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AN INVESTIGATION OF THE
GENETIC BASIS OF ALCOHOLISM

by

Daniel F. Malamud

A thesis presented to the
Faculty of the School of Graduate
Studies in partial fulfillment
of the
Degree of Master of Arts

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INTRODUCTION

Alcoholism: The Disease

"Alcoholism is a chronic disease manifested by repeated implicative drinking so as to cause injury to the drinker's health or to his social or economic functioning" (53). Such a definition of alcoholism points to the disease concept which went unrecognized until recent years. In addition to its medical implications, alcoholism has been the subject of considerable writing and research by academicians in such diverse fields as sociology, psychology, physiology, psychiatry, theology, and law.

At the outset it should be noted that the writer is aware of the arguments and opinions expressed by the advocates of the several disciplines as mentioned above, and it is fully realized that all of the above have a proper and just place within the scope of the problem of alcoholism. It should be realized that any problem may be approached from a variety of positions, and in the case of a disease, several different etiologies, pathologies, and treatments may be valid. Thus, although the writer is concerned

with the physiological-genetic aspects of alcoholism, it should be understood that sociological, psychological, and other factors play an important role in the precipitation of the disease.

There remains a great deal of uncertainty in the realm of the physiology and biochemistry of alcoholism, particularly with respect to the etiology of the disease. If it were possible to define clearly the role of biochemistry and genetics with respect to the onset of alcoholism one would have a valuable tool at hand to use in the treatment and prevention of this disease which affects some five million Americans.

The Role of Genetics in Disease

The science of genetics as it applies to human disease has only recently become an important consideration. Early studies in genetics were confined to plants and the lower animals mainly because man is a difficult form in which to study inheritance. As Stern (98) points out, man demonstrates a great deal of genetic diversity and humans mate without concern

for the experiments of geneticists.

Following Mendel's rediscovery, early in the twentieth century, it was possible to illustrate the inheritance of dominant and recessive traits as well as the resulting 9:3:3:1 or 3:1 ratios. As the study of genetics advanced, it became clear that one could not describe all inheritance, particularly in the realm of human genetics, on the basis of simple Mendelian genetics. At the present time a genetic analysis is complicated by such factors as the existence of polygenes, incomplete penetrance, sex linkage, variable expressivity, modifying genes and other factors that make it difficult to say definitely whether or not a given trait or disease has a genetic basis.

It should be stated that when reference is made to a genetic basis for alcoholism, the reference is not to inheritance of the disease per se, but rather to the inheritance of a gene(s) which confers a pre-disposition to the disease, which then may or may not be manifest depending on the environment. It is now becoming clear that many diseases which were not thought to have a genetic basis due to the lack

of clear and simple Mendelian patterns, do in fact owe their expression, in part at least, to the genotype. Thus research has been directed towards an investigation of the role of genetics in lung cancer, leukemia, schizophrenia, epilepsy, diabetes mellitus, tuberculosis, and many other diseases.

Nature of the Present Study

The present study is designed to investigate the genetic basis of alcoholism, and, to a lesser extent, the relationship between smoking and alcoholism and the genetic basis of smoking.

Although there is some evidence suggesting a relationship between smoking and drinking (16, 17, 67) the writer has been unable to locate any studies relating to smoking and alcoholism. It was thus believed feasible to collect data relevant to smoking and alcoholism and by administering several genetic tests to the subjects, relate smoking and alcoholism as well as to determine if any relationship existed between the traits investigated and either smoking or alcoholism. If one or more of the genetic traits investigated was found to occur with greater frequency

in the experimental group than in the control group, linkage would be suggested, whereby the gene(s) responsible for the genetic trait was located on the same chromosome(s) as the gene(s) predisposing to the conditions investigated.

Many studies have been undertaken to investigate linkage between two particular traits and in general the experimenter has concluded that no evidence for linkage was found. This result may be expected if two traits are selected at random and an attempt is made to show linkage between them. Since there are twenty-three pairs of chromosomes in man, each of which "contains" an enormous number of genes responsible for a wide variety of traits, the chance of selecting two such traits at random and finding them to be linked is extremely improbable.

Prior to the selection of the genetic traits to be investigated, the writer visited several meetings of Alcoholics Anonymous in an attempt either to eliminate or select certain characteristics which might be representative of alcoholics. In this manner eye color, ear lobe structure, hair texture, body type, baldness, height, and congenital deformations

were eliminated. This elimination process was by no means infallible since under ideal conditions data would have to be collected and analyzed statistically before a definite conclusion could be drawn. It was assumed, however, that the above characteristics were not distinctive for the alcoholics observed. Two characteristics did tend to stand out. The first, which is fairly well documented in the literature (2, 31, 51, 52, 59, 66, 119) is that there are more male than female alcoholics, the ratio being on the order of six to one (2). In addition, it was noted that there was an excessive amount of cigarette smoking, particularly "chain smoking." These observations led to the present study.

The fact that male alcoholics outnumber female alcoholics six to one suggests that perhaps some type of sex linkage is involved. Red-green color blindness was selected as the sex linked trait to be investigated because it is relatively easy to determine (as opposed to hemophilia) and also because the number of color blind individuals roughly approximates the number of alcoholics (In the United States an estimated 8 per cent of the males and 0.5 per cent of

the females are color blind. This would be approximately 6.8 million individuals as compared with an estimated 5-6 million alcoholics).

The reasons for selecting the second trait to be investigated, the ability to taste phenylthiocarbamide (PTC), were somewhat more involved. As will be demonstrated, both alcoholism and the ability to taste PTC are related to hyperthyroidism.

Richter (87) noted that one rarely finds alcoholics among hyperthyroid patients. This observation led him to experiment on the role of thyroid extract in alcohol consumption by rats. He found that thyroid treatment (1 per cent of total diet) resulted in essentially stopping the intake of alcohol in a free-choice situation. Richter noted that thyroxine and triiodothyroxine were equally effective in reducing the rats' intake of a 10 per cent alcohol solution as well as wine, whiskey, and beer. According to Richter, the results suggest that excessive thyroid secretion in hyperthyroid individuals inhibits the appetite for alcohol. It should also be noted that PTC is an anti-thyroid substance which inhibits the formation of thyroxine and causes the condition

known as goiter (29). Fischer, et al. (22, 23), in a series of experiments found that the ability to taste PTC and other related compounds is associated with the enzymatic activity of the saliva, this activity being greater in non-tasters. They further demonstrated that certain thyroid precursors lower the taste thresholds for PTC and related compounds. The above reports, along with the finding that the ability to taste PTC is higher in heavy smokers (99), led to the decision to investigate thresholds for PTC in alcoholics.

The final trait to be investigated in the present study concerned the manner of clasping the hands. Two possible positions of hand clasping are possible - the fingers of the right hand may be over the fingers of the left hand, the right thumb then being uppermost (type R) or the fingers of the left hand may be placed over the fingers of the right hand, the left thumb being on top (type L). The trait seems to have some genetic basis (26, 27). The reason for selecting this characteristic for use in the present study lies in the relative ease of collecting the data, and the possibility that any such readily ob-

servable and inconspicuous trait might show a relationship with one or more of the other traits being investigated. Also, in dealing with the data, evidence might be obtained which would help to establish whether or not this trait is indeed inherited.

REVIEW OF THE LITERATURE

The Genetotrophic Concept

Without a doubt the most vociferous claims suggesting the importance of genetics in the etiology of alcoholism have come from Williams (105-118). Together with his associates at the University of Texas Biochemical Institute, Williams has propounded the genetotrophic concept of disease and has applied this concept primarily to the etiology of alcoholism. Basic to the formation of Williams' theory is an understanding of the related concept of biochemical individuality as it applies to alcohol selection in choice experiments with animals and distinctive metabolic patterns among individuals. Prior to a consideration of the genetotrophic concept itself, attention will be focused on the related ideas mentioned which have led to the formulation of the theory.

In order to show that metabolic patterns differ in different individuals, Williams (110) performed a series of experiments in which he analyzed the blood, urine, and saliva of various organisms (both

rats and humans) by chromatographic techniques. These experiments showed that several characteristics were distinctive for each individual tested. Rats which were kept on identical diets were found to have different urinary patterns with respect to amino acids as well as to other substances excreted. Similar results can be observed in young children fed milk or identical formulas. Although only one set of twins was studied, they were found to have metabolic patterns which were more similar than any other two individuals. Williams' studies also included members of Alcoholics Anonymous and a group of schizophrenics, each of whom were observed to have metabolic patterns distinctive from control subjects. On the basis of these studies, Williams concluded that the patterns seemed to be inherent, since even when the environmental factors were minimized by keeping the subjects on identical diets, the patterns showed marked individual differences. Williams further believed that changes observed to occur with age were inherent and that the individual's metabolic pattern was of prime importance in his susceptibility to mental or physical disease.

One of these experiments mentioned above by Williams, and performed by Reed (82), involved several strains of inbred rats in terms of alcohol consumption. The diets of these rats were carefully controlled so as to minimize environmental differences. Reed found that there was a striking difference among the individual rats and also among the various strains of rats used with respect to alcohol consumption in a choice situation and also with respect to the urinary excretory products. The differences between strains involved differences in phosphate, lysine, taurine, and methionine excretion. Reed claimed that these findings substantiated the notion of a polygenic basis for the metabolic patterns.

Williams (111) carried out the investigation of metabolic differences further and found that in the serum of alcoholics, the amounts of sodium and uric acid were higher than in the serum of control subjects. Urine analysis showed higher levels of hippuric acid, uric acid, thiamine, citrate, pigment/creatinine, and weak acids whereas the levels of gonadotrophin, citrulline, and taurine were lower in the controls. In another experiment Williams, et al. (115), analyzed

a group of 53 alcoholic males and 41 male controls who had demonstrated an ability to drink in moderation. The results showed significant differences between the alcoholics and the controls in the following determinations:

1. Total leukocyte count.
2. Lymphocyte count.
3. Eosinophil count.
4. Serum sodium.
5. Serum calcium.
6. Serum potassium.
7. Blood glucose.
8. Urinary creatinine.
9. Urinary hippuric acid.
10. Urinary sodium.
11. Urinary chloride.

Although the evidence is not conclusive, it is thought that several of the above are genetically determined (115).

Barlow and Wooten (9) analyzed the serum and red cells of alcoholics and compared their results with those of a control group. They found the plasma electrolytes and hematocrit values to be signifi-

cantly lower in the alcoholics. In the erythrocytes the sodium level was normal but the potassium values were higher and those of the chloride lower for the alcoholic group.

A numerical system was devised whereby an index number was assigned to each value determined for an individual for a particular metabolic trait (116). By adding up these numbers it was possible to determine an individual's "alcoholism-proneness" strictly on the basis of his metabolic pattern. Although it is possible that alcohol consumption over the years has something to do with the character of the metabolic pattern, the fact that inbred strains of mice show similar patterns is support for the genetic nature of metabolic patterns.

Williams (117) sums up the subject of biochemical individuality by stating that the genetic basis of metabolism leads to distinctive amino acid requirements for every individual. Indirect evidence for these distinctive needs is given in terms of the existence of substances in characteristic amounts in the body fluids. He also suggests that in addition to quantitative differences in needs, there may also

be qualitative distinctions. Williams (118) lists seven areas in which individual differences may be found, thus he notes differences in (1) anatomy, (2) blood and body composition, (3) enzyme systems, (4) endocrine activity, (5) excretion patterns, (6) responses to drugs, and (7) nutritional needs.

It has been shown that there are individual metabolic patterns which are at least to some extent genetically determined. These patterns have been shown to differ between individuals and also between alcoholics, as a group, and non-alcoholics.

Rats differ in terms of their preference for a 10 per cent solution of ethyl alcohol over pure water, the position of the two liquids in the cage being switched daily (106). These preferences seem to be genetically determined because inbred strains behave similarly and distinct differences exist among strains. It was also shown that the preference for alcohol could be abolished by adding certain factors to the diet. Many substances seem to play a role in abolishing the rats' appetite for alcohol. Foremost of these substances were the B vitamins, anti-pernicious anemia vitamin, linoleic and linolenic acid (106).

McClearn and Rodgers (68, 69) have provided strong evidence for genetic control of the mechanism of alcohol preference in mice. They showed that animals of the C57BL/Crg1/2 strain preferred 10 per cent solutions of alcohol whereas four other strains showed strong preferences for plain water. In a genetic analysis of McClearn and Rodgers' data (69), it was shown that inbred C57BL mice showed a greater tendency to consume the alcohol solution than any of the other strains. When the F_1 's from a C57BL crossed with a non-preferring strain were tested their consumption was found to be between that of inbred C57BL's and the other strain. The reciprocal crosses, C57BL X C3H/2 and C3H/2 X C57BL, permit an assessment of the maternal effects. The offspring of the C57BL X C3H/2 cross develop in the uteri of, and are raised by, C57BL mothers. The fact that there was no significant difference in the alcohol consumption by the offspring of these two crosses shows that maternal variables have little if any effect on alcohol preference. In another part of this experiment, two heterogeneous groups of mice were compared, one of which had some C57BL ancestors and the other of which did not. It was shown that the heterogeneous

group of mice which had some C57BL ancestry showed stronger preferences for alcohol than the group which had no such ancestry. In the final part of this experiment the generations beyond the F_1 's were observed. On the basis of simple Mendelian genetics the F_2 's would be expected to show a greater variance than had been shown by the F_1 generation. This was not observed. These results, as well as the fact that high values of alcohol consumption were not observed in the F_2 generation, seem to indicate a polygenic system rather than a single locus type of inheritance.

In a more recent study (92) the preference for alcohol over plain water was investigated with a series of alcohol solutions varying from 2.5 to 15 per cent. It was found that the concentration most preferred by C57BL mice was 12.5 per cent, higher than the preference of any other strain. Over a three week period, C57BL and C3H/2 strains demonstrated a progressive increase with respect to amount of alcohol ingested whereas mice of two other "non-prefering" strains showed a progressive decrease. In previous experiments C3H/2 mice had shown a low preference for a 10 per cent solution of ethyl alcohol.

Here their preferences were shown to be moderately high, falling between that of C57BL mice and the non-preferring A/3 and BALB/c strains. The results here also suggest that alcohol preference in mice is influenced by a multiple allele and/or a multiple gene system.

Arvola and Forsander (7) expanded the principle of the preceding experiments to various species of animals. They found that whereas rabbits tended to drink as much water as alcohol, hamsters showed a "pronounced preference" for alcohol. Hedgehogs, guinea pigs, rats, and mice tended to prefer water.

It is now possible to look at the genotrophic concept as it applies to alcoholism. Williams, et al. (107), pointed out that each individual has a characteristic metabolic pattern which is genetically determined. These patterns can then lead to the possibility that an individual could suffer from nutritional deficiencies on a diet which would be adequate for another individual. On the basis of experiments with rats, it seemed that the appetite for alcohol had a physiological basis tied in with inadequate nutrition. Such unusually high require-

ments make the individual vulnerable, and once he begins to consume alcohol, more nutrients are crowded out of the diet and a greater deficiency results. Thus the genetotrophic concept encompasses both genetic and nutritional factors in the etiology of disease.

The inheritance could be one of a particular type of endocrine activity. This would be similar to the cravings which result from a deficiency of salt or calcium. The hereditary trait then which predisposes to the disease is a high requirement for certain food elements. A vulnerable person could, however, escape alcoholism if, for social, cultural, or psychological reasons, he were to keep his drinking to a minimum or avoid it entirely. Here is an example of the importance of various environmental factors in the expression of a genetic trait (108).

As a possible mechanism behind the genetotrophic concept, Williams (109) suggests the existence of a partial genetic block. These are described as blocks which "involve a heritable characteristic by diminution (though not complete failure) of ability to carry out some specific enzymatic transformation.

Since a functional deficiency of this kind may increase the need of the body for some specific nutritional factor or factors, the existence of such partial genetic blocks can explain why different species require different quantities of nutrients."

It would be worthwhile to inject here some information concerning partial genetic blocks or "leaky genes" as they are sometimes called. First the notion must be accepted that an alteration of the velocity of a particular reaction in the midst of a whole series of biochemical reactions is sufficient to cause major modifications in the final metabolic pattern. If a mutation causes the loss of the capacity for carrying out some biochemical reaction, and this loss in turn affects the organism deleteriously due to a failure to synthesize a particular metabolite, then a nutritional supplement containing this metabolite will alleviate the effect of the mutation (102). In studies with Neurospora, many mutants investigated with regard to faulty metabolic patterns exhibited partial genetic blocks. One example concerns the ability of Neurospora to grow without riboflavin at one temperature but not

at another. At temperatures intermediate between the two extremes a partial requirement for riboflavin was demonstrated. It was also shown that lower quantities of riboflavin would have to be added as one approached the critical temperature. From these and similar experiments on tryptophan synthesis it seems that partial genetic blocks play an important role in the control of metabolism (102).

Beerstetcher (10) performed further studies relevant to the genetotrophic concept, specifically with respect to which nutrients would abolish an experimental preference for alcohol. He found that riboflavin, thiamine, pantothenic acid and pyridoxine were all important factors. Rogers, et al. (90), experimenting with the effect of glutamine on alcohol consumption in a free choice situation with rats, found that it was possible to reduce the animal's intake of alcohol. Oral glutamine, and to a lesser extent, injected glutamine, were effective during the period of administration. After discontinuing the glutamine supplement the alcohol consumption once again increased. The effects of glutamine on humans has also been tested and it seems that this substance may be one of the nutrients which is effective in the

control of alcoholism (91).

In another study (84) it was shown that the voluntary intake of alcohol by rats was decreased following the addition of a yeast supplement to the diet. At least part of this effect was attributed to lipoic acid since synthetic lipoic acid alone had been shown to cause a slight decrease in alcohol consumption (84). An interesting relationship was discovered by Reed, et al. (83), whereby glutamine was effective in reversing the toxic effects of ethanol on cultures of Streptococcus faecalis.

The above findings show the effect of various nutrient supplements upon the preference for alcohol and tend to support the genetotrophic theory. The following studies deal with other types of evidence for Williams' proposals.

Mardones (64) noted that certain deficiency diseases appeared with greater frequency among alcoholics: namely, cirrhosis, polineuropathy and other forms of thiamin deficiency, and pellagra. He also observed that rats increased their alcohol consumption when kept on vitamin B deficient diets. This

led to the conclusion that the difference in appetite for alcohol was determined by genetic constitution as well as by such factors as experience, pathological events, and pharmacological actions. Mardones (64) states that the increased sensitivity to deficiency disease as expressed by alcoholics is not the direct result of the action of alcohol. He likewise concluded that the voluntary intake of alcohol by mice was genetically determined.

Williams, et al. (112), points out that partial genetic blocks and the genetotrophic concept of disease is not limited to alcoholism. He suggests that there may be similar etiological bases for cancer, diabetes mellitus, rheumatoid arthritis, multiple sclerosis, and many other diseases. In summing up the genetotrophic concept as it applies to alcohol preference in rats, Williams (114) states:

- "1. Individual rats have requirements which are quantitatively distinctive.
2. Deficiencies too mild to produce overt lesions are sufficient to reduce materially the wisdom*of the body of the individual rats.

*Williams apparently uses "wisdom" in a physiological sense.

3. Nutritional substances, not yet recognized, are needed by the rats in order that all individuals exhibit a maximum wisdom of the body with respect to food choices."

In his latest publication, Williams (118) discusses the recommended dietary supplement and the effects of his treatment on alcoholics. The complete vitamin supplement is shown below:

Thiamine (B ₁)	3.30 mg.
Riboflavin (B ₂)	2.67
Nicotinamide	20.00
Calcium pantothenate (B ₃)	20.00
Pyrodoxin	3.30
Biotin	0.05
Folic acid	1.10
p-Aminobenzoic acid	11.00
Inositol	53.00
Choline	53.00
Vitamin B ₁₂	5.00 μ g.
Vitamin A	6,667.00 units
Vitamin C	66.70 mg.
α -Tocopherol	6.67 mg.
Vitosterol	333.00 units
Lipoic acid	0.10 mg.

The above vitamins should be taken from three to nine times daily depending on the individual case. In addition it is suggested that a daily intake of glutamine and a mineral supplement containing manganese, iron, copper, cobalt, zinc, iodine, and molybdenum to taken daily. Williams also provides several suggestions with respect to diet. Specifically,

the alcoholic should eat large amounts of high protein foods such as meat, fish, poultry, eggs, and dairy products. Foods such as sugar, white rice, spaghetti, macaroni, and white-flour products, all of which comprise a class of refined nutrients, should be kept to a minimum. Williams (118) cites individual cases where the dietary supplement has been applied successfully in the treatment of alcoholism. He notes, however, that in some cases the results have been incomplete or unsuccessful and attributes this to a failure on the part of the subject to maintain an adequate diet and also to refrain from all drinking. In experimental studies one is never certain whether or not the subject is taking all of the required vitamin capsules, and this has invalidated some of the experimental work which has been performed. This was the case in one study (100) where of 25 alcoholics treated over a 13 month period, diagnosis showed 7 were abstinent, 7 controlled, 2 improved and 9 showed no change.

In summary of the genetotrophic theory it can be pointed out that cravings with a physiological basis are well known in living organisms. Hunger and

thirst are the most common of such cravings. Williams speaks of the "wisdom of the body" with respect to these cravings. Thus a rat which suffers from a salt deficiency will begin to crave this substance. Williams has also shown that individuals differ with respect to physiological or metabolic patterns. These patterns seem to be genetically determined since inbred organisms display similar patterns. In humans, certain blood and urine determinations of alcoholics are distinctive from those of non-alcoholics. In mice and rats, the patterns of those strains which select alcohol over water are different from those which choose only water. Further studies seem to indicate that the crucial factor is associated with nutrition, since an animal can be made to select alcohol more often by removing certain substances from its diet. Likewise an animal which originally chooses an alcohol solution can have this appetite abolished by supplying an adequate diet. On the basis of these findings Williams has proposed the genotrophic theory. Genetically the organism has a high requirement for certain substances. If these substances are provided by an enriched diet the tendency to consume alcohol disappears. It is also suggested

(118) that this theory provides a means for the prevention of alcoholism. By testing youngsters it would be possible to identify those individuals possessing metabolic patterns which predispose towards alcoholism. These individuals could then be raised on a special supplemented diet and alcoholism could be prevented. In the case of the person already having the disease, the administration of the special diet would serve to abolish the craving for alcohol.

Criticism of the Genetotrophic Concept

Lester and Greenberg (62), experimenting with ten rats, observed that alcohol consumption could be increased by placing the animals on a deficient diet. These results seemed in accord with earlier findings by Williams (108, 109, 111, 118). It was further noted, however, that the addition of a third solution (an emulsion of fat or solution of saccharin or sucrose) significantly decreased the preference for alcohol. On the basis of this finding it was concluded that the preferences expressed were probably due to the caloric content of the choice solutions, palatability, or other unidentified factors. This

experiment showed that there was no specific preference for alcohol, and according to Lester and Greenberg, it was impossible to assume that the etiology of alcoholism in humans is connected with dietary deficiencies.

Popham (79) in a similar series of experiments came up with the same results. He also concluded that since the laboratory animals do not seek intoxication, their behavior does not parallel human behavior with respect to alcoholic beverages.

As a result of another series of investigations in which the addition of sucrose led to a decrease in the preference for alcohol, Lester and Greenberg (33) stated that the genetotrophic concept was an oversimplification. They agreed that increased alcohol consumption in vitamin deficient rats was an example of an alteration of metabolism to new needs, but since the organism did not specifically choose alcohol, the validity of the genetotrophic concept was questioned.

Additional criticism of the genetotrophic theory (72, 104) relies on the same assumptions as above;

namely, the effect of sugar as a third choice.

In another study a group of 650 boys was followed over a 24 year period. This group was carefully observed at the beginning of the study and various characteristics were noted and compared at the end of the study. On the basis of these findings it was concluded that nutritional deficiencies are not causally related to alcoholism. It was also concluded that glandular disorders do not lead to alcoholism and that the evidence for a hereditary explanation is lacking (70,71).

Williams (113) attempted to justify his original findings in the light of the experiments mentioned above. He repeated Lester and Greenberg's experiment and observed that sugar consumption as well as alcohol consumption increased as a result of a deficient diet. He pointed out that some rats exhibit a "sweet tooth" and this results in diminished growth. Some animals tended to consume more alcohol and likewise became more deficient. It was also pointed out that it was not necessarily the same rats consuming the extra sugar as were consuming extra alcohol. In another study by Williams (114) the new findings with

regard to sugar consumption were used as another demonstration of nutritional deficiency leading to an increased craving.

Frequency of Alcoholism in Families of Alcoholics

The studies in this category, which consist of a comparison of the frequency of alcoholism in the relatives of alcoholics and in the general population, are extremely numerous. They are among the earliest studies in the genetic analysis of any disease, and are also the least conclusive since environmental factors are at a maximum. Consequently, when early analyses pointed to the fact that alcoholism seems to run in families it was suggested that this was due to the example set by the parents and the neglect to which children of alcoholics are subjected. Although an increased amount of alcoholism in families of alcoholics does not prove that the disease is inherited, it would be a necessary requirement if other evidence did in fact prove alcoholism to be inherited.

An investigation of the family history of 500 alcoholics, 200 non-alcoholic psychiatric patients,

and 22 "normal" controls showed that alcoholism was four times as frequent in the families of alcoholics than it was in the general population. Psychiatric patients gave a family history of alcoholism twice as often as normal drinkers. According to this study there was a tendency for alcoholism to be transmitted down the male line, the inheritance being one of an abnormal reaction to alcohol and taking the form of an increased attractiveness of the beverage (58).

In another study of 100 alcoholics it was found in 30 cases alcoholism had been a problem in the male ancestry, in 17 cases it had been a problem in the female ancestry, and in 8 cases there had been an alcoholism problem in the combined ancestry; this was a total of 55 out of the 100 cases studied (8).

Amark (5) made a comprehensive study of the family history of alcoholics with respect to incidence of alcoholism as well as other "character deviations." He found that the siblings of alcoholics consumed from three to eight times as much alcohol as the general population. Amark points out that a genetic analysis is difficult because:

1. The environmental effects of a parent's alcoholism upon the children is marked.
2. Alcoholism is common in those groups where there is a large amount of alcohol consumption.
3. There is a close connection between the constitution and the environment.

He showed that the frequency of alcoholism in families of alcoholics was considerably higher than in a control group. In addition, Amark noted that the morbidity risk for alcoholism among brothers is greater when the parent matings are unaffected X alcoholic, unaffected X compulsive drinker, and unaffected X periodic alcoholism than when the mating is unaffected X unaffected. These results were statistically significant, indicating, according to Amark, the importance of genetic factors.

In addition to the preceeding studies several investigations have been reported with similar findings (13, 34, 46, 49, 54, 65, 94, 96). There seems to be little argument that alcoholism occurs more frequently in families of alcoholics than in the general population. The debate centers on the meaning of these findings, i.e., is it the environment or the genotype which determines familial alcoholism?

Analysis of Family Structure

The principal factors considered in family analyses include the family size, birth order, sex of sibling, parental age at birth, age of father in relation to mother, and other elements of this type. There are two ways of interpreting such data. One can say that if the genotype is of prime importance then there should be a random distribution of the disease in the family regardless of the above factors. Or, on the other hand, one can explain certain genetic traits in terms of family structure. The classic example of this latter point of view occurs in mongolism where the maternal age appears to play an important role (98). It is also possible, and perhaps even more justifiable, to explain differences in family structure as affecting the sociological aspects of development. Such interpretations attribute different susceptibilities among members of a family to the first, or in some cases, the last born.

Although the results on the subject of structure of the family of the alcoholic remain diverse and unclear, the fact that much work has been done in this

area suggests that their implications be considered.

In Prout's (80) study of 100 alcoholics there were 12 only children, 12 only male children, and in only 36 cases were there more than two siblings. On the basis of this study it was concluded that small families were characteristic of the alcoholic.

In another study of 109 alcoholics it was observed that 25 per cent of the alcoholics were ordinal children, 21 per cent ultimate, 13 per cent preultimate, 13 per cent only children, and all other possibilities accounted for 27 per cent of the cases. In 49 per cent of the families there were 4 or more children. Thus, although there was no conspicuous cluster with respect to place in the sibling hierarchy, the data strongly suggests that alcoholism occurs more frequently in large families (103).

Bakan (8) found that the probability of contributing to the alcoholic population increased as the number of older siblings increased. In addition he found that the oldest children contribute least while the youngest children contributed most to the alcoholic population sampled.

Navatrill (73) studied 720 male alcoholics. Excluding 14 only children, 32 per cent were last born whereas the expected number was only 22 per cent. He claims the difference is statistically significant and could be due to the mother-child relationship with the last born as well as to the constitutional defects which occur with lateborn children. Three years later the same experimenter (74) studied a group of 600 alcoholics. He found that 29.9 per cent of them, a statistically significant number, were first born. He claims that this could be due to the fact that first born children are overly protected and often are "mother's favorite." Navatrill goes on to discuss the importance of overdependence in the development of alcoholism.

Another study was designed to determine a systematic family constellation which might favor the onset of alcoholism (65). Among 518 male alcoholics 50 were found to be only children, 99 had no brothers, and 139 were last born. This last figure was 25 per cent greater than was to be expected on the basis of a chance occurrence. The analysis is carried on to maternal and paternal grandparents, the conclusion

being that by careful analysis of the family structure it is possible to determine alcoholism-prone individuals.

Gregory (34) observed that there was a statistically significant number of only children among the group of alcoholics that he studied. He noted that there was an apparent vulnerability to alcoholism in the youngest child. On the basis of his observations Gregory concluded that the susceptibility to the disease was not determined solely by genetic factors and that more research was necessary to elucidate the role of the various factors in the etiology of alcoholism.

Association of Alcoholism with Other Diseases

In this section of the literature review, attention will first be directed to a number of different diseases which are found to occur frequently in association with alcoholism. Following this, the literature relevant to two particular diseases will be considered: namely, schizophrenia and epilepsy. It should be pointed out that the purpose of this analy-

sis of diseases, many of which are or seem to be genetic in nature, occurring with alcoholism, is to propose a hypothesis which suggests a common basis for one or more of these diseases and alcoholism.

Investigators noted some time ago that certain diseases, particularly mental ailments, seemed to occur more frequently in alcoholics and their families. Bourrat (15) noted that among the factors which predispose to alcoholism were such diseases as infantile encephalopathy (a constitutional nervous fragility) and mental debility. He stated that if it were possible to observe hereditary factors in the parents of alcoholics it would be in the form of dipsomania and epilepsy. Bourrat went as far as to say that alcoholism was a familial disease, the alcoholic inheriting a particular craving in some cases, and in others, the alcoholism of the parents being responsible for neuropsychiatric disabilities in the descendants.

In an even earlier study it was concluded that dipsomania, in one Dutch family, was a sex-linked condition expressed in hemizygous males or else recessive in females (55). In a study of luxatio-coxae (congenital dislocation of the hip) in 29

pedigrees and 189 individual cases, Roch (88) claimed that the anomaly seemed to be recessive and occurred most frequently in families whose ancestors contained drinkers and epileptics.

An interesting association was noted by Hyde and Chisholm (43). They found the Chinese to be free from alcoholism and also characterized by a low rate of psychopathy. The Irish, Negroes, and Italians were highest in both psychopathy and alcoholism.

Jager and King (45) studied 24 members of a family with hereditary tremor over a period of four generations. Ten of these were aware of the fact that a small amount of alcohol lessened the shaking. Only four of the entire family were considered to drink to excess. One member was considered an alcoholic but he had no tremor. The writers point out that alcoholism is frequently observed in persons with hereditary tremor and they postulated that an emotional instability may be inherited. The relief of the tremor due to the alcohol could then lead to alcoholism. It was also pointed out that in this particular family the incidence of alcoholism was lower than is usually found in association with the

disease.

In a study of 50 alcoholics and their 1,313 relatives various factors were compared with those of the general population. It was found that the incidence of mental disease among the relatives was no greater than in the control group. On the basis of this study it was concluded that there was no evidence that alcoholism causes epilepsy or oligophrenia in the offspring, and that the genetics of alcoholism was closely related to the genetics of abnormal personality development (13).

Alvarez (4) studied the family history of patients complaining of mild psychosis and found a host of anomalies from eccentricity to alcoholism. He stated that a genetic trait was operating in many of these instances and was expressing itself in different ways. Among the relatives of 99 epileptic patients Alvarez found 15 per cent were alcoholics as compared with 7 per cent of the relatives of psychotics and alcoholics.

A recent investigation of 130 alcoholics revealed that 18.5 per cent of them had peptic ulcer

or had had it as compared with 8.1 per cent in the general population. In addition it is pointed out that in most cases the ulcer had preceeded the alcoholism, thus invalidating the assertion that the alcohol had precipitated the ulcer. Alcoholism and peptic ulcer are regarded by the investigators as manifestations of a common basic disturbance (35).

As a final note in the consideration of diseases in general associated with alcoholism, mention should be made of tuberculosis. Brown and Campbell (16) noted a relationship between the incidence of tuberculosis and heavy consumption of alcoholic beverages. The incidence of tuberculosis was observed to increase with the amount of alcohol consumed.

Having looked at some general findings with respect to diseases associated with alcoholism, attention will now be focused specifically on schizophrenia and epilepsy.

Heath and Leach (38) consider schizophrenia to be an inborn error in metabolism, the defect being basically a genetic one. This defect in turn is manifest as an alteration in the molecular configu-

ration of one of the proteins in the serum. The investigators demonstrated that this defect is one of amine metabolism by virtue of a comparison of the serum and urine of schizophrenics with controls. It is also pointed out that the electroencephalogram results suggest that schizophrenia, as well as other forms of psychoses, arise from a common metabolic disorder.

In a study of 100 children of alcoholic parents, Heuyer, et al. (41), found 10 cases of epilepsy, 30 instances of retarded children with respect to psychomotor development, and 60 cases where behavioral problems existed. The experimenters have eliminated the possibility of "genetic heredity" and suggest that parental alcoholism "produces damage by killing or weakening the fetus." Bourrat (15), Alvarez (4), and Berry (11), also noted an association between alcoholism and epilepsy.

A study of families of schizophrenics in which a second person besides the proband had been hospitalized for oligophreny, psychopathy, suicide, toximania, or chronic alcoholism was undertaken by Vazire (101). Among all the traits mentioned only alcoholism was

found to be more prevalent in the families of schizophrenics than in the general population. Alcoholism affects 26.2 per cent of the parents (46 per cent of the fathers!), 11.5 per cent of the grandparents, 12.7 per cent of the uncles and aunts, 6.2 per cent of the brothers and sisters, and 8.2 per cent of the children of the proband. On the basis of these results Vazire suggests four hypotheses:

1. There is a genetic relationship between schizophrenia and alcoholism.
2. Alcoholism could be a larval manifestation of schizophrenia.
3. The family environment, having been disturbed by alcoholism would be favorable for the onset of schizophrenia.
4. The alcoholism would foster a deteriorating environment which would provide ideal conditions for the precipitation of schizophrenia in genetically predisposed individuals.

Vazire thinks that the first hypothesis is unlikely since it has been found that alcoholism is a symptom common to many psychiatric maladies. He believes that the last hypothesis, suggesting that alcoholism serves to manifest the genetically predisposed schizophrenics, is most likely.

There is considerable evidence suggesting a

genetic basis for schizophrenia and epilepsy and attention will be directed to these areas.

Heath (39) considers schizophrenia to be a "genetically determined metabolic disease, or, more specifically, a disease characterized by alterations in the metabolic pathway for the breakdown of certain (as yet unidentified) endogenously occurring compounds." He suggests that the genetic defect is manifest by the presence of taraxein, a protein found in the blood stream of schizophrenics which may alter the physiology of the activity of the brain. It has further been shown that the administration of taraxein to normal subjects results in symptoms of catatonic stupor, hebephrenia, delusions of persecution and grandiosity, all characteristic of schizophrenic behavior (40).

Studies of the incidence of schizophrenia in families of schizophrenics show that where both parents are affected the risk for the children is forty per cent. In the general population the morbidity risk for the disease is about 1 per cent; for siblings of schizophrenics, 7-15 per cent are affected. Twin studies show a concordance rate of 76-91 per

cent for monozygotic and 10-17 per cent for dizygotic pairs. The mode of inheritance seems to be one of reduced penetrance for the heterozygotes. There also seems to be a correlation between schizophrenia and tuberculosis (14).

According to Stern (98), on the basis of results of six authors, there is a concordance of 80 per cent with respect to schizophrenia in identical twins as compared with 13 per cent in fraternal twins. He points out that the fact there is discordance in 20 per cent of the identical twins shows that non-genetic factors are also important. It is postulated that schizophrenia is inherited as a single recessive gene with a limited amount of penetrance in homozygotes. Stern refers to one study investigating twins who were separated before the onset of the disease. When not separated the morbidity risk for the other identical twin was 85.8 per cent, whereas if separated the risk is only 77.6 per cent. This again shows the role of environment in the disease.

In a review of the literature dealing with the genetic basis of schizophrenia, Altshuler (3) presents the following statistics:

<u>Relationship to schizo-</u> <u>phrenic proband.</u>	<u>Incidence</u> <u>in per cent</u>
General population	0.85
Half-sibs	7.00 - 8.00
Full-sibs	5.00 - 15.00
Parents	5.00 - 10.00
Children (of one index case)	8.00 - 16.00
Children (of two index cases)	53.00 - 68.00
Dizygotic twins (one index case)	3.30 - 16.70
Monozygotic twins (one index case)	66.60 - 86.20

Rosenthal (93) has suggested that perhaps there are two broad types of schizophrenia. In one type the genetic contribution is absent or minimal, while in the other the contribution is significant.

The genetic interpretation of the etiology of schizophrenia is not universally accepted. Jackson (44) states that since in only two cases have twins been reared apart, the environmental factors have not been truly eliminated. He also notes that in many of the studies reported there is a question of monozygosity. Jackson further suggests that monozygotic twins inhabit a unique environment as compared to dizygotic twins. Monozygotic twins may also respond with symptoms of schizophrenia out of "biological sympathy." It is also mentioned that investigators tend to record concordancy in monozygotic twins due to a nature of sameness.

Lennox (60) investigated the hereditary nature of epilepsy. He noted a history of seizures in 3.2 per cent of the relatives of 4,231 epileptic patients. This was 3.6 per cent if evidence of brain damage prior to the first seizure is lacking and 1.8 per cent if there is such evidence. These figures are respectively 7 and 3.5 times those found in controls. In 122 pairs of twins without brain damage, both were epileptic in 84 per cent of the monozygotic and 10 per cent of the dizygotic twins. In monozygotic twins there was concordance as to the type of seizure and the electroencephalograph pattern. On the basis of these findings Lennox concluded that genetic factors were important in the etiology of epilepsy.

In a later account Lennox (61) reported that epilepsy occurs in 0.5 per cent of the population of the United States. The onset of the disease is usually in childhood and although the number of affected males is approximately equal to the number of affected females, the onset is generally earlier in the females. The size of the family as well as the birth order have been shown to be unimportant. As to

the etiology, it seems that there is a genetic and also an acquired form of the disease, but the genetic etiology is the more frequent of the two. Of 2,500 patients, 35 per cent had a family history of epilepsy, 11 per cent had both genetic and acquired history, and in 38 per cent there was no definite etiology. Epilepsy, according to this study, is three times more prevalent in the relatives of epileptics than in the general population.

Correlation of Alcoholism with Blood Groups

In a study of patients at Colorado State Hospital, 5,637 patients were classified according to diagnosis, age, sex, and both ABO blood group and Rh₀(D) type. There was no relationship between the blood groups and schizophrenia or mental deficiency. There was, however, a correlation between alcoholism (939 patients) and blood group A ($p = 0.004$). It is pointed out by the investigator that many pitfalls are encountered in an analysis of blood groups. For instance variations in ethnic and racial composition may account for differences of 20 per cent. In addition errors are introduced by mistyping and the use

of small samples. In this study it is suggested that the sampling error was minimized due to the large sample used and technical errors due to mistyping were negligible. Although the male alcoholics in this study outnumbered the females six to one, there was no difference between the sexes with respect to type A blood. Twenty-five per cent of the patients were Mexican, but since this group is characterized by an increase in type O, this should not affect the nature of the results (75).

Achté (1) appears to be the only other investigator to look at the question of alcoholism and blood groups. The results of his study are presented in Table 1 below.

Table 1. Association of Alcoholism and Blood Groups.

Type	<u>Alcoholics</u>		<u>Controls</u>	
	<u>No.</u>	<u>%</u>	<u>No.</u>	<u>%</u>
A	89	42.0	591	42.7
O	66	31.2	463	33.5
B	39	18.3	232	16.8
<u>AB</u>	<u>18</u>	<u>8.5</u>	<u>97</u>	<u>7.0</u>
Totals	212	100.0	1383	100.0

Alcoholism and Twin Studies

In order to show clearly that alcoholism is inherited it would be desirable to have several studies investigating the frequency of the disease in monozygotic and dizygotic twins. Kaij (47, 48) was the only investigator to undertake this experiment. In a preliminary report (47) Kaij presented only a brief tabulation of his results and the comment that monozygotic twins were more concordant than dizygotic twins with respect to drinking habits. Three years later a book was published containing the final results along with discussion and interpretation of the data (48). In the study 174 twin pairs, 48 monozygotic (MZ) and 126 dizygotic (DZ) pairs were investigated. The results with respect to concordance and discordance of drinking habits are shown in Figure 1, which presents samplings at all levels, including the average and above average consumers as well as the alcoholics.

DIZYGOTIC

MONOZYGOTIC

DIZYGOTIC							MONOZYGOTIC						
**0	1	2	3	4	?		**0	1	2	3	4	?	
* ?		2	1		5	8	* ?					1	1
4	1	2	1	10		14	4		1	1	10		12
3	1	3	7	6	3	20	3	1	4	7	1		13
2	6	4	6	6		22	2	3	10	3	2		18
1	1	19	22	10	7	59	1	4	5	2	1		12
0		7	5	6	5	23	0		1	2			3
total	2	36	42	30	31	5	146	9	22	13	14	1	59

Classes

- 0 - Abstainers or below average consumers
- 1 - Average consumers
- 2 - Weekend drinkers - above average consumers
- 3 - Addicts and heavy drinkers
- 4 - Chronic alcoholics
- ? - Not examined or unable to determine

Fig. 1. Comparison of drinking habits of monozygotic and dizygotic twins. The results are tabulated below in order of increasing discordance.

<u>DIZYGOTIC TWINS</u>		<u>MONOZYGOTIC TWINS</u>	
<u>Number</u>	<u>Per cent</u>	<u>Number</u>	<u>Per cent</u>
39	28.3	31	53.5
53	38.4	18	31.0
26	18.8	8	13.8
15	10.9	1	1.7
5	3.6	=	0.0

*Classes of twin I (partner)
 **Classes of twin II (proband)

When these data are broken down into classes of drinking behavior the results are even more significant. Table 2 shows the concordance rate among MZ and DZ pairs, the samples being taken at different levels of drinking behavior.

Table 2. Concordance Rate among Monozygotic and Dizygotic Twins.

Concordance Rates	All	Classes			Classes	Class
	Classes	2	3	4	3 and 4	4
measured in per cent						
Monozygotic pairs	53.5		55.6		63.0	71.4
Dizygotic pairs	28.3		20.0		26.7	32.3
Difference between DZ and MZ pairs	25.2		35.6		36.3	39.1

The above data show that the differences between monozygotic and dizygotic twins become more pronounced as the amount of drinking increases. It can be seen that class 4, representing chronic alcoholics, shows the greatest differences between the two types of twins.

According to Kaij the findings imply that not only "drinking habits but also the social manifestations of alcohol abuse are determined by genetic factors." The high concordance of MZ twins with respect to DZ

twins and also of DZ twins as compared with that in the general population suggests the existence of genetic factors. It is not necessary to assume that a single gene or even a number of genes is directly responsible for the results of this study. It is possible that unspecific factors relating to overall personality are basic to drinking behavior. The fact, however, that there is increasing concordance with an increase in alcohol abuse suggests the specificity associated with genetic influence. Observing that 54.2 per cent of the MZ probands and 31.5 per cent of the DZ probands had partners who were also probands, Kaij concluded "that the development of alcohol abuse and chronic alcoholism...is greatly influenced by genetic factors."

Of the monozygotic twins there was positive information of alcohol abuse or chronic alcoholism in the fathers of eighteen pairs. In 7 pairs there was no evidence and in the remaining 23 pairs the fathers were either abstainers or moderate drinkers. It was clear, Kaij claimed, that twins having advanced drinking habits were more likely to have a father who was an abuser than were twins with moderate

drinking habits.

Only three pairs of monozygotic twins were studied who were reared apart. In one pair both twins were in class 2 (weekend drinkers). In a second pair, both twins being brought up in an environment where there was alcohol abuse, the twins were both classified as chronic alcoholics. The third pair, in which there was some question of monozygosity, one twin was a chronic alcoholic while the other one was a class 1 (average) drinker. Kaij claims that no conclusions can be drawn from these results because of the small sample.

Miscellaneous Studies Relating to the Genetics of Alcoholism

One of the earliest writings on the subject of genetics and alcoholism was a book by Keeley entitled The Non-Hereditry of Inebriety (50). Keeley believed that alcohol was the cause of alcoholism. He believed that a person would begin to drink and this would poison the body cells. The craving which results is one of poisoned cells for more poison. Keeley realized that many of the relatives of alcoholics

were alcoholic, but he points out that many relatives suffered from other diseases and many were normal. Keeley observed that alcoholism did not follow any of the inheritance patterns known at that time.

Most of the reports from the years around the 1940's and early 1950's, especially those papers appearing in non-scientific or lay publications, refer to the interplay which exists between genetics and environment. Jellinek (46) noted that it is difficult to distinguish the effects of heredity and environment in alcoholism. He reported that 52 per cent of all alcoholics were born of inebriate parents. With regard to psychopathological deviations among the parents of alcoholics, Jellinek stated that about 35 per cent showed a "hereditary taint." Roe (89) attempted to look at the occurrence of alcoholism in children of alcoholic parents raised in foster homes. The results showed no significant differences between the experimental and the control group, suggesting that hereditary factors were unimportant. However, as Roe points out, there were large differences between the experimental and control groups with respect to age and also as to whether the foster home was in the city or in a rural

area.

Rice and Harger (85) also state that one must not jump to conclusions regarding the genetic nature of alcoholism. They claim that excessive drinking by the female prior to birth may lead to congenital defects but these are not genetic in nature. In conclusion Rice and Harger state that it is "pretty well established that alcoholism is not inherited" but rather of acquired etiology.

Similar conclusions were reached by Christiaens, et al. (18), in a study of 100 children of alcoholic parents. They noted that premature births and congenital debility were most frequent in cases where both parents were alcoholics. The fact that inferior size and weight are characteristic of the offspring of alcoholic females is attributed to congenital and postnatal effects of alcohol rather than genetics.

Greenberg (32) emphatically states that there is no genetic basis for alcoholism, claiming:

"There is no evidence that the use of alcohol has any effect on the human gene. The high mortality rate among children of alcoholic parents is due primarily to environmental conditions. The fact that children of alco-

holics are more likely to become alcoholic than children of temperate families is due to poor home environment, poor parental example and the fact that in some families a predisposition to various forms of abnormalities, which may lead to alcoholism, is inherited. Abnormal drinking and craving for alcohol are acquired traits which cannot be transmitted genetically."

The preceding references, largely from workers at the Yale School of Alcohol Studies, tended to refute the genetic hypotheses of alcoholism. The following studies concern investigations which tended to substantiate the role of heredity in the etiology of alcoholism.

Williams (105), prior to the formulation of the genetotrophic concept, suspected that the inheritance predisposing to alcoholism was not based on a single gene but was rather one of multiple factors with a gradient rather than a discontinuous pattern of inheritance. This, he stated, is evidenced by the fact that some individuals seem to crave more alcohol than others.

In another report (6) alcoholism was considered to be a concomitant of other mental disorders, a genetic factor operating in nonsymptomatic cases such that alcohol is more tempting to the alcoholic than to

the moderate drinker.

In a study relating physique and alcohol consumption, Parnell (77) noted certain significant trends. Healthy students, mental patients, and young delinquents were studied with respect to body build and alcoholism. Consistent relationships were noted whereby the greatest alcohol consumption was in the endomorph group and the least consumption was by linear ectomorphs, while mesomorphs of a more muscular make-up comprised the middle group.

Roussel (94) points out that the most serious consequences of alcoholism to man involves hereditary transmission. Alcoholic males and females produce more alcoholics, and in addition one finds degeneration, epilepsy, predisposition to tuberculosis, and moral degeneration in the families of alcoholics.

The following studies concern nutritional and physiological aspects of alcoholism and are thus related to the genetotrophic concept.

Richter (86) referred to several earlier studies in which it was demonstrated that rats preferred certain concentrations of glucose, maltose, sucrose,

galactose, sodium chloride, and dibasic sodium phosphate. All these compounds were considered to be important in nutrition. Richter found that when given a choice between water and alcohol solutions of various concentrations, rats chose the alcohol solution up to a concentration of 4.8 per cent.

In a later experiment, Richter (87) attempted to force rats to become addicted to alcohol by forcing them to drink an alcohol solution. He found that addiction could not be produced in this manner. The rats did, however, reduce their intake of the stock diet in direct proportion to the calories received from the alcohol.

In one study investigating alcohol consumption in rats it was claimed that the intake of alcohol could be related either to psychological or to physiological causes. If it is true that an organism selects those substances which are good for it, then those organisms which are observed to consume alcohol should be extracting some benefit from this source. Since alcohol and fats are metabolized in the Krebs cycle, it would seem logical to look at the different enzymes and hormones controlling this system. In this experiment it was shown that alcohol consumption

could be changed by altering the balance of hormones. Whereas an untreated rat was found to consume only small amounts of alcohol, a rat which had been given insulin was observed to consume large quantities of ethyl alcohol. Insulin then seemed to alter the metabolism which in some manner then induced the alcohol consumption. It was further observed that alloxan-treated animals showed a distaste for alcohol. This was explained by assuming that alloxan blocks the utilization of acetate, and since in the oxidation of alcohol, acetate is one of the substances produced, the animal tends to avoid the intake of alcohol which would be stored in the body, and after accumulation, would induce various physiological disturbances (24). Although only a hypothesis, this interpretation offers a possible explanation for the mechanism of the genetotrophic concept.

Zarrow, et al. (120), also investigated the role of hormones in preference for alcohol by rats. They found that castration, adrenalectomy, and alloxan diabetes would not induce an increase in the consumption of alcohol in free-choice situations. Rats treated with cortisone, formaldehyde, or exposed to

low temperatures were found to show an increase in their preference for solutions containing alcohol, but this was decreased when dextrose was provided as a third choice. It was concluded from this study that the hormones from the testis, ovary, and adrenal gland were ineffectual in the production of increased alcohol consumption.

Olson, et al. (76), have found evidence for a defect in tryptophan metabolism in chronic alcoholics. Tryptophan is metabolized to nicotinic acid and serotonin, and 5-hydroxyindolacetic acid (5-HIAA) is one of the major urinary metabolites of these two compounds. Sixteen healthy social drinkers experienced euphoria and lightheadedness after the administration of 10 grams of tryptophan whereas 34 alcoholics showed no such effects. In addition, the patients with chronic alcoholism excreted significantly less 5-HIAA than the controls, the average being 40 per cent less. It was also noted that abstinence of up to four months (on a hospital diet) did not change the low excretion rate thus ruling out poor nutrition as an explanation. The investigators report that the amount of 5-HIAA excreted does not appear to be related to the duration of the disease.

As possible explanations for the results observed, the experimenters suggested depression of enzyme activity due to long standing alcoholism or else that this was a somatic trait associated with chronic alcoholism. The fact that the low level of 5-HIAA excretion does not rise after 6 months abstinence tended to favor the latter possibility. Since a decreased rate of 5-HIAA excretion was also noted in patients suffering from phenylketonuria, the subjects were tested for a defect in phenylalanine metabolism. The results of this test were negative, indicating that this same amino acid was not affected in alcoholism.

Genetic Basis of Smoking

The literature suggesting a genetic predisposition to smoking may be considered in two general categories: the association of smoking with the ability to taste phenylthiocarbamide (PTC), and the smoking habits of monozygotic twins as compared to dizygotic twins.

There has been a great deal written concerning the relationship, if any, between smoking and the taste sensitivity for PTC. As Maia (63) points out,

there are two points to consider with regard to smoking and PTC. First, the changes in taste sensitivity following the smoking of a cigarette, and second, the taste sensitivity of smokers as compared to non-smokers. In general, no correlation has been found between smoking and PTC taste sensitivity (25, 56, 57, 78, 95). It has been reported that the non-smokers among the PTC tasters were more sensitive than the smokers (56) and also that a systematically higher frequency of non-tasters occurs among the smokers as compared to the non-smokers (25), but in both cases the differences were not statistically significant.

Only two studies have demonstrated a relationship between smoking and PTC sensitivity. Hall and Blakeslee (36) tested 60 subjects, then allowed them to smoke and repeated the PTC tests immediately and at 15 minute intervals. They found that there was a marked effect, 73.3 per cent of the subjects requiring stronger solutions following the cigarette. The results were explained in terms of a direct dulling of the taste buds.

Thomas and Cohen (99) looked at the frequency of tasters among smokers as compared to non-smokers. Using filter paper impregnated with a Number 2 solution of PTC (650 mg/liter), subjects were tested and a questionnaire relevant to smoking habits was filled out. In both 597 white and 232 Negro male subjects there were significant differences in the ability to taste PTC between smokers and non-smokers. Of the white males, 52.6 per cent of the tasters were heavy smokers in contrast to 29.7 per cent of the non-tasters. Among heavy smokers, 65.9 per cent were tasters as compared to 42.7 per cent of the non-smokers. These differences were statistically significant. The investigators point out that the former, occasional, and light smokers resembled the non-smokers as to proportion of tasters. The following table shows the approximate per cent of tasters in each group of subjects, results being taken from a graph by Thomas and Cohen (99).

Table 3. Variation in Ability to Taste PTC.

<u>Classification</u>	<u>Per cent PTC Tasters</u>
Non-smokers	42
Former smokers	41
Occasional smokers	43

Table 3. (continued)

Light smokers	41
Moderate smokers	50
Heavy smokers	67
Cigarette, pipe, cigar	68
Pipe	68
Cigar	40

In another study (19) the same investigators refer to unpublished findings on 408 white males in which the same trends appeared.

Several investigators have looked at the smoking habits of twins in an attempt to discover if heredity is a factor in the predisposition to smoking. Fisher (21) cites the following data of E. Slater with respect to smoking:

	<u>Like</u>	<u>Unlike</u>
Monozygotic pairs	44	9
Dizygotic pairs	9	9

Fisher goes on to show that the effects are not solely due to similar environment by looking at the monozygotic pairs which were separated at birth as compared with those who were brought up together:

	<u>Like</u>	<u>Unlike</u>
Separated	23	4
Not separated	21	5

Friberg, et al. (28), studied 59 pairs of monozygotic and 59 pairs of dizygotic twins with respect to smoking habits. The figure below shows their results.

Monozygotic Pairs

		Twin II			
		A	B	C	D
Twin I	A	15			
	B	3	3		
	C	3	0	1	
	D	4	1	3	26

Dizygotic Pairs

		Twin II			
		A	B	C	D
Twin I	A	15			
	B	0	0		
	C	7	0	0	
	D	11	2	5	19

Classes

- A - regular smokers
- B - sporadic smokers
- C - former smokers
- D - other non-smokers

Fig. 2. Comparison of Smoking Habits of Monozygotic and Dizygotic Twins.

The results showed that monozygotic twins belonged to the same group in 45 cases whereas dizygotic twins had the same habits in only 34 cases. These results were statistically significant.

In another study (81), 984 pairs of twins were studied. It was shown that there was a greater concordance among monozygotic twins both for amount smoked as well as for type (cigar, cigarette, or pipe). The investigator also cites a personal communication from Juel-Nielsen on a study of 12 pairs of monozygotic twins reared apart in which the same rate of concordance was found as in the twins who were raised together.

Before concluding the review of the literature dealing with the genetic basis of smoking the following two studies are worthy of citation.

Cohen and Thomas (19) investigated the blood groups of 1,398 healthy males and then attempted to correlate their findings with smoking habits. The smokers were grouped into five categories: non-smokers, occasional smokers, heavy cigarette smokers, other smokers (pipe and cigar), and former smokers.

When the results of the white occasional and non-smokers were pooled and compared with the heavy cigarette smokers, a significant difference was found. There was a deficiency of group B among the heavy smokers and an excess of group B among the non-smokers and occasional smokers. In addition, among the white males, a high frequency of Rh negative individuals was found in the occasional smoker group. Although no significant differences were observed in the Negro group, the investigators state that it was noteworthy that the same trends were observed in this group.

In another study (97) an association was noted between the smoking of mentholated cigarettes and alcoholism. In order to demonstrate this relationship the investigators cited the following data for four populations.

Table 4. Cigarette Consumption; Mentholated versus Non-Mentholated.

Group	Mentholated cigarettes as per cent of total
Normal population	5
Drug dependent patients	5
State hospital with 3% alcoholics	14
State hospital with 12% alcoholics	21

It is suggested that the most likely hypothesis explaining the above association is a synergistic effect between mentholated cigarettes and alcoholism. Although it is not clear exactly what such a relationship indicates, it was believed to be sufficiently important to be included in the present study dealing with the genetics of smoking and alcoholism.

Discussion of the Findings in the Literature

The genetotrophic concept as proposed by Williams and his co-workers is an appealing hypothesis and seems to be regarded by most investigators as a possible explanation. It is cited by many of the new textbooks on nutrition, metabolic diseases, and human genetics as a plausible hypothesis. The lack of adequate evidence for the mechanism whereby the genetotrophic concept functions, leaves the proposal in the realm of speculation. One question which can and has been proposed is why the nutritional deficiency should lead to a specific craving for alcohol when alcohol is not the deficient substance. It is conceivable that somewhere in the series of

chemical reactions in the metabolism of some as yet unidentified substance, there is a compound formed which is either identical with, or closely resembles, ethyl alcohol or one of the substances of its breakdown (e.g. acetaldehyde). Another possibility might be that ethyl alcohol or one of the products of its metabolism is needed as a catalyst, co-factor, or inhibitor in a series of reactions concerned with the metabolism of the deficient substance. These suggestions, while purely hypothetical, serve to demonstrate that a specific craving for alcohol as the result of a nutritional deficiency is not an impossibility. The fact that no mechanism has as yet been proposed to explain the functioning of the genotrophic concept does not invalidate the hypothesis or make it any less valid. It simply suggests that more research is necessary in order to clarify the concept as proposed by Williams..

The studies which show that alcoholism is more common in families of alcoholics than in the general population do not prove that there is a genetic basis for alcoholism. As has been pointed out, the environment created by alcoholic parents will have a

marked effect on the lives of their offspring. There may be some debate as to whether this effect would be one of fostering alcoholism or discouraging it, but it cannot be denied that environmental influence is marked. It should be pointed out, however, that in the event that alcoholism was shown to be affected by genetic predispositions, the finding that there are an increased number of alcoholics in the family of the alcoholic would be a necessary one. These investigations then, along with other relevant information, suggest a genetic factor is operating. If it is shown that alcoholism does in fact have some genetic basis, these studies may be useful in investigating the nature of the inheritance.

The literature dealing with the family structure is extremely ambiguous. Some studies show that alcoholism is more prevalent in small families and others that there is a preponderance of the disease in large families. Two investigators maintain that the youngest child is most susceptible (8, 65) and a third claims that there is no conspicuous difference between youngest and oldest children (103). One worker reported that younger children were more often affected

and three years later claimed that the first born has the greatest chance of becoming an alcoholic (73, 74). The results of these studies do not suggest any meaningful conclusions.

The literature dealing with the occurrence of other diseases in association with alcoholism suggests several interpretations. Emphasis was placed on diseases of known or suspected genetic origin, and in particular, schizophrenia and epilepsy. Although there is considerable evidence for a genetic basis for these latter diseases, many investigators tend to overlook the importance of heredity. The single fact that schizophrenia and epilepsy, as well as the other conditions referred to, are found to be associated with alcoholism does not prove that there is a genetic basis for alcoholism. Such an observation does suggest that there may be a common form of inheritance, but this is by no means the only possible explanation. Most investigators are inclined to disregard the genetic interpretation in favor of the psychological or sociological one.

The studies which are most strongly suggestive of a genetic basis for alcoholism are the twin studies

carried out by Kaij (27, 28). The only type of data which are still lacking consist of information on separated twins. Although monozygotic-dizygotic twin comparisons are by no means infallible, this remains one of the most reliable tools available for research in human genetics. More research is needed in order to establish whether or not there is a relationship between alcoholism and blood groups. The two studies presented, the only ones found in the literature, seem to be valid, both based on large experimental groups. It should be noted that Nordimo's (75) study was performed with a considerably larger group of alcoholics. He failed, however, to show a tabulation of his results, merely claiming that there was a correlation between alcoholism and blood group A with $p = 0.004$.

With respect to the literature dealing with a genetic predisposition to smoking, it is believed that no correlation has been demonstrated between smoking and PTC taste sensitivity. The findings of Hall and Blakeslee (36) have been seriously questioned by the findings of a later study by Maia (63) in which it was shown that variations in the taste

threshold occur over 15 minute intervals regardless of whether or not a cigarette is smoked during the interval. The writer also questions the study by Thomas and Cohen (99) in which only one concentration of PTC was used. It should be noted that other investigators have used only one solution, but this is either solution Number 5 or 6 (81.25 mg/liter and 40.63 mg/liter respectively). In the study by Thomas and Cohen the solution used was an extremely concentrated one (solution Number 2, 650 mg/liter) which does not accurately differentiate between tasters and non-tasters.

The results of the twin studies, however, seem to be quite conclusive. In every study reported the concordance among monozygotic twins was significantly higher as compared with the concordance among dizygotic twins. In addition, the fact that the concordance is not affected by separation of monozygotic twins supports the hypothesis of genetic factors predisposing to smoking.

The validity of the findings by Cohen and Thomas (19) regarding a relationship between blood groups and smoking is questioned by the writer. It should

be noted that these are the same investigators who studied smoking and PTC taste sensitivity using only one solution. It should also be noted that both studies were supported by grants from the Tobacco Industry Research Committee. The writer feels that the study dealing with smoking and blood groups is questionable, since the investigators indulged in considerable manipulation of the data. When an analysis of the five groups of smokers showed no significant trends with respect to blood groups, the investigators proceeded to pool the data from two of the groups and compare this with another selected group. They also showed a statistically significant relationship between the Rh blood groups and white male occasional smokers. This does not seem to be a meaningful result unless the investigators are suggesting a genetic basis for occasional smoking.

MATERIALS AND METHODS

In order to obtain information from experimental and control subjects, questionnaires (see appendix II) were filled out by the investigator during an interview.

Questions 4 through 9 were designed to assess the smoking habits of the subjects. Question 8 was included in an attempt to determine the subject's dependency upon smoking. In the interviewing session this was usually phrased as: "Have you ever tried to stop smoking?" If the answer was affirmative the next question was, "Was it difficult to give it up?" If the person had never tried to stop smoking he was then asked, "Do you think it would be difficult to stop smoking if you wanted to?" The writer realizes the subjective nature of these questions and the difficulty in obtaining a clear-cut response; however it was felt that this was the best way of determining whether or not the subject was a compulsive smoker.

In order to test the results of an earlier study (97) with respect to a correlation between alcoholism

and mentholated cigarettes, question 9 was included. The questions designed to assess the drinking habits (10 through 14) were included in the experimental group questionnaire, but were eliminated from that given the control group due to the personal nature of the inquiries. The final questions, relevant to the regular use of vitamin pills, were an attempt to relate the study to Williams' genetotrophic concept. In other words, it was thought possible that some individuals might be found who were genetically predisposed to alcoholism but had avoided the disease due to vitamin supplements. At the bottom of the questionnaire a notation was made of the hand-clasping type, the sensitivity to PTC, and for the experimental group a record of the color perception test.

The experimental group consisted of alcoholic in-patients at Detroit Receiving Hospital. The patients were first interviewed and told of the nature of the study. If they desired, and were physically able to be tested, they were taken to a room in a remote part of the ward for the test session. The control group, as indicated below, consisted of students and faculty at Western Michigan University.

Phenylthiocarbamide (PTC)

Since it was first noted that some individuals can taste PTC while others cannot, a vast number of studies have been undertaken with respect to the ability to taste this substance. It was shown (12) that the ability to taste PTC is genetically determined, and follows a bimodal distribution, approximately 70 per cent of the individuals tested being classified as tasters and 30 per cent as non-tasters. In a review of research studies involving PTC (42) it was pointed out that many diverse techniques have been employed in order to test PTC taste sensitivity. These methods include direct application of the crystals to the subject's tongue, the placing of drops of solution on the tongue with various types of droppers, the use of PTC impregnated filter paper, and the sipping of PTC solutions from paper cups.

Harris and Kalmus (37), in an attempt to standardize PTC taste tests, devised the following procedure. A stock solution of 0.13 per cent PTC was prepared in boiled tap water. From this, fourteen serial solutions were prepared, each one being one-half as concentrated as the preceeding one. In

the testing session the subject was presented with paper cups containing the solutions, the test being started with the most dilute solution (#14). The subject was then given the more concentrated solutions in serial order until he claimed to perceive a taste. This was the approximate threshold. The subject was then given 8 cups, 4 containing water and 4 with the PTC just determined. If the subject was able to separate the cups correctly, then the test was repeated with the next most dilute solution until he was no longer able to differentiate between the two. This then represented the actual taste threshold. Since the introduction of this standard method most investigators have adopted the procedure either entirely or in part.

Prior to the beginning of the present study the writer attempted to assess the method of Harris and Kalmus as well as the use of filter paper soaked in the various concentrations of PTC. The latter method was found to be entirely unsatisfactory due to the taste imparted by the paper itself. Two difficulties were encountered with the method designed by Harris and Kalmus. The first, a practical consideration, was

that this technique required that too much equipment be transported from one test site to the next. In situations where the subjects come to a central location for testing it would be feasible to use the set-up of Harris and Kalmus, but when the investigator must call on the subjects individually it becomes difficult to carry fourteen bottles and sets of paper cups. Furthermore, without the use of a sink, the problem of disposing of the groups of eight cups becomes bothersome. The second difficulty encountered with the taste test concerns the odor associated with the PTC solutions. Phenylthiocarbamide, being a urea compound, has a rather unpleasant odor, particularly at the higher concentrations. When the subject is presented with a cup containing the solution it is possible that olfaction rather than taste is the basis for differentiation.

After several failures, the following method was devised for the testing of taste sensitivity to PTC. The solutions were prepared according to the method of Harris and Kalmus (37), autoclaved distilled water being used in place of tap water. In addition, a reagent blank (boiled distilled water) and a sucrose

solution (25 gm sucrose/liter distilled water) were prepared. The three most dilute solutions (solutions #12, 13, and 14) were eliminated in order to reduce the amount of apparatus and time required for testing. Since the taste area sensitive to bitter is localized at the base of the tongue it was felt that any method of application which centered on the tip of the tongue (as with sipping) was questionable. In order to apply the solution to all parts of the tongue, as well as eliminate olfaction as much as possible, atomizers were used.

For the present study the DeVillbiss economy atomizer No. 82 was selected. This device had the advantage of being compact as well as providing a heavy and reasonably constant spray. Several difficulties were encountered with this atomizer. It was not adapted for heat sterilization which necessitated the longer process of washing in 95 per cent ethyl alcohol. Furthermore, the atomizer bulbs did not hold up under prolonged use and it was necessary to replace several of the sprayers. The advantages of the technique, however, outweighed the faults. It was possible to transport thirteen bottles in a small

valise and it was only necessary to refill the bottles once daily.

The reagent blank and sucrose solution were used to aid in the discrimination. It was noted, as previously reported (37), that many subjects perceive a sweet taste in the solutions below the threshold, but this taste was readily distinguishable from that of the sucrose solution. Before the subject's actual threshold was determined he was required to distinguish between that solution and the one preceeding it as well as between the threshold solution and the distilled water blank. Thus in the testing procedure the subject was presented with the solutions beginning with distilled water and then the most dilute solution (#11). If he perceived a sweet taste this was differentiated from the sucrose solution. When the subject reported a bitter taste he was asked to compare it with the preceeding solution, if this one also tasted bitter, the next most dilute solution was offered for comparison and this process was repeated until he could distinguish the two solutions. Finally the subject was asked to differentiate the PTC solution from distilled water. It is believed

that this method eliminated most errors since the subject ~~was~~ required to identify the PTC solution three times. In cases of inconsistency or apparently confused reports the results were omitted. This was found to occur only twice during the entire experiment. Occasionally, after reaching the taste threshold the subject retained a foul taste. In these instances the interview was continued, the subject being offered a drink of water, and the trials were completed after a lapse of several minutes.

Ordinarily it would not be necessary to run a control group since the literature contains adequate results with respect to taste sensitivity which can be compared with any experimental results obtained. Since a new method was being used, however, it was felt desirable to test a control group and see if the present method yielded results comparable to those in the literature. For this purpose a group composed of students and faculty at Western Michigan University was tested..

Color Vision

In order to test for color blindness the Dvorine Color Perception Testing Charts (20) were used. The book containing the charts was held in front of the subject who was instructed to call off the numbers. The responses were recorded on a mimeographed sheet according to the form suggested by Dvorine (20). An analysis of the scored sheet enabled the writer to classify the subjects as normal, protanoid, or deuteranoid. Due to the large amount of data relevant to the incidence of color blindness in the general population, and also to the length of time required for the test, it was not believed necessary to administer this test to the control group.

Hand Clasping

The subject was asked to clasp his hands in front of him and a notation was made as to whether the right thumb (type R) or the left thumb (type L) was placed uppermost. Following the initial hand clasp the subject was told that some people place the fingers of the other hand on top and he was asked to

try this. In every case the subject responded by claiming that the second method felt "uncomfortable," "funny," or some other such reply.

In addition to the hand clasping data obtained from the experimental and control groups, one generation pedigree data was obtained in order to determine the importance of genetic factors in hand clasping (see Appendix I).

RESULTS

Table 5 contains the information obtained from thirteen alcoholic male subjects. It will be noted that 9 were classified as smokers, 2 as former smokers, and 1 each as non-smoker and cigar smoker. That would mean that 69 per cent of the present sample were cigarette smokers, a figure which would not seem significantly different from the figure of 75 per cent reported in the literature (17).

The PTC taste sensitivity of the control group is shown in Figure 3. As pointed out previously, it was felt necessary to include a control group for this part of the experiment because a new technique was being used. The results compare favorably with those in the literature (25, 26, 37, 98), the antimode in the present study falling between solutions 4 and 5. Figure 4 depicts the taste sensitivity for the alcoholic subjects. There is a greater percentage of non-tasters among the alcoholics ($\chi^2 = .0083$, $p < .95$), and the mean taste threshold is lower ($t = .99$, $p > .30$). Neither of these differences is significant.

In order to determine the relationship, if any, between smoking and PTC taste sensitivity Figures 5

and 6 were prepared, representing a breakdown of the control group with respect to smoking. The smokers are those subjects currently smoking ten or more cigarettes per day. Light smokers (under 10 cigarettes per day), former smokers, and other smokers (cigar or pipe) have not been included in these figures. The smoking group have a smaller percentage of tasters and a lower mean taste threshold, however the differences between smokers and non-smokers are not significant ($t = 1.7$, $p = .10$) and the percentage of tasters as compared to non-tasters do not differ significantly from those expected* ($X^2 = .92$, $p > .30$; $X^2 = .14$, $p = .70$ for smokers and non-smokers respectively). The finding of less sensitive tasters among smokers, but not significantly less, has been reported in the literature (25). It was thought that this might be due to some small effect upon taste sensitivity which might arise following prolonged smoking. To test this hypothesis the smokers were divided into two groups based on the number of years that they had been smoking. The results are shown in Table 6.

*For PTC the expected values were 70 per cent tasters; 30 per cent non-tasters. For hand clasping the expected values were 50 per cent R : 50 per cent L.

Table 5. Results of Experimental Findings.

Subject Number	Age	Category	Smoking Brand(s)	Duration	Alcohol Preference	Duration	PTC	Color Vision	Hand Clasp
101	47	former-heavy	-----	10-15 yrs.	Beer	24 yrs.	8	normal	L
102	54	heavy	-----	42 yrs.	Beer	17 yrs.	5	deuter-anoid	L
103	57	non-smoker	-----	-----	Beer	25 yrs.	-1	normal	R
104	46	heavy	-----	29 yrs.	Beer & Wine	27 yrs.	2	deuter-anoid	R
105	58	heavy	Camels Pall Mall	45 yrs.	Distilled	15 yrs.	6	deuter-anoid ?	R
106	43	moderate	Pall Mall	16 yrs.	Beer	16 yrs.	11	normal	R
107	35	heavy	Winston Pall Mall	20 yrs.	Distilled	15 yrs.	6	normal	R
108	36	heavy	Old Gold	20 yrs.	Beer	20 yrs.	6	normal	R
109	51	cigars	-----	25 yrs.	Distilled	37 yrs.	1	normal	R
110	54	heavy	Pall Mall Kools	30 yrs.	Distilled	35 yrs.	-1	normal	L
111	68	former-heavy	-----	?	Beer	?	3	?	?
112	33	heavy	Pall Mall	19 yrs.	Beer	10 yrs.	7	normal	R
113	47	heavy	Pall Mall	27 yrs.	Distilled	25 yrs.	6	normal	R

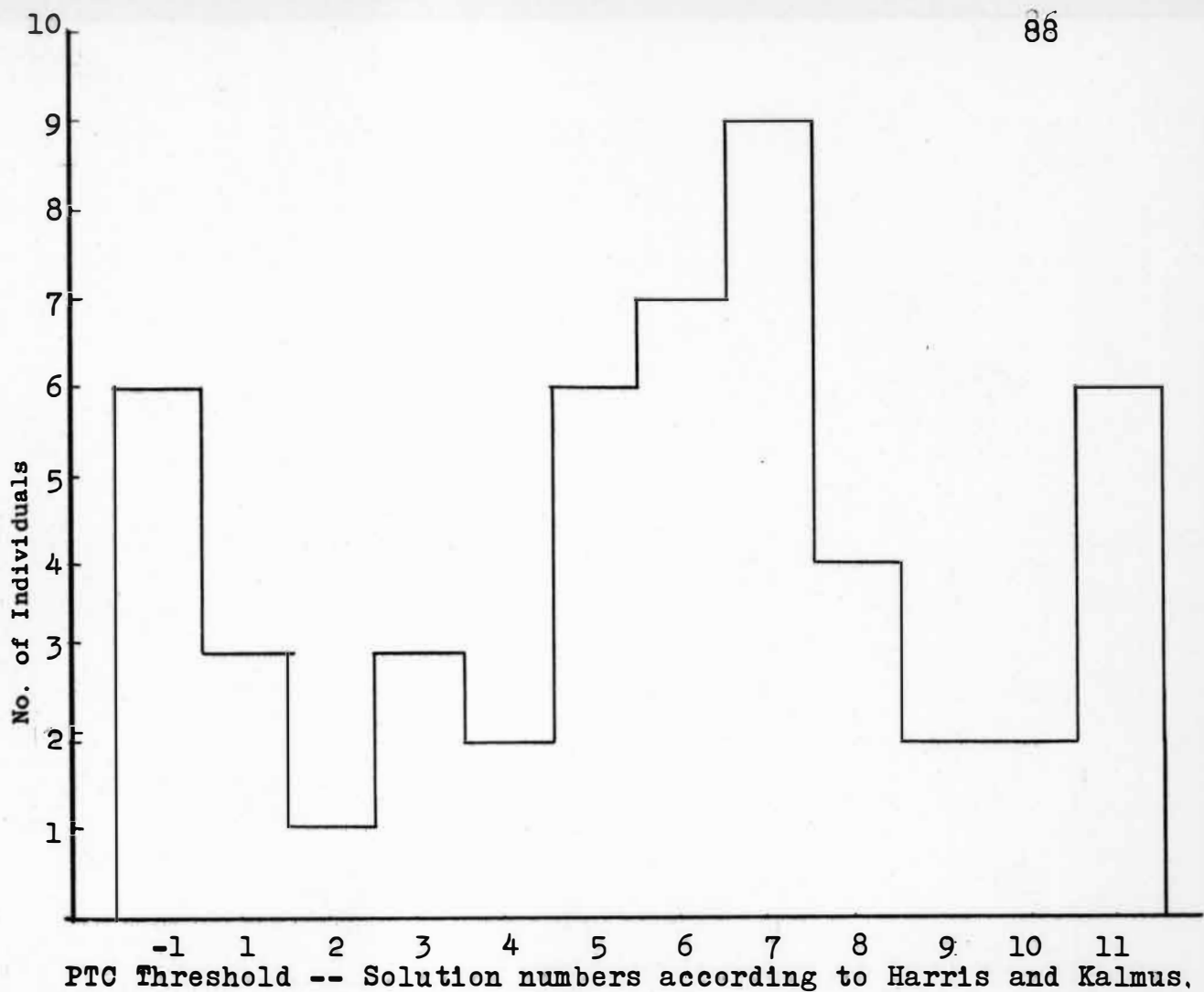


Fig. 3. PTC Thresholds in Control Group. 71% Tasters : 29% Non-Tasters.

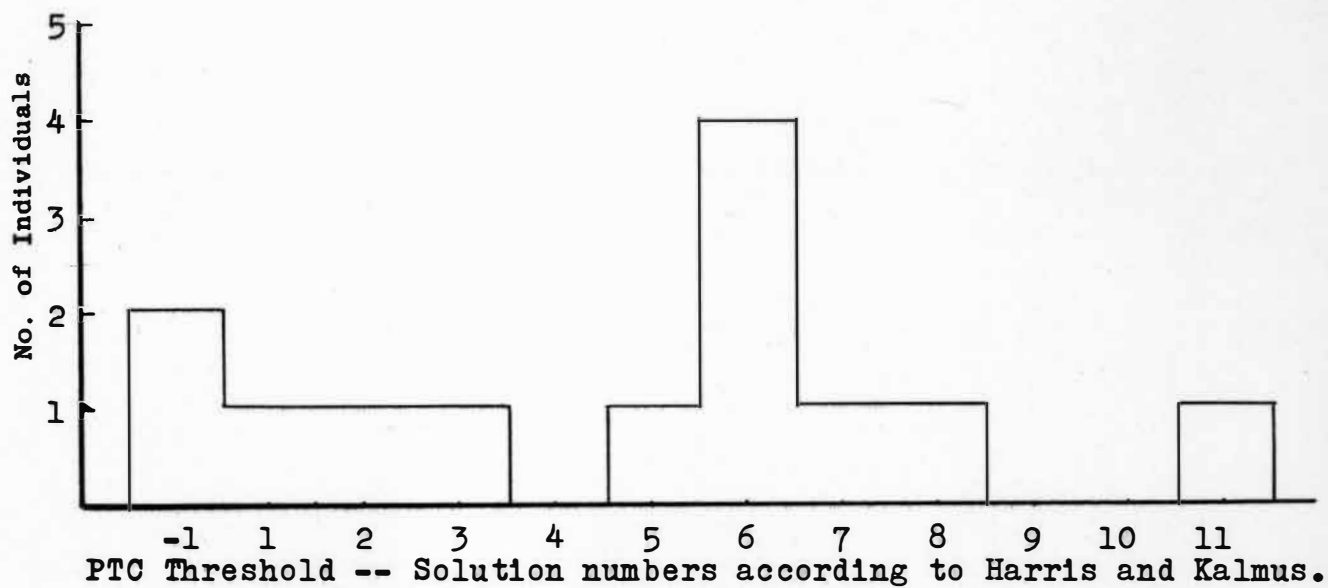


Fig. 4. PTC Thresholds in Alcoholic Group. 62% Tasters : 38% Non-Tasters.

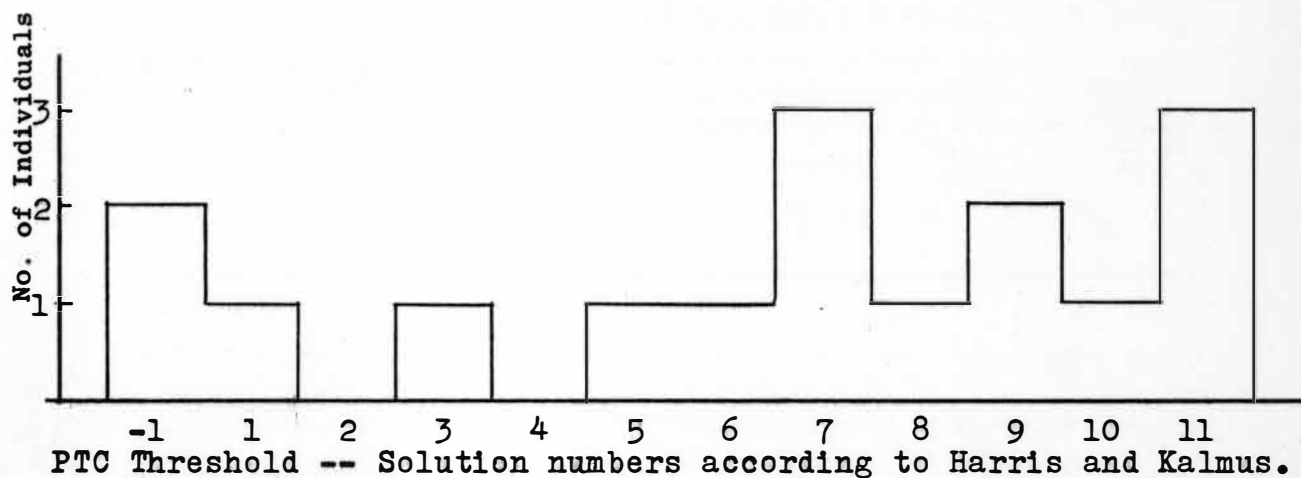


Fig. 5. PTC Thresholds in Non-Smoking Group. 75% Tasters : 25% Non-Tasters.

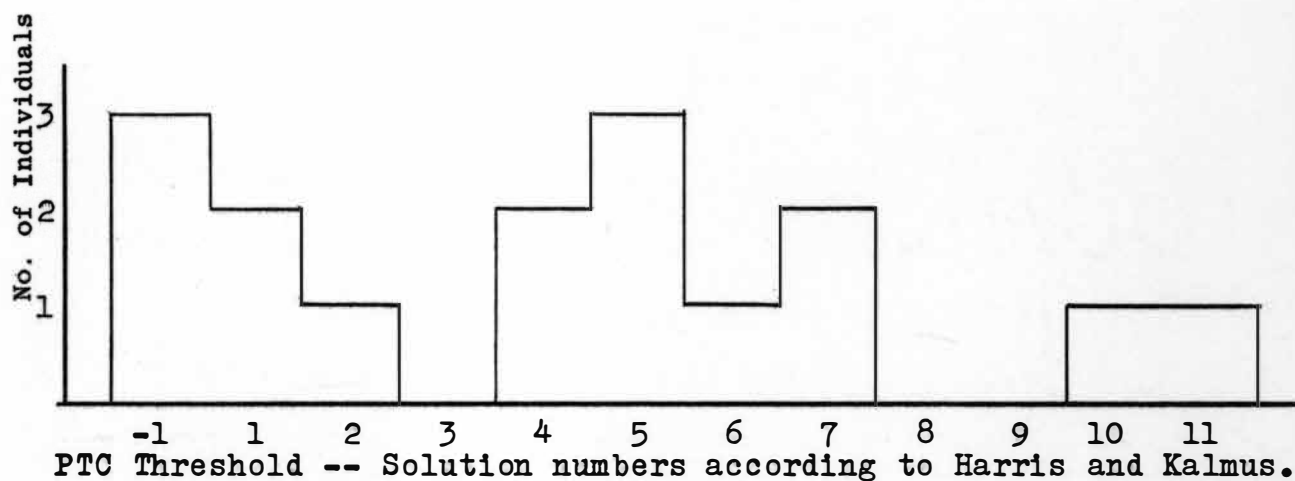


Fig. 6. PTC Thresholds in Smokers. 50% Tasters : 50% Non-Tasters.

Table 6. PTC Thresholds Related to Duration of Smoking Habit.

Average Number Years Smoking	Tasters : Non-Tasters	Mean Taste
2.3	37.5 : 62.5%	4.12
20.0	75.0 : 25.0%	5.12

Of the smokers among the alcoholics, 77.7 per cent were tasters and 22.2 per cent were non-tasters. These results do not differ significantly from the expected values ($\chi^2 = .26$, $p < .50$). The mean taste threshold of this group (5.2) does not differ significantly from the smokers in the control group ($t = .802$, $p = .40$). The mean taste threshold was lower among the non-alcoholic smokers than among the alcoholic smokers, an unexpected result which suggests that "abuse" to the taste buds is not the only factor involved affecting the taste sensitivity to PTC.

Three subjects in the control group indicated that they preferred mentholated cigarettes while only one subject (subject 110) in the alcoholic group listed a mentholated cigarette among the brands preferred. No evidence was obtained to substantiate the claim (97) that there was an association between alcoholism and the smoking of mentholated cigarettes.

It was noted that the brands preferred by the alcoholics were generally in the classification of strong cigarettes, six of the nine current smokers indicating Pall Mall as their brand.

Among the controls 55 per cent were of hand clasping type R and 45 per cent were of type L. The results were not significantly different from those expected ($X^2 = .40$, $p = .50$). Among the alcoholics 75 per cent were of type R as compared to only 25 per cent of type L; however these values were not significantly different from the expected ($X^2 = 3.0$, $p < .10$). When the control group was divided into smokers and non-smokers and hand clasping types analyzed, the smokers were found to consist of 50 per cent type R and 50 per cent type L (as theoretically expected) while the non-smokers were comprised of 63 per cent type R and 37 per cent type L. The latter results do not differ significantly from 50 - 50 ($X^2 = 1.0$, $p = .30$). The hand clasping types for the smokers among the alcoholics were found to be the same as for the total alcoholic group (75 per cent R and 25 per cent L), the differences still being insignificant ($X^2 = 3.0$, $p < .10$). The non-smoking alcoholics

did not constitute a sufficiently large group to be statistically analyzed.

The only statistically significant results obtained became apparent when the results for several of the traits were combined. Among the non-alcoholic smokers the ratio of PTC tasters to non-tasters was 50 : 50, the mean taste threshold being 4.1. When this group was analyzed according to hand clasping types it was found that among type R individuals 75 per cent were tasters as compared to 25 per cent who were non-tasters. The mean taste threshold was 5.1. Among the type L individuals 14 per cent were tasters and 86 per cent were non-tasters ($\chi^2 = 11.1$, $p < .001$), the mean taste threshold being only 2.0 ($t = 1.89$, $p > .05$). The results are highly significant.

Figs. 7-8 show the pooled data (alcoholics and non-alcoholics) for smokers analyzed with respect to hand clasping type and PTC taste sensitivity. It will be seen that among smokers type L individuals were significantly less sensitive PTC tasters than type R individuals ($\chi^2 = 9.7$, $p > .001$; $t = 2.83$, $p = .01$). If the criterion for selecting smokers is changed so that only individuals smoking in excess of

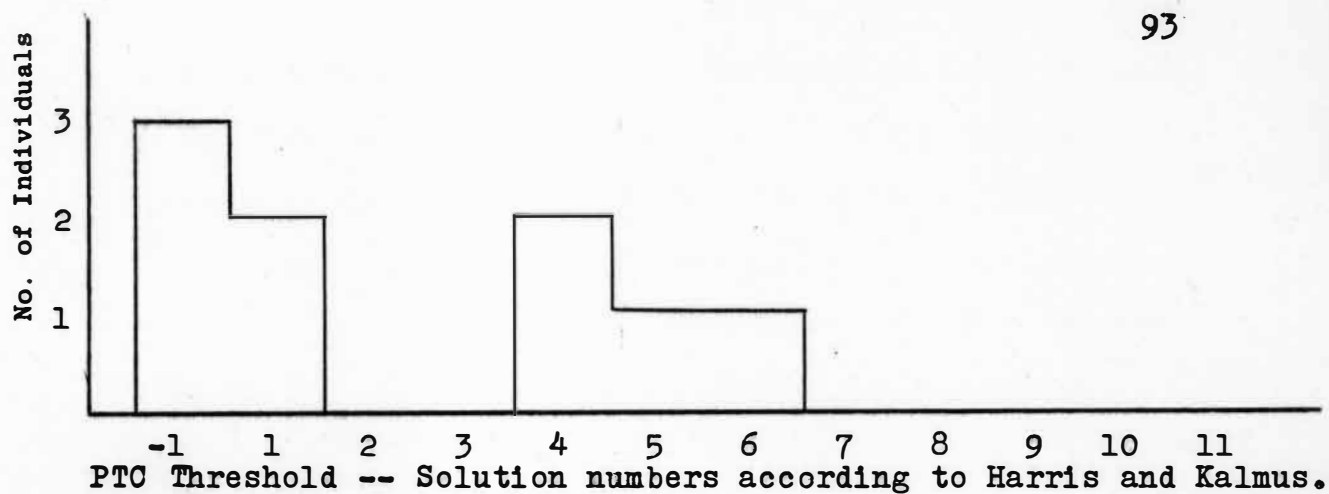


Fig. 7. PTC Thresholds in Type L Smokers. 22.2% Tasters :
77.7% Non-Tasters.

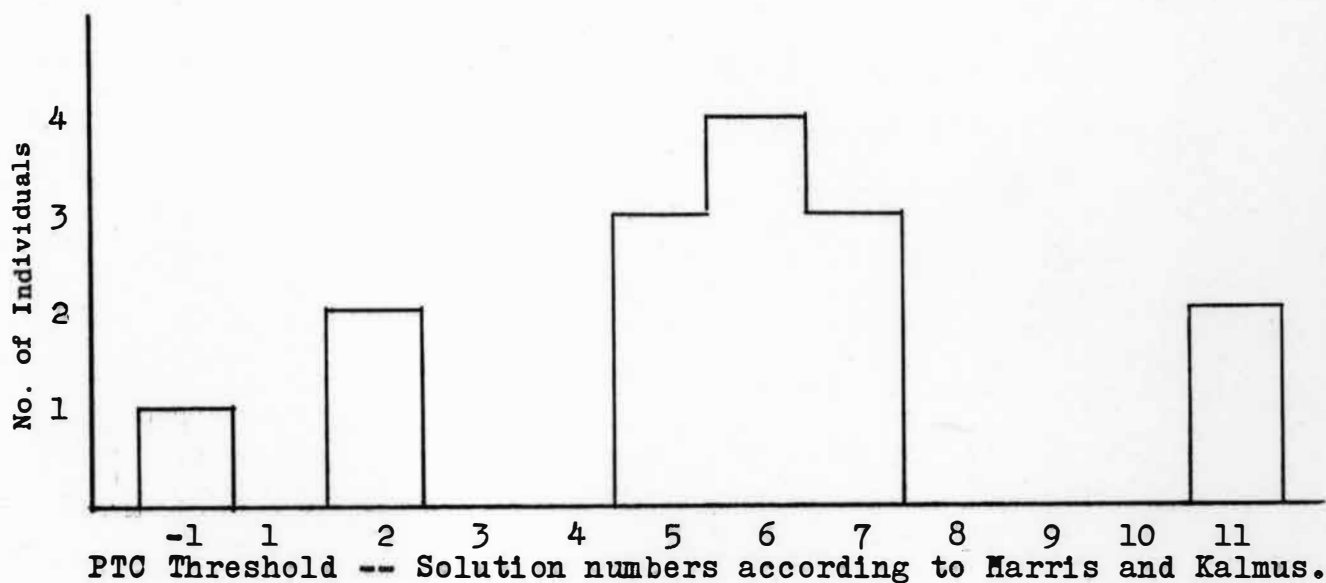


Fig. 8. PTC Thresholds in Type R Smokers. 80% Tasters :
20% Non-Tasters.

20 cigarettes per day are classified as heavy smokers, the mean taste threshold, as well as the per cent of tasters, is increased in the type R group, thus increasing the differences between type L and type R individuals. A comparison of the means in this case shows the results to be statistically significant ($t = 3.1$, $p < .01$).

When the alcoholics were tested it was also possible to examine their medical records. The only common affliction was avitaminosis. The only condition with a known or suspected genetic basis was von Recklinghausen's disease which occurred in subject 106. All of the subjects had been taking thiamine and were placed on a vitamin regimen. It was also possible to obtain plasma glucose and white blood cell values. These values, as obtained from 16 alcoholic patients, 11 of whom were subjects for the remainder of this study, are presented in Table 7. In addition the control averages and alcoholic averages as obtained by Williams, et al. (116), are included for comparison.

Table 7. Blood Values in Control and Alcoholic Subjects.

Blood	Williams Control Average	Williams Alcoholic Average	Present Study Alcoholic Average
Total leukocyte count (mm ³)	6,450	8,420	7,644
Plasma glucose mg/100 ml	96	106	115

The final consideration in this section concerns the incidence of red-green color blindness. Of the thirteen alcoholics tested, two were classified as deuteranoid, one as a possible deuteranoid, and one who apparently had some defect of color vision but could not be clearly placed in any particular category. Subject 102 was classified as a deuteranoid because he replied incorrectly to plates 2, 4, and 10 of the Dvorine charts (20). Subject 104 missed plates 2, 3, 4, and 24. Individuals having difficulty with green will fail to see the "5" on plate 2 and will report a "3" instead of "8" on plate four. Both of the above subjects failed to see the "5" and reported the "3" as described above. Subject 105 missed plates 4 and 24, reporting a "3" on plate four. Subject 111 failed to see any number on plates 2, 3, 8, 9, 10, 14, and 18. No consistent pattern of errors was noted. Due to the small sample size no statistical analysis of these data has been undertaken.

DISCUSSION

The foremost problem encountered in the present study stemmed from the stigma associated with the problem itself. Few people are ready to accept the disease concept of alcoholism, let alone a genetic interpretation. The alcoholic becomes disturbed when it is suggested that his condition is inherited, probably because he does not like to think of passing the disease on to his children. Most investigators are content to explain alcoholism in terms of personality factors. A few are willing to attribute some importance to physiology. Only a handful have attached serious consideration to the genetic factors. This was the basic problem encountered because it resulted in a lack of enthusiasm and consequently a small experimental group. The members of Alcoholics Anonymous were hesitant to cooperate in a biological experiment although they were more than willing to submit to a personality evaluation. One doctor, with access to a large number of alcoholics, refused to cooperate because the idea of a genetic basis of alcoholism was "absurd."

The results of the PTC taste sensitivity test on the control group demonstrated the validity of the method used. It is felt that the spraying of solutions directly into the mouth yields more accurate results since the effects of olfaction have been essentially removed.

The finding that there was no significant difference between alcoholics and controls with respect to PTC tasting ability suggests that these traits are not linked genetically.

It was not possible to determine if a relationship exists between smoking and alcoholism. It is the writer's belief that any association which exists is one between smoking and drinking. This was indicated by the observation that there was not an excessive amount of smoking among the alcoholics tested or other alcoholics observed in the hospital ward. It will be noted that only 9 of the 13 subjects were current cigarette smokers. During the course of the interviews it was noted that most of the subjects claimed to smoke more while they were drinking. The large amount of smoking observed at Alcoholics Anonymous meetings could most likely be attributed

to substitution of smoking for drinking, the extent of the former increasing after alcohol withdrawal. This latter hypothesis would have to be tested by interviewing alcoholics who have stopped drinking.

The results with respect to smoking and PTC are as reported in the literature, namely a decrease in taste sensitivity among smokers. In a review of the literature (25) it was found that several studies had yielded the same results, but in each case the differences had been insignificant. As noted in the results of the present study, the data on smokers were divided into two groups on the basis of number of years smoking. It was found that the group which had been smoking for an average of 2.3 years were less sensitive tasters than the group which had been smoking for an average of 20 years. This suggests that prolonged effects of smoking are not an important factor in diminishing taste sensitivity.

The results with respect to brand of cigarettes smoked did not substantiate the association between alcoholism and the smoking of mentholated cigarettes. It was not possible to disprove this relationship due to the small sample size.

Differences were noted with respect to hand clasping among alcoholics as compared to non-alcoholics. There was an excess of type R; however the differences were not statistically significant.

The association between PTC non-tasting and type L hand clasping in smokers is statistically significant and suggestive of linkage. The writer is hesitant to claim that linkage does in fact exist, since as pointed out previously, the chances of selecting two traits and finding linkage between them is improbable. It is possible that this finding is merely an artifact due to the small size of the sample. Furthermore, it is not certain that hand clasping is under genetic control, although there is some evidence for this hypothesis (85, 86, Appendix I). It is possible, however, that the above finding is indicative of linkage between genes predisposing to smoking, PTC taste sensitivity, and hand clasping. Further studies will be necessary to determine the implication of these results. The fact remains that the results are highly significant.

It will be noted that in all the data dealing with smoking the writer has eliminated the subjects

who smoke less than ten cigarettes per day and also the former smokers regardless of how long they had smoked and the extent of their habits. It would be desirable to have a separate group for light smokers and another one for former smokers; however the number of subjects in these categories was too small to be analyzed. While it is not known for certain that there are differences between smokers and former smokers the possibility exists that one who has stopped smoking is not as dependent on cigarettes as one who has not. Of course there is no way of determining how many of the current smokers will have stopped smoking by next year, and this introduces another variable into the data. However the investigator believed that whereas it was impossible to determine "future-former-smokers" it was simple to eliminate former smokers. Furthermore there were only four of these former smokers in the entire study.

Another consideration with respect to the association between smoking, PTC non-tasting, and type L hand clasp exists and should be mentioned. It will be noted (Fig. 8) that three individuals among the type R smokers have been classified as

non-tasters. In the literature on hand clasping, Fujiki (30) has suggested that a small number of the type L genotype manifest the R situation by virtue of a phenocopy. This means that some of the individuals classified as type R might be genotypically type L and this might increase the significance of the findings. This is merely a thought but it would be interesting to test type R offspring from two type L parents.

The significance of the findings of blood values as compared with Williams' data is questionable. It was noted that these blood values varied widely among the alcoholics from high levels at admittance to lower levels after abstinence. It is likely that the differences observed in blood values were the result of the temporary condition of the individual and not inherently characteristic.

The results with respect to color blindness might prove to be the most significant. As stated previously the reason for selecting this trait was to test the hypothesis that the predisposition to alcoholism was sex-linked. Two difficulties in the present study make any conclusions with respect to

color blindness impossible. First, and most important, is the size of the sample. It is possible to deal with PTC tasting due to the gradient of results obtained. With color blindness no such analysis is possible. The second difficulty resides in the method used to test color blindness. The Dvorine charts are useful in obtaining some idea of an individual's color perception, but for a research investigation more accurate methods are necessary. Thus, on the basis of this study, it can only be stated that further work is required in order to determine the relationship, if any, between color blindness and alcoholism.

In conclusion, no evidence has been found supporting the hypothesis of a genetic basis for alcoholism. No significant relationship has been found between alcoholism and PTC taste sensitivity or between alcoholism and hand clasping. A relationship between alcoholism and red-green color blindness has been suggested. A significant relationship between PTC non-tasting and type L hand clasping has been found among individuals smoking ten cigarettes per day or more. The possibility of linkage is thus suggested.

SUMMARY

1. A review of the literature consisting of the following topics has been presented:
 - a) The genetotrophic concept.
 - b) Frequency of alcoholism in families of alcoholics.
 - c) Analysis of family structure.
 - d) Association of alcoholism with other diseases.
 - e) Twin studies on alcoholism.
 - f) Alcoholism and blood groups
 - g) Miscellaneous studies relating to genetics of alcoholism.
 - h) The genetic basis of smoking.
2. The present study has investigated the relationships among smoking, alcoholism, red-green color-blindness, phenylthiocarbamide (PTC) taste sensitivity, and hand clasping. The purpose was an attempt to define linkage between any one or more of the above traits thus providing evidence for the genetic basis of alcoholism.
3. A new method has been devised to test PTC taste sensitivity. The technique, using a series of atomizers, has been found successful.
4. No significant relationship has been found between PTC taste sensitivity and alcoholism.
5. No significant relationship has been found between

hand clasping and alcoholism.

6. A relationship between red-green color blindness and alcoholism has been suggested, but further study with a larger experimental group will be necessary.
7. The PTC taste sensitivity of smokers was found to be lower, but not significantly lower, than non-smokers.
8. A highly significant relationship has been shown between PTC non-tasting and type I hand clasping among smokers.
9. Family data on hand clasping is included (Appendix I) which suggests that genetic factors are important in determining this trait.

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APPENDIX I

Genetic Data on Hand Clasping

The following data were collected in order to determine if hand clasping is under genetic control. Two possibilities exist with respect to clasping the hands; the fingers of the right hand may be placed over the fingers of the left hand with the right thumb uppermost (type R); or the reverse situation with the left thumb on top (type L).

The results were obtained from college students at Western Michigan University. The students were requested to report their hand clasping types and those of their families. The analysis is based on a total of 90 individuals, the 47 offspring of 22 matings.

The four possible mating types ($\text{♀} \times \text{♂}$) along with the number of each type in the present sample were 6(R X R), 8(R X L), 3(L X R), and 5(L X L). There were no significant differences among the four mating types ($X^2 = 2.36$, $p = .70$) and for this reason types R X L and L X R can be considered together as comprising the heterogeneous mating type.

The breakdown of results with respect to hand clasping type as well as to sex is shown in Table 8.

Table 8. Handclasping Types.

Type	Number Male	Number Female	Total	
			No.	%
Type R	22	25	47	52.22
Type L	23	20	43	47.78

Analysis showed no statistically significant differences between males and females with respect to hand clasping type ($X^2 = .10$, $p = .70$; $X^2 = .21$, $p = .70$ for types R and L respectively).

The pooled data (52.22 per cent R, 47.78 per cent L) do not differ significantly from the data reported by Freire-Maia, et al. (26), ($X^2 = 2.09$, $p = .15$).

The genetic nature of the trait is suggested by the results shown in the table below.

Table 9. Frequency of Type L Individuals Resulting from the Three Mating Types.

Parents	Number of L Offspring	Per cent of L Offspring
R X R	2	18.2
R X L	9	52.9
L X L	10	83.3

The foregoing results are highly significant ($\chi^2 = 11.33$, $p > .005$).

Fujiki (30) has suggested that the "homozygous dominants, heterozygotes, and a part of the homozygous recessives (the genotype of the L-situation) manifest the R-situation by a phenocopy." The present results are consistent with Fujiki's proposal as well as with the suggestion by Freire-Maia, et al. (27), whereby RR would be expressed as type R, rr as type L, and the heterozygotes would clasp their hands indifferently. Regardless of the type of inheritance, the present results suggest the existence of genetic factors in the control of hand clasping.

APPENDIX II

QUESTIONNAIRE (Control group)

1. Code No. _____.
 2. Age _____.
 3. Check: _____ Male. _____ Female.
 4. If you have never smoked check here _____ and skip to question 10.
 5. Check appropriate statement:
 I now smoke _____.
 I used to smoke but no longer do _____.
 6. I smoke (smoked):
 5 cigarettes a day or less _____.
 10 cigarettes a day or less _____.
 20 cigarettes a day or less _____.
 30 cigarettes a day or less _____.
 over 30 cigarettes a day _____.
 - If you smoke (smoked) a pipe or cigar, please
 estimate daily usage _____.
 7. I have been, smoking (had smoked) for _____ years.
 8. Check: Are you a "compulsive" smoker _____ or a
 "casual" smoker _____.
 9. If you smoke (smoked) one or two particular brands
 of cigarettes please indicate which brand(s).

 10. If you do not take vitamin pills regularly check
 here _____.
 11. I have been taking _____ (indicate brand
 name or type) for _____ years.
- _____
 tt _____ . clasp _____ . misc. _____ .

QUESTIONNAIRE (Experimental group)

1. Code No. _____.
2. Age _____.
3. Check: _____ Male. _____ Female.
4. If you have never smoked check here _____ and skip to question 11.
5. Check appropriate statement:
I now smoke _____. I used to smoke but no longer do _____.
6. I smoke (smoked):
5 cigarettes a day or less _____.
10 cigarettes a day or less _____.
20 cigarettes a day or less _____.
30 cigarettes a day or less _____.
more than 30 cigarettes a day _____.
If you smoke (smoked) a pipe or cigar please estimate daily usage _____.
7. I have been smoking (had smoked) for _____ years.
8. Check: Are you a "compulsive" smoker _____ or a "casual" smoker _____.
9. If you smoke (smoked) one or two particular brands of cigarettes please indicate which brand(s).

10. If you started smoking before drinking became a problem, or at about the same time you started drinking check here _____. If you have only been smoking since you've stopped drinking check here _____.
11. My preference was:
_____ Beer. _____ Wine. _____ Distilled spirits
12. I drank for _____ years. I have not had a drink for _____ (please specify time).
13. If you do not take vitamin pills regularly check _____.
14. I have been taking _____ (indicate brand name or type) for _____ years.

- tt _____ . CB/+ _____ . Clasp _____ . Misc. _____