Dietetic Treatment of Phenylketonuria: a Follow-up Study

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This is a factual study of 57 children with phenylketonuria (31 boys and 26 girls) seen during the period 1955 to the end of 1965. Most of them were under the care of one of us (A.M.), but other physicians at the Hospital for Sick Children have allowed us to use their records. With this small number under various physicians, the reasons for not treating some children or terminating treatment in others necessarily varied. Only those who were treated, or at least given a trial of treatment, are included in this report. Some patients born or detected late in 1965 were not included, as the results obtained were too recent for any satisfactory assessment. One patient (Case 55), detected at 6 years and 4 months, had an I.Q. of 105 and is the subject of a special note.

Methods of Treatment

The basis of the dietetic treatment of phenylketonuria is the exclusion of phenylalanine from the diet save for a minimal amount necessary to sustain life and progress. After a positive test for phenylpyruvic acid in the urine, confirmation is sought by examining the phenylalanine content of the blood. Normally this is about 2 mg./100 ml. serum when a chromatographic method of estimation is used, but in affected children it is much higher. The aim of dietary treatment has been to maintain the level below 4 mg. It is generally advisable to admit the child to hospital for "stabilization."

In the early days of the treatment, when affected children mostly past infancy were being discovered and treated, the practice was to eliminate all phenylalanine by using a synthetic "milk" very low in phenylalanine and a careful selection of other items free from or very low in phenylalanine. When a satisfactory low blood level had been achieved—and sometimes this regimen resulted in the complete disappearance of phenylalanine from the blood—ordinary cow's milk (liquid or dried) was added to the diet until the level of phenylalanine rose; but such a rise was restricted to a maximum of 4 mg./100 ml. serum and the amount of milk adjusted accordingly by frequent estimations of the serum phenylalanine level. An early account of experience in this programme at the Hospital for Sick Children has been published (Woolf, Griffiths, and Moncrieff, 1955). Further experience led to a full account of the methods used and the results achieved (Woolf, Griffiths, Moncrieff, Coates, and Dillistone, 1958).

When treatment of quite young babies was started, however, complete exclusion of phenylalanine from the daily diet produced alarming results, which included skin rashes, loss of appetite, and wasting. An account of some of these difficulties was published (Moncrieff and Wilkinson, 1961). Because of these findings it is necessary to add a calculated amount of milk to the diet, the basis of which is one of the special casein hydrolysates. Full accounts of the methods used have been published as a report of a conference to the

Medical Research Council (1963). A short, simple account of a method for feeding the phenylketonuric infant was published from the Hospital for Sick Children by Clayton, Francis, and Moncrieff (1965). It can be assumed that all the children whose cases are reported in the present series have been treated according to the methods in the publications cited.

No mention is made here of methods employed elsewhere than at the Hospital for Sick Children, as this is essentially a report of personal experiences. For the same reason no attempt has been made to review the literature.

The main detailed results are shown in Table I, and the patients are arranged in order of the age of detection, beginning with the youngest. The "quality" of treatment

TABLE I.—Summary of Effect of Treatment

Case No.	Age Detected (Weeks)	Initial I.Q.	Duration of Treatment (Weeks)	Quality of Treatment	Last I.Q.	Epilepsy	Placement
1	2	107	37	Good	111	—	Preschool
2	3	119	376	"	79	—	Ordinary school
3	3	74	30	"	104	—	Preschool
4	4	133	16	"	119	—	"
5	5	111	45	"	120	—	"
6	6	108	104	"	95	—	"
7	6	94	52	"	106	—	"
8	6	83	158	Fair	90	—	"
9	8	90	108	Good	100	—	"
10	8	95	104	"	98	—	"
11	17	70	17	"	85	—	"
12	18	65	476	"	82	—	Ordinary school
13	19	83	320	"	78	—	"
14	26	74	212	"	65	—	Preschool
15	28	102	260	Fair	109	—	Ordinary school
16	28	15	160	"	39	—	Preschool
17	28	18	221	Good	30	—	"
18	37	31	292	"	61	+	E.S.N.
19	38	29	396	"	55	—	"
20	38	65	208	"	73	+	Ordinary school
21	41	41	372	"	51	+	E.S.N.
22	52	8	368	"	27	+	T.C.
23	52	51	87	"	65	—	Preschool
24	55	45	132	Fair	36	+	Hospital
25	57	21	260	Good	23	+	"
26	59	44	360	"	44	+	"
27	61	45	106	"	44	+	T.C.
28	62	58	15	"	58	+	Preschool
29	64	36	464	"	33	+	Rudolph Steiner
30	66	32	364	"	27	+	Hospital
31	68	57	520	"	68	—	Ordinary school
32	69	28	416	"	41	+	T.C.
33	70	11	78	"	8	+	Hospital
34	71	33	104	Fair	30	+	Preschool
35	88	57	60	Good	70	—	"
36	88	42	156	Fair	38	—	T.C.
37	104	24	468	Good	20	+	Hospital
38	104	71	520	"	82	—	Ordinary school
39	104	70	296	"	98	—	"
40	104	34	72	Fair	46	—	Preschool
41	113	36	220	Good	71	—	Ordinary school
42	114	20	104	"	18	+	Hospital
43	122	23	264	Fair	19	+	T.C.
44	122	48	224	"	61	—	E.S.N.
45	124	35	256	Abandoned	26	—	T.C.
46	128	49	212	Fair	53	—	E.S.N.
47	128	70	268	Good	100	—	Ordinary school
48	138	47	288	Fair	67	—	E.S.N.
49	146	40	120	"	61	—	"
50	168	36	184	Good	39	+	Preschool
51	196	92	112	"	105	—	Ordinary school
52	199	67	160	"	70	—	E.S.N.
53	213	64	72	Fair	56	—	"
54	305	38	312	"	53	—	T.C.
55	321	105	16	Good	104	—	Ordinary school
56	450	49	320	Fair	45	—	Preschool
57	496	47	28	Abandoned	49	—	T.C.

Ordinary school indicates placement with the normal educational system.
E.S.N. indicates placement in a school for the educationally subnormal.
T.C. indicates placement at a training centre.
Hospital indicates placement in a hospital for the subnormal.
Rudolph Steiner indicates placement in a special unit.

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was assessed as good, fair, or bad. This assessment is necessarily subjective, but it was made from our knowledge of the parents together with the views of the ward sister and the dietitians. Thus in 40 instances the standard of maternal care was good, in 15 it was fair, and in two the treatment was abandoned.

Intelligence Testing

The assessment of developmental progress and/or intelligence in children of all ages, but especially in the neonatal period, is fraught with difficulty. Nevertheless, in assessing the progress of children being treated for phenylketonuria, some objective evaluation has to be made, though the limitations of such procedures are well recognized. In particular the standard tests used do not measure the more subtle aspects of behaviour and "intelligence" that may result from dietary treatment.

In the longitudinal study various tests have been used, depending on the age of the child. These tests have included the Griffiths, the Stanford-Binet, the Merrill-Palmer, and the Wechsler. For the purpose of this paper the "score," whatever the test, is expressed as "I.Q." for reasons of convenience.

It must be recognized, however, that the determination of an I.Q. in numerical terms is related to placement within the educational system. It may be that in future, for infants and small children, the term "developmental" tests would be more appropriate.

In the early days in the treatment of phenylketonuric children, before screening tests were introduced on a more or less national scale, it was surprising to find such variable levels of intelligence at the initial testing. One child (Case 55), with an I.Q. of 105 at the age of 321 weeks, has already been mentioned, and this case has been fully reported (Coates, Norman, and Woolf, 1957).

Case 55.—A boy, the fourth child of a family of five, was affected by Gowers's muscular dystrophy. At the time of this diagnosis, when he was 6 years old, the urine was examined for amino-acids, and phenylpyruvic acid was detected. The level of phenylalanine in the blood was raised. Other children in the family were given intelligence tests and were all higher in rating than the patient. It is perhaps significant that just over two years after the initial intelligence testing the level in this patient had fallen by an average of 18 points and a low phenylalanine diet, previously abandoned after three months, was reinstituted.

The parents of this child had above average levels of intelligence, especially the mother. Unfortunately, the intelligence level of other parents in the present series was not estimated.

Effects of Treatment

In general terms the best results, as might be expected, were obtained when treatment was started in early infancy, though some surprisingly good results were obtained in older children, with a rise in intelligence level which enabled them to go to a school for the educationally subnormal (Cases 18, 19, 21, 44, 46, 48, 49, 52, and 53) and to an ordinary school (Cases 2, 12, 13, 15, 20, 31, 38, 39, 41, 47, 51, and 55). Some of these results are shown in the Chart. The final placements of all the children are shown in Table I.

Additional Comments

The reasons for referral to hospital are shown in Table II, which illustrates clearly that the patients are by no means always referred because of mental subnormality alone. Table III shows how and where the disorder was initially diagnosed. It was disappointing to find that during the whole period only 10 patients were detected in infant welfare centres and only

two of these were under 6 weeks of age. Seven were detected because of the presence of a previous sibling with the condition, five in the first three weeks of life, and these have done well. The majority, however, have been detected because of the presence of mental subnormality, unfortunately only becoming apparent from 6 months of age onwards.

TABLE II.—Main Reasons for Referral to Hospital

Mental subnormality	32
Epilepsy (in each case "infantile spasm")	4
Failure to thrive	3
Speech retardation	1
Eczema	1
Muscular dystrophy	1
Asymptomatic	7
1. From infant welfare centre	7
2. Known to be "at risk"	7
Total	57

TABLE III.—How, Where, and Why the Diagnosis Was Made

Age	Infant Welfare Centre		Hospital Services			Health Visitor ? M/S	Family Doctor ? M/S
	Routine	? M/S	Routine Investigation	Screened for M/S	At Risk Child		
< 3 weeks	1				5		
3-6 weeks	1						
6-8 "	3						
8-12 "	1						
3-6 "	1		1		1		
6-9 months			1			1	
9-12 "				4			1
12-18 "		1	1	3			
18-24 "				8			
2-2½ years		2		3			
2½-3 "			1	2	1		
3-4 "				1			
4-5 "				1			
5-6 "							
6-7 "			1	1			
7-8 "							
8-9 "				1			
9-10 "				1			

M/S = Mental subnormality. At risk = Previously affected sibling.

Reasons for failure or partial failure of the treatment are perhaps as important as reasons for success. Several possibilities, or associated phenomena, must be taken into account when assessing the progress of an individual child.

1. **Epilepsy.**—All but three children with epilepsy appear to have responded badly to dietary treatment (see Table I). Eighteen of the 57 children suffered from epilepsy. The progress of some of these is shown in the Chart. A statistical analysis was carried out to see whether the final I.Q. score differed in the two groups of children (epileptics and non-epileptics) after adjusting for initial I.Q., duration of treatment, and age at detection. The results of an analysis of covariance were as follows:

(F-test) $F=14.6$ (D.F. 1,49)

Very highly significant, $P<0.001$.

Difference between groups for adjusted final I.Q. = 16.4

Developmental progress of the patients on treatment who had been regularly assessed. — Denotes non-epileptics. ---- Denotes the presence of epilepsy.

Hence the results indicate that the final I.Q. is higher in non-epileptic children after allowance is made for initial I.Q., duration of treatment, and age at detection. The type of epilepsy and the ages of onset are shown in Table IV. The high incidence of infantile spasms is noteworthy.

TABLE IV.—*Type of Epilepsy and Age of Onset*

Type of Epilepsy	Age of Onset (Months)						Total No.
	5	6	7	8	9	12-18	
"Infantile Spasms"							10
Grand mal	1	2	1	1	4	2	6
Petit					2	2	2

2. *Infection.*—Because the blood phenylalanine level is found to rise temporarily during acute infections, it was thought that the presence of chronic infection—for example, chronic tonsillitis or discharging ears—might militate against the success of dietetic treatment in keeping the blood phenylalanine at a satisfactory low level. So far as the records examined show, however, there was no evidence of this.

3. *Dietetic Difficulties.*—Difficulties with the diet were not infrequently present, often requiring admission to hospital for further stabilization, but, unless breaks in diet lasted more than a week or so, no obvious unsatisfactory results were observed. Infants and young children alleged to refuse the special diet took it in hospital, and intensive instruction of the mothers was necessary. Children of school age presented some difficulties over the midday meal at school, but the education authorities and teachers were always most helpful. Occasional raiding of the larders at home probably does no permanent harm. It is interesting to note that in two affected young children there was a clear history of a severe dislike for ordinary milk from an early age, and later for all protein-containing foods, including eggs. A few parents either refused to co-operate or claimed that it was impossible to get the children to take the special diet. This was the case in certain older children rather than in babies. In one instance the reason given was that a child was no more backward than an elder sister. Investigations showed that the latter child was also affected and untreated. They were members of a migrant gipsy family and were best left alone.

Physical Progress

The records examined have not always shown details of height and weight. When available, heights and weights were converted into percentile groups (Tanner and Whitehouse, 1959). The results are shown in Table V. In general there is no evidence that phenylalanine-restricted diet resulted in poor physical development. In the case of twins, one of whom was affected and treated from the age of 17 days (the other twin being normal), the treated child at the age of 9 was actually 1 in. (2.5 cm.) taller than her sister.

TABLE V.—*Height and Weight of Treated Patients*

Percentile Status	No. of Patients	
	Height	Weight
Not recorded	15	3
below the 3rd	3	3
3-9	4	7
10-24	11	13
25-49	12	11
50-74	9	14
75-89	2	1
90-96	1	3
97 and over	1	2
Total	57	57

Criteria for Treatment

In the early days of the treatment of phenylketonuria patients, most of the children found with this abnormality were past the age of infancy, and some "rule of thumb" had to be devised. As experience developed it seemed likely in most instances that a rise of about 20 points in the intelligence level might be achieved by treatment, and even if this did not raise the child into the educational level (educationally sub-normal or fit for ordinary school) it seemed worth while even to raise the child from the severe to the moderately sub-normal level. In the report of Woolf *et al.* (1958) a rough guide was set out as follows: "We consider treatment worth initiating if the child is 2 years old or under and the G.Q. not less than 20, or 3 years old with a G.Q. of 30 or over, or 4 years old with a G.Q. of 40 or over. In any border-line cases it is probably wise to try six months' treatment with careful psychological testing at the beginning, at 3 months and at the end of this period."

The paper went on to state that it was important to rule out any other form of brain disease such as that due to birth trauma in the widest sense. In the light of further experience it is probably wise to add that the presence of "fits" would make a favourable outcome unlikely. With this reservation, however, it would be fair to state that the policy set out in 1958 is still valid. In addition, all young babies detected by routine screening should certainly be treated.

When to Stop Treatment

This question is of increasing importance as the number of children under treatment grows and the children get older. We have not felt that ethically we could yet stop treatment in any of the patients here reported as doing well. Theoretically it is possible that there is a point in maturation of the brain when a raised phenylalanine level in the blood ceases to cause damage or, to put it another way round, the brain cells develop some degree of tolerance. An attempt to test this by a consideration of the immediate effects of a dose of phenylalanine on the electroencephalogram has been made in the department of electroencephalography at the Hospital for Sick Children (Clayton, Moncrieff, Pampiglione, and Shepherd, 1966). Twelve children received dietetic treatment for phenylketonuria were selected and in seven a considerable increase in the abnormality of the electroencephalogram occurred after a phenylalanine load. It would seem unwise to relax dietetic restrictions in these children. Five children showed only mild or negligible changes during the phenylalanine-tolerance test. These were all children whose intelligence quotients at the time of the test were around normal. Three had started treatment in the first two months of life, and in the other two, though starting treatment at nearly 2 and 3 years old respectively, a remarkable improvement had occurred in their measured intelligence levels. Even in these children we are still hesitant to increase their phenylalanine intake at present.

Summary

From 1955 to the end of 1965 57 children with phenylketonuria, who were treated or at least given a trial of treatment, were studied.

Only 10 of the patients were detected in infant welfare centres, and only two of these were under 6 weeks of age. Seven were detected because a previous sibling had the condition. Unfortunately, the majority were discovered after mental subnormality had become apparent.

The best results were obtained when treatment was started in early infancy.

Sometimes surprisingly good results occurred in older children, with a rise in intelligence level which enabled them to go to a school for the educationally subnormal or to a normal school.

All but three of the 18 children with epilepsy responded badly to dietary treatment.

There was no evidence that dietary treatment resulted in poor physical development.

Thanks are due to the physicians at the hospital for permission to study their patients; to Mr. H. Goldstein for help with the statistical analysis; to the staff of the Department of Psychological

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Studies in the Epidemiology of Tinea Pedis. VIII: Fungal Infection in a Long-stay Hospital

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Tinea pedis has been studied in many different types of community, each yielding different but complementary information about the epidemiology of the disease. It now seems certain that the most common means of transmission is the direct contact of healthy feet with small fragments of skin shed by infected persons (Gentles, 1957; English and Gibson, 1959b; Gip, 1966). This may happen in various ways, the relative importance of which will differ in different communities. It is also known that the incidence of infection is higher in persons living a communal life (Marples and di Menna, 1949; English, Gibson, and Warin, 1961; Wrede, 1965) or using communal washing facilities or swimming-baths (Tritsmans and Vanbreuseghem, 1955; Gentles and Holmes, 1957; English, Gibson, and Duncan, 1960) than in those not doing so; and that, in children, incidence rises with age (English and Gibson, 1959a; Munro-Ashman and Clayton, 1962; Polemann, 1955). There is dispute about the extent to which fungi are carried on, and hence dispersed by, lesion-free feet (Rosenthal, Baer, Litt, Rogachefsky, and Furnari, 1956; English, 1962). That many people have a natural resistance to the disease is a constantly observed fact, though the nature of this resistance and the proportion of the population protected by it are unknown.

The two fungi responsible for the overwhelming majority of cases of tinea pedis in this country are *Trichophyton interdigitale* and *T. rubrum*. The incidence of *T. rubrum* is increasing rapidly, and recent figures from dermatological clinics in Bristol show that it now occurs more often in them than *T. interdigitale*. However, English and Gibson (1959a) and English *et al.* (1961) have shown that both in day schools and in boarding-schools *T. interdigitale* was by far the most common fungus, and this has been confirmed in another boarding-school by Munro-Ashman and Clayton (1962). Similar figures for a sample of the adult population not attending skin clinics are not available, but English and Turvey (work to be published) have recently shown that in patients attending a chiropody clinic, almost entirely for complaints other than tinea pedis, 20 of the 33 infections found were attributable to *T. interdigitale* and only five to *T. rubrum*. *T. interdigitale*, there-

fore, is still the most common cause of tinea pedis in the population at large. *Epidermophyton floccosum*, the third causal organism, is comparatively rare and its incidence seems to be changing little. The clinical manifestations and epidemiology of these three species differ, but only very tentative suggestions regarding the reasons for this have been put forward.

It seemed possible that information on some of the above points might be provided by the study of a large, relatively stable community of adults living communally for most or all of their lives. During 1964 the attention of one of us (R. R. W.) had been attracted by the large number of patients in one section of a long-stay hospital for mentally retarded men who had clinically severe tinea pedis, and it was decided that a detailed epidemiological study of this hospital should be undertaken.

Subjects

The hospital housed some 400 male patients of all degrees of mental subnormality, some of whom also had mild to severe physical handicaps.

Patients were grouped in "lodges," each housed in separate buildings or parts of buildings. Lodge 7, the largest, was also used for the supervision and discipline of difficult patients, and it was therefore likely that patients from most other lodges spent periods there. Other transfers between lodges occurred at intervals, but many patients had been in the same lodge for a very long time. Lodge 9 was reserved for the elderly sick.

Lodges 7 and 8 each had a 60-bed dormitory; other dormitories ranged in size from 6 to 24 beds. Bathrooms were communal and each contained a number of baths. Up to the end of 1964 one bathroom served lodges 1–5, another lodges 6–8, and lodge 9 had its own. In December of that year additional bathrooms were brought into use so that one was shared by lodges 1 and 2, another by lodges 3–5, and lodges 6, 7, and 8 had one each.

Of the 358 patients included in the survey, 7 were under 20 years old and 276 (77%) were over 40; 326 (91%) had lived in the hospital for three years or more and 236 (66%) for 11 years or more.

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