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COMMITTEE ON PROBLEMS OF ALCOHOL

A Report of its Activities from 1949 to 1955, the Research Work it has Supported and the Place of this Work in the Field of Alcoholism

by

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I. INTRODUCTION

The problems posed by alcohol have undoubtedly been present to one degree or another since man first discovered the process of fermentation. In various cultural settings, of course, alcohol is used to varying extents and for differing purposes. The wild and violent drunkenness of the plains Indian in the early days of the fur trade and the heavily ritualized and quite modest alcohol consumption of the orthodox Jew illustrate well the variations existing in the use of alcohol from one social group to another.

The recognition of chronic alcoholism as a social problem goes back at least to the days of Hogarth and the development of distilled liquors, while the great "experiment" of prohibition in this country is probably the most radical attempt ever made to solve the problems presented by alcohol. In recent years a variety of organizations, such as Alcoholics Anonymous, the Yale Center of Alcohol Studies, and the National Committee on Alcoholism, have arisen which have attempted in one way or another to help those with serious drinking problems. As of 1955, twenty-seven states and the District of Columbia had state programs concerned with the disease of alcoholism, while several other states have had commissions studying the problem. (38)

The seriousness of the problem in the U.S.A. must to a large extent be related to the proportion of the population suffering from chronic alcoholism. Because of the social stigmata attached to the condition and the frequency with which confirmed alcoholics strenuously deny having any drinking problem at all, direct polling of the population cannot be expected to provide any accurate assessment of the magnitude of the problem. Dr. E. M. Jellinek (20) has developed an indirect method for estimating the total number of chronic alcoholics in a given state or country based on the area's autopsy statistics for cirrhosis of the liver and for alcoholism as well as the percentage of active chronic alcoholics suffering from liver disease. By this method, in an article published in 1952 (21), he estimated that in 1948 there were 3,808,000 chronic alcoholics in the United States. The prevalence rate was calculated as 3,952 alcoholics per every 100,000 inhabitants over twenty-one years of age, a rate which approaches closely four per cent of the adult population. In comparing this figure with those for other diseases in that year (39), it becomes evident that there were 130 times as many chronic alcoholics in the U.S.A. as there were cases of poliomyelitis (only 27,726).

There were, by these calculations, six times as many alcoholics in this country as there were hospitalized psychiatric patients (only 554,454).

An alternate method devised by Ipsen, Moore, and Alexander (16), based on the frequency with which medical examiners report alcoholism as a cause of death, arrived at the slightly more modest estimate of 1,240 chronic alcoholics per 100,000 total population (for the State of Massachusetts).

These authors felt that the medical examiners' autopsy diagnoses were sufficiently reliable and unbiased to give an adequate picture of the relative incidence of the problem in the state as a whole. Their figures, although lower than Jellinek's, still indicate that a very substantial problem exists.

In the best actual survey of a given population made to date, R. J. Gibbins (9), by using very careful case-finding methods, discovered that a county in Ontario had sixteen seriously abnormal drinkers for every 1,000 inhabitants over twenty years of age. By using Jellinek's formula the alcoholism rate for Ontario in 1948 was estimated as being 18* per thousand people over twenty, a figure which closely approximated that arrived at by Gibbins in his actual counting of specific individual cases. Gibbins' work would therefore support the validity of the figures arrived at by Jellinek.

Of course, further studies like the one conducted in Ontario are badly needed so that the exact extent of the problem can be reliably determined; but at present it seems at least strongly possible that one out of every 25 adult Americans is a chronic alcoholic. If this is true, it is indeed a problem of mammoth dimensions, urgently needing further study.

Recent research aimed at a better understanding of both the etiology of chronic alcoholism and the effects of alcoholism on the individual can be grouped under four main headings: clinical, sociological, psychological, and metabolic-pharmacologic-physiologic.

Clinical research has included studies on the psychopathology of the chronic alcoholic, and studies of the organic diseases commonly found associated with chronic alcoholism, such as cirrhosis of the liver, polyneuritis, and delirium tremens. In addition, various methods of treatment based on a variety of different rationales have been attempted and have been evaluated with varying degrees of success and reliability. Attempts have been made to cause an aversion to alcohol by producing vomiting immediately after the patient has had a drink. (24, 43) Vitamins have been given in large doses (42) both because chronic alcoholics often show evidences of vitamin deficiencies and because certain animal experiments have indicated that rats deprived of certain vitamins may voluntarily increase their alcohol intake. (28, 48) Adrenal hormones and adrenocorticotrophic hormones have been used because some alcoholics show evidence of mild to moderate adrenal insufficiency. (35) The effectiveness of these forms of treatment has varied

*The difference between this figure and Jellinek's figure of 1,000 for the U.S.A. in 1948 is due to differences between the autopsy statistics for Ontario and those for the U.S.A. as a whole.

somewhat from one unit to another, and the rationales behind them remain unclear, since it is not known whether any observed phenomenon such as adrenal insufficiency is a predisposing factor in chronic alcoholism or a secondary effect of prolonged heavy drinking.

Formal psychoanalysis of a relatively small number of patients has been only moderately effective, (22, 33) while other forms of psychotherapy, including group therapy, have achieved some measure of success. (41)

Antabuse, the drug which can make those taking it vomit violently if they drink alcohol, has been widely used with some success since its introduction from Denmark in 1949. (12, 18)

Institutional treatment, varying from simple confinement within a state hospital (3) to hospitalization in units organized specifically for the rehabilitation of the chronic alcoholic, is being carried out in various parts of the country, but detailed studies evaluating the effectiveness of the various aspects of such programs are badly needed.

Lurking beneath all these methods of treatment, as well as beneath the nonmedical and relatively non-research-oriented AA movement, is the problem of motivation for cure in the alcoholic. Whether this motivation is dependent on biochemical, hormonal, or psychological factors, its presence is often considered the sine qua non of successful treatment in the chronic alcoholic. (10)

Sociological research into the drinking habits and attitudes toward alcohol of various cultural groups has been being actively carried out. There seems to be no doubt concerning the effect of such factors on the incidence of alcoholism within various subgroups, although this approach does not explain the occurrence of alcoholism in specific individuals with a given cultural group. (2, 8)

Psychological research in chronic alcoholism has been relatively active, but has been handicapped by at least two major difficulties. There have been attempts to differentiate alcoholics as a group from normal individuals as a group by means of various psychological tests, and there have been attempts to define "the alcoholic personality". Because of the considerable variability in personality and behavior found in any large series of chronic alcoholics such attempts have met with little success. The other major problem has been the interpretation of such abnormal personality traits as are found in some chronic alcoholics. Are these traits the reason for the patient's drinking, or are they the result of prolonged alcohol consumption? (8, 40)

This question of "which came first, the chicken or the egg" pervades metabolic and physiological studies of the alcoholic as well. Whenever abnormalities of any sort are found in chronic alcoholics the same problem arises. Attempts have been made to study incipient or "early" alcoholics, but these cases are hard to define or identify and are open to some of the same doubts. Perhaps large-scale studies of great numbers of "normal" adolescents or young adults will be necessary, utilizing prolonged follow-up

studies of these individuals to determine which ones become alcoholics in later life. The various psychological and physiological findings obtained at the inception of the study could then be statistically evaluated to determine their association with the eventual development of chronic alcoholism.

On the biochemical side, despite the importance of the problem and the considerable amount of work devoted to it, a number of gaps exist in our knowledge concerning the process by which alcohol is metabolized in the normal human body. Such knowledge is vitally necessary before one can even begin to investigate the often-suggested possibility that the bodies of chronic alcoholics may handle alcohol in an abnormal manner.

Our knowledge of the effects of alcohol consumption on salt and water balance in the body, on the secretions of the endocrine glands, and on the functioning of the central nervous system contains equally large loopholes.

From the time of its organization within the National Research Council, the Committee on Problems of Alcohol has been acutely aware of these defects in our knowledge of the metabolic, physiological, and pharmacological effects of alcohol, and has felt that knowledge in these areas must be expanded and solidified before possible metabolic or physiologic factors in the etiology of chronic alcoholism can begin to be explored. Since other organizations in the field of chronic alcoholism, both state and national, tend, because of their charters and the groups which they serve, to place emphasis on clinical, sociological, and psychological aspects of the problem, the Committee on Problems of Alcohol has felt even more strongly that the encouragement and support of work in the metabolic, physiological, and pharmacological aspects of the problems was a useful and even vital function for the National Research Council's Committee on Problems of Alcohol to perform.

This general theoretical approach to the problem fitted in well with the specific research projects which the Committee inherited from its predecessor, the Research Council on Problems of Alcohol, in 1949. Four of these were of this nature: Dr. R. J. Williams' work on biochemical individuality in alcoholism, Dr. J. J. Smith's work on adrenal insufficiency in chronic alcoholics, Dr. W. L. Voegtlin's work on allergies to alcohol, and Dr. O. Diethelm's study of the relationship between certain biochemical components of the blood, certain emotions, and chronic alcoholism.

Within its general area of interest the Committee on Problems of Alcohol has supported a variety of projects ranging from studies of the enzymes which metabolize alcohol to the factors influencing the spontaneous drinking of alcohol by laboratory animals. The general state of knowledge in the field, together with the place of the various studies supported by this Committee with the generous gifts of the Licensed Beverage Industries, will now be reviewed. The specific studies supported are also listed in Appendix A.

The descriptions of the work and ideas of the various grantees which are presented in this report are taken from either the progress reports submitted to the Committee or from their comments at the Colloquium on the Metabolic and Pharmacological Aspects of Alcoholism held by the Committee on

Problems of Alcohol on April 5, 1955. Reference numbers are included to indicate results which have already been published. All other comments not supported by published articles should be considered as personal communications, not to be utilized for publication reference without the expressed permission of the investigator in question.

II. THE METABOLISM OF ALCOHOL*

Following the taking of an alcoholic solution into the stomach the alcohol is absorbed from the stomach and small intestine at a rate influenced by the presence of food in the stomach and a variety of other factors. (11) This variability has been at least one factor which has caused different results to be obtained from similar experiments studying the effects of alcohol on the organism.

Once in the body, alcohol is almost certainly metabolized first to acetaldehyde, although the exact enzyme or enzymes causing this change are not known with certainty.

In almost all animals, including man, with the notable exception of the dog, acetaldehyde is found in the blood stream in small amounts after alcohol has been ingested. The fact that the dog is different in this respect highlights another problem which confronts those working in this field. Different species show significant variations in the way they handle alcohol, so that experimental findings derived from studies of a single species cannot be applied to man indiscriminately. (19)

In any event, the metabolism of alcohol to acetaldehyde is an interesting process posing several unsolved problems.

First, ethyl alcohol is burned by the body at an almost steady rate, approximating 100 mg. per Kg. per hour in man, or about one pint of 100-proof liquor per day, (17) regardless of the concentration of alcohol in the blood. Almost all other substances metabolized by the body are metabolized much faster at high concentrations than at low ones. This implies that there may be in the body only a limited amount of the enzyme or enzymes which change alcohol to acetaldehyde; this small amount could act as a limiting factor, keeping the rate of alcohol metabolism down at its observed constant level.

The situation becomes still more complicated. Some animals (especially dogs) will start out with a somewhat higher rate of alcohol metabolism if they are given a large dose of alcohol to start with than if they are given a small one. (45) But in either case the rate at which they burn alcohol when their blood concentration is highest remains constant as they metabolize the whole dose they were given. It is possible that some of these animals are not burning alcohol to the best of their ability initially and that the

*For more detailed review articles on the metabolism of ethyl alcohol, the interested reader is referred to the excellent review articles by Jacobsen (19) and Westerfeld (45) as well as Goodman and Gillman's textbook of pharmacology (10).

larger dose of alcohol may produce secondary effects, perhaps through stimulation of the adrenal glands or changes in liver function, which enable the body to increase its alcohol metabolism to its full capacity. In other species (and in some individual dogs) the rate of metabolism seems to be constant and unaffected by either the size of the dose or by the giving of hormones or other substances to the animal.

In some animals the rate of metabolism of alcohol will deviate a little from the constant rate described above, making people suspect that two different enzymes may perhaps be involved.

There are two known enzymes, catalase and alcohol dehydrogenase, which can convert alcohol to acetaldehyde in the test tube. In many ways alcohol dehydrogenase would appear to be the enzyme primarily involved; it has been calculated to be present in the liver (of the horse) in amounts just proper to account for the limited rate of alcohol metabolism described above. To allow this reaction to occur, diphosphopyridine nucleotide, a molecule containing the vitamin nicotinic acid, must be present; but for unknown reasons, the effects of nicotinic acid deficiency on alcohol metabolism have not yet been specifically investigated. (19)

The other enzyme, catalase, if it were the only enzyme responsible, would cause a quite different relative rate of alcohol metabolism than that which is observed; but it is possible that it also metabolizes alcohol to a limited extent and may account for some of the unexplained deviations from the steady rate of alcohol metabolism sometimes found.

Dr. Kinard of the Medical College of South Carolina (aided by a grant from the Committee on Problems of Alcohol) has been studying the relationships between the rate at which the living dog metabolizes alcohol, the rate at which the dog's liver will metabolize alcohol in vitro after the dog has been sacrificed, and the amount of catalase activity present in the liver as determined by a method not involving alcohol. His initial results in the living dog have indicated a positive relationship between the rate of alcohol metabolism and the catalase content of the liver, a finding at variance with the theoretical formulation presented above. He plans to expand these observations and to attempt to alter the amounts of catalase and alcohol dehydrogenase in the liver by a variety of methods. His work should constitute a definite step toward the better understanding of the inter-relationships of these two enzymes.

The next step in the metabolism of alcohol is the conversion of the acetaldehyde formed as described above, perhaps by way of acetic acid, to acetyl coenzyme A (CoA). From the acetyl CoA stage the metabolism of the molecule to carbon dioxide and water is in no way different from the end steps in the metabolism of fat or carbohydrate, and so ceases to be of special concern to those interested in alcohol or alcoholism.

The metabolism of acetaldehyde, however, is of considerable importance for at least three reasons. First, acetaldehyde is itself a substance with potent pharmacological effects. It has a narcotic action on the central nervous system and is a much more poisonous substance than alcohol, the fatal

blood level of acetaldehyde being less than one-eighth the fatal blood level of alcohol. Some of the effects of intoxication, as well as the hangover itself, have been blamed on acetaldehyde, but without proof. The levels normally present in the blood of an intoxicated person or animal are not high enough in themselves to produce the symptoms of intoxication.

Secondly, the fact that acetaldehyde is found in the blood at all is in itself a mystery, since liver slices or homogenates in the laboratory metabolize acetaldehyde at a much faster rate than it could possibly be produced from the limited amount of alcohol the liver can metabolize in a given unit of time.

Thirdly, the metabolism of acetaldehyde in the body is interfered with by Antabuse (disulfiram), the violent nausea and flushing the patient experiences in the alcohol-Antabuse reaction being caused by the accumulation of unmetabolized acetaldehyde in his blood.

The enzyme or enzymes metabolizing acetaldehyde are also unclear. Six enzymes capable of this function (in vitro) are known to exist in the body. Three of these are found in muscle in considerable quantities. Since in actuality living muscle barely metabolizes acetaldehyde at all, it seems unlikely that these enzymes play any important role in the metabolism of acetaldehyde by the living animal. The three others are all present in the liver, which is the primary site of acetaldehyde metabolism, and are called, respectively, xanthine oxidase, aldehyde oxidase and aldehyde dehydrogenase (or mutase).

The enzyme actually metabolizing acetaldehyde must be inhibited by antabuse in low concentrations. This condition rules out xanthine oxidase to start with. Both of the other known enzymes are inhibited by antabuse in this way, but cause acetaldehyde to be converted to acetic acid in the test tube. Since acetic acid is not formed in the living animal in measurable amounts by the metabolism of acetaldehyde, it is suspected either that the acetic acid itself is metabolized very rapidly by the body or that acetaldehyde is converted directly to acetyl CoA without acetic acid ever being formed. The latter theory would imply the existence of another enzyme, as yet undiscovered.

Under a grant from the Committee on Problems of Alcohol, Dr. Hulpieu of the Indiana University Medical Center has been working with animal (bone) charcoal, a substance which in moderate doses will produce an antabuse-like reaction to alcohol in both dogs and men. In a clinical trial he has found the symptoms produced by the two substances to be essentially identical. However, antabuse could not be isolated from animal charcoal, nor could any substance with an antabuse-like action be extracted from the charcoal by any of a variety of procedures. The active principle in animal charcoal therefore still remains a mystery.

Only two vitamins appear to be directly concerned in the metabolism of alcohol, nicotinic acid as mentioned above, and riboflavin in the conversion of acetaldehyde to acetic acid. There has been a surprising dearth of studies

on the effects of vitamin deficiencies on the metabolism of alcohol, especially considering the frequency with which vitamin deficiency states are found associated with chronic alcoholism.

Aided by a grant from the Committee on Problems of Alcohol, Dr. Richter at the Johns Hopkins Hospital has shown that rats fed an alcohol solution alone did not live appreciably longer if thiamine (vitamin B_1) was added to it, whereas rats fed dextrose and water and thiamine lived several times longer than those given dextrose and water alone. He feels that in some deficiency states alcohol may be more easily metabolized than glucose.

Dr. Hulpieu, (15) in addition to his work with bone charcoal, has studied the effects of thiamine (B_1) deficiency on the metabolism of alcohol in dogs, both by giving them a diet without thiamine in it and by giving them one of two other compounds (oxythiamine and neopyrithiamine) which act to block the action of the thiamine in the body and so produce a sudden artificial thiamine deficiency. One of these two compounds, oxythiamine, caused a sharp drop in blood sugar to occur when alcohol or acetaldehyde were given as well. He has postulated that thiamine plays some role in the metabolism of alcohol beyond the acetaldehyde stage.

In clinical medicine insulin and glucose have been used extensively in the treatment of acute alcoholic intoxication on the assumption that the metabolism of alcohol was speeded by this procedure. Well-defined studies of the actual metabolic effects of this treatment in man have unfortunately been few. (19) In the dog this method is effective if the animal is metabolizing alcohol at an initially subnormal rate, as described above, but is not effective otherwise. In man it would seem that large doses of insulin may increase the rate of alcohol metabolism by 50 per cent, but many patients do not show this effect.

III. CENTRAL NERVOUS SYSTEM ASPECTS OF ALCOHOL AND ALCOHOLISM

Despite the very obvious effects of alcohol on brain function, in producing good cheer in some people, violence in others, and ataxia or stupor in still others, it was, until recently, difficult to demonstrate any effect of alcohol on the metabolism of brain slices until massive levels, never found in the blood stream of any living alcoholic, were reached. However, a piece of brain by itself, in a solution in a laboratory bottle, is not being constantly stimulated by nerve impulses as it would be in the intact brain. The brain piece therefore shows only a basal - i.e. minimum - rate of oxygen consumption. It is now found that if this piece of brain is artificially stimulated, its metabolic rate rises sharply, and it can then be observed that alcohol levels equivalent to those found in moderate intoxication will markedly reduce this rise in metabolism. (30)

Beside this evidence, there is evidence that, in the sympathetic ganglionic nerve cells which act as a relay station in the transmission of nerve impulses from the spinal cord to the intestines, the passage of nerve impulses is blocked by levels of alcohol still too low to affect the metabolic rate of these cells. (23) So the question is open as to whether alcohol affects the

brain by interfering with the oxygen metabolism of brain cells or by blocking the transmission of nerve impulses from one cell to another by some other method.

One problem which may have influenced some of the results reported in the literature of the past is the failure of investigators to allow for the evaporation of alcohol from the solutions in which the brain slices were being incubated, as Dr. Grenell of the University of Maryland Medical School has pointed out. Under a grant from this Committee, he is currently working on the effects of both alcohol and acetaldehyde on slices of brain tissue and on small areas of the intact brain. He will study the changes produced in metabolism and electrical activity as well as in the concentration of adenosine triphosphate, a coenzyme shown to be of great importance in providing energy to nerve cells. He plans to compare the effects of alcohol to those of other narcotics. He has a number of animals being maintained on high, steady doses of alcohol for long periods, and is planning to compare the metabolism of their brains with those of animals getting a single dose of alcohol as well as with those of normal animals.

Using a technique developed for the study of anti-epilepsy drugs, Dr. Swinyard (1) of the University of Utah College of Medicine, with the aid of a grant from the Committee on Problems of Alcohol, has been studying the effect of the chronic administration of alcohol upon the amount of electrical stimulation needed to produce a convulsion in the rat. He has found that the amount of electric current needed was at first much greater in the alcohol-fed rat than in the normal rat, but this difference dropped gradually back to the normal level after about two weeks of daily convulsions and constant alcohol intake. No lowering of the convulsion threshold occurred after the alcohol was stopped. These findings imply that the brain adapts to alcohol over a period of time, and support the common observation that heavy drinkers can often function well at blood alcohol levels that would cause intoxication in a relative abstainer. More work on this problem of "tolerance" to higher blood levels of alcohol is badly needed.

The effect of alcohol on a particular property of the brain was studied in the cat by Drs. A. E. Walker and W. J. Horsey (13) of The Johns Hopkins Medical School under a Committee on Problems of Alcohol grant. Most soluble substances, salts, drugs, dyes, etc., spread out through most of the body in a uniform manner; but between the blood and the central nervous system there is a "barrier" through which many substances move at a very slow rate and through which some substances, like dyes, cannot pass at all.

Now, in autopsies done on alcoholics, what is called a "wet brain" is generally found, i.e. a brain which is swollen with extra water. The reason for this is unknown. Dr. Walker hypothesized that alcohol might break down this blood-brain barrier, allowing more water and salts to pass through, therefore producing the observed "wet brain". In his experiments on cats, however, he could find no significant increase in brain weight or water content in "alcoholic" cats, nor could he observe any change in the permeability of the barrier to certain dyes. He felt, therefore, that the "wet brain" could not be attributed to alcohol per se, and wondered whether lack of vitamins or other

factors contributing to death in chronic alcoholics might be the cause of the observed cerebral changes at post-mortem examinations. He also studied the brain wave changes which occurred when cats were studied at various blood alcohol levels and found the expected gradual depression of brain function. (14)

One possible approach to the problem of alcoholism, as well as to drug addiction and to the observed differences in the effects of drugs with potent psychological effects in differing individuals, is the more detailed study of the effects of these drugs on specific centers and pathways in the central nervous system. Work of this sort is complex and difficult, but techniques of neurophysiology necessary for such work are rapidly improving. It seems at least possible that the hypothalamus, the part of the brain which most directly controls endocrine gland function and cardiovascular, gastro-intestinal, and other autonomic functions of the body may be involved and that alcohol, at least in some alcoholics, serves to decrease or eliminate such painful emotions as anxiety, tension, resentment, or depression.

Good work along these lines will most often be done by investigators who plan to study a number of different drugs along with ethyl alcohol itself. To obtain the knowledge needed in the field of chronic alcoholism it will be necessary to support work by investigators who are not always working with alcohol alone.

Dr. Oskar Diethelm (45) of Cornell University Medical College has been working with three "autonomic" substances found in the blood, which affect the contractions of isolated rabbit intestine and rat uterus in specific ways. The blood levels of these three substances correlate well with clinically observed levels of anxiety, tension, and resentment, respectively, in psychiatric patients. A group of fifty-seven chronic alcoholics have been studied. Many of these showed consistently higher "resentment" substance levels in their blood than did other psychiatric patients, and appeared clinically resentful as well. This substance was found to be especially elevated before the patients went on a drinking spree, and, in the laboratory, six ounces of alcohol given to these patients would usually bring the resentment substance level in the blood almost to zero. Tension substance along with observed tension was also markedly reduced in some alcoholic patients by alcohol feeding.

In nonalcoholic psychiatric patients neither tension nor resentment was dramatically changed by drinking alcohol (whiskey).

Other drugs such as dexedrine (a stimulant), sodium amytal (a sedative-barbiturate), and mephenesin (a muscle relaxant) were able to cut down both observed tension and "tension substance" in some alcoholic and some nonalcoholic patients, but no drug other than alcohol has been found which has affected resentment substance levels appreciably. The blood substances involved in the above research are currently being isolated for further study by special biochemical procedures in the Department of Pharmacology at Cornell.

It should be cautioned that tests of the pharmacological activities of shed blood are full of hazard because slight differences in the way the tests are made may make large differences in the results obtained. Therefore, many members of the Committee on Problems of Alcohol believe that this work needs confirmation before too much weight should be put upon the results.

However, work of this sort on the brain and the autonomic nervous system offers considerable hope that in the future the gap between the personality problems of the chronic alcoholic and the biochemical-physiological maladjustments related to his drinking may be narrowed and finally closed.

A grant has recently been awarded to Dr. Leon Greenberg of the Laboratory of Applied Psychology at Yale to study the effects of alcohol on conditioned behavior in rats. The use of laboratory animals in a standardized environment (the Skinner Box) under standardized training conditions will make possible a more detailed and specific study of the effects of alcohol on behavior than would be feasible in the human subject.

IV. FACTORS INFLUENCING VOLUNTARY ALCOHOL CONSUMPTION

A number of attempts have been made to create "chronic alcoholism" in laboratory animals, in the hope that the means by which it could be produced would throw light on the etiology of the condition in man.

The most commonly used technique in these studies has been the multiple choice feeding method. In this the rat (or other animal) has access to a number of bottles containing differing solutions, which in the simplest experiment would be two bottles, one containing an alcohol solution and one filled with water. The consumption of fluid from these bottles can be measured and compared at regular intervals.

In an attempt to investigate possible effects of constitution and heredity in alcoholism, the spontaneous alcohol consumptions of a variety of types of animals have been studied by Drs. Williams, Emerson, and Richter, among others, the latter two being aided by the Committee on Problems of Alcohol grants. The rat may consume small amounts spontaneously but never enough to produce intoxication. However, Dr. Emerson of the University of Texas Medical Branch in Galveston, has found that hamsters, wood rats, and deer mice all drink significantly more alcohol than do the conventional laboratory rats and mice. Work aimed at studying the possible effects of heredity on alcohol consumption in the hamster has produced equivocal results. The offspring of "heavy drinking" hamster parents seem to be quite variable in their alcohol consumption. This has led Dr. Emerson to feel that if genetic factors in alcohol intake are present, they are very complex and obscure.

Dr. R. J. Williams (47) of the University of Texas had received a small grant-in-aid from the RCPA which was still in effect at the inception of the National Research Council committee. His work has been based in general on the thesis that alcoholism is a deficiency disease caused by differing requirements for vitamins in different individuals, probably on a hereditary basis. In his past work with rats he has shown that vitamin deficiencies will

cause an increase in voluntary alcohol consumption in white rats. This increase is not great, and his work has since been criticised by other workers in the field. (25) The RCPA grant was made to enable him to investigate further his theories on biochemical individuality in man, work which he hoped would help in the identification of the biochemical abnormalities which might exist in alcoholics.

Dr. Curt P. Richter of The Johns Hopkins University has tried by a variety of methods to influence the alcohol consumption of the rat. He has been able, in a few individual wild rats only, to produce a large and eventually fatal appetite for alcohol solutions by making the rats drink a 20% alcohol solution for a long period of time in order to get drinking water. When again given access to straight water, a few of these animals continued drinking alcohol by preference, stopped eating, and eventually died.

Dr. Richter warns that anything used in experiments of this sort which makes the rat's food taste badly will force him to obtain more of his calories from alcohol. In that type of situation a sugar solution will be preferred to the alcohol solution if both are offered. Dr. Richter (31) has found that if rats are forced to take alcohol in their water they will cut down on their other food intake by the exact number of calories they must take in with their water in the form of alcohol.

Recently Dr. Richter has found that rats given thyroid extract will stop drinking alcohol entirely, although they have previously been voluntarily consuming small but definite amounts daily. He is interested in determining whether hyperthyroidism or the giving of thyroid hormone can be shown to have an effect on human alcoholism.

Under a grant from the Committee on Problems of Alcohol, Dr. M. X. Zarrow (50) of Purdue University has studied the effects of castration, diabetes, removal of the adrenal glands, administration of cortisone, exposure to cold, and administration of thiouracil on the voluntary alcohol consumption of the rat. Of these, only thiouracil caused any increase in alcohol consumption, and even this increase disappeared when the animal was offered sugar solution as well. It can, therefore, be presumed that the bad taste of thiouracil in the food induced the animal to seek calories elsewhere, and did not produce any specific craving for alcohol by making the animal's thyroid underactive.

V. PHYSIOLOGICAL EFFECTS OF ALCOHOL

The general physiological actions of alcohol, both short-term and long-term, are of considerable interest. The changes in the salt and water balance in the body in the alcoholic have been subjected to a good deal of study, much of it controversial. The question of the diuretic action of alcohol (i.e., does alcohol make the body pass more urine than it otherwise would?) has also not been settled adequately.

Early German experiments with beer drinkers showed that their subjects passed identical amounts of urine after drinking the same large quantities of either beer or water.

Dr. Knoefel of the University of Louisville School of Medicine, under a Committee on Problems of Alcohol grant, has been re-exploring the subject in dogs and has been able to demonstrate a definite diuretic action of alcohol much in excess of the diuretic effect of a comparable amount of water. He will be pushing forward this work, which had been delayed while he worked out some of the problems involved in measuring total body water and extracellular body water, data necessary for the proper interpretation of water, salt, and other electrolyte excretion figures obtained in such experiments.

A grant-in-aid has recently been given to Dr. L. A. Sapirstein of Ohio State University to study other aspects of this problem, including the action of alcohol in cardiac patients who retain too much water in their bodies.

Related to the salt-retaining ability of the body as well as many other of the bodies' self-regulating mechanisms is the cortex of the adrenal gland. Dr. J. J. Smith (36) of Bellevue Hospital had been studying the adrenal function of chronic alcoholics under a grant from the RCPA, which was continued for an additional two years under the present Committee. He found some evidence of impaired adrenal function in about one-third of a large group of chronic alcoholics and evidences of pituitary malfunction in about another third. In addition, he felt that certain physical findings frequently found in chronic alcoholics could be related to partial adrenal insufficiency or other hormonal imbalance.

The adrenal cortex, and the pituitary-hypothalamic system which controls its activity, are both very complex structures with many and diverse actions. Great strides have been made in the understanding of pituitary and adrenal physiology in the last few years, and perhaps the time is now ripe for a more detailed and complex appraisal of the situation which Dr. Smith has explored with less refined techniques. Work in this area is so complex and expensive however, that it may be necessary for the Committee to interest one of the centers actively engaged in this work in using their methodology in studying chronic alcoholism. The cost of setting up a new alcoholism research unit capable of handling this problem would be prohibitive.

Dr. Smith (37) also evaluated the therapeutic effects of both an extract of the adrenal cortex and ACTH (adrenocorticotrophic hormone, the hormone from the pituitary which stimulates the adrenal cortex to excrete its own hormones) on acute alcoholic intoxication, the hangover, delirium tremens (D.T.'s), and Korsakoff's psychosis (a serious chronic organic mental illness sometimes occurring in chronic alcoholics). He observed beneficial results in all these conditions. His results have been challenged elsewhere since that time, and further study by other investigators would be desirable. (34, 29, 44)

Dr. F. W. Ellis of the School of Medicine of the University of North Carolina has recently been given a grant to study the effects of both acute and chronic alcohol intoxication on adrenal function in the dog. He will also study the effects of both acute and chronic alcohol intoxication on carbohydrate and alcohol metabolism, and will endeavor to determine whether prolonged intoxication over a six-month period can produce adrenal insufficiency as hypothesized by Smith (36) and by Tintera and Lovell (26).

With the aid of a grant from the Committee on Problems of Alcohol, Dr. J. C. Forbes of the Medical College of Virginia has studied the effects of various vitamin deficiences on the response of the adrenal cortex to alcohol administration in rats and guinea pigs. The adrenal cortex, in addition to its hormones, contains considerable amounts of ascorbic acid (vitamin C). When the normal adrenal cortex is stimulated by a stress - injury, cold, fright, or alcohol injection - its ascorbic acid content drops sharply. This drop is assumed to accompany the release of the protective hormones by the adrenal cortex which enable the body to handle stress effectively.

Dr. Forbes (6, 7) has shown that ascorbic acid itself does not protect guinea pigs against lethal doses of alcohol, but it does appear to hasten full recovery in those animals which survive large doses.

Using somewhat smaller doses of alcohol, he has studied the effects of severe thiamine (vitamin B_1), pantothenic acid, riboflavin (vitamin B_2), and pyridoxine (vitamin B_6) deficiencies on the adrenal response to alcohol administration as determined by the drop in adrenal ascorbic acid. There was no appreciable change in the amount of this response after alcohol administration in either the thiamine deficient animals or the pyridoxine-deficient animals. The pantothenic-acid-deficient animals showed a variable change in the response, while the riboflavin-deficient animals showed a complete lack of response to the alcohol injection.

VI. CLINICAL RESEARCH IN CHRONIC ALCOHOLISM

In recent years the general trend of the Committee on Problems of Alcohol has been away from the support of clinical research in the field of alcoholism. This trend has been in part due to the Committee's predominant concern with the metabolic, physiologic, and pharmacologic aspects of chronic alcoholism and in part due to the considerable expense involved in the support of good clinical research.

However, two of the six projects which the RCPA had been supporting at the time it transferred its research functions to the NRC were clinical studies. One, under Dr. J. J. Smith, has been described. The other, under Dr. Oskar Diethelm, was a five-year project of considerable scope whose support under the CPA ended in 1953. A full report of this work has recently appeared in the form of a book, "Etiology of Chronic Alcoholism," edited by Dr. Diethelm and published by C C Thomas in 1955. The work described therein on emotions and biochemical changes in the blood has already been outlined above.

In addition to a detailed report of that work, the book contains reports on Dr. Mary Jane Sherfey's clinical classification of chronic alcoholics, Dr. Manfred Bleuler's work on constitution and heredity in chronic alcoholism, and Dr. Milton Barnett's work on alcoholism among the Cantonese in New York City.

Dr. Sherfey presented the results of her detailed study of the case records of 161 chronic alcoholic patients who had been treated at Payne-Whitney Clinic since 1932. (27 of these were treated by the writer and 49 by her colleagues during the period of her study). She found that 42.8% of this group could be given conventional psychiatric diagnoses, as follows:

Paranoid Schizophrenia	14 Cases	8.7%
Manic Depressive Reaction	11 "	6.8%
Poorly Organized Asocial Psychopathic Personality	11 "	6.8%
Poorly Organized Psychoneurotic Psychopathic Personality	15 "	9.3%
Epilepsy and Epileptoid Reactions	7 "	4.3%
Brain Damage	5 "	3%

The remaining 59.6% (92 cases) fell into the group generally classified under the less exact term "character disorder" (meaning people with distorted personalities rather than more obvious psychiatric symptoms). These patients were descriptively classified into five groups. The first group consisted of rigidly organized "obsessive compulsive" personalities (males, 22 cases, 13.6% of total groups studied). These were relatively successful men in the middle life period (41 - 60) in whom the problems of their age group had upset their pre-existing rigid, neurotic life adjustment.

The second group was composed of rigidly organized neurotic personalities with paranoid features (females, 17 cases, 10%). These women had strongly masculine personality strivings which they were unable to satisfy adequately, which resulted in marked resentment. They were controlling and domineering women, given to suspiciousness and the misintrepretation of things happening about them.

The third group of poorly organized, inadequate psychoneurotic personalities (males, 30 cases, 18.6%) resembled most closely the frequently described "typical alcoholic". They were passive, dependent, and neurotic, and had vague life goals and poor life achievements despite high intelligence.

The fourth group consisted of dependent psychoneurotic personalities with depression and tension (females, 12 cases, 7.4%). These passive women were quite immature and had reacted with depression, tension, and alcoholism when their marked need to be dependent was not satisfied.

The fifth group (5 males, 6 females; 11 cases, 6.8%) consisted of individuals who had developed depressions of milder intensity than those usually given formal psychiatric diagnoses and had concurrently begun to drink excessively, becoming chronic alcoholics. These illnesses occurred in the middle or later life periods in reaction to threats to their security.

Dr. Sherfey felt strongly that alcoholism was a symptom rather than a single disease, and that it occurred in a variety of psychiatric conditions and personality disorders. She felt that all the patients in her series showed personality defects prior to the onset of their chronic alcoholism which were causally related to the development of their alcoholism. There was a high incidence of alcoholism in the families of her patients, this occurring in 68% of the women and 44.9% of the men. In almost all these cases the alcoholism of a family member occurred during the patient's childhood, thereby producing a strong psychological influence in addition to the possible constitutional influence.

Dr. Manfred Bleuler of the University of Zurich and the Burghölzli Psychiatric Clinic, after working in cooperation with Dr. Diethelm for a year at the Payne-Whitney Clinic, reported in this volume on his endocrinologic evaluation of fifty American alcoholics treated at Payne-Whitney Clinic. Of these, fourteen showed mild but distinct endocrine derangements, while four others showed questionable ones. Some causal relationship between the endocrine problem and the alcoholism seemed probable in twelve of these eighteen patients and a questionable relationship existed in three others, while in the remaining three patients the two conditions appeared definitely unrelated. The endocrine abnormalities found, however, included such diverse conditions as questionable hyperthyroidism, hypothyroidism, sexual underdevelopment, early menopause, diabetes mellitus, and physical characteristics of the opposite sex. No one condition appeared with any significant frequency, and Dr. Bleuler did not feel able to state definitely that these endocrinologic disturbances were either a cause of the alcoholism or a secondary result of either an accompanying morbid psychological condition or of the alcoholism itself.

In his study of familial incidence of various diseases among these fifty American chronic alcoholics, Dr. Bleuler failed to find any evidence that alcoholism in the first generation led to either epilepsy or feeble-mindedness in the second generation. There was no increase in the frequency of occurrence of schizophrenia in the relatives of these chronic alcoholics, while the frequency of alcoholism among the relatives of this group was much higher than that found in the general population.

In general, he felt that the long-standing scientific hope that the effects of constitution could be separated from those of the environment in the causation of chronic alcoholism was doomed to failure because of the striking interweavings of these factors found in both his Swiss and American patients.

It should be noted that the work of Dr. Diethelm's group has been done on privately hospitalized chronic alcoholics whose intellectual and educational levels were far above the average for the general population. Dr. Bleuler contrasted his findings in the fifty patients of the Payne-Whitney group with those he had obtained on Swiss alcoholics with a considerably different, generally lower middle class, background.

In the last section of the book, Dr. Barnett described in an interesting manner the use and abuse of alcohol in New York's Chinatown, giving a good deal of background information on Chinese culture and its interactions with American culture. Of especial interest was the Chinese use of drinking as a competitive phenomenon at banquets and parties, at which they would try to get others drunk without becoming so themselves. A number of drinking "games" were used to achieve this end. The man who withdrew from this competition was not ridiculed, but would admit by implication that he could not hold his liquor as well as his challenger. However, the man who became intoxicated would be subjected to considerable disgrace and ridicule from the group.

The Cantonese culture placed a far greater stigma on drunkenness than did the American culture, with apparent resultant reduction in the incidence of chronic alcoholism. The Cantonese clannishness and their strong need to conceal anything so disgraceful as alcoholism from outside eyes made any valid estimate of the real prevalence of chronic alcoholism impossible, however.

VII. COMPLICATIONS OF CHRONIC ALCOHOLISM

Dr. S. Mallov of the State University of New York at Syracuse has been studying the causation of one of the most important complications of chronic alcoholism, cirrhosis of the liver. It had been generally assumed in recent years that all the complications of chronic alcoholism - cirrhosis of the liver, delirium tremens, nerve paralyses, et cetera - were due to the vitamin deficiencies so commonly found in chronic alcoholics. This concept has recently been shaken in the case of delirium tremens by the work of Dr. H. Isbell (17) of the Drug Addiction Research Unit at Lexington, Kentucky, who has demonstrated that delirium tremens could occur in volunteer subjects, who have been kept on a constant high level of alcohol consumption, when the alcohol was withdrawn. This could occur despite the fact that these subjects were kept on high doses of vitamins throughout the entire experiment.

Dr. Mallov (27) has been currently studying in rats the effects of alcohol substituted calorie for calorie for some of the carbohydrate in their standard diet. He has found that these alcohol-fed rats would develop fatty livers (which is believed but not proven to be the beginning stage of cirrhosis of the liver) on diets which should be quite adequate in all necessary vitamins. A deficiency in choline, a vitamin-like substance, would also produce fatty liver. Choline appears to be necessary for the proper metabolism of fat. It may be, as suggested by Dr. Westerfeld of our Committee, that alcohol is metabolized in many ways more like a fat than like a carbohydrate and may therefore increase the amount of choline needed by the body. This hypothesis is partially confirmed by Dr. Mallov's finding that this action of alcohol in producing a fatty liver in the rat could be counteracted by giving large supplementary doses of choline.

He has observed that the rats which took some of their calories as alcohol did not grow as rapidly as control rats receiving diets with the same calorie content but without alcohol.

In longer-term experiments in which both the alcohol-fed rats and their controls were given diets very low in choline, it was observed that the alcohol-fed rats developed increased liver fat much more rapidly than did their controls, but in the long run both groups developed about equally fatty livers.

Dr. Mallov has also observed that the adrenals of his chronically intoxicated rats are enlarged, and that rats whose adrenals have been removed do not develop fatty livers from alcohol. He plans to investigate further the manner in which the various endocrine glands influence the deposition of fat in the liver.

VIII. OTHER WORK SUPPORTED

Work has been supported also in other areas related to alcoholism. In view of the considerable usage of disulfiram (Antabuse) in the treatment of chronic alcoholism, a grant was made to Dr. H. Holck of the College of Pharmacy of the University of Nebraska for the study of the effects of disulfiram on the growth rate, fertility, and length of life of the white rat. The initial experiments used amounts of Antabuse in the rat's diet equivalent to 5 to 10 times the normal human daily dose.

At these high levels definite deleterious effects were noted on both growth and fertility, with questionable effects on life span.

When rats were fed dosages more nearly equal to those used in clinical medicine no significant harmful effect on either growth or fertility could be detected, although the number of rats used in the fertility study was too small to permit the drawing of definite conclusions.

One other project supported by the Committee on Problems of Alcohol illustrates well the impossibility of confining research rigidly to one specific field. The findings, although not pertinent to alcoholism, are of very definite scientific interest.

Dr. V. A. Najjar of The Johns Hopkins Hospital in Baltimore was given a grant in 1952 to investigate the following hypothesis. It had been shown that certain bacteria, if raised in a medium containing large amounts of a given substance, would develop large amounts of the enzyme needed to metabolize this substance. Dr. Najjar therefore wondered if rats fed large amounts of alcohol over a prolonged period would develop increased amounts of the alcohol dehydrogenase enzyme in their livers. His first group of rats did just the opposite; their liver alcohol dehydrogenase dropped strikingly as compared with normal controls. He attempted to repeat this observation with other groups of rats and also with mice, but was unable to obtain similar results.

In the course of this work an epidemic of infectious dysentery occurred in his mouse colony. He noted that the alcohol-fed mice almost all died, while their normal controls remained healthy. He wondered whether the alcoholic mice were unable to make antibodies and therefore unable to protect themselves against infection.

Using rabbits as subjects and alcohol dehydrogenase enzyme found in yeast as an antigen (a foreign substance against which the body must make antibodies to protect itself), he found that chronic alcohol intoxication did not affect the rabbit's ability to make antibodies.

In working with this problem, however, he was able to demonstrate that the organism produced two types of antibodies instead of the single type heretofore described. His animals initially produced antibodies which reacted with the antigens to form single larger molecules, as would be expected. He detected, however, a second type of antibody which would be formed several days after the antigen was injected. This antibody would react to the antigen-antibody combinations described above to form a still larger molecule, but would not react to the original antigen by itself. This phenomenon may be related to the delayed symptoms appearing in certain diseases, and is a finding of considerable importance to the study of the processes of immunity and hypersensitivity. Dr. Najjar has therefore understandably shifted his interest from problems of alcohol to the field of immunology.

IX. OTHER RCPA PROJECTS

Other projects in effect at the time of transfer of the research functions of the Research Council on Problems of Alcohol to the NRC in addition to the three described above included a three-year grant to Drs. M. R. Fields and J. B. Nash of New York University School of Education to provide scholarships to a course on alcohol education and a single small grant to Dr. W. Voegtlin of the University of Washington School of Medicine to study the hypothesis that an allergy to alcohol existed in chronic alcoholics.

The grant for alcohol education was productive of a number of unpublished student reports outlining techniques, methods, and course materials to be used in alcohol education. The course ran as a special course in the academic years 1949-1950 and 1950-1951. Twelve graduate students took the course the first year and thirteen the second. In the third year of the program only enough fellowship money was available to provide scholarships for four students. The material on alcohol education was therefore incorporated in a course, "Methods and Materials of Teaching for Health."

Dr. Voegtlin's work, supported only in part by RCPA funds, attempted to confirm studies suggesting that allergic reactions to alcohol could be produced in experimental animals and that alcoholics would show, by skin tests, evidence of allergy to alcohol. Drs. Voegtlin and Robinson (32) were completely unable to reproduce any of the results previously reported by either Loiseleur or Maniloff. They concluded that no allergy to ethyl alcohol (they used a highly purified alcohol prepared from sugar cane) could be produced in experimental animals or demonstrated in human alcoholics by the methods

suggested in the above papers. They suggested that other constituents of certain alcoholic beverages might conceivably account for the earlier results reported, but did not feel that a true allergy could produce chronic alcoholism.

X. SUMMARY

In conclusion it may be stated that 18 research projects have been supported by the National Research Council's Committee on Problems of Alcohol for periods of from one to four years. Three of the five projects which began under the Research Council on Problems of Alcohol were continued under this Committee for two or three years. Fourteen scientific articles and one book have been published reporting work supported wholly or in part by grants from the CPA. This work has been made possible by the generous gifts of the Licensed Beverage Industries, which have shown their faith and interest in the Committee's work through their continued support of its grant-in-aid program over the six-year period of the CPA's existence.

The Committee feels that, although much is known about the metabolic, physiologic, and pharmacologic aspects of the problems of alcohol, many important gaps in our knowledge still exist. Work in these areas warrants continued and expanding support, both to maintain present workers in the field and to encourage new research personnel to undertake work of this sort. Experienced investigators in adjacent fields should also be encouraged to include work on alcohol and alcoholism in their research programs.

The Committee will in the future have to consider further how best to expand its activities in stimulating and coordinating work in the metabolic, physiological, and pharmacological aspects of alcoholism. One research colloquium was held by the Committee in the spring of 1955, which was attended by all current grantees and a few selected guests. The Committee felt that the discussion and interchange of ideas which took place at that meeting was most beneficial, and has been considering organizing further conferences of this sort.

In addition, the Committee will have to consider again expanding its activities into more clinical areas, since laboratory results in experimental animals will in the future point out the need both for specific investigations of the metabolism and physiology of the alcoholic patient and for the scientific testing of proposed methods of treatment for chronic alcoholism.

Appendix A

List of Grants

COMMITTEE ON PROBLEMS OF ALCOHOL

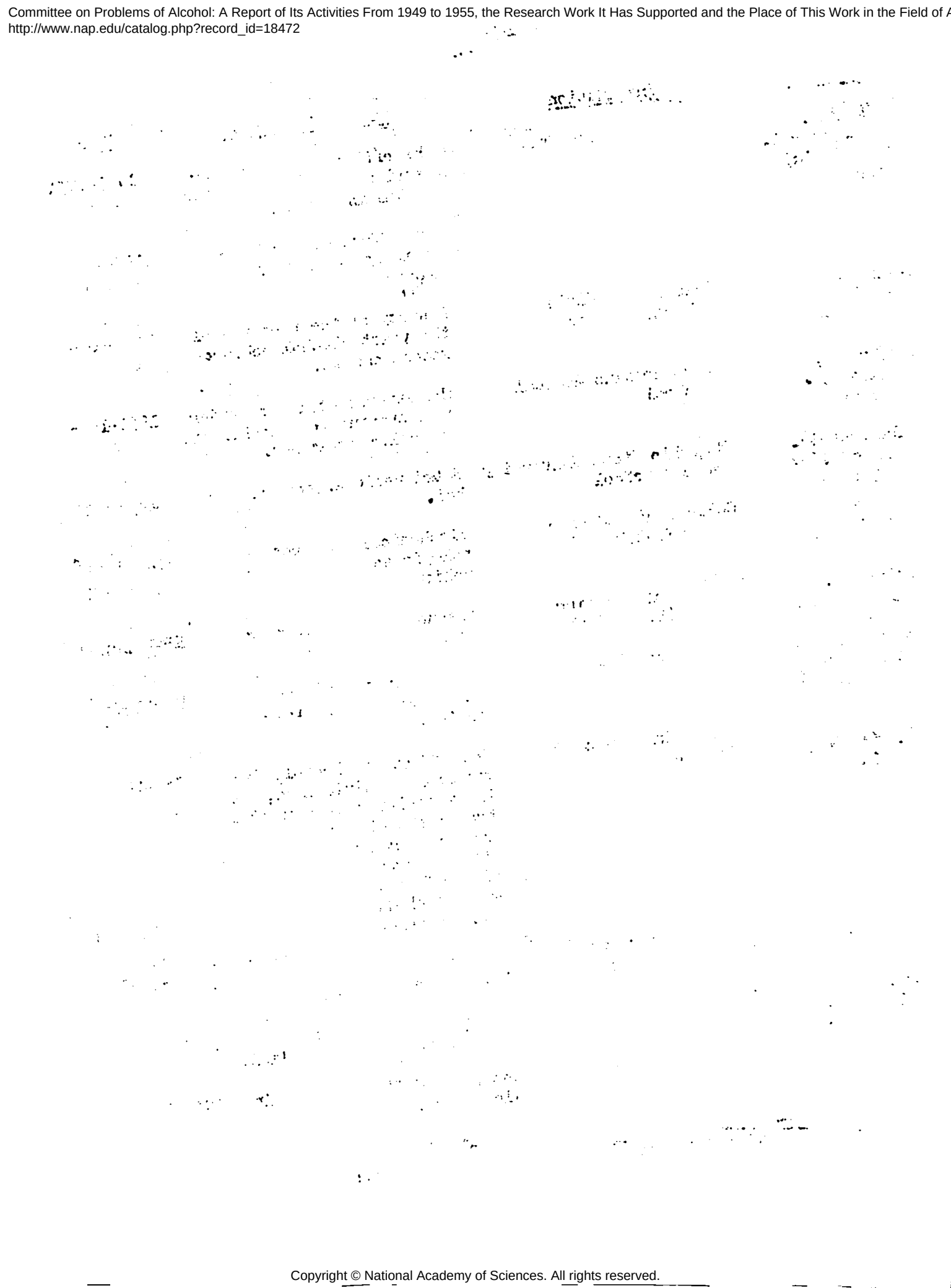
Grantee	Institution	Title of Research	Year
Diethelm, Oskar	Cornell University Medical College - New York Hospital	Research on the etiology of chronic alcoholism.	1947-1951*
		Pharmacologically active substances found in the blood of alcoholic subjects.	1952-1953
Ellis, Fred W.	School of Medicine University of North Carolina	The possible relationship between adrenal cortical function and experimental alcoholism.	1955-1956
Emerson, G. A.	The University of Texas Medical Branch	Factors affecting voluntary intake of alcohol in experimental animals.	1953-1955
Fields, Morey B. and Nash, Jay B.	New York School of Education	Grant for the establishment of a course in alcohol education, to run for a 3-year period.	1949-1951*
Forbes, J. C.	Medical College of Virginia	The effect of ascorbic acid intake on (a) the concentration of ascorbic acid and cholesterol in the adrenal glands of the guinea pig following a state of acute alcoholic intoxication, and (b) the LD_{50} of ethyl alcohol for guinea pigs .	1951-1952
		The role of pantothenic acid and vitamin C in alcoholism.	1952-1954
Greenberg, Leon A.	Yale University	The effects of small and moderate amounts of alcohol as influenced by accommodation and oxygen tension.	1955-1956
Grenell, Robert G.	University of Maryland Medical School	The effects of alcohol on fundamental properties of the nervous system.	1951-1955
		Effects of alcohols on cerebral neurons.	1955-1956

* Support initiated under Research Council on Problems of Alcohol.

Grantee	Institution	Title of Research	Year
Hine, Charles Henri	School of Medicine University of California	The metabolism of ethanol in vivo and in vitro.	1952-1956
Holck, Harald	College of Pharmacy University of Nebraska	The inhibitory effect of tetraethylthiuram disulfide (Antabuse) upon reproduction of the albino rat.	1953-1954
Hulpieu, H. R.	School of Medicine Indiana University	Pharmacological comparison of agents which have been reported to increase the toxicity of alcohol.	1951-1953
		Studies on an Antabuse-alcohol reaction produced by animal charcoal followed by the ingestion of alcohol.	1953-1956
Kinard, Fredrick W.	Medical College of South Carolina	The role of catalase in ethanol metabolism.	1954-1955
		The effects of alcohol dehydrogenase and catalase levels on the ethanol oxidizing capacity of the liver.	1955-1956
Knoefel, Peter K.	School of Medicine University of Louisville	The changes in water and electrolytes in experimental alcoholism.	1953-1956
Mallov, Samuel	The Research Foundation of State University of New York	The production of fatty livers in rats by chronic ethanol intoxication, and the role of lipotropic agents.	1953-1955
		The role of hormones in the production of fatty infiltration of the liver in rats by means of acute ethanol intoxication.	1955-1956
Najjar, Victor A.	Johns Hopkins University	The identification and purification of the enzymes responsible for alcohol utilization and study of their biochemical characteristics.	1952-1953

Grantee	Institution	Title of Research	Year
Najjar, Victor A. (Cont'd)	Johns Hopkins University	The effect of alcohol ingestion on the dehydrogenase system in tissues.	1953-1954
		The effect of alcohol on the antibody to alcohol dehydrogenase.	1954-1955
Racker, Efraim	School of Medicine Yale University	A study of the property of the yeast alcohol dehydrogenase enzyme.	1953-1954
Richter, Curt P.	Johns Hopkins Medical School	The experimental production of a craving for alcohol and alcoholic beverages.	1951-1955
Sapirstein, Leo A.	The Ohio State University Medical School	Natriuretic effects of alcohol.	1955-1956
Smith, James J.	College of Medicine New York University	Biochemical and endocrinologic aspects of alcoholism.	1948-1951*
Swinyard, Chester A.	College of Medicine University of Utah	Tissue tolerance to alcohol.	1954-1956
Voegtlin, Walter L.	University of Washington	Studies on the allergic factor in chronic alcoholism.	1948-1949*
Walker, A. Earl	Johns Hopkins Medical School	The effect of alcohol, parenterally administered, upon the vascular system of the brain; the effect of alcohol upon cerebral vascular permeability; and the pathogenesis of the "wet brain" seen in some alcoholics and its relation to cerebral edema.	1951-1953
Williams, Roger J.	Biochemical Institute University of Texas	Metabolic factors in the etiology of alcoholism.	1947-1949*
Zarrow, M. X.	Purdue University	The relationship of the adrenal gland to alcoholism.	1951-1953
		The role of the hormones in alcoholism.	1953-1954

*Support initiated under Research Council on Problems of Alcohol.



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