

heart disease without rheumatic and congenital heart disease or cor pulmonale indicates a poor prognosis.

4. Another mechanism altering the electrical axis of the heart may be widespread necrosis of one ventricle which can completely nullify the effects of hypertrophy of that ventricle.

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### THE TREATMENT OF ALCOHOLISM BY ESTABLISHING A CONDITIONED REFLEX.

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THE utilization of the principle of the conditioned reflex in the treatment of alcoholism was first suggested by Markovnikov<sup>1</sup> and by Ichok,<sup>2</sup> in 1934. The former author cited some experimental results, but Ichok presented only a philosophic discussion of the subject.

A conditioned reflex may be defined as the eliciting of a normal or unconditioned reflex response by means of a strange or unnatural stimulus. Thus if salivation in an experimental animal is made to result solely from the stimulus of a ringing bell, a conditioned reflex has been established. These reflexes are called conditioned reflexes because they require a period of training or conditioning before they may become manifest. The fundamental concept of the conditioned reflex and the importance of its several peculiar characteristics has been studied most exhaustively by Pavlov.<sup>3</sup>

**Method of Treatment.** In applying the foregoing physiologic considerations to the treatment of alcoholism, the action of certain nauseant drugs is utilized to elicit the unconditioned reflex of nausea and vomiting. The sight, smell and taste of alcoholic beverages serve as the conditioned stimulus, and thus, a conditioned reflex can be established. The physical properties of alcoholic beverages when utilized as the conditioned stimulus will, upon exhibition, initiate reflex activity of the centers of nausea and vomiting. A distaste is thus created for the conditioned stimulus, amounting to a strong and definite aversion to the sight, smell and taste of liquor. It is interesting to note in passing that an analogous con-

ditioned reflex occurs spontaneously in nature in certain cases of food poisoning. It is probable that every one after partaking of certain foods too abundantly or of "tainted" food, has experienced nausea and vomiting. It is true that after such an unfortunate experience there is left in the mind of the person an aversion or distaste, that may last for years, for the particular food in question. It is of further interest to observe that the person may experience no distaste whatever for the food actually causing the illness should it escape his suspicion. His dislike may center upon an entirely blameless and innocent food that was eaten just prior to his illness. This observation indicates the importance of suggestion in establishing the conditioned reflex.

The establishment of a conditioned reflex aversion to alcohol is undertaken during a number (usually 5 to 7) of seances or treatments with rest periods between. The average hospital stay is 5 days. No food except liquids and no sedative drugs are given for at least 12 hours prior to each treatment. Our choice of nauseant drugs lies between emetine and apomorphine. We have chosen emetine because its action is more prolonged and it produces no hypnotic effect following its use to complicate the interpretation of the results. However, small doses of apomorphine given in conjunction with the emetine achieve a degree of nausea and emesis impossible with emetine alone. Each treatment should be given only by a physician especially trained and experienced in this work. Experience has taught that a certain hazard exists in the administration of the treatments. Alarming though not dangerous collapse may follow the injudicious administration of the suggested medication.

The treatment room is constructed with special attention given to the physical comfort of the patient during treatment. The room is soundproofed in order to avoid extraneous stimuli, such as conversation, street noises and all other distracting influences. The lighting is subdued with the exception of the treatment table. It is believed worth while to have the treatment table with its array of liquors "spot lighted" in plain view. The patient's attention is thereby constantly focused on our conditioned stimulus. This attention to the visual sense will cause the sight of liquor to become one element of our conditioned stimulus. Similarly, by forcing the patient to smell deeply of various liquors at every possible opportunity during the treatment, the olfactory sense may also be utilized as still another element of the conditioned stimulus. These points are of vital importance. In our experience we have found aversion to the sight and smell of liquor to be very marked following completion of the course of treatments. Usually this aversion to sight and smell is sufficient to cause the patient to avoid alcohol without the more dangerous experiment of tasting liquor that he may satisfy his curiosity relative to his inability to drink.

Since the conditioned stimulus is specific, it is necessary to use every conceivable type of liquor as our conditioned stimulus. However, the particular type of beverage usually consumed should receive the greatest stress. If this technique were not observed it would be possible to create a successful aversion to whiskey, for example, and none to other liquors or beer.

The drugs used during the treatment are made up in 40 cc. ampules from which individual doses may be drawn with ease and accuracy. The proportions used are as follows:

Emetine HCl . . . . .	50 grains	Ephedrine SO <sub>4</sub> . . . . .	23 grains
Pilocarpine . . . . .	25 grains	Water . . . . .	qs 40 cc.

Pilocarpine is included not only because of the psychic effect of its producing profuse diaphoresis and sialorrhoea, but also because of the feeling among older writers that it helps combat the physical taste for liquor. The ephedrine is used to combat the fall in blood pressure experienced by some patients after emetine administration. We feel that a fall in systolic blood pressure below 100 is indication for rest and continued ephedrine medication until a near normal level is again reached.

In administering the actual treatment the following routine is used. The patient is made comfortable in the treatment room and the appropriate dose of the emetine-pilocarpine-ephedrine mixture is given (Minims vi to xii) hypodermically. Variations in dosage depend not so much on body weight as upon the personality of the patient. Selection of the proper amount is largely based on previous experience and observation of the effect obtained during the first treatment. It is well to mention casually to the patient that this medication is merely a stimulant to support him during the ensuing violent nausea. Such a remark serves not only to remove the injection as a possible source of the following nausea but also suggests to the patient that the drinking of the liquor is going to make him acutely ill. Experience alone will enable one to judge the exact moment when the emetine nausea will begin (usually 2 to 8 minutes) and consequently the exact moment when the first drink of liquor should be offered. It is of paramount importance that this first offering of liquor should be given within several seconds before the onset of nausea and certainly under no conditions should it be withheld until either nausea or salivation has appeared. An error of only a few seconds in the first admission of alcohol will not only annul the effect of the treatment but will, according to our experience, make the patient recalcitrant to further efforts to establish a satisfactory conditioned reflex. If an error in timing has been committed and the liquor is given prematurely the onset of nausea may be hastened by administering 1 to 2 grains of emetine orally in whiskey. Since this drug apparently acts centrally to lower the threshold of mucosal irritability the effect after oral adminis-

tration at this time is more quickly manifest than would be an additional hypodermic injection. Since this oral intake of emetine is almost entirely rejected before absorption can take place one can disregard the effect of this administration from a systemic point of view. Following the onset of nausea all types of liquor are forced on the patient, making certain that each empty glass is smelled deeply. Warm water is given frequently in order to afford easy emesis and to avoid retching. After emesis is completed the above routine is repeated until the nauseant effect has begun to wane. The stomach is then thoroughly emptied and washed with warm water using the Ewald tube. The patient is then covered carefully and left in the treatment room until the pilocarpine diaphoresis has ceased.

Occasionally a patient is unable to regurgitate in spite of deep nausea. In these instances the stomach must be emptied promptly via the Ewald tube. Absorption of alcohol to the point where an effect is noted by the patient will vitiate the entire treatment. The necessary use of the Ewald tube does not in any way render the treatment less effective.

It has been found that an occasional patient develops little or no nausea following the administration of emetine. In these cases it has been noted that the hypodermic injection of a small dose of apomorphine (grains 1/20 to 1/40) in conjunction with emetine will invariably initiate severe nausea. This procedure must be used with much caution due to the fact that approximately 30% of the patients so treated develop alarming syncope coupled with marked bradycardia amounting in a few instances to complete momentary cardiac standstill coincident with the onset of nausea. This is of course on the basis of strong vagus stimulation of central origin and may be overcome largely with preliminary atropine medication. Pilocarpine should not be given when the mixed treatment with emetine and apomorphine is used.

Routine laboratory work was performed on each patient, including daily chemical and microscopic urinalysis, blood pressure determinations 3 to 5 times daily, as well as the indicated blood-chemistry studies.

Contraindications to the treatment comprise in the main the cardio-vascular-renal syndrome, hepatic cirrhosis with or without esophageal varices, hernia (unless guarded), active peptic ulcer or history of recent hematemesis and active psychosis.

**Results.** In the past 4 years 685 patients with chronic alcoholism have been treated by the foregoing method. Of this total number the exact status of 538 of these patients is known. The latter figure will form the basis of the statistical data to be presented.

The answer to the question as to results is of course based on the percentage of cures obtained. Chart 1 shows graphically the percentage of complete abstinence among patients treated during each

6-month period for the past 4 years. Examination of these data will reveal that with the exception of the most recent and the most remote periods, the percentage of sobriety is remarkably constant, varying only between 62 and 69%. It is felt that the low percentage (50%) noted in the most remote period (48 months) is due to the fact that this group represents the first cases treated more or less experimentally and that certain mistakes and omissions of technique occurred, which have later proven to be most important, and that a relatively poor result was thereby obtained. While the percentage

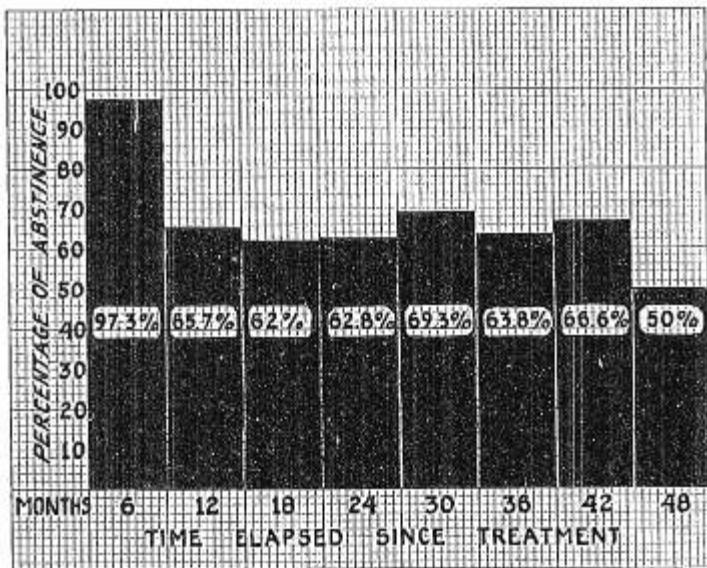


CHART 1.—Showing the percentage of abstinence at the present time among patients treated during each 6-month period during the past 4 years.

of abstinence for the 6-month period immediately following treatment is found to be 97.3%, the percentage during the second 6-month period is seen to be only 65.7%. This indicates clearly, in view of the number of cases reported, that the great majority of relapses occurred between the sixth and twelfth months following treatment. It is believed in view of these figures that if a relapse does not occur during the first year, the subsequent danger of a relapse is not great. The slight fluctuations shown after the first year in the graphic representation of the data are due to variations

in personality types vagariously included in any particular period with a corresponding tendency to make the results of that period better or worse, as the case may be. It would be illogical to consider these variations as a function of the factor of elapsed time following treatment. By obtaining an average figure for all of the 6-month periods after the end of the first 6 months, and even including the remote period of experimentation, it would seem from the data presented that by this method we have a conservative expectation of 64.3% of total and permanent cures. By a "cure" in this sense is meant total and permanent abstinence from alcohol of all types.

The average age of admission was 41.5 years. The average age of those returning to drink was 38.0 years, showing the tendency for younger patients to relapse. It is interesting to note that among the entire series of cases we have been unsuccessful in treating a single individual under 28 years of age. The percentage of abstinence among women patients was found to be 57% following treatment, which is somewhat below the average for the entire series. No correlation was found to exist between relapses and either duration or severity of addiction. Relapses are more common, however, among wine drinkers than beer drinkers and least frequent among patients who are users of distilled liquors such as whiskey.

Many of the patients who have returned to drinking following treatment have presented themselves for retreatment. While we have as yet no authoritative data to report in this connection, it is indicated from experience that the prognosis in these cases is poorer than in the untreated group. Many of these patients have relapsed a second time soon after treatment.

Considering the fact that the majority of patients presenting themselves for an alcoholic cure are confirmed and heavy drinkers and that they usually come during a prolonged spree, and considering, further, that alcohol is withdrawn suddenly during treatment, it is surprising that delirium tremens developed in only 14 (2%) of the total number of treated cases. Twenty-one patients were admitted in acute delirium. We have felt in the past that our freedom from delirium was due to the spontaneous dehydration<sup>2</sup> of the patient following profuse pilocarpine diaphoresis and emesis. Chart 2 showing the average of 100 unselected cases indicates the extent of dehydration in spite of the fact that fluids are forced during the treatment. That the sedative action of alcohol on the central nervous system is not the sole factor as suggested by Tatum<sup>8</sup> is indicated by the fact that only rarely is it necessary to administer sedative medication. Recent advice, however,<sup>1,6</sup> would indicate that dehydration *per se* is not the factor that controls the incidence of delirium tremens. The further investigation of pilocarpine in the therapy of delirium is indicated. The mortality in our series of 35 cases of delirium tremens was a single case that expired before

treatment could be instituted. This represents a mortality of 2.8%, if this untreated case is included.

The mortality of the entire series of cases receiving the complete treatment was a single death (0.14%) due to cardiac failure.

Laboratory studies show that while 36.8% of patients on admission show albuminuria only 3.9% have this finding upon being discharged.

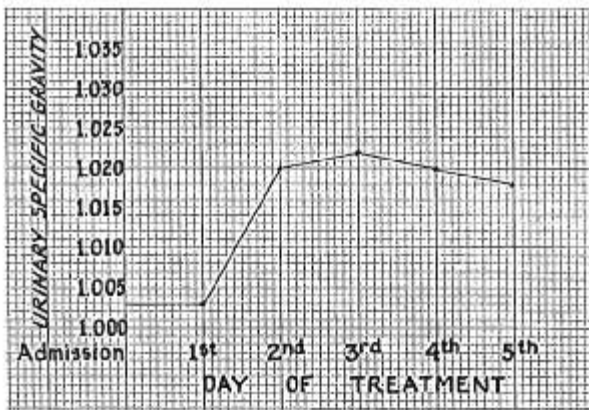


CHART 2.—Showing the increase in urinary specific gravity (dehydration) in 100 unselected cases during treatment.

**Discussion.** Failures under this method of treatment are due in very few instances to the inability to establish a satisfactory conditioned reflex. The greater proportion of failures are due to the natural breaking down and weakening of the conditioned reflex due to the lack of periodic reënfocement. This is indicated by the fact that the relapses occur during the sixth to twelfth months when the reflex might be expected to weaken or disappear. Relapses occurring before the sixth month are almost without exception characterized by gross psychopathic traits. Those cases of permanent cure are seen in individuals who possess sufficient residual psychic balance spontaneously and automatically to repair the fundamental personality defect which is the basis of their drinking during the period of enforced abstinence before the mechanism of the conditioned reflex becomes weakened to the point where it is no longer effective. This suggests the desirability of reënfocement by secondary treatment after the sixth month following the original treatment. It is felt that this practice would greatly enhance the value of the results obtained.

In our experience there are two main causes for relapse. The first is the feeling on the part of a patient that following a variable period of abstinence without conscious effort on his part, he is now able to drink socially and in a controlled manner. Only 4 of the total number (175) of relapse cases have been able to accomplish this. The second cause is curiosity on the part of the patient as to whether liquor will actually make him ill, if it should be taken. Needless to say either experiment on the part of the patient is a most dangerous procedure and will almost certainly lead to a relapse.

A most interesting sidelight on the mechanism of the conditioned reflex is furnished by the chance observation that during the development of an aversion to alcohol a simultaneous aversion to snuff is often acquired. If the latter aversion is desired by the patient, the snuff is given only before each treatment, whereas if the patient wishes to retain the habit he is instructed to chew snuff between but not immediately before the treatment. Because of the lesser psychiatric significance of the snuff habit as compared with alcoholism, we have never in our knowledge known a patient to revert to the habit of chewing snuff even though he may revert to drinking.

The medical literature is remarkable for the paucity of statistical data relating to cures by various methods of treatment for alcoholism. The gold chloride type of treatment so popular about the turn of the century, and still practiced sporadically in some parts of the country, claimed a success of 95%. Examination of further data, however, reveals that only 55% of these patients remained sober at the end of the first year and only 10% of abstinence was noted at the end of the third year. Other data<sup>7</sup> show successful results in 61% of a series of 1100 cases. These and other data, while open to error, suggest that approximately 33.3% may be reasonably considered as permanently cured. Sajous<sup>7</sup> by employing hypnotic suggestion in 1284 cases obtained favorable results in 80%. The length of abstinence and criterion of cure were not included in the data and it is assumed that the favorable results mentioned did not necessarily constitute total and permanent abstinence.

It is not the intention of this paper to claim superiority of this method over any other or to compare the results obtained by various methods of therapy. The primary interest is to present the results of treatment obtained by a method based upon the principle of the conditioned reflex. Other methods of treatment have probably unwittingly included the principle in some phase of the treatment but have apparently never premeditatively based their immediate treatment on this factor alone.

It should be noted that no attempt at psychiatric care was made with any patients of this series. It is our opinion that if appropriate mental care could have been furnished this series of cases, our percentage of relapses would have been much smaller. We have, however, made systematic efforts through social service workers to do



rehabilitation work in those cases where it is necessary that assistance be given in such matters as regaining lost positions, smoothing out domestic incompatibilities and obtaining employment, etc. It is felt that this work is of the greatest importance in aiding the reclaimed alcoholic to find his lost position in society.

**Summary.** 1. The technique of a new physiologic approach to the problem of the treatment of alcoholism, the conditioned reflex, is given.

2. Younger individuals and women are less promising patients from the standpoint of ultimate cure than are mature men.

3. The treatment is safe; having a mortality of less than 0.15%.

4. About 64% of permanent cures may be expected as a result of this treatment when rehabilitation measures are practiced following discharge.

5. Psychotherapy and routine reinforcement after the sixth month following treatment will probably improve these results markedly.

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### STUDIES ON A PURIFIED ANTIGEN FROM BRUCELLA.\*

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CUTANEOUS hypersensitiveness to specific antigen as a test for brucella infection has been used by several authors.<sup>1,2,3b,4,6,7,10b,12,15,19,20</sup> Unfortunately, a diversity of preparations<sup>3a,8,10a,13</sup> has been used as antigens, making correlation of results difficult. We have tried to obtain a standard preparation which could be measured accurately, would be a good antigen, would be stable and could be prepared easily and with the least possible denaturation.

This has been made possible by following a modification of Seibert's method<sup>18</sup> for the preparation of P.P.D. (purified protein derivative from tuberculin). Since brucella organisms cannot be

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