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OBSERVATIONS ON PHENYLKETONURIA IN ONTARIO

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IT IS now generally agreed that, although the most prominent feature of phenylketonuria is mental deficiency, the primary lesion is an inborn error of metabolism. Patients with phenylketonuria are unable to metabolize phenylalanine adequately because of a deficiency of the enzyme phenylalanine hydroxylase. In consequence, phenylalanine accumulates in the blood and various phenylalanine metabolites appear in the urine. One of these metabolites is phenylpyruvic acid which gives a characteristic green colour with ferric chloride and so provides a simple means of identifying the disease.

In the last few years it has become clear that the early treatment of phenylketonuria with a low phenylalanine diet will prevent the development of mental defect.[1] For this reason alone phenylketonuria has assumed an importance out of proportion to its actual frequency.

Several full reviews of phenylketonuria have been published[2-5] but relatively few observations about the disease have been reported from Canada. This paper describes some studies on a series of 98 phenylketonuric patients, all of whom came from Ontario.

MATERIAL AND METHODS

The series was made up of 98 patients with phenylketonuria drawn from three main sources. The first group (20 cases) were patients seen at the Hospital for Sick Children, Toronto. The second group (50 cases) were inpatients at the Ontario Hospital Schools at Orillia, Ontario (33 cases), and Smiths Falls, Ontario (17 cases). The third group (28 cases) consisted of 17 patients known only by hospital case-notes and 11 patients known by case-notes and interviews or correspondence with the parents. All of the patients were, or had been, resident in Ontario. Limited observations on 44 of these patients have been published previously.[6-9]

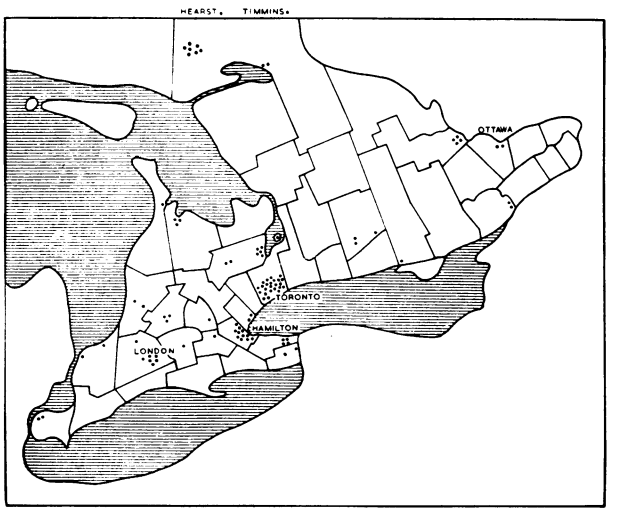

Fig. 1.—Phenylketonuria in Ontario. Present geographical location or that just prior to hospitalization. Each dot represents one patient.

In all cases, except one, the diagnosis was made by testing the urine for phenylpyruvic acid with ferric chloride or Phenistix. In the one exception (Case 2, Table II), there was strong circumstantial evidence for the diagnosis (a phenylketonuric sibling, mental retardation, fair hair, blue eyes, infantile eczema). A significantly raised fasting plasma phenylalanine level was demonstrated in 69 patients (method of Udenfriend and Cooper[10]).

INCIDENCE AND LOCATION

Several estimates have been made of the incidence of phenylketonuria in populations of predominantly European descent.[2, 11, 12] These agree reasonably well and vary from 2 to 6 per 100,000 persons, with an average of 4 per 100,000 or 1 in 25,000. On this basis, Ontario, with a population in 1960 of just over six million, should have some 240 cases. It seems clear that the 83 living patients from this series represent only about one-third of the phenylketonuric subjects in the province.

Although the incidence of phenylketonuria in the general population is about 0.004%, most patients with phenylketonuria eventually find their way to institutions for retarded children and here form from 0.1 to 2.7% of the population.[2] In

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Canad. M. A. J.
May 6, 1961, vol. 84

TABLE I.—ESTIMATED NUMBER OF CHILDREN WITH PHENYLKETONURIA BORN 1959 - 1974, ONTARIO

Year	Estimated* live births (thousands)	Number‡ born with phenyl-ketonuria	Number still§ alive this year with phenyl-ketonuria	Number born and alive this year with phenyl-ketonuria
1959	157†	6	—	6
1960	162	6	6	12
1961	166	7	12	19
1962	171	7	19	26
1963	176	7	26	33
1964	181	7	32	39
1965	185	7	39	46
1966	190	8	46	54
1967	195	8	54	62
1968	199	8	62	70
1969	204	8	69	77
1970	209	8	77	85
1971	214	9	85	94
1972	218	9	93	102
1973	223	9	102	111
1974	228	9	110	119
		123		

*Assuming an average annual increase of 4700 live births.
†Tentative figure, Registrar-General's office.
‡Based on 4 per 100,000 born with this condition.
§Based on Ontario Life Table, Dominion Bureau of Statistics, 1956.

this series, 50 phenylketonuric individuals were found in two Ontario Hospital Schools with a combined population (in 1959) of 5061, an incidence of 1%.

Fig. 1 shows the geographical distribution of the cases in this series. The positions indicated refer to the present location of the patient or that just prior to hospitalization. In general, most of the patients came from the most densely populated areas. The small clusters of cases in outlying areas usually reflect the fact that more than one case may be found in the same family.

Using a birth rate of 1 phenylketonuric per 25,000 births and best current estimates of population increase and mortality, Dr. A. H. Sellers of the Division of Medical Statistics, Ontario Department of Health, has made an estimate of the number of children with phenylketonuria who have been, or will be, born in Ontario between 1959 and 1974 (Table I). It can be seen that in these 15 years some 123 new cases of phenylketonuria are to be expected.

TABLE II.—PHENYLKETONURIA: AGE DISTRIBUTION OF THE 83 LIVING PATIENTS

Age group	Number of patients Male	Female	Total	%
0 - 4	10	10	20	24
5 - 9	10	13	23	28
10 - 14	10	6	16	19
15 - 19	1	5	6	7
20 - 24	1	3	4	5
25 - 29	0	3	3	4
30 - 34	4	0	4	5
35 - 39	0	4	4	5
40 - 44	0	2	2	2
45 - 49	0	0	0	0
50 - 54	1	0	1	1
Totals	37	46	83	100

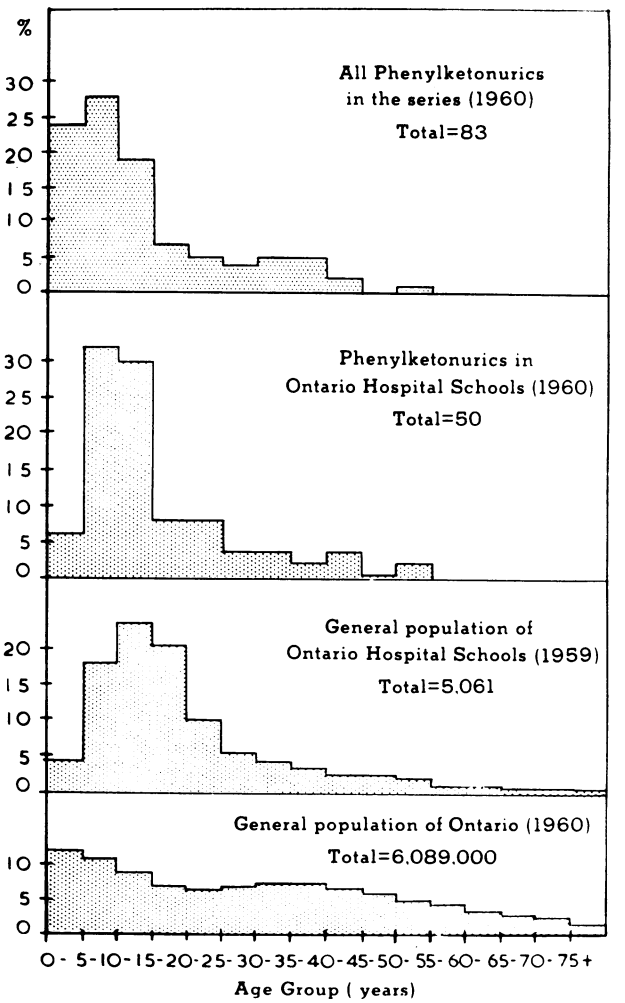

Fig. 2.—Phenylketonuria. Comparison of percentage age distributions of the whole series, the phenylketonuric patients in the Ontario Hospital Schools, the general population of these schools and the general population of Ontario.

MORTALITY

The foregoing estimate is based on an average life expectancy. There is some evidence from the age distribution of reported cases of phenylketonuria that the life expectancy of untreated patients is diminished.[5] Table II shows the age and sex distribution of the 83 living patients in this series. The percentage age distribution is compared with the percentage age distribution of the general population of Ontario in the top and bottom sections of Fig. 2. It can be seen that, compared with the general population, there is a relative excess of the younger phenylketonurics and a relative deficiency of the older patients. This is presumably due to an increased mortality in phenylketonuria, but other factors may be involved.[13]

This type of age distribution is characteristic of mental defect in general.[13] Since the great majority of untreated phenylketonurics are mentally defective, a further comparison can be made between the age distribution of the phenylketonurics in the Ontario Hospital Schools and the age distribution of the general population of these schools. This is shown in the middle two sections of Fig. 2. There

TABLE III.—PHENYLKETONURIA: AGE AND CAUSE OF DEATH IN 15 PATIENTS

Patient	*Sex*	*Age in years*	*Autopsy*	*Cause of death*	*Clinical history*
1. W.W.	M	8/12	Yes	Pneumonia	Severe infantile eczema
2. S.F.	F	1 5/12	No	Unknown	Found dead in bed. Infantile eczema
3. J.S.	M	3 5/12	Yes	Acute interstitial pneumonia	Sudden death. Severe infantile eczema
4. D.Wa.	F	3 7/12	Yes	Staphylococcal septicemia with skin lesions, empyema, renal abscesses	Pre-terminal measles and bronchopneumonia
5. D.F.	F	4 5/12	No	Pneumonia	Infantile eczema. Sib of S.F.
6. D.So.	F	4 10/12	Yes	Lobar pneumonia	Mild infantile eczema
7. V.I.	M	8	Yes	Lobar pneumonia	
8. J.V.	M	11	Yes	Bronchopneumonia	5 previous attacks of pneumonia
9. W.H.	M	12	Yes	Uremia, chronic pyelonephritis, terminal bronchopneumonia	
10. C.T.	M	16	Yes	Bronchopneumonia	2 attacks of bronchitis
11. M.L.	F	17	No	"Exhaustion and intestinal intoxication"	
12. M.Ta.	F	19	No	Diabetic coma	
13. G.T.	M	22	Yes	Bronchopneumonia and empyema	Sib of C.T.
14. I.H.	F	26	No	Repeated convulsions associated with measles	
15. R.Ta.	M	28	Yes	Ruptured esophageal ulcer and hemothorax. Duodenal ulcer found	Sib of M.Ta.

is obviously less discrepancy between the two age distributions, and a comparison of the absolute figures by a chi-square test showed that there was no significant difference.

Observations on the age and causes of death in phenylketonuria are scanty.[5] Table III gives some of these details for 15 patients. Most of the data were taken from case records of the Ontario Hospital Schools.

In 8 of the 15 cases the cause of death was ascribed to an acute respiratory disease, and pneumonia was cited as a contributory cause in two others. Two patients had a past history of repeated respiratory infections. Two deaths were associated with measles. Two deaths were sudden and were largely unexplained. It is of great interest that five of the six children under the age of five years had a definite history of infantile eczema.

Cases 12 and 15 were patients from an interesting family originally described by Penrose.[7] There were 12 children in the sibship of whom five were shown by Penrose to have phenylketonuria. This was also a likely diagnosis in a sixth sib who had died as a young child. Three of the affected sibs are still alive. Case 15 died suddenly in 1959 from a ruptured esophageal ulcer and a massive hemothorax; an associated duodenal ulcer was found. Case 12, the youngest sib, had diabetes mellitus as well as phenylketonuria. The diabetes began at the age of four years and she was admitted to the Hospital for Sick Children, Toronto, on five occasions, once in coma, for regulation and readjustment of her diet and insulin. She died in coma in 1952, 48 hours after discontinuing insulin on the advice of a religious fanatic.

ASSOCIATED CONDITIONS

Single cases of phenylketonuria have been reported in association with neurofibromatosis,[14] Gower's muscular dystrophy,[15] diabetes mellitus,[7] and polydactyly.[9] Jervis[16] found three cases of congenital dislocation of the hip in a survey of 200 phenylketonuric subjects. Six phenylketonuric babies are now reported to have had a Ramstedt operation for pyloric stenosis.[9, 17] It seems likely that the association of phenylketonuria with these conditions is no more than coincidental. There is a closer relationship between phenylketonuria and infantile eczema.

Infantile Eczema

Folling,[18] in his original description of phenylketonuria, found that four of 10 patients had rough, dry skins with papular or eczematous lesions. Other workers have noted a tendency to dermatitis,[2, 7] dermatographia or urticaria factitia,[3, 19] photosensitivity[19] or eczema, and eczema is now regarded as an integral part of the clinical picture of phenylketonuria. According to Knox,[5] the incidence of eczema in published series of phenylketonurics varies from 17% to 34%. It is not always clear from the reported cases what skin diseases the patients did suffer from or whether these were any different from the skin lesions often found in badly retarded patients with poor hygiene.[3] In this series, particular attention was paid to the occurrence of infantile eczema.

By infantile eczema in this context is meant a skin lesion starting in the first 18 months of life and characterized by itching, erythema, papules and vesicles, oozing, crusting and lichenification. Secondary infection is common. The course of the disease is protracted and marked by remissions and exacerbations. In general, the lesions in the younger child tend to be mainly exudative and are found on the face and trunk, whereas in the older child the lesions tend to be drier and are often confined to the flexures.

Canad. M. A. J.
May 6, 1961, vol. 84

The series was divided into two groups according to whether the dermatological history was regarded as adequate or inadequate. The term adequate implied that the history had been taken personally or that the hospital case records were explicit about the presence or absence of infantile eczema. Forty-three patients were thought to have adequate dermatological histories and of these 13 (31%) had a history of infantile eczema (Table IV). This is probably an overestimate of the overall incidence, since those children who had eczema would be more likely to have hospital records describing the state of the skin. Fifty-five patients were thought to have inadequate dermatological histories and of these 3 (6%) were said to have had infantile eczema. This is probably an underestimate because the hospital records were mainly concerned with the neurological and social aspects of the patients' histories. The combined incidence of infantile eczema in the two groups was 16%.

TABLE IV.—PHENYLKETONURIA. THE MORTALITY OF PATIENTS WITH AND WITHOUT A HISTORY OF INFANTILE ECZEMA

	Patients with					
	Eczema		*No eczema*		*Total*	
Dermatological history	*Number*	*Number of deaths*	*Number*	*Number of deaths*	*Number*	*Number of deaths*
Adequate.....	13	5	30	2	43	7
Inadequate....	3	0	52	8	55	8
Total.....	16	5	82	10	98	15

The percentage death rate amongst the phenylketonurics with infantile eczema was 31% compared with a mortality of 12% for the rest of the series. Using the absolute figures (Table IV), the difference is not significant ($x^2 = 2.27$; $n = 1$; $0.2 > p > 0.1$). The difference is significant if the analysis is confined to the 43 patients with an adequate dermatological history ($x^2 = 4.68$; $n = 1$; $0.05 > p > 0.02$).

SEX

There were 44 male and 54 female patients with phenylketonuria. There has been a slight excess of females in most reported series, which is attributed to a slightly higher death rate in male patients. The age and sex distribution of this series (Table II) shows a slightly higher ratio of females to males in the older age groups and is thus consistent with this explanation.

RACE

The first patients that Folling described with phenylketonuria were Norwegian.[18] Since then it has become clear that the disease is predominantly one of North Europeans and their descendants. Phenylketonuria is quite common among Italians but is rare in Jews.[2, 20, 21] Several cases have been reported from Japan[5, 22] but there are only single examples of patients of Mexican[3] or part-Spanish descent.[23] Phenylketonuria has been described in a Brazilian Negro,[24] a mulatto[25] and a child whose parents were Negro-white and Negro-Indian.[16]

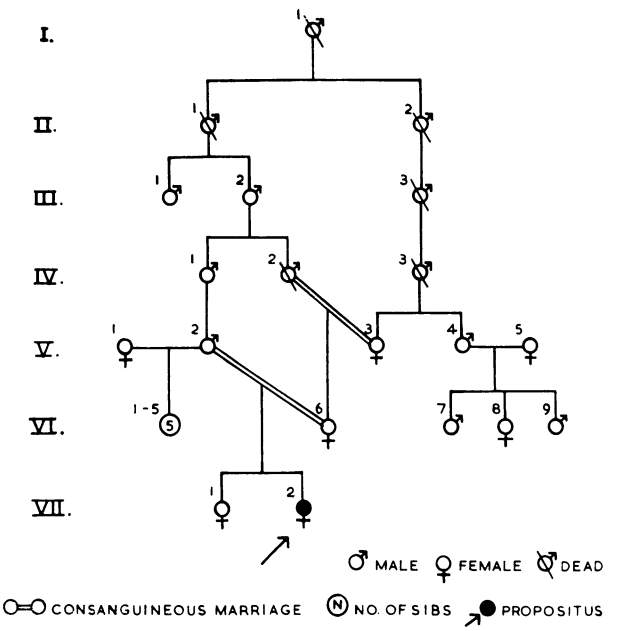

Fig. 3.—Pedigree of Myra B-C., the Ojibwa Indian.

This series conformed to a similar pattern. A racial background was recorded in some 50 families. In order of decreasing frequency these were said to be English, Irish, Scottish, French, Italian, Dutch, Polish and Russian. There were several mixed marriages between these groups and single Polish-German, Danish-English, Scottish-Ukrainian and Scottish-Syrian families. One child was a North American Indian and is apparently the first pure-blood Indian with phenylketonuria to be reported.

CASE REPORT

Myra B-C. was born on February 2, 1950. Her pedigree is shown in Fig. 3. She was apparently a pure-blood Ojibwa Indian. Her parents are first cousins and are further related by having a common ancestor four generations previously on the paternal side and five generations previously on the maternal side of the family. There was a history of diabetes mellitus on the maternal side.

She was born of a seven-months' pregnancy: delivery was normal and birth weight was 5 lb. 6 oz. (2.4 kg.). She was breast fed for three months without difficulty. Her development throughout infancy was slow, and she was given thyroid for one year from the age of 12 months. At 2 years of age she was restless and agitated, and was given phenobarbitone. This was withdrawn for a week at the age of 5 years and she had several major convulsions. Between the ages of 2 and 5 years she had four bouts of pneumonia. She was admitted to the Ontario Hospital School, Orillia, on January 30, 1956. Phenylketones were found in her urine by ferric chloride test on February 1, 1956.

Examination in 1960 (see Fig. 4) revealed a retarded child at the idiot level. She walked about the ward, was toilet-trained, fed herself and was easy to manage, but showed no evidence of speech. Her

TABLE V.—PHENYLKETONURIA: PERCENTAGE OF AFFECTED SIBS ESTIMATED BY 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	1	1	0	0	26	6	2	10	2	51	11	3	30	6
2	3	2	4	2	27	2	2	2	2	52	3	1	2	0
3	2	1	1	0	28	3	1	2	0	53	12	3	33	6
4	1	1	0	0	29	3	3	6	6	54	2	1	1	0
5	3	2	4	2	30	5	1	4	0	55	2	1	1	0
6	5	2	8	2	31	2	1	1	0	56	4	1	3	0
7	1	1	0	0	32	3	1	2	0	57	2	1	1	0
8	3	1	2	0	33	3	1	2	0	58	5	1	4	0
9	2	2	2	2	34	1	1	0	0	59	1	1	0	0
10	3	2	4	2	35	2	1	1	0	60	2	1	1	0
11	3	1	2	0	36	3	3	6	6	61	2	1	1	0
12	7	1	6	0	37	3	1	2	0	62	2	1	1	0
13	2	1	1	0	38	4	1	3	0	63	1	1	0	0
14	2	1	1	0	39	4	1	3	0	64	6	1	5	0
15	2	1	1	0	40	2	1	1	0	65	1	1	0	0
16	5	1	4	0	41	3	2	4	2	66	1	1	0	0
17	4	2	6	2	42	3	1	2	0	67	6	2	10	2
18	3	1	2	0	43	3	1	2	0	68	12	5	55	20
19	2	1	1	0	44	5	1	4	0	69	2	2	2	2
20	3	1	2	0	45	2	2	2	2					
21	1	1	0	0	46	2	1	1	0		232	95	292	72
22	4	2	6	2	47	4	2	6	2					
23	3	1	2	0	48	5	1	4	0					
24	3	1	2	0	49	4	1	3	0					
25	2	1	1	0	50	8	1	7	0					

$$P = \frac{\Sigma t(t-1)}{\Sigma t(s-1)} \times 100 = 24.65$$

$$\text{S.E.} = \sqrt{\frac{P(100-P)}{\Sigma s}}$$

$$= \pm 2.83$$

s = No. of sibs in each family.
t = No. of sibs with phenylketonuria.
P = estimated % of sibs with phenylketonuria.
S.E. = standard error of the estimate.

height was 48 in. (1.22 m.) and weight 66 lb. (30 kg.). Her head was somewhat pointed. Head circumference was 19 in. (48 cm.). She had very dark brown hair and dark brown irides. Her skin was medium brown; no eczema was present. There was early breast development. No abnormalities were detected on general physical examination. Her teeth were normally spaced.

Urine examination: phenylketones were detected by 10% ferric chloride test and Phenistix; no sugar present. Her fasting blood sugar level was 104 mg. %. A fasting plasma phenylalanine determination was 28.7 mg. %.

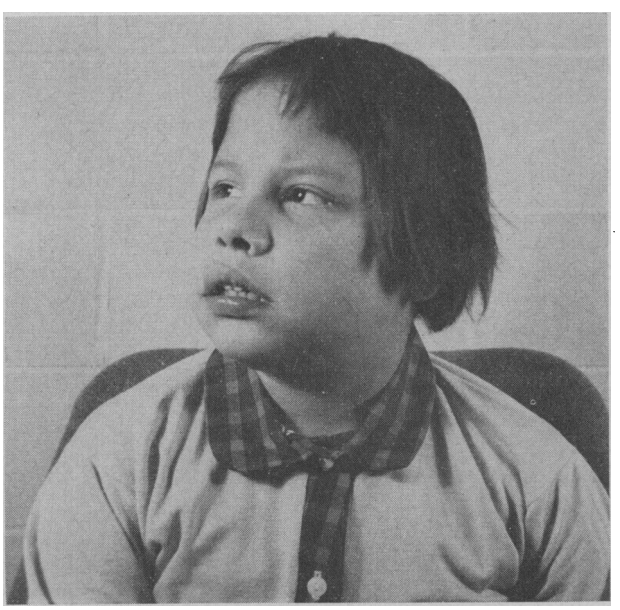

Fig. 4.—Phenylketonuria in an Ojibwa Indian girl.

Unfortunately, only the patient has been seen and examined. Two further members of the family (V, 4 and VI, 9) who are also retarded have had negative ferric chloride and Phenistix tests on the urine. The details of the family were obtained by the public health nurse for the reservation; an attempt is being made to find and examine the other members.

The pedigree shows the consanguineous marriages. The maternal grandfather (IV, 2) died at the age of 40 years from an accident in a sawmill. The maternal great-grandfather (IV, 3) and the maternal grandmother (V, 3) both suffer from diabetes mellitus. The maternal great uncle (V, 4) is said to be a low-grade moron who has had three children by a mentally defective girl (V, 5). Two out of these three children (VI, 8 and VI, 9) are said to be mentally defective.

GENETICS

Phenylketonuria is thought to be inherited as an autosomal recessive. If this is so, then the ratio of unaffected to affected sibs should be 3 to 1. In this series (excluding one family of three patients for reasons described later), 95 patients came from 69 sibships with a total of 232 sibs. This is a ratio of 137 unaffected to 95 affected sibs or about 1.4 to 1, which is a far greater proportion of affected sibs than expected on the recessive hypothesis. The reason is that those families that are potentially able to produce phenylketonuric children, but in fact produce only normal children, escape notice.

Various ways of allowing for this situation have been devised. Two different methods used by

Canad. M. A. J.
May 6, 1961, vol. 84

Jervis[2] and Munro[11] on somewhat similar case material in the United States and England, respectively, have been applied to the present series. In the first method (Table V), a correction is applied to each sibship throughout the series and the corrected percentage of affected sibs is compared to the expected 25%. In this case the corrected percentage worked out to be 24.65. The agreement is close and the difference between the observed and expected figures (0.35) is well within the standard error.

TABLE VI.—PHENYLKETONURIA: FACTORIAL METHOD FOR TESTING THE EXPECTED 3 TO 1 RATIO OF NORMAL TO AFFECTED SIBS[2, 11]

Size of sibship S	*No. of sibships of size S, N_s*	*Total No. of sibs, $S.N_s$*	*Number of sibs with phenylketonuria*		*Variance of No. expected $N_s.K_s$**
			Observed	*Expected**	
1	9	9	9	9.0	0.0
2	20	40	24	22.86	2.44
3	19	57	27	24.65	5.0
4	7	28	10	10.24	2.94
5	6	30	7	9.83	3.55
6	3	18	5	5.48	2.33
7	1	7	1	2.02	0.97
8	1	8	1	2.22	1.17
9	0	0	0	0.0	0.0
10	0	0	0	0.0	0.0
11	1	11	3	2.87	1.81
12	2	24	8	6.20	4.04
Total.....	69	232	95	95.37	24.25

Standard error = $\sqrt{24.25} = \pm 4.92$

* = Values given by Penrose.[13]

In the second method (Table VI), the *a priori* assumption is made that the ratio of unaffected to affected sibs is, in fact, 3 to 1. The theoretically expected frequency of cases is then calculated over the series for sibships of various sizes, and the expected number of affected cases compared with that actually observed. In this series the expected number of cases worked out to be 95.37. Ninety-five cases were in fact observed; the difference is again small and well within the standard error.

CONSANGUINITY

It is a characteristic of a recessively inherited condition that the frequency of consanguineous marriages amongst the parents of affected patients is greater than in the general population. The rate of consanguineous marriages in the general population is hard to estimate but in the United States (and probably in Canada) it is now thought to be less than 1%.[26] In this series, out of 69 marriages, 4 (or 5.8%) were between first cousins.

One female phenylketonuric was a twin; her co-twin was a normal boy. There were two sets of first cousins with phenylketonuria, but the total number of cousins for the series as a whole is not known. There was one family with two uncles, an aunt and a nephew with phenylketonuria, and one family (omitted from the estimation of the Mendelian ratios) in which a mother and two out of her three children all had phenylketonuria.

DISCUSSION

Since the 83 living patients in this series probably represent only one-third of Ontario's population of phenylketonuric individuals, it may be of interest to speculate on the whereabouts of the other two-thirds. There would seem to be four likely groups of patients. For this purpose, children and adults are considered separately.

Children

1. At home; not under medical care; not diagnosed. This is the most important group from the point of view of useful therapy. The problem of the early diagnosis of such cases is not easy. Mass screening tests for phenylketonuria have been advised and several are in progress.[27-29] Another useful approach would seem to be a high index of suspicion on the part of the doctors and nurses who care for children, together with facilities close at hand for testing the urine for phenylketonuria.[30]

2. At home; under medical care; may or may not be diagnosed. Such children might be found in doctors' offices, among the outpatients of pediatric hospitals, in schools for retarded children, at occupation centres, at neuroconvulsive clinics or at skin clinics with eczema or well-baby clinics with feeding problems.[9] The importance of diagnosis in this group is twofold. In the first place, treatment with a low phenylalanine diet may well alleviate eczema and seizures and, in some cases, prevent intellectual deterioration. In the second place, the discovery of a patient with phenylketonuria should immediately lead to testing of all present and future siblings and so to a really early diagnosis of other patients.

Adults

3. The Ontario Hospitals; may or may not be diagnosed. By this is meant mental hospitals as opposed to the Hospital Schools for retarded children. Two patients from this series are in this group. As a general rule, however, it seems unlikely that the adult psychotic population contains any large number of undiagnosed phenylketonurics.[5]

4. At home; may or may not be diagnosed. Three cases from this series fit into this group. The first two are sibs who live in a rural area. The brother, aged 36 years, can do little and has a disability pension. The sister, aged 28 years, does housework and helps look after children. Both patients are retarded but they have been raised in an undemanding environment and so have avoided hospitalization. By contrast, the third case, a woman of 36 years, lives in an urban area and can in no way be described as *suffering* from phenylketonuria. She is a bright and active housewife with an I.Q. of 102 who has had three children. One of her children is a 13-year-old girl with phenylketonuria who is in an Ontario Hospital School. One child is a normal schoolboy and the third is a four-month-old phenylketonuric patient on treatment with a

low phenylalanine diet. The proportion of untreated phenylketonurics who have normal intelligence is not yet known but, according to Knox,[1] is probably less than 5%.

The practical importance of case-finding in these last two groups is that, once more, it may lead to an early diagnosis in others.

The age distribution of the patients indicates that the mortality of untreated phenylketonuria is about the same as that of mental deficiency in general. This suggests that the biochemical lesion in phenylketonuria has no specific lethal effect except insofar as it causes mental deficiency. The immediate cause of death was attributed to a respiratory infection in over half the patients. Case 15 had a duodenal and perforated esophageal ulcer. One other phenylketonuric has been reported in the literature as dying from a perforated peptic ulcer.[5]

The present figures indicate that the mortality rate of phenylketonuric patients with a history of infantile eczema is higher than those with phenylketonuria alone. The whole relationship of phenylketonuria to eczema, and possibly other skin lesions, is of great interest and would clearly bear much further investigation. A recent paper failed to demonstrate any increased sensitivity of the phenylketonuric person's skin to ultraviolet light.[31]

The Indian patient with phenylketonuria had a brown skin and very dark brown hair and eyes. Several other patients had dark hair. This emphasizes the fact that, although phenylketonurics have lighter coloured hair than other members of their families,[32] fair hair and blue eyes are not essential to the clinical picture and are of little diagnostic value.

The close agreement between the observed and expected ratios of normal to affected sibs provides further evidence that phenylketonuria is transmitted as a Mendelian recessive. As Knox[5] points out, this lends considerable weight to estimates of the expected frequency of phenylketonuria in the relatives of known cases.[3] These estimates depend, first, on the assumption that phenylketonuria is recessively inherited and, second, on the incidence of the disease in the general population. The accuracy of these estimates could be increased by a precise knowledge of the incidence of phenylketonuria in the population concerned. Furthermore, the identification of the heterozygotes by means of phenylalanine loading tests[33] now seems a real possibility, at least in many cases, and this should improve the accuracy and value of eugenic advice.

SUMMARY

Details are given of the age, sex and racial distribution, geographic location and mortality of 98 patients with phenylketonuria from Ontario. By current estimates of the incidence of the disease, the 83 living patients in this series represent about one-third of the province's phenylketonuric population.

The age distribution of the patients suggests that untreated phenylketonuria has an increased mortality rate but that this is no higher than that associated with mental defect in general. There is some evidence that a history of infantile eczema worsens the prognosis.

Phenylketonuria is reported in an apparently pure-blood Ojibwa Indian.

The corrected ratio of patients affected with phenylketonuria to their unaffected sibs agreed closely with the ratio of 1 to 3 expected in a recessively inherited disorder.

The findings are discussed and suggestions put forward as to where the remainder of the cases in the province may be sought.

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