of sickness are shown as a function of order of treatment sessions.

Thus, in the later sessions of the present treatment, if no conditioned sickness developed to the alcohol, the lithium sickness should have taken longer to develop and have been of shorter duration. That the opposite pattern was evident after the fourth session suggests that the alcohol was now eliciting its own conditioned sickness which preceded the sickness elicited by the lithium. This would account for the decrease in latency of sickness evident after the fourth session. Furthermore, since the total sickness now included that which was alcohol produced and that which was lithium produced, the duration of sickness showed a corresponding increase. Other clinicians have reported the development of conditioned sickness around the fourth alcohol-sickness pairing and in the present treatment there is a further reason why it should be evident after the fourth session. The procedure of administering the alcohol generally involved the introduction of different alcoholic beverages in each of the first four sessions. Thus except for generalization from the taste of one to the taste of another alcoholic beverage, the level of aversions reached in these first four sessions should have been similar. However, in each session after the fourth, all previously used alcoholic beverages were usually paired with the sickness in order to strengthen the overall aversion. Thus, it is after the fourth session that the conditioned sickness should have become most obvious.

DISCUSSION

In the strictest sense the present study cannot be considered a test of the effectiveness of a sophisticated lithium aversion therapy but as a preliminary study showing that such a therapy is likely to be possible. This is necessarily so because the clinical determination of effective dosage and patterns of administration resulted in not all patients receiving equally effective treatment procedure. That lithium can produce aversions to alcohol with considerable strength and safety even when the alcohol is introduced a considerable time before the onset of sickness has been amply verified. However, the observations and experience gained from this study suggest further modifications of the procedure and several openings for clinical research.

Higher Dosages and Safety: The safety of the present dosage levels, together with clinical reports of the use of lithium in mood disorders suggest that dosages higher than those used here could be administered safely. The serum lithium levels showed that 1500 - 1800 mg. of lithium carbonate administered once every two or three days during this study, was about as conservative as administering 750 - 900 mg. daily. Twice these daily dosages (Schou and Baastrup, 1967), and three times these dosages (Gershon, 1968) are commonly recommended in the treatment of acute mania. Gershon (1968) found that manics can tolerate more lithium

during the acute phase than normals. However, it is worth noting that when this phase is over a lithium free day is commonly recommended to avoid toxic buildup. In the present treatment a lithium free day followed every acute dosage even though the daily dosage averaged out to be much less than the dosage used in mania. In another study, normals acting as controls, have taken 900 mg. of lithium carbonate daily for six weeks and then continued at 1800 mg. for a further week (Schou, Amdisen, and Thomsen, 1970). Finally, groups of alcoholics have been treated with lithium for bouts of depression at dosages similar to those used in the treatment of mood disorders (personal communication, J.C. Wren). In these examples the lithium was probably administered on a three or four times daily basis, since this is the recommended procedure for minimizing aversive side effects (Prien et. al., 1971). However whether the dosage is given all at once or spread out over the 24 hours seems to make little difference to the overall excretion pattern and the major difference seems to be the accentuation or attenuation of the side effects (Trautner, et. al., 1955). There is however a major difference between the use of lithium in aversion treatment and its use in mood disorders; in aversion treatment there is no need to build up and maintain a specific serum lithium level. Because of this it is possible to allow any number of lithium free days between treatment sessions. Indeed, if dosages of 2100 mg. and 2400 mg. of lithium carbonate are eventually

used in aversion treatment we would recommend at least three days between treatment sessions. Considering that the biological half-life of lithium is in the vicinity of 24 hours this should leave ample time for safe excretion. Furthermore, with the present procedure of daily monitoring serum lithium levels it would be difficult for unsafe levels to go undetected.

Lithium Excretion Test: It will be recalled that there was a strong inverse relationship between the percentage of lithium excreted and the intensity of the sickness reaction. This relationship ought to be used to determine initial dosage level for high and low excretors. The same dosage of lithium should be safer for high excretors than for low excretors since they eliminate the lithium more rapidly. It follows however, that proportionally higher dosages would be necessary for high excretors to react with the same degree of sickness. For example, high excretors might be started at 1800 mg. and raised to 2100 mg. and 2400 mg. of lithium carbonate with the progression of treatment. Furthermore, we suggest an eight hour lithium excretion test based on a non-aversive dosage of 600 mg. of lithium carbonate since we feel that it would be more sensitive than the four hour test used in this study.

Avoidance of Habituation: The experience gained from this study indicated that a decline in intensity of reaction at the 1500 mg. level could be avoided by raising the patients' dosage to 1800 mg. of lithium carbonate around the third

or fourth session. However, since 1800 mg. of lithium carbonate was the a priori limit set for this study, any decline in intensity of reactions evident at this level could not be avoided by further increases in dosage. Had 2100 mg. of lithium been used, this decline in intensity of reaction evident in some patients in the later sessions could have been anticipated and their dosage routine raised to this level at the sixth session. If 2400 mg. of lithium also proved safe the number of treatment sessions could be extended to eight or nine without lowering and possibly increasing the intensity of reaction. This may prove desirable as a means of strengthening an overall aversion or allowing more treatment sessions to be devoted to a particular beverage.

Beer Flavours Hardest to Condition: Although two known relapses reported repeated nausea and vomiting when drinking was initiated with beer, observations made during this study indicated that aversions to beer were hardest to condition. The patients would usually report spontaneously during the later sessions of treatment, that the odors and flavours of spirits and wines used in previous sessions smelled and tasted extremely unpleasant. However, this was least often reported of beer, and when reported, was judged to be less unpleasant than the odors and flavours of other beverages. Furthermore, two relapsed patients who were considered resistant to lithium sickness during treatment, reported aversions to spirits and wines but not to beer. Kant (1944)

has reported that other practitioners of chemical aversion treatment have experienced this problem. Animal studies indicate that the best explanation may be weakness of flavour (Dragoin, 1971; Garcia, 1970). In the present sample of patients this was further confounded by greater familiarity since most patients indicated that beer was the least novel of the beverages sampled. The best way to overcome this problem would be to devote more conditioning sessions exclusively to beer flavours.

Outpatient Treatment: There are two considerations which suggest that aversion treatment with lithium could be carried out in part, on an outpatient basis.

1) Lithium, at the dosages used in the present study appears to be safe.

2) The lack of necessity for temporal contiguity between the flavour and the sickness greatly increases the flexibility of the treatment procedure. This flexibility can be appreciated when constrasted with this description of Voegtlin and Lemere's training procedure with emetine aversion treatment.

> "In developing technicians for this type of work we feel that observation and participation in at least several hundred conditioning sessions are prerequisite to administration of even the earlier and relatively unimportant treatments. The most single technical detail to be mastered is the proper timing of the first administration of liquor...Experience alone will enable one to judge the exact moment when the emetine nausea will begin (usually 2-8 minutes) and consequently the exact moment when the first drink of liquor should be offered" (Voegtlin, Lemere, and Broz, 1940).

Under medical supervision, technicians could carry out the present procedure with very little training. As an outpatient treatment we would recommend that the patient be dried out, complete his medical and psychiatric examinations, be given his lithium excretion test, and receive his first two aversion treatment sessions while still in hospital. He would then receive the remainder of his treatment sessions as well as any booster treatments on an outpatient basis. In communities such as this one, where no detoxification centers or alcoholism clinics exist, the freeing of beds and facilities would certainly be of value.

BIBLIOGRAPHY

Amdisen, A. Serum lithium determinations for clinical use. Scandinavian Journal of Clinical Laboratory Investigations, 1967, 20, 104-108.

Blake, B.G. A follow-up of alcoholics treated by behavior therapy. Behavior Research and Therapy, 1967, 5 (2), 89-94.

Boland, F.J. Saccharin aversions induced by lithium chloride toxicosis in a backward conditioning paradigm. Animal Learning and Behavior, 1973, 1, 34.

Braveman, N., and Capretta, P.J. The relative effectiveness of two experimental techniques for the modification of food preferences in rats. Proceedings of the 73 rd. Annual Convention of the American Psychological Association, 1965, 129-130.

Capretta, P.J. An experimental modification of food preference in chickens. Journal of Comparative and Physiological Psychology, 1961, 54, 238-242.

Dietz, M.N., and Capretta, P.J. Modification of sugar and sugar-saccharin preference in rats as a function of electrical shock to the mouth. Proceedings of the 75th Annual Convention of the American Psychological Association, 1967, 161-162.

Domjan, M. and Wilson, N.E. The contribution of ingestive behaviors to taste-aversion learning in the rat. Journal of Comparative and Physiological Psychology, 1972, 80, 403-412. (a)

Domjan, J., and Wilson, N.E. Specificity of cue to consequence in taste-aversion learning in the rat. Psychonomic Science, 1972, 26, 143-145 (b).

Dragoin, W.B. Conditioning and extinction of taste aversions with variations in intensity of the CS and the UCS in two strains of rats. Psychonomic Science, 1971, 22, 303-305.

Franks, C.M. Behavior modification and treatment of the alcoholic. In R.Fox (Ed.), Alcoholism: Behavioral Research, Therapeutic Approaches. Springer, New York, 1967.

Franks, C.M. (Ed.), Behavior Therapy: Appraisal and Status. McGraw-Hill, New York, 1969.

Garcia, J., Ervin, F.R., and Koelling, R.A. Learning with prolonged delay of reinforcement. Psychonomic Science, 1966, 5, 121-122.

Garcia, J., Kimeldorf, D.J., and Koelling, R.A. Conditioned aversions to saccharin resulting from exposure to gamma radiation. Science, 1955, 122, 157-158.

Garcia, J., and Koelling, R.A. Relation of cue to consequence in avoidance learning. Psychonomic Science, 1966, 4, 123-124.

Garcia, J., and Koelling, R.A. A comparison of aversions induced by X-rays, toxins, and drugs in the rat. Radiation Research, 1967, 7, 439-450.

Garcia, J., Kovner, R., and Green, K.F. Cue properties versus palatability of flavors in avoidance learning. Psychonomic Science, 1970, 20, 313-314.

Garcia, J., McGowan, B.K., Ervin, F.R., and Koelling, R.A. Cues: Their effectiveness as a function of the reinforcer. Science, 1968, 160, 794-795.

Garcia, J., McGowan, B.K., and Green, K.F. Biological constraints on learning. In A.H. Block, and W.F. Prokasy, (Eds.), Classical Conditioning II: Current Theory and Research, Appleton-Century-Crofts, New York, 1972.

Gattozzi, A.A. Lithium in the treatment of mood disorders. National Clearinghouse for Mental Health Information, Washington, (Publication No. 5033), 1970.

Gershon, S. Use of lithium salts in psychiatric disorders. Diseases of the Nervous System, 1968, 29, 51-66.

Gershon, S. Lithium in mania. Clinical Pharmacological Therapy, 1970, 11, 168-187.

Green, K.F., and Garcia, J. Recuperation from illness: Flavour enhancement for rats. Science, 1971, 173, 749-751.

Grollman, A., and Grollman, E.F. Pharmacology and Therapeutics. Lea and Febiger, Philadelphia, 1965.

Hammersley, O.W. Conditioned reflex therapy. In Wallerstein, R.S. (Ed.) Hospital Treatment of Alcoholism. Menninger Clinic Monographs, 1957.

Kalat, J. and Rozin, P. Role of interference in taste aversion learning. Journal of Comparative and Physiological Psychology, 1971, 71, 53-58.

Kant, F. Further modifications in the technique of conditioned reflex treatment of alchol addiction. Quarterly Journal of Studies on Alcohol, 1944, 5, 229-232.

Lemere, F. and Voegtlin, W. An evaluation of the aversion treatment for alcoholism. Quarterly Journal of Studies on Alcohol, 1950, 11, 199-204.

MacCulloch, M.J., Feldman, M.P., Orford, J., and MacCulloch, M.L. Anticipating avoidance learning in the treatment of alcoholism. A record of therapeutic failure. Behavior Research and Theory, 1966, 4, 187-196.

McCance, C. and McCance, P.F. Alcoholism in north-east Scotland: Its treatment and outcome. British Journal of Psychiatry, 1969, 115, 189-198.

McLaurin, W.A. Postirradiation saccharin avoidance in rats as a function of the interval between ingestion and exposure. Journal of Comparative and Physiological Psychology, 1964, 57, 316-317.

McLaurin, W.A., Farley, J.A. and Scarborough, B.B. Inhibitory effect of preirradiation saccharin habituation on conditioned avoidance behavior. Radiation Research, 1963, 18, 473-478.

Nachman, M. Learned taste and temperature aversions due to lithium chloride sickness after temporal delays. Journal of Comparative and Physiological Psychology, 1970, 73, 31-37.

Nachman, M. and Ashe, J.H. Learned taste aversions in rats as a function of dosage, concentration and route of administration of lithium chloride. Physiological Behavior, 1973, 10, 73-78.

Pavlov, I.P. Conditioned Reflexes. (Translated by G.V. Anreys.) London and New York: Oxford University Press, 1927.

Peacock, L.J. and Watson, J.A. Radiation-induced aversion to alcohol. Science, 1964, 143, 1462-1463.

Platman, S.R. and Fieve, R.R. Biochemical aspects of lithium in affective disorders. Archives of General Psychiatry, 1968, 19, 659-663.

Prien, R.F., Chaffey, E.M., and Klett, C.J. Lithium carbonate: A survey of the history and current status of lithium in treating mood disorders. Diseases of the Nervous System, 1971, 32, 521-531.

Quinn, J. and Henbest, R. Partial failure of generalization in alcoholism following aversion therapy. Quarterly Journal of Studies on Alcohol, 1967, 28, 70-75.

Rachman, S. Aversion therapy: Chemical or electrical? Behavior Research and Therapy, 1965, 2, 289-300.

Rachman, S. and Teasdale, J. Aversion therapy and behavior disorders: An analysis. University of Miami Press, Coral Gables, Florida, 1969.

Revusky, S.H. Aversions to sucrose produced by contingent x-irradiation: Temporal and dosage parameters. Journal of Comparative and Physiological Psychology, 1968, 65, 17-22.

Revusky, S. The role of interference in association over a delay. In Honig, W., and James, P.H.R. (Eds.) Animal Memory. Academic Press, New York, 1971, 155-213.

Revusky, S.H. Some laboratory pointers for chemical aversion treatment of alcoholism. Journal of Behavior Therapy and Experimental Psychiatry, 1973, 4, 15-17.

Revusky, S.H. and Garcia, J. Learned associations over long delays. In G.H. Bower (Ed.), The Psychology of Learning and Motivation, Vol. 4, New York: Academic Press, 1970, 1-84.

Revusky, S.H., and Gorry, T. Flavor aversions produced by contingent drug injection: Relative effectiveness of apomorphine, emetine, and lithium. Behavior Research and Therapy, 1973, 2, 17-19.

Rimon, R., and Rakkolainen, V. Lithium iodide in the treatment of confusional states. British Journal of Psychiatry, 1968, 114, 109-110.

Robinson, J. and Tripoli, W. The sensory aspects of lithium sickness. Paper delivered at the 43rd. annual meeting of the Eastern Psychological Association, Boston, 1972.

Rozin, P. Central or peripheral mediation of learning with long CS-US intervals in the feeding system. Journal of Comparative and Physiological Psychology, 1969, 67, 421-429.

Rozin, P., and Kalat, J.W. Specific hungers and poison avoidance as adaptive specializations of learning. Psychological Review, 1971, 78, 459-486.

Schou, M. Special review: Lithium in psychiatric therapy and prophyloxis. Journal of Psychiatric Research, 1968, 6, 67-95.

Schou, M., Amdisen, A., Thomsen, K. The effect of lithium on the normal mind. In P. Baudis, E. Peterova, V. Sedivec, and V. Plzen (Eds.), Psychiatria Progrediens, 1970.

Schou, M., and Baastrup, P.C. Lithium treatment of manic depressive disorders: Dosage and control. Journal of the American Medical Association, 1967, 201, 696-698.

Seligman, M.E.P. On the generality of the laws of learning. Psychological Review, 1970, 77, 406-418.

Smith, J.C. and Roll, D.L. Trace conditioning with x-rays as the aversive stimulus. Psychonomic Science, 1967, 9, 11-12.

Solomon, R.L., and Brush, E.S. Experimentally derived conceptions of anxiety and aversion. In M.R. Jones (Ed.), Nebraska Symposium on Motivation. Lincoln: University of Nebraska Press, 1956.

Stojiljkovic, S. Conditioned aversion treatment of alcoholics. Quarterly Journal of Studies on Alcohol, 1969, 30, (4-A), 900-904.

Straus, R., and Bacon, S.D. Index of social stability. Quarterly Journal of Studies on Alcohol, 1951, 12, 231.

Tapper, D.N. and Halpern, B.A. Test stimuli: A behavioral categorization. Science, 1968, 161, 708-709.

Taukulis, H.K. Odor aversions produced over long CS-US delays. Behavioral Biology, 1974, 10, 505-510.

Thimann, J. Conditioned-reflex treatment of alcoholism: its rationale and technique. New England Journal of Medicine, 1949, 214, 368-370, 406-410.

Traunter, E. M., Morris, R., Noack, C.H., and Gershon, S. The excretion and retention of ingested lithium and its effect on the ionic balance of man. Medical Journal of Australia, 1955, 42, 280-291.

Tupin, J. The use of lithium for manic-depressive psychosis. Hospital Community Psychiatry, 1970, 21, 73-80.

Voegtlin, W.L., Lemere, F., and Broz, W.R. Conditioned reflex therapy of alcohol addiction. III: An evaluation of present results in the light of previous experience with the method. Quarterly Journal of Studies on Alcohol, 1940, 1, 501-515.

Volger, R.E., Lunde, S.E., and Martin, P.L. Electrical aversion conditioning with chronic alcoholics: Follow-up and suggestions for research. Journal of Consulting and Clinical Psychology, 1971, 36 (3), 450.

Williams, E.Y. Management of chronic alcoholism. Psychiatric Quarterly, 1947, 21, 190-198.

Wilson, G.T., and Davison, G.C. Aversion technique in behavior therapy: Some theoretical and metatheoretical considerations. Journal of Consulting and Clinical Psychology, 1969, 33, 3, 327-329.

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Saccharin aversions induced by lithium chloride toxicosis in a backward conditioning paradigm*

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Seven experimental groups of seven rats each were allowed to consume saccharin solution at different times relative to intubation of lithium chloride solution. Six backward conditioning (BWD) groups were intubed 0.5, 1, 2, 3, 4, and 8 h before saccharin consumption, and a forward conditioning (FWD) group was intubed 0.5 h after saccharin consumption. A no-lithium control group of 14 rats received no intubation. Only the 0.5-h FWD and the 0.5-h BWD groups showed an aversion to saccharin relative to the no-lithium controls. The aversion to saccharin in the 0.5-h FWD group was more pronounced than that in the 0.5-h BWD group. This shows that the aversive effects of lithium toxicosis dissipate far sooner than the aversive effects of X-irradiation.

If ingestion of a flavored substance, such as saccharin solution, is followed by toxicosis induced by some independent means, such as X-irradiation, rats will avoid the flavored substance on subsequent occasions (Revusky & Garcia, 1970). With saccharin, this is true even if the interval between ingestion and exposure is extended up to 12 h (Smith & Roll, 1967). Furthermore, it has been shown that rats will form an aversion to saccharin solution when the solution is consumed up to 12 h after exposure to radiation ceases (Scarborough, Whaley, & Rogers, 1964). It was initially suspected that the reduced preference was due to unlearned factors (McLaurin, 1964), or to backward conditioning, which is generally considered impossible (Kimble, 1961). A better explanation is that the aversive physiological aftereffects of the radiation continue long after exposure ceases (Scarborough et al, 1964; Smith, Taylor, Morris, & Hendricks, 1965; Revusky & Garcia, 1970). Thus, although the operational paradigm may involve backward conditioning, consumption of the saccharin solution may well precede the peak of the sickness.

Lithium chloride is the most effective known chemical toxicosis for producing flavor aversions in animals (Nachman & Ashe, in press). Nachman (1970) has shown that forward conditioning can take place when the interval between saccharin consumption and lithium toxicosis is up to at least 4 h. However, the backward conditioning curve for lithium has not been investigated. The best guess is that the backward curve for lithium would be much shorter than that for X-irradiation. In radiation sickness with humans, the prodromal symptoms of nausea and vomiting do not become pronounced until approximately 7 h after radiation (Gerstner, 1960). According to reports of investigators who themselves consumed lithium, lithium sickness lasts approximately 2 h and has a sharper peak than radiation sickness; within 10-20 min of this peak, which is correlated with the peak lithium concentration in the blood, all symptoms disappear (Trautner, Morris, Noack, & Gershon, 1955). Thus, although there is no guarantee that the absorption pattern of lithium is identical for humans and rats, the human data offer a strong hint that the backward curve will be much shorter for lithium than for X-irradiation. The present experiment deals with the extent of an aversion to saccharin solution which may occur if lithium is intubed directly into the stomachs of rats at various intervals prior to consumption of the saccharin solution.

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METHOD

Subjects and Preexperimental Preparation

Two strains of rats were used to increase generality. They consisted of 36 adult male Sprague-Dawleys familiar with sucrose from a previously unrelated T-maze experiment and 27 naive adult male Fisher inbreds. All animals were gentled and housed in individual home cages where food was available except on the day of conditioning. Four Sprague-Dawleys and three Fishers were assigned randomly to each of seven experimental groups, leaving eight and six, respectively, for controls. Six days before conditioning, all animals were placed on a water-deprivation schedule designed to insure rapid and complete consumption of a saccharin solution on the day of conditioning. All Ss received 1 h of water on Day 1, 0.5 h on Day 2, and 10 min on Days 3, 4, and 5. Water was introduced at a regular time in stainless steel cups attachable to the cages. To insure empty stomachs and therefore rapid absorption of the lithium, food was removed 8 h before treatment started.

Conditioning and Recovery

On Day 6, all experimental groups received identical intubations (for procedure, see Braveman & Capretta, 1965) of 20 ml/kg of .3 molar (1.27%) lithium chloride solution. Intubation times differed for each group relative to consumption of 3 ml of 0.5% saccharin solution at their regular drinking time. Six backward conditioning (BWD) groups were intubed 0.5, 1, 2, 3, 4, and 8 h before saccharin consumption, and one forward conditioning (FWD) group was intubed 0.5 h after saccharin was introduced. Controls received no intubation. Food and water were returned to the Ss 16 h after consumption of the saccharin solution, and a 24-h period of recovery followed. Due to

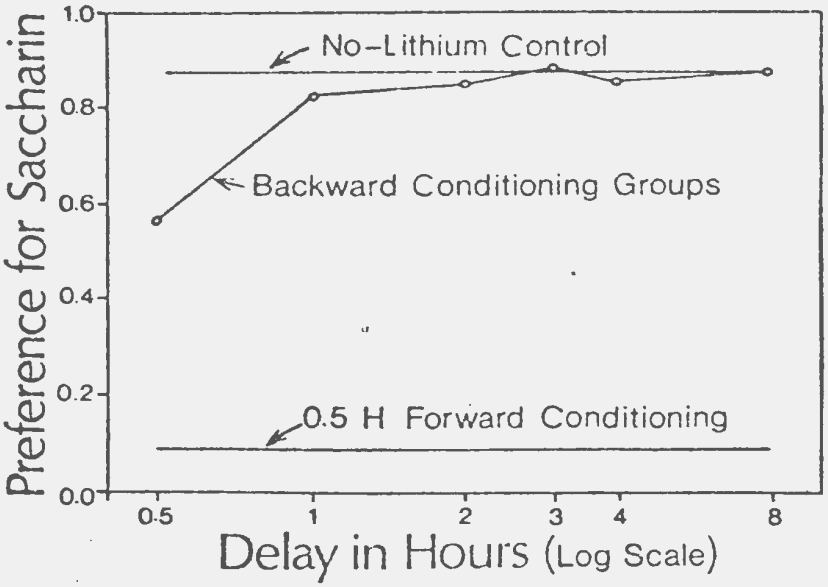

Fig. 1. Mean preference for saccharin solution relative to tap water among six BWD groups as a function of the delay between intubation of lithium chloride and subsequent ingestion of saccharin solution. The mean preferences for the no-lithium controls and a ½-h FWD group are shown as horizontal lines.

improper intubation, one Sprague-Dawley from the 3-, 4-, and 8-h BWD groups and one Fisher from the 0.5-h FWD group died.

Testing

On Day 8, a 48-h two-bottle choice test between saccharin solution and tap water began. The water bottles were weighed and placed on the left position of the cage front. At the same time, previously weighed bottles of 0.5% saccharin solution were placed in the right position. Every 12 h, the bottles were weighed and the positions of the two bottles were interchanged. Preference for saccharin was computed by dividing the total saccharin consumed by the total fluid consumed.

RESULTS AND DISCUSSION

The two strains differed in overall preference for saccharin by only 0.3% and were pooled for statistical purposes. No extinction was observed, and the saccharin preference for each group was averaged over the four test sessions. In Fig. 1, the no-lithium controls and the 0.5-h FWD group are represented by straight lines. The only groups to show an aversion to saccharin solution relative to the controls were the 0.5-h FWD group ($t = 14.35$, $df = 18$, $p < .0001$) and the 0.5-h BWD group ($t = 3.31$, $df = 19$, $p < .005$). Furthermore, the aversion obtained in the 0.5-h FWD group was much greater than that in the 0.5-h BWD group ($t = 3.21$, $df = 17$, $p < .005$). None of the other groups yielded significantly lower preferences than did the controls, the largest being the 1-h BWD group ($t = .693$, $df = 19$, $p \gg .05$). These results agree with an independent study by Domjan and Wilson (in press). They noted that one of their control groups introduced to saccharin solution 1.5-3 h after injection of lithium chloride did not form an aversion.

In conclusion, the aversive effects of lithium chloride toxicosis dissipate far sooner than toxicosis induced by X-irradiation. If consumption of saccharin solution is delayed by more than 0.5 h after intubation of lithium chloride solution, rats will not form a flavor aversion.

REFERENCES

Braveman, N. S., & Capretta, P. J. The relative effectiveness of two experimental techniques for the modification of food preferences in rats. Proceedings of the 73rd Annual Convention of the American Psychological Association, 1965, 129-130.

Domjan, M., & Wilson, N. E. The contribution of ingestive behaviors to taste-aversion learning in the rat. Journal of Comparative & Physiological Psychology, in press.

Gerstner, H. B. Reactions to short-term radiation in man. Annual Review of Medicine, 1960, 11, 289-302.

Kimble, G. A. *Hilgard and Marquis' conditioning and learning.* (2nd ed.) New York: Appleton-Century-Crofts, 1961.

McLaurin, W. A. Postirradiation saccharin avoidance in rats as a function of the interval between ingestion and exposure. Journal of Comparative & Physiological Psychology, 1964, 57, 316-317.

Nachman, M. Learned taste and temperature aversions due to lithium chloride sickness after temporal delays. Journal of Comparative & Physiological Psychology, 1970, 73, 31-37.

Nachman, M., & Ashe. Learned taste aversions in rats as a function of dosage, concentration and route of administration of lithium chloride. Physiology & Behavior, in press.

Revusky, S. H., & Garcia, J. Learned associations over long delays. In G. H. Bower (Ed.), *Psychology of learning and motivation: Advances in research and theory.* New York: Academic Press, 1970. Pp. 1-83.

Scarborough, B. B., Whaley, D. L., & Rogers, J. G. Saccharin-avoidance behavior instigated by X-irradiation in backward conditioning paradigms. Psychological Reports, 1964, 14, 475-481.

Smith, J. C., & Roll, D. L. Trace conditioning with X-rays as the aversive stimulus. Psychonomic Science, 1967, 9, 11-12.

Smith, J. C., Taylor, H. L., Morris, D. D., & Hendricks, J. Further studies of X-ray conditioned saccharin aversion during the post exposure period. Radiation Research, 1965, 24, 423-431.

Trautner, E. M., Morris, R., Noach, C. H., & Gershon, S. The excretion and retention of ingested lithium and its effects on the ionic balance in man. Medical Journal of Australia, 1955, 42, 280-291.

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APPENDIX B

To The Volunteer for Aversion Treatment

There is a discouragingly high rate of early relapse among alcoholics discharged from hospital treatment. St. Clare's is now testing a new experimental treatment in conjunction with its usual program of recovery. It is called aversion treatment and is aimed specifically at increasing your chances of not having an early relapse.

What is aversion treatment?

Aversion therapy is a treatment procedure through which an alcoholic patient loses his taste and craving for alcohol by forming an aversion to alcoholic beverages. The outcome of aversion treatment has often been compared with the outcome of food poisoning in that a person who has been poisoned by a toxic food often forms a longstanding aversion to the flavor and smell of the particular food that caused his sickness. For many months after the completion of an aversion treatment there is a strong tendency for the alcoholic patient to react to the flavor, smell, sight, and sometimes even the thought of an alcoholic drink with nausea and repulsion. Hopefully, the alcoholic will use this period of time away from the active craving for alcohol to reorient his life in such a way that alcohol is unnecessary.

How is an aversion produced?

You will be given approximately six treatments spaced two or three days apart. At each session, you will be asked

to taste and drink a small amount of liquor. Just after you taste the liquor you will be given a dose of lithium carbonate, which within 20 minutes should make you feel sick. You will continue to taste, smell, and occasionally drink a small amount of liquor until approximately 10 minutes after the start of sickness. For about 1½ hours after this you will feel as if you were suffering a cross between seasickness and a hangover. You will eventually come to associate the flavor, smell and sight of alcohol with this sickness and form an aversion to the alcohol. About two hours after the start of treatment all symptoms of sickness should leave and you should be ready to eat lunch.

Why haven't my hangovers produced an aversion to alcohol?

You have probably been sick more often and more severely with hangovers than with the sickness sessions associated with aversion treatment, yet there are several reasons why your hangovers did not produce an aversion to alcohol:

1. Between drinking and your hangover there was a period of intoxication which research has shown to interfere with the formation of an aversion.
2. Instead of becoming associated with the sickness, the drink you take as a "straightener" to relieve your hangover becomes associated with the relief of sickness.
3. The time interval between your drinking and your hangover is probably too long for an effective association to form

between drinking and sickness.

In essence aversion treatment avoids these difficulties by arranging for an artificial hangover to follow drinking immediately.

Does aversion treatment make it impossible to drink?

The answer is No. If you persist for a long enough period through the nausea, vomiting and repulsion which will occur if you attempt to drink, you may eventually succeed in breaking down the aversion to alcohol. Aversion treatment does not make it "impossible to drink" it makes it "possible not to drink".

Is aversion treatment widely used?

Aversion treatment has a long history and has been used quite extensively in the U.S.A. and many European countries. For example, the Shadel clinic in Seattle, Washington has treated over 17,000 alcoholics with this method as the core of their program.

Should your desire to stop drinking motivate you to volunteer for this new treatment you will be given the necessary medical and psychological examinations to determine your fitness as a volunteer. If you have any questions regarding any aspect of treatment please contact the personnel in charge. They will be glad to discuss it with you.