THE GENETICS OF PHENYLPYRUVIC OLIGOPHRENIA.

(A CONTRIBUTION TO THE STUDY OF THE INFLUENCE OF HEREDITY ON MENTAL DEFECT.)

By GEORGE A. JERVIS, M.D., Ph.D.

From the Research Department of Letchworth Village, Thiells, New York.

(Received May 3, 1939.)

INTRODUCTION.

ALTHOUGH considerable attention has been devoted during the past years to the problems of the influence of heredity on mental deficiency, no final conclusions have yet been reached. It appears well established at the present time, first, that in a large percentage of cases, variously estimated at from 40 to 80%, mental deficiency is significantly determined by genetic mechanisms, and second, that recessive genes seem to play a considerable role in such mechanisms (Lokay, 1929; Brugger, 1930*a*; Smith, 1930; Luxemburg, 1931; Juda, 1934; Kreyenberg, 1935).

However, the value of studies which arbitrarily investigate mental deficiency as a whole is impaired by the consideration that mental deficiency is far from fulfilling the essential Mendelian postulate of a "unit character". Even when clearly exogenous types are carefully excluded and investigations are limited to the so-called primary forms, mental defect constitutes no entity in a biological sense. It consists, rather, of a group of heterogeneous conditions, differing essentially in ætiology, symptomatology and pathology. Hence, it is most likely that different genetic mechanisms operate in the various groups. The first requirement for any adequate approach to this problem, therefore, appears to consist of a painstaking clinico-pathological investigation aiming to separate clear-cut nosological entities so that each condition may be tested to Mendelian ratios.

A second obstacle to the study of heredity in mental deficiency lies in the difficulty of a rigorous identification, by means of exact criteria, of the character under study. In numerous investigations mental deficiency was a graded character, and the distinction between normal and affected individuals was determined according to an arbitrary policy, based upon psychological tests or sociological distinctions.

The Mendelian requirements of a rigorous selection and identification of a unit character have been adequately met in recent studies that bear witness to the variety of the mode of inheritance of mental defect. Thus, epiloia appears

to be determined by dominant genes (Penrose, 1934), amaurotic idiocy by a single recessive autosomal gene (Sjøgren, 1931 ; Slome, 1934), whereas in other particular types of oligophrenia two recessive genes are involved—a rare autosomal and a more common sex-linked gene (Sjøgren, 1932–35).

The present paper presents a genetic study of 200 cases of a recently recognized type of mental deficiency—"phenylpyruvic oligophrenia".

Fölling in 1934 reported the finding of phenylpyruvic acid in the urine of 10 mentally defective patients ; in 6 of these the condition was present in two members of the sibship. In 1935 Penrose, on the basis of a pedigree, suggested that the disease may be due to recessive genes. The present author (Jervis, 1937), basing his conclusion on a study of 50 cases, offered evidence for the hypothesis of a single recessive gene substitution.

The disease is characterized by an alteration of the metabolism of phenylalanine. There is strong evidence indicating that this amino-acid is not oxidized by the organism. An abnormally high amount of phenylalanine, in fact, is found in the blood. The phenylalanine is then transformed into phenylpyruvic acid mainly by the kidney, and this last acid is excreted in the urine. Clinically, the disease shows a fairly well-defined symptomatology. In the majority of cases anomalies of the motor system are demonstrable ; increase of the muscle tonus, hyperactivity of the deep reflexes, knee and ankle clonus, hyperkinetic and dyskinetic manifestations (athetotic and choreatic movements, tremors, etc.). Pronounced intellectual defect is present in all the cases ; in the present material, two-thirds of the patients were at the idiot, and one-third at the imbecile level.

This disease seems to fulfil the initial condition required by Mendelism, its biochemical characteristic constituting a unity in a biological sense. In the second place, the identification of the individual showing the character is made by exact laboratory methods, i.e., the test for phenylpyruvic acid. Thus, a very clear-cut difference can be drawn between affected and non-affected members of a family.

Material.

Cases of phenylpyruvic oligophrenia were collected in the following way : All the inmates of fourteen State Institutions for treatment and care of mental defectives were examined ; a sample of urine of each patient was tested for the presence of phenylpyruvic acid. The procedure consists of adding a few drops of a diluted solution of ferric chloride to the acidified urine ; in the positive cases a green colour results which gradually fades. When a case gave a positive result to the ferric chloride test, additional evidence was obtained with the more specific test of formation of 2 : 4 dinitrophenylhydrazone. This is secured by adding to 100 c.c. of filtered urine 300 mgrm. of 2 : 4 dinitrophenylhydrazine dissolved in 50 c.c. of hot 2N HCl. When phenylpyruvic acid is present there forms immediately a precipitate of its dinitrophenylhydrazone, which can be identified by its melting-point.

The inmates of the following institutions were examined : in the State of New York—Letchworth Village, Wassaic, Rome and Newark State Schools ; in the

State of New Jersey—Vineland, Woodbine, Totowa, New Lisbon State Schools, and Vineland Training School; in the State of Massachusetts—Fernald, Wrentham and Belchertown State Schools; in the State of New Hampshire—Laconia State School. 20,300 patients were thus examined, of whom 161 were found to show a positive reaction.

Next, the family of each patient was personally visited, and all the living parents and siblings were examined and tested for phenylpyruvic acid. Moreover, in a large number of cases other relatives of the patients, including uncles, aunts and first cousins, could be personally examined. School records and hospital notes were secured. Twenty-seven additional cases were thus observed. They were, in the great majority, siblings of hospitalized patients. Twenty-five more cases are taken into account which died prior to the undertaking of the present study. Although biochemical proof was lacking, these patients were considered affected by the disease, since they were siblings of identified patients, to whom they bore striking similarities in both physical and mental features; they had shown physical development and severe mental defect, which had occurred without apparent cause. This brought the total number of cases to 213.

In two families the data available were so scanty that dead members, although mental defectives, were not included in the material.

Table I shows the distribution of the cases in the various institutions.

TABLE I.—*Distribution of the Patients in the Various Institutions.*

Institution.	Patients examined.			Positive cases.									
				Total.		In institution.		At home.		Deceased.			
	Total.	Male.	Female.	M.	F.	M.	F.	M.	F.	M.	F.		
Letchworth	3,568	1,874	1,694	11	20	8	15	2	4	1	1		
Wassaic	3,194	1,649	1,545	7	10	5	8	..	1	2	1		
Rome	1,614	1,029	585	7	5	4	3	..	..	3	2		
Newark	1,965	818	1,147	8	16	4	11	4	1	..	4		
Vineland	1,440	352	1,088	4	19	3	15	1	3	..	1		
Woodbine	760	760	..	11	..	9	..	2	..	..	..		
New Lisbon	762	762	..	6	1	6	..	..	1	..	..		
Totowa	574	..	574	..	1	..	1	..	..	..	..		
Mansfield	1,123	559	564	12	3	8	2	2	1	2	..		
Laconia	580	262	318	2	4	1	3	..	1	1	..		
Fernald	1,553	786	767	6	15	6	14	..	..	..	1		
Wrentham	1,865	972	893	12	20	11	13	1	3	..	4		
Belchertown	1,302	515	787	2	11	..	11	..	..	2	..		
Total	20,300	10,338	9,962	88	125	65	96	12	15	11	14		

Presentation of the Material.

For reasons of space only a brief summary of the constitution of each family and a few clinical data of each case are reported. Thirteen cases are omitted, since the data concerning their families were incomplete.

The families are divided into four groups according to the four States in which they were observed. Families and patients are indicated with progressive numbers, and each patient with the number of the record of the institution in which he was hospitalized. The abbreviations "Ph. neg." and "Ph. pos." indicate that the subject had been tested for phenylpyruvic acid with negative or positive result respectively. "G.S." and "H.S." stand for graduated from grammar school or high school respectively. "O.B." means

"order of birth in the sibship". Sibs who died within the first year of life are arbitrarily excluded (since no reliable data concerning their mentality could be secured), and are designated with the abbreviation "d.i." (died in infancy). If not otherwise indicated, individuals Ph. neg. were mentally within normal limits. In cases in which samples of urine could not be secured, graduation from grammar school was considered tentatively as evidence against the presence of phenylpyruvic acid in the urine. As a matter of fact, thus far, no individual showing phenylpyruvic acid in the urine was able to graduate from grammar school, and the examination of thousands of samples of urine of mentally normal individuals never showed a positive test for phenylpyruvic acid. If not otherwise indicated, the personal history of the patient was negative, i.e., no conditions were reported that might be suspected to be of any significance in the causation of mental defect.

State of New York.

Family I.—Father, Ph. neg.: one brother, G.S., with eight children, G.S. Mother, Ph. neg.: one sister, Ph. neg., with two children, Ph. neg. Fraternity, seven sibs: a boy, dissimilar twin of Case 1, died at 12 years of age, G.S.; four, two males and two females, Ph. neg.; one sib, similar (?) twin of Case 2, d.i.

Case 1: A. Edna, Letchw. 2772. Female, aged 21, Ph. pos., O.B. 1. Muscular hypertonicity. Increase of deep reflexes with bilateral clonus of the patella. Tremors of hands. I.Q. 20.

Case 2: A. Edgar, Letchw. 762. Male; died of tuberculosis, aged 12, O.B. 6. Increase of deep reflexes. Tremors of hands. I.Q. 20. Physical and mental features very similar to Case 1.

Family II.—Parents died in old age, G.S. No collaterals traced. Fraternity, three sibs: two, a male and a female, died of tuberculosis, aged 20, G.S.

Case 3: B. Winifred, Wass. 593. Female, aged 58, Ph. pos., O.B. 3. Symptoms of precocious senility. Bilateral Babinski sign. I.Q. 23. Apathetic low-grade imbecile.

Family III.—Father, Ph. neg.: two brothers, Ph. neg., with five children, G.S. Mother, G.S.; died, aged 37; two brothers, no information. Fraternity, four sibs: two males and one female, Ph. neg. Three sibs, d.i. One half sib, Ph. neg.

Case 4: B. Floyd, Rom. 9026. Male, aged 34, Ph. pos., O.B. 3. Marked muscular hypertonicity. Increase of deep reflexes with bilateral clonus of patella and foot. Tremors of hands. I.Q. 13. Passive, quiet idiot.

Family IV.—Father, Ph. neg.: four sibs with ten offspring, G.S. Mother, Ph. neg.: one sib., Ph. neg. Fraternity, two sibs.

Case 5: B. Robert, New. 1350. Male, aged 6, Ph. pos., O.B. 1. Increase of deep reflexes with clonus of patella and foot. Athetosis. I.Q. 38. Hyperactive and excitable imbecile.

Case 6: B. Joseph. Male, aged 4, Ph. pos., O.B., 2. Increase of deep reflexes with clonus of patella. I.Q. 10. Tremors of hands. Quiet, apathetic, low-grade idiot.

Family V.—Father dead, G.S.: one sister, Ph. neg. Mother, Ph. neg.: two brothers, G.S., with one offspring, Ph. neg. Fraternity, one sib. Another sib, d.i.

Case 7: B. Joseph, Letchw. 2856. Male, aged 28, Ph. pos. Congenital luxation of the left hip. I.Q. 43. Apathetic high-grade imbecile.

Family VI.—Father dead, G.S.: no information concerning his fraternity. Mother, Ph. neg., schizophrenic: no sibs. Fraternity, three sibs: one boy, Ph. neg.; one girl (mentally defective ?), dead at 8 years. Two half sibs, G.S.

Case 8: B. Mary, Letchw. 7430. Female, aged 34, Ph. pos., O.B. 3. Underdevelopment. Emaciation. Increase of deep reflexes. Tremors of hands. I.Q. 33. At times almost catatonic, at others emotional outburst with intense expression of fear.

Family VII.—Father died of heart disease, aged 45, H.S.: no fraternity. Mother, Ph. neg.: one brother and one sister, Ph. neg., with two children, Ph. neg. Fraternity, one sib. Two half sibs, Ph. neg.

Case 9: C. William, Letchw. 6385. Male, aged 14, Ph. pos. Hypertonicity of the lower extremities with increased deep reflexes. Choreo-athetotic movements of hands. I.Q. 10. Restless, destructive low-grade idiot.

Family VIII.—Father, Ph. neg.: two sisters, Ph. neg.; with nine offspring, G.S. Mother, G.S., died of tuberculosis, two sibs, H.S. Fraternity, two sibs: one girl, Ph. neg.

Case 10: C. Norma, New. 3779. Female, aged 9, Ph. pos., O.B. 2. History of rickets. Increase of deep reflexes. Athetoid movements. I.Q. 10. Hyperactive, destructive idiot.

Family IX.—Father dead, G.S. Mother, Ph. neg. No information about collaterals. Fraternity, eight sibs: one boy and five girls, Ph. neg.

Case 11: C. Anna, Letchw. 3846. Female, aged 25, Ph. pos., O.B. 5. Generalized convulsions, three to four times a year until the age of 10. Diffuse rigidity with increase of deep reflexes and tendency to catatonic postures. I.Q. 12. Passive, even-tempered idiot.

Case 12: C. Florence. Female, aged 23, Ph. pos., O.B. 6. Living at home. Physical examination negative. I.Q. 48. Apathetic, good-natured imbecile. History of convulsions.

Family X.—Father, Ph. neg.: five sibs, Ph. neg., with twenty-five offspring, Ph. neg. One of these schizophrenic. Mother, Ph. neg.: one brother, G.S., with one child, Ph. neg. Parents first cousins. Fraternity, two sibs.

Case 13: D. Benjamin, Letchw. 2538. Male, aged 26, Ph. pos., O.B. 1. Convulsive seizures three to four times a year. Increase of deep reflexes, tremor of hands. Bilateral keratitis. I.Q. 10. Hyperactive, destructive, low-grade idiot.

Case 14: D. Mary, O.B. 2. Female, died at 10 years of age of pneumonia. Low-grade idiot girl with a negative history. Physical development normal. Physical and mental features very similar to Case 13.

Family XI.—Parents, Ph. neg. No information concerning collaterals. Fraternity, seven sibs: four girls and one boy, Ph. neg.

Case 15: D. Albert, Was. 1882. Male, aged 13, Ph. pos., O.B. 5. Increase of deep reflexes. Choreo-athetoid movements of hands. I.Q. 19. Excitable and mischievous idiot.

Case 16: D. Anna, Letchw. 7331. Female, aged 6, Ph. pos., O.B. 7. History negative. Rigid gait with increased deep reflexes. Athetoid movements of hands. I.Q. 10. Usually apathetic idiot. Occasional short fits of violent temper.

Family XII.—Father, G.S., died of uræmia. Mother, Ph. neg. No collaterals. Fraternity, seven sibs: two boys and one girl, Ph. neg.

Case 17: D. Henry, Letchw. 153. Male, aged 35, Ph. pos., O.B. 1. Physical examination negative. I.Q. 46. Passive, even-tempered imbecile.

Case 18: D. Anna, Was. 358. Female, aged 31, Ph. pos., O.B. 3. Muscular rigidity with increased deep reflexes. Choreo-athetoid movements of hands. I.Q. 17. Excitable, apprehensive idiot. Occasional severe temper tantrums.

Case 19: D. Margaret, Was. 2387. Female, aged 28, Ph. pos., O.B. 4. Generalized hypertonicity. Increase of deep reflexes with clonus of patella. Athetoid movements and tremors of hands. I.Q. 20. Transient episodes of aggressiveness.

Case 20: D. Albert, O.B. 7. Died at 8 years of appendicitis. Low-grade imbecile with a negative history. Physical development normal. The physical examination was reported negative but for tremors of both hands.

Family XIII.—Father, Ph. neg.: no information concerning his fraternity. Mother, Ph. neg.: two sibs with six offspring, G.S. Fraternity, five sibs: one female and one male, Ph. neg. One sib d.i.

Case 21: D. Mary. Female, aged 20, Ph. pos., O.B. 2. Increase of deep reflexes. Tremors of hands. I.Q. 20. Quiet, apathetic idiot.

Case 22: D. Kate. Female, died at 8 years of age of pneumonia, O.B. 2. Twin (probably similar) of Case 21. Low-grade idiot: at 8 years she was untidy and showed no speech. Physical and mental features very similar to those of Case 21.

Case 23: D. Peter, New. 314. Male, aged 12, Ph. pos., O.B. 5. Athetoid movements. I.Q. 12. Pleasant, quiet, idiot.

Family XIV.—Parents and collaterals, no reliable information. Fraternity, two sibs: one female, Ph. neg., with two children, G.S.

Case 24: D. Emma. Female, aged 35, living at home, Ph. pos., O.B.1. Physical examination negative. I.Q. 49. Apathetic imbecile with occasional emotional outbursts.

Family XIVa.—Father, Ph. neg.: two sisters, G.S. Fraternity, four sibs: one boy and one girl, Ph. neg.

Case 25: D. Elizabeth, Letchw. 2885. Female, aged 19, Ph. pos., O.B. 1. Increase of deep reflexes. I.Q. 33. Apathetic, well-behaved imbecile.

Case 26: D. John. Male, aged 17, living at home, Ph. pos., O.B. 2. Physical examination essentially negative. I.Q. 50. Passive, quiet, even-tempered imbecile.

Family XV.—Parents, Ph. neg. No information concerning collaterals. Fraternity, two sibs: one boy, Ph. neg.

Case 27: F. Joseph, Rom. 10113. Male, aged 13, Ph. pos., O.B. 1. History of convulsions. Muscular hypertonicity. Increase of deep reflexes with bilateral clonus of patella. I.Q. 13. Quiet and passive low-grade idiot.

Family XVI.—Parents, Ph. neg. No collaterals. Fraternity, two sibs: a male, Ph. neg., with two children, Ph. neg.

Case 28: F. Lilly, Letchw. 4630. Female, aged 16, Ph. pos., O.B. 2. Instrumental delivery. Muscular hypertonicity. Increase of deep reflexes with clonus of patella. Right Babinski. I.Q. 17. Apathetic, well-behaved idiot.

Family XVII.—Parents dead, G.S. No collaterals. Fraternity, three sibs: two boys, Ph. neg. Four sibs d.i.

Case 29: F. Edna, Letchw. 1759. Female, aged 30, Ph. pos., O.B. 2. Marked tremors of hands. Rigid gait. I.Q. 13. Hyperactive, destructive idiot.

Family XVIII.—Father, Ph. neg.: no sibs. Mother, Ph. neg.: one brother, G.S., died of general paralysis. Fraternity, one sib. Another sib, d.i. One half sib, Ph. neg.

Case 30: G. Philip, Was. 3474. Male, aged 13, Ph. pos. Tremors of hands. Rigid gait. I.Q. 13. Hyperactive, destructive idiot.

Family XIX.—Parents, Ph. neg. No collaterals. Fraternity, two sibs: one male, Ph. neg.

Case 31: G. Elizabeth, Letchw. 5405. Female, aged 19, Ph. pos., O.B. 2. Athetoid movements of hands. Increased deep reflexes of lower extremities. I.Q. 10. Quiet, even-tempered, low-grade idiot.

Family XX.—Father, G.S., died, aged 68. Mother, Ph. neg. No information concerning collaterals. Fraternity, three sibs: one male, Ph. neg., with two children, H.S.; one female, Ph. neg.

Case 32: G. George, New. 264. Male, aged 52, Ph. pos., O.B. 2. Rigid gait and posture. Marked tremors of hands and body. I.Q. 34. Well-behaved, agreeable imbecile.

Family XXI.—Parents dead, G.S. No information concerning relatives. Fraternity, ten sibs: one female, Ph. neg.; two males and two females, G.S., dead of tuberculosis.

Case 33: H. Mary, Rom. 906. Female, aged 65, Ph. pos., O.B. 2. Marked tremors of hands. Pronounced signs of senility. Ps. Ex.: I.Q. 31. Quiet and well-behaved imbecile.

Case 34: H. Emile. Female, died at 6 years, O.B. 4. History of convulsions. Well developed physically. Low-grade idiot.

Case 35: H. Joseph. Male, dead at 8 years, O.B. 6. History of convulsions. Low-grade idiot, well developed physically.

Case 36: H. Clara. Female, dead at 15 years, O.B. 8. History negative. Low-grade idiot. Physical development normal.

Case 37: H. Gertrude. Female, dead at 17 years, O.B. 9. History of convulsions. Low-grade idiot.

Family XXII.—Father, Ph. neg.: four sibs, G.S. Mother, Ph. neg.: two sisters with four children, Ph. neg. Fraternity, four sibs: one boy and two girls, Ph. neg.

Case 38: H. Peter, Was. 1311. Male, aged 16, Ph. pos., O.B. 2. Dystonic movements involving head, arms and hands. Hypertonicity of lower extremities. I.Q. 10. Apathetic, even-tempered, low-grade idiot.

Family XXIII.—Father, Ph. neg.: no fraternity. Mother, Ph. neg.: three sibs, G.S. Fraternity, four sibs: one boy and two girls, Ph. neg.

Case 39: H. Harry, New. 855. Male, aged 5, Ph. pos., O.B. 4. History negative. Unsteady gait. Increase of deep reflexes. Athetoid movements. I.Q. 25. Hyperactive, unco-operative imbecile.

Family XXIV.—Father, Ph. neg.: two sisters, Ph. neg. with five children, Ph. neg.; one brother living abroad with four children, one of them low-grade mental defective. Mother, Ph. neg.: no information concerning her family. Fraternity, five sibs: one male and one female, Ph. neg.

Case 40: H. Michael, Rom. 4240. Male, aged 24, Ph. pos., O.B. 2. Tremor of hands. Muscular hypertonicity with increased deep reflexes and clonus of patella and foot. I.Q. 10. Apathetic, quiet idiot.

Case 41: H. Kamil, Rom. 4241. Male, O.B. 3. Died of tuberculosis, aged 9. Tremors and athetoid movements of hands. I.Q. 20.

Case 42: H. Julia, New. 2400. Female, O.B. 5. Died of appendicitis, aged 10. History of generalized convulsive seizures. Unsteady gait. Tremors of hands. I.Q. 16.

Family XXV.—Parents, Ph. neg. No information concerning relatives. Fraternity, two sibs: one girl, Ph. neg.

Case 43: I. Thomas, Rom. 9946. Male, aged 16, Ph. pos., O.B. 1. Convulsive seizures from the age of 4 months to 2 years. Physical examination negative. I.Q. 51. Quiet, even-tempered, co-operative imbecile.

Family XXVI.—Parents dead, G.S. No collaterals. Fraternity, two sibs: one girl, Ph. neg. Four half sibs, G.S.

Case 44: K. Alice, Letchw. 6208. Female, aged 18, Ph. pos., O.B. 2. Physical examination, negative. I.Q. 48. Passive, even-tempered imbecile.

Family XXVII.—Father, Ph. neg.: five sibs with seventeen offspring, Ph. neg. Mother, Ph. neg.: five sibs with twenty-four offspring, Ph. neg. (one a defective boy, post-encephalitic syndrome). Fraternity, five sibs: one male and two females, Ph. neg.

Case 45: K. Charlotte, Letchw. 4549. Female, aged 29, Ph. pos., O.B. 3. Increase of deep reflexes. Tremors of hands. I.Q. 20. Hyperactive, occasionally destructive idiot.

Case 46: K. Walter, Letchw. 4471. Male, aged 22, Ph. pos., O.B. 4. Increase of deep reflexes. I.Q. 23. Apathetic, quiet, low-grade imbecile.

Family XXVIII.—Father, Ph. neg.: no sibs. Mother, Ph. neg.: four sibs, Ph. neg., with two offspring, Ph. neg. Fraternity, three sibs: two girls, Ph. neg. One half sib, Ph. neg.

Case 47: K. Rose, Letchw. 5473. Female, aged 7. Ph. pos., O.B. 2. Absent gait but no paralysis. Hyperactivity of deep reflexes. I.Q. 10. Apathetic, low-grade idiot; occasional fits of temper.

Family XXIX.—Father, G.S.: died of cerebral hæmorrhage; no sibs. Mother, Ph. neg.: two sibs with nine offspring, Ph. neg. Parents, first cousins. Fraternity, three sibs: two females, Ph. neg., with four children, Ph. neg. Five sibs, d.i.

Case 48: K. Artje, Rom. 1721. Female, aged 40, Ph. pos., O.B. 1. Increase of deep reflexes with clonus of patella and foot. Choreo-athetoid movements. I.Q. 13. Restless, excitable, destructive, low-grade idiot.

Family XXX.—Father, G.S.: dead, no sibs. Mother, G.S.: dead. Three sisters with seven offspring: one schizophrenic, Ph. neg., and one low-grade mental defective (not examined). Fraternity, five sibs: two males and two females, Ph. neg.

Case 49: L. Grace, Was. 1162. Female, aged 44, Ph. pos. O.B. 4. Increase of deep reflexes with clonus of patella. I.Q. 41. Apathetic, quiet imbecile.

Family XXXI.—Father, Ph. neg.: one brother with three children, Ph. neg. Mother, Ph. neg.: no information concerning her sibs. Fraternity, two sibs, one girl, Ph. neg.

Case 50: L. Catherine, New. 4311. Female, aged 18. Ph. pos., O.B. 2. *Petit mal* attacks from three to seven years of age. Athetoid movements of hands. I.Q. 22. Quiet, apathetic idiot.

Family XXXII.—Father, Ph. neg. Mother, G.S.: died of tuberculosis. No information concerning collaterals. Fraternity, six sibs: three boys and two girls Ph. neg. Four sibs, d.i.

Case 51: M. Rose, Letchw. 4195. Female, aged 16, Ph. pos., O.B. 3. Underdevelopment. Athetosis. I.Q. 10. Hyperactive, excitable low-grade idiot.

Family XXXIII.—Parents, Ph. neg. No information concerning collaterals. Fraternity, four sibs: one boy and two girls, Ph. neg.

Case 52: M. Johanna, New. 2301. Female, aged 30, Ph. pos., O.B. 2. Tremors and athetosis of hands. I.Q. 17. Hyperactive, at times destructive idiot.

Family XXXIV.—Parents, Ph. neg., second cousins. All collaterals (uncles, aunts and cousins of patient, 35 members), Ph. neg. Fraternity, twelve sibs: four boys and four girls, Ph. neg.

Case 53: M. Madelaine, Letchw. 7208. Female, aged 17, Ph. pos., O.B. 3. Marked athetosis. Rigid gait. I.Q. 13. Apathetic, quiet idiot.

Case 54: M. Clotilde. Female, aged 13, living at home, Ph. pos., O.B. 5. Tremors of hand. I.Q. 54. Co-operative, well-behaved imbecile.

Case 55: M. Julia, Female, aged 5, living at home, Ph. pos., O.B. 10. Physical examination negative. I.Q. 51. Quiet, submissive imbecile.

Case 56: M. Ernest. Male, aged 4, living at home, Ph. pos., O.B. 11. Increase of deep reflexes. Tremors of the whole body. I.Q. 20. Hyperactive, destructive idiot.

Family XXXV.—Father, G.S.: died of cerebral hæmorrhage, aged 50: three sibs with two offspring, G.S. Mother, G.S., died of childbirth, aged 28: three sisters with twelve offspring, G.S.; another sister is the mother of Family XXXV*a*. Fraternity, six sibs: two males and two females, Ph. neg.

Case 57: M. Genevieve, New. 123, O.B. 1. Female, died at 26 years of age of tuberculosis (?). History negative. Physical examination essentially negative. Low-grade idiot.

Case 58: M. Margaret, New, 1124. Female, aged 45, Ph. pos., O.B. 5. Hypertonicity of muscles. Tremors of hands. I.Q. 12. Resistive, unco-operative idiot.

Family XXXVa.—Father, same as Family XXXV. Mother, Ph. neg.: sister of mother of family XXXV. Fraternity, eight sibs: four females and two males, Ph. neg. The two males had four offspring, Ph. neg., one of whom mental defective with bilateral cataract. Two sibs d.i.

Case 59: M. Joseph. Male, aged 43, Ph. pos., O.B. 1. Increase of deep reflexes. Rigid gait and posture. I.Q. 35. Well-behaved, apathetic imbecile, living at home.

Case 60: M. Ruth, New. 2401. Female, aged 36, Ph. pos., O.B. 6. Marked tremors. Increase of deep reflexes with clonus of foot. I.Q. 10. Unco-operative, resistive, low-grade idiot.

Family XXXVI.—Father, Ph. neg.: two sibs, Ph. neg. Mother, Ph. neg. No information concerning relatives. Fraternity, four sibs: one boy and one girl, Ph. neg. Four half sibs, Ph. neg.

Case 61: M. Ilma, New. 4274. Female, aged 7, Ph. pos., O.B. 2. Tremors of hands, at times diffusing to the whole body. Unable to walk. I.Q. 10. Occasional outbursts of screaming.

Case 62: M. Wesley. Male, aged 5, Ph. pos., O.B. 3. Increase of deep reflexes. Athetosis. Unable to walk. I.Q. 20. Quiet, passive low-grade idiot, living at home.

Family XXXVII.—Father, G.S.: died of pneumonia: one sib, G.S., with two mentally defective children, who could not be examined. Mother, G.S.: died of cancer, aged 58. No information concerning her fraternity. Fraternity, five sibs: two male and one female, Ph. neg., with six offspring, G.S.; another female is the mother of Family 48.

Case 63: P. John, New. 563. Male, aged 45, Ph. pos., O.B. 3. Instrumental delivery. Under-development. Rachitic symptoms. Marked tremors of face, tongue and hands. I.Q. 27. Well-behaved, agreeable, low-grade imbecile.

Family XXXVIII.—Father, Ph. neg.: two sibs, G.S. Mother, Ph. neg.: four sibs with fourteen offspring, G.S. Parents, first cousins. Fraternity, six sibs: two girls and one boy, Ph. neg.

Case 64: P. Nettie, New. 3200. Female, aged 30, Ph. pos., O.B. 1. Rigid gait and posture. Tremors of hands. I.Q. 25. Quiet, passive, low-grade imbecile.

Case 65: P. Concetta. Female, died, aged 6, of appendicitis, O.B. 4. History negative. Gait unsteady with hypertonicity of legs. I.Q. below 20.

Case 66: P. Victoria, New. 3198. Female, aged 14, Ph. pos., O.B. 5. Increased deep reflexes. Rigid gait and posture. Athetosis. I.Q. 26. Hyperactive, destructive, low-grade imbecile.

Family XXXIX.—Parents, Ph. neg. No collaterals examined. Fraternity, three sibs: one boy, Ph. neg.

Case 67: Q. Anna, Was. 1162. Female, aged 11, Ph. pos., O.B. 2. Tremors of hands. Increase of deep reflexes. I.Q. 13. Apathetic, quiet, low-grade idiot.

Case 68: Q. William. Male, died of pneumonia, aged 6, O.B. 3. History negative. Well-developed low-grade idiot. Physical examination reported negative except for athetosis.

Family XL.—Father, Ph. neg.: two brothers, Ph. neg. Mother, G.S.: died at 38 years of age of pneumonia. Fraternity, four sibs: one boy and two girls, Ph. neg. One sib d.i.

Case 69: R. William, Letchw. 5861. Male, aged 16, Ph. pos., O.B. 1. Physical examination negative. I.Q. 50. Co-operative, even-tempered imbecile.

Family XLI.—Father, Ph. neg.: two sibs with eight offspring, G.S. Mother, G.S.: died of Bright's disease, aged 63. No information concerning her sibs. Fraternity, four sibs: two boys and one girl, Ph. neg. Two sibs, d.i.

Case 70: R. Peter, Rom. 1525. Male, aged 38, Ph. pos., O.B. 2. Marked generalized rigidity of muscles. Tremors of hands. I.Q. 10. Quiet, passive idiot.

Family XLII.—Father, Ph. neg.: three sibs with four offspring, Ph. neg. Mother, Ph. neg. Fraternity, four sibs: one boy and one girl, Ph. neg.

Case 71: S. Nora, Was. 1078. Female, aged 14, Ph. pos., O.B. 1. Instrumental delivery. Increase of deep reflexes with clonus of patella. Choreo-athetosis. I.Q. 20. Passive, quiet idiot.

Case 72: S. Mary. Female, died at 4 years of pneumonia. History negative. Low-grade idiot girl bearing striking similarities to Case 71.

Family XLIII.—Father, Ph. neg. Mother, G.S.: died of heart disease. No collateral examined. Fraternity, three sibs: one boy, Ph. neg.

Case 73: S. Bertha, Was. 623. Female, aged 21. Ph. pos., O.B. 1. Marked tremors. Increase of deep reflexes with clonus of patella and foot. I.Q. 40. Quiet, even-tempered imbecile.

Case 74: S. Elsie, Was. 624. Female, aged 16, Ph. pos., O.B. 2. Choreo-athetosis and tremors. Increase of deep reflexes with clonus of patella and foot. Congenital dislocation of the hip. I.Q. 32. Hyperactive, emotionally unstable imbecile.

Family XLIV.—Father, Ph. neg.: three sibs with ten offspring, H.S. Mother, Ph. neg.: one sib, Ph. neg.

Case 75: S. Paul, Letchw. 4999. Male, aged 22, Ph. pos., O.B. 2. Meningitis (?) at 8 months. Friedreich-like deformation of both feet. Choreo-athetosis. I.Q. 13. Hyperactive, destructive idiot.

Family XLV.—Parents, Ph. neg. Collaterals, no information. Fraternity, six sibs: two boys and two girls, Ph. neg.: one of these schizophrenic.

Case 76: V. Paul, Was. 3652. Male, aged 17, Ph. pos., O.B. 4. Muscular hypertonicity. Increase of deep reflexes with clonus of the patella. I.Q. 17. Emotionally unstable, idiot.

Case 77: V. Hilda. Female, aged 12, Ph. pos., O.B. 5. Physical examination negative. Ps. Ex. I.Q. 48. Marked speech defect. Quiet, timid imbecile living at home.

Family XLVI.—Parents, G.S.: both dead. No collaterals traced. Fraternity, three sibs: two boys, Ph. neg.

Case 78: V. Mary, Letchw. 702. Female, aged 23, Ph. pos., O.B. 3. Underdevelopment. Diffuse tremors. I.Q. 10. Passive, quiet, low-grade idiot.

Family XLVII.—Parents died in old age, G.S. No collateral traced. Fraternity, one sib.

Case 79: W. William, Was. 1184. Male, aged 39, Ph. pos., physical examination negative. I.Q. 42. Apathetic, well-behaved imbecile.

Family XLVIII.—Father, Ph. neg.: no collaterals. Mother, see Family XXXVII. Fraternity, three sibs.

Case 80: W. Albert. Male, aged 16, Ph. pos., O.B. 1. Physical examination essentially negative. I.Q. 38. Quiet, well-behaved imbecile.

Case 81: W. Rita, New. 4444. Female, aged 14, Ph. pos., O.B. 2. Obesity of the hypopituitary type. Increase of deep reflexes. I.Q. 25. Quiet, passive, low-grade imbecile.

Case 82: W. Florence, New. 4443. Female, aged 10, Ph. pos., O.B. 3. Rigid, unsteady gait. Increase of deep reflexes. I.Q. 16. Indolent, passive idiot.

State of New Jersey.

Family XLIX.—Father, G.S.; died of cerebral hæmorrhage: one brother with four children, Ph. neg. (one of them schizophrenic). Mother, Ph. neg.: two sisters with eight offspring, Ph. neg. Fraternity, four sibs: one male, Ph. neg. Three sibs, d.i.

Case 83: B. William, Wood. 42. Male, aged 39, Ph. pos., O.B. 2. History of epilepsy. Increase of deep reflexes. Left Babinski. I.Q. 20. Passive, quiet idiot.

Case 84: B. Sadie, Vin. St. 996. Female, aged 36, Ph. pos., O.B. 3. Diffuse tremors. Increase of deep reflexes with patella clonus. I.Q. 35.

Case 85: B. Anna. Female, married, without children, aged 34, Ph. pos., O.B. 4. Marked tremors of hands. I.Q. 39. Submissive, emotionally unstable imbecile living at home.

Family L.—Father, G.S.: died of uræmia. Mother, Ph. neg. No collateral investigated. Fraternity, six sibs: two boys and two girls, Ph. neg. One sib, d.i.

Case 86: B. William. Male, aged 27, Ph. pos., O.B. 5. Physical examination negative. I.Q. 50. Apathetic, well-behaved imbecile, living at home.

Case 87: B. Helen, Vin. St. 2049. Female, aged 19, Ph. pos., O.B. 6. Choreatic movements. Generalized hypertonicity with increased deep reflexes and clonus of patella and foot. Right Babinski. I.Q. 10. Hyperactive destructive idiot.

Family LI.—Father, Ph. neg.: one brother, G.S. Mother, Ph. neg.: five sibs with nine offspring, G.S. Fraternity, five sibs: three boys, Ph. neg.

Case 88: B. James, New Lis. 676. Male, aged 19, Ph. pos., O.B. 1. Scoliosis. Increase of deep reflexes. Tremors of hands. I.Q. 16. Quiet, passive idiot.

Case 89: B. Eleanore. Female, aged 13, Ph. pos., O.B. 4. Marked tremors. Increase of deep reflexes. I.Q. 20. Quiet, apathetic idiot, living at home.

Family LII.—Parents, G.S.: died in old age. No collateral examined. Fraternity, two sibs: one male, Ph. neg.: one sib, d.i.

Case 90: B. Anna, Vin. St. 923. Female, aged 40, Ph. pos., O.B. 2. Marked tremors of hand. Blood Wassermann positive. I.Q. 54. Passive, even-tempered, high-grade imbecile.

Family LIII.—Father, H.S.: three sibs with six offspring, G.S. Mother, Ph. neg.: one sister with three offspring, Ph. neg. One of these low-grade mental defective (birth injury ?). Fraternity, one sib.

Case 91: B. Carol, Vin. Tr. 2257. Female, aged 17, Ph. pos. History of epilepsy. Increase of deep reflexes. Tremors of hands. I.Q. 25. Excitable, hyperactive low-grade imbecile.

Family LIV.—Parents, G.S.: died in old age. Of three collateral families only one examined: five members, Ph. neg. Fraternity, six sibs: two males, Ph. neg.

Case 92: C. Florence. Female, aged 34, living at home, Ph. pos., O.B. 2. Epileptic attacks twice a month. Tremors of hand. I.Q. 42. Quiet, apathetic imbecile.

Case 93: C. Harold, New Lis. 864. Male, aged 27, Ph. pos., O.B. 4. Increase of deep reflexes with clonus of patella. I.Q. 24. Quiet, passive low-grade imbecile.

Case 94: C. Ruth, Vin. St. 1854. Female, aged 25, Ph. pos., O.B. 5. Athetosis and tremors of hands. Increase of deep reflexes with patellar clonus. I.Q. 16.

Case 95: C. Jack, Wood. 1210. Male, aged 23, Ph. pos., O.B. 6. Marked athetoid movements. I.Q. 20. Quiet, idiot, occasional temper tantrums.

Family LV.—Parents, Ph. neg. One father's sib with three children, Ph. neg. Fraternity, four sibs: one boy and two girls, Ph. neg.

Case 96: C. Lucy, Vin. St. 2351. Female, aged 12, Ph. pos., O.B. 4. Increase of deep reflexes with bilateral clonus of foot and patella. Marked tremors. I.Q. 10. Hyperactive and emotionally unstable idiot.

Family LVI.—Father, Ph. neg.: three brothers with four offspring, Ph. neg. Mother, Ph. neg.: first cousin of Case 119. Fraternity, three sibs: two girls, Ph. neg.

Case 97: C. Caroline, Vin. St. 2289. Female, aged 15, Ph. pos., O.B. 1. Paralysis of the right brachioradialis. Tremors of hands. I.Q. 20. Hyperactive, emotionally unstable idiot.

Family LVII.—Father, Ph. neg., of mixed Negro-Indian race. Mother, G.S. (?) of mixed Negro-White race. No collaterals traced. Fraternity, two sibs: one girl, Ph. neg.

Case 98: C. Ernest, Wood. 980. Male, aged 10, Ph. pos., O.B. 1. Physica examination negative I.Q. 19. Quiet, agreeable idiot.

Family LVIII.—Father, H.S.: died of heart disease. Mother, Ph. neg. No collaterals examined. Fraternity, four sibs: one boy and two girls, H.S.

Case 99: E. Frank, Wood. 482. Male, aged 40, Ph. pos., O.B. 1. Epileptic attacks three to four times a year. Muscular hypertonicity with increased reflexes and clonus of patella and foot. I.Q. 25. Quiet, well-behaved imbecile.

Family LIX.—Father, G.S.: died of cancer. Mother, Ph. neg.: four sibs with nineteen offspring, Ph. neg. Fraternity, two sibs: one female, Ph. neg., with one child, Ph. neg.

Case 100: F. Helen, Vin. St. 2624. Female, aged 23, Ph. pos., O.B. 2. Rigid posture and gait. Increase of deep reflexes. I.Q. 19. Passive, quiet idiot.

Family LX.—Father, Ph. neg.: two sibs with three offspring, Ph. neg. Mother, Ph. neg.: two brothers with six offspring, G.S. Fraternity, two sibs: one girl, Ph. neg.

Case 101: H. Margaret, Vin. St. 2471. Female, aged 9, Ph. pos., O.B. 2. Epileptic convulsions three to four times a year. Hypertonicity of lower extremities with increase of deep reflexes. Tremors of hands. I.Q. 25. Apathetic, low-grade imbecile.

Family LXI.—Father, Ph. neg.: six sibs with twenty-eight offspring, twenty, G.S., and eight, Ph. neg. Mother, Ph. neg.: five sibs with ten offspring, G.S. Fraternity, seven sibs: one boy and four girls, Ph. neg.

Case 102: H. Edward, Wood. 972. Male, aged 12, Ph. pos., O.B. 3. History negative. Rigid gait and posture. Increase of deep reflexes with clonus of patella. I.Q. 20. Quiet, passive idiot.

Case 103: H. Raymond. Male, aged 5, living at home. Ph. pos., O.B. 6. Unsteady gait with diffuse tremors of the body. I.Q. 26. Passive idiot; occasional temper tantrums.

Family LXII.—Father, Ph. neg. Mother, G.S.: died of uræmia, aged 45. No collaterals examined. Fraternity, one sib.

Case 104: H. Ralph, Wood. 1197. Male, aged 12, Ph. pos. Hyperactivity of deep reflexes with clonus of patella. I.Q. 10. Quiet, apathetic idiot.

Family LXIII.—Parent, Ph. neg. No collaterals examined. Fraternity, two sibs: one girl, Ph. neg.

Case 105: H. Margaret, Vin. St. 2471. Female, aged 25, Ph. pos., O.B. 1. Increase of deep reflexes with clonus of patella. Tremor of hands. I.Q. 20. Hyperactive, excitable idiot.

Family LXIV.—Father, G.S.: died of cerebral hæmorrhage, aged 44: three sibs, no information. Mother, Ph. neg.: one brother with four children, G.S. Fraternity, three sibs: one female, Ph. neg. with two children, Ph. neg.

Case 106: G. Selma. Female, aged 50, living at home. Married with a child, apparently normal, who died at 5 years of pneumonia, Ph. pos., O.B. 1. Tremors of hands. Precocious senility. I.Q. 50. Apathetic, well-behaved imbecile.

Case 107: G. August, Vin. T1. 690. Male, aged 45, Ph. pos., O.B. 3. Increase of deep reflexes. Tremors of hands. I.Q. 32. Passive, even-tempered imbecile.

Family LXV.—Father, Ph. neg.: three sibs, G.S. Mother, Ph. neg.: two sibs with three offspring, G.S. Fraternity, one sib.

Case 108: G. Allen, Vin. Tr. 2270. Male, aged 36, Ph. pos., instrumental delivery. Increase of deep reflexes with clonus of foot and patella. Marked tremors of hands. I.Q. 36. Well-behaved, emotionally unstable imbecile.

Family LXVI.—Father, G.S.: died in old age: five sibs with fourteen offspring; thirteen, G.S.: one girl, low-grade, physically normal idiot (not examined). Mother, G.S.: died in old age; four sibs with twelve offspring, G.S. Fraternity, nine sibs: one girl, G.S., died at 18 years of pneumonia: four boys and two girls, Ph. neg.

Case 109: L. Bertha. Female, died at 16 years in the Village for Epileptics, Skillman, N.J., O.B. 6. History of severe convulsions. Unsteady gait. Tremors of hands. I.Q. 10.

Case 110: L. Catherine, Vin. St. 2169. Female, aged 11, Ph. pos., O.B. 8. Epileptic attacks in late infancy. Marked, diffuse tremors. Choreo-athetoid movements. I.Q. 10. Excitable and hyperactive, low-grade idiot.

Family LXVII.—Father, Ph. neg. Mother, G.S.: died of cancer. Parents, first cousins. Collaterals, no information. Fraternity, four sibs: one boy and one girl, Ph. neg.

Case 111: M. Josephine, Totow. 580. Female, aged 19, Ph. pos., O.B. 2. Increase of deep reflexes. I.Q. 52. Well-behaved, even-tempered, co-operative imbecile.

Case 112: M. Alphonse, New Lis. 1234. Male, aged 12, Ph. pos., O.B. 4. Increase of deep reflexes. Tremors of hands. I.Q. 36. Restless, excitable imbecile.

Family LXVIII.—Father, Ph. neg.: no fraternity. Mother, Ph. neg.: two sibs, Ph. neg. Fraternity, one sib.

Case 113: M. Betty, Vin. St. 2574. Female, aged 12, Ph. pos. Diffuse muscular rigidity. Increase of deep reflexes with clonus of patella. I.Q. 20. Excitable and emotionally unstable idiot.

Family LXIX.—Father, Ph. neg.: five sibs with sixteen children, G.S. Mother, H.S., died of tuberculosis: two sibs with two children, G.S. One of three mother's first cousins was a low-grade mental defective (not examined). Fraternity, two sibs: one girl, Ph. neg.

Case 114: M. Robert, Wood. 572. Male, aged 14, Ph. pos., O.B. 1. Epileptic attacks three to four times a year. Rigid gait. Athetoid movements of hands and feet. I.Q. 26. Quiet, passive, low-grade imbecile.

Family LXX.—Parents, G.S., dead; no collateral. Fraternity, three sibs: one boy and one girl, Ph. neg.

Case 115: O. Terrance, Wood. 891. Male, aged 16, Ph. pos., O.B. 1. Increase of deep reflexes with clonus of patella. Tremors and myoclonic movements of hands. I.Q. 31. Quiet, well-behaved imbecile.

Family LXXI.—Father, Ph. neg.: three sibs with six offspring, G.S. Mother, Ph. neg.: five sibs, G.S., with three offspring, Ph. neg. Fraternity, six sibs: three boys and one girl, Ph. neg.

Case 116: R. Gerald, Wood. 664. Male, aged 17, Ph. pos., O.B. 1. Increase of deep reflexes with clonus of patella and foot. Left Oppenheim. Tremors of hands. Apathetic, low-grade imbecile.

Case 117: R. Eugene, male, aged 6, Ph. pos., O.B. 4. Marked tremors. I.Q. 22. Quiet, passive, low-grade imbecile, living at home.

Family LXXII.—Father, Ph. neg.: three sibs with nine offspring, Ph. neg. One of these is the mother of Family LVI. Mother, Ph. neg.: three sibs, G.S. The parents were cousins. Fraternity, four sibs: one boy and two girls, Ph. neg.

Case 118: R. Evelyn, Vin. St. 2290. Female, aged 11, Ph. pos., O.B. 2. Rigid gait. Marked athetosis. I.Q. 12. Quiet, passive idiot.

Family LXXIII.—Parents, Ph. neg. Collaterals, no information. Fraternity, three sibs: two boys, ph. neg. Two sibs, d.i.

Case 119: S. Anna, Vin. St. 2383. Female, aged 18, Ph. pos., O.B. 2. Increase of deep reflexes with clonus of patella. Tremors of hands. I.Q. 20. Hyperactive, excitable idiot.

Family LXXIV.—Father, H.S. Mother, Ph. neg. No collaterals examined. Fraternity, three sibs: two girls, Ph. neg.

Case 120: W. Buster, Vin. Tr. 1789. Male, aged 25, Ph. pos., O.B. 1. Premature birth. Rigid gait and posture. Tremors of hand. I.Q. 46. Quiet, emotionally unstable imbecile.

Family LXXV.—Father, Ph. neg.: two sibs, ph. neg. Mother, Ph. neg.: four sibs with six offspring, G.S. Fraternity, three sibs: two girls, Ph. neg.

Case 121: W. Lee, New Lis. 693. Male, aged 19, Ph. pos., O.B. 1. Physical examination, essentially negative.

Family LXXVI.—Father, Ph. neg.: one sister inmate of Rome State School (I.Q. 68), Ph. neg. Mother, G.S.: died, aged 46. Fraternity, two sibs: one female, Ph. neg., with five children, Ph. neg.

Case 122: Y. Percy, New Lis. 1258. Male, aged 37, Ph. pos., O.B. 2. Unsteady gait. Increase of deep reflexes. Tremors of hands. I.Q. 30. Quiet, passive imbecile.

State of Connecticut.

Family LXXVII.—Father, G.S., died of pneumonia, aged 34: three sibs with fifteen offspring, G.S. Mother, Ph. neg.: three sibs, Ph. neg. Fraternity, three sibs: one boy, Ph. neg. One half sister, Ph. neg.

Case 123: F. Wilfred. Male, aged 35, Ph. pos., O.B. 1. Rigid gait and posture. Tremors of hands. I.Q. 46. Quiet, passive imbecile, living at home.

Case 124: F. Clifton, Mans. 553. Male, aged 28, Ph. pos., O.B. 3. History of convulsions. Increased deep reflexes. Tremors and athetoid movements of hands. I.Q. 10. Hyperactive, destructive, low-grade idiot.

Family LXXVIII.—Parents, Ph. neg. Collaterals, no information. Parents, cousins. Fraternity, three sibs: one boy and one girl, Ph. neg.: one sib, d.i.

Case 125: G. George, Mans. 949. Male, aged 26, Ph. pos., O.B. 2. Diffuse tremors. I.Q. 12. Excitable, hyperactive idiot.

Family LXXIX.—Parents, Ph. neg. Collaterals not examined. Fraternity, three sibs: one boy, Ph. neg. One sib, d.i.

Case 126: K. Philip, Mans. 2211. Male, died, aged 13, of pneumonia, O.B. 1. History of convulsions. Unable to walk, no paralysis. I.Q. 10. Quiet, passive, low-grade idiot, similar to Case 127.

Case 127: K. Robert, Mans. 2228. Male, aged 10, Ph. pos., O.B. 2. Instrumental delivery. Athetoid movements. Increase of deep reflexes. Bilateral Babinski. I.Q. 10. Hyperactive idiot.

Family LXXX.—Parents, G.S.: died in old age. Collaterals, no information. Fraternity, four sibs: three boys, Ph. neg.

Case 128: M. Edward, Mans. 1517. Male, aged 20, Ph. pos., O.B. 3. Generalized rigidity of muscles. Increase of deep reflexes with clonus of patella. Diffuse tremors. I.Q. 10. Excitable, unco-operative, low-grade idiot.

Family LXXXI.—Father, Ph. neg.: two sibs, G.S. Mother, Ph. neg.: two sibs, no information. Fraternity, five sibs: two boys, Ph. neg.

Case 129: P. John. Male, died at 6 years of pneumonia, O.B. 1. History negative. Well-developed boy unable to walk and talk. Tremors of hands. Low-grade idiot.

Case 130: P. Florence, Mans. 2271. Female, aged 14, Ph. pos., O.B. 4. Rigid posture and gait. Increase of deep reflexes. Diffuse tremors. I.Q. 10. Hyperactive, emotionally unstable, low-grade idiot.

Case 131: P. Michael. Male, aged 10, Ph. pos., O.B. 5. Increase of deep reflexes. Tremors of hands. I.Q. 20. Quiet, passive idiot. Living at home.

Family LXXXII.—Parents, Ph. neg. Father, alcoholic. Collaterals, no information. Fraternity, one sib. Three half sibs, Ph. neg.

Case 132: S. Harry, Mans. 1688. Male, aged 12, Ph. pos. Unable to walk. No motor paralysis. Increase of deep reflexes with clonus of foot. Diffuse tremors. I.Q. 10. Apathetic, quiet, low-grade idiot.

Family LXXXIII.—Father, schizophrenic, Ph. neg.: four sibs, H.S. Mother, G.S. No information concerning her relatives. Fraternity, two sibs.

Case 133: V. Louis, Mans. 1171. Male, aged 22, Ph. pos., O.B. 1. Instrumental delivery. Marked hypertonicity of muscles. Increase of deep reflexes with clonus of patella and foot. Kyphosis. Physical under-development. I.Q. 10.

Case 134: V. Floyd. Male, aged 15, Ph. pos., O.B. 2. History of convulsions. Increase of deep reflexes. Rigid gait and posture. I.Q. 20. Passive, quiet idiot.

Case 135: V. Alexander, Mans. 2260. Male, aged 12, Ph. pos., O.B. 4. Convulsive seizures at 2 years of age. Increase of deep reflexes with clonus of patella and foot. I.Q. 15. Excitable, destructive idiot.

State of New Hampshire.

Family LXXXV.—Father, Ph. neg.: two sibs, H.S. Mother, Ph. neg.: seven sibs, G.S. Fraternity, eight sibs: four boys and two girls, Ph. neg. Two sibs, d.i. Two half sibs. G.S.

Case 136: C. Francis, Lac. 710. Male, aged 19, Ph. pos., O.B. 2. Convulsive seizures at 18 years. Increase of deep reflexes with clonus of patella. Generalized tremors. I.Q. 10. Excitable, destructive, low-grade idiot.

Case 137: C. George, Lac. 711. Male, died at 12, O.B. 4. History of convulsions. Physical features similar to those of Case 136. I.Q. 10. Restless, low-grade idiot.

Family LXXXVI.—Parents, Ph. neg. Cousins. Collaterals, no information, but for a schizophrenic cousin. Fraternity, five sibs: four girls, Ph. neg. Four sibs, d.i.

Case 138: T. Stella, Lac. 1028. Female, aged 25, Ph. pos., O.B. 3. Congenital dislocation of the hip. Athetoid movements. I.Q. 14. Quiet, passive idiot.

Family LXXXVII.—Father, G.S.: died of heart disease. Mother, Ph. neg. Collaterals, no information. Fraternity, six sibs: one male and three females, Ph. neg. Four sibs, d.i.

Case 139: V. Eva, Lac. 508. Female, aged 32, Ph. pos., O.B. 2. Increase of deep reflexes with clonus of patella. Tremors of hands. I.Q. 10. Excitable, destructive idiot.

Case 140: V. Lillian. Female, aged 30, O.B. 3. Tremors of hand. Rigid posture. I.Q. 42. Quiet, unassuming imbecile. Living at home.

State of Massachusetts.

Family LXXXVIII.—Parents, G.S. Collaterals, no information. Fraternity, five sibs: two boys and one girl, Ph. neg. One sib, d.i.

Case 141: A. Vincent, Fern. 796. Male, aged 15, Ph. pos., O.B. 4. Increase of knee-jerks. Athetoid movements. I.Q. 20. Well-behaved, apathetic idiot.

Case 142: A. Peter, Fern. 7965. Male, aged 12, Ph. pos., O.B. 5. Increase of deep reflexes with clonus of patella. I.Q. 10. Placid, passive idiot.

Family LXXXIX.—Father, G.S.: died of accident, aged 35. Mother, Ph. neg.: one sib with three children, Ph. neg. Fraternity, five sibs: one boy, Ph. neg.; another boy, G.S., died at 12 years of typhoid. One sib, d.i.

Case 143: B. Mary, Wrenth. 3498. Female, aged 34, Ph. pos., O.B. 1. Instrumental delivery. Increase of knee-jerks. Tremors of hands. I.Q. 35. Quiet, well-behaved imbecile.

Case 144: B. Virginia. Female, aged 31. Physical examination essentially negative, Ph. pos., O.B. 3. I.Q. 60. Well-behaved, apathetic, high-grade defective. Living at home.

Case 145: B. Philomena. Female, aged 28, Ph. pos., O.B. 4. Tremors of hands. I.Q. 48. Quiet, unassuming, high-grade imbecile. Living at home.

Family XC.—Parents, Ph. neg. Collaterals not examined (one of father's sibs said to be defective). Fraternity, four sibs: one girl and one boy, Ph. neg. One sib, d.i.

Case 146: B. Lillian, Fem. 6989. Female, aged 25, Ph. pos., O.B. 2. Instrumental delivery. Increase of deep reflexes with clonus of patella. Athetosis. I.Q. 10. Destructive, hyperactive, low-grade idiot.

Case 147: B. Anna, Fern. 6031. Female, aged 23, Ph. pos., O.B. 3. Convulsions since the age of 3 years. Athetosis and tremors of hands. I.Q. 10. Excitable, restless, low-grade idiot.

Family XCI.—Parents, Ph. neg. Relatives, no information. Fraternity, four sibs: three girls, Ph. neg. Two sibs, d.i.

Case 148: C. Catherine, Fern. 6112. Female, aged 23, Ph. pos., O.B. 2. Convulsions three to four times a year. Increase of deep reflexes. Rigid posture. I.Q. 10. Quiet, passive, low-grade idiot.

Family XCII.—Father, Ph. neg.: six sibs, H.S., with seven children. G.S. Mother, Ph. neg.: five sibs, H.S., with five offspring, G.S. Fraternity, three sibs: one boy and one girl, Ph. neg.

Case 149: C. Robert, Wrenth. 3537. Male, aged 13, Ph. pos., O.B. 3. Convulsions at 3 years. Increase of deep reflexes with clonus of patella and foot. I.Q. 10. Destructive, low-grade idiot.

Family XCIII.—Parents, Ph. neg.: no collateral investigated. Fraternity, few sibs: one boy and one girl, Ph. neg.

Case 150: C. Elizabeth, Wrenth. 862 Female aged 30, Ph. pos., O.B. 1. Instrumental delivery. Increase of deep reflexes with clonus of patella. Tremors of hands. I.Q. 20. Excitable, destructive idiot.

Case 151: C. Alice, Wrenth. 1512. Female, aged 26, Ph. pos., O.B. 3. Convulsions at 2 years. Rigid posture and gait. Increase of knee-jerks. I.Q. 10. passive, occasionally destructive idiot.

Family XCIV.—Father, Ph. neg.: four sibs with nine offspring, G.S.: another sib is the father of Case 154. Mother, Ph. neg.: three sibs with five children, Ph. neg.; two other sibs, G.S. Fraternity, six sibs: two boys and two girls, Ph. neg.

Case 152: D. Nora, Belch. 1550. Female, aged 12, Ph. pos., O.B. 2. Increase of deep reflexes with clonus of foot. Athetoid movements of hands. I.Q. 12. Quiet, passive idiot.

Case 153: D. Jeremiah. Male, died at 6 years of dysentery, O.B. 4. History negative. Physical development normal. Physical examination reported negative. I.Q. below 10. Physical and mental features similar to Case 152.

Family XCIVa (This family was not examined personally).—Parents, H.S. Father, uncle of Cases 152, 153. Fraternity, four sibs: two girls and one boy, H.S.

Case 154: D. Thomas. Male, died of pneumonia, aged 5 years, O.B. 4. History negative. The patient was a well-developed, physically normal, low-grade idiot, who, in the opinion of the attending physician, had striking similarities to Case 153.

Family XCV.—Parents, Ph. neg.: ten sibs, G.S. Fraternity, one sib.

Case 155: D. Pauline, Wrenth, 4306. Female, aged 12, Ph. pos. Choreatic movements. Slight tremors of hands. Echolalia. I.Q. 32. Hyperactive imbecile.

Family XCVI.—Parents, Ph. neg. Collaterals, no information. Fraternity, one sib.

Case 156: D. Leo, Fern. 3808. Male, aged 35, Ph. pos. Instrumental birth. Convulsions in late infancy. Increase of deep reflexes with clonus of patella. I.Q. 10. Excitable, destructive, low-grade idiot.

Family XCVII.—Father, Ph. neg.: two sibs with three offspring, H.S. Mother, Ph. neg.: two sibs with three offspring, H.S. Fraternity, three sibs.

Case 157: F. Anna. Female, died at 12 years, O.B. 1. Low-grade idiot, well developed and physically normal. History negative. Striking similarities to Case 158.

Case 158: F. John, Wrenth. 3195. Male, aged 13, Ph. pos., O.B. 2. Tremors of hands. Increase of deep reflexes. I.Q. 20. Quiet, passive idiot.

Case 159: F. Tom. Male, aged 13. Ph. pos., O.B. 3. Dissimilar twin of Case 158. History negative. The urine was tested, but the patient was not personally examined. The I.Q. was not available. He began to talk at 5 years.

Family XCVIII.—Parents, Ph. neg. Collaterals, no information. Fraternity, three sibs: one boy and one girl, Ph. neg.

Case 160: F. Elen, Fern. 6171. Female, aged 38, Ph. pos., O.B. 3. Convulsions in late infancy. Marked tremors. Increase of deep reflexes with clonus of patella. I.Q. 10. Passive, low-grade idiot.

Family XCIX.—Father, Ph. neg.: four sibs with four offspring, Ph. neg. Mother, Ph. neg.: three sibs, G.S. Fraternity, three sibs: one boy and one girl, Ph. neg.

Case 161: F. Charles, Wrenth. 4275. Male, aged 16, Ph. pos., O.B. 1. History negative. Tremors of hands. I.Q. 32. Quiet, well-behaved imbecile.

Family C.—Both parents dead, G.S. Collaterals, no information. Fraternity, six sibs: two girls, Ph. neg.; two boys, G.S.: three sibs, d.i.

Case 162: F. Edna, Belch. 623. Female, aged 38, Ph. pos., O.B. 1. Convulsions in childhood. Increase of knee-jerks. Tremors of hands. I.Q. 32. Quiet, well-behaved imbecile.

Case 163: F. Mildred, Belch. 1637. Female, aged 27, Ph. pos., O.B. 6. Physical examination essentially negative. I.Q. 60. Well-behaved, unassuming, high-grade defective. The patient had an illegitimate child, aged 2, Ph. neg.

Family CI.—Father, Ph. neg.: one sib with three children, H.S. Mother, G.S.: died at 42 years. Fraternity, three sibs: two girls, H.S.

Case 164: F. Marjorie, Wrenth, 3331. Female, aged 15, Ph. pos., O.B. 3. Athetoid movements. I.Q. 10. Quiet, passive idiot.

Family CII.—Father, Ph. neg.: two sibs, H.S. Mother, Ph. neg.: two sibs with eight offspring, G.S. Fraternity, two sibs: one boy, Ph. neg.

Case 165: G. David, Fern. Male, aged 15, Ph. pos., O.B. 1. History of convulsions. Increase of deep reflexes with clonus of patella. Tremors. I.Q. 20.

Family CIII.—Parents, Ph. neg. Collaterals not investigated. Fraternity, four sibs: two boys, Ph. neg.

Case 166: G. Miriam, Fern. 6136. Female, aged 24, Ph. pos., O.B. 1. Increase of deep reflexes. Right Babinski. I.Q. 10.

Case 167: G. Barbara, Fern. 6137. Female, aged 19, Ph. pos., O.B. 4. Diffuse tremors. Increase of deep reflexes. I.Q. 10. Low-grade, unco-operative idiot.

Family CIV.—Father, Ph. neg.: four sibs with five offspring, G.S. Mother, Ph. neg.: four sibs, H.S. Fraternity, four sibs: two boys and one girl, Ph. neg.

Case 168: H. Catherine, Belch. 2139. Female, aged 6, Ph. pos., O.B. 4. Unsteady gait. Tremors of hands. I.Q. 12. Quiet, passive idiot.

Family CV.—Parents, H.S.: five sibs, H.S. Fraternity, one sib.

Case 169: H. Joseph, Wrenth, 4172. Male, aged 14, Ph. pos. Choreatic movements of hands. I.Q. 14. Passive, occasionally restless idiot.

Family CVI.—Father, G.S.: died at 55 years of heart disease: one sib, Ph. neg. Mother, Ph. neg.: no sibs. Fraternity, four sibs: two boys and one girl, Ph. neg. One sib, d.i.

Case 170: H. Frances, Fern. 6739. Female, aged 27, Ph. pos., O.B. 2. Tremors of hands. I.Q. 24. Quiet, phlegmatic, low-grade imbecile.

Family CVII.—Father, Ph. neg. Mother, G.S.: dead. Collaterals, no information. Fraternity, three sibs: one boy, Ph. neg.

Case 171: H. Vincent, Wrenth. 2553. Male, aged 24, Ph. pos., O.B. 2. Increase of deep reflexes. I.Q. 10. Quiet, passive idiot.

Case 172: H. Nancy, Wrenth. 4015. Female, aged 22, Ph. pos., O.B. 3. Convulsions at 3 years. Increase of deep reflexes with clonus of patella. Marked tremors. I.Q. 18. Well-behaved, passive idiot.

Family CVIII.—Father, Ph. neg.: sibs not examined. Mother, Ph. neg.: four sibs with six children, G.S. Fraternity, seven sibs: four boys and one girl, Ph. neg. Two half sibs, Ph. neg.

Case 173: K. Inez. Female, died in Monson State Hospital, Palmer, Mass., aged 8, O.B. 2. Epileptic attacks two to three times a month. Physical examination essentially negative. I.Q. 26.

Case 174: K. David, Wrenth. 4088. Male, aged 11, Ph. pos., O.B. 5. Increase of deep reflexes with clonus of patella. I.Q. 14. Quiet, passive idiot.

Family CIX.—Father, Ph. neg.: two sibs with three children, G.S. Mother, Ph. neg.: one sib with two children, G.S. Fraternity, two sibs.

Case 175: K. Katherine, Wrenth. 1885. Female, aged 17, Ph. pos., O.B. 1. Marked tremors. Increase of deep reflexes with clonus of patella. I.Q. 10. Quiet, passive idiot.

Case 176: K. Frieda. Female, died at 6 years of pneumonia, O.B. 2. History negative. Low-grade idiot. Physical and mental features strikingly similar to Case 175.

Family CX.—Parents, Ph. neg. Collaterals not examined. Fraternity, two sibs: one girl, Ph. neg.

Case 177: K. Roberta, Wrenth. 3490. Female, aged 17, Ph. pos., O.B. 2. Increase of deep reflexes. Marked athetoid movements of hands. I.Q. 10. Quiet, passive idiot.

Family CXI.—Father, H.S. Mother, Ph. neg. Collaterals, not examined (a mother's sib reported mentally defective). Fraternity, one sib.

Case 178: K. Margaret, Belch. 1788. Female, aged 14, Ph. pos. Diffuse tremors. Increase of knee-jerks. I.Q. 20. Quiet, apathetic idiot.

Family CXII.—Father, Ph. neg.: one sib with four children, Ph. neg. Mother, Ph. neg.: no information concerning her sibs. Fraternity, five sibs: four boys, Ph. neg. One sib, d.i.

Case 179: J. Helen, Belch. 2121. Female, aged 5, Ph. pos. Instrumental delivery. Increase of deep reflexes with clonus of patella. Diffuse tremors. Inability to walk. I.Q. 10. Apathetic, quiet idiot.

Family CXIII.—Father dead, G.S. Mother, Ph. neg.: five sibs, G.S. Fraternity, one sib.

Case 180: J. William, Fern. 7490. Male, aged 22, Ph. pos. Convulsions at the age of 2 years. Increase of deep reflexes with clonus of patella. Athetoid movements. I.Q. 10. Quiet, passive idiot.

Family CXIV.—Parents dead, G.S. No information concerning collaterals. Fraternity, four sibs: one male, Ph. neg., with five children, Ph. neg. Three sibs, d.i.

Case 181: J. Mary, Wrenth. 1231. Female, aged 42, Ph. pos., O.B. 2. Tremors of hands. I.Q. 40. Well-behaved, apathetic imbecile.

Case 182: J. Ellen, Wrenth. 799. Female, aged 40, Ph. pos., O.B. 3. Increase of deep reflexes with clonus of patella and foot. Tremors of hands. I.Q. 22. Quiet, passive, low-grade imbecile.

Case 183: J. Tracy. Female, aged 35, O.B. 4. Tremors of hands. I.Q. 48. Well-behaved, submissive imbecile. Living in an orphanage.

Family CXV.—Father, Ph. neg.: three sibs with five children, G.S. Mother, Ph. neg. Fraternity, six sibs: two girls and one boy, Ph. neg.

Case 184: L. Margaret, Wrenth. 3154. Female, died of *status epilepticus*, aged 13, O.B. 3. Increase of deep reflexes. I.Q. 10. Quiet, low-grade idiot.

Case 185: L. Francis, Wrenth. 3764. Male, aged 14, Ph. pos., O.B. 4. Cæsarian birth. Increase of knee-jerks. Choreic movements of hands. I.Q. 10. Hyperactive, destructive, low-grade idiot.

Case 186: L. Anthony, Wrenth. 3722. Male, aged 14, Ph. pos., O.B. 4. Identical twin of Case 185. Increase of knee-jerks. Choreic movements of hands. I.Q. 10. Hyperactive, low-grade idiot.

Family CXVI.—Father, Ph. neg.: no fraternity. Mother, Ph. neg.: one sib, H.S. Fraternity, two sibs: one boy, Ph. neg.

Case 187: M. John, Wrenth. 4897. Male, aged 9, Ph. pos., O.B. 2. Instrumental delivery; induced premature birth because of toxæmia in the mother. Increase of deep reflexes with clonus of patella. I.Q. 10. Apathetic, at times destructive, low-grade idiot.

Family CXVII.—Parents, Ph. neg. Collaterals, no information. Fraternity, four sibs: one boy and two girls, Ph. neg.

Case 188: M. Peter Wrenth. 2038. Male, aged 18, Ph. pos., O.B. 3. History negative. Choreo-athetoid movements of hands. Tics of the facial muscles. I.Q. 10. Passive idiot.

Family CXVIII.—Father, Ph. neg.: one sib with three children, Ph. neg. Mother, Ph. neg.: one sib with three children, G.S. Fraternity, four sibs: two girls, Ph. neg. Two sibs, d.i.

Case 189: M. Mary. Female, died at 4 years, O.B. 2. Low-grade idiot, physically normal, with a negative history.

Case 190: M. John, Fern. 6788. Male, aged 21, Ph. pos., O.B. 2. Increase of deep reflexes, I.Q. 10. Hyperactive, excitable idiot.

Family CXIX.—Father, Ph. neg.: two sibs with two children, G.S. Mother, Ph. neg.: one sib with one child, G.S. Fraternity, five sibs: two boys and two girls, Ph. neg.

Case 191: M. Valentine, Wrenth. 4346. Female, aged 16, Ph. pos., O.B. 4. Slight tremors of hands. I.Q. 36. Apathetic, well-behaved imbecile.

Family CXX.—Father, Ph. neg.: no sibs. Mother, G.S.: died at 38 years of Bright's disease; two sibs with two children, G.S. Fraternity, four sibs: two males, H.S.

Case 192: O. Sartene, Fern. 8158. Female, aged 28, Ph. pos., O.B. 1. Increase of deep reflexes. I.Q. 33. Quiet, seclusive imbecile.

Case 193: O. Isabelle, Fern. 8159. Female, aged 20, Ph. pos., O.B. 3. Physical examination essentially negative. I.Q. 44. Well-behaved, shy imbecile.

Family CXXI.—Parents dead, H.S. Collaterals not examined. Fraternity, three sibs: one boy and one girl, Ph. neg.

Case 194: P. Robert, Wrenth. Male, aged 17, Ph. pos., O.B. 1. Instrumental delivery. Increase of knee-jerks. I.Q. 18. Quiet, passive idiot.

Family CXXII.—Father, Ph. neg.: one sib died of epilepsy; his son was schizophrenic, Ph. neg. Mother, Ph. neg. Fraternity, one sib.

Case 195: R. Louise, Belch. 1911. Female, aged 6, Ph. pos. Increase of deep reflexes. Diffuse tremors. Unsteady gait. I.Q. 14. Quiet idiot.

Family CXXIII.—Father, Ph. neg.: one sib, G.S. Mother, G.S.: died of cerebral hæmorrhage: one sib with two children, G.S. Fraternity, three sibs: one boy, Ph. neg.

Case 196: R. Anstra, Wrenth. 1271. Female, aged 33, Ph. pos., O.B. 2. Jerking movements of legs and arms. Increase of knee-jerks. I.Q. 10. Excitable, hyperactive, low-grade idiot.

Case 197: R. Lidia. Female, died in Wrenth., aged 10, O.B. 1. Convulsions from four to eight years of age. Increase of deep reflexes with clonus of patella. Tremors. I.Q. 16. Well-behaved, quiet idiot.

Family CXXIV.—Father, Ph. neg.: four sibs with six children, G.S.; another child, I.Q. 65, Ph. neg., hemiplegic. Mother, Ph. neg.: three sibs with fourteen children, G.S. Fraternity, two sibs: one boy, Ph. neg.

Case 198: S. Effe, Fern. 6818. Female, aged 12, Ph. pos., O.B. 1. Convulsions from four years to eight years of age. Increase of deep reflexes with clonus of patella. Tremors. I.Q. 16. Well-behaved, quiet idiot.

Family CXXV.—Father, Ph. neg.: two sibs with eleven children, Ph. neg. Mother, Ph. neg.: six sibs, no information. Fraternity, three sibs: one boy, Ph. neg.

Case 199: W. Stephanie, Belch. 1593. Female, aged 11, Ph. pos., O.B. 1. Instrumental delivery. Convulsions at four years. Physical examination essentially negative. Gait normal. I.Q. 10.

Case 200: W. Martha, Belch. 1902. Female, aged 6, Ph. pos., O.B. 3. History of convulsions. Increase of deep reflexes. Unco-ordinated gait. I.Q. 32. Quiet, lethargic imbecile.

Elaboration of the Material.

There is enough justification in assuming that in some instances conclusive evidence may be obtained whereby types of mental deficiency which are significantly determined by the structure of the sexual cells (i.e., hereditary) can be distinguished from types which are determined by external agencies operating during the course of development. On the basis of this assumption, the problem underlying this study is to investigate whether genetic mechanisms or environmental factors play a determinant role in the causation of phenylpyruvic oligophrenia.

There are factual data proving that the condition runs in families. Out of 125 families which have been examined, 51 have two or more members affected. If the sibships with only one member are excluded, 46% of sibships have two or more affected sibs and 68% of the cases show familial incidence.

Mere chance may be considered an explanation of high familial incidence of a disease only when the condition is frequent. Since phenylpyruvic oligophrenia shows a frequency of the order of 0·004% (p. 721), this explanation is easily ruled out.

Familial incidence of a disease may be caused by genetic mechanisms. However, its possible causation by environmental factors, when there occurs joint exposure of several siblings to determining causes existing in the environment, should be first taken into account.

(*a*) Environmental Factors.

Under this heading, the various factors which are usually considered to be instrumental in detecting the influence of environmental agencies will be briefly analyzed.

(1) *Order of birth.*—When a disease occurs with great frequency with relation to a particular position in the order of birth, environmental factors operating only, or mainly, during that particular period of time may be suspected. If a condition is due solely to genetic mechanisms, it is reasonable to expect that it should be found at random in a sibship without relation to the order of birth.

Table II represents the order of birth of the patients in the present material. The expected number has been calculated according to Weinberg (1913) and

Brugger's (1930*b*) method, in which the expectation for each birth position in S-membered family is calculated, adding the ratio between affected sibs (R) and number of members (S).

TABLE II.—*Order of Birth (Weinberg-Brugger's Method).*

S.	R.	R/S.	Expected number.	Observed number.
1	15	15·00	64·20	59
2	27	13·50	49·20	48
3	41	13·88	35·70	35
4	40	10·00	21·92	26
5	25	5·00	11·92	16
6	22	3·66	6·92	8
7	12	1·71	3·26	2
8	6	0·50	1·55	2
9	2	0·22	1·05	1
10	5	0·50	0·83	1
11	0	0·00	0·33	1
12	4	0·33	0·33	0

It will be seen that the fit between observed and expected values is satisfactory enough to assume that the disease occurs at random.

In Table III the number of first- and last-born affected sibs is presented according to Schulz's (1931) method. The figures are obtained by summing the first, and last-born affected sib of each family with the exclusion of one-membered families. The expectation is calculated by dividing the sum of the affected sibs in each group of families of the same number of members by this number.

It will be seen that the number of the first- and last-born affected sibs (43 and 50 respectively) is not far from the theoretical expectation (49·5). It appears, therefore, that factors usually associated with excess of affected first-born (trauma at birth) or with excess of affected last-born sibs (maternal exhaustion) are unlikely to play a role in the causation of the disease.

(2) *The age of the parents* at the time of conception is considered to have a similar significance. A great frequency of affected individuals among offspring of old parents suggests the possibility of environmental factors connected with parental exhaustion.

Table IV shows the distribution of parental ages of these patients. It will be seen that the figures do not differ significantly from the normal.

(3) *High prolificity of the parents* of affected children may also offer some indirect evidence in favour of exogenous factors as a cause of the condition. The total number of children in the present material averages 3·6 as compared with 4·9 in mongolism (Penrose, 1932). However, owing to the method of

TABLE III.—*First- and Last-born Affected Sibs (Weinberg-Schulz Method)*

Size of sibship.	Number of affected sibs with order of birth. 1.	2.	3.	4.	5.	6.	7.	8.	9.	10.	11.	12.	Expected number.
1	15	..	..	..	..	..	..	..	..	..	..	..	..
2	12	15	..	..	..	..	..	..	..	..	..	..	13·5
3	14	13	14	..	..	..	..	..	..	..	..	..	13·7
4	7	13	10	10	..	..	..	..	..	..	..	..	10·0
5	3	2	6	9	6	..	..	..	..	..	..	..	5·2
6	4	3	2	5	5	3	..	..	..	..	..	..	3·7
7	2	1	2	1	2	2	2	..	..	..	..	..	1·7
8	1	1	0	1	1	2	0	0	..	..	..	..	0·7
9	0	0	0	0	0	1	0	1	0	..	..	..	0·2
10	0	1	0	1	0	1	0	1	1	0	..	..	0·5
11	0	0	0	0	0	0	0	0	0	0	0	..	0·0
12	0	0	1	0	1	0	0	0	0	1	1	0	0·3
	43 : number of first-born.								Number of last-born :			50	49·5

TABLE IV.—*Age of Parents at Birth of Patients.*

Age of father.	Age of mother. –19.	20–24.	25–29.	30–34.	35–39.	40–44.	Total.	In %.
20–24	8	27	2	..	..	..	37	18·5
25–29	1	20	22	2	..	..	45	22·5
30–34	..	4	24	21	1	..	50	25·0
35–39	1	2	7	16	6	1	33	16·5
40–44	..	1	2	7	11	1	22	11·0
45–49	..	..	..	2	2	2	6	3·0
50–	..	2	1	2	1	1	7	3·5
Total	10	56	58	50	21	5	200	..
%	5	28	29	25	10·5	2·5	..	..

https://doi.org/10.1192/bjp.85.357.719 Published online by Cambridge University Press

collecting the data, this figure needs a correction, since obviously the larger the family, the higher the probability of its being taken into consideration. In Table V the data are shown corrected according to the method of Lenz (1925).

TABLE V.—*Corrected Number of Children per Family (Lenz's Method).*

No. of children (*a*)	1	2	3	4	5	6	7	8	9	10	12	.	Total
No. of families (*b*)	15	23	29	26	13	10	5	3	1	1	1	.	127
b/*a* (*c*) .	15	11·5	9·66	6·5	2·6	1·66	0·71	0·37	0·11	0·10	0·08	.	48·29

Correct ratio (*b* : *c*) = 2·6

It will be seen that the correct ratio (*b* : *a*) is 2·6. If childless families are accounted for, the ratio is 2·2, 15 being considered the average percentage of childless families. Therefore, the corrected average number of children in families with oligophrenic members is not above the average of families in the general population.

(4) *High percentage of miscarriages and stillborn* among the sibs of affected individuals may suggest the presence of conditions connected with local pathology of the uterus or with hormonic exhaustion. In the present material in 10 families there was a record of miscarriage or stillbirth. In 26 families one or more sibs died in early infancy. These figures are not significantly above expectation.

(5) *Syphilis.*—Wassermann reaction in the blood was available in the great majority of the cases. Only one patient (No. 90) had a positive test—a woman who had been sexually promiscuous for several years. That syphilis was acquired during this period is therefore probable. In 30 patients the spinal fluid was also examined; globulin reactions, Wassermann and colloidal tests always gave negative results. Moreover, no clinical signs of congenital lues were found in any of the patients. Clinical evidence of parental syphilis was lacking in the whole series of cases except in two instances, where there was a suspicion of syphilis in the father.

(6) *Alcoholism* in the father was observed in too few cases (2%) to constitute a significant factor.

(7) *Diseases of the mother* during pregnancy were observed in a very few cases (2%). In only 1 case (187) was the condition sufficiently serious to require premature delivery. This case and Case 121 are the only instances in the whole material of premature birth.

(8) *Trauma at birth* might be suspected in 10 cases where a history of instrumental delivery was given. In no case, however, were signs of intracranial injury observed in the early life of the patient. Moreover, the percentage of difficult deliveries is not significantly above expectation.

(9) *Post-natal diseases.*—In the great majority of cases no diseases were

observed in infancy and childhood. In fact, the discrepancy between physical and mental development was striking. Throughout the series, exanthematic diseases, when occurring, were unaccompanied by cerebral symptoms. Severe diseases with probable symptoms of cerebral involvement were observed in 4 cases. However, there was some evidence that mental defect was established prior to the disease.

There was a high percentage of epileptic seizures (21%) among these patients. These seizures were of the *grand mal* type, and occurred irregularly. In all but two cases, there were clear signs of mental retardation prior to the occurrence of fits, so that a causal relationship of the seizures to oligophrenia can hardly be suspected.

(10) The distribution of the patients according to *geographical environment* failed to show significant data: 41% of the families lived in large cities, 35% in small towns and 24% in rural environment.

That patients were derived from populations of variable social standing is shown by examining the distribution of patients according to paternal occupation: 10% belong to the professional class, 26% to the minor professional and the clerical, 32% to the skilled labour, 32% to the unskilled labour.

(11) *The race distribution* shows: Irish 21%, Italian 18%, English 12%, German 6%, Slavonic 10%, Dutch 3%, Scandinavian 2%, mixed 28%. This distribution, when compared with the figures of the population of the institutions visited, fail to show any important variation in susceptibility among Aryan races. It will be noted that the Jewish race is not represented, although over a thousand Jewish defectives were examined.

(12) *Twins.*—Among patients in the series there was one pair of uniovular twins (185 and 186), both affected. Of another pair (Cases 21 and 22), also both affected, uniovularity was doubtful, since one member had died. There were also two pairs of binovular twins; one pair had two members affected (Cases 158 and 159). The second pair had one member affected (Case 1) and the other normal; although this last had died, school reports were available showing high scholastic performances. These observations on twins are not a proof for the hereditary causation of the disease. However, there are no elements in these data excluding genetic mechanisms.

Summarizing the findings with regard to the importance of various environmental agencies, it may be concluded that without exception the data indicate the improbability that factors due to the external environment play a significant role in the causation of the disease.

(*b*) Hereditary Factors.

The high familial incidence of phenylpyruvic oligophrenia strongly suggests the possibility of a genetic mechanism. The material will be examined, therefore, for evidence of genetic factors, to determine whether the data are

consistent with the quantitative requirements of the theory of a particular hypothesis of inheritance.

(1) *Single dominant gene.*—This hypothesis is readily excluded. In fact, there is no direct transmission from one generation to another; with the only exception of one sibship (No. 14) all affected children have normal parents. Moreover, the ratio of affected to normal children is far from the theoretical expectation.

(2) *Two complementary dominant genes.*—If a condition is due to the interaction of two independent genes whose presence is not manifest when either is present without the other, the expected percentage of affected offsprings of normal parents is expressed by the formula (Hogben, 1932)—

$$\frac{1}{4 - 2I - 2m + Im},$$

where I and m are the respective frequencies of the two complementary dominant genes. It will readily be seen that, when the genes are rare and of the same order of magnitude, the percentage approaches 25—a figure which appears in agreement with the observation in the present material. Moreover, of the three matings of one affected and one normal parent (Families 14, 64, 100), one resulted in two affected and two normal offsprings as expected in this type of heredity.

The excess of cousin-marriages among parents of affected individuals offers some evidence against the intervention of dominant genes. More decisive evidence, however, is offered by the ratio of affected individuals having one affected parent to affected individuals having no affected parents. From the frequency of the dominant genes and the frequency of the different types of matings between one affected and one normal parent, Hogben (1932) deduces the following formulæ expressing the frequencies of affected individuals with one affected parent and with two normal parents respectively:

$$\frac{2(1-m)^2[(m^4+10m^3)(1-m)+15m^2(1-m)^2+8m(1-m)^3+(1-m)^4]}{m^2+4m(1-m)+4(1-m)^2}$$

$$\frac{2m^2(1-m)^4+4m(1-m)^5+2(1-m)^6}{m^2+4m(1-m)+4(1-m)^2},$$

where m is the frequency of both genes, supposedly of the same order of magnitude. It will readily be seen that if m is very small, both formulæ approximate the same value. In other words, when the condition is rare the number of affected individuals having one affected parent (in the present material, 2) equals the number of affected individuals having normal parents (in the present material, 197). Therefore, the observed figures are far from the theoretical expectation, even when the fact is taken into account that a

certain number of patients are low-grade or segregated and therefore prevented from parenthood.

(3) *Sex-linked genes.*—This hypothesis may be also excluded, since it is not consistent with the ratio of males and females affected. The percentage is 58·2 females to 41·8 males, 10,338 males having been examined against 9,962 females. The slight excess of females is not significant. The ratio of affected males to affected females, as compared with that of normal males to normal females, in the sibships, with two or more affected sibs, is 1 : 2 and 5 : 4 respectively. In these families, therefore, there is a clear excess of affected females over affected males, the real cause of which remains undetermined.

(4) *Partially sex-linked recessive gene.*—Recently Haldane (1936) offered strong evidence in favour of the hypothesis that incomplete sex-linkage occurs in man. According to this theory, the X and Y chromosomes possess a homologous segment in which chiasmata occur. The genes carried in these pairing segments, then, exhibit incomplete sex-linkage, since if chiasma occurs between the locus of this gene and the sex-determining segment it crosses over from the X to the Y chromosome and conversely.

In order to investigate such a possibility in the present material, Haldane's indirect method will be used, since the genotype of the father is unknown.

Applying Fisher (1935) treatment of Haldane's (1934) procedure in the detection of linkage, the function—

$$u = (a - 3b - c + 3d)^2 - (a + 9b + c + 9d)$$

(where $a\ b\ c\ d$ are the four classes, namely, male normal, male affected, female normal, female affected and $a - b - c - d = s$) is calculated for each sibship.* The sum of u is -16. Fisher's first method, which is used when a complete census of the population had been made, gives—

$$1 - 4x = \frac{S(u)}{S(k)} = \frac{-16}{4310{\cdot}9} = 0{\cdot}0037,$$

where x is the estimate of $\xi = \chi - \chi^2$ (χ being the cross-over frequency) and $k = s(s-1)\dfrac{4^s - 3^{s-2}}{4^s - 3^s}$. The second method, used when each family has been ascertained only singly, gives—

$$1 - 4x = \frac{S(u)}{S[(s-1)\ (s\ 4)]} = \frac{-16}{3148} = -0{\cdot}00508.$$

Fisher's third method, which is used when ascertainment is complete, each family being brought into record through each of its affected members (r), gives—

$$1 - 4x = \frac{S(ru)}{S[r(s-1)\ (s\ 4)]} = \frac{-181}{16166} = -0{\cdot}011.$$

* The table giving the value of u, $s\ (-1)\ (s-4)$, and k has been omitted.

https://doi.org/10.1192/bjp.85.357.719 Published online by Cambridge University Press

It will be seen that in no case the value of $1 - 4x$ is significantly different from 0. These data seem to exclude, therefore, partially sex-linked genes.

(5) *Recessive autosomal gene.*—This hypothesis seems the most probable one at a first examination of the data. Each element of the present material, therefore, will be analyzed in order to determine whether the observation is consistent with the theoretical expectation on this particular hypothesis. A rare recessive gene can be recognized by (*a*) the ratio of affected to normal children in the sibship; (*b*) the rate of consanguinity among the parents of affected individuals; (*c*) the distribution of the character among ascendant and collateral relatives of affected individuals.

(A) *Ratio of affected to normal children.*—The theoretical expectation of this ratio in the sum of sibships that have one or more affected sibs follows the well-known Mendelian figures. Thus, on the hypothesis of a single recessive gene, without influence on viability, three-quarters of the sibs will be normal and a quarter affected when both parents are heterozygous, half will be normal and half affected when one of the parents is affected and one heterozygous, no sib will exhibit the character when one parent is affected and the other normal, and finally, all sibs will be affected when both parents are affected. In the present material, all parents of affected individuals, with the exception of Family 14*a*, were normal; i.e., on the hypothesis of a single recessive gene, all but two of the recessive homozygotes are the result of the mating of two heterozygous parents. Therefore it is expected that 25% of the offspring will show the character. However, in the present material the observed raw percentage is 42. That in human recessive traits such high percentages occur is a well-known fact. Since human families are small, a certain number of heterozygous parents will have no affected children; these families, therefore, escape consideration, whereas other families in which the proportion of affected children is in excess of expectation will be included in the count. Moreover, sibships containing more than one affected member are more likely to be recorded than those in which only one is affected.

Corrections of the raw percentage by special methods of statistical analysis have been suggested. The following will be considered:

Methods of Weinberg (1925).

"*Sib method.*"—Since sibships have been taken into account because they contain an affected sib, its occurrence is not merely probable, but certain. Representating an excess due to the method of collecting material, this sib is eliminated in the calculation. The remaining sibs will have the same probability of being affected as before this elimination had been made, since the hereditary character of a sib depends upon the genetic constitution of the parents, but is independent from the genetic constitution of the other siblings. The ratio of recessives, then, is drawn from all the siblings of the affected sib,

with the exclusion of this last. If two or more affected individuals occur in the same sibship, each of these and its sibship is considered independently. In fact, since a sibship has been selected only because of the occurrence of one affected individual, if another occurs the sibship has to be considered as a new one.

In brief, the calculation is made as follows: From the number of siblings (s) in a family, one affected is eliminated. The result ($s - 1$) is taken as many times as the number of recessive (t) occurring in the sibship, with the exclusion of the one previously eliminated. The figure $t\ (s - 1)$ is thus obtained, which expresses the normal siblings of affected children; the figure $(t - 1)$ will then express the affected siblings of affected children, and the ratio,

$$100\ \frac{t(r-1)}{t(s-1)},$$

will indicate the percentage of affected to normal siblings. The mean quadratic error is given by the formula:

$$P\ \frac{(100 - P)}{S} \text{ where } P = 100\ \frac{(t-1)}{(s-1)} \text{ and } S = \text{the total number of sibs.}$$

The present material is ordered in Table VI according to this method.

The ratio thus obtained is 28·8%, the mean error 2·14. The difference between observation and expectation, therefore, is less than twice the mean error.

"*Proband-method.*"—The "sib method" is correctly used only when all the affected offspring are ascertained at random. In the present material a certain number of cases were collected mediately, i.e., starting from an affected individual, who was observed in an institution, and investigating its family, which was not taken at random, but was selected on account of having this affected sib. Where the procedure of ascertainment involves such a choice the so-called "proband method" is indicated. The affected individuals are divided into "proband", i.e., individuals from which the genetic investigation starts, and "secondary cases", i.e., affected sibs who have been collected mediately. As in the previous method the "proband" is not computed, but only his sibs. When a "proband" happens to be a sib of another "proband", he is considered in this relation as an affected sib.

The formula, $100\ \frac{p(t-1)}{p(s-1)}$, expresses the method, where p is the number of "probands", t the number of affected sibs and s the number of sibs. The mean error may be calculated with the formula used for the "sibs method".

In Table VII the present material has been arranged according to the "proband method". All the cases observed outside the institution are considered secondary cases.

https://doi.org/10.1192/bjp.85.357.719 Published online by Cambridge University Press

TABLE VI.—*Weinberg's "Sib Method".*

Family.	*s.*	*t.*	*t*(*s*−1).	*t*(*t*−1).	Family.	*s.*	*t.*	*t*(*s*−1).	*t*(*t*−1).	Family.	*s.*	*t.*	*t*(*s*−1).	*t*(*t*−1).
1	7	2	12	2	46	3	1	2	0	92	3	1	2	0
2	3	1	2	0	47	1	1	0	0	93	4	2	6	2
3	4	1	3	0	48	3	3	6	6	94	6	2	10	2
4	2	2	2	2	49	4	3	9	6	94*a*	4	1	3	0
5	1	1	0	0	50	6	2	10	2	95	1	1	0	0
6	3	1	2	0	51	5	2	8	2	96	1	1	0	0
7	1	1	0	0	52	3	1	2	0	97	3	3	6	6
8	2	1	1	0	53	1	1	0	0	98	3	1	2	0
9	8	2	14	2	54	6	4	20	12	99	3	1	2	0
10	2	2	2	2	55	4	1	3	0	100	6	2	10	2
11	7	2	12	2	56	3	1	2	0	101	3	1	2	0
12	7	4	24	12	57	2	1	1	0	102	2	1	1	0
13	5	3	12	6	58	4	1	3	0	103	4	2	6	2
14	2	1	1	0	59	2	1	1	0	104	4	1	3	0
15	2	1	1	0	60	2	1	1	0	105	1	1	0	0
16	2	1	1	0	61	7	2	12	2	106	4	1	3	0
17	3	1	2	0	62	1	1	0	0	107	3	2	4	2
18	1	1	0	0	63	2	1	1	0	108	7	2	12	2
19	2	1	1	0	64	3	2	4	2	109	2	2	2	2
20	3	1	2	0	65	1	1	0	0	110	2	1	1	0
21	10	5	45	20	66	9	2	16	2	111	1	1	0	0
22	4	1	3	0	67	4	2	6	2	112	5	1	4	0
23	4	1	3	0	68	1	1	0	0	113	1	1	0	0
24	5	3	12	6	69	2	1	1	0	114	4	3	9	6
25	2	1	1	0	70	3	1	2	0	115	5	2	8	2
26	2	1	1	0	71	6	2	10	2	116	2	1	1	0
27	6	2	10	2	72	4	1	3	0	117	4	1	3	0
28	3	1	2	0	73	3	1	2	0	118	4	2	6	2
29	3	1	2	0	74	3	1	2	0	119	5	1	4	0
30	5	1	4	0	75	3	1	2	0	120	4	2	6	2
31	2	1	1	0	76	2	1	1	0	121	3	1	2	0
32	6	1	5	0	77	3	2	4	2	122	1	1	0	0
33	4	1	3	0	78	3	1	2	0	123	3	2	4	2
34	12	4	44	12	79	3	2	4	2	124	2	1	1	0
35	6	2	10	2	80	4	1	3	0	125	3	2	4	2
35*a*	8	2	14	2	81	5	3	12	6					
36	4	2	6	2	82	1	1	0	0	Total	467	197	652	188
37	5	1	4	0	83	2	2	2	2					
38	5	3	15	6	84	4	1	3	0					
39	3	2	4	2	85	8	2	14	2					
40	4	1	3	0	86	5	1	4	0					
41	4	1	3	0	87	6	2	10	2					
42	4	2	6	2	88	5	2	8	2					
43	3	2	4	2	89	5	3	12	6					
44	2	1	1	0	90	4	2	6	2					
45	5	2	8	2	91	4	1	3	0					

$$P = 100\,\frac{t(t-1)}{t(s-1)} = 28{\cdot}8$$

$$\sigma = \sqrt{\frac{100-P}{\Sigma s}} = \pm\, 2{\cdot}14$$

The ratio thus obtained is 24·8, the mean error 1·99. Expectation and observation, therefore, are strikingly agreed.

A modification of Weinberg's methods has been devised by Dahlberg (1930). The principle of this procedure, known as the method of the "late sibs" (*Spätere Geschwister*), is the independence of a character of a recessive from the genetic composition of its sibs. The probability of occurrence of recessive in a family remains unchanged in any subdivision of the sibship performed

https://doi.org/10.1192/bjp.85.357.719 Published online by Cambridge University Press

TABLE VII.—*Weinberg's "Proband Method".*

Family.	s.	t.	p.	p(s−1).	p(t−1).	Family.	s.	.	p.	p(s−1).	p(t−1).	Family.	s.	.	p.	p(s−1.	p(t−1).
1	7	2	2	12	2 .	46	2	1	1	2	0 .	93	4	2	2	6	2
2	3	1	1	2	0 .	47	1	1	1	0	0 .	94	6	2	1	5	1
3	4	1	1	3	0 .	48	3	3	2	4	4 .	94a	4	1	0	0	0
4	2	2	1	1	1 .	49	4	3	2	6	4 .	95	1	1	1	0	0
5	1	1	1	0	0 .	50	6	2	1	5	1 .	96	1	1	1	0	0
6	3	1	1	2	0 .	51	5	2	1	4	1 .	97	3	3	1	2	2
7	1	1	1	0	0 .	52	3	1	1	2	0 .	98	3	1	1	2	0
8	2	1	1	1	0 .	53	1	1	1	0	0 .	99	3	1	1	2	0
9	8	2	1	7	1 .	54	6	4	3	15	9 .	100	6	2	2	10	2
10	2	2	1	1	1 .	56	3	1	1	2	0 .	101	3	1	1	2	0
11	7	2	2	12	2 .	57	2	1	1	1	0 .	102	2	1	1	1	0
12	7	4	3	18	9 .	58	4	1	1	3	0 .	103	4	2	2	6	2
13	5	2	1	4	2 .	59	2	1	1	4	0 .	104	4	1	1	3	0
14	2	1	0	0	0 .	60	2	1	1	1	0 .	105	1	1	1	0	0
15	2	1	1	1	0 .	61	7	2	1	6	1 .	106	4	1	1	3	0
16	2	1	1	1	0 .	62	1	1	1	0	0 .	107	3	2	2	4	2
17	3	1	1	2	0 .	63	2	1	1	1	0 .	108	7	2	12	12	2
18	1	1	1	0	0 .	64	3	2	1	2	1 .	109	2	2	1	1	1
19	2	1	1	1	1 .	65	1	1	1	0	0 .	110	2	1	1	1	0
20	3	1	1	2	0 .	66	9	2	2	16	2 .	111	1	1	1	0	0
21	10	5	1	9	4 .	67	4	2	2	6	2 .	112	5	1	1	4	0
22	4	1	1	3	0 .	68	1	1	1	0	0 .	113	1	1	1	1	0
23	4	1	1	3	0 .	69	2	1	1	1	0 .	114	4	3	2	6	4
24	5	3	3	12	6 .	70	3	1	1	2	0 .	115	5	2	2	8	2
25	2	1	1	1	0 .	71	6	2	1	5	1 .	116	2	1	1	1	0
26	2	1	1	1	0 .	72	4	1	1	3	0 .	117	4	1	1	3	0
27	6	2	2	10	2 .	73	3	1	1	2	0 .	118	4	2	1	3	1
28	3	1	1	2	0 .	74	3	1	1	2	0 .	119	5	1	1	4	0
29	3	1	1	2	0 .	75	3	1	1	2	0 .	120	4	2	2	8	2
30	5	1	1	4	0 .	76	2	1	1	1	0 .	121	3	1	1	2	0
31	2	1	1.	1	0 .	77	3	2	1	2	1 .	122	1	1	1	0	0
32	6	1	1	5	0 .	78	3	1	1	2	0 .	123	3	2	1	2	1
33	4	1	1	3	0 .	79	3	2	2	4	2 .	124	2	1	1	1	0
34	12	4	1	11	3 .	80	4	1	1	3	0 .	125	3	2	2	4	2
35	6	2	2	10	2 .	81	5	3	1	4	2 .						
35a	8	2	1	7	1 .	82	1	1	1	0	0 .	Total	467	197	155	464	115
36	4	2	1	3	1 .	83	2	2	1	1	1 .						
37	5	1	1	4	0 .	84	4	1	1	3	0 .						
38	6	3	3	15	6 .	85	8	2	2	14	2 .						
39	3	2	1	2	1 .	86	5	1	1	4	0 .						
40	4	1	1	3	0 .	87	6	2	1	5	1 .						
41	4	1	1	3	0 .	88	5	2	2	8	2 .						
42	4	2	1	3	1 .	89	5	3	1	4	2 .						
43	3	2	2	4	2 .	90	4	2	2	6	2 .						
44	2	1	1	1	0 .	91	4	1	1	3	0 .						
45	5	2	1	4	1 .	92	3	1	1	2	0 .						

$$P = 100\,\frac{p(t-1)}{p(s-1)} = 24{\cdot}8$$

$$\sigma = \sqrt{\frac{100-P}{Ss}} = \pm 1{\cdot}99$$

according to some determined criterion—for instance, after the birth of a first recessive. Therefore, the Mendelian ratio of affected to normal children is to be expected in a group of children consisting of all the siblings born after the first recessive, i.e., with the exclusion of both the first recessive and the sibs born before it.

The material is arranged in Table VIII according to this method; s is the number of sibs per family, sB the number of sibs born before the first recessive, sA the number of recessives born after the first one.

https://doi.org/10.1192/bjp.85.357.719 Published online by Cambridge University Press

TABLE VIII.—*Dahlberg's "Late Sibs" Method.*

Family.	s.	sB.	sA.	rA.	Family.	s.	sB.	sA.	rA.	Family.	s.	sB.	sA.	rA.
1	7	0	6	1	45	5	3	1	1	89	5	0	4	2
3	4	2	1	0	48	3	0	2	2	90	4	1	2	1
4	2	0	1	1	49	4	1	2	2	91	4	1	2	0
9	8	4	3	1	50	6	4	1	1	93	4	0	3	1
10	2	0	1	1	51	5	0	4	1	94	6	1	4	1
11	7	4	2	1	52	3	1	1	0	97	3	0	2	2
12	7	0	6	3	54	6	1	4	3	99	3	0	2	0
13	5	1	3	2	56	3	0	2	0	100	6	0	5	1
15	2	0	1	0	57	2	0	1	0	102	2	0	1	0
17	3	1	1	0	58	4	0	3	0	103	4	0	3	1
20	3	1	1	0	61	7	2	4	1	106	4	1	2	0
21	10	1	8	4	63	2	0	1	0	107	3	1	2	1
22	4	1	2	0	64	3	0	2	1	108	7	1	5	1
24	5	1	3	2	66	9	5	3	1	109	2	0	1	1
25	2	0	1	0	67	4	1	2	1	114	4	1	2	2
27	6	3	2	1	69	2	0	1	0	115	5	2	2	1
28	3	1	1	0	70	3	0	2	0	117	4	2	1	2
29	3	0	2	0	71	6	0	5	1	118	4	1	2	1
30	5	3	1	0	72	4	1	2	0	119	5	3	1	0
32	6	2	3	0	73	3	1	1	0	120	4	0	3	1
33	4	1	2	0	74	3	0	2	0	121	3	0	2	0
34	12	2	9	3	75	3	0	2	0	123	3	1	1	1
35	6	0	5	1	77	3	0	2	1	124	2	0	1	0
35a	8	0	7	1	78	3	1	1	0	125	3	0	2	1
36	4	1	2	1	79	3	0	2	1					
37	5	2	2	0	80	4	2	1	0	Total	386	79	219	70
38	6	0	5	2	81	5	0	4	2					
39	3	1	1	1	83	2	0	1	1					
40	4	0	3	0	85	8	1	6	1					
41	4	1	2	0	86	5	2	2	0					
42	4	0	3	1	87	6	1	4	1					
43	3	0	2	1	88	5	3	1	1					

$$\text{Percentage} = 100\frac{PA}{SA} = 31{\cdot}9$$

$$\sigma = \sqrt{\frac{100-P}{S}} = \pm 2{\cdot}38$$

It will be seen that the percentage of recessives accordingly is 31·9 with a standard error 2·38.

When a "proband" material is used, Dahlberg suggested a modification of this procedure, consisting of excluding all the sibs which are born before the proband. In Table IX this method is presented.

With this modification, the ratio 29·4% is obtained with a mean error 2·36. The observation is therefore slightly above the expected figure.

It appears evident that Weinberg's methods suffer from the defect of partial utilization of the material, since all the sibships with one affected sib are eliminated. Moreover, single families with numerous affected children (as No. 21) acquire a great numerical significance, involving a risk of error.

"*A priori methods.*"—A second group of statistical methods, known as "*a priori*" methods (Apert, Bernstein, Hogben) is based upon a different treatment of the problem. A certain ratio theoretically determined on a certain type of heredity is assumed "a priori", and the number of affected children which is theoretically to be expected on that particular Mendelian hypothesis is calculated in each sibship. If there is agreement between expectation and

TABLE IX.—*Dahlberg's Method (Corrected for "Proband" Material).*

Family.	*s.*	*sB.*	*sA.*	*rA.*	Family.	*s.*	*sB.*	*sA.*	*rA.*	Family.	*S.*	*sB.*	*sA.*	*rA.*
1	7	0	6	1	42	4	0	3	1	88	5	3	1	1
3	4	2	1	1	43	3	0	2	1	89	5	0	4	2
4	2	0	1	1	45	5	3	1	1	90	4	1	2	1
9	8	4	3	1	48	3	1	1	1	91	4	1	2	0
10	2	0	1	1	49	4	1	2	2	93	4	0	3	1
11	7	4	2	1	51	5	0	4	1	94	6	1	4	1
12	7	0	6	3	52	3	1	1	0	97	3	1	1	1
15	2	0	1	0	54	6	3	2	2	99	3	0	2	0
17	3	1	1	0	56	3	0	2	0	100	6	0	5	1
20	3	1	1	0	57	2	0	1	0	102	2	0	1	0
21	10	3	6	3	58	4	0	3	0	103	4	0	3	1
22	4	1	2	0	61	7	2	4	1	106	4	1	2	0
24	5	1	3	2	63	2	0	2	1	107	3	1	2	1
25	2	0	1	0	66	9	7	1	0	108	7	4	2	0
27	6	3	2	1	67	4	1	2	1	109	2	0	2	2
28	3	1	1	0	69	2	0	1	0	114	4	1	2	1
29	3	0	2	0	70	3	0	2	0	115	5	3	1	0
30	5	3	1	0	71	6	0	5	1	117	4	2	1	0
32	6	2	3	0	72	4	1	2	0	118	4	2	1	0
33	4	1	2	0	73	3	1	1	0	119	5	3	1	0
34	12	2	9	3	74	3	0	2	0	120	4	0	3	1
35	6	4	1	0	75	3	0	2	0	121	3	0	2	0
35*a*	8	5	2	0	78	3	1	1	0	123	3	1	1	1
36	4	1	2	1	79	3	1	1	0	124	2	0	1	0
36	4	1	2	1	80	4	2	1	0	125	3	0	2	1
37	5	2	2	0	81	5	3	1	1					
38	6	0	5	2	83	2	0	1	1	Total	371	100	187	55
39	3	1	1	1	85	8	1	6	1					
40	4	0	3	0	86	5	2	2	0	Percentage		$100\frac{rA}{sA} = 29{\cdot}4$		
41	4	1	2	0	87	6	1	4	1					

observation, it is inferred that the character follows the Mendelian law according to which the expectation has been computed.

The expectation is calculated according to a general formula which corrects the error due to the small size of human families. In families with two heterozygous parents, if p expresses the theoretical probability that the offspring of two heterozygous parents will be affected, and q the probability that they will be normal, then q^s will represent the probability that all the members of a family of s individual will be normal, and $(1 - q^s)$ the probability that a sibship contains at least one affected sib. The ratio $\frac{sp}{1 - q^s}$ will represent the theoretical expectation of recessives. This last figure is compared with the actual observation.

Bernstein's method (1929).—In Table X the present material is arranged according to the "*a priori*" method following Bernstein: p is assumed, *a priori*, to be 0·25 on the recessive monomeric hypothesis; s is the number of children per sibship; n_s the number of sibships of s members; t_s the observed number of affected children; $x = \frac{sp}{1 - q^s}$, the expected number of affected sibs in each s-membered sibship; $x_s n_s$ the expected number of affected sibs

in all s-membered sibships; m^2 the quadratic error per sibship; $m^2 n_s$ the quadratic error in all s-membered sibships. Δ is the difference between observation and expectation. The calculation of the standard error follows the formula—

$$m^2 = x_s (q - xsq^s).$$

TABLE X.—*Bernstein Method.*

$S.$	$n_s.$	$x_s.$	$x_s n_s.$	$t_s.$	$m^2.$	$m^2 n_s.$	$\Delta.$
1	15	1·000	15·000	15	0·000	0·000	0·000
2	23	1·143	26·289	27	0·122	2·806	0·711
3	29	1·297	37·613	41	0·263	7·627	3·387
4	26	1·463	38·038	38	0·420	10·920	−0·038
5	13	1·639	21·307	25	0·592	7·096	3·693
6	10	1·825	18·250	22	0·776	7·760	3·750
7	5	2·020	10·100	12	0·970	4·850	1·900
8	3	2·223	6·669	6	1·172	3·516	−0·669
9	1	2·433	2·433	2	1·380	1·380	−0·433
10	1	2·649	2·649	5	1·592	1·582	2·351
12	1	3·098	3·098	4	2·020	2·020	0·902
Total	127		181·446	197		49·557	

It will be seen that the difference between expectation and observation is 15·554, i.e., more than twice the standard error ±7·09.

Lenz's method.—A similar method for investigating recessive human characteristics has been devised by Lenz (1929).

The theoretical number of sibships with two heterozygous parents which are not included in the investigation because no member of them exhibits the character is calculated. These sibships are, then, computed with the observed sibships, and the percentage of affected individuals thus theoretically obtained in the sum of sibships is compared with the observed number of affected sibs. The method may be expressed as follows: If n_s is the number of families with at least one recessive, then $n_s \frac{q^s}{1 - q^s}$ is the number of families with two heterozygous parents but no affected members, and $n_s - n_s \frac{q^s}{1 - q^s}$ is the total number of offspring of two heterozygous parents. Hence the percentage of recessive children (R) will be—

$$\frac{100\,R}{n_s - n_s \frac{q^s}{1 - q^s}} \quad \text{or} \quad \frac{100\,R}{n_s \frac{s}{1 - q^s}}$$

https://doi.org/10.1192/bjp.85.357.719 Published online by Cambridge University Press

In Table XI the present material is arranged following Lenz's method, assuming $q = 0{\cdot}75$, on the recessive monomeric hypothesis.

TABLE XI.—*Lenz's Method.*

$S.$	$n_s.$	$\frac{1}{1-q^s}.$	$n\frac{s}{1-q^s}.$	$R.$	%.
1	15	4·000	60·0000	15	25·000
2	23	2·2857	105·1422	27	26·156
3	29	1·7397	151·3539	41	27·088
4	26	1·4629	152·1416	38	24·976
5	13	1·3116	85·2540	25	29·324
6	10	1·2165	72·9900	22	30·141
7	55	1·1540	40·3900	12	29·710
8	3	1·1113	26·6712	6	22·495
9	1	1·0812	9·7308	2	21·477
10	1	1·0597	10·5970	5	47·183
12	1	1·0328	12·3936	4	32·274
Total	177		726·6643	197	27·11

It will be seen that the percentage is 27·11. The standard error which may be calculated with the same formula used in Weinberg's method is ±2·05. The difference between observation and expectation is not above the standard error.

Weinberg's correction of Bernstein's method.—The *a priori* method, as Weinberg (1931) pointed out, is correctly applied only when all the material has been collected at random. When, as in the present material, a certain choice occurred, the formula $x_s = \frac{sp}{1-q^s}$ is to be written, according to the correction of Weinberg, thus :

$$x_s = \frac{sp[1-(1-r)(1-rp)^{s-1}]}{1-(1-rp)^s},$$

where the new figure r represents the degree of choice ("*Grad der Stichprobenauslese*"), and is expressed by the ratio—

$$\frac{P(P-1)}{P(R-1)} \qquad \text{(see Table VII).}$$

The quadratic error is given by the formula—

$$m^2 = \frac{x_s(1-x_s)}{s} - \frac{(s-1)p^2q^2r^2(1-pr)^{s-2}}{s^2\ 1-(1-pr)^{s-2}}.$$

In Table XII the present material is arranged according to this correction. The degree of choice of the random sample is 57% (see Table VII).

TABLE XII.—*Bernstein's Method* (*Weinberg's Correction*).

s.	n_s.	x_s.	$x_s n_s$.	t_s.	m^2.	$m^2 n_s$.	Δ.
1	15	1·000	15·000	15	0·000	0·0000	0·000
2	23	1·192	27·416	27	0·1123	2·5829	−0·416
3	29	1·389	40·281	41	0·1585	4·5965	0·719
4	26	1·590	41·340	38	0·2145	5·5670	−3·340
5	13	1·789	23·467	25	0·2443	3·1759	1·533
6	10	1·993	19·930	22	0·3062	3·0620	2·070
7	5	2·201	11·005	12	0·3469	1·7345	0·995
8	3	2·2412	7·236	6	0·4152	1·2456	1·235
9	1	2·621	2·621	2	0·4650	0·4650	−0·621
10	1	2·841	2·841	5	0·5182	0·5182	2·159
12	1	3·280	3·280	4	0·6229	0·6229	0·720
Total	127		194·417	197		23·5705	

The difference 2·6 is less than the standard error ±4·85. Expectation and observation, therefore, are agreed.

Sjögren's correction of Lenz' method.—The method of Lenz may be also corrected to include material collected not entirely at random (Sjögren, 1931). Instead of the number of recessive (R), the ratio between probands and recessives is used. The total number of children is then expressed by the formula—

$$\frac{s}{1-q^s} \cdot \frac{P}{R'}$$

the total number of affected children being represented by $\frac{P}{R}R$, i.e., by the total number of probands. The percentage will be—

$$\frac{100P}{\frac{s}{1-q^s} \cdot \frac{P}{R}}$$

In Table XIII the material is presented according to Sjögren correction.

It will be seen that the percentage of affected sibs is 25·48%, as expected on the Mendelian recessive hypothesis.

Haldane's method.—In comparison with Weinberg's procedure, Bernstein's method and its modifications suffer from the defect of an "*a priori*" assumption. In single cases of Mendelian heredity involving one gene the *a priori*

https://doi.org/10.1192/bjp.85.357.719 Published online by Cambridge University Press

TABLE XIII.—*Lenz's Method (Sjögren Correction).*

s.	n_s.	$\frac{P}{R}$.	$\frac{1}{1-q^s}$.	$\frac{s}{1-q^s} \cdot \frac{P}{R}$.	P.	%.
1	15	15	4·000	60·000	15	25·000
2	23	20·000	2·2857	91·428	22	24·062
3	29	24·333	1·7397	127·196	32	25·158
4	26	27·833	1·4629	162·867	38	23·335
5	13	9·666	1·3116	63·389	18	28·396
6	10	7·141	1·2165	52·122	16	30·690
7	5	3·750	1·1540	30·292	9	29·710
8	3	2·000	1·1113	17·781	4	22·496
9	1	1·000	1·0812	9·731	2	20·553
10	1	0·2000	1·0597	2·119	1	27·183
12	1	0·250	1·0328	3·098	1	32·278
Total	..	..	..	620·023	158	25·48

ratios are easily determined, but when more complicated types of heredity come into question the formulation of an *a priori* figure may offer serious difficulties. Haldane (1932–1938*a*) devised an alternative method, which does not involve the expected value of p. He demonstrates that in a group of families having heterozygous parents and each containing one or more affected members, the most likely value of q is the real root other than unity of the equation:

$$\frac{R}{1-q} = \Sigma \frac{sn_s}{1-q^s},$$

where ns is the number of families of s members, R is the total number of affected, and q $(= 1 - p)$ the proportion of normal individuals. The standard error of q is given by the equation—

$$\sigma^{-2} = \frac{R}{q(1-q)^2} - \frac{s^2q^s - 2}{(1-q^s)^2} \cdot n_s.$$

Applying this procedure to the present material, and excluding the families with $s = 1$, in which obviously the terms of the equation are cancelled, the following equation is to be solved in order to find the value of q:

$$\frac{182}{1-q} = \frac{46}{1-q^2} + \frac{87}{1-q^3} + \frac{104}{1-q^4} + \frac{65}{1-q^5} + \frac{60}{1-q^6} + \frac{35}{1-q^7} + \frac{24}{1-q^8} + \frac{9}{1-q^9} + \frac{10}{1-q^{10}} + \frac{12}{1-q^{12}}.$$

https://doi.org/10.1192/bjp.85.357.719 Published online by Cambridge University Press

The equation is most easily solved by the method of trial and error. The first approximation of q may be offered by a formula derived by Weinberg :

$$1 - q = r \frac{(r-1)\, n_s}{(s-1)\, r_s}$$

Therefore : $1 - q = (2{\cdot}39 + 6{\cdot}9 + 12{\cdot}3 + 20{\cdot}1) \div (1{\cdot}27 + 2{\cdot}41 + 3{\cdot}38 + 4{\cdot}25 + 5{\cdot}22 + 6{\cdot}12 + 7{\cdot}6 + 8{\cdot}2 + 9{\cdot}5 + 11{\cdot}4) = 0{\cdot}288$.

After few iterations the most likely value of q is found to be 0·69. Hence $p = 0{\cdot}31$. The standard error is $\pm$ 0·025. Therefore, p deviates from the expected value of 0·25 by 0·06, or more than twice its standard error. It will be noted, however, that this value (p_1) is valid in one limiting case, i.e., when the probability that a recessive in the population is brought into the record is equal to 1. In the other limiting case, when the ascertainment is proportional to the frequency of recessives, so that the probability of recording approached 0, p is, according to Haldane $\frac{R-N}{T-N}$, where R is the total number of recessives, T the total number of sibs and N the total number of sibships. The standard error is $\sigma^{-2} = \frac{(T-N)}{(T-R)\,(R-N)}$. Therefore, $p_o = \frac{182-112}{452-112} = 0{\cdot}2058 \pm 0{\cdot}016$. Obviously, neither limiting case occurs in the present material, although the first is the better approximation. However, according to Haldane, the data are consistent with Mendelian expectations, provided $p_1 + 2\sigma_{p_1} > 0{\cdot}25 > p_o - 2\sigma_{p_o}$ as is verified in the present material : $0{\cdot}36 > 0{\cdot}25 > 0{\cdot}17$.

If Haldane's formula is corrected to include the " degree of choice " of the material, we have Weinberg's formula :

$$\frac{R}{p} = \frac{1 - (1-r)\,(1-rp)^{s-1}}{1-(1-rp)^s}\, sn_s.$$

Substituting, as first approximation of p, 0·25, we have $2{\cdot}384{\cdot}46 + 1{\cdot}850{\cdot}87 + 1{\cdot}590{\cdot}104 + 1{\cdot}431{\cdot}65 + 1{\cdot}328{\cdot}60 + 1{\cdot}258{\cdot}35 + 1{\cdot}206{\cdot}24 + 1{\cdot}165{\cdot}9 + 1{\cdot}136{\cdot}10 + 1{\cdot}093{\cdot}12 = 717{\cdot}6$, which closely approaches the left hand side (728). The value of p corresponds, therefore, to Mendelian expectation.

In considering these data the question may be raised of the possibility that the condition is genetically determined only in the families that show two or more affected children, whereas other factors are operating in families with only one affected sib. In this case the material would not be homogeneous. To rule out this possibility, Bernstein (1933) suggested a method (" double case method ") whereby the theoretical expectation is calculated only in families with two or more recessives. Expectation and observation are in agreement if the material is uniform. For the calculation of the expected figures the usual formula $\frac{sp}{1-q^s}$, is used, from both terms of which

https://doi.org/10.1192/bjp.85.357.719 Published online by Cambridge University Press

spq^{s-1} is subtracted. Therefore $x_s = \frac{sp - spq^{s-1}}{1 - q^s - spq^{s-1}} = \frac{sp\,(1 - q^{s-1})}{1 - q^s - spq^{s-1})}$.

The quadratic error is—

$$x - x^2 + \frac{p^2\,s(s-1)}{1 - q^s - spq^{s-1}}.$$

TABLE XIV.—*Bernstein's Method ("Double Case").*

$S.$	$n_s.$	$x_s.$	$x_s n_s.$	$t_s.$	$m^2.$	$m^2 n_s.$	$\Delta.$
2	4	2·000	8·0000	8	0·0000	0·0000	0·0000
3	10	2·1006	21·0060	20	0·0900	0·9000	−1·0060
4	9	2·2090	19·8819	20	0·1959	1·7541	0·1181
5	8	2·3271	18·6168	20	0·3160	2·5288	1·3832
6	8	2·4547	20·0376	19	0·4521	3·6168	−1·0376
7	5	2·5917	12·9585	12	0·6041	3·0205	0·9585
8	3	2·7382	7·2146	6	0·7704	2·3112	1·2146
9	1	2·8939	2·8939	2	0·9509	0·9509	0·8939
10	1	3·0587	3·0587	5	1·1438	1·1438	1·9413
12	1	3·4140	3·4140	4	1·5612	1·5612	0·5860
Total		..	117·0820	116	..	17·7873	1·0820

It will be seen that the difference (1·082) between observed and expected figures is less than the standard error 4·2. The same value of p is thus obtained in the total material as well as in the series of sibships with two or more recessives. It is reasonable to infer, therefore, that the same factors are operating in both groups.

In conclusion, the application of statistical methods clearly indicates that the ratio of affected to normal children in sibships derived from the mating of two unaffected (heterozygous) individuals is compatible with the hypothesis of a single recessive Mendelian inheritance. It seems noteworthy to stress the striking agreement between observation and expectation obtained with methods which are particularly adapted to the present material. (Weinberg's proband method, Weinberg correction of Bernstein method and Sjögren correction of Lenz's method.)

The mating of affected individuals offers scanty data in the present material. Matings of two affected individuals, theoretically resulting in all affected children, were not observed. Mating of one affected and one normal individual occurred in three cases. In one instance (Case 163) the offspring was living and normal. In the second instance (Case 106) the offspring was also apparently normal, although no biochemical test could be made, the child having died. In the third instance (Case 24) four children resulted from the union: two were affected (Cases 25, 26) and two were normal. While the two first

https://doi.org/10.1192/bjp.85.357.719 Published online by Cambridge University Press

instances conform to expectation on the hypothesis of a rare recessive gene, the third instance can be explained only by assuming that one parent was heterozygous. Although this explanation seems hardly acceptable in the absence of consanguinity, it is not impossible, when one considers that the frequency of heterozygotes in the general population is probably above 1%. However, a simple calculation will show that about 1 in 70 families with one affected and one normal parent will contain affected children. Therefore, more data on mating of affected individuals are necessary to warrant a conclusion.

(B) *Rate of consanguinity.*—As pointed out by Dahlberg (1930*b*), if the gene frequency is p, and p^2 is the frequency of the character among the progeny of unrelated parents, when inbreeding occurs the frequency is $ap\ (1 - p) + p^2$, where a is the coefficient of inbreeding. If p diminishes, as in the case of rare conditions, the ratio of the frequency of the condition among the progeny of cousins to that among the progeny of unrelated parents obviously increases. Therefore, high frequency of cousin marriages in the families of affected individuals is a valuable criterion for the detection of rare recessive genes.

In the present material the parents were cousins in seven of 125 families.* They had 10 affected offspring. Therefore, 5% cousin marriages were observed against a theoretical expectation which is generally considered of the order 0·5%. This discrepancy is significant. Using Lenz (1919) formula, indicating the incidence of cousin marriages among parents of rare recessive traits,

$$\frac{a}{a \quad 16p}$$

(where a is the incidence of cousin marriage in the general population and p the incidence of the condition), the expected incidence of cousin marriage among parents of affected individuals is 5% (if $a = 0{\cdot}5$, and the frequency of phenylpyruvic oligophrenia of the order of 0·04% [p.]). Expectation and observation, therefore, are agreed.

(C) *The distribution of the condition among ascendant and collateral relatives.*—A rare recessive character occasionally appears in ascendants and collaterals. This frequency can be determined by exact formulæ when the frequency of the character in the general population is known, assuming the distribution of the gene to be uniform and mating to occur at random.

The frequency of phenylpyruvic oligophrenia in the general population can be determined only on the basis of the approximate incidence of mental deficiency in the general population. Estimates for this, according to various authorities, range from 3 to 0·5%. Assuming a frequency of 1%, of which half are in institutions, and since 0·793% (161 in 20·300) is the incidence of phenylpyruvic oligophrenia among institutionalized mental defectives, the

* An additional family in which the parents were cousins was not included.

https://doi.org/10.1192/bjp.85.357.719 Published online by Cambridge University Press

frequency of this condition in the general population is of the order ·004%. The frequency of the heterozygote (*b*) is, according to Johannsen's (1926) formula, $2\sigma\sqrt{a} - 2a = 1{\cdot}26\%$, where *a* is the frequency of the homozygote.

According to Dahlberg's (1926) formulæ, the probability that both parents of affected individual are also affected is $\left(\frac{2a}{2a+b}\right)^2 = 0{\cdot}04\%$. In the present material no such occurrence was observed.

The probability that both parents be heterozygous is $\left(\frac{b}{2a+b}\right)^2 = 9{\cdot}93\%$. This figure agrees with the observed 99% of the present material.

The probability that one parent be affected and one heterozygous is $\frac{2ab}{(a\ b)^2} = 0{\cdot}63\%$. In the present material the observed frequency is 1%.

The theoretical incidence of the condition among uncles and aunts of patients is, according to Hultkrantz and Dahlberg's (1927) formula,

$$\sqrt{a} \cdot \frac{1+\sqrt{a}}{2} = 0{\cdot}3.$$

In the present material only in one family was there an uncle affected (Family 48).

The theoretical incidence of the condition in cousins is, according to Weinberg (1920), about of the same order. In two cases (97 and 153) were cousins found affected. In several other families history of mental defect among uncles and cousins was obtained, but no test could be made.

It should be noted that the figures concerning collaterals are rough approximations, since the data are incomplete.

Of considerable importance is the distribution of the condition among half-brothers and half-sisters. In the case of a rare recessive character, as Rüdin (1916) pointed out, when the parents are heterozygous, if one of them marries again, it is most unlikely that he will marry another heterozygote. The half sibs of affected individuals, therefore, are generally normal. However, when one parent marries again a blood relation of the other parent, it is likely that he will marry again another heterozygote. In this case the half sibs will be affected. In the present material, of 130 half sibs examined, 28 were normal; the two exceptions occurred in one family (35 and 35*a*) where the father had married two sisters, both matings resulting in affected children.

The distribution of the disease among ascendants and collaterals, therefore, satisfies the theoretical expectation on the recessive monomeric hypothesis.

In view of a recent hypothesis of Penrose (1938) that a gene responsible for mental defect might be expressed in the heterozygote by some form of insanity, it appears of some interest to note the incidence of schizophrenia among relatives of individuals affected by phenylpyruvic oligophrenia. In three cases (8, 133, 134) one of the parents was schizophrenic; the uncle of

Cases 133, 134, the brother of Cases 76, 77, and the cousin of Cases 13, 50, 83, 84, 85, 138, 195 were likewise certified schizophrenics. Although the data are too scanty to warrant a statistical analysis of these figures, it appears possible that schizophrenia is more frequent than might be expected in a random sample of the population.

In conclusion, the data are consistent with the quantitative requirements of the theory of monomeric recessivity, since (*a*) the ratio of affected to normal sibs in families with normal parents, when corrected by specific method of statistical analysis, is found to be 25%; (*b*) the rate of consanguinity among the parents of affected individuals is significantly higher than normal; (*c*) the distribution of the character among ascendant and collateral relatives follows the rules of monomeric recessivity. *Phenylpyruvic oligophrenia, therefore, appears to be a clear illustration of a type of mental deficiency determined by a single autosomal recessive gene.*

The practical implications of this conclusion are obvious. Parents of children affected with phenylpyruvic oligophrenia should be discouraged from having other children. Parenthood should be also discouraged in brothers and sisters, uncles and aunts of affected individuals. Consanguineous marriages among members of families of patients should particularly be prevented. Moreover, the patients should be segregated to prevent child-bearing, since the great majority reach sexual maturity.

A final consideration concerning some theoretical implications of this study may be added. As stated in the introduction, phenylpyruvic oligophrenia is biochemically characterized by a lack of oxidation of phenylalanine. There is little doubt that this oxidation is brought about in the normal organism by an enzyme system, which is likely to be absent in affected individuals. Much evidence has been offered in favour of the opinion expressed by Haldane (1938*b*) and others that the effect of a genic action may be the production of a specific enzyme, although the chain of processes leading from the gene to the final phenotypic expression of its activity is still unknown. Further, genetic experiments have proven that in some instances the enzyme is dominant to its absence; thus, Onslow (1915), and more recently Koller (1930), found that in rabbits an enzyme is present which oxidizes tyrosin to melanin, whereas in recessive white rabbits this enzyme is absent. It appears, therefore, that one is on safe experimental ground in assuming that the absence of the enzyme system bringing about the oxidation of phenylalanine may be recessively determined.

It will be noted that in other metabolic disorders due to faulty metabolism of some particular substance (such as alkaptonuria, cystinuria, lævulosuria and albinism), evidence has been offered that a genetic mechanism, recessive in character, is responsible for the condition. Of particular interest for the study of heredity in mental deficiency is the fact that amaurotic idiocy, a condition recessively determined (Sjögren, 1931), is also due to a faulty

metabolism. Phenylpyruvic oligophrenia and amaurotic idiocy appear to be analogous conditions. Both are characterized by a biochemical error involving the metabolism of proteins in the former, the metabolism of lipoids in the latter; in both an enzymatic system is probably at fault, and finally both behave as recessive Mendelian characters. In the group of "familial mental deficiency" other conditions may exist showing similar biochemical and genetical characteristics, the study of which is likely to throw much light on the whole problem of the influence of heredity on mental deficiency.

The investigation was helped by a grant from Child Neurology Research (Friedsam Foundation).

I am indebted to the superintendents of the various institutions for permission to examine the patients and perform laboratory tests.

My thanks are due to Dr. H. C. Storrs (Wassaic), Dr. Charles Bernstein (Rome), Dr. C. L. Vaux (Newark), Dr. B. W. Baker (Laconia), Dr. G. B. Thorn (Vineland State), Prof. E. R. Johnstone (Vineland Training), Dr. E. L. Johnstone (Woodbine), Dr. A. H. Meese (Totowa), Dr. C. T. Jones (New Lisbon), Dr. C. S. Raymond (Wrentham), Dr. R. A. Greene (Fernald), and Dr. C. T. LaMoure (Mansfield).

REFERENCES.

BERNSTEIN, F.—"Variationen und Erblichkeitstatistik" in *Handbuch der Vererbungwissenschaft*, Berlin, 1929.

Idem.—"Korrekturen bei erblichkeitsmatematischer Untersuchung von Krankheiten mit recessivem Erbgang," *Arch. Rassenbiol.*, 1933, xxvii, p. 25.

BRÜGGER, C.—"Genealogische Untersuchungen an Schwachsinnigen," *Zeitschr. Neur. u. Psychiat.*, 1930*a*, cxxx, p. 66.

Idem.—"Die Stellung der Schwachsinnigen in der Geburtenheitenfolge," *ibid.*, 1930*b*, cxxxiii, p. 537.

DAHLBERG, G.—*Twin Births and Twins from a Hereditary Point of View*, Stockhom, 1926.

Idem.—"Eine neue Methode zur familienstatistischen Analyse bei der Vererbungsforschung," *Hereditas*, 1930*a*, xiv, p. 73.

Idem.—"Inzucht bei Polyhybridität beim Menschen," *ibid.*, 1930*b*, xiv, p. 83.

FISHER, R. A.—"The Detection of Linkage with Recessive Abnormalities," *Ann. Eugen.*, 1935, vi, p. 26.

FÖLLING, A.—"Ueber Ausscheidung von Phenylbrenztraubensäure in den Harn als Stoffwechselanomalie in Verbindung mit Imbezillität," *Zeitschr. Phys. Chem.*, 1934, ccxxvii, p. 169.

HALDANE, J. B. S.—"A Method for Investigating Recessive Characters in Man," *Journ. Genet.*, 1932, xxv, p. 251.

Idem.—"Methods for the Detection of Autosomal Linkage in Man," *Ann. Eugen.*, 1934, vi, p. 26.

Idem.—"A Search for Incomplete Sex-linkage in Man," *ibid.*, 1936, vii, p. 28.

Idem.—"The Estimation of the Frequencies of Recessive Conditions in Man," *ibid.*, 1938*a*, viii, p. 255.

Idem.—In *Perspectives of Biochemistry*, Cambridge, 1938*b*.

HOGBEN, L.—"Genetic Analysis of Family Traits," *Journ. Genet.*, 1932, xxv, p. 211.

HULTKRANTZ, J., and DAHLBERG, G.—"Die Verbreitung eines monohybriden Erbmerkmals in einer Population und in der Verwandtschaft von Merkmalsträger," *Arch. Rassenbiol.*, 1927, xix, p. 129.

JERVIS, G. A.—" Phenylpyruvic Oligophrenia," *Arch. Neur. and Psychiat.*, 1937, xxxviii, p. 944.

JOHANNSEN, W.—*Elemente der exakten Erblichkeitslehre*, Jena, 1926.

JUDA, A.—" Über Anzahl und psychische Beschaffenheit der Nachkommen von schwachsinnigen u. normalen Schülern," *Zeitschr. Neur. u. Psychiat.*, 1934, cli, p. 244.

KOLLER, P.—" On Pigment Formation in the D Black Rabbit," *Journ. Genet.*, 1930, xxii, p. 103.

KREYENBERG, E.—" Die Erblichkeitverhältnisse bei endogenem u. exogenem Schwachsinn," *Zeitschr. mensch. Vererbung u. Konstit.*, 1935, xix, p. 40.

LENZ, F.—" Die Bedeutung der statistisch ermittelten Belastung mit Blutverwandtschaft der Eltern," *Münch. med. Wochenschr.*, 1919, lxvi, p. 1340.

Idem.—" Erhalten die Begabten Familien Kaliforniens ihren Bestand ? " *Arch. Rassenbiol.*, 1925, xvii, p. 397.

Idem.—" Methoden der menschlichen Erblichkeitforschung " in *Handbuch der hygienischen Untersuchungmethoden*, Jena, 1929.

LOKAY, A.—" Über die hereditären Beziehungen der Imbezillität," *Zeitschr. Neur. u. Psychiat.*, 1929, cxxii, p. 90.

LUXEMBURG, H. —" Zur Frage der Manifestationwahrscheinlichkeit der erblichen Schwachsinns," *ibid.*, 1931, cxxxv, p. 767.

ONSLOW, H.—"A Contribution to our Knowledge of the Chemistry of Coat Colour in Animals and of Dominant and Recessive Whiteness," *Proc. Roy. Soc. Lond.*, 1915, xiii, p. 189.

PENROSE, L.—" On the Interaction of Heredity and Environment in the Study of Human Genetics, with Special Reference to Mongolian Idiocy," *Journ. Genet.*, 1932, xxv, p. 407.

Idem.—*The Influence of Heredity on Diseases*, London, 1934.

Idem.—" Inheritance of Phenylpyruvic Amentia," *Lancet*, 1935, ccxxix, p. 192.

Idem.—" Some Genetical Problems in Mental Deficiency," *Journ. Ment. Sci.*, 1938, lxxxiv, p. 693.

RÜDIN, E.—*Zur Vererbung und Neuenstehung der Dementia Præcox*, Berlin, 1916.

SCHULZ, B.—" Zur Genealogie des Mongolismus," *Zeitschr. Neur. u. Psychiat.*, 1931, cxxxiv, p. 268.

SJÖGREN, T.—" Die juvenile amaurotische Idiotie," *Hereditas*, 1931, xiv, p. 197.

Idem.—" Klinische u. vererbungmedizinische Untersuchungen über Oligophrenia in einer Nordschwedische Bauernpopulation," *Acta Psychiat*, 1932, Suppl. 2.

Idem.—" Investigations of the Heredity of Psychoses and Mental Deficiency in Two North Swedish Parishes," *Ann. Eugen.*, 1935, vi, p. 253.

SLOME, D.—" The Genetic Basis of Amaurotic Family Idiocy," *Journ. Genet.*, 1934, xxvii, p. 363.

SMITH, J. C.—" Das Ursachen-Verhältnis des Schwachsinns," *Zeitschr. Neur. u. Psychiat.*, 1930, cxxv, p. 678.

WEINBERG, W.—*Die Kinder der Tuberkulösen*, Leipzig, 1913.

Idem.—" Methodologische Geschichtpunkte für die statischen Untersuchungen der Dementia Præcox," *Zeitschr. Neur. u. Psychiat.*, 1920, lix.

Idem.—In *Handbuch der sozialen Hygiene und Gesundheitfürsorge*, Berlin, 1925.

Idem.—" Zur Probandenmethode," *Arch. Rassenbiol.*, 1931, xxiii, p. 281.