Negative microfilm
received from university

67-12,678

FRENCH, Jean Gilvey, 1926-
A STUDY OF FAMILIAL AGGREGATION OF SERUM URIC ACID LEVELS IN THE POPULATION OF TECUMSEH, MICHIGAN, 1959-1960.

The University of Michigan, Dr.P.H., 1965
Health Sciences, public health

University Microfilms, Inc., Ann Arbor, Michigan

PLEASE NOTE:

The negative microfilm copy of this dissertation was prepared and inspected by the school granting the degree. We are using this film without further inspection or change. If there are any questions about the film content, please write directly to the school.

UNIVERSITY MICROFILMS

A STUDY OF FAMILIAL AGGREGATION OF SERUM URIC ACID LEVELS IN THE POPULATION OF TECUMSEH, MICHIGAN 1959-1960

by
Jean Gilvey French

Submitted in partial fulfillment of the
requirements for the degree of
Doctor of Public Health
Department of Epidemiology
School of Public Health
The University of Michigan
Ann Arbor, Michigan
1965

Doctoral Committee:

Professor Horace J. Dodge, Chairman
Assistant Professor Marcus O. Kjelsberg
Associate Professor William M. Mikkelsen
Professor William J. Schull

ACKNOWLEDGMENTS

The author wishes to express sincere appreciation to all those who helped to make this study possible. Special thanks are given to:

1. Doctor Thomas Francis, Jr., Chairman of the Department of Epidemiology, for his approval and support of this project.
2. Members of the Doctoral Committee for their help, guidance and constructive criticism:

   Doctor Horace J. Dodge, Chairman
   Doctor Marcus O. Kjelsberg
   Doctor William M. Mikkelsen
   Doctor William J. Schull.

3. Mr. Jacob Keller for his help with statistical methods.
4. Mr. James Wood for help in the processing of the data.
5. Mrs. Ida Yeh for help in preparing programs for the computer.
6. Mrs. Rebecka Andress for typing the manuscript.

TABLE OF CONTENTS

Page

ACKNOWLEDGMENTS ii

LIST OF TABLES v

LIST OF FIGURES xi

INTRODUCTION 1

Chapter

I. URIC ACID METABOLISM 4

A. Purine Metabolism in Relation to Uric Acid

1. Purine Anabolism
2. Purine Catabolism

B. Factors Influencing Uric Acid Metabolism

1. Hyperuricemia

a. Gout
b. Other Conditions Associated with Hyperuricemia

2. Hypouricemia
3. Variations of Serum Uric Acid with Time

II. HISTORICAL REVIEW OF GENETIC STUDIES IN HYPERURICEMIA AND GOUT 17

III. DESCRIPTION OF THE TECUMSEH COMMUNITY HEALTH STUDY . . . 25

A. Purpose of the Tecumseh Community Health Study
B. Description of the Community of Tecumseh
C. Methods Used in Collection of Data

IV. STUDY OF THE DISTRIBUTION OF SERUM URIC ACID LEVELS IN THE TECUMSEH COMMUNITY HEALTH STUDY 28

A. Method of Handling Blood Specimens
B. Method of Determining Serum Uric Acid Concentrations

Chapter Page

C. Delineation of Members of Study Population with Satisfactory Serum Uric Acid Determinations
D. Distribution of Serum Uric Acid Levels
E. Method of Computing Scores for SUA

V. PRESENTATION OF METHODS AND RESULTS IN THE STUDY OF FAMILIAL AGGREGATION OF SERUM URIC ACID IN TECUMSEH COMMUNITY HEALTH STUDY 34

A. Cursory Analysis to Determine Evidence for Familial Aggregation
B. Identification of Subjects with Secondary Hyperuricemia
C. Measurement of the Degree of Association Between Parent and Child
D. Measurement of the Degree of Association in Siblings
E. Measurement of the Degree of Association in Spouse Pairs
F. Measurement of the Degree of Association of SUA Scores Within Kindreds
1. Kindred Analysis in Probands with Hyperuricemia
2. Kindred Analysis in Probands with Hypouricemia
3. Kindred Analysis in Probands with Gout
4. Kindreds with Both Hypo- and Hyperuricemic Probands
G. Measurement of the Degree of Association Between Serum Uric Acid and Other Variables

VI. DISCUSSION 92

A. Interpretation of Findings
B. Limitations of the Study

SUMMARY 104

APPENDIX 106

BIBLIOGRAPHY 127

LIST OF TABLES

Table		Page
I.1	Serum Uric Acid Values for Ten Healthy Subjects Taken at Four Different Times Over Eight Hours	15
I.2	Mean Serum Uric Acid Values for Eleven Healthy Subjects During a Two Month Period	16
II.1	Published Studies of Hyperuricemia in Relatives of Gouty Patients	19
III.1	Distribution by Age and Sex of Subjects Examined in Tecumseh from April 1959 to October 1960	27
IV.1	Age-Sex Distribution of Persons Having a Technically Satisfactory Serum Uric Acid Determination, Absolute and Relative to the Number of Persons Examined, TCHS, 1959-60	30
V.1a, V.1b	Per Cent Distribution of SUA Scores by Age and Sex Based on SUA Score of Parents with SUA Scores of Both Offspring and Parents Grouped by the Number of Standard Deviations from the Mean	36, 37
V.2	Mean Serum Uric Acid Scores of Offspring, All Ages by Sex Based on Serum Uric Acid Scores of Parents	43
V.3	Mean Serum Uric Acid Scores of Children Ages 0 to 9 Based on Serum Uric Acid Score of Parents	44
V.4	Mean SUA Scores of Children Ages 10-19 by Sex Based on Serum Uric Acid Score of Parents	45
V.5	Mean SUA Scores of Offspring Ages 20-39 by Sex Based on SUA Score of Parents	46
V.6	Regression Coefficient, F Test and Correlation Coefficient of SUA Score of One Offspring in Family on SUA Score of Parents (based on formula a + bx)	51

Table | Page

V.7 Least Squares Second and Third Degree Polynomial of Child's SUA Score on Parents SUA Score by Sex of Child 52

V.8 Heritability of Child's SUA Score with Parents SUA Score 53

V.9 Regression Analysis of SUA Score of One Offspring per Family on SUA Score of Parent Based on Formula $a + b_1x_1 + b_2x_2 + b_3x_1x_2$ 54

V.10 Intraclass Correlation Coefficient of SUA Scores of Sibships by Age 56

V.11 Analysis of Variance Considering the Variation Among Superfraternities, Among Fraternities within Superfraternities and within Fraternities 58

V.12 Correlation Coefficients of Spouse Pairs Based on Age of Wife and Test for Homogeneity 59

V.13 Distribution of Hyperuricemic Probands by Sex and Relationship When More than One Proband in a Kindred . . . 62

V.14 Number and Per Cent of Relatives of Hyperuricemic Probands with SUA Scores of 5.6-7.0 mg. and 2.5-3.4 mg. by Sex of the Relatives 62

V.15 Number and Per Cent of Kindreds with More than One Hyperuricemic Proband or with One or More Relatives with SUA Scores of 5.6-7.0 mg. 63

V.16 Computation to Determine the Expected Number of Kindreds with More than One Proband and/or One or More Members with SUA Scores of 5.6-7.0 mg./100 ml. 64

V.17 Distribution of Hypouricemic Probands by Sex and Relationship of Probands When More than One Proband/Kindred 71

V.18 Number and Per Cent of Relatives of Hypouricemic Probands with SUA Scores of 5.6-7.0 mg. and 2.5-3.4 mg. by Sex of the Relatives 72

V.19 Number and Per Cent of Kindreds of Hypouricemic Probands Containing Members with SUA Scores of 5.6-7.0 mg. or 2.5-3.4 mg. 72

Table		Page
V.20	Computation to Determine the Expected Number of Kindreds with More than One Proband and/or One or More Members with SUA Scores of 2.5-3.4 mg./100 ml. . .	74
V.21	Distribution of Gout Probands by Sex	78
V.22	Number and Per Cent of Relatives of Gout Probands with SUA Scores of 5.6-7.0 mg. and 2.5-3.4 mg./100 ml. . .	78
V.23	Number and Per Cent of Kindreds of Gout Probands Containing Members with SUA Scores of 5.6-7.0 mg. or 2.5-3.4 mg.	79
V.24	Relationship of Probands when Both a Hyperuricemic and Hypouricemic Proband Occur in the Same Kindred	81
V.25	Number of Relatives with SUA Scores of 5.6-7.0 mg. or 2.5-3.4 mg. in Kindreds with Hyperuricemic and Hypouricemic Probands	81
V.26	Correlation Coefficients of Serum Uric Acid with Fourteen Variables by Age and Sex	84
V.27	Regression Coefficients and Correlation Coefficients of SUA on Relative Weight by Age and Sex	85
V.28	Regression Coefficient and Correlation Coefficient of SUA on Weight by Age and Sex	85
V.29	Mean Serum Uric Acid Scores for Subjects, All Ages, Above the 80th and Below the 20th Percentile in Relative Weight by Sex	88
V.30	Student T Test--Comparing Mean Relative Weight of Hyperuricemic Probands with that of Hypouricemic Probands .	90
	Student T Test--Comparing Mean Serum Uric Acid Scores of Immediate Family Members of Hyperuricemic Probands with Immediate Family Members of Hypouricemic Probands	90
	Student T Test--Comparing Mean Relative Weight of Immediate Family Members of Hyperuricemic Probands with Mean Relative Weights of Immediate Family Members of Hypouricemic Probands	91

LIST OF APPENDIX TABLES

Table		Page
A.1	Number and Per Cent of Sons and Daughters of Female Hyperuricemic Probands with SUA Scores of 5.6-7.0 mg. and 2.5-3.4 mg./100 ml.	107
A.2	Number and Per Cent of Sons and Daughters of Male Hyperuricemic Probands with SUA Scores of 5.6-7.0 mg. and 2.5-3.4 mg./100 ml.	107
A.3	Number and Per Cent of Sons and Daughters of Hyperuricemic Probands with SUA Scores of 5.6-7.0 mg. and 2.5-3.4 mg./100 ml.	108
A.4	Number and Per Cent of Male Hyperuricemic Probands with SUA Scores of 5.6-7.0 mg. and 2.5-3.4 mg.	108
A.5	Number and Per Cent of Female Hyperuricemic Probands with SUA Scores of 5.6-7.0 mg. and 2.5-3.4 mg.	109
A.6	Number and Per Cent of Mothers and Fathers of Male Hyperuricemic Probands with SUA Scores of 5.6-7.0 mg. and 2.5-3.4 mg.	109
A.7	Number and Per Cent of Fathers and Mothers of Female Hyperuricemic Probands with SUA Scores of 5.6-7.0 mg. and 2.5-3.4 mg.	110
A.8	Number and Per Cent of Mothers and Fathers of Hyperuricemic Probands with SUA Scores of 5.6-7.0 mg. and 2.5-3.4 mg./100 ml.	110
A.9	Number and Per Cent of Cousins of Hyperuricemic Probands with SUA Scores of 5.6-7.0 mg. and 2.5-3.4 mg. by Sex	111
A.10	Number and Per Cent of Grandsons and Granddaughters of Hyperuricemic Probands with SUA Scores of 5.6-7.0 mg. and 2.5-3.4 mg./100 ml.	112
A.11	Number and Per Cent of Aunts and Uncles of Hyperuricemic Probands with SUA Scores of 5.6-7.0 mg. and 2.5-3.4 mg.	113

Table		Page
A.12	Number and Per Cent of Nieces, Nephews, Grandnieces and Grandnephews of Hyperuricemic Probands with SUA Scores of 5.6-7.0 mg. and 2.5-3.4 mg.	114
A.13	Number and Per Cent of Sons and Daughters of Female Hypouricemic Probands with SUA Scores of 5.6-7.0 mg. and 2.5-3.4 mg.	114
A.14	Number and Per Cent of Sons and Daughters of Male Hypouricemic Probands with SUA Scores of 5.6-7.0 mg. and 2.5-3.4 mg.	115
A.15	Number and Per Cent of Sons and Daughters of Hypouricemic Probands with SUA Scores of 5.6-7.0 mg. and 2.5-3.4 mg.	115
A.16	Number and Per Cent of Mothers and Fathers of Male Hypouricemic Probands with SUA Scores of 5.6-7.0 mg. and 2.5-3.4 mg.	116
A.17	Number and Per Cent of Mothers and Fathers of Female Hypouricemic Probands with SUA Scores of 5.6-7.0 mg. and 2.5-3.4 mg.	116
A.18	Number and Per Cent of Siblings of Male Hypouricemic Probands with SUA Scores of 5.6-7.0 mg. and 2.5-3.4 mg.	117
A.19	Number and Per Cent of Siblings of Female Hypouricemic Probands with SUA Scores of 5.6-7.0 mg. and 2.5-3.4 mg.	117
A.20	Number and Per Cent of Nieces, Nephews, Grandnieces, and Grandnephews of Hypouricemic Probands with SUA Scores of 5.6-7.0 mg. and 2.5-3.4 mg.	118
A.21	Number and Per Cent of Uncles and Aunts of Hypouricemic Probands with SUA Scores of 5.6-7.0 mg. and 2.5-3.4 mg.	118
A.22	Number and Per Cent of Grandparents of Hypouricemic Probands with SUA Scores of 5.6-7.0 mg. and 2.5-3.4 mg.	119
A.23	Number and Per Cent of Cousins of Hypouricemic Probands with SUA Scores of 5.6-7.0 mg. and 2.5-3.4 mg.	120

Table Page

A.24 Number and Per Cent of Mothers and Fathers of Gout Probands with SUA Scores of 5.6-7.0 mg. and 2.5-3.4 mg. 121

A.25 Number and Per Cent of Sons and Daughters of Female Gout Probands with SUA Scores of 5.6-7.0 mg. and 2.5-3.4 mg. 121

A.26 Number and Per Cent of Sons and Daughters of Male Gout Probands with SUA Scores of 5.6-7.0 mg. and 2.5-3.4 mg. 122

A.27 Number and Per Cent of Sons and Daughters of Female Gout Probands with SUA Scores of 5.6-7.0 mg. and 2.5-3.4 mg. 122

A.28 Number and Per Cent of Siblings of Gout Probands with SUA Scores of 5.6-7.0 mg. and 2.5-3.4 mg. 123

A.29 Number and Per Cent of Grandchildren of Gout Probands with SUA Scores of 5.6-7.0 mg. and 2.5-3.4 mg. 123

A.30 Number and Per Cent of Aunts and Uncles of Gout Probands with SUA Scores of 5.6-7.0 mg. and 2.5-3.4 mg. 124

A.31 Number and Per Cent of Nieces, Nephews, Grandnieces, Grandnephews of Gout Probands with SUA Scores of 5.6-7.0 mg. and 2.5-3.4 mg. 124

A.32 Number and Per Cent of Cousins of Gout Probands with SUA Scores of 5.6-7.0 mg. and 2.5-3.4 mg. 125

A.33 Student T Test--To Test the Difference Between b_1 (Sons' SUAS on Midparent Scores) and b_2 (Daughters' SUAS on Midparent Scores) 126

Student T Test--To Test the Difference between b_1 (Sons' SUAS on Midparent Scores) and β (Expected Regression Coefficient for Multifactor Inheritance) and b_2 (Daughters' SUAS on Midparent Scores) and β (Expected Regression Coefficient for Multifactorial Inheritance). 126

LIST OF FIGURES

Figure		Page
IV.1	Distribution of Serum Uric Acid Levels by Sex Tecumseh, 1959-60	33
IV.2	Distribution of Serum Uric Acid Scores by Sex Tecumseh, 1959-60	33
V.1	Per Cent Distribution of Serum Uric Acid Scores of Offspring, All Ages, by Sex Based on Serum Uric Acid Scores of Parents	38
V.2	Per Cent Distribution of Serum Uric Acid Scores of Offspring 0-9 Years Based on Serum Uric Acid Score Parents	39
V.3	Per Cent Distribution of Serum Uric Acid Scores of Offspring 10-19 Years Based on Serum Uric Acid Scores of Both Parents	40
V.4	Per Cent Distribution of Serum Uric Acid Scores of Offspring 20-39 Years Based on Serum Uric Acid Scores of Parents	41
V.5	Mean Serum Uric Acid Scores of Sons and Daughters, 0-19, Based on Serum Uric Acid Score of Father	48
V.6	Mean Serum Uric Acid Scores of Sons and Daughters, 0-19, Based on Serum Uric Acid Score of Mother	48
V.7	Mean Serum Uric Acid Scores of Sons and Daughters, 0-19, Based on Serum Uric Acid Score of Mother and Father	48
V.8	Key to Geneologies	65
V.9	Geneologies of Hyperuricemic Probands	66
V.10	Geneologies of Hyperuricemic Probands	67
V.11	Geneologies of Hyperuricemic Probands	68

Figure		Page
V.12	Geneologies of Hyperuricemic Probands	69
V.13	Geneologies of Hyperuricemic Probands	70
V.14	Geneologies of Hypouricemic Probands	75
V.15	Geneologies of Hypouricemic Probands	76
V.16	Geneologies of Hypouricemic Probands	77
V.17	Geneologies of Gout Probands	80
V.18	Geneologies with Both Hyperuricemic and Hypouricemic Probands	82
V.19	Per Cent Distribution of Percentile Rank in Relative Weight in Males Grouped According to the Number of Standard Deviations from the Mean in Serum Uric Acid Scores	86
V.20	Per Cent Distribution of Percentile Rank in Relative Weight in Females Grouped According to the Number of Standard Deviations from the Mean in Serum Uric Acid Scores	86
VI.1	Distribution of Serum Uric Acid Scores of Relatives of Probands with Hyperuricemia	94
VI.2	Distribution of Serum Uric Acid Scores of Relatives of Probands with Hypouricemia	95
VI.3	Distribution of Serum Uric Acid Scores of Relatives of Probands with Gout	96

INTRODUCTION

> One that's sick o' the gout would rather
> Groan so in perplexity than be cured
> by th' one sure physician, Death.
>
> William Shakespeare, Cymbeline

In the 400 years that have passed since these lines were written, remarkable advances have been made in the treatment of the disease, gout, once it is established. Death is no longer the "one sure physician." Available to all physicians are colchicine for terminating the acute attacks of the disease and the uricosuric drugs for prevention of the development of subsequent acute attacks.

While these advances in secondary prevention--that is, prevention of disability resulting from acute attacks of the disease--have been notable, advances along the lines of primary prevention--that is, prevention of the development of the first attack--have not kept pace.

In a recent editorial, Cobb[1] has urged that the serum uric acid determinations be added to the battery of screening tests used as a routine for hospital admissions, periodic health examinations and multiple screening surveys. He points out that recent, but unpublished, data from the Framingham Heart Study have shown a direct relationship between the frequency of gout and the level of uric acid in the serum. Cobb has estimated that there is a 100-fold increase in the frequency of gout as

one goes from persons with less than 6 mg. per 100 ml. of serum uric acid (SUA) to those with 8 or more mg. per 100 ml. The evidence from Framingham also suggests that one-third of the persons with SUA of 8 or more mg. per 100 ml. will develop gout within the next ten years. Cobb states that,

> Since prevention is (of) primary (concern) in public health, we find ourselves in a fine situation for it is clear that people with levels (of SUA) over 8 mg. per cent should be investigated and should probably be treated with uricosuric drugs before they develop their disease,

and that

> . . . since Barry, et al.,[2] have also demonstrated that persons with gout are more subject to myocardial infarctions than others, the importance of screening is enhanced.

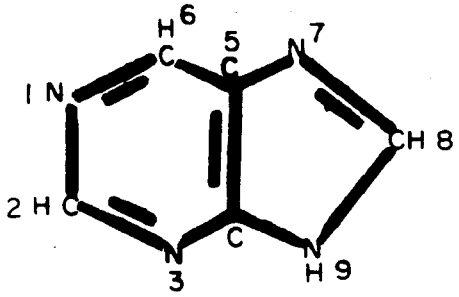
As a screening device to signal the need for consideration of primary preventive measures, the SUA must be regarded as being something less than an ideal test. It is generally recognized that an elevated SUA is a "necessary but not sufficient" condition for the development of acute episodes of gout. Other hall marks of susceptibility to gout should be discovered and utilized in the decision as to the need for primary preventive measures. In the search for other indicators of susceptibility to gout, consideration must be given to the role of genetic and environmental factors as well as their interactions. Whichever of these factors are found to be operative in the pathogenesis of gout, it is reasonable to assume that susceptible individuals may cluster about the identifiable index case in the same family or household. A study of such families may then provide a means for identifying potential victims to the disease.

The purpose of the present study is to determine the nature and extent of familial aggregation of serum uric acid levels in the population of Tecumseh, Michigan. It is hoped that such a study will provide knowledge of the influence of genetic forces on the serum uric acid level and some measure of the interaction between genetic and environmental factors. The knowledge acquired from such a study might then prove useful in the prevention and control of hyperuricemia and gout.

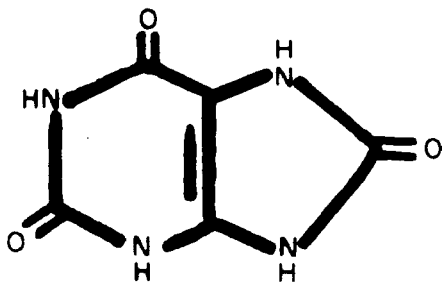
CHAPTER I

URIC ACID METABOLISM

Uric acid is the end product of the oxidation of purines in the body. The oxidation process can be accomplished in one of two ways. The first is by the synthesis of purines, their incorporation into nucleic acids (or polynucleotides) and the subsequent degradation of nucleic acids and the oxidation of their purines to uric acid. The second way is by the synthesis of purines and their direct oxidation without the obligatory interaction of nucleic acids.



Purine



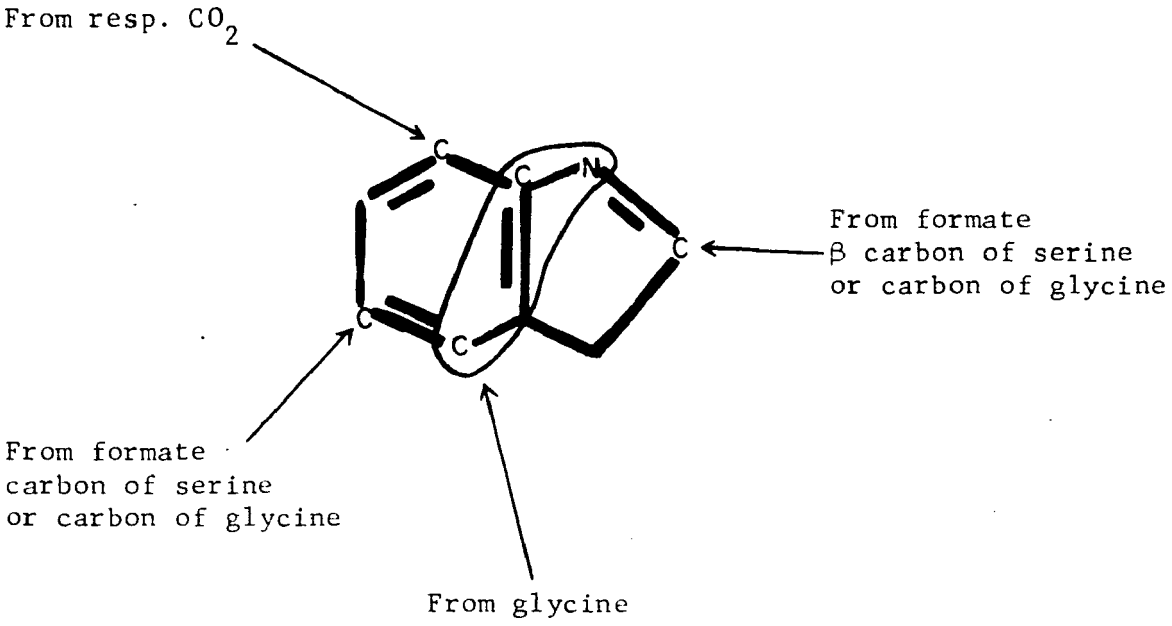
Uric Acid

A. Purine Metabolism in Relation to Uric Acid

1. Purine Anabolism

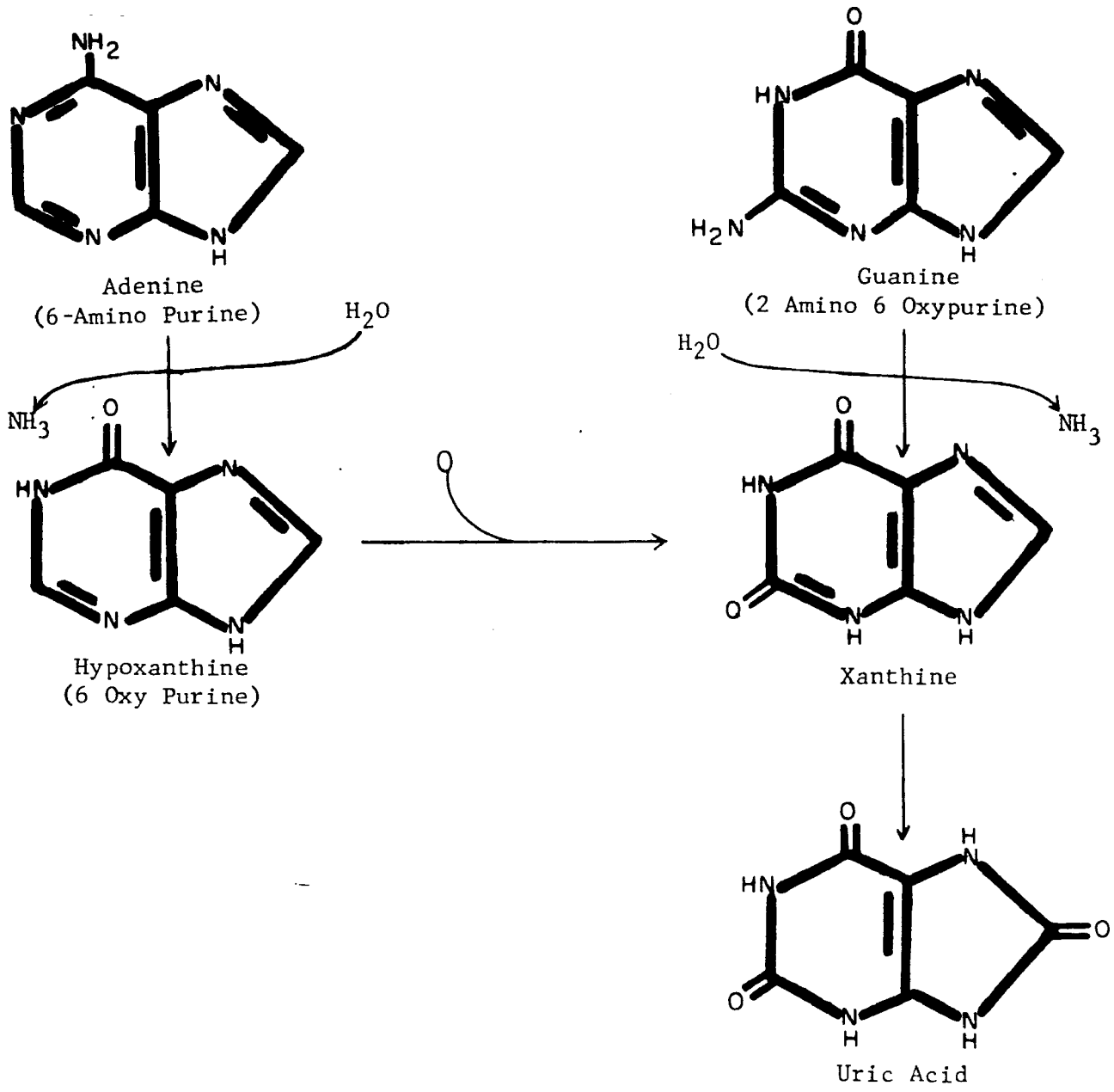
Information on the sources of the various atoms of the purine nucleus have been obtained by tracer studies in birds, rats, and man. The amino acid glycine is utilized intact to form the carbons in position 4 and 5 (shown above) while its alpha-nitrogen forms position 7. The nitrogen at position 1 is derived from the amino nitrogen of

aspartic acid; those at positions 3 and 9 from the amide nitrogen of glutamine. The carbon atom in position 6 is derived from respiratory CO_2 while the carbons in positions 2 and 8 come from a one carbon compound such as formate or from the beta carbon of serine, which is itself derived from a one carbon moiety when glycine is converted to serine.



2. Purine Catabolism

Adenine and guanine are the two purines found in all nucleic acids. The following illustrates the breakdown of adenine and guanine to uric acid.



The metabolism of uric acid in man has been studied by the use of isotopically labeled uric acid (N^{15} in carbons 1 and 3). Single doses of the labeled uric acid were injected intravenously into a normal subject and into patients suffering from gout, a disease which is characterized by a disturbance in purine metabolism. The dilution of the injected labeled compound was used to calculate the quantity of uric

acid which is present in the body water. This quantity, referred to as the "miscible pool," contained in the normal subjects an average of 1131 mg. of uric acid. It is estimated that 200-300 mg. of this pool is exogenous from the ingestion of nucleotides; the remainder is endogenous from the breakdown of nucleoproteins and nucleotides. The plasma was found to be considerably higher in uric acid than other portions of the body water. In gouty subjects the miscible pool was much larger; for example, 4,742 mg. in a mild case having a serum uric acid of 6.9 mg./100 ml. and no symptoms of the disease; up to 31,000 mg. in a patient with severe symptoms of gout.[3]

From the rate at which N^{15} declined in the uric acid, it was possible to estimate the "turnover" of this compound or the rate at which uric acid is synthesized and lost to the body. The uric acid formed in the normal subject was 500-580 mg. per day. It was also noted that the quantities of uric acid entering the miscible pool exceeded those which were lost by the urinary route by 100 to 250 mg. per day. This suggested that about 20 per cent of the uric acid lost to the body is not excreted as such but is chemically broken down. This conclusion is supported by the finding of N^{15} in urea and ammonia. It is known that some uric acid is excreted in the gut. This would then be subject to degradation by intestinal bacteria and the liberated N^{15} would be absorbed and reappear in various nitrogenous metabolites. More recent experiments indicate that breakdown of uric acid in man may be independent of the bacteria of the intestinal tract. When administered intravenously to a normal human subject, 18 per cent of the labeled uric acid was degraded to other nitrogenous products and 6 per cent of the

label was recovered in the urine unchanged. The experiment was repeated in the same subject, but sulfonamides were given by mouth to induce a reduction in the activity of the intestinal bacteria. The results were the same as had been obtained in the original experiment. It was concluded that some uricolysis does occur in normal human beings and that the intestinal flora does not make a major contribution to the process.[4,6]

Uric acid in the plasma is filtered by the glomeruli but is later partially reabsorbed by the renal tubules. Glycine is believed to compete with uric acid for tubular reabsorption.

There is now good evidence for tubular secretion of uric acid by the kidney; therefore, uric acid may be considered to be cleared from the plasma both by glomerular filtration and by tubular secretion.[5,6]

B. Factors Influencing Uric Acid Metabolism

1. Hyperuricemia can be induced in man by any one of four abnormalities in the metabolic process: an increase in the degradation of nucleoproteins and nucleic acids, an increase in the shunt pathway (the synthesis of purines and their direct oxidation to uric acid without the obligatory intervention of nucleic acids), decreased glomerular filtration, or decreased tubular secretion.

a. Gout

Gout is characterized by elevated levels of uric acid in blood and urine. Urates tend to deposit in cartilage (ears, joints, rarely the nose) epiphyseal bone, other articular structures and

kidneys. Crystalline urates produce local necrosis and an ensuing foreign body reaction with proliferation of fibrous tissue. Cartilagenous degeneration, synovial proliferation, destruction of subchondral bone (destructive arthritis), proliferation of marginal bone (hypertrophic arthritis), often synovial pannus and sometimes fibrous or bony ankylosis may slowly develop. In the kidneys one finds gross and microscopic urate deposits in tubules, medulla and interstitial tissues. Secondary destructive and inflammatory reactions develop.[7]

The miscible pool of uric acid in the gouty patient is much larger than in the normal subject. This excess is largely stored in the tophi. The uric acid in the body fluids is in some degree equilibrated with that in the tophi, since the miscible pool can be decreased by the administration of uricosuric drugs even though these changes may not be reflected in the serum uric acid levels.

The administration of N^{15} labeled glycine has been used to study the rate of synthesis of uric acid in the gouty patient.[9] In some patients there were findings which were interpreted as evidence not only for an increased rate of incorporation of dietary glycine nitrogen into uric acid but also of a cumulative incorporation of N^{15} into uric acid which was three times greater than in normal subjects. It was suggested, because of the rapidity and extent of the isotope incorporation, that in some gouty subjects there may be a metabolic alteration whereby glycine nitrogen can enter the purine nucleus of uric acid more readily than in normal individuals. A diet rich in protein would be expected to increase the formation of uric acid and it has, in fact, been found that uric acid synthesis from glycine is

accelerated both in normal individuals and in gouty individuals when the protein content of the diet is increased. Gutman[10] has hypothesized from more recent findings that in primary metabolic gout the kidney is partially blocked in the formation of ammonia from glutamine thus diverting glutamine to de novo purine biosynthesis and resulting in over production of uric acid.

In primary metabolic gout the mechanisms for the elimination of uric acid are normal, but are inadequate to cope with the increased load. However, there is now increasing evidence that in a smaller number of cases the primary defect may be in the kidney where there is faulty enzymatic transport of urates by the renal tubules.[11] In consequence there is a lowering of the rate of excretion of urates even though other functions of the kidney appear to be normal. This type of primary renal hyperuricemia or gout is to be distinguished from secondary renal hyperuricemia or gout as may occur in the patient with progressive renal failure.

b. Other Conditions Associated with Hyperuricemia

Hyperuricemia occurs in patients with psoriasis, and these patients show a greater than normal incorporation of glycine into urinary uric acid.[12]

Elevated blood levels of uric acid may occur in other diseases in which there is abnormally great turnover of nucleic acids. Examples are polycythemia, myeloid metaplasia and chronic leukemia. In the case of leukemia, hyperuricemia is found in chronic granulocytic leukemia but not in chronic lymphocytic leukemia. Studies carried out with labeled sodium formate showed that in granulocytic leukemia there is

increased incorporation of the isotope into the nucleic acids of the leukemic granulocytes and the isotope is then released as the granulocytes degenerate.[13] Granulocytic turnover is the principal factor in the overproduction of uric acid in this case. In chronic lymphocytic leukemia, leukocyte turnover does not contribute substantially to uric acid production. Occasionally in these hematopoietic diseases there may be attacks of gout. Such cases are referred to as secondary metabolic gout. If gout is not present, the observed hyperuricemia should be referred to as secondary metabolic hyperuricemia. This form of hyperuricemia and gout is thought to be due to increased catabolism of nucleic acids and a sudden flooding of the organism with the products of nucleic acid breakdown. The etiology of the secondary metabolic gout is therefore different from that of primary metabolic gout which is presumably due to an inherited metabolic error.

A number of conditions can give rise to impaired uric acid excretion. A decrease in glomerular filtration which accompanies diseases such as glomerular nephritis and arteriolar nephrosclerosis can cause an elevation of the serum uric acid level. Obesity is often associated with hyperuricemia and reduced renal clearance of urate.[15] Starvation produces a further decrease in urate excretion and an enhanced hyperuricemia. In this case the renal retention of uric acid may be mediated by the accumulation of the β hydroxy butyrate. The study conducted by Leiber et al.[16] on the interrelationship of uric acid and ethanol metabolism in man showed that five of twelve acutely intoxicated subjects had uric acid concentrations above normal. During recovery uric acid concentrations decreased in all. These investigators

proposed that the hyperuricemia observed in patients spontaneously intoxicated with alcoholic beverages is due, at least in part, to the oxidation of ethanol to acetylaldehyde generating diphosphopyridine nucleotide hydrogenase which reduces pyruvate to lactate. The resulting rise in blood lactate decreases urinary uric acid output which leads to an increase in serum uric acid concentration. It is thought that an increased blood lactate level is also the reason for the hyperuricemia associated with toxemia of pregnancy and glycogen storage disease. Myxedematous patients demonstrate a significant hyperuricemia and this group shows a decreased urinary excretion of urate and a decreased renal excretion rate.[18] Certain drugs have been shown to reduce the renal excretion of uric acid. Salicylates (in small doses), pyrozinamide, chlorthiazide, anti-hypertensives and sulfonamide diuretics have all been shown to elevate the serum uric acid level.

Hyperuricemia accompanies several other disease entities but the mechanism for the increased serum uric acid level has not been established. There is an association of hyperuricemia with hyperparathyroidism and hypoparathyroidism but thus far studies have revealed no direct physiologic correlation between parathyroid function and uric acid metabolism. Elevated uric acid levels are present throughout most of the life of mongoloids but thus far the reason for this has not been sufficiently studied. Berkowitz[27] has found a high correlation between hyperuricemia and hypertriglyceridemia but a very low correlation with cholesterol levels. This suggests a close association between uric acid and triglyceride metabolism. Elevated serum uric acid levels and the symptoms of gout have been observed in patients with diabetes. An

explanation which has been offered for this association is that an intermediary product of nucleoprotein breakdown which results from the disturbance of the metabolism in gout acts as a diabetogenic agent or that the metabolic aberration responsible for gout is also responsible for a subsidiary abnormality in carbohydrate metabolism. A syndrome consisting of hyperuricemia, mental retardation, chorioathetoidosis and self destruction biting has been described in two brothers aged five and eight years.[31] The uric acid pools in these patients were found to be similar in size to those reported for gouty adult patients. The formation of uric acid from glycine in these patients exceeded control patients by 200 times. It is possible that an excess of uric acid or one of its precursors could produce marked toxicity in early infancy.

2. Hypouricemia

Hypouricemia has received little attention and little study. It is possible to suppose that a reversal of any one of the four metabolic abnormalities found in hyperuricemia could contribute to a hypouricemic state. Abnormalities of xanthine metabolism have been reported in several patients who excreted only minute quantities of uric acid although the amounts of xanthine excreted were about equal to the amount of uric acid expected in a normal individual. The disease was considered to be a congenital metabolic defect possibly caused by a lack of xanthine oxidase. The extremely low levels of blood uric acid are believed to be due to the rapid glomerular filtration of xanthine together with a failure of reabsorption by the renal tubules, so that little or no xanthine remains to form uric acid. In the xanthinuric

patient xanthine stores may be formed in the kidney and the patient may develop urinary calculi. Low serum uric acid levels have also been associated with Wilson's Disease and the Fanconi Syndrome. Certain uricosuric drugs block reabsorption of uric acid, e.g., large doses of salicylates, cenhophen, neocenhophen, caronamide and probenecid. The urinary excretion of urate by human subjects can be increased by the administration of hormones of the adrenal cortex (the 11 oxysteroids) as well as by corticotropin (A.C.T.H.).

3. Variations of Serum Uric Acid with Time

The variation of serum uric acid levels in subjects over an extended period of time was studied by Dunn et al.[32] in several different groups. One group of ten males, all of whom were in good health and not receiving any medication, had determinations done at four different times during an eight hour period. Each subject ate an ordinary breakfast at about 7:30 A.M., lunch about 12 noon, and abstained from food between meals. The major component of variation was among subjects and there was no significant difference between times of day. Some subjects, however, may vary appreciably even during an eight hour period. There was no consistent effect of fasting or ingestion of food on serum uric acid levels. The mean serum uric acid levels and standard deviation for each subject is shown in Table I.1.

The subjects mentioned above were followed for two months with a total of four to six serum uric acid determinations. The major component of variation again was between subjects rather than with time. However, some subjects are quite constant while others fluctuate. The

TABLE I.1

SERUM URIC ACID VALUES FOR TEN HEALTHY SUBJECTS TAKEN AT FOUR DIFFERENT TIMES OVER EIGHT HOURS

Subject	Mean Serum Uric Acid mg. %	Standard Deviation
A	6.1	±0.48
B	5.6	±0.05
C	4.6	±0.00
D	6.1	±0.44
E	6.6	±0.28
F	5.7	±0.06
G	4.8	±0.08
H	7.4	±0.26
I	5.6	±0.03
J	5.2	±0.28

mean serum uric and value and standard deviation for each subject is shown in Table I.2.

Two other groups were used to supplement the above observations. One group of ten medical students were studied with seven uric acid determinations over a 24 hour period. For these students the mean values for each time period showed no evidence of a diurnal pattern. Another group consisting of 58 executives had two determinations of serum uric acid levels done at an interval of one year and these determinations did now show variation with time.

TABLE I.2

MEAN SERUM URIC ACID VALUES FOR ELEVEN HEALTHY SUBJECTS DURING A TWO MONTH PERIOD

Subject	Number of Determinations	Mean Serum Uric Acid Level	Standard Deviation
A	6	5.8	± 0.14
B	5	5.5	± 0.05
C	6	4.8	± 0.08
D	5	6.1	± 0.20
E	5	6.6	± 0.22
F	6	5.8	± 0.10
G	6	4.8	± 0.16
H	6	7.6	± 0.19
I	6	5.1	± 0.28
J	6	5.4	± 0.14
K	4	4.7	± 0.20

CHAPTER II

HISTORICAL REVIEW OF GENETIC STUDIES IN HYPERURICEMIA AND GOUT

Gout has been recognized as a familial disorder since Galen (AD 131-201) ascribed the origin of gout to "debauchery, intemperence, and a hereditary trait."[33] Thomas Sydenham (1624-1689) who himself suffered from the malady of gout, described the distribution of the disease by the following:

> But the gout does not only seize those that are corpulent; for sometimes it invades those that are in the flower of their age when they have received the ill seeds of this disease from their parents by inheritance.[34]

One observer, Cadogen,[35] (1675-1726) did differ from other early British writers in believing that gout was not hereditary, but in this view he stands in the small minority among the thousands who have written on the subject.

Uric acid was first recognized by Scheele[36] in 1776 when he detected this chemical in the urine of gouty patients. This led to recognition of the association of uric acid with gout. Later Garrod[37] showed an excess of uric acid in the blood of gouty subjects by his famous "cotton string test." He suggested that gout was probably due to a factor which expresses itself fairly regularly in hyperuricemia but only occasionally in gouty arthritis. This prediction was followed

by many subsequent observations clearly establishing hyperuricemia as a common finding in the relatives of gouty individuals and opening the way for further genetic studies based on biochemical tests. The major portion of the genetic studies on serum uric acid have been carried out in relatives of patients with gout.

Many observers have reported a familial incidence of gout in close relatives of patients with gout, ranging from six to 81 per cent. The reason for these wide differences may be attributed to the fact that these reports are based upon the statements of the patient or other members of the family; only rarely has the diagnosis of gout in the relatives been confirmed by a physical examination, a uric acid determination, or a roentgenographic study. They are valuable only in that they strongly suggest the hereditary tendency of gout; they do not permit an accurate analysis nor do they indicate the exact mode of transference of the genetic factor.

Shortly after the development of quantitative methods for determining uric acid in the blood, Folin and Lyman[38] (1913) reported hyperuricemia in a man in whose family there had been gout. Jacobson[39] (1938) studied a son of each of two men with clinical gout and a brother of a third patient; all of these individuals had elevated serum urate levels.

Table II.1 contains a summary of several recent investigations of hyperuricemia in the immediate relatives of gouty individuals.

The first extensive study was by Talbot[40] who reported observations on 136 nongouty relatives of 27 patients with gout. He found that 34 of these close relatives (25 per cent) had serum uric acid levels which were abnormally high. Similar findings were reported by

TABLE II.1

PUBLISHED STUDIES OF HYPERURICEMIA IN RELATIVES OF GOUTY PATIENTS

Reference	Year	Number of Gout Patients	Number of Relatives	Number of Gouty Relatives	Number with Hyperuricemia	Per cent with Hyperuricemia
Talbot[40]	1940	27	136	3	34	25
Smyth, Freyberg, Cotterman[41]	1948	19	87	3	21	24
Stecher, Hersch, Solomon[44]	1949	44	136	0	16	11
Wilson[45]	1951	3	29	11	21	72
Hague and Harvald[46]	1955	32	261	16	71	27

Smyth, Cotterman and Freyberg[41]. They collected data from 87 relatives of 19 gouty male patients. Of the male parents, siblings and children, an elevated serum urate (greater than 6 mg. per cent) was present in 12 out of 29. Of the female parents, siblings, and children, hyperuricemia (greater than 5 mg. per cent) was present in eight out of 21. In every instance where both parents of a hyperuricemic individual were studied, at least one parent showed an elevated serum urate. These observations were interpreted as indicating that hyperuricemia is due to a single dominant gene with incomplete penetrance. A follow up study of this group was conducted during 1961-62 and it was possible to examine all nine surviving propositi and 69 of the surviving 86 relatives as well as 193 additional relatives who were studied for the first time.[42] The results of this follow up are similar to those of the previous investigation in suggesting that the prevalence of gout and asymptomatic hyperuricemia is increased among the relatives of gouty patients. The prevalence rate for asymptomatic hyperuricemia in the relatives studied was 17.2 per cent. Gout had developed in 12 per cent of the 99 relatives in the original study, in eight or 16 per cent of the 50 male relatives and in four or 8 per cent of the 48 female relatives. Of eleven male and nine female subjects found to be hyperuricemic during the original study, four or 20 per cent had developed frank gout by the time of follow up. This follow up study also showed that hyperuricemia tends to persist as a fixed trait thus subjecting the individual to a chronic risk of developing overt gout.

A reconsideration of the distribution of serum uric acid values in the families of Smyth, Cotterman, and Freyberg was carried out by

Neel et al.[43] and although the data revealed a significant skewing to the right, the evidence for bimodality was thought less convincing than the earlier report implied.

Another extensive survey of 136 asymptomatic members of families of 44 patients with gout by Stecher, Hersch, and Solomon[44] recorded similar results. Hyperuricemia was found in a total of 16 of 136 relatives.

Wilson[45] in the first British study of hyperuricemia in gouty families investigated the relatives of three gouty patients. In 11 members of the first family uric acid estimations were carried out and among these eight had hyperuricemia. In the second family out of eight relatives examined, four had a high serum uric acid value. The third family had ten members examined; nine of them had high serum uric acid. Thus, of the 29 relatives studied, 21 or 72 per cent had an elevated serum uric acid level.

Hague and Harvald[46] conducted a comprehensive study of 32 probands with gout and 261 immediate relatives. They agree with other investigators that heredity is an etiologic factor in this disease. The uric acid of brothers was 1.0 mg. per cent greater than controls and sisters 1.4 mg. per cent greater than controls; the distribution of urate levels showed a normal distribution with no suggestion of bimodality. These investigators interpret their results as failing to support the view that hyperuricemia is transmitted as a Mendelian dominant trait. They consider that dominance with incomplete penetrance and recessive heredity are excluded by their study and suggest that a cumulative gene action may be operative.

The study of Popert and Hewett[47] in Britain is one of the few studies of the distribution of serum uric acid levels carried out in a population other than in the relatives of gouty patients. These investigators estimated the prevalence of hyperuricemia and clinical gout in an area sample of a rural population of Wensleydale in Yorkshire and a random sample of an urban population in Leigh, Lancashire. The distribution of serum uric acid levels in these samples showed that in males the mean serum uric acid levels remained constant from age 15 through age 75 while in females lower values are found up to the time of the menopause. After the age of 50 years, the distribution in females begins to approximate that found in males. Despite a relatively high incidence of hyperuricemia in both localities, no cases of clinical gout were found in Wensleydale and only two definite cases were found in Leigh. A follow up study of the individuals with hyperuricemia and of gouty individuals together with their blood relatives revealed evidence of familial hyperuricemia in eight of 33 families but clinical gout was only seen in the relatives where the proband was already suffering from gout. These authors concluded that the inheritance of familial hyperuricemia does not necessarily determine the inheritance of clinical gout and that other factors, especially diet, may be concerned.

A study to determine whether hyperuricemia is inherited and, if so, what the mechanism of inheritance might be was carried out by O'Brien, Burch and Bunim[48] on two populations: The Blackfeet Indians of Montana and the Pima Indians of Arizona. They found the uric acid values for the two populations were normally distributed, the mean being 4.89 in Blackfeet and 4.22 in Pimas. Using values of 6 mg. per cent in

females and 7 mg. per cent in males as the cutting point, they found 7 per cent of the Blackfeet and about 3 per cent of the Pimas to have hyperuricemia. Of 31 Pimas with hyperuricemia two had definite gout and 14 had mono- or poly-arthritis compatible with gout and without signs diagnostic of other rheumatic diseases. Of 73 Blackfeet with hyperuricemia, 12 had possible gout. The uric acid levels of relatives of hyperuricemic individuals were determined and although the mean uric acid of these individuals was 0.25 mg. per cent higher than the population average there was no suggestion of bimodality in their distribution. These investigators concluded that the trait of hyperuricemia, if a genetic one at all, would most likely be determined by several genes.

The studies described here suggest that there is some familial aggregation of serum uric acid levels whether it be on a genetic or environmental basis. There are certain obvious limitations inherent in these studies:

1. The earlier studies were carried out mainly on relatives of patients with gout and did not provide an opportunity to see how serum uric acid levels were distributed in the so-called "normal population."

2. Many of these investigations were based upon relatively small numbers.

3. In some studies, as already mentioned, the propositi and their relatives did not have serum uric acid determinations but diagnosis was made on the basis of clinical history.

4. Most of these studies did not standardize for differences in serum uric acid levels by age and sex.

5. In none of these studies has anyone looked at the aggregation of very low serum uric levels.

6. These studies (with the exception of the follow up study) have been cross sectional studies taken at one point in time and do not provide an opportunity to determine if individuals maintain their relative position in their age and sex group with respect to their serum uric acid levels.

7. Complete medical examinations were very seldom available on the subjects in these studies. Thus it was difficult to determine if a person was suffering from primary or secondary hyperuricemia.

8. No attempt was made to differentiate between environmental and genetic influences in the major portion of these studies.

The Tecumseh Community Health Study affords an opportunity to look at the aggregation of serum uric acid levels in a relatively large population in a context which obviates some of the limitations noted above.

CHAPTER III

DESCRIPTION OF THE TECUMSEH COMMUNITY HEALTH STUDY

A. Purpose of the Tecumseh Community Health Study

The Tecumseh Community Health Study (TCHS) is a comprehensive longitudinal study of the health of the entire population of Tecumseh, Michigan, and the immediate surrounding area. The purpose of the project is to study the origin, course and distribution of disease and disability in a natural community. The focus has been on the family unit and the kindred.

The study is an undertaking by the faculty and departments of the School of Public Health and the Medical School of the University of Michigan and it is supported by grants from the National Institutes of Health.

B. Description of the Community of Tecumseh

Tecumseh was selected in 1957 as a community in which it seemed feasible and practical to conduct such a study; Tecumseh with its immediate surrounding area comprises 56 square miles and a population of about 9,500 persons, 3,000 of whom live outside the city limits. Tecumseh is located in Lenawee County, 27 miles southwest of Ann Arbor. It is predominantly a rural agricultural area but also has one large and

several small manufacturing plants. This provides varied socio-economic groups. The study area is relatively stable in terms of population mobility, an important factor in long term studies.

C. Methods Used in Collection of Data

A census was conducted in 1957 to identify individuals by household and kindreds. A system was then developed for assembling individuals related to each other in various ways, so that attributes of these persons could be compared. Kindred charts were prepared and each member of the kindred was given a ten digit code which identified his position within the kindred[50]. Households were identified independently. This system makes it possible to analyze the data on living and deceased individuals by biological relatedness, households, and examination status. The population in Tecumseh could be assigned to a total of some 4,500 overlapping kindreds

The area was divided into five strata based on geographical and socio-economic considerations. The dwelling units were stratified and ten random samples of dwelling units, about 900 persons each, were drawn. Thus each sample represented a cross sectional unit of the total population. The subjects within each sample were examined consecutively.

For the first round examination, of 1959-60, a trained interviewer visited each home and obtained a detailed medical history from each respondent. After the completion of the questionnaire, the interviewer made an appointment for the entire household to come to the special clinic set up at Herrick Memorial Hospital in Tecumseh.

Carefully trained personnel took the electrocardiogram, recorded blood pressure, determined a variety of pulmonary function measurements and took various anthropometric measurements. The physicians then conducted a complete physical examination after checking and annotating the history taken by the interviewer. A blood sample was taken, X-ray of the chest was made and a urine sample was collected.

During the time period from April 1959 to October 1960, detailed medical histories and general medical examinations were obtained on 8,641 persons (4,238 males and 4,403 females) representing 88 per cent of the Tecumseh population. Table III.1 shows the age distribution of these subjects.

TABLE III.1

DISTRIBUTION BY AGE AND SEX OF SUBJECTS
EXAMINED IN TECUMSEH FROM
APRIL 1959 TO OCTOBER 1960

Age at Time of Exam	Total	Males	Females
Total all ages	8,641	4,238	4,403
Under 10 years	2,345	1,192	1,153
10-19 years	1,608	807	801
20-29 years	1,040	455	585
30-39 years	1,384	679	705
40-49 years	942	468	474
50-59 years	659	332	327
60-69 years	374	178	196
70 years and older	289	127	162

CHAPTER IV

STUDY OF THE DISTRIBUTION OF SERUM URIC ACID LEVELS IN THE TECUMSEH COMMUNITY HEALTH STUDY 1959-60

Drs. William Mikkelsen, Horace Dodge and Hans Valkenberg undertook to study the serum uric acid (SUA) concentration of the study subjects in the Tecumseh population.[52] The purpose of this study was to define the distribution characteristics of serum uric acid levels in a "normal population" and to evaluate the importance of age and sex as variables in relation to serum uric acid levels.

A. Method of Handling Blood Specimens

The clotted blood specimens were refrigerated and transmitted from the examination clinic in Tecumseh to Ann Arbor at the conclusion of each clinic session. There the serum was separated and divided into aliquots and the aliquots for serum uric acid determination were frozen at minus 20° C. The estimated interval between freezing and serum uric acid determinations ranged from 20 to 44 months.

B. Method of Determining Serum Uric Acid Concentrations

Serum uric acid concentration was determined by the enzymatic spectrophotometric method of Liddle, Seegmiller and Laster[53]. The procedure was modifed only insofar as the measurement of optical

density five minutes after addition of enzyme was omitted and both 25 and 30 minute readings were taken. Determination of standard uric acid solutions added to human serum over the range 6.0 to 60 mg. per 100 ml. resulted in an average error of minus 0.54 per cent. The standard deviation of the method based on the differences between 24 duplicate determinations was ± 0.18 mg. per 100 ml.

Since the Tecumseh sera were not analyzed for their uric acid content immediately, two control experiments were instituted to determine the effect of storage. In the first of these, ten serum specimens were divided into six aliquots, the first of which was analyzed immediately while the others were refrigerated at 4° C and analyzed at 3, 10, 17, 24, and 31 days. The mean values for these determinations were 7.2, 7.0, 7.0, 6.9 and 6.9 mg. per 100 ml. In the second experiment ten sera were analyzed immediately and after freezing at minus 20° C for one week and 3, 6, 9, 12, 18, 24, 26, 30, and 36 months. The mean values for these determinations were 6.35, 6.8, 6.4, 6.0, 6.2, 6.2, 6.2, 6.2, 6.05 and 0.1 mg. per 100 ml.

C. Delineation of Members of Study Population with Satisfactory Serum Uric Acid Determinations

In the examinations, individuals of all ages were included. An attempt was made to obtain a blood sample on all examined individuals four years of age or older but with varying degrees of success, especially among children. Since the determination of serum uric acid was begun late, relative to the collection of blood, the supply of serum from some individuals was already exhausted. For a relatively small

number of sera, there were technical factors that cast doubt on the reliability of the serum uric acid concentration. These were excluded from the subsequent analysis.

It should be emphasized that the eventual 6,000 persons who had technically satisfactory serum uric determinations were not selected because of any knowledge or suspicion of the presence of hyperuricemia or gout, but were selected entirely on the basis of the availability of serum.

The age and sex distribution of these study subjects are shown in Table IV.1 and are related to the distribution of those persons examined.

TABLE IV.1

AGE-SEX DISTRIBUTION OF PERSONS HAVING A TECHNICALLY SATISFACTORY SERUM URIC ACID DETERMINATION, ABSOLUTE AND RELATIVE TO THE NUMBER OF PERSONS EXAMINED
TCHS, 1959-60

Age in Years	Males			Females		
	Number		Per cent (2)/(1)	Number		Per cent (2)/(1)
	Examined (1)	With SUA (2)		Examined (1)	With SUA (2)	
0- 9	1,192	365	30.6	1,153	319	27.7
10-19	807	683	84.6	801	618	77.2
20-29	455	391	85.9	585	495	84.6
30-39	679	581	85.5	705	590	83.7
40-49	468	407	87.0	474	414	87.3
50-59	332	283	85.2	327	281	85.9
60-69	178	166	93.2	196	163	83.2
70 or more	127	111	87.4	162	133	82.1
All ages	4,238	2,987	70.5	4,403	3,013	68.4

D. Distribution of Serum Uric Acid Levels

The mean concentration of SUA for subjects of both sexes was 4.5 ± 1.8 (S.D.) mg. per 100 ml. The mean value for males was 4.9 ± 2.0 and that for all females 4.2 ± 1.35. The difference of 0.7 mg. per 100 ml. is statistically significant. The difference between males and females as to serum uric acid values is significant at each five year age interval with the exception of ages 4-14, for ages 60-64 years, and for ages 75 and over. In this study 21 per cent of all males age four and over were found to have values 6.0 mg. per 100 ml. or greater and 22 per cent of all female subjects had values of 5.0 mg. per 100 ml. or greater. Among male subjects of every age group except for the youngest and next to the oldest, there are individuals with values in excess of 8.0 mg. per 100 ml. In females every age group, except for the youngest, had individuals with values in excess of 7.0 mg. The male mean serum uric acid values rise steadily with age from 4 to 16 years, decline slightly and then rise to peak at 21-23 years. The female mean serum uric acid values rise more slowly to a minor peak at 15-19 years following which they decline slightly and level out until about 40 years when the curve rises slowly again to peak levels at 50-54 and later at 60-64 years. The distribution curves for all males and females, ages four years and over, suggest a continuous distribution of serum uric acid values with some degree of skewing toward high values. They do not show any clear evidence of two populations, one normouricemic and one hyperuricemic.

E. Method of Computing Scores for SUA

The serum uric acid value for each subject was standardized by taking into account his position in his age-sex group. Five year age classes were used for each sex with the exception of age four and an open ended classification of 80 and over. The formula used in computing this standardized value or score is:

$$\frac{\text{(Observed SUA of the individual subject) minus (Mean SUA of his age-sex group)}}{\text{Standard Deviation of the SUA for his age-sex group}} + 4.5 \text{ mg./100 ml.}$$

The 6,000 serum uric acid scores are distributed about the mean score of 4.5 mg. per 100 ml. in a nearly symmetric curve whose standard deviation is 1.0 mg. per 100 ml. The value 4.5 mg. was so chosen because it is the overall mean of the serum uric acid levels.

Figure IV.1 shows the distribution of the serum uric acid levels for males and females. Figure IV.2 shows the serum uric acid scores for each sex. The scoring process has shifted the female distribution to the right and the male distribution to the left so they are almost superimposed one upon the other. There is a slightly higher per cent of males in the lower serum uric acid scores and a slightly higher per cent of females with scores 6.5 mg. and greater.

The serum uric acid score is the measurement used in the study of familial aggregation of serum uric acid levels in the Tecumseh population, as of the examination period of April 1959 to October 1960.

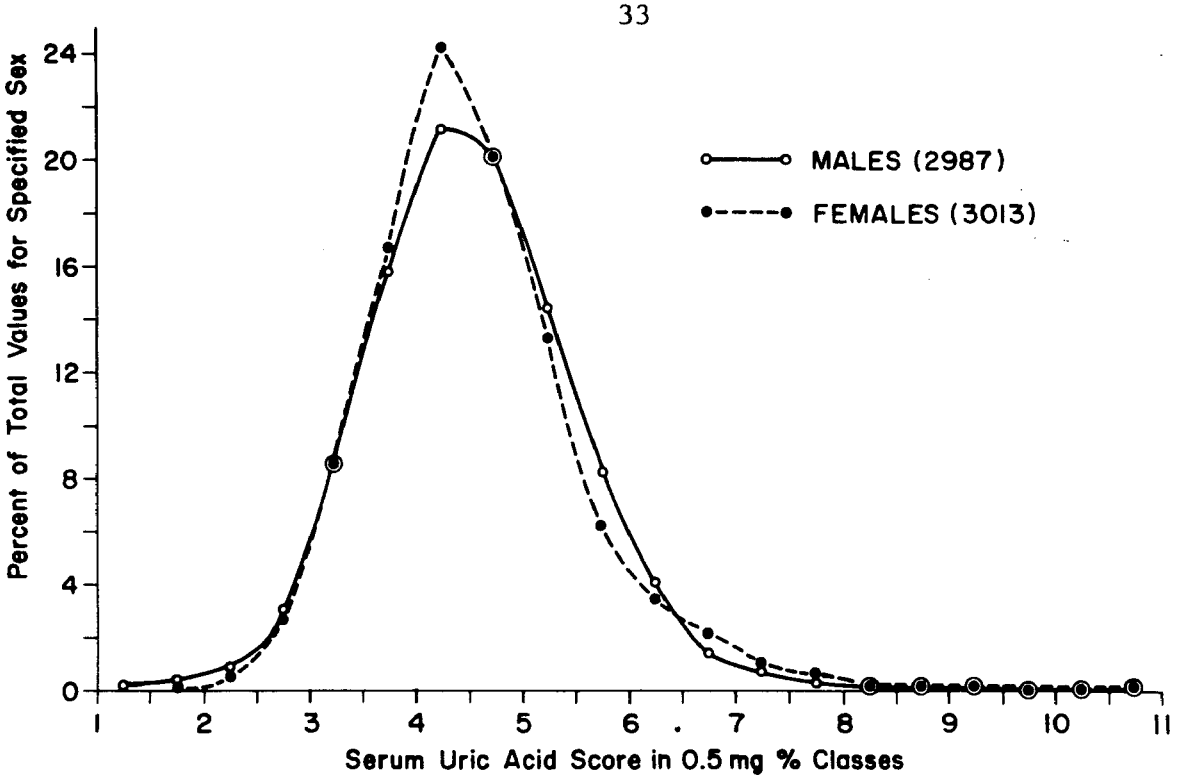


Fig. IV.1 Distribution of Serum Uric Acid Levels by Sex. Tecumseh, 1959-60.

*Used by permission of Dr. Mikkelsen and the American Journal of Medicine.

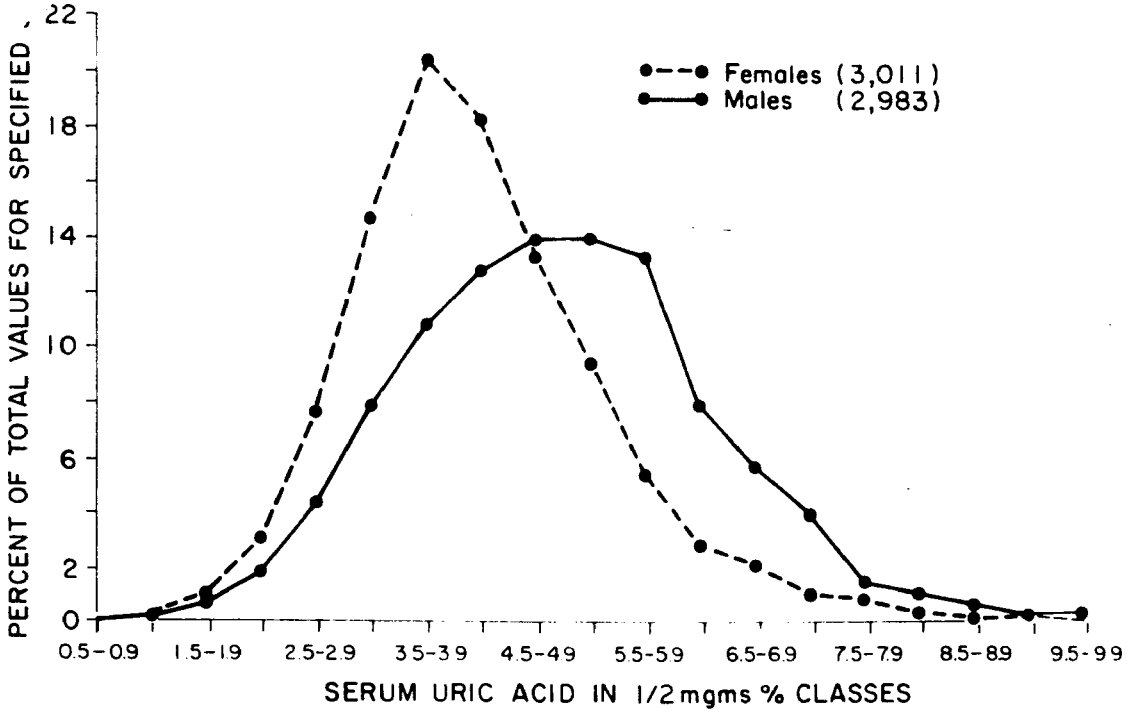


Fig. IV.2 Distribution of Serum Uric Acid Scores by Sex. Tecumseh, 1959-60.

CHAPTER V

PRESENTATION OF METHODS AND RESULTS IN THE STUDY OF FAMILIAL AGGREGATION OF SERUM URIC ACID IN TECUMSEH COMMUNITY HEALTH STUDY

This chapter is a description of the methods of analysis used in the study of familial aggregation of serum uric acid score levels carried out on the 6,000 study subjects with technically satisfactory serum uric acid determinations in the Tecumseh Community Health Study during the 1959-60 examinations. The results obtained from such analysis are included.

The plan of study was first to conduct a cursory analysis to determine if there was any evidence for the existence of aggregation in the population under study. If aggregation was shown to be present, then the next step was to obtain some measure of the degree of aggregation. Since clustering could be due to genetic or environmental factors or from their interaction, appropriate tests would then be applied to determine the extent to which each of these factors was operating.

The serum uric acid score was the measurement used in this study since it standardized both for age and sex and in many instances obviated the need for age-sex specific analysis.

A. Cursory Analysis to Determine Evidence for Familial Aggregation

The serum uric acid score of each parent was classified according to its distance in standard deviations from the overall mean of 4.5 mg./100 ml. Those classified as one denoted scores one standard deviation or more below the mean, those classified as two denoted scores within one standard deviation of the mean and those classified as three represented scores one standard deviation or more above the mean. The parents were then grouped according to the combination of their score classifications giving rise to nine different parental groups which were as follows:

Father 1	Mother 1
Father 1	Mother 2
Father 1	Mother 3
Father 2	Mother 1
Father 2	Mother 2
Father 2	Mother 3
Father 3	Mother 1
Father 3	Mother 2
Father 3	Mother 3

The serum uric acid scores of the offspring were also classified into the one, two, three system and the per cent distribution of these values was computed for the offspring by age and sex within each parental group. The results of this analysis are shown in Table V.1 and in Figures V.1, V.2, V.3, and V.4. Figure V.1 shows the per cent distribution of SUA scores of offspring of all ages. When both parents have scores classified as one, a high per cent of their children's scores are classified as one. None of the females and only three per cent of

TABLE V.1a

PER CENT DISTRIBUTION OF SUA SCORE OF OFFSPRING BY AGE AND SEX
BASED ON SUA SCORE OF PARENTS WITH SUA SCORES OF BOTH OFFSPRING AND PARENTS
GROUPED BY THE NUMBER OF STANDARD DEVIATIONS FROM THE MEAN
TCHS 1959-60

Age of Offspring	Child	Males																	
		F_1	M_1	F_1	M_2	F_1	M_3	F_2	M_1	F_2	M_2	F_2	M_3	F_3	M_1	F_3	M_2	F_3	M_3
		N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%
0-9	1	5	50.0	1	4.2	0		3	27.3	15	9.8	4	13.8	0		2	7.1	0	
	2	5	50.0	22	91.6	2	100.0	6	54.5	115	75.1	21	72.4	2	100.0	25	89.2	3	60.0
	3	0	0.0	1	4.2	0		2	18.1	23	15.0	4	13.8	0		1	3.6	2	40.0
10-19	1	6	40.0	4	10.3	2	20.0	4	8.9	32	12.5	4	11.1	1	20.0	3	8.6	0	
	2	8	53.4	32	82.0	6	60.0	38	84.4	191	74.9	26	72.2	4	80.0	26	74.2	3	50.0
	3	1	6.6	3	7.7	2	20.0	3	6.7	32	12.5	6	16.6			6	17.1	3	50.0
20-39	1			1	8.3			2	22.2	11	13.9	1	7.1	0				0	
	2	2	100.0	8	66.6	2	100.0	7	77.7	59	74.5	12	85.7	2	66.6	9	64.3	2	100.0
	3			3	25.0			0	0.0	9	11.4	1	7.1	1	33.3	5	35.7	0	
Total	1	11	40.7	6	8.0	2	14.3	9	13.6	58	11.9	9	11.3	1	10.0	5	6.4	0	
	2	15	55.5	62	82.6	10	71.4	51	78.7	365	74.9	59	74.6	8	80.0	60	77.9	8	61.5
	3	1	3.7	7	9.3	2	14.3	5	7.6	64	13.1	11	13.9	1	10.0	12	15.3	5	38.4

F = Father
M = Mother

1 = SUAS < 3.5 mg./100 ml. One or more than one standard deviation below the mean.
2 = SUAS 3.5 - 5.5 mg./100 ml. Within one standard deviation from the mean.
3 = SUAS > 5.5 mg./100 ml. More than one standard deviation above the mean.

TABLE V.1b

PER CENT DISTRIBUTION OF SUA SCORE OF OFFSPRING BY AGE AND SEX
BASED ON SUA SCORE OF PARENTS WITH SUA SCORES OF BOTH OFFSPRING AND PARENTS
GROUPED BY THE NUMBER OF STANDARD DEVIATIONS FROM THE MEAN
TCHS 1959-60

Age of Offspring	Child	Females																	
		F_1	M_1	F_1	M_2	F_1	M_3	F_2	M_1	F_2	M_2	F_2	M_3	F_3	M_1	F_3	M_2	F_3	M_3
		N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%
0-9	1	3	33.3	3	15.8	0		4	16.7	13	10.7	1	3.5	0		1	4.5	0	
	2	6	66.6	15	78.9	4	100.0	18	75.0	93	76.9	21	80.1	0		18	81.8	4	66.6
	3	0	0.0	1	5.3	0		2	8.3	15	12.4	4	15.4	0		3	13.6	2	33.3
10-19	1	4	33.3	8	22.2	0		10	27.7	22	10.0	3	8.6	0		2	7.4	0	
	2	8	66.6	26	72.2	6	100.0	22	61.1	167	75.9	23	65.7	2	100.0	15	55.5	9	60.0
	3	0		2	5.6	0		4	11.1	31	14.1	9	25.7	0		10	37.0	6	40.0
20-39	1	0	0	5	33.3	0		4	36.4	12	17.6	1	7.7	0		0		0	
	2	31	100.0	8	53.3	0		6	54.5	50	73.5	10	76.9	0		5	100.0	4	100.0
	3	0	0	2	13.3	0		1	9.1	6	8.8	2	15.4	1	100.0	0		0	
Total	1	7	13.4	16	22.5	0		18	25.3	47	11.4	5	6.7	0		3	5.5	0	
	2	45	86.5	49	70.4	10	100.0	46	64.7	310	75.7	54	72.9	2	66.6	38	70.3	17	68.0
	3	0	0.0	5	7.0	0		7	9.6	52	12.7	15	20.1	1	33.3	13	24.0	8	32.0

F = Father
M = Mother

1 = SUAS 3.5 mg./100 ml. One or more than one standard deviation below the mean.
2 = SUAS 3.5 - 5.5 mg./100 ml. Within one standard deviation from the mean.
3 = SUAS > 5.5 mg./100 ml. More than one standard deviation above the mean.

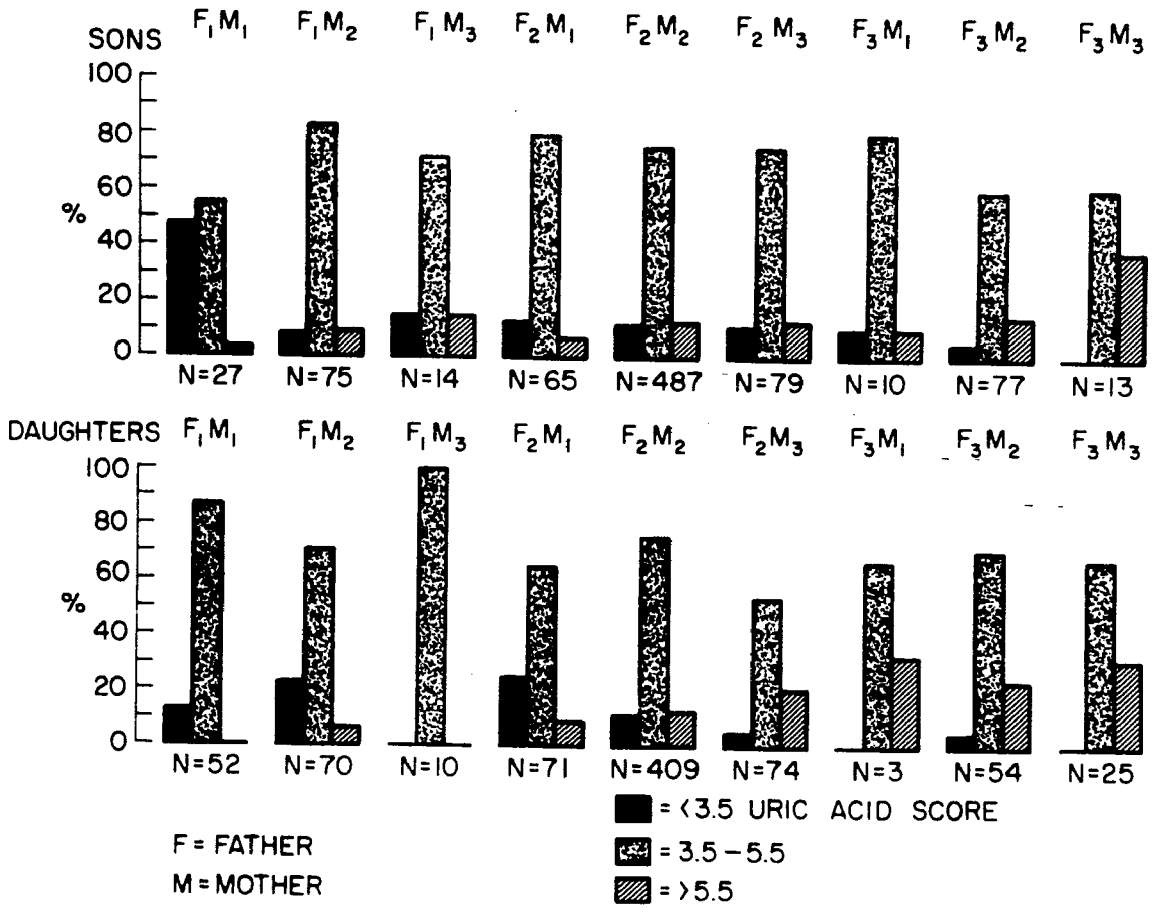


Fig. V.1 Percent Distribution of Serum Uric Acid Scores of Offspring, All Ages, by Sex Based on Serum Uric Acid Scores of Parents.

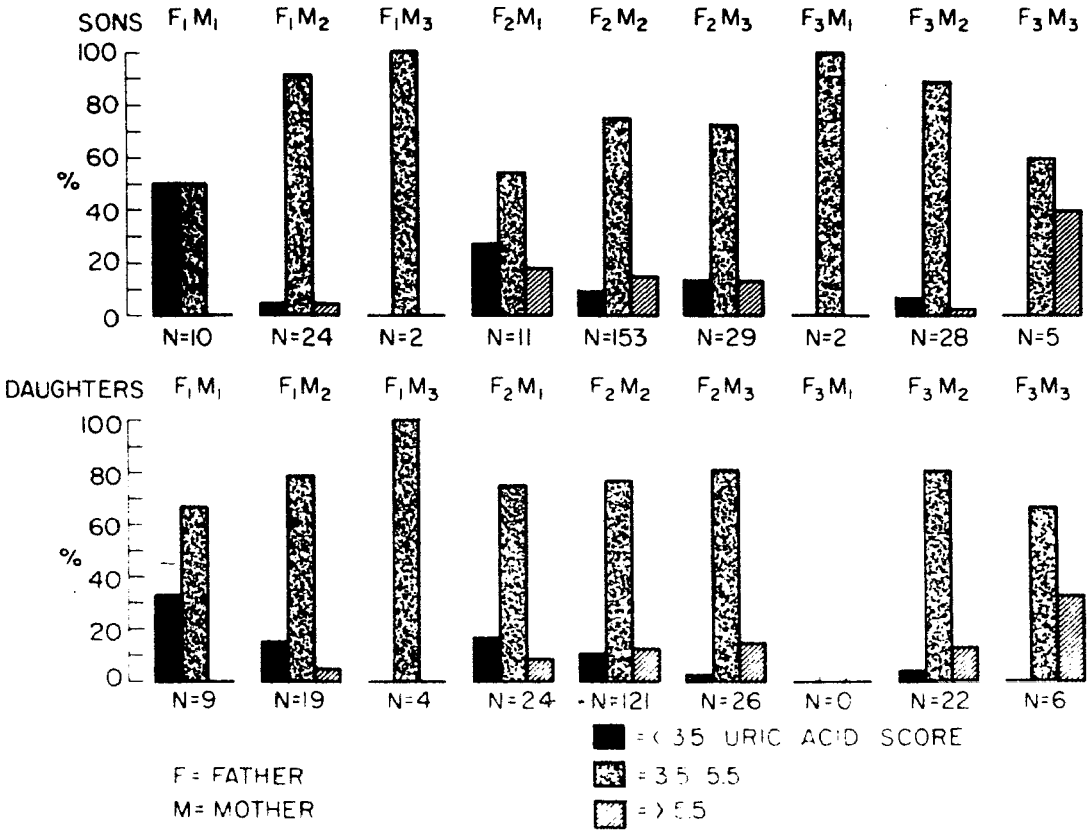


Fig. V.2 Percent Distribution of Serum Uric Acid Scores of Offspring 0-9 Years Based on Serum Acid Scores of Parents.

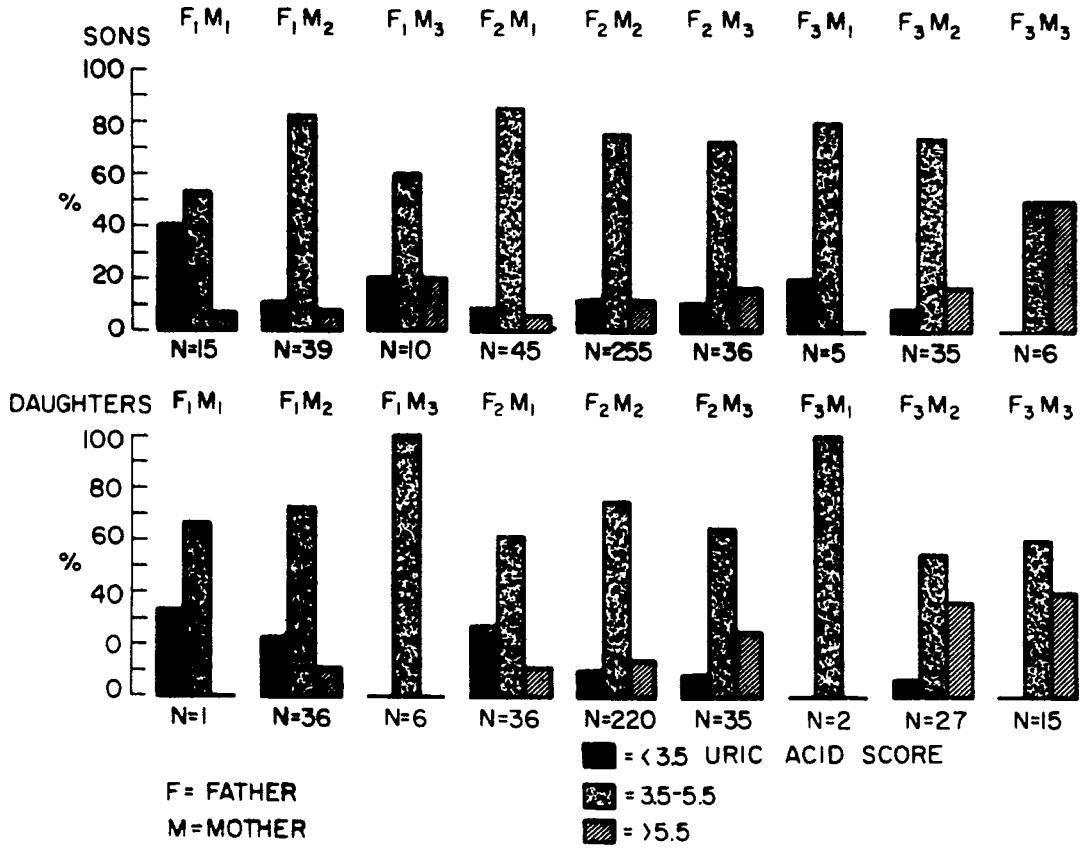


Fig. V.3 Percent Distribution of Serum Uric Acid Scores of Offspring 10-19 Years Based on Serum Uric Acid Scores of Both Parents.

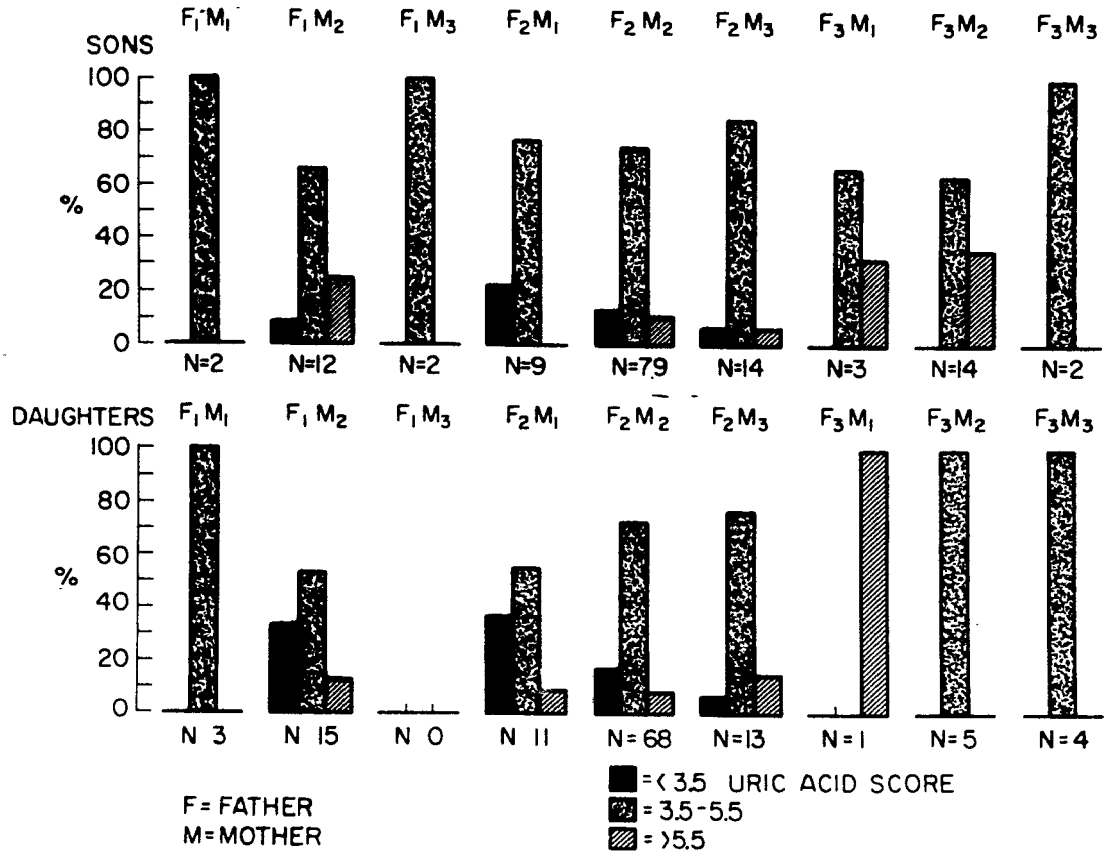


Fig. V.4 Percent Distribution of Serum Uric Acid Scores of Offspring 20-39 Years Based on Serum Uric Acid Scores of Parents.

the male offspring are classified as three. As the parents' scores increase, the children's scores also show an increase in value. In the situation where both parents have scores classified as three, a higher percentage of their children have scores classified as three than in the other parental groups and none of their children have scores classified as one. When one of the parents has a score classified as one and the other parent has a score classified as three, the child's score tends to reflect the average of the parents' scores with a high per cent of the children classified as two (75 per cent of the males and 100 per cent of the females). It did not seem to matter which parent had the high or the low score. This pattern prevailed in both male and female offspring in each of the age groups studied.

In a subsequent analysis the same scheme was used for classifying the parents' scores but within each parental group the mean of the scores of the offspring were computed by age and sex. The results of this computation are shown in Tables V.2, V.3, V.4, and V.5. The mean serum uric acid score of offspring (all ages combined) as seen in Table V.2 is 3.4 in males and 3.9 in females when both their parents have scores classified as one. There is a gradual increase in the child's mean score as the parents' values increase and when both parents have scores classified as three, the mean of their children's SUA score is 5.2 for both males and females. This pattern was observed in both sexes in the age groups 0 to 9 and 10 to 19. The age group 20-39 failed to follow this trend but this may be due to the small number of subjects in this age group or possibly to the fact that a greater proportion of children of this age no longer share the home environment with their

TABLE V.2

MEAN SERUM URIC ACID SCORES OF OFFSPRING, ALL AGES, BY SEX BASED ON SERUM URIC ACID SCORES OF PARENTS

MALES

		Mother 1		Mother 2		Mother 3	
		N	$\bar{X}$	N	$\bar{X}$	N	$\bar{X}$
Father	1	27	3.4	82	4.5	14	4.5
	2	66	4.3	496	4.4	82	4.7
	3	10	4.0	78	4.7	13	5.2

N = 868

FEMALES

		Mother 1		Mother 2		Mother 3	
		N	$\bar{X}$	N	$\bar{X}$	N	$\bar{X}$
Father	1	24	3.9	71	4.3	10	4.4
	2	73	4.1	425	4.4	77	4.8
	3	5	3.9	55	4.8	25	5.2

N = 765

Key: 1 = SUAS < 3.5 mg./100 ml.
2 = SUAS 3.5 - 5.5 mg./100 ml.
3 = SUAS > 5.5 mg./100 ml.

TABLE V.3

MEAN SERUM URIC ACID SCORES OF CHILDREN 0-9
BY SEX BASED ON SERUM URIC SCORE OF PARENTS

MALES

		Mother 1		Mother 2		Mother 3	
		N	$\bar{X}$	N	$\bar{X}$	N	$\bar{X}$
Father	1	10	3.5	24	4.5	2	4.1
	2	11	4.3	153	4.6	29	4.7
	3	2	4.3	28	4.2	5	5.3

N = 264

FEMALES

		Mother 1		Mother 2		Mother 3	
		N	$\bar{X}$	N	$\bar{X}$	N	$\bar{X}$
Father	1	9	3.9	19	4.4	4	4.3
	2	24	4.1	121	4.5	26	4.9
	3	2	4.0	22	4.6	6	5.1

N = 233

Key: 1 = SUAS < 3.5 mg./100 ml.
2 = SUAS 3.5 - 5.5 mg./100 ml.
3 = SUAS > 5.5 mg./100 ml.

TABLE V.4

MEAN SERUM URIC ACID SCORES OF CHILDREN 10-19
BY SEX BASED ON SERUM URIC ACID SCORE
OF PARENTS

MALES

		Mother 1		Mother 2		Mother 3	
		N	$\bar{X}$	N	$\bar{X}$	N	$\bar{X}$
Father	1	15	3.8	39	4.5	10	4.6
	2	45	4.4	255	4.5	36	4.7
	3	5	3.4	35	4.7	6	5.2

N = 446

FEMALES

		Mother 1		Mother 2		Mother 3	
		N	X	N	X	N	X
Father	1	12	3.6	36	4.2	6	4.5
	2	36	4.2	220	4.5	35	4.7
	3	1	6.4	27	5.0	15	5.5

N = 388

Key: 1 = SUAS < 3.5 mg./100 ml.
2 = SUAS 3.5 - 5.5 mg./100 ml.
3 = SUAS > 5.5 mg./100 ml.

TABLE V.5

MEAN SERUM URIC ACID SCORES OF OFFSPRING, AGES 20-39, BY SEX BASED ON SERUM URIC ACID SCORES OF PARENTS

MALES

		Mother 1		Mother 2		Mother 3	
		N	$\bar{X}$	N	$\bar{X}$	N	$\bar{X}$
Father	1	2	4.6	12	4.5	2	4.6
	2	9	4.1	79	4.4	14	4.4
	3	3	5.0	14	5.6	2	4.7

N = 137

FEMALES

		Mother 1		Mother 2		Mother 3	
		N	$\bar{X}$	N	$\bar{X}$	N	$\bar{X}$
Father	1	3	5.0	15	4.4	0	
	2	11	4.1	68	4.4	13	4.6
	3	2	2.7	5	4.6	4	4.2

N = 121

Key: 1 = SUAS < 3.5. mg./100 ml.
2 = SUAS 3.5 - 5.5 mg./100 ml.
3 = SUAS > 5.5 mg./100 ml.

parents to the same degree as do the younger children.

In another analysis the serum uric acid scores of mothers and fathers were grouped separately into 0.5 mg. per 100 ml. intervals. The mean of the sons' SUA scores was computed for each maternal and each paternal grouping and for the mid parent average. Similar computations were carried out for daughters. This analysis was limited to offspring aged 0 to 19 because of the small number of offspring beyond the age of 19. The open ended class interval of 5.5 mg. per 100 ml. and over was used because there were insufficient numbers of offspring with high scores to permit meaningful groupings beyond this point. The results of this analysis are shown in Figures V.5, V.6, and V.7. The strongest suggestion of regression seems to be in the mean scores of both sons and daughters based on the average of the scores of the parents (Figure V.7). The relation of the daughters' mean score to the mid parent score appears to be more nearly linear than that of the sons'.

The question may be raised here as to whether one or two children with unusually high scores were responsible for the observed trend by exerting undue weight in the analysis. Such was not the case since there are no children in this distribution with SUA scores greater than three standard deviations above the mean.

B. Identification of Subjects with Secondary Hyperuricemia

Since the presence of subjects with <u>secondary</u> hyperuricemia and gout would limit the precision of the measurement of the degree of association of hyperuricemia and gout in relatives of probands, an attempt was made to identify such secondary cases so that they might be excluded

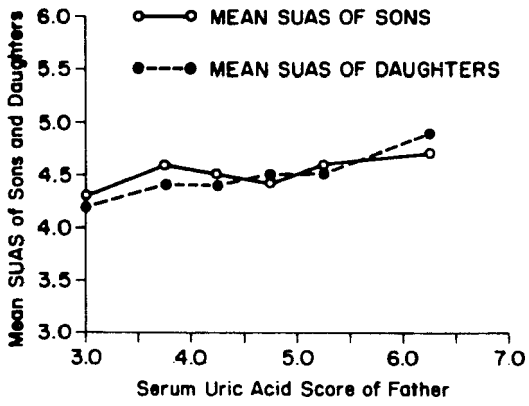


Fig. V.5 Mean Serum Uric Acid Scores of Sons and Daughters, 0-19, Based on Serum Uric Acid Score of Father.

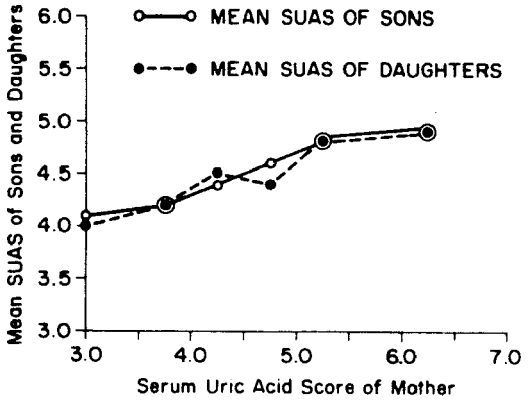


Fig. V.6 Mean Serum Uric Acid Scores of Sons and Daughters, 0-19, Based on Serum Uric Acid Score of Mother.

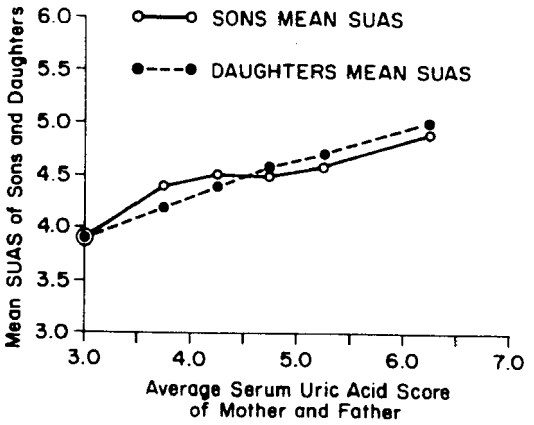


Fig. V.7 Mean Serum Uric Acid Scores of Sons and Daughters, 0-19, Based on Serum Uric Acid Score of Mother and Father.

from this study. It was decided that only those conditions known to cause secondary hyperuricemia would be considered rather than conditions, such as diabetes, which have been incriminated only by association (Chapter I).

A medical history and a diagnostic summary were available on each subject of the first round of examinations carried out in 1959 and 1960 (Chapter III). No subjects with SUA determinations were found to have granulocytic leukemia, polycythemia, myeloid metaplasia or glycogen storage disease.

Serum creatinine levels were obtained on subjects with serum uric acid concentrations greater than 6 mg./100 ml. for whom sufficient serum was available for such further analysis. These creatinine determinations were used as a means of identifying patients with hyperuricemia secondary to renal dysfunction. It was decided that those subjects with a serum creatinine level of 1.3 mg. per cent or greater and who had a history of kidney disease would be removed from the study. This decision eliminated only two persons from further study. An abnormal serum creatinine alone was not thought sufficient evidence for removal since this might be a reflection of kidney dysfunction resulting from primary hyperuricemia.

Although information was recorded on the intake of alcohol as part of the history, no information was available on those who might have been under the influence of alcohol at the time of examination. Information on the intake of drugs was not consistently recorded. For this reason it was impossible to screen subjects on the bases of ethanol intoxication and the use of drugs known to influence Serum Uric Acid.

Obesity has been known to contribute to a hyperuricemic state but there is no consistent criterion for defining the term obesity. If those subjects who were above the 80th percentile in relative weight (as defined for TCHS) were arbitrarily withdrawn, this would result in the loss of some 1,800 subjects from the study. It was therefore decided that obesity would not be considered at this time but relative weight would be reckoned with in another form of analysis later on in the study.

Although attempts were made to identify and withdraw subjects with secondary hyperuricemia, the limitations were such that only a very coarse screening was accomplished.

C. Measurement of the Degree of Association Between Parent and Child

To assess the degree of association of parents' and children's SUA scores, three least squares regression lines of the form $y = a + bx$ and three correlation coefficients were computed for children of each sex. These were based on the child's score and father's score, child's score and mother's score and the average of the scores of both parents. Only one offspring was selected from a family to allow each family to have equal weight in the analysis. Since the serum uric acid score standardizes for age, the oldest child in each family was arbitrarily selected. This assumes that the first born is no different from other children in the family with respect to serum uric acid.

The results of the regression and correlation analysis are shown in Table V.6. Although the correlation coefficients are significantly

TABLE V.6

REGRESSION COEFFICIENT, F TEST AND CORRELATION COEFFICIENT OF SUAS OF ONE OFFSPRING[a] IN FAMILY ON SUAS OF PARENTS (Based on formula a + bx)

Variables Dependent vs Independent	N	Regression Coefficient	F Value	Correlation Coefficient
Son on father	324	.1285	4.45*	.128*
Son on mother	324	.1495	6.73*	.143*
Son on average of both parents	324	.2859	11.977***	.190**
Daughter on father	321	.1661	9.584**	.171**
Daughter on mother	321	.2345	19.40***	.239**
Daughter on average of both parents	321	.3384	24.408***	.266**

[a] = oldest child in family with SUA determination.
* = significant at $P \leq .05$.
** = significant at $P \leq .01$.
*** = significant at $P \leq .005$.

different from 0 at $P \leq .05$, the correlation of daughter's score with the score of each parent is higher than that of son's with each parent. There is a higher correlation of offspring with mother's score than with father's score. However, none of these differences is significant. The highest correlation in both sons and daughters is with the mid parent value (.190 in males and .266 in females).

To determine more specifically the relation of the child's SUA score to that of his parents, the least squares second degree and third degree polynomial regression lines were computed for each of the three groups in each sex. Out of the six regressions computed, only that of son on mother showed a quadratic component significant at the 0.05 level as seen in Table V.7.

TABLE V.7

LEAST SQUARES SECOND AND THIRD DEGREE POLYNOMIAL OF CHILD'S SUAS ON PARENT'S SUAS BY SEX OF CHILD

Variables Dependent vs Independent	Third Degree vs Second Degree		Second Degree vs Linear	
	df	Regression Mean Sq. / Residual Mean Sq.	df	Regression Mean Sq. / Residual Mean Sq.
Son vs father	1, 706	.158	1, 707	.1647
Son vs mother	1, 706	3.431	1, 707	9.748*
Son vs average of parents	1, 706	1.172	1, 707	.945
Daughter vs father	1, 618	.271	1, 619	.185
Daughter vs mother	1, 618	2.76	1, 619	.060
Daughter vs average of parents	1, 618	.867	1, 619	.001

* = Significant at $P \leq 0.05$.

Hence no evidence was found for any consistent nonlinear component.

Table V.8 shows the heritability of the child's SUA score with his parents'.

TABLE V.8

HERITABILITY OF CHILD'S SUAS
WITH PARENTS' SUAS

Dependent vs. Independent Variable	h^{2*}
Son with Father's SUAS	25.7
Son with Mother's SUAS	29.9
Son with Average of Mother and Father's SUAS	28.5
Daughter with Father's SUAS	33.2
Daughter with Mother's SUAS	47.9
Daughter with Average of Mother and Father's SUAS	33.8

* $\frac{1}{2} h^2 = 100\ b$ for offspring and one parent.

$h^2 = 100\ b$ for offspring and mid parent where b is the regression coefficient.

Heritability is derived from the formula $\frac{1}{2} h^2 = 100\ b$ where h^2 is the heritability and b is the regression coefficient of the child's SUA score with that of his parent. Perfect heritability would be 100 per cent. The heritability of son's SUA score on the mid parent score is 28.5 per cent and that of daughter's is 33.8 per cent.

In order to determine further the interaction of the child's SUA score on the parents' SUA score, a multiple regression analysis was

carried out of the form $y = a + b_1x_{1j} + b_2x_{2j} + b_3x_{3j}$ where x_{1j} is the father of the jth family, x_{2j} is the mother of the jth family and x_{3j} is the product of the measurements on the father and the mother. This analysis showed that b_3 did not contribute significantly to the regression of the child's value on mother's and father's values. The results of this analysis are shown in Table V.9.

TABLE V.9

REGRESSION ANALYSIS OF SUA SCORE OF ONE OFFSPRING[a] PER FAMILY ON SUA SCORE OF PARENT BASED ON THE FORMULA $a + b_1x_1 + b_2x_2 + b_3x_1x_2$

	d.f.	S. Square	Mean Square
	Sons		
Due to Regression	3	.14447	.04816
Due to Regression	2	.13518	.06759
Test of b_3	1	.00929	.00929
Error	320	3.58565	.01120
	F Ratio $\frac{.00929}{.01120}$ = .829 Not Significant		
	Daughters		
Due to Regression	3	.22874	.07625
Due to Regression	2	.22090	.11045
Test of b_3	1	.00784	.00784
Error	317	2.76250	.008714
	F Ratio $\frac{.00784}{.008714}$ = .90011 Not Significant		

[a] = oldest child in each family with SUA Determination.

D. Measurement of the Degree of Association in Siblings

To assess the degree of association in siblings an intraclass correlation coefficient of the form

$$\frac{\sigma_B^2}{\sigma_B^2 + \sigma_w^2}$$

was computed for sibships* of size two and three for ages 0 to 15, 16 to 39 and $\geq$ 40. The sibship size is a function of those members of the sibship with serum uric acid determinations. In some instances the ages of the sibship members fell into two different age groups. In sibships of size two, the age of the younger member determined the age group for the sibship. In sibships of size three, the two members in the same age group determined the grouping for the sibship. There were no instances where the ages of the members of the sibship fell into three different age groups. Sibships of size four or greater were not included in this analysis because of insufficient numbers. The intraclass correlation coefficients for ages 0 to 15 and 16 to 39 were significant at $P \leq 0.05$ based on an F test of one way analysis but the age group, 40 and over failed to yield a $P \leq 0.05$. These results are shown in Table V.10.

In an attempt to assess the contribution of genetic and environmental influences to the serum uric acid scores, sibships of size two ranging in age from 16 to 39 were divided into two groups: those

---

*Sibship = all the children with the same father and mother.

TABLE V.10

INTRACLASS CORRELATION COEFFICIENT
OF SUAS OF SIBSHIPS[a] BY AGE

Sibship Size	Age Group	Number of Sibships (Sample size)	Intraclass Correlation	F Value
2	≤ 16	263	.175	1.425**
	16-39	212	.167	1.40*
	≥ 40	103	.143	1.33
3	≤ 16	184	.261	2.05**
	16-39	96	.173	1.63*
	≥ 40	32	.189	1.70

[a] = sibship--all the children with the same mother and father.

* = significant at P ≤ .05.
** = significant at P ≤ .01.

siblings sharing the same household and those living in different households. An intraclass correlation was then computed for these two groups. This analysis was limited to ages 16 to 39 because this was the only group that provided sufficient numbers of both household and nonhousehold sibships. The intraclass correlation of the 26 sibships representing siblings sharing the same household was .393 and the F test based on one way analysis was significant at P ≤ .01. The intraclass correlation of 167 sibships representing siblings living in different households was 0.099 and the F test was not significant.

In another form of analysis the sibships of fraternities* were

*Fraternity is synonomous with sibship.

grouped into superfraternities which then represented all of the children, related and unrelated, whose parents had a common combination of scores. There were as many superfraternities as there were different combinations of parental measurements grouped on the bases of 0.5 mg. intervals. The assumption underlying the superfraternity grouping is that those groups of parents with similar scores reflect families that are exposed to similar environments. If such an assumption is correct, then the superfraternity grouping minimizes environmental differences so that genetic influences can be better measured.

An analysis of variance was carried out which permitted comparisons of the variation among superfraternities, the variation among fraternities within superfraternities and the variation within fraternities. The variation among superfraternities was significantly higher than the variation among fraternities within superfraternities and the variation among fraternities within superfraternities was significantly higher than the variation within fraternities. The level of significance for these differences was $P \leq 0.01$. Components of variance were estimated as follows: among superfraternities 0.09, among fraternities within superfraternities 0.120 and mean square within fraternities 0.77. The results of this analysis are shown in Table V.11.

E. Measurement of the Degree of Association in Spouse Pairs

The study of spouses provides a way of comparing persons of essentially different genetic structure who are exposed to similar environmental influences. The length of time married should be considered as the length of time of exposure to the common environment. Since

TABLE V.11

ANALYSIS OF VARIANCE CONSIDERING THE VARIATION AMONG SUPERFRATERNITIES,[a] AMONG FRATERNITIES[b] WITHIN SUPERFRATERNITIES, AND WITHIN FRATERNITIES

Source of Variation	Sums of Squares	d.f.	Mean Square	F Value	Expectation	Estimation
Among Super Fraternities	197.17500	94	A) 20.976	A/B 1.86**	$\frac{\sigma_e^2 + 2.767\sigma_f^2 \quad 13.191\sigma_s^2}{\sigma_e^2 + a.455\sigma_f^2}$	$S_s^2 = .090799$
Between Fraternities within Super Fraternity	439.20125	390	B) 1.12615	B/C 1.456**	$\frac{\sigma_e^2 + 2.767\sigma_f^2}{\sigma_e^2}$	$S_f^2 = .12760$
Within Fraternities	606.86031	785	C) .77307	A/C 2.713**	σ_e^2	$S_e^2 = .77307$
Total	1243.23656	1269				

[a]Superfraternity--all the children, related and unrelated, whose parents had a common combination of scores.

[b]Fraternity--all the children with the same mother and father.

**Significant at $P < 0.01$.

information on the length of time married had not been obtained on subjects in the TCHS, the age of the wife was used as an approximation of the length of marriage. Correlation coefficients were computed for spouse pairs based on wives aged 16-19, 20-29, 30-39, and ≥40 and these results are shown in Table V.12. A test for homogeneity of the correlation coefficients showed no significant differences among the four correlations.

TABLE V.12

CORRELATION COEFFICIENTS OF SPOUSE PAIRS BASED ON AGE OF WIFE AND TEST FOR HOMOGENEITY

Age of Wife	N Spouse Pairs	r	$\bar{z}$	$(N-3)\bar{z}$	$(N-3)\bar{z}^2$
16-19	21	.0211	.021	.378	.008
20-29	378	.1203	.121	45.738	5.534
30-39	487	.1182	.119	57.953	6.854
≥ 40	628	.1007	.101	63.428	6.406
Total	1,511			167.497	18.802

Average $\bar{z}$ = .111. Average r = .110.

$[\Sigma(N-3)\bar{z}]$ (avg. $\bar{z}$) = (167.497)(.111) = 18.592.

$(N-3)\bar{z}^2 - [\Sigma(N-3)\bar{z}]$ (avg. $\bar{z}$) = 18.802 - 18.592 = χ^2 .210

F. Measurement of Degree of Association of SUA Scores Within Kindreds

Analysis was made of the kindreds of probands with hyperuricemia, hypouricemia and gout. The hyperuricemic probands comprised those study subjects with SUA scores ≥ 7.1 mg./100 ml. and the hypouricemic probands

comprised those with SUA scores $\leq$ 2.4 mg./100 ml. There were 27 subjects who were diagnosed as having gout on the basis of a careful screening carried out on the total study population by Drs. Mikkelsen and Dodge. Of these 27 cases only 24 had serum uric acid determinations and it is this latter group which comprised the gout probands in this analyses. In some instances there was more than one proband in a kindred. Those kindreds which contained both hypo and hyperuricemic probands were analyzed separately. The kindreds of some probands were deleted from further analysis if none of their relatives had serum uric acid determinations.

The study of kindreds was made possible from the information collected in 1957 as part of the TCHS and described in Chapter III of this paper.

Within each kindred, attention was given to those relatives with scores ranging from 5.6 to 7.0 mg./100 ml. and from 2.5 to 3.4 mg./100 ml. These values represent scores more than one standard deviation above the mean and more than one standard deviation below the mean respectively.

1. Kindred analysis of probands with hyperuricemia.

There were 72 hyperuricemic probands who had relatives with serum uric acid determinations and in seven instances there was more than one proband in a kindred. Table V.13 shows the distribution of probands by sex and the relationship of probands when there was more than one proband in a kindred.

Sixty-five kindreds were studied and the serum uric acid scores of 284 relatives were assessed. Of these relatives, 17.6 per cent had

scores ranging from 5.6 to 7.0 mg./100 ml. and 9.5 per cent had scores of 2.5 to 3.4 mg./100 ml. Thirty-three or 50.7 per cent of the 65 kindreds had one or more members with SUA scores ranging from 5.6 to 7.0 mg./100 ml. and 22 or 33.8 per cent had one or more members with scores ranging from 2.5 to 3.4 mg./100 ml. These results are shown in Tables V.14 and V.15.

In order to obtain an expected value for the proportion of kindreds with more than one proband or at least one member of the kindred with a SUA score of 5.6 to 7.0 mg./100 ml., the proportion of subjects within this range of scores was determined from the total TCHS and found to be .13. Using this proportion as the P value, binomial tables gave the probability of at least one person having a score within the stated range, for a kindred of a given size. This probability was then weighted by the frequency of kindreds of that size in the distribution. The average of all such weighted probabilities was computed. This average proportion, then, was the expected proportion. There is no appropriate measurement for computing the standard error of a weighted value such as the observed $\hat{P}$ value in this analysis. Therefore the use of the student t test for determining the significance of the difference between the observed and the expected proportions should be interpreted as a rough approximation of the significance of the difference between the two values. The t test failed to yield a P value $\leq .05$. This computation is shown in Table V.16.

The geneologies of these hyperuricemic probands are shown in Figure V.9 through Figure V.13.

TABLE V.13

DISTRIBUTION OF HYPERURICEMIC PROBANDS BY SEX AND RELATIONSHIP WHEN > ONE PROBAND/KINDRED

Total Number of Probands with Kindred Members with SUAS	Male	Female	Relationship of Probands Where > One Proband/Kindred				
			Father and Son	Mother and Daughter	Two Sisters	Brother and Sister	Two Female Paternal Cousins
72	28	44	1	2	2	1	1

TABLE V.14

NUMBER AND PER CENT OF RELATIVES OF HYPERURICEMIC PROBANDS WITH SUA SCORES OF 5.6 - 7.0 mg. and 2.5 - 3.4 mg. BY SEX OF THE RELATIVES

Number of Kindreds Studied	Number of Relatives with SUAS	SUAS	N	%	Males	SUAS	N	%	Females	SUAS	N	%
65	284	2.5-3.4	27	9.5	128	2.5-3.4	13	10.9	156	2.5-3.4	14	9.0
		5.6-7.0	50	17.6		5.6-7.0	23	18.0		5.6-7.0	27	17.3

TABLE V.15

NUMBER AND PER CENT OF KINDREDS WITH MORE THAN ONE HYPERURICEMIC PROBAND OR WITH ONE OR MORE RELATIVES WITH SUA SCORES OF 5.6 - 7.0 mg.

Total Number of Kindreds with > One Proband or One or more Relatives with SUAS 5.6 - 7.0		Number of Members/Kindred with SUAS 5.6 - 7.0 mg.				Total Number of Kindreds with Relatives with SUAS 2.5 - 3.4 mg.		Number of Members/Kindred with SUA Scores 2.5 - 3.4 mg.	
N	%	1 Member	2 Members	3 Members	4 Members	N	%	1 Member	2 Members
33	50.7	20	8	4	1	22	33.8	16	6

TABLE V.16

COMPUTATION TO DETERMINE THE EXPECTED NUMBER OF KINDREDS WITH MORE THAN ONE PROBAND AND/OR ONE OR MORE MEMBERS WITH SUA SCORES OF 5.6 to 7.0 mg./100 ml.

Size of Kindred	N_i Number of Kindreds of Such Size	P_i Probability of More than One Proband or One or More than One Member with a SUAS 5.6 to 7.0 mg./100 ml.	$N_i P_i$
1	8	.13	1.04
2	15	.24	3.60
3	7	.34	2.38
4	10	.42	4.20
5	5	.50	2.50
6	8	.57	4.56
7	4	.62	2.48
8	1	.67	.67
9	2	.71	1.42
10	1	.75	.75
12	2	.81	1.62
14	1	.86	.86
17	1	.91	.91
	65		26.99

$$\text{Expected } P = \frac{\Sigma N_i P_i}{N} = \frac{26.99}{65} = .415$$

$$\text{t test } \frac{p - \hat{p}}{\sqrt{\frac{Pq}{N}}} = \frac{.415 - .507}{\sqrt{\frac{(.415)(.585)}{65}}} = \frac{.092}{.0610739} = 1.51$$

SEE TEXT PAGE 61 FOR FURTHER EXPLANATION.

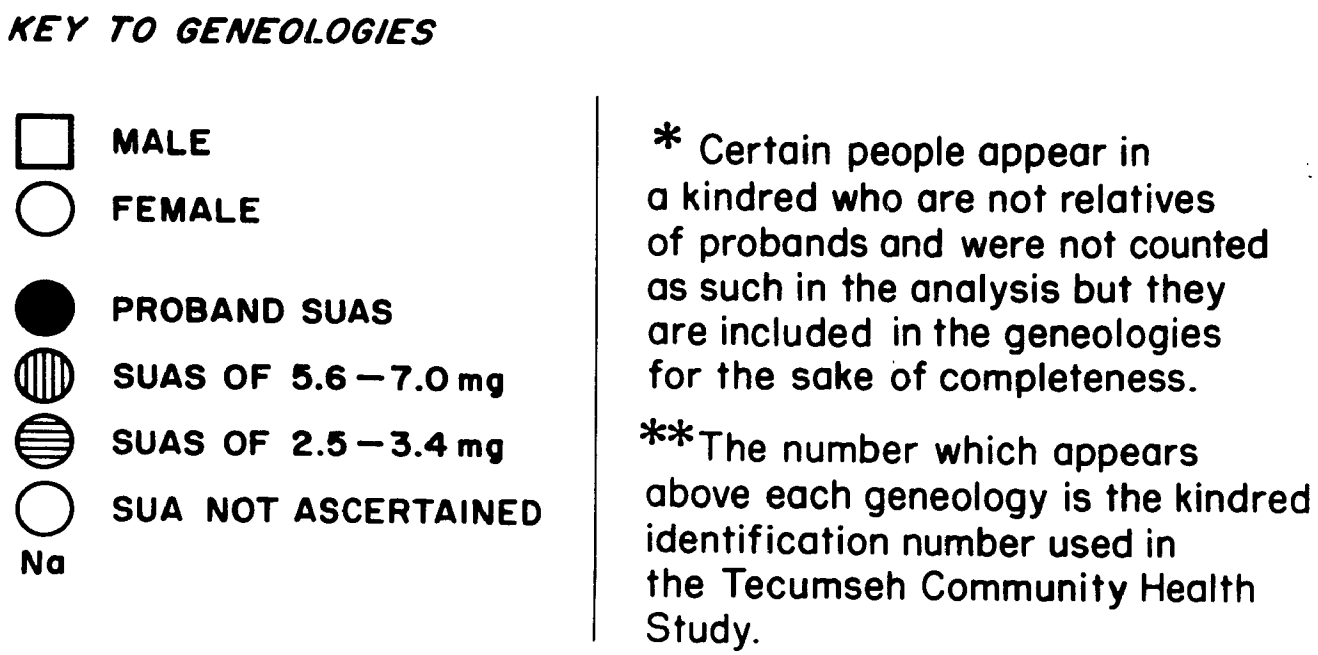


Fig. V.8 Key to Geneologies.

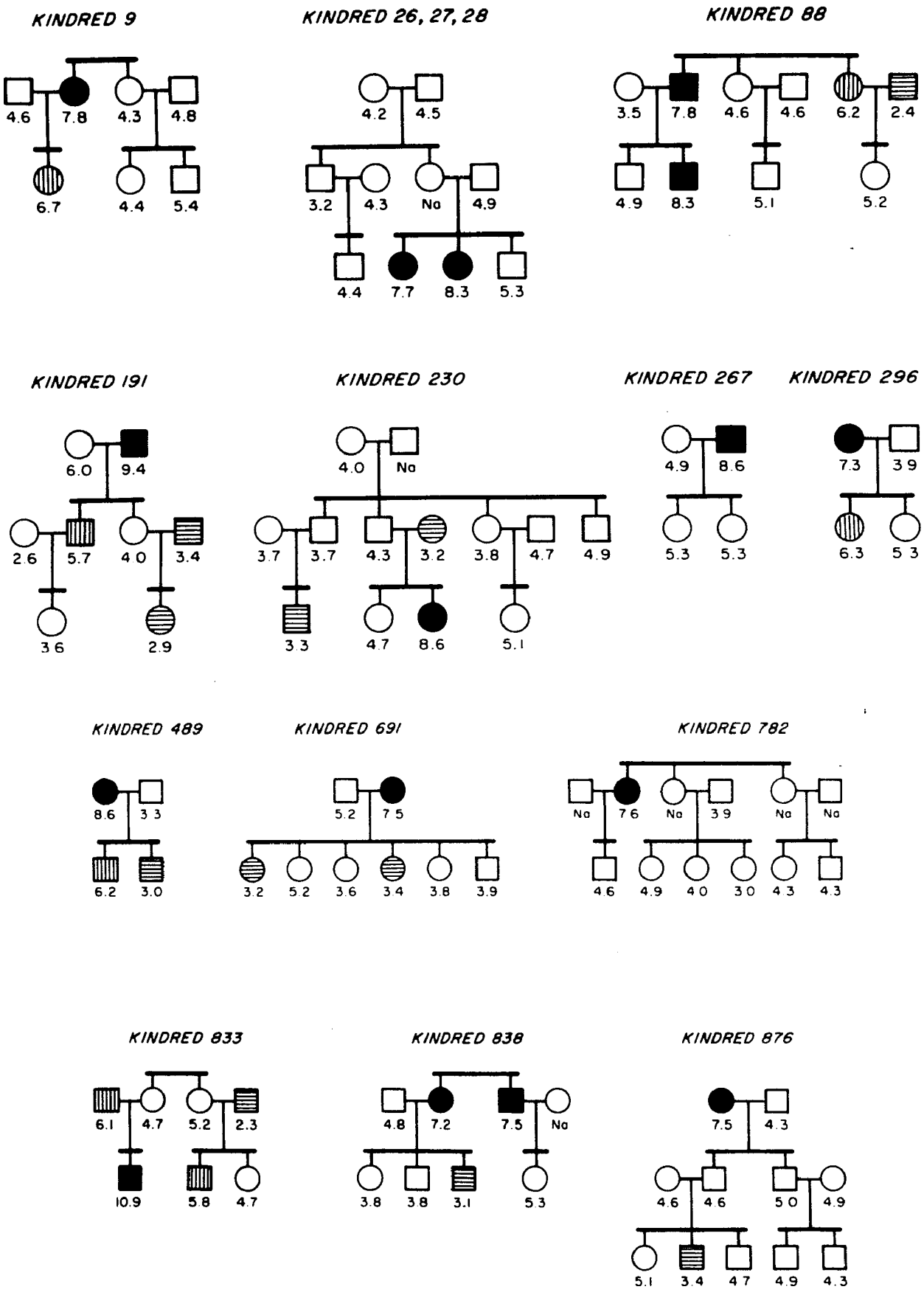


Fig. V.9 Geneologies of Hyperuricemic Probands.

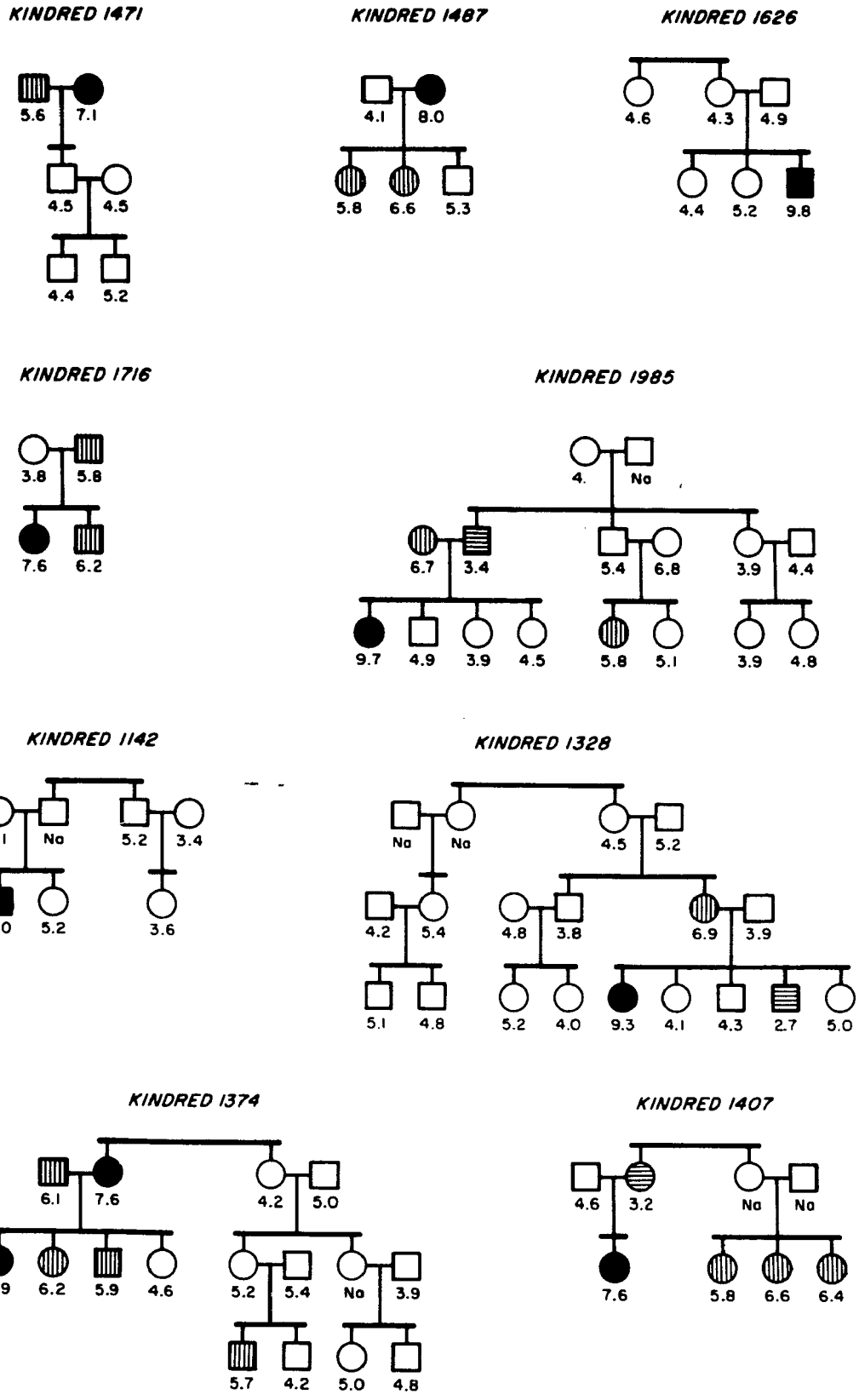


Fig. V.10 Geneologies of Hyperuricemic Probands.

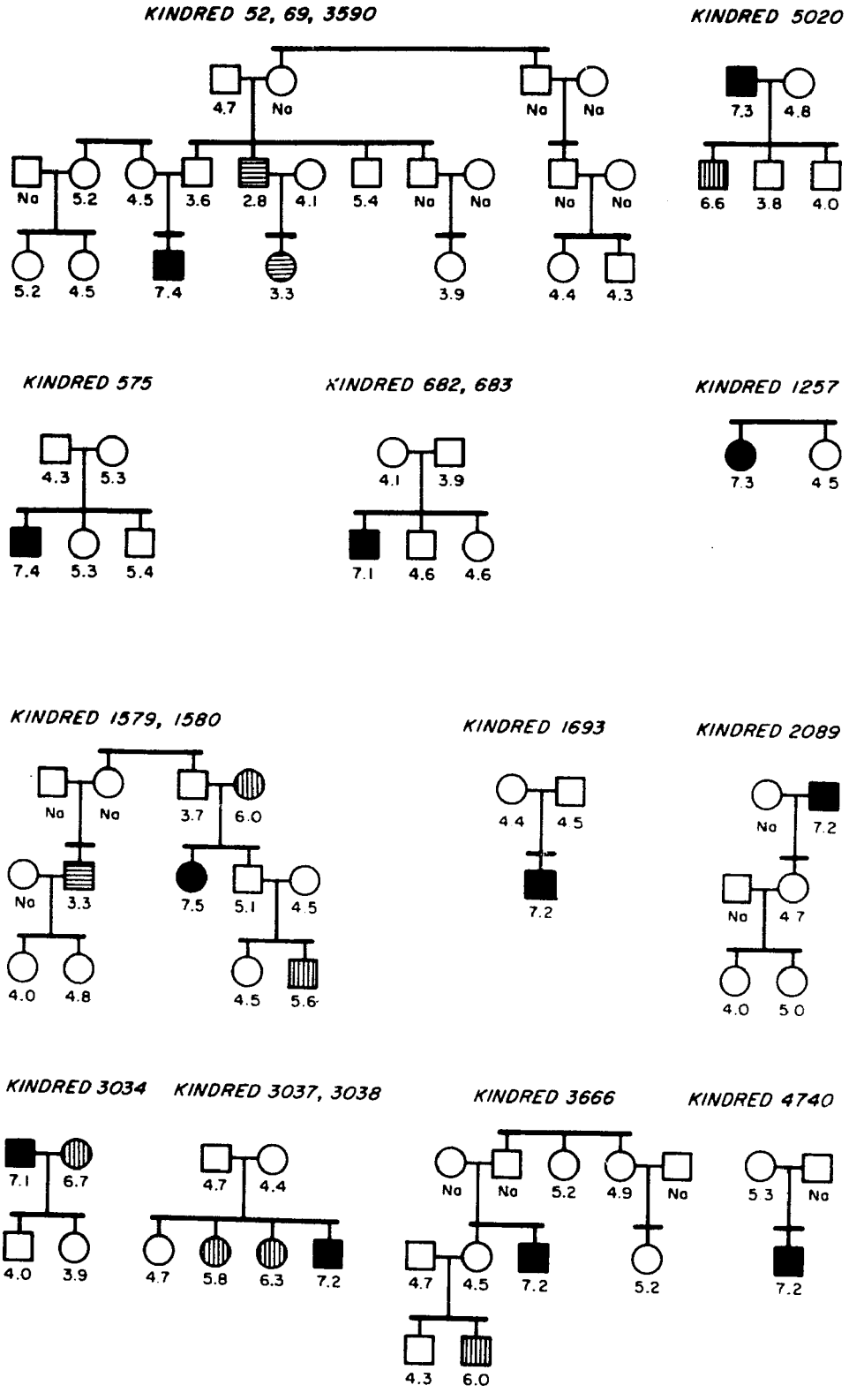


Fig. V.11 Geneologies of Hyperuricemic Probands.

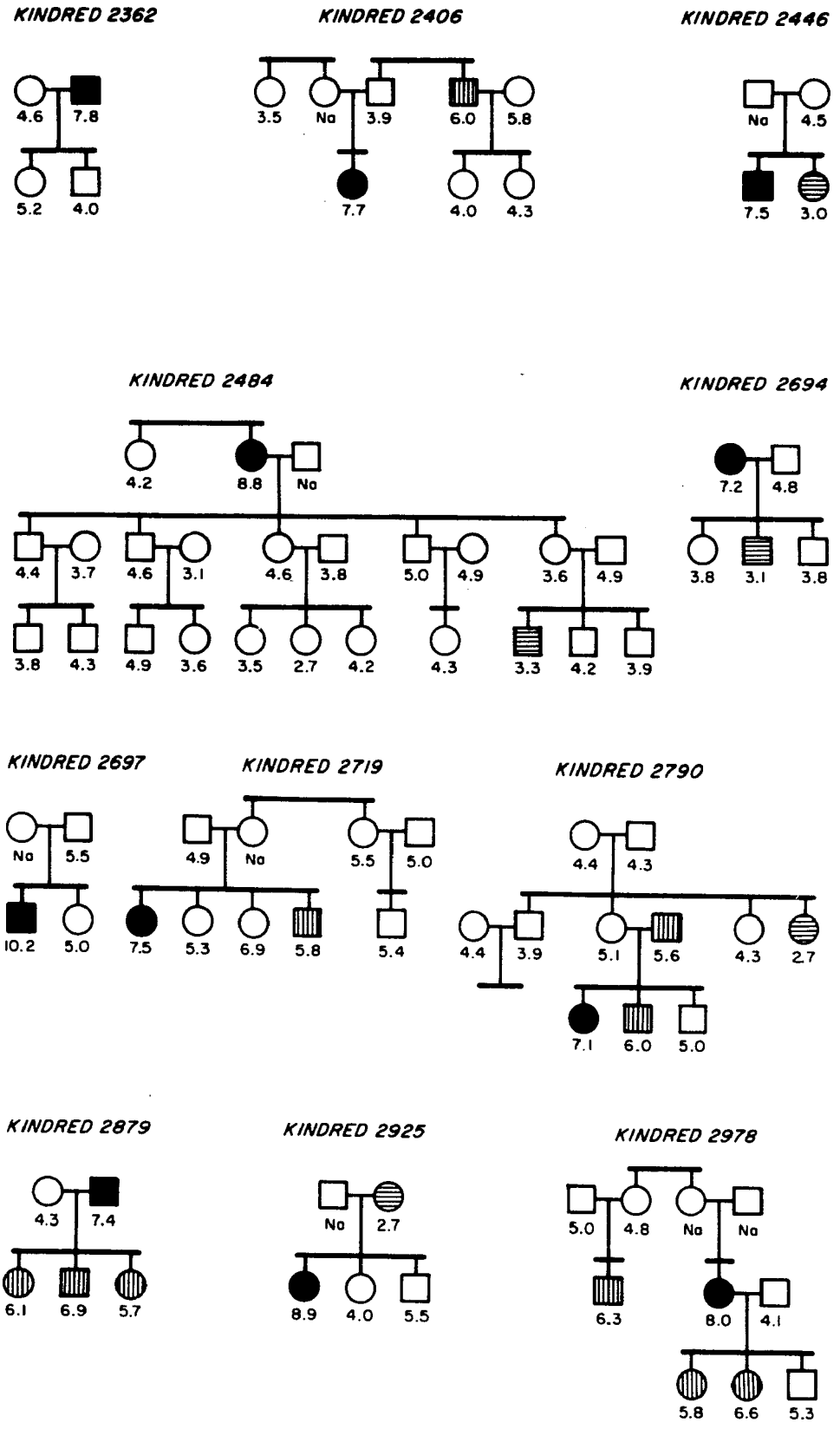


Fig. V.12 Geneologies of Hyperuricemic Probands.

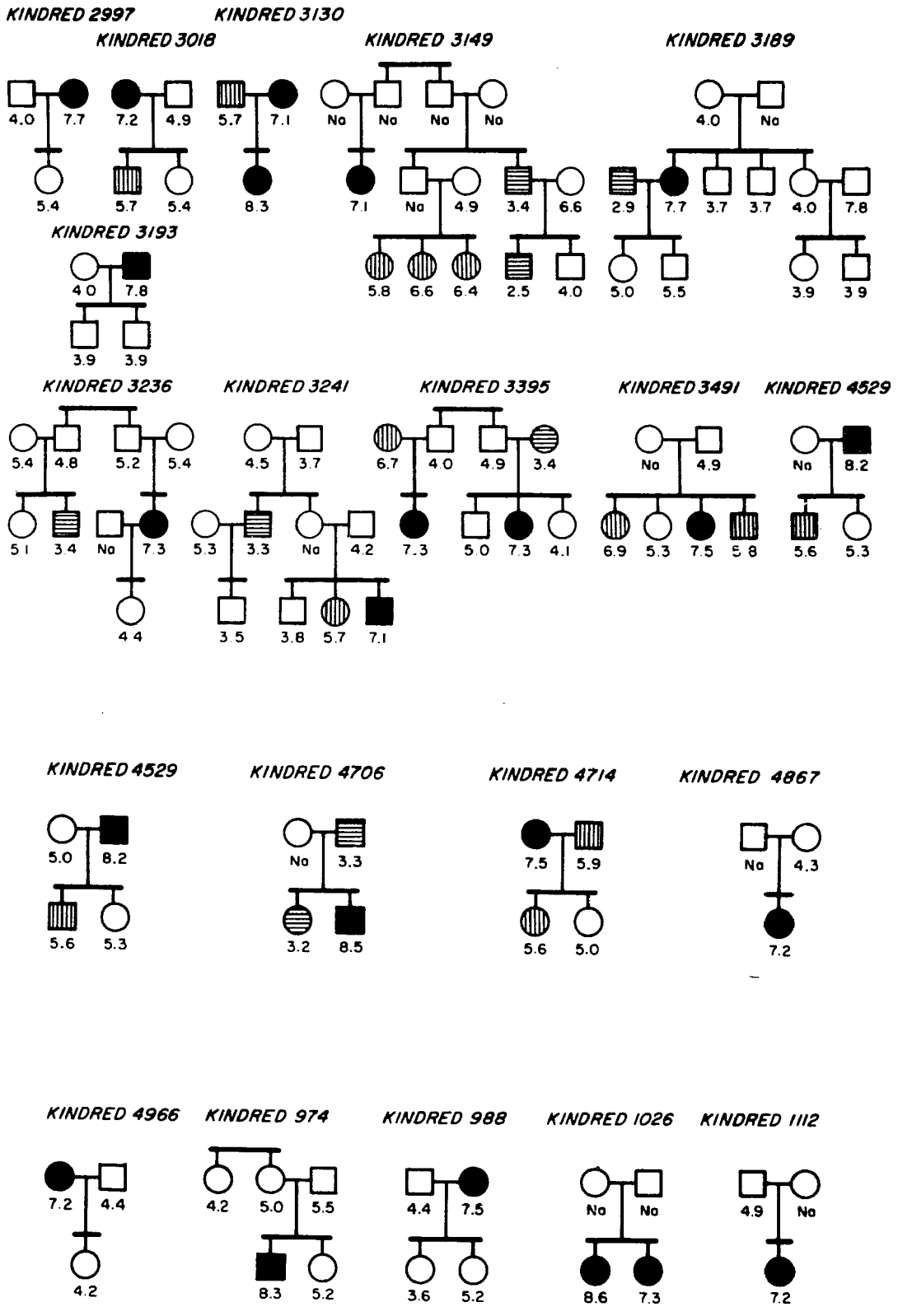


Fig. V.13 Geneologies of Hyperuricemic Probands.

The number and per cent of those kindred members with SUA scores 5.6 to 7.0 and 2.5 to 3.4 mg. by relationship to the hyperuricemic proband are shown in Appendix Tables A.1 through A.12.

2. Kindred Analysis in Probands with Hypouricemia

There were 42 hypouricemic probands who had relatives with SUA determinations and there were two instances where more than one hypouricemic proband occurred in a kindred. The sex distribution of the probands is shown in Table V.17 as well as the relationship of probands when there was more than one proband in a kindred.

TABLE V.17

DISTRIBUTION OF HYPOURICEMIC PROBANDS BY SEX AND RELATIONSHIP WHEN MORE THAN ONE PROBAND/KINDRED

Total Number of Probands with Members in Kindred with SUAS	Males	Females	Number of Kindreds with Two Probands	Relationship When > 1 Proband/Kindred	
				Two Male Cousins	Aunt and Grand Nephew
42	28	14	2	1	1

Forty kindreds were studied resulting in the assessment of SUA scores of 169 relatives. Of these relatives 27.2 per cent had scores of 2.5 - 3.4 mg./100 ml. and 7.1 per cent had scores of 5.6 - 7.0 mg./100 ml. The per cent distribution of these relatives by sex is shown in Table V.18. Twenty-two of the 40 kindreds or 55 per cent had at least one member with a SUA score of 2.5 - 3.4 mg./100 ml. and 7 or 17.5 percent had at least one member with a SUA score of 5.6 - 7.0 mg./100 ml. These results are shown in Table V.19. The number and per cent of

TABLE V.18

NUMBER AND PER CENT OF RELATIVES OF HYPOURICEMIC PROBANDS WITH SUAS OF 5.6 - 7.0 mg. and 2.5 - 3.4 mg. BY SEX OF THE RELATIVES

Total Number of Kindreds Studied	Number of Relatives with SUAS	SUAS	N	%	Males	SUAS	N	%	Females	SUAS	N	%
40	169	2.5 - 3.4	46	27.2	80	2.5 - 3.4	23	28.8	89	2.5 - 3.4	23	25.8
		5.6 - 7.0	12	7.1		5.6 - 7.0	7	8.8		5.6 - 7.0	5	5.6

TABLE V.19

NUMBER AND PER CENT OF KINDREDS OF HYPOURICEMIC PROBANDS WITH $\geq$ ONE HYPOURICEMIC PROBANDS OR ONE OR MORE RELATIVES WITH SUA SCORES OF 2.5 - 3.4 mg.

Total Number of Kindreds with Members 2.5-3.4 SUAS or One Hypouricemic Proband		Number of Members/Kindred with SUAS 2.5-3.4 mg.					Total Number of Kindreds with Members 5.6-7.0 SUAS		Number of Members/Kindred with SUAS 5.6-7.0 mg.		
N	%	1 Member	2 Members	5 Members	7 Members	10 Members	N	%	1 Member	2 Members	5 Members
22	55.0	13	6	1	1	1	7	17.5	5	1	1

kindred members with SUA scores of 5.6 - 7.0 mg. and 2.5 - 3.4 mg. by their relationship to the hypouricemic proband are shown in Appendix Tables A.13 through A.23.

In order to arrive at the expected proportion of kindreds with at least one member with a SUA score of 2.5 mg./100 ml. to 3.4 mg./100 ml. similar computations were carried out as described in the previous section on hyperuricemic probands. The t test carried out on the significance of the difference between the observed and expected proportions showed significance at $P \leq 0.05$. These computations are shown in Table V.20. A t test was carried out to determine if the observed proportion of kindreds with scores of 5.6 - 7.0 mg./100 ml. was significantly lower than would be expected based on the proportion of these values in the total Tecumseh study population. The results of this test showed the difference to be significant at $P \leq .05$.

The geneologies of these hypouricemic probands are shown in Figures V.14 through V.16.

3. Kindred Analysis in Probands with Gout

Fifteen of the twenty-four probands with gout had relatives with SUA determinations. Seven of these probands had hyperuricemic serum uric acid levels. Each kindred had only one proband with gout. The number of relatives with SUA determinations was 65 and 13.8 per cent of these relatives had SUA scores 5.6 - 7.0 mg./100 ml. and 12.3 per cent had values of 2.5 - 3.4 mg./100 ml. These results are shown in Tables V.21 and V.22. Of the fifteen kindreds studied, six or 40 per cent had one or more members with SUA scores of 5.6 - 7.0 mg./100 ml.

TABLE V.20

COMPUTATION TO DETERMINE THE EXPECTED NUMBER OF KINDREDS WITH MORE THAN ONE PROBAND AND/OR ONE OR MORE MEMBERS WITH SUA SCORES OF 2.5 to 3.4 mg./100 ml.

Size of Kindred	N_i Number of Kindreds of Such Size	P_i Probability of More than One Proband or At Least One Member with a SUAS 2.5 to 3.4 mg./100 ml.	$N_i P_i$
1	8	.13	1.04
2	9	.24	2.16
3	6	.34	2.04
4	6	.42	2.52
5	4	.50	2.00
6	2	.57	1.14
8	1	.67	.67
10	1	.75	.75
11	1	.78	.78
15	1	.88	.88
25	1	.97	.97
	40		14.95

$$\text{Expected } P = \frac{\Sigma N_i P_i}{N} = \frac{14.95}{40} = .373$$

$$\hat{p} = .55$$

$$\text{t test } \frac{p - \hat{p}}{\sqrt{\frac{pq}{N}}} = \frac{.373 - .555}{\sqrt{\frac{(.373)\ (.627)}{40}}} = \frac{.177}{.0763} = 2.33^*$$

*Significant $P \leq .05$.

SEE TEXT PAGE 61 FOR FURTHER EXPLANATION.

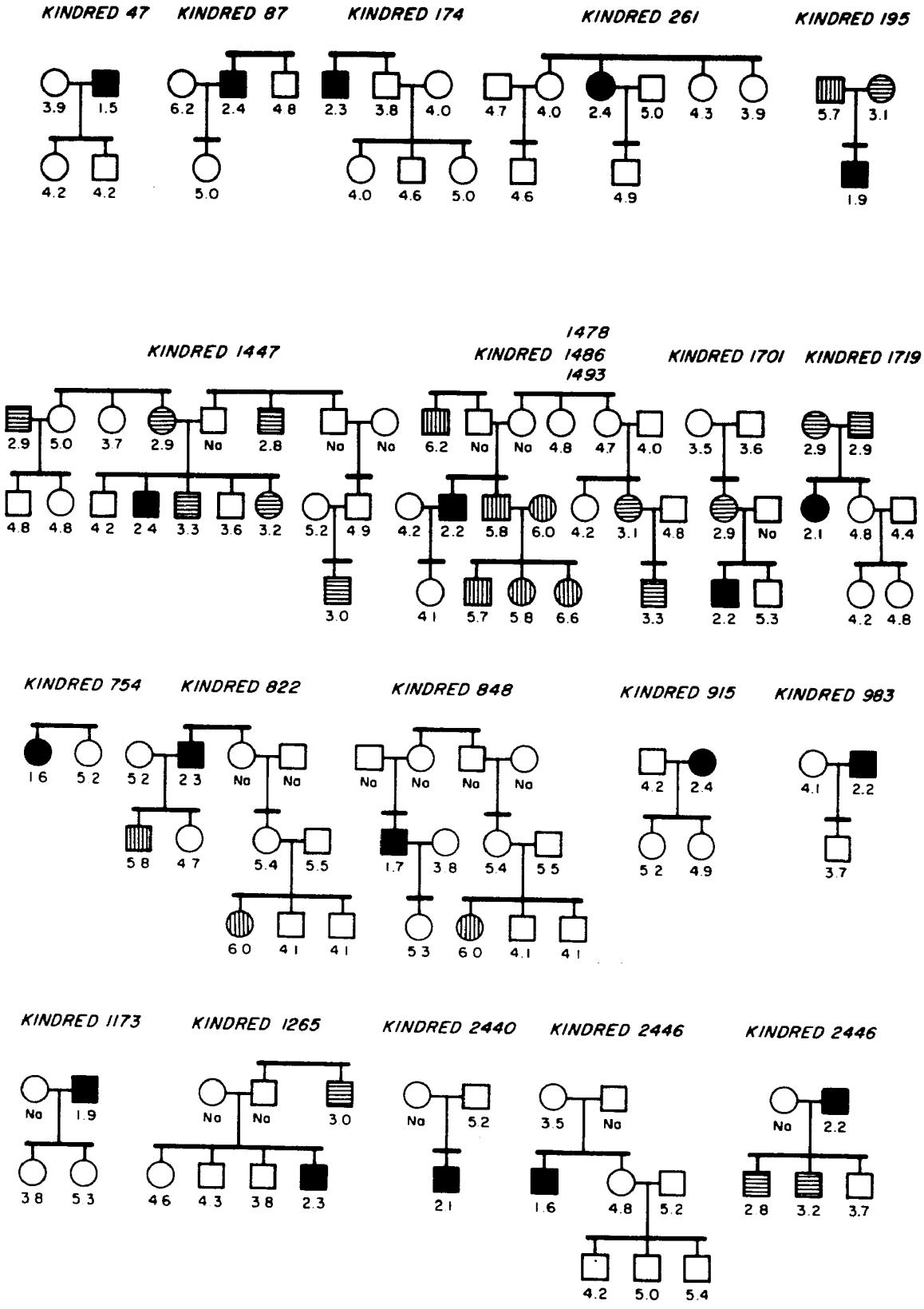


Fig. V.14 Geneologies of Hypouricemic Probands.

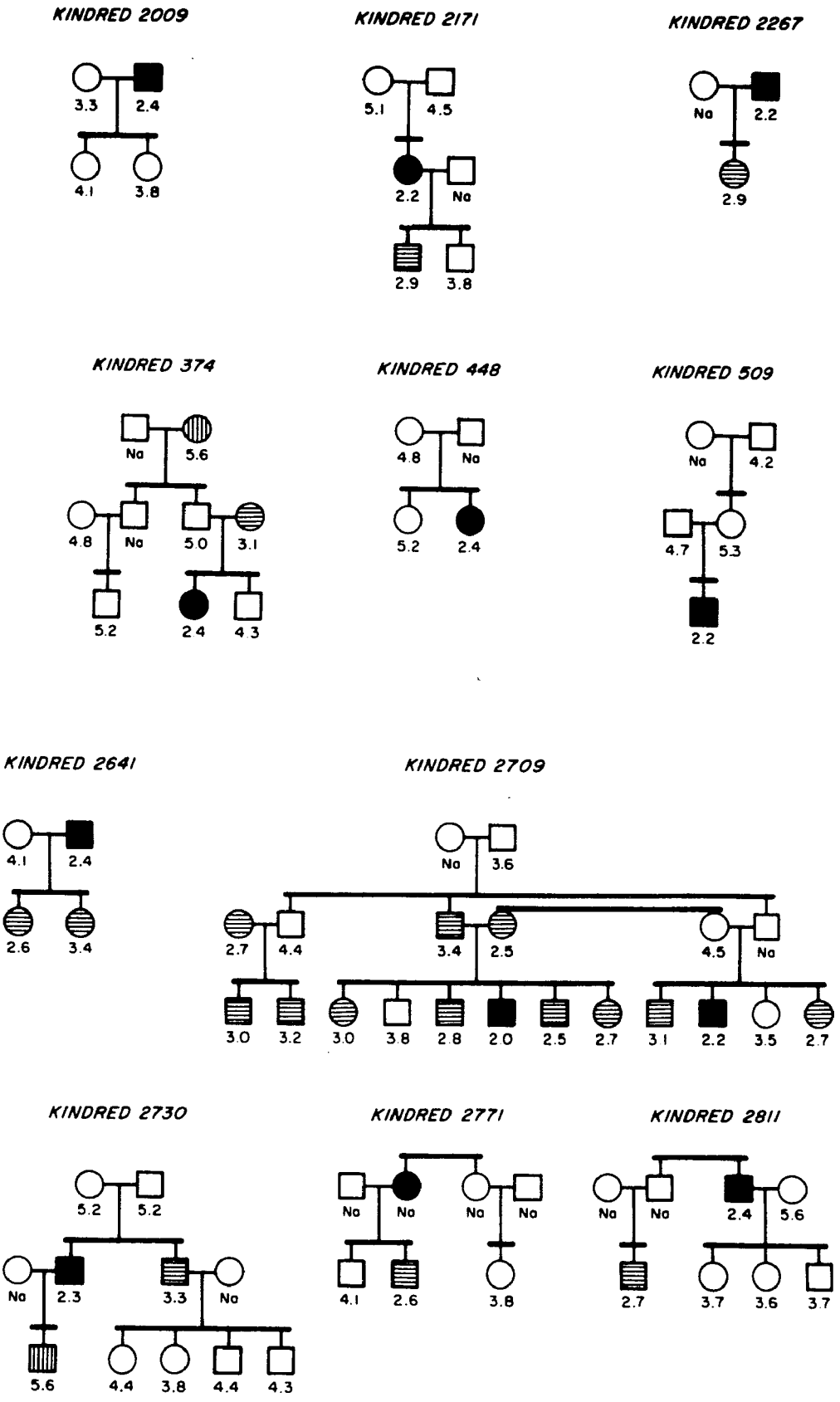


Fig. V.15 Geneologies of Hypouricemic Probands.

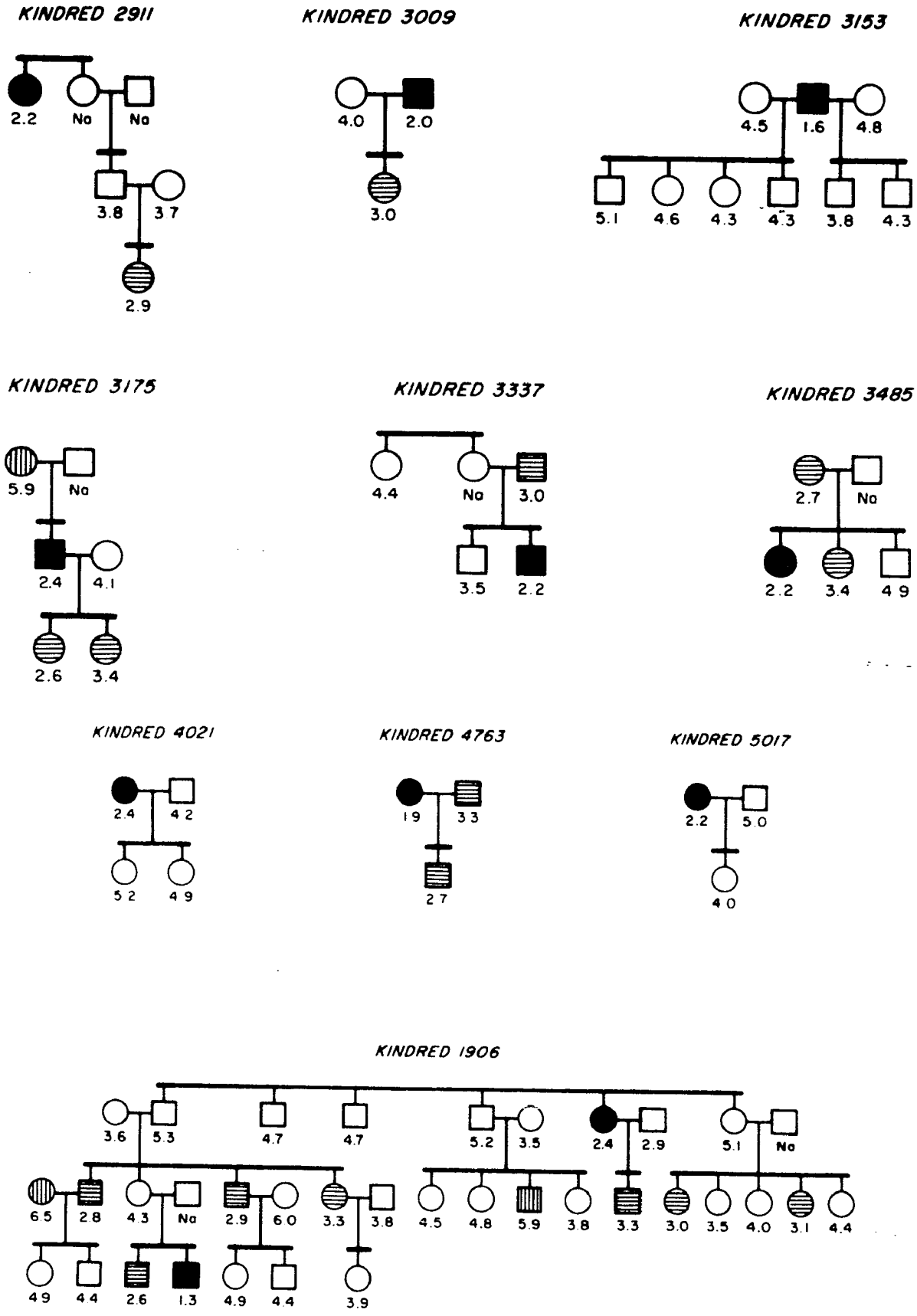


Fig. V.16 Geneologies of Hypouricemic Probands.

TABLE V.21

DISTRIBUTION OF GOUT PROBANDS BY SEX

Total Number of Probands with Members in Kindred with SUAS	Males	Females	Number of Kindreds with More than One Proband	Number of Probands with Hyperuricemic SUAS Levels
15	11	4	0	7

TABLE V.22

NUMBER AND PER CENT OF RELATIVES OF GOUT PROBANDS
WITH SUAS OF 5.6 -7.0 and 2.5 - 3.4 mg.

Total Number of Kindreds Studied	Total Number of Relatives*	SUAS	N	%	Males	SUAS	N	%	Females	SUAS	N	%
15	65	2.5-3.4	8	12.3	34	2.5-3.4	4	11.8	31	2.5-3.4	4	12.9
		5.6-7.0	9	13.8		5.6-7.0	4	11.8		5.6-7.0	5	16.1

*Mean number of relatives/kindred = 7.4 Range = 2-15

and five or 33.3 per cent had scores of 2.5 - 3.4 mg./100 ml. as shown in Table V.23.

TABLE V.23

NUMBER AND PER CENT OF KINDREDS OF GOUT PROBANDS CONTAINING MEMBERS WITH SUAS OF 5.6 - 7.0 mg./100 ml.

Total Number of Kindreds with Members with SUAS 5.6 -7.0 mg.		Number of Members/Kindred with SUAS 5.6 - 7.0 mg.			Total Number of Kindreds with Members 2.5 - 3.4 mg.		Number of Members/Kindred with SUAS 2.5 - 3.4 mg.	
N	%	1 Member	2 Members	3 Members	N	%	1 Member	2 Members
6	40.0	4	1	1	5	33.3	3	2

The observed proportion of kindreds with one or more members with SUA scores of 5.6 to 7.0 mg./100 ml. was the same as the expected proportion.

The geneologies of these gout probands are shown in Figure V.17

The number and per cent of kindred members with SUA scores of 5.6 to 7.0 and 2.5 to 3.4 mg. by their relationship to the gout proband are shown in Appendix Tables A.24 through A.32.

4. Kindreds Containing Both Hypo- and Hyperuricemic Probands

Five kindreds contained both a hyper and a hypouricemic proband. The relationship of these probands, shown in Table V.24, consisted of a father and daughter, a brother and sister, an aunt and nephew, a husband and wife and two sets of male cousins. Table V.25 shows the number of relatives in each kindred with SUA scores of 5.6 - 7.0 mg./100 ml. or

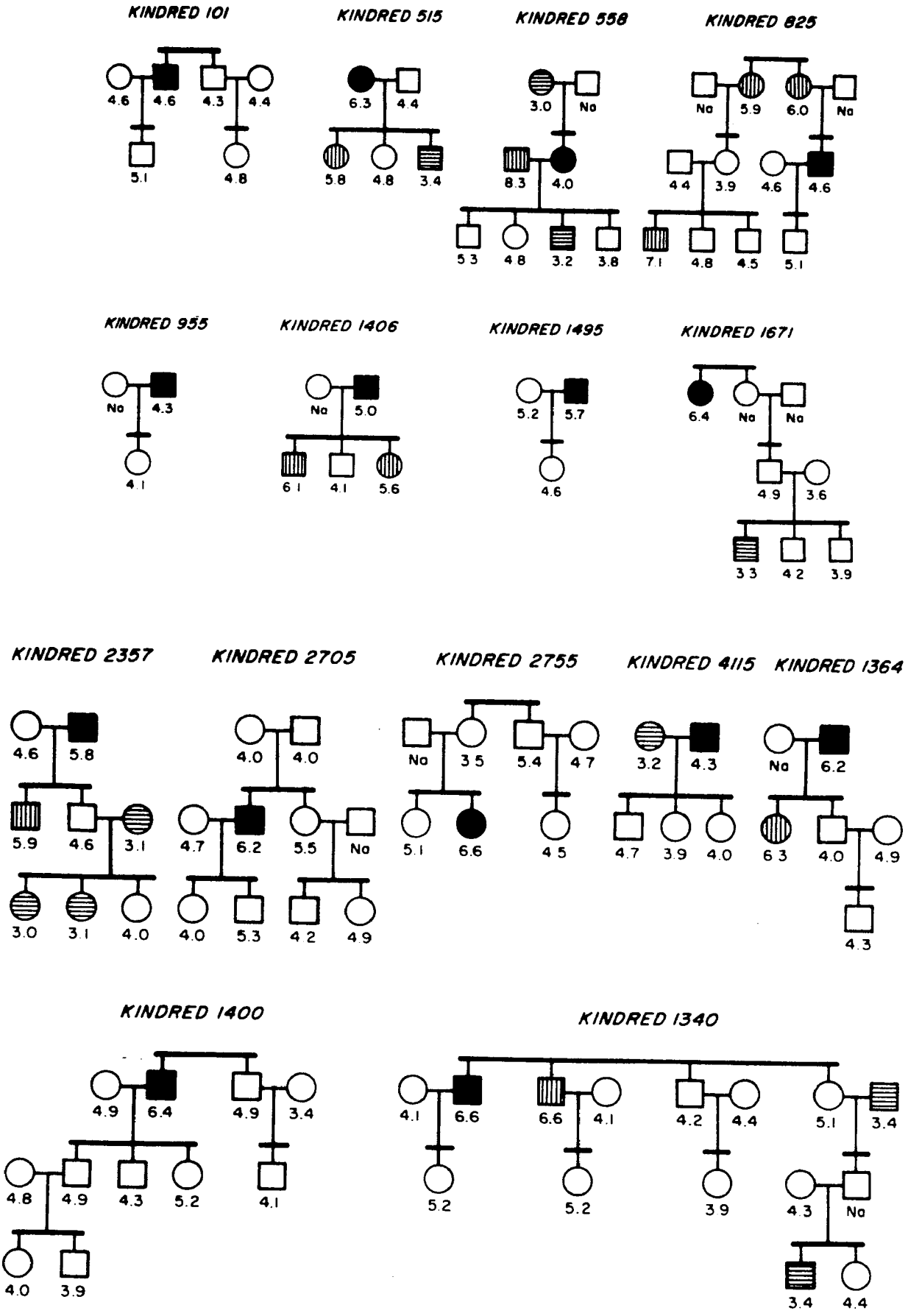


Fig. V.17 Geneologies of Gout Probands.

TABLE V.24

RELATIONSHIP OF PROBANDS WHEN BOTH A HYPER- AND A HYPOURICEMIC PROBAND OCCUR IN THE SAME KINDRED

Number of Kindreds	Relationship of High and Low Probands			
	Father and Daughter*	Brother and Sister	Male Cousins	Husband and Wife
5	1	1	2	1

*This kindred has two high probands (grandfather and grandson). grand

TABLE V.25

NUMBER OF RELATIVES WITH SUAS OF 5.6 - 7.0 mg. or 2.5 - 3.4 mg. IN FIVE KINDREDS WITH HIGH AND LOW PROBANDS

SUA Scores						Total
5.6 - 7.0 mg./100 ml.	0	1	1	1	0	3
2.5 - 3.4 mg./100 ml.	2	0	3	0	0	5

2.5 - 3.4 mg./100 ml. One kindred contained two relatives with SUA scores of 2.5 to 3.4 mg./100 ml., two kindreds each had one member with a SUA score of 5.6 to 7.0 mg./100 ml. and one kindred contained relatives with both high and low scores. The geneologies of these kindreds are shown in Figure V.18.

G. Measurement of the Degree of Association Between Serum Uric Acid and Other Variables

In order to determine the degree of association between the unstandardized serum uric acid levels and other measurements, the

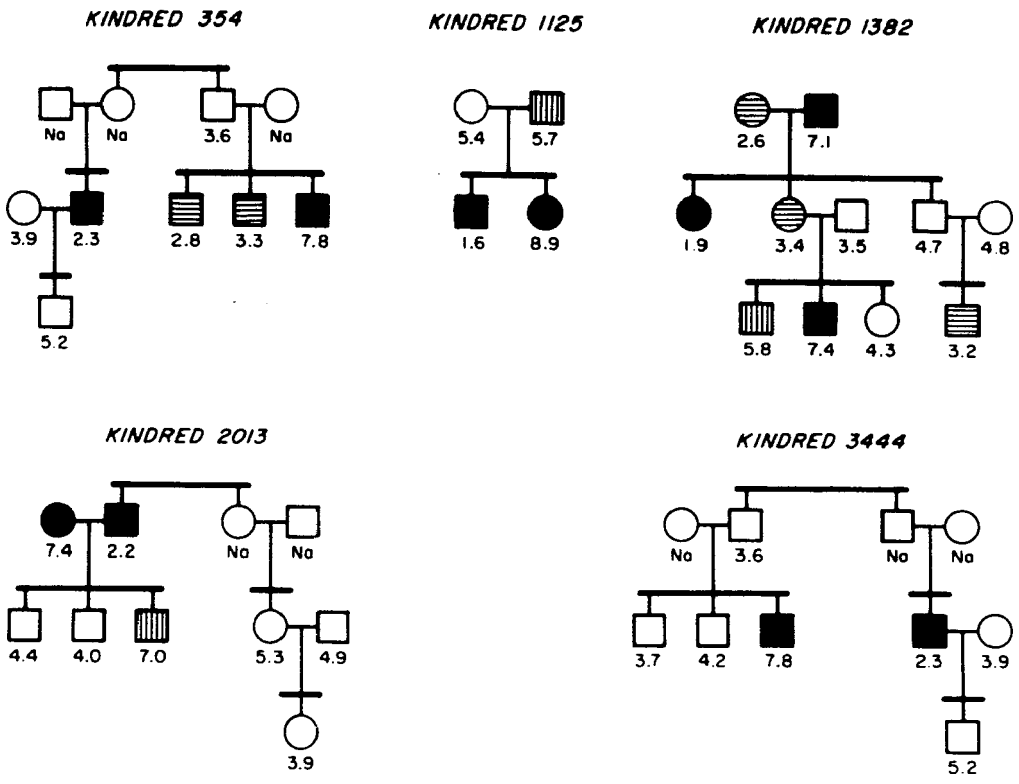


Fig. V.18 Geneologies with Both Hyperuricemic and Hypouricemic Probands.

statistical staff of the TCHS correlated uric acid by age and sex with fourteen other variables. The results of these computations are shown in Table V.26.

The highest correlation coefficients were those of serum uric acid with weight and serum uric acid with relative weight. The regression coefficients and correlation coefficients of SUA on relative weight and weight are shown in Tables V.27 and V.28, respectively. The relative weight was computed as a ratio of the subject's weight to his ideal weight. This predicted weight was determined from a regression equation of weight on height, biacromial and bicristal diameter for men and women of ages 20-29.[55]

It is possible that an associated factor such as relative weight may be responsible for the observed aggregation of serum uric acid in families. In order to explore further this possibility, analyses were carried out on the relation of serum uric acid scores to relative weight.

In the first of these analyses serum uric acid scores were divided into six groups based on their distance in standard deviations from the mean. The per cent distribution of the three percentile ranks in relative weight (below the 20th percentile, 20th to 80th percentile, above the 80th percentile) was then obtained for each of the six serum uric acid groups. The results of this analysis are shown in Figure 19 and Figure 20.

There was a higher per cent of subjects with SUA scores one or more standard deviations above the mean (groups 4, 5, 6) among those who were above the 80th percentile in relative weight than among those

TABLE V.26

CORRELATION COEFFICIENTS OF SERUM URIC ACID WITH FOURTEEN VARIABLES BY AGE AND SEX[a]

Observed Serum Uric Acid Correlated with:	Men						Women					
	20-29	30-39	40-49	50-59	60-69	70-79	20-29	30-39	40-49	50-59	60-69	70-79
Weight	.144**	.198**	.217**	.228**	.290**	.217*	.241**	.340**	.230**	.270**	.222**	.224*
Height	-.052	.003	.062	.006	.032	.194*	-.007	-.009	-.045	-.009	-.018	.112
Cholesterol	.087	.126**	-.027	.103	.133	.078	.083	.042	.042	.034	-.078	.039
Heart Diameter	.050	.122*	.123*	.139*	.282**	.076	.233**	.252**	.188**	.216**	.160*	.283*
Biacromial Diameter	.038	.064	.030	.086	.022	.265**	.162**	.174**	.089	.111	.018	.232*
Bicristal Diameter	-.053	.086*	.082	-.013	.107	.103	.126**	.118**	.134**	.161*	.128	.178
Cardiac-thoracic Ratio	.069	.081	.105*	.107	.222**	-.009	.152**	.161**	.095*	.108	.042	.167
Relative Weight	.195**	.225**	.230**	.248**	.314**	.127	.188**	.314**	.235**	.251**	.218**	.114
Systolic Blood Pressure	.083	.199**	.072	.131*	.086	-.007	.066	.211**	.167**	.083	-.048	.081
Diastolic Blood Pressure	.046	.164**	.134	.128*	.023	-.056	.142**	.260**	.174**	.148**	-.068	.057
Triceps Skinfold	.201**	.069	.015	.058	.118	.127	.146**	.343**	.102*	.254**	.170*	.157
Subscapular Skinfold	.156**	.168**	.066	.124	.278**	.293**	.241**	.377**	.143**	.259**	.190*	.188
Forced Expiratory Volume	.047	-.016	-.065	-.034	.035	.185	-.018	-.021	-.030	-.091	.081	-.215
1 Hour Glucose Tolerance	.046	.008	-.054	-.069	.018	.026	-.019	.069	.061	.107*	.059	-.183

[a]From unpublished data by statistical staff of TCHS.

*$P \leq .05$.

**$P \leq .01$.

TABLE V.27

REGRESSION COEFFICIENT AND CORRELATION COEFFICIENT
OF OBSERVED SUA ON RELATIVE WEIGHT
BY AGE AND SEX

Males			Females		
Age	r	b	Age	r	b
20-29	.195	.01987	20-29	.188	.01425
30-39	.225	.0225	30-39	.314	.0194
40-49	.230	.02168	40-49	.235	.0164
50-59	.248	.0258	50-59	.251	.0189
60-69	.314	.0299	60-69	.218	.0177
70-79	.127	.01311	70-79	.114	.0071

TABLE V.28

REGRESSION COEFFICIENT AND CORRELATION COEFFICIENTS
OF OBSERVED SUA ON WEIGHT
BY AGE AND SEX

Males			Females		
Age	r	b	Age	r	b
20-29	.144	.0161	20-29	.241	.021256
30-39	.198	.0194	30-39	.340	.028832
40-49	.217	.0216	40-49	.230	.0175950
50-59	.228	.0246	50-59	.270	.0238410
60-69	.290	.0308	60-69	.222	.0224886
70-79	.217	.0239	70-79	.224	.0211232

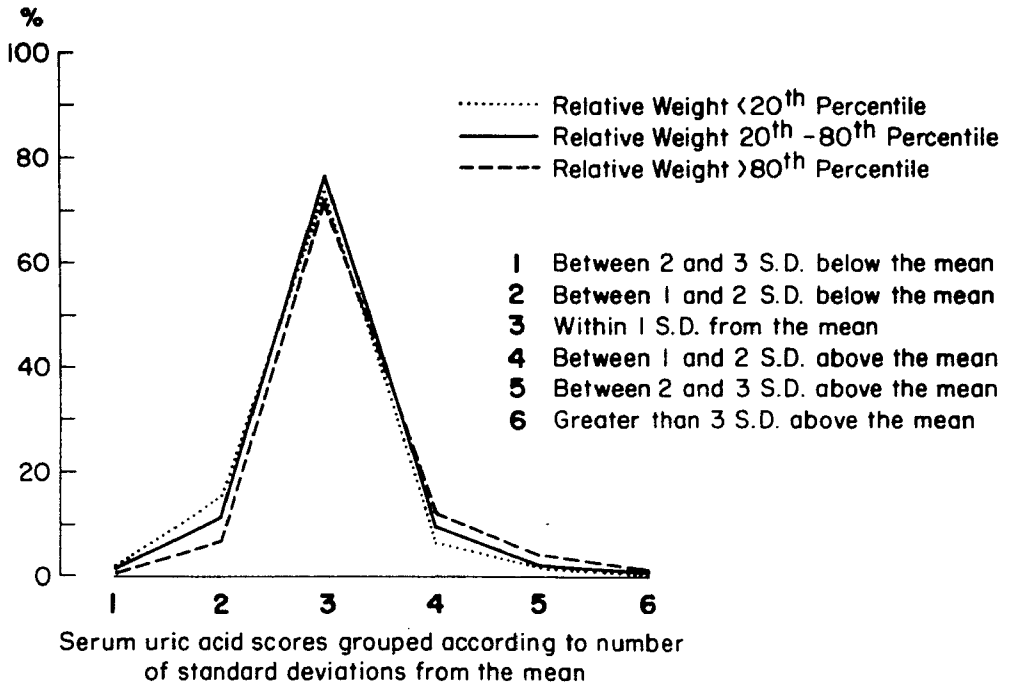


Fig. V.19 Percent Distribution of Percentile Rank in Relative Weight in Males Grouped According to the Number of Standard Deviations from the Mean in Serum Uric Acid Scores.

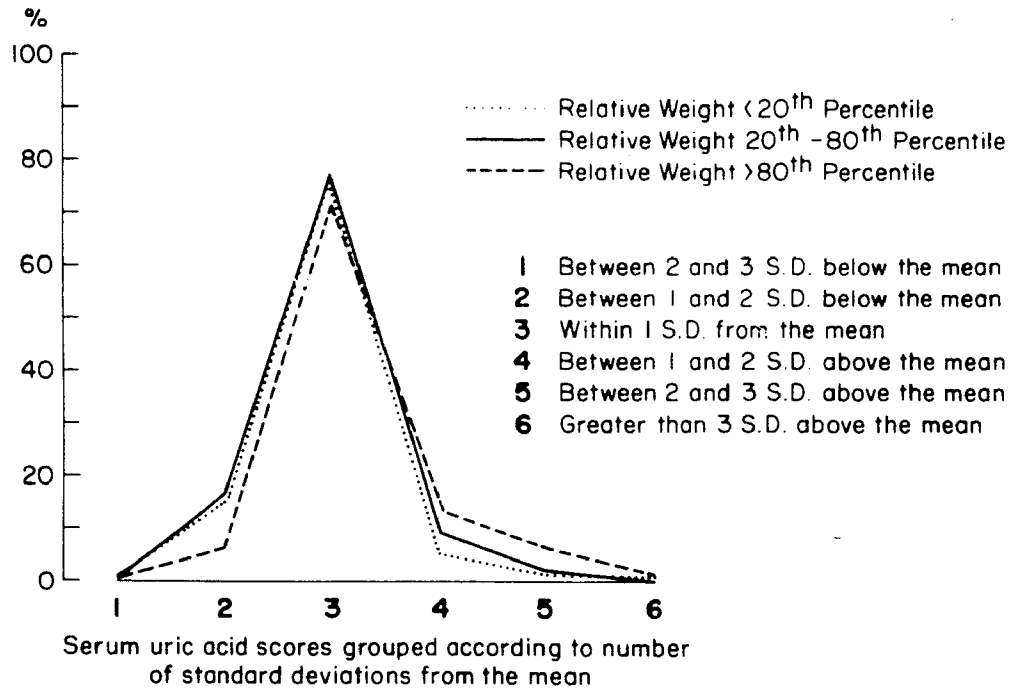


Fig. V.20 Percent Distribution of Percentile Rank in Relative Weight in Females Grouped According to the Number of Standard Deviations from the Mean in Serum Uric Acid Scores.

who were below the 20th percentile in relative weight. Conversely there was a higher per cent of subjects with serum uric acid scores one or more standard deviations below the mean (groups 1 and 2) among those who were below the 20th percentile in relative weight.

In order to determine if the association between serum uric acid and relative weight occurs only in those subjects with extremely high or low values in relative weight, the mean serum uric acid scores were computed by relative weight units for all subjects above the 80th percentile and all those below the 20th percentile in relative weight. This is shown in Table V.29.

There was a difference between the SUA scores of subjects below the 20th percentile compared to those above the 80th percentile in relative weight. However, this difference was not due to a few individuals within each group with outlying values in both relative weight and SUA scores. There was no consistent increase in mean serum uric acid score with increase in relative weight within each of these percentile groups.

Since the greatest difference in relative weight values has been shown, in this study, to occur between hypouricemic and hyperuricemic probands, then a study of the relative weights and serum uric acid scores of the immediate family members of these two groups should be of some value in assessing the role of relative weight in the familial aggregation of serum uric acid scores.

The relative weights of subjects with SUA scores 7.6 mg./100 ml. or greater were compared with the relative weights of subjects with SUA scores $\leq$ 2.4 mg./100 ml. The mean relative weight of the hyperuricemic

TABLE V.29

MEAN SERUM URIC ACID SCORES FOR SUBJECTS, ALL AGES, ABOVE THE 80TH AND BELOW THE 20TH PERCENTILE IN RELATIVE WEIGHT BY SEX

Relative Weight Percentile	Relative Weight	Males		Females	
		Mean SUA	N	Mean SUA	N
Below 20th Percentile	<80	4.01	63	4.12	89
	80- 84	4.20	117	4.22	177
	85- 89	4.28	262	4.33	268
	90-100	4.31	157	4.21	81
Total	< 100	4.25	599	4.25	615
Above 80th Percentile	105-114	4.59	140	4.77	88
	115-119	4.71	161	4.68	118
	120-124	4.71	117	4.82	112
	124-129	5.02	86	4.90	93
	130-134	4.80	37	4.91	60
	135-139	4.84	17	5.58	26
	140-144	5.22	9	4.97	27
	145-149	4.88	6	5.56	8
	≥ 150	4.24	11	4.81	26
Total	≥ 105	4.75	584	4.86	558

subjects was significantly higher ($P \leq 0.01$) than the mean relative weight of the hypouricemic probands. Because relative weight values gradually increase with age up to the age of 60 years when they begin to decrease, the age distribution of the two groups of probands was examined to determine if the ages of the probands might be responsible for the observed differences in their relative weight values. However, the age destribution was such that one would have expected the hypouricemic probands to have higher relative weight values than the hyperuricemic probands. Since the converse was observed, the difference in relative weight values between hyper- and hypouricemic probands should be considered independent of age. The mean SUA score of the immediate family members of the hyperuricemic probands was significantly higher than the SUA score mean for the immediate family members of the hypouricemic probands ($P \leq 0.05$) but the difference in the mean relative weights between these two groups failed to yield significance. These results are shown in Table V.30.

An association was found between body surface and serum uric acid by O'Brien et al.[48] in their study in the Pima and Blackfeet Indians. Attention was not given to body surface in the present study because the precision of the present method for measuring body surface is questionable. It was felt that a study of the association between serum uric acid and body surface should be postponed until such time that a more precise measurement is available for body surface.

TABLE V.30

STUDENT'S T TEST--COMPARING MEAN RELATIVE WEIGHT OF HYPERURICEMIC PROBANDS WITH THAT OF HYPOURICEMIC PROBANDS

$$t_{(n_1 + n_2 - 2)} = \frac{\bar{X}_1 - \bar{X}_2}{\sqrt{\frac{s_p^2}{n_1} + \frac{s_p^2}{n_2}}}$$

Relative Weight Values Hyperuricemic Probands	Relative Weight Values Hypouricemic Probands
$\bar{X}_1 = 108$	$\bar{X}_2 = 97.2$
$s_1^2 = 2.15$	$s_2^2 = 1.91$
$n_1 = 43$	$n_2 = 60$

$$t_{(n_1 + n_2 - 2)} = \frac{108 - 97.2}{\sqrt{\frac{2.00}{43} + \frac{2.00}{60}}} = 2.713^{**}$$

**Significant at $P \leq .01$.

STUDENT'S T TEST--COMPARING MEAN SERUM URIC ACID SCORES OF IMMEDIATE FAMILY MEMBERS OF HYPERURICEMIC PROBAND WITH IMMEDIATE FAMILY MEMBERS OF HYPOURICEMIC PROBANDS

Serum Uric Acid Score Values of Family Members of Hyperuricemic Probands	Serum Uric Acid Score Values of Family Members of Hypouricemic Probands
$\bar{X}_1 = 4.88$	$\bar{X}_2 = 3.92$
$s_1^2 = 1.1$	$s_2^2 = 1.63$
$n_1 = 33$	$n_2 = 39$

$$t_{(n_1 + n_2 - 2)} = \frac{4.88 - 3.92}{\sqrt{\frac{1.41}{33} + \frac{1.41}{39}}} = 2.44^{*}$$

*Significant at $P \leq .05$

TABLE V.30--(CONTINUED)

STUDENT'S T TEST--COMPARING MEAN RELATIVE WEIGHT OF IMMEDIATE FAMILY MEMBERS OF HYPERURICEMIC PROBAND WITH MEAN RELATIVE WEIGHT OF IMMEDIATE FAMILY MEMBERS OF HYPOURICEMIC PROBANDS

Relative Weight Values of Immediate Family Members of Hyperuricemic Probands	Relative Weight Values of Immediate Family Members of Hypouricemic Probands
$\bar{X}_1 = 97.1$	$\bar{X}_2 = 102$
$s_1^2 = 1.0309$	$s_2^2 = 1.69$
$n_1 = 33$	$n_2 = 39$

$$t_{(n_1 + n_2 - 2)} = \frac{102 - 97.1}{\sqrt{\frac{1.33}{33} + \frac{1.33}{39}}} = 1.80$$

Not significant

CHAPTER VI

DISCUSSION

A. Interpretation of Findings

This study fails to support the findings of early investigators such as Smyth et al. who concluded that hyperuricemia was inherited as a simple monofactorial dominant in which only a portion of the heterozygotes manifested the trait. It also fails to corroborate the findings of Stetcher et al. that hyperuricemia and gout are dominant with varying penetrance in some families and recessive with varying penetrance in others.

It is an accepted genetic principle that monogenic traits are discontinuous and the distribution of discontinuous traits usually show bimodality. The metric character of serum uric acid casts doubt on the hypothesis of monogenic inheritance in hyperuricemia. The distribution of serum uric acid levels in the study population of Tecumseh as shown in Chapter IV suggests a continuous unimodal curve with slight skewness at high values. Such continuous variation cannot be explained on the basis of single genes but must, if the trait is hereditary, depend on the combined action of a number of genes. However, the observation of a continuous bell shaped curve for the total population does not rule out the possibility that bimodality may be present in the tails of the

distribution due to the presence of single rare genes with overriding effects.

The study of the kindreds of hyperuricemic, hypouricemic and gout probands may be viewed as a study of the individuals who constitute the tails of the distribution. Although there was significant aggregation of low serum uric acid levels in the relatives of probands with hypouricemia, there was no significant aggregation of high serum uric acid levels or gout in the relatives of probands with hyperuricemia and gout. The distribution of the serum uric acid scores of these relatives as shown in Figures VI.1, VI.2, and VI.3 fail to show evidence of bimodality by inspection. The observation of a continuous unimodal curve for SUA scores both in the population as a whole and in the relatives of hyperuricemic and gout probands substantiates the finding of O'Brien et al. in their study of SUA levels in Pima and Blackfoot Indians.[48] There are three possible reasons for this continuous variation: the simultaneous segregation of many genes affecting the serum uric acid level, the superimposition of truly continuous variation arising from nongenetic causes or the interaction of both of these factors.

In multifactor inheritance many genes are acting additively or nonadditively to produce the observed phenotype. On the average half of the genes are making the sibling or parent just like the subject while half are making them no more like the subject than would be an unrelated person. When a trait is determined wholly by multifactorial inheritance the regressions between parent and offspring are the same as the proportion of genes in common.[55] This is only true for large numbers

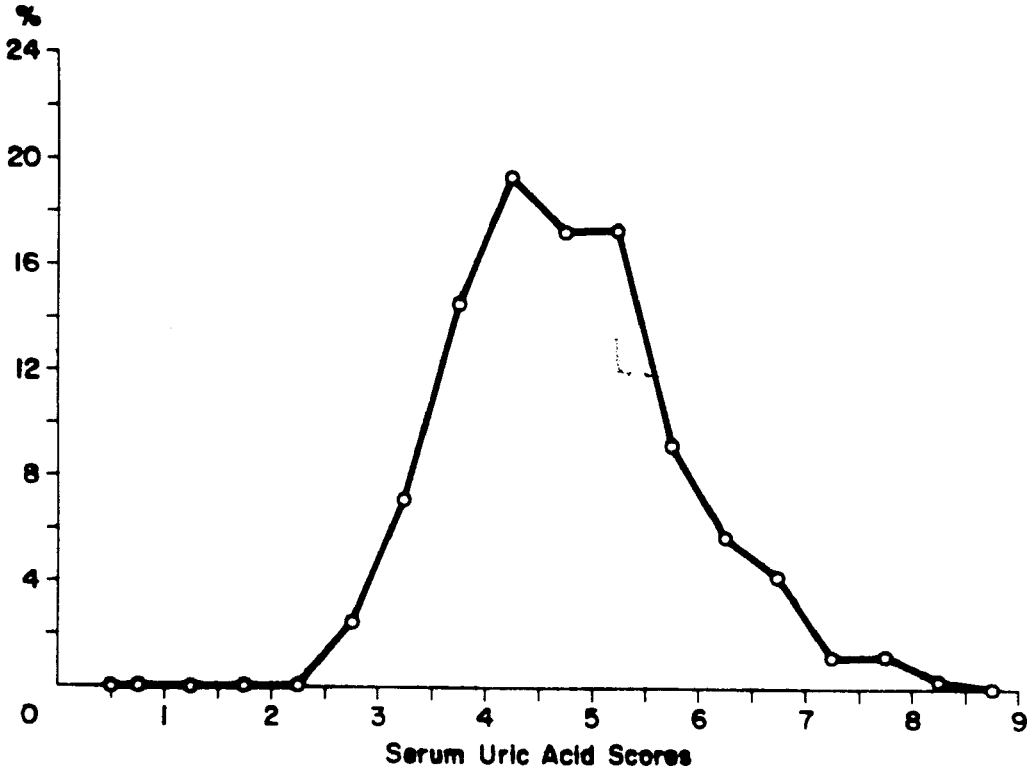


Fig. VI.1 Distribution of Serum Uric Acid Scores of Relatives of Probands with Hyperuricemia.

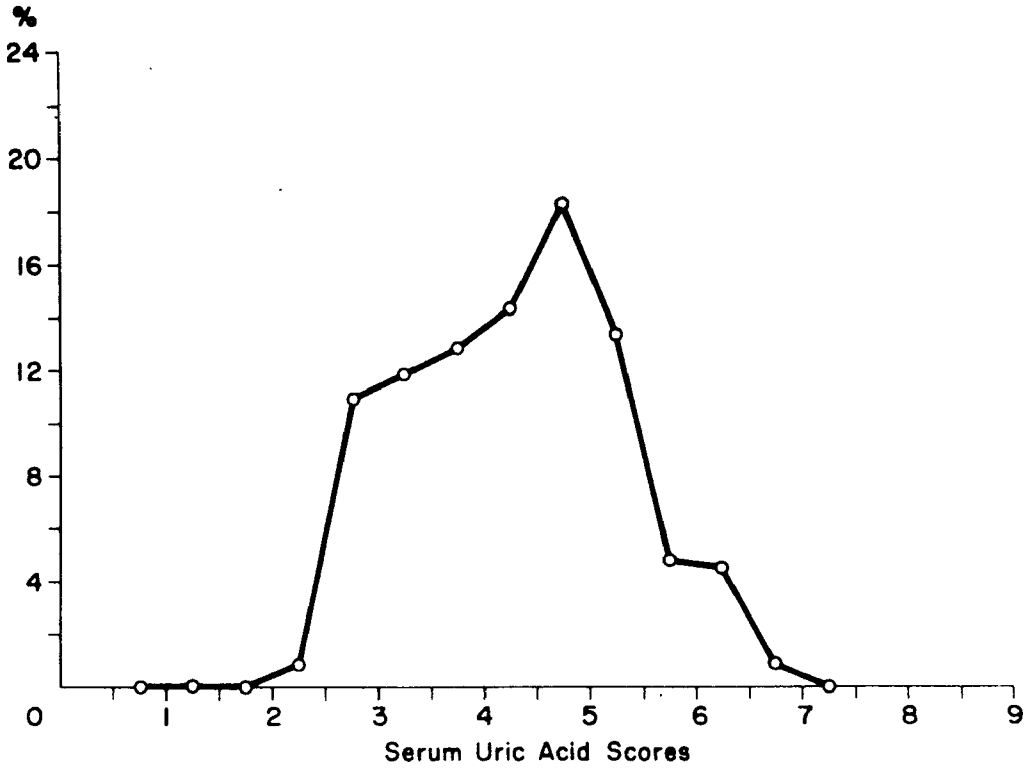


Fig. VI.2 Distribution of Serum Uric Acid Scores of Relatives of Probands with Hypouricemia.

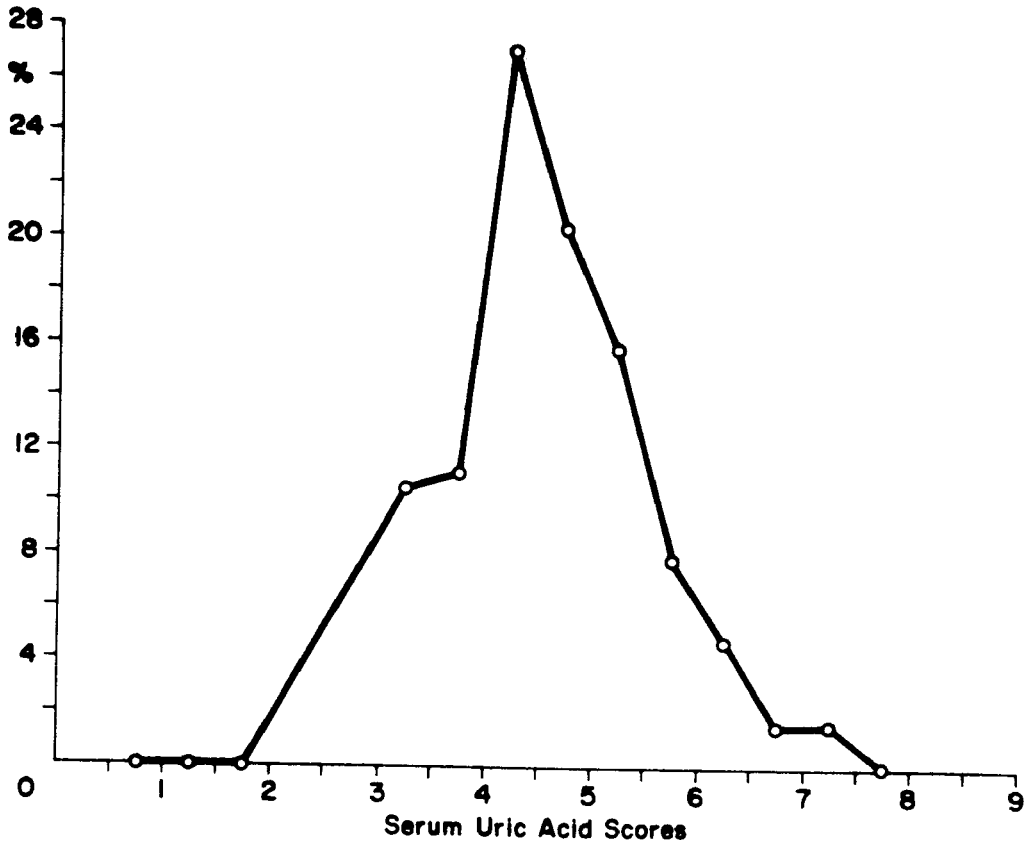


Fig. VI.3 Distribution of Serum Uric Acid Scores of Relatives of Probands with Gout.

of additive, nonlinked genes when the gene pairs do not display dominance or epistasis. The heritability of a metric character is an expression of the total variance that is attributable to the average effects of genes. In this study the estimates of heritability based on the regression of a child's SUA score on the mid parent SUA score is 28.5 per cent for sons and 33.8 per cent for daughters. These two estimates are not significantly different from each other and they do not deviate significantly from the expected value of 50 per cent for multifactorial inheritance. These tests of significance are shown in Appendix Table A.33.

If genes were present with any degree of dominance or epistasis, then one would expect the interaction of the parents' SUA scores to contribute significantly to the regression of the child's SUA score on his parents' SUA score. In order to test this, a regression analysis was computed of the form $a + b_1x_1 + b_2x_2 + b_3x_1x_2$ where x_1 is the serum uric acid score of the father and x_2 is the serum uric acid score of the mother. This computation indicated that the product term (x_1x_2) did not contribute significantly to the regression. The implication of this result is that genetic factors are additive with no evidence for dominance or epistasis in the gene pairs.

Although these data support the hypothesis of multifactorial inheritance with additive gene action, the influence of nongenetic factors must also be given due consideration in these findings.

In the intraclass correlation of SUA scores in sibships aged 0 to 15, 16 to 39, and 40 and over, there was a decrease in the intraclass correlation with increase in age. Possible explanations for this finding may be that the older sibship group represents siblings that are

in large measure living in different households and thus exposed to different environmental factors or it may be a reflection of the increased incidence of secondary conditions influencing the serum uric acid with increase in age which would tend to offset the association in siblings due to genetic factors. The intraclass correlation for ages 16 to 39 based on siblings living in the same or different households helps clarify which of these explanations is most plausible. The intraclass correlation for siblings living in the same household was 0.39 with an F test significant at $P \leq 0.01$ while that for nonhousehold sibships was 0.098 with a nonsignificant F test. These results indicate that environmental factors influence the serum uric acid and the degree of association is greater in siblings who are exposed to similar environments.

If environmental factors alone were responsible for determining the serum uric acid level and if spouse pairs share an environment which is similar, then one would expect the degree of association of SUA scores in spouse pairs to be comparable to that of siblings who share similar environments. One would also expect the length of time of exposure to the common environment to influence the degree of association in spouse pairs. Information on the length of time married was not available on the study subjects but the age of the wife was used as an approximation of the length of time married. It was possible to use age of wife in this way because the SUA score standardizes for age. The correlation coefficients of spouse pairs were much lower than the intraclass correlation of siblings who shared similar environments. The highest correlation coefficients for spouse pairs was 0.12 whereas the intraclass correlation coefficient for siblings who shared the same household

was 0.39. A test for homogeneity failed to show any significant differences in the correlation coefficients of spouse pairs by age of the wife. If the exact length of time of marriage had been known a more powerful test could have been used here. This would have consisted of computing a regression of the difference in serum uric acid scores between spouse pairs on length of time married. If the length of exposure to a common environment influenced the serum uric acid then one would expect the differences in scores between spouse pairs to decrease with increased length of marriage and this would result in a negative regression coefficient. Although there are certain limitations in the analysis of spouse pairs, the results of the analysis provide sufficient evidence to support the argument that environment alone is not responsible for determining the serum uric acid level but rather there appears to be an interaction between genetic and environmental factors.

The analysis of variance based on sibships grouped into superfraternities helps provide some measure of the contribution of each of these factors. If a genetic trait is influenced by environmental factors there is a component of environmental variance that contributes to the variance between means of families but not to the variance within families who share a common environment. When sibships are grouped into superfraternities, the superfraternity represent all the children, related and unrelated, whose parents have a common combination of serum uric acid scores. Since environmental factors are influencing the serum uric acid scores, one may assume that those groups of parents with similar scores reflect families that are exposed to similar environments. The superfraternity grouping then minimizes the variance between means

of families due to the environmental component and the children within each superfraternity are assumed to be similar with respect to the environmental component and parental phenotype. There are certain limitations in the underlying assumptions in this analysis. Not all siblings in a fraternity share the same household as their parents. However, the major portion of those families in TCHS in which both mother and father and their offspring have serum uric acid determinations represent younger families living in the same household. The assumption that similar phenotypes in unrelated persons indicates exposure to similar environments certainly is subject to some error. In light of the limitations underlying the analysis of variance based on superfraternities, the components of variance arising from such analysis should be viewed, at best, as approximations of the contribution of environmental and genetic factors to the serum uric acid level.

The major source of variation within a fraternity represents individual differences due to gene segregation and the among fraternity variation is attributed to differences due to the expression of genotypes, while the variation among superfraternities represents largely differences due to the environmental component. The components of variance in this analysis were: within fraternity variation 0.77, variation between fraternities within superfraternities 0.12 and variation among superfraternities 0.09. The implication of this finding is that in the interaction between genetic and environmental factors, the genetic component is playing a larger role than the environmental component in determining the serum uric acid of an individual.

Attempts at identifying the nongenetic factors which might be contributing to the familial aggregation of serum uric acid levels were based on those variables which showed the strongest association with SUA levels among the fourteen variables tested as shown in Table V.26 of Chapter V. Only the correlation coefficients of weight and relative weight were thought sufficiently large to warrant further consideration of those variables. Relative weight was singled out for study because it represents a measure of the weight which in part is corrected for body size.

Since the greatest difference in both serum uric acid scores and relative weight values appeared between hyperuricemic and hypouricemic probands, it seemed reasonable to assume that if relative weight were contributing to familial aggregation then the immediate family members of these two groups of probands would also show significant differences between both SUA scores and relative weight values. The analysis showed these two groups of relatives were significantly different with respect to their serum uric acid scores but there was no significant difference in their relative weights. The interpretation of this result is that the familial aggregation of SUA scores is independent of relative weight and presumably independent of weight.

The higher rate of association of serum uric acid in mothers and daughters (r.239) as compared to that of father and sons (r.128) raises the question of possible sex linkage. In order to support the argument for sex linkage the rate of association in fathers and daughters should be comparable to that of mothers and daughters since females get their sex linked genes equally from fathers and mothers while males get their

sex linked genes only from their mothers. However, the observations in this study fail to support this argument. The correlation coefficients of fathers and daughters was only .171 and that for mothers and sons was only slightly larger than that for fathers and sons (r.143).

In the absence of other evidence for sex linkage, these observed sex differences in transmission of a serum uric acid trait suggest maternal influences in such things as dietary habits. Since the mother usually prepares the food for her family, it is reasonable to assume that she influences the eating habits of her children more than the father who is out of the home part of the time. Daughters no doubt adopt many of the cooking habits of their mothers and maintain the same eating patterns even after they leave home while sons are subjected more to the cooking habits of others and thus would be less apt to maintain the same food habits as their mothers. The role of diet as a factor in influencing the serum uric acid deserves further study.

The implications of the findings in this study suggest that the serum uric acid level is determined by multifactorial inheritance with additive gene action which is interacting with certain environmental factors to produce the observed phenotype.

B. Limitations of the Study

A major limitation of this study was the inability to screen subjects more closely for secondary conditions which influence the SUA level. As mentioned previously, there was a significant number of low serum uric acid scores in the relatives of hypouricemic probands but there was not a significant number of high serum uric acid scores in

the relatives of probands with hyperuricemia and gout. In the absence of differences in the numbers of household and nonhousehold members within each of these three groups, the most plausible explanation for the failure to observe significant aggregation in relatives of hyperuricemia and gout probands is that many of these probands may have secondary hyperuricemia and gout. No attempt was made to follow up on relatives of these probands who reside outside of Tecumseh. It may well be that some cases of gout and hyperuricemia in relatives were missed because of this. Although this study failed to show evidence for the action of rare single dominant or recessive genes in hyperuricemia and gout, the existence of such genes cannot be completely ruled out until further studies are carried out in a group comprised solely of individuals with a confirmed diagnosis of primary hyperuricemia and gout.

Another limitation of this study is that observations are based on a single measurement taken at one point in time. Although the score standardizes for differences in age and sex it is not known if an individual maintains the same relative position in his age-sex group throughout life or if his position shifts with time. It may be that children resemble parents with respect to serum uric acid levels only after they reach a certain age. The prospective nature of the Tecumseh Community Health Study hopefully will provide additional information along these lines in future studies.

SUMMARY

A study of familial aggregation of serum uric acid levels was made on 6,000 study subjects from the Tecumseh Community Health Study, Tecumseh, Michigan 1959-1960. These 6,000 subjects represent a natural population without prior selection for either hyperuricemia or gout. A measurement which standardizes for both age and sex was used in the analyses and is referred to as the serum uric acid score. Subjects thought to have secondary hyperuricemia and gout were removed from the study but limited information permitted only a coarse screening of such subjects.

The distribution curve of serum uric acid scores for all male and female subjects aged four years and over is continuous with no suggestion of bimodality.

There was significant aggregation of low serum uric acid scores in relatives of probands with hypouricemia (scores ≤ 2.4) but there was no suggestion of bimodality in the distribution curves of these relatives.

There was no significant aggregation of high serum uric acid scores in the relatives of probands with hyperuricemia (SUA scores ≥ 7.1). The distribution of the SUA scores of these relatives showed no evidence for bimodality.

There was no significant aggregation of gout or high SUA scores in the relatives of probands with gout and there was no evidence of

bimodality in the distribution curve based on the SUA scores of these relatives.

The estimate of heritability of SUA scores on mid parent is 28.6 per cent for sons and that for daughters is 33.8 per cent. These estimates are not significantly different from the expected value for multifactorial inheritance.

Analysis of the data indicates the gene action to be additive with no suggestion of dominance or epistasis in the gene pairs.

There is evidence for interaction between genetic and environmental factors and the data suggest that genetic factors may play a larger role than environmental factors in determining the serum uric acid plenotype.

Of fourteen variables correlated with SUA levels only that of weight and relative weight showed an association strong enough to warrant further consideration. Subsequent analysis suggested that the familial aggregation of SUA levels was independent of relative weight and presumably independent of weight.

The highest degree of correlation of parents and offspring was found in mothers and daughters. The data failed to support the argument that this was due to sex linkage.

The findings in this study suggest that multifactorial inheritance with additive gene action is interacting with certain environmental factors to produce the serum uric acid phenotype. There is no evidence in this study to suggest the action of rare dominant or recessive genes in hyperuricemia and gout.

APPENDIX

TABLE A.1

NUMBER AND PER CENT OF SONS AND DAUGHTERS OF FEMALE HYPERURICEMIC PROBANDS WITH SUA SCORES OF 5.6-7.0 OR 2.5-3.4 mg. BY SEX OF RELATIVES

Sons				Daughters				Number per Family		
Total with SUA Scores	SUAS	N	%	Total with SUA Scores	SUAS	N	%	One Son	One Daughter	Two Daughters
20	2.5-3.4	3	20.0	27	2.5-3.4	2	7.2	3	1	0
	5.6-7.0	3	20.0		5.6-7.0	9	37.4	3	6	3

TABLE A.2

NUMBER AND PER CENT OF SONS AND DAUGHTERS OF MALE HYPERURICEMIC PROBANDS WITH SUA SCORES OF 5.6-7.0 OR 2.5-3.4 mg.

Sons				Daughters				Number per Family		
Total with SUA Scores	SUAS	N	%	Total with SUA Scores	SUAS	N	%	One Son	One Daughter	Two Daughters
8	2.5-3.4	0	0.0	9	2.5-3.4	0	0.0	0	0	0
	5.6-7.0	4	50.0		5.6-7.0	2	22.0	3	1	1

TABLE A.3

NUMBER AND PER CENT OF SONS AND DAUGHTERS OF MALE AND FEMALE HYPERURICEMIC PROBANDS WITH SUA SCORES of 5.6-7.0 OR 2.5-3.4 mg.

Sons				Daughters				Number per Family		
Total with SUA Scores	SUAS	N	%	Total with SUA Scores	SUAS	N	%	One Son	One Daughter	Two Daughters
28	2.5-3.4	3	10.7	36	2.5-3.4	2	5.6	3	1	0
	5.6-7.0	7	25.0		5.6-7.0	11	30.2	6	8	3

TABLE A.4

NUMBER AND PER CENT OF SIBLINGS OF MALE HYPERURICEMIC PROBANDS WITH SUA SCORES OF 5.6-7.0 mg. AND 2.5-3.4 mg.

Brothers				Sisters				Total Siblings			
Total with SUA Scores	SUAS	N	%	Total with SUA Scores	SUAS	N	%	Total with SUA Scores	SUAS	N	%
2	2.5-3.4	0	0.0	9	2.5-3.4	2	22.2	11	2.5-3.4	2	18.2
	5.6-7.0	0	0.0		5.6-7.0	2	22.2		5.6-7.0	2	18.2

TABLE A.5

NUMBER AND PER CENT OF SIBLINGS OF FEMALE HYPERURICEMIC PROBANDS WITH SUA SCORES OF 5.6-7.0 mg. AND 2.5-3.4 mg.

Brothers				Sisters				Total Siblings			
Total with SUA Scores	SUAS	N	%	Total with SUA Scores	SUAS	N	%	Total with SUA Scores	SUAS	N	%
14	2.5-3.4	1	17.1	17	2.5-3.4	0	0.0	21	2.5-3.4	1	4.8
	5.6-7.0	5	35.6		5.6-7.0	3	17.7		5.6-7.0	8	38.0

TABLE A.6

NUMBER AND PER CENT OF MOTHERS AND FATHERS OF MALE HYPERURICEMIC PROBANDS WITH SUA SCORES 5.6-7.0 mg. AND 2.5-3.4 mg.

Mother				Father				Both Parents 5.6 - 7.0
Total with SUA Scores	SUAS	N	%	Total with SUA Scores	SUAS	N	%	
7	2.5-3.4	0	0.0	6	2.5-3.4	1		1
	5.6-7.0	0	0.0		5.6-7.0	1		

TABLE A.7

NUMBER AND PER CENT OF MOTHERS AND FATHERS OF FEMALE HYPERURICEMIC PROBANDS WITH SUA SCORES 5.6-7.0 mg. AND 2.5-3.4 mg.

Mothers				Fathers				One Parent High, One Parent Low
Total with SUA Scores	SUAS	N	%	Total with SUA Scores	SUAS	N	%	
12	2.5-3.4	4	33.3	15	2.5-3.4	1	6.6	1
	5.6-7.0	3	25.0		5.6-7.0	4	26.3	

TABLE A.8

NUMBER AND PER CENT OF MOTHERS AND FATHERS OF HYPERURICEMIC PROBANDS WITH SUA SCORES OF 5.6-7.0 AND 2.5-3.4 mg.

Mothers				Fathers				Both Parents 5.6 - 7.0	One Parent 2.5-3.4 One Parent 5.6-7.0
Total with SUA Scores	SUAS	N	%	Total with SUA Scores	SUAS	N	%		
19	2.5-3.4	4	21.0	21	2.5-3.4	2	9.5	1	1
	5.6-7.0	3	15.8		5.6-7.0	5	23.4		

TABLE A.9

NUMBER AND PER CENT OF COUSINS OF HYPERURICEMIC PROBANDS WITH SUA SCORES OF 5.6-7.0 AND 2.5-3.4 mg. BY SEX

	Maternal	Paternal	SUAS	Maternal N	%	Paternal N	%	Total N	%
Total with SUA Scores 35	15	20	2.5-3.4	0	0.0	3	20.0	3	9.3
			5.6-7.0	6	35.0	4	29.6	10	34.9
Female Cousins with SUA Scores 20	9	11	2.5-3.4	0	0.0	0	0.0	0	0.0
			5.6-7.0	3	36.4	4	26.7	7	30.8
Male Cousins with SUA Scores 15	6	9	2.5-3.4	0	0.0	4	44.4	4	23.5
			5.6-7.0	0	0.0	3	33.3	3	41.2

TABLE A.10

NUMBER AND PER CENT OF GRANDSONS AND GRANDDAUGHTERS OF HYPERURICEMIC PROBANDS WITH SUA SCORES OF 5.6-7.0 mg. AND 2.5-3.4 mg.

Grandsons				Granddaughters			
Total with SUA Scores	SUAS	N	%	Total with SUA Scores	SUAS	N	%
12	2.5-3.4	3	25.0	7	3.5-3.4	2	35.0
	5.6-7.0	0	0.0		5.6-7.0	0	0.0

TABLE A.11

NUMBER AND PER CENT OF AUNTS AND UNCLES OF HYPERURICEMIC PROBANDS WITH SUA SCORES OF 5.6-7.0 mg. AND 2.5-3.4 mg.

		Uncles					
Total with SUA Scores	Maternal	Paternal	SUAS	Maternal N	Paternal N	Total N	%
16	3	13	2.5-3.4	0	1	1	6.3
			5.6-7.0	0	1	1	6.3
			Aunts				
14	9	5	2.5-3.4	1	0	1	100
			5.6-7.0	1	0	1	100

TABLE A.12

NUMBER AND PER CENT OF NIECES, NEPHEWS, GRANDNIECES, AND GRANDNEPHEWS OF HYPERURICEMIC PROBANDS WITH SUA SCORES OF 5.6-7.0 mg. AND 2.5-3.4 mg.

Nieces				Nephews				Grandniece				Grandnephew			
Total with SUA Scores	SUAS	N	%	Total with SUA Scores	SUAS	N	%	Total with SUA Scores	SUAS	N	%	Total with SUA Scores	SUAS	N	%
10	2.5-3.4	1	10.0	6	2.5-3.4	0	0	1	2.5-3.4	0	0	2	2.5-3.4	0	0
	5.6-7.0	0	0.0		5.6-7.0	0	0		5.6-7.0	1			5.6-7.0	0	

TABLE A.13

NUMBER AND PER CENT OF [illegible] SONS AND DAUGHTERS OF FEMALE HYPOURICEMIC PROBANDS WITH SUA SCORES OF 5.6-7.0 mg. AND 2.5-3.4 mg.

Sons				Daughters				Total Offspring			
Total with SUA Scores	SUAS	N	%	Total with SUA Scores	SUAS	N	%	Total with SUA Scores	SUAS	N	%
[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	2.5-3.4	3	27.3
									5.6-7.0	0	0.0

TABLE A.14

NUMBER AND PER CENT OF SONS AND DAUGHTERS OF MALE HYPOURICEMIC PROBANDS WITH SUA SCORES OF 5.6-7.0 mg. AND 2.5-3.4 mg.

Sons				Daughters				Total Offspring			
Total with SUA Scores	SUAS	N	%	Total with SUA Scores	SUAS	N	%	Total with SUA Scores	SUAS	N	%
12	2.5-3.4	2	16.6	19	2.5-3.4	6	31.6	31	2.5-3.4	8	25.8
	5.6-7.0	2	16.6		5.6-7.0	0	0.0		5.6-7.0	2	6.5

TABLE A.15

NUMBER AND PER CENT OF SONS AND DAUGHTERS OF HYPOURICEMIC PROBANDS WITH SUA SCORES OF 5.6-7.0 AND 2.5-3.4 mg.

Sons				Daughters				Total Offspring			
Total with SUA Scores	SUAS	N	%	Total with SUA Scores	SUAS	N	%	Total with SUA Scores	SUAS	N	%
18	2.5-3.4	5	31.5	24	2.5-3.4	6	25.0	43	2.5-3.4	12	27.9
	5.6-7.0	2	10.5		5.6-7.0	0	0.0		5.6-7.0	2	4.7

TABLE A.16

NUMBER AND PER CENT OF MOTHERS AND FATHERS OF MALE HYPOURICEMIC PROBANDS WITH SUA SCORES OF 5.6-7.0 mg. AND 2.5-3.4 mg.

Mothers				Fathers				Father and Mother Both 2.5-3.4	Mother Low Father High
Total with SUA Scores	SUAS	N	%	Total with SUA Scores	SUAS	N	%		
9	2.5-3.4	4	44.4	7	2.5-3.4	2	28.5	0	1
	5.6-7.0	0	0.0		5.6-7.0	1	14.3		

TABLE A.17

NUMBER AND PER CENT OF MOTHERS AND FATHERS OF FEMALE HYPOURICEMIC PROBANDS WITH SUA SCORES OF 5.6-7.0 mg. AND 2.5-3.4 mg.

Mothers				Fathers				Father and Mother Both 2.5-3.4	Mother Low Father High
Total with SUA Scores	SUAS	N	%	Total with SUA Scores	SUAS	N	%		
[illegible]	[illegible]	3	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	1	0
[illegible]	[illegible]	0	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]		

TABLE A.18

NUMBER AND PER CENT OF SIBLINGS OF MALE HYPOURICEMIC PROBANDS WITH SUA SCORES OF 5.6-7.0 mg. AND 2.5-3.4 mg.

Brother				Sister				Two Brothers 2.5-3.4	Two Sisters 2.5-3.4	Brother and Sister 2.5-3.4
Total with SUA Scores	SUAS	N	%	Total with SUA Scores	SUAS	N	%			
15	2.5-3.4	6	40.0	17	2.5-3.4	4	23.5	3	2	1
	5.6-7.0	1	6.3		5.6-7.0	0				

TABLE A.19

NUMBER AND PER CENT OF SIBLINGS OF FEMALE HYPOURICEMIC PROBANDS WITH SUA SCORES OF 5.6-7.0 mg. AND 2.5-3.4 mg.

Brother				Sister				None with more than one brother or sister
Total with SUA Scores	SUAS	N	%	Total with SUA Scores	SUAS	N	%	
6	2.5-3.4	0	0.0	7	2.5-3.4	1	14.3	
	5.6-7.0	0	0.0		5.6-7.0	0	0.0	

TABLE X.20

NUMBER AND PER CENT OF NIECES, NEPHEWS, GRANDNIECES, AND GRANDNEPHEWS OF HYPOURICEMIC PROBANDS WITH SUA SCORES OF 5.6-7.0 mg. AND 2.5-3.4 mg.

Nieces				Nephews				Grandnieces				Grandnephews			
Total with SUA Scores	SUAS	N	%	Total with SUA Scores	SUAS	N	%	Total with SUA Scores	SUAS	N	%	Total with SUA Scores	SUAS	N	%
16	2.5-3.4	4	25.0	11	2.5-3.4	0	0.0	2	2.5-3.4	2	100	4	2.5-3.4	0	0
	5.6-7.0	0	0.0		5.6-7.0	1	9.1		5.6-7.0	0	0		5.6-7.0	0	0

TABLE X.21

NUMBER AND PER CENT OF NIECES AND AUNTS OF HYPOURICEMIC PROBANDS WITH SUA SCORES OF 5.6-7.0 mg. AND 2.5-3.4 mg.

Nieces								Aunts					
Total with SUA Scores	Maternal	Paternal	SUAS	N	%	SUAS	N	%	Total with SUA Scores	Maternal	Paternal	SUAS	N	%
			2.5-3.4	4	57.1	2.5-3.4	4	57.1				2.5-3.4	4	57.1
			5.6-7.0	0	0.0	5.6-7.0	0	0.0				5.6-7.0	0	0.0

TABLE A.22

NUMBER AND PER CENT OF GRANDPARENTS OF HYPOURICEMIC PROBANDS WITH SUA SCORES OF 5.6-7.0 mg. AND 2.5-3.4 mg.

Grandfathers

Total with SUA Scores	Maternal	Paternal	SUAS	Maternal		Paternal		Total	
				N	%	N	%	N	%
4	3	1	2.5-3.4	0	0.0	0	0.0	0	0.0
			5.6-7.0	0	0.0	1	20.0	1	20.0

Grandmothers

3	2	1	2.5-3.4	0	0.0	0	0.0	0	0.0
			5.6-7.0	0	0.0	0	0.0	0	0.0

TABLE A.23

NUMBER AND PER CENT OF COUSINS OF HYPOURICEMIC PROBANDS WITH SUA SCORES OF 5.6-7.0 AND 2.5-3.4 mg.

	Maternal	Paternal	SUAS	Maternal N	%	Paternal N	%	Total N	%
Total with SUA Scores 22	15	7	2.5-3.4	3	20.0	4	57.1	7	31.8
			5.6-7.0	1	6.7	0	0.0	1	4.5
Female Cousins with SUA Scores 8	6	2	2.5-3.4	1	16.6	1	50.0	2	20.0
			5.6-7.0	0	0.0	0	0.0	0	0.0
Male Cousins with SUA Scores 14	9	5	2.5-3.4	2	22.2	3	60.0	5	35.7
			5.6-7.0	1	11.1	0	0.0	1	7.1

TABLE A.24

NUMBER AND PER CENT OF MOTHERS AND FATHERS OF GOUT PROBANDS WITH SUA SCORES OF 5.6-7.0 mg. AND 2.5-3.4 mg.

Mother				Father			
Total with SUA Scores	SUAS	N	%	Total with SUA Scores	SUAS	N	%
4	2.5-3.4	1	25.0	1	2.5-3.4	0	0.0
	5.6-7.0	1	25.0		5.6-7.0	0	0.0

TABLE A.25

NUMBER AND PER CENT OF SONS AND DAUGHTERS OF FEMALE GOUT PROBANDS WITH SUA SCORES OF 5.6-7.0 mg. AND 2.5-3.4 mg.

Sons				Daughters				Total Offspring			
Total with SUA Scores	SUAS	N	%	Total with SUA Scores	SUAS	N	%	Total with SUA Scores	SUAS	N	%
4	2.5-3.4	2	50.0	3	2.4-3.4	0		7	2.5-3.4	2	28.5
	5.6-7.0	0			5.6-7.0	1	33.3		5.6-7.0	1	14.2

TABLE A.26

NUMBER AND PER CENT OF SONS AND DAUGHTERS OF MALE GOUT PROBANDS WITH SUA SCORES OF 5.6-7.0 mg. AND 2.5-3.4 mg.

Sons				Daughters				Total Offspring			
Total with SUA Scores	SUAS	N	%	Total with SUA Scores	SUAS	N	%	Total with SUA Scores	SUAS	N	%
12	2.5-3.4	0	0.0	10	2.5-3.4	0	0.0	22	2.5-3.4	0	0.0
	5.6-7.0	3	25.0		5.6-7.0	3	30.0		5.6-7.0	6	27.2

TABLE A.27

NUMBER AND PER CENT OF SONS AND DAUGHTERS OF FEMALE GOUT PROBANDS WITH SUA SCORES OF 5.6-7.0 mg. AND 2.5-3.4 mg.

Sons				Daughters				Total Offspring			
Total with SUA Scores	SUAS	N	%	Total with SUA Scores	SUAS	N	%	Total with SUA Scores	SUAS	N	%
16	2.5-3.4	2	12.5	13	2.5-3.4	0	0.0	29	2.5-3.4	2	6.8
	5.6-7.0	3	18.7		5.6-7.0	4	30.8		5.6-7.0	7	24.1

TABLE A.28

NUMBER AND PER CENT OF SIBLINGS OF GOUT PROBANDS WITH SUA SCORES OF 5.6-7.0 mg. and 2.5-3.4 mg.

Brothers				Sisters				Total Siblings			
Total with SUA Scores	SUAS	N	%	Total with SUA Scores	SUAS	N	%	Total with SUA Scores	SUAS	N	%
6	2.5-3.4	0	0.0	3	2.5-3.4	0	0.0	9	2.5-3.4	0	0.0
	5.6-7.0	1	16.6		5.6-7.0	0	0.0		5.6-7.0	1	11.1

TABLE A.29

NUMBER AND PER CENT OF GRANDCHILDREN OF GOUT PROBANDS WITH SUA SCORES OF 5.6-7.0 mg. AND 2.5-3.4 mg.

Grandsons				Granddaughters			
Total with SUA Scores	SUAS	N	%	Total with SUA Scores	SUAS	N	%
[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	2	50.0
[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]

TABLE A.30

NUMBER AND PER CENT OF AUNTS AND UNCLES OF GOUT PROBANDS WITH SUA SCORES OF 5.6-7.0 mg. and 2.5-3.4 mg.

Uncles				Aunts			
Total with SUA Scores	SUAS	N	%	Total with SUA Scores	SUAS	N	%
1	2.5-3.4	0	0.0	1	2.5-3.4	0	0.0
	5.6-7.0	0	0.0		5.6-7.0	0	0.0

TABLE A.31

NUMBER AND PER CENT OF NIECES, NEPHEWS, GRANDNIECES, AND GRANDNEPHEWS OF GOUT PROBANDS WITH SUA SCORES OF 5.6-7.0 mg. AND 2.5-3.4 mg.

Nieces				Grandnieces				Nephew				Grandnephew			
Total with SUA Scores	SUAS	N	%	Total with SUA Scores	SUAS	N	%	Total with SUA Scores	SUAS	N	%	Total with SUA Scores	SUAS	N	%
7	2.5-3.4	0	0	1	2.5-3.4	0	0	4	2.5-3.4	0	0.0	4	2.5-3.4	2	50.0
	5.6-7.0	0	0		5.6-7.0	0	0		5.6-7.0	1	25.0		5.6-7.0	0	0.0

TABLE A.32

NUMBER AND PER CENT OF COUSINS OF GOUT PROBANDS
WITH SUA SCORES OF 5.6-7.0 mg. AND 2.5-3.4 mg.

Male Cousins				Female Cousins				Total Cousins			
Total with SUA Scores	SUAS	N	%	Total with SUA Scores	SUAS	N	%	Total with SUA Scores	SUAS	N	%
3	2.5-3.4	1		2	2.5-3.4	0	0.0	5	2.5-3.4	1	20.0
	5.6-7.0	0	0.0		5.6-7.0	0	0.0		5.6-7.0	0	0.0

TABLE A.33

STUDENT T TEST--TO TEST THE DIFFERENCE BETWEEN b_1 (SONS SUAS ON MIDPARENT SCORES) AND b_2 (DAUGHTERS SUAS ON MIDPARENT SCORES)

$$t = \frac{b_1 - b_2}{\frac{s^2_{S\cdot M}}{s^2_M(n-1)} + \frac{s^2_{D\cdot M}}{s^2_M(n_2-1)}} = \frac{.338 - .286}{\sqrt{\frac{1.127}{.5113} + \frac{.869}{.5788}}} = .0270 \text{ not significant}$$

STUDENT T TEST--TO TEST THE DIFFERENCE BETWEEN b_1 (SONS SUAS ON MIDPARENT SCORES) AND β (EXPECTED REGRESSION COEFFICIENT FOR MULTIFACTOR INHERITANCE) AND b_2 (DAUGHTERS SUAS ON MIDPARENT SCORES) and β (EXPECTED REGRESSION COEFFICIENT FOR MULTIFACTOR INHERITANCE)

$$\frac{b_1 - \beta}{\frac{s_{x\cdot y}}{s_x\sqrt{n-1}}} = \frac{.286 - .50}{1.48} = .108 \text{ not significant}$$

$$\frac{b_2 - \beta}{\frac{s_{x\cdot y}}{s_x\sqrt{n-1}}} = \frac{.338 - .50}{\sqrt{1.22}} = .175 \text{ not significant}$$

BIBLIOGRAPHY

BIBLIOGRAPHY

1. Cobb, S. The Prevention of Gout, American Journal of Public Health. 55:353-54, March 1965.

2. Barry, P. From a paper read by Barry at a meeting of the American Public Health Association in New York, October 8, 1964. Uric Acid, Gout and Coronary Heart Disease--Observations from the Framingham Study by Daubler, T., Barry, P. and Hall, A.

3. Wyngaarden, J. B. Intermediary Purine Metabolism and the Metabolic Defects of Gout, Metabolism. 6:245, 1957.

4. Sorenson, L. B. Degradation of Uric Acid in Man, Metabolism. 8:687-703, September 1959.

5. Sorenson, L. B. The Elimination of Uric Acid in Man Studied by Means of C-14 Labeled Uric Acid Uricolysis, Scandinavian Journal of Clinical Laboratory Investigation. 12(suppl. 54):1-214, 1960.

6. Harper, H. A Review of Physiological Chemistry. Ninth edition. Lange Medical Publication, 1963, pp. 291-94.

7. Cecil, R. and Loeb, R. A Textbook of Medicine. Tenth edition. Philadelphia, Pa.: W. B. Saunders Co., 1959, pp. 595-608.

8. Seegmiller, J. E., Howell, R. R. and Malawesta, S. E. The Inflammatory Reaction to Sodium Urate, Journal of the American Medical Association. 80:460-75, 1962.

9. Wyngaarden, J. B. The Metabolic Basis of Inherited Disease. Edited by Stanbury, J. B., Frederickson, D. S. and Wyngaarden, J. B. New York: McGraw-Hill, 1960, pp. 679-760.

10. Gutman, A. and Yu Ts'ai, F. Uric Acid Metabolism in Normal Man and Primary Gout, The New England Journal of Medicine. 273(6): July 29 and August 5, 1965.

11. Willoughby, L. and Rodan, G. Impairment of Uric Acid Excretion in Gout, Journal of Clinical Investigation. Vol. 41, 1955-1963, 1962.

12. Eisen, A. Z. and Seegmiller, J. E. Uric Acid Metabolism in Psoriasis, Journal of Clinical Investigation. 40:1486, 1961.

13. Krakoff, Irwin and Boles, M. Abnormalities of Purine Metabolism in Human Leukemia, Annals of New York Academy of Science. 1043-52, February 1964.

14. Talbot, J. H. Gout and Blood Dyscrasia, Medicine. 38:173,

15. Shapiro, J. B., Klineberg, J. R., Peck, W., Goldfinger, S. Seegmiller, J. E. Hyperuricemia Associated with Obesity and Intensified by Caloric Restriction, Arthritis and Rheumatism. 7:343, 1964.

16. Leiber, C., Jones, D., Losowsky, M. S. and Davidson, C. tionship of Uric Acid and Ethanol Metabolism in Man, Journal Clinical Investigation. 41:1863-69, 1962.

17. Alepa, F. P., Howell, R. R. and Seegmiller, J. E. The Occur of Glycogen Storage Disease with Tophaceous Gout, Arthritis Rheumatism. 5:634 (abstract 1962).

18. Leiper, R. D., Binua, R. S., Brener, J. L. and Rawson, Hyperuricemia in Myxedema, Journal of Clinical Endocrin 20:1457, 1960.

19. Yu, T. F., Berger, L. and Gutman, A. B. A study of Effects of Salicylate in Low Intermediate and High Do Renal Mechanisms for Excretion of Urate in Man, Journal Investigation. 38:1298, 1959.

20. Yu, T. F. and Gutman, A. B. Suppression of Tubular Urate by Pyrazinamide in the Dog, Proceedings of the Experimental Biology and Medicine. 107:905, 1961.

21. Healy, L. A., Magil, G. J. and Decker, J. L. Uric A Due to Hydrochlorothiazide, New England Journal of 1358, 1959.

22. Dollery, C. F., Duncan, H. and Sumner, B. Hyperuri to the Treatment of Hypertension, British Medical Jou 1960.

23. Bryant, J. M., Yu, T. F., Berger, L., Schwartz, M., Fletcher, L., Fertig, H., Schwarz, M. S. and Quan, R. uricemia Induced by the Administration of Chlorothiazide Other Sulfonamide diuratics, American Journal of Medic 1962.

24. Mintz, D. H., Canary, J. J., Cameron, G. and Kyle, L. H. uricemia in Hyperparathyroidism, New England Journal of 265:112, 1961.

25. Dubin, A., Kushner, D. S., Bronsky, D. and Pascale, L. R. Hyperuricemia in Hypoparathyroidism, Metabolism. 5:703, 1956.

26. Mertz, E. T., Fuller, R. W. and Concon, J. M. Serum Uric Acid in Young Mongoloids, Science. 141:535, 1963.

27. Berkowitz, D. Blood Lipid and Uric Acid Interrelationships, Journal of the American Medical Association. Vol. 190, Number 9, November 30, 1964.

28. Gertler, M. M., Garn, S. M. and Leving, S. A. Serum Uric Acid in Relation to Age and Physique in Health and in Coronary Heart Disease, Annals of Internal Medicine. 34:1421-31, 1951.

29. Beckett, A. G. and Lewis, J. G. Gout and Serum Uric Acid Values in Diabetes Mellitus, Quarterly Journal of Medicine. 29:443, 1960.

30. Herman, J. B. Gout and Diabetes, Metabolism. 7:707, 1958.

31. Lesch, M. and Nyhan, W. A Familial Disorder of Uric Acid Metabolism and Central Nervous System Function, American Journal of Medicine. Vol. 36, January-June, 1964.

32. Dunn, J. P., Brooks, G. W., Mausner, J., Rodnan, G. P. and Cobb, S. Social Class Gradient of Serum Uric Acid Levels in Males, Journal of the American Medical Association. 185:431-36, August 1963.

33. Galen, Claudius (quoted by Schmtker, M. A.). Opera Omnia. Editonem Curavit Carol Gottlieb Kuhn. Tomi 1-20, Leipsig 1821-33.

34. Sydenham, T. The Whole Works of that Excellent Practical Physician Dr. Thomas Sydenham. Translated by John Pechery. 7th ed. London, 1717.

35. Cadogan, William. A Dissertation on the Gout and All Chronic Diseases Jointly Considered. Boston: Henry Knox, 10th ed., 1772.

36. Schule, K. W. Examen Chemicism Calculi Urinarii Opuscula 11, 73. Leipsig, 1776.

37. Garrod, A. B., Med-Chir. Translated. London, 1841. The Nature and Treatment of Gout and Rhumatic Gout. London: Walton and Mayberly, 1859.

38. Folin, O. and Lyman, H. On the Influence of Phenylquinolin Carbonic Acid (Atophan) on Uric Acid Elimination, Journal of Pharmacology. 4:539, 1913.

39. Jacobson, B. M. Uric Acid in Serum of Gouty and Non-gouty Individuals; Its Determination by Folin's Recent Method and Its

Significance in the Diagnosis of Gout, Annals of Internal Medicine. 11:1277, 1938.

40. Talbot, J. H. Serum Urate in Relatives of Gouty Patients, Journal of Clinical Investigation. 19:645, 1940.

41. Smyth, C. J., Cotterman, C. W. and Freyberg, R. H. The Genetics of Gout Hyperuricemia--An Analysis of 19 Families, Journal of Clinical Investigation. 27:749, 1948.

42. Rakic, M., Valkenberg, H., Davidson, R., Engels, J., Mikkelsen, W., Neel, J. and Duff, I. Observations on the Natural History of Gout and Hyperuricemia, American Journal of Medicine. 37:862, 1964.

43. Neel, J., Rakic, M. T., Davidson, R. T., Valkenberg, H. A. and Mikkelsen, W. M. Studies on Hyperuricemia II. A Reconsideration of the Distribution of Serum Uric Acid Values in the Families of Smyth, Cotterman, and Freyberg, American Journal of Human Genetics. 17:14-21, January 1965.

44. Stecher, R. M., Hersch, A. H. and Solomon, W. M. Heredity of Gout and Its Relationship to Familial Hyperuricemia. Annals of Internal Medicine. 31:595, 1949.

45. Wilson, D., Collins, D. H. and Mason, R. M. Gout: Discussion Proceedings of the Royal Society of Medicine. 44:285, April 1951.

46. Hague, M. and Harvald, B. Heredity in Gout and Hyperuricemia, Acta Medica Scandinavica.

47. Popert, A. J. and Hewett, J. V. Gout and Hyperuricemia in Rural and Urban Populations, Annals of Rheumatic Diseases. 21:154, 1962.

48. O'Brien, W., Burch, T. and Bunim, J. Genetics of Hyperuricemia in Blackfeet and Pima Indians. (Unpublished paper)

49. Francis, T., Jr. Aspects of the Tecumseh Study, Public Health Reports. 76:963, Washington, 1961.

50. Napier, J. A. Field Methods and Response Rates in the Tecumseh Community Health Study, American Journal of Public Health. 52:208, 1962.

51. Epstein, F. H. Epidemiologic Research in Total Communities: Settings and Perspectives, Meth. Inform. in Med. 3:18, 1964.

52. Mikkelsen, W. M., Dodge, H. J. and Valkenberg, H. The Distribution of Serum Uric Acid Levels in a Population Unselected for Hyperuricemia or Gout, American Journal of Medicine. 39(2):242-51, August 1965.

53. Liddle, L., Seegmiller, V. E. and Laster, L. The Enzymat photometric Method for Determination of Uric Acid, Jour Laboratory and Clinical Medicine. 54:903-13, 1959.

54. Dodge, H. J. and Mikkelsen, W. M. The Relationship Acid Scores to Occupation, Smoking and Drinking Habi Michigan, 1959-1960. Presented in part at a panel the "Epidemiology of Gout" at the Annual Meeting of Public Health Association, New York City, October

55. Montoye, H., Epstein, F. and Kjelsberg, M. The Meas Fatness--A Study in a Total Community, American Jour Nutrition. Vol. 16, May 1965.

56. Falconer, D. S. Introduction to Quantitative Genet The Ronald Press, 1960.