General Conclusions

The experiences of the past few years suggest that early detection of phenylketonuria and treatment of these very young infants offer a reasonable chance of preventing mental retardation. There are certain difficulties about early detection which should be overcome. More troublesome is the fact that the diet of the actively developing young baby may have to be more generous in phenylalanine, even to the extent of exceeding the normal blood level, if the child is to survive and thrive. Why some babies are more difficult than others is not yet clear. The dietetic control must be most closely followed by serial estimations of phenylalanine levels in the blood. Probably the simplest dietary treatment would be to use the available phenylalanine-free casein preparations but to add more milk than is usual (more than the maximum of 3 oz. (85 ml.) daily allowed in older children). Whether or not we should also give more tyrosine and tryptophan is not yet clear. Alternatives to the present casein-hydrolysates might help with the cost of the diet. We should like to know more about the enzyme deficiency present, and experimental work may help here. What everyone working in this field would like to know is whether or not dietetic restrictions can ever be relaxed. Evidence on this may be difficult to get, although it is beginning to accumulate.

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REFERENCES

- Auerbach, V. H., Waisman, H. A., and Wyckoff, L. B., jun. (1958). *Nature (Lond.)*, **182**, 871.
 Berry, H. K., Sutherland, B. S., Guest, G. M., and Umbarger, B. (1958). *Pediatrics*, **21**, 929.
 Blainey, J. D., and Gulliford, R. (1956). *Arch. Dis. Childh.*, **31**, 452.
Brit. med. J., 1958, **2**, 736.
 Clements, F. W. (1949). *Infant Nutrition*, p. 82. Wright, Bristol.
 Geisler, E., and Ströder, J. (1958). *Ann. paediat. (Basel)*, **191**, 147.
 Gibbs, N. K., and Woolf, L. I. (1959). *Brit. med. J.*, **2**, 532.
 Hansen, J. D. L., Howe, E. E., and Brock, J. F. (1956). *Lancet*, **2**, 911.
 Horner, F. A., and Streamer, C. W. (1959). *Amer. J. Dis. Childh.*, **97**, 345.
 Hsia, D. Y.-Y., Knox, W. E., Quinn, K. V., and Paine, R. S. (1958). *Pediatrics*, **21**, 178.
 Hudson, F. P., and Ireland, J. (1959). *Brit. med. J.*, **2**, 885.
 Kenney, F. T., and Kretchmer, N. (1959). *J. clin. Invest.*, **38**, 2189.
 Macdonald, D. B. Personal communication.
 Moncrieff, A. (1958). *Brit. med. J.*, **2**, 917.
 — and Wilkinson, R. H. (1960). *Lancet*, **1**, 282.
 Paine, R. S., and Hsia, D. Y.-Y. (1957). *Amer. J. Dis. Childh.*, **94**, 224.
 Pare, C. M. B., Sandler, M., and Stacey, R. S. (1957). *Lancet*, **1**, 551.
 — (1958). *Ibid.*, **2**, 1099.
 — (1959). *Arch. Dis. Childh.*, **34**, 422.
 Snyderman, S. E., Pratt, E. L., Cheung, M. W., Norton, P., Holt, L. E., jun., Hansen, A. E., and Panos, T. C. (1955). *J. Nutr.*, **56**, 253.
 Waisman, H. A., Wang, H. L., Harlow, H., and Sponholz, R. R. (1959). *Proc. Soc. exp. Biol. (N.Y.)*, **101**, 864.
 Wilkinson, R. H. (1961). To be published.
 Woolf, L. I., Griffiths, R., Moncrieff, A., Coates, S., and Dillistone, F. (1958). *Arch. Dis. Childh.*, **33**, 31.

RESULTS OF TREATMENT IN PHENYLKETONURIA

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This paper reports on further experience in the dietary treatment of phenylketonuria at The Hospital for Sick Children, and follows the papers by Woolf, Griffiths, and Moncrieff (1955) and Woolf, Griffiths, Moncrieff, Coates, and Dillistone (1958). This experience is considered in the light of a review by Knox (1960), especially our successes and failures in treatment. As Knox gives an evaluation of treatment based on all the treated cases published up to the end of 1959, it is not necessary to review the literature here. The neurological aspects of the patients will be dealt with in a later paper. Moncrieff and Wilkinson (1961) discuss our current views on the biochemistry of the disease, and the present paper is concerned mainly with the psychological aspects.

Material

Up to October, 1960, 35 cases of phenylketonuria have been considered for treatment at The Hospital for Sick Children since the dietary treatment was started in October, 1953. These are listed in Table I. Case 34 has already been the subject of a paper (Coates, Norman, and Woolf, 1957), and Case 35 is mentioned by Moncrieff and Wilkinson (1961). These are not discussed here. Of the remaining 33, two (Cases 32 and 33) have only had their initial test before starting treatment: they will therefore be used only in calculating the level of abilities found before treatment.

Thirty-one cases have been treated and had their second test, but in six of these (Cases 26–31) treatment has been ended for various reasons:

Material from our earlier papers is repeated. The case numbers of the present series and the corresponding numbers in those papers are as follows:

Present Series	1958	1955
Case 1	Case 11	
" 3	" 6	
" 9	" 3	Case 2
" 10	" 2	
" 20	" 9	
" 24	" 8	
" 25	" 1	
" 26	" 4	" 1
" 28	" 10	
" 29	" 5	" 3
" 31	" 7	

The children are tested for intelligence before treatment starts, then three months later, three months later again, six months later, and then yearly. Originally we tested much more often, but the additional information is no longer useful. The Griffiths mental development scale is used on children with a mental age below 2 years: 75% of 192 tests up to date. The Merrill-Palmer scale and the Revised Stanford-Binet intelligence scale are used for children of higher mental age.

Results of Treatment

The results of treatment are given in Table I. Cases 1 to 25 are still being treated and have had more than one test. They are listed in order of the size of the increase in the intelligence quotient from the initial to the latest test.

Whether or not the final outcome is improvement, the test measures in any one case naturally vary above and below the trend of that particular case. The latest measure used in this paper may therefore not always be the highest, to some extent as a result of chance. The latest score is in fact less than the highest in 10 of these cases. In assessing results the latest measure has been used—therefore making the results slightly less satisfactory—but the highest scores are also given in Table I. It will be seen, from Cases 26, 27, and 28, that a child may temporarily improve and then revert to a measure so close to the original that eventually treatment is stopped. It therefore seemed better to use the latest rather than the highest measure in assessing the effects of the diet.

Case 25 is a special one. Since this patient's elder sister was a known phenylketonuric (Case 20 of this series) the patient was herself diagnosed at 17 days and has been on the diet since she was 4 weeks old. The quotient dropped to 81 after two years, but has since climbed fairly steadily to the latest figure of 94, her present age being 5 years 6 months. We naturally did not expect an improvement in her intelligence, and the loss of 25 points is not important, since the first test would inevitably be unreliable at so early an age. Her normal non-identical twin sister began with a quotient of 113, and on last testing at 4 years of age this had dropped to 108.

Discontinued Cases

Treatment has been stopped, after various periods, in six cases (Nos. 26–31). The latest quotients tabulated are the last before treatment stopped. The reasons for

TABLE I

Case No.	Sex	Initial Quotient	Latest Quotient	Change in Quotient	Highest Quotient if Different from Latest	Age at Initial Test (Weeks)	Period of Treatment (Weeks)	Rate of Improvement*
1	M	36	74	38		118	166	0.23
2	M	57	88	31		70	288	0.14
3	M	29	57	28	65	42	190	0.15
4	M	31	58	27	62	43	119	0.23
5	F	8	31	23		54	214	0.11
6	F	28	48	20	50	69	78	0.26
7	M	41	61	20		47	165	0.12
8	F	47	64	17	72	152	304	0.06
9	F	71	85	14	93	152	295	0.05
10	M	48	60	12		130	132	0.09
11	F	34	46	12		106	77	0.16
12	M	18	27	9		37	109	0.08
13	F	67	71	4		327	30	0.13
14	F	83	87	4		65	42	0.10
15	M	42	45	3		63	70	0.04
16	M	74	77	3		28	28	0.11
17	M	21	23	2	32	63	220	0.01
18	M	38	40	2	41	307	96	0.01
19	F	32	32	0		234	97	0.02
20	F	24	23	-1	31	94	218	
21	M	32	31	-1		68	241	
22	F	49	48	-1		455	95	
23	F	44	39	-5	51	64	163	
24	F	63	56	-7	83	19	216	
25	F	119	94	-25		4	274	
26	M	20	29	9	30	138	142	0.06
27	F	23	31	8	34	124	112	0.07
28	M	20	25	5	34	80	220	0.02
29	F	11	14	3		279	221	0.01
30	F	33	33	0		85	0	
31	F	49	49	0		132	4	
32	M	15				44		
33	M	40				42		
34	M							
35	F							

* The rate of improvement is the rise in quotient per week of treatment, derived by dividing the increase in the quotient by the period of treatment. It is not the same as the progress rate, which is the increase in mental age divided by the increase in chronological age multiplied by 100. It seemed (Woolf *et al.*, 1955) that this latter figure might stay constant for a particular child and enable us to predict the final adult intelligence level, but this has been disproved. The situation is too complex for such simple mathematical predictions, and the rate varies from month to month.

stopping in Cases 26, 28, and 31 have already been stated in our last paper (Woolf *et al.*, 1958). The mother of Case 30 never really tried the diet, as she would not agree that her child was very backward.

Two patients (Cases 27 and 28) showed slight initial improvement, but this was not maintained, the measures finishing at a slightly higher level. In both cases it was difficult to keep the child on the diet and pointless to continue the uneven struggle.

All these children have been tested since stopping the diet, with results (Table II) which may be compared with three cases quoted by Knox (1960) from Armstrong *et al.* (1957).

TABLE II

Case No.	Age (Weeks)		Duration of Treatment (Weeks)	Period after Treatment (Weeks)	Intelligence Quotient		
	When Diet Started	When Last Seen			Initial	When Diet Stopped	At Follow-up
26	138	280	142	?	20	29	21
27	124	323	112	87	23	31	21
28	80	356	220	56	20	25	32
29	279	300	221	90	11	14	10
30	85	182	0	97	33	33	30
31	132	278	4	142	49	49	37

It would seem that there are no effects, all the differences being accountable for by chance. Improvement, such as it may be, is not usually maintained, but there is also no appreciable loss of ability.

Organic Psychosis

There are five children (Table III) whose behaviour warrants the diagnosis of autism or juvenile psychosis. They are withdrawn, unable to make a relationship even with their mothers, fairly wild and unmanageable, non-speaking, and given to uttering peculiar noises and displaying many kinds of mannerisms, often of an auto-erotic kind. These are Cases 11, 17, 20, 21, and 27.

TABLE III

Psychotic Cases				Non-psychotic Cases of Comparable Initial Quotient			
Case No.	Initial Quotient	Latest Quotient	Age at Start of Treatment (Weeks)	Case No.	Initial Quotient	Latest Quotient	Age at Start of Treatment (Weeks)
11	34	46	106	3	29	57	42
17	21	23	63	4	31	58	43
20	24	23	94	5	8	31	54
21	32	31	68	6	28	48	69
27	23	31	124	12	18	27	37
				19	32	32	234
				28	20	25	80
Means	27	31	91		24	40	80

They are all of low initial intelligence quotient—the average is 27—but this cannot be held responsible for their condition, since there are seven children of comparable initial intelligence who are not similarly affected (Cases 3, 4, 5, 6, 12, 19, and 28). There is a tendency for the psychotic to have started treatment at a later age than these seven non-psychotic. Five of the seven non-psychotic were treated early (before 70 weeks), whereas only two of the five psychotics were treated so early.

It may be that we have prevented a psychosis in Cases 3, 4, 5, 6, and 12 by starting treatment early, though the fact that we failed to prevent it in Cases 17, 20, and 21 suggests that there may be selective brain damage and that in some children there is an organically induced psychosis as well as an organically caused mental deficiency. That the two conditions are not necessarily

related is shown by Cases 5, 12, 19, and 28, where the final quotient is still very low but the child is clinically by no means psychotic. In some of the psychotic cases the mothers were unable to provide the optimum environment, but this failure, as also their failure to keep the child strictly on the diet, was by no means restricted to these cases. Thus Case 3 has been very poorly handled by a mother preoccupied with her own personal problems, and the child has not always been kept strictly to the diet, but there is no psychosis and there is improvement. It seems that where there is this selective damage to the personality any change in the brain is not accompanied by improvement in the intellect, probably because the intellect cannot improve if the mind is diseased. But when the mind is not diseased, for all that the brain is damaged, as in Case 3, then the intellect can improve.

Rapid Changes

It has happened that in four cases there has been a considerable rise in the quotient between the initial and the second test, and this has led to an overoptimistic prognosis at the time of the second test. These cases are shown in Table IV. There are three other cases

TABLE IV

Case No.	Age at Start (Weeks)	Initial Quotient	Interval between Tests	Second Quotient	Latest Quotient
3	42	29	33 weeks	55	57
4	43	31	16 "	59	58
5	54	8	17 "	19	31
6	69	28	17 "	47	48

(Nos. 7, 15, and 17) of comparable age, initial intelligence, and interval which do not show this sudden jump. Presumably in the "jumping" cases we are seeing the effects of the removal of intoxication from a damaged brain: the immediate effects are dramatic, but the permanent damage is such that complete repair is impossible, and though further permanent damage may be prevented the result is still a child who is considerably retarded intellectually.

Sub-scale Differences

The Griffiths scale consists of five subscales: A, locomotor; B, personal-social; C, hearing and speech; D, eye and hand; and E, performance. In the normal child there will be only slight differences in the scores across these five subscales. Children with specific defects show up early by a relative failure on one subscale. Thus spastic children will fail on the locomotor scale and deaf children on the hearing and speech scale. We investigated discrepancies on 87 tests carried out by 25 of the patients. The major discrepancies are on the locomotor scale and the performance scale. The locomotor scale tends to be the highest of the five on any one testing and the performance scale tends to be the lowest. The three other tests behave in no consistent fashion beyond being between these two extremes. Of the 87 tests, only 21 (24%) showed no discrepancy—that is, neither the locomotor scale, the highest, nor the performance scale, the lowest. On the other hand, 25 (29%) have both a high locomotor and a low performance at the same testing. These discrepancies are much more pronounced in the second year. Thus 15 (33%) of the 45 tests yielding a mental age less than 52 weeks show no discrepancies but only 5 (14%) of the 42 tests yielding a mental age between 52 and 104 weeks. The results of this investigation are shown in

Table V. It will be seen that the chances are that three-quarters of all tests on these children will show a discrepancy of either scale A or scale E, and that the possibilities are greater (3:2) that it will be in scale A.

TABLE V

	No. of Tests	Locomotor High	Performance Low	Locomotor High and Performance Low	No Discrepancies
All tests ..	87	55 (63%)	36 (41%)	25 (29%)	21 (24%)
1st-year tests ..	45	20 (44%)	21 (47%)	11 (24%)	15 (33%)
2nd- " " ..	42	35 (83%)	15 (36%)	14 (33%)	6 (14%)

It will also be seen that the chances of obtaining a discrepancy are greater in the second year than in the first (9:7). In the first year the discrepancies which will probably occur in 67% of tests will be equally divided between a high locomotor and a low performance score, with a quarter of the cases showing both at once. In the second year the great majority (83%) will have a high locomotor score, but the 36% with a low performance score are probably no more than would be expected by chance.

Two conclusions can be drawn. In the first place it is clear that the locomotor scale alone would be a very inadequate indication of intellectual status in the second year of mental life. Assessments based on locomotor skills—crawling, walking, climbing stairs—will be misleadingly optimistic. Inferences from low performance scale scores may well be unduly pessimistic in some cases, though this scale is most like a normal intelligence test; but these inferences are less likely to be made.

In the second place it is worth noting that the damage to the brain in these children seems not to affect physical development. We do not find paralyses or disturbances of locomotion. In another series of brain-damaged children, hydrocephalics, there is a close correspondence between degree of mental defect and degree of physical handicap (Laurence and Coates, in preparation). It would be interesting to know why a metabolic abnormality which causes irreversible damage to the brain (Crome and Pare, 1960*; Hsia *et al.*, 1958) should selectively be less damaging to locomotor development, relatively speaking, than to the intellect as a whole, while other post-natal diseases of the brain seem to affect intellect and locomotion equally.

Evaluation of Results

In order that our series might be compared with the 43 cases collected by Knox (which included eight cases from our 1958 paper, which are repeated here), our results have also been assembled in Table VI in the form he uses.

It is immediately apparent that the distribution of our untreated cases is very different from that of 466 untreated cases collected by Knox. Presumably our cases are younger and therefore show less deterioration. We do not know the average age of the 466 patients, but they include a large number of adults, whereas our sample consists entirely of children varying in age from 4 weeks to 8 years 9 months, 80% being under 3 years old. It seems quite invalid to compare treated cases with those 466 untreated, since such a comparison would give a falsely optimistic view of the effects of the diet.

We can claim to have had some moderate success from the diet. Table VI shows that, taking all 31 treated

*Crome and Pare (1960) refer in their bibliography to a non-existent paper: Woolf, Griffiths, and Moncrieff, *Brit. med. J.*, 1954, 1, 1957.

cases (which include 6 whose treatment was ended, two of them never really on diet), the shift in proportions of cases in the various quotient categories is clearly significant. From Table I it can be seen that 22 cases improved (Nos. 1-18 and 26-29). Some of these were only borderline successes (Cases 13-18). Eight cases appear to be failures (Cases 19-24 and 30-31). These failures and borderline failures are discussed in detail.

TABLE VI

Intelligence Quotient	Untreated Cases		Treated Cases (31)		Treated Started Before 3 Years			
	466 (Knox, 1960)	All Our Cases (33)	Before Treatment	After Treatment	Before Treatment (26 Cases)	After Treatment (26 Cases)	Started Before 16 Mths (14 Cases)	Started After 16 Mths (12 Cases)
0-20	64.4	18.2	19.5	3.0	15	0	0	0
21-40	23.2	39.4	35.0	39.0	38	39	36	42.0
41-60	9.7	24.2	26.0	29.4	27	31	36	25.0
61-80	1.9	12.1	13.0	16.0	12	15	14	16.5
81+	0.6	6.1	6.5	12.6	8	15	14	16.5

Failures

In Cases 30 and 31 the failure was clearly attributable to the diet never having been properly tried. They are cases of failure of our treatment of the parents but not necessarily failure of the diet.

The loss of ability in Cases 23 and 24 may not be permanent. It will be seen that both have shown higher quotients in the past. Case 23 went up from 44 to 51 in the course of the first year of treatment, and Case 24 from 63 to 83 over three years. There is no explanation for the subsequent drop to 39 in Case 23. There has been good dietary control and the blood phenylalanine levels have always been satisfactory. The drop in Case 24 is more easily understood, since the diet had not been adhered to, there had been many upheavals in the home, with the mother very disturbed and the child being cared for by different people. The situation is better now. We may see some improvement in both these children, and so we are keeping them on the diet.

Cases 19 and 22 were probably too old to benefit from the diet (234 weeks and 455 weeks), though age is not the only factor, as we shall see below.

Cases 20 and 21 failed apparently because they became psychotic; so that, though they were fairly young (94 and 68 weeks respectively) when they started the diet, the damage to the personality, the organic psychosis, made it impossible for the intellect to improve.

Borderline Cases

Cases 13, 14, and 16 are all high-grade (initial quotients of 67, 83, and 74) and have been on the diet for only short periods (30, 42, and 28 weeks), so that very much change should not be anticipated as yet. Their rates of improvement are all 0.10 or more, so we could hope to get Cases 14 and 16 into the average range of intelligence, since they were young when they started the diet (65 and 28 weeks), but we would not be too optimistic with Case 13, since she is much older (327 weeks: 6 years 3 months). In her case we hope to prevent further deterioration rather than aim for improvement, which is unlikely to continue at the present rate.

Case 18 is another of the psychotic children, and the relative failure here has probably the same causes as in Cases 20 and 21. Case 15 was probably too old.

Dietary Control.—In all these last cases (Nos. 13-24) the dietary control has been satisfactory, so far as we know, except in the cases already mentioned.

Effect of Age

In an earlier paper (Woolf *et al.*, 1958) we suggested the rule that treatment should be tried if the quotient was more than 20 at 2 years, more than 30 at 3 years, and more than 40 at 4 years. In other words, we were clearly of the opinion that as early a start as possible was essential. As a result of his work with Hsia *et al.* (1958) Knox uses 3 years of age at the start of treatment as a point above which improvement is negligible. Our figures are rather too disproportionate to assist in the investigation of this suggestion, since so few of our patients are over 3 years old. The relationship between age and change is shown in Table VII for 28 cases (excluding Nos. 25, 30, and 31), adopting 3 years as a dividing-line.

Therefore, using the criterion of any rise in the quotient between initial and final test (Cases 1-18 and 26-29), 5 out of 7 of those over 3 years (71%) and 17 out of 21 of those under 3 years (81%) improved; or, using the criterion of exclusion of all borderline and terminated cases (Cases 1-12) 2 out of 7 of those over 3 years (29%) and 10 out of 21 of those under 3 years (48%) improved.

It is apparent that better results are obtained in those under 3 years, but 71% of our small number of those over 3 years show some (at times only temporary) improvement, and 29% show quite definite improvement—not a negligible proportion. Our number of cases, however, is so small that these proportions must be treated with caution.

Though these figures suggest that the younger children do better, this is not true for our cases as a whole. Knox obtained a high correlation of -0.67 between the age at the start of treatment and the final quotient, using 43 patients under 3 years of age. Our figures do not give the same result. The correlation on our similar cases—there are 26 cases if we include Case 25—is only -0.08 . Even if we include all 31 of our cases there is no correlation between initial age and final quotient ($r = -0.15$).

Table VI suggests that those who started treatment before 16 months did better than those who started later, which would be consistent with the results Knox collected. But this difference is spurious, since the 14 children who started before 16 months and appeared to do better were in fact better to begin with, their average initial quotient being 45, whereas the average of the 12 who started after 16 months was 39.

TABLE VII

Improved	No. of Cases	% of 28	Failed	No. of Cases	% of 28	Totals	
						No. of Cases	% of 28
Over 3 Years							
Quotient rise of 9 or more points	2		No rise or a fall in quotient	2			
Quotient rise of less than 5 points	2						
Quotient rise but case terminated	1						
	5	18		2	7	7	25
Under 3 Years							
Quotient rise of 9 or more points	10		ditto	4			
Quotient rise of less than 5 points	4						
Quotient rise but case terminated	3						
	17	61		4	14	21	75
	22	79		6	21	28	100

By calculating the rate of improvement we have attempted to find out what does influence the result (Table I). Unfortunately, this tells us very little. It is negatively correlated with the age at which treatment was started ($r = -0.32$), meaning that the lower the age the greater the rate of improvement, but the figure is not statistically significant. The rate, which is naturally correlated with the size of change from which it is derived ($r = 0.66$), is not correlated with the initial quotient ($r = 0.11$). It is negatively correlated with the period of treatment (-0.28), but this again is not significant, though one would expect the rate of improvement to slow down as the figure suggests. From our figures it is extremely difficult to say on what the final outcome does depend.

In other words, we would still recommend starting treatment as early as possible. But the fact that it is begun early is no criterion by which to assess how successful the treatment will be. If it is delayed the results are less likely to be good, but they may well be good in about a quarter of the cases.

The explanation may possibly be found in two facts. First, though it may be agreed that 75% of the variation in intelligence between normal people is genetic in origin (Burt and Howard, 1956), it is nevertheless probable that this relationship does not obtain much before the age of 3 or 4 (Skodak and Skeels, 1949; Honzik, 1957), as is also true of the genetically determined proportion of variations in height (Bayley, 1954; Tanner, 1960). If the genetic influence is by no means completely effective before 3 years of age we would, theoretically, not be able to predict intelligence levels within these years. The second fact suggests that this is largely true. Longitudinal studies have shown that predictions based on tests within the first 18 months will be very uncertain—only about 36% correct (Hindley, 1960). With these doubts in mind it is not surprising that the addition of variables—such as degree of biochemical intoxication, degree of detoxication, hospitalization, lowering of intelligence—makes prediction impossible. Some of the children who fail, though treatment was started early, may well have been going to be dull, and were therefore more susceptible to the disease; some who do well, though treatment was started late, may well have been born to be very intelligent, and our pleasure at an I.Q. of 90 may mask the fact that the child may have lost 50 genetic I.Q. points. Probably we can never know in any one case. We can only say that treatment should be tried, and be given up if no improvement of any kind occurs (Moncrieff and Wilkinson, 1961).

The lack of predictive power from infant tests does not in the least lessen their value in this type of work. Without some objective measurement we cannot assess whether any particular child is benefiting from the diet. It may not be valid to compare a child's test score at 12 months with the normal, but we can more validly compare a child with itself and watch for changes in the degree of backwardness. For this purpose the Griffiths scale seems by far the most useful instrument.

Summary

Up to October, 1960, 35 cases of phenylketonuria have been treated at The Hospital for Sick Children since dietary treatment was started in October, 1953; 31 are discussed.

Treatment was terminated in six cases.

One patient (Case 25) born with average intelligence and treated since she was 4 weeks old has retained that level up to 5 years of age.

Of 28 cases in which the diet was given a fair trial, 22 (79%) showed improvement; in 12 (43%) this improvement was marked—a rise in I.Q. of 9 or more points—and appeared to be permanent.

The reasons for the variations in result are discussed; to some extent these variations are attributed to the impossibility of accurate prediction in young babies.

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REFERENCES

- Armstrong, M. D., Low, N. L., and Bosma, J. F. (1957). *Amer. J. clin. Nutr.*, **5**, 543.
 Bayley, N. (1954). *J. educ. Psychol.*, **45**, 1.
 Burt, C., and Howard, M. (1956). *Brit. J. statist. Psychol.*, **9**, 95.
 Coates, S., Norman, A. P., and Woolf, L. I. (1957). *Arch. Dis. Childh.*, **32**, 313.
 Crome, L., and Pare, C. M. B. (1960). *J. ment. Sci.*, **106**, 862.
 Hindley, C. B. (1960). *Child Psychol. Psychiat.*, **1**, 99.
 Honzik, M. P. (1957). *Child Develop.*, **28**, 215.
 Hsia, D. Y.-Y., Knox, W. E., Quinn, K. V., and Paine, R. S. (1958). *Pediatrics*, **21**, 178.
 Knox, W. E. (1960). *Ibid.*, **26**, 1.
 Moncrieff, A., and Wilkinson, R. H. (1961). *Brit. med. J.*, **1**, 763.
 Skodak, M., and Skeels, H. M. (1949). *J. genet. Psychol.*, **75**, 85.
 Tanner, J. M. (1960). *Growth at Adolescence*. Stuttgart.
 Woolf, L. I., Griffiths, R., and Moncrieff, A. (1955). *Brit. med. J.*, **1**, 57.
 ———, Coates, S., and Dillistone, F. (1958). *Arch. Dis. Childh.*, **33**, 31.

PHENYLKETONURIA: CITY OF BIRMINGHAM SCREENING SURVEY

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The possibility of the prevention of mental retardation associated with phenylketonuria by early diagnosis and treatment (Blainey and Gulliford, 1956; Woolf *et al.*, 1958; Brimblecombe *et al.*, 1959) has resulted in local health authorities carrying out tests for phenylketonuria on a wide scale. In Birmingham arrangements were made to test every infant born in 1959 and living in the city at the age of 6 weeks. In order to ensure early diagnosis it was planned to carry out the test as soon after that age as possible, and certainly before the age of 3 months, so that treatment by suitable diet could be instituted before cerebral damage occurred.

In an extensive screening survey it is rarely practicable to apply more than one test per infant. Testing at 6 weeks of age was therefore chosen to ensure that no case would be missed because of insufficient excretion of phenylpyruvic acid to give a clear positive test. Baird (1958) suggests that all known phenylketonuric children excrete more than 30 mg. of phenylpyruvic acid per 100 ml. after the age of 34 days.