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FURTHER EXPERIENCES IN THE TREATMENT OF PHENYLKETONURIA

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Since the last paper from the group at the Hospital for Sick Children, Great Ormond Street, was published (Woolf *et al.*, 1958), further experience has been gained. The patient on whom they reported (their Case 1), and who has an unaffected twin, continues to make good progress and has gone to an ordinary primary school with the twin sister. (The affected twin, born in February, 1955, gave a positive test for phenylpyruvic acid in the urine on the seventeenth day of life, and the special diet was started shortly after her admission to hospital at the age of 3 weeks.) Her I.Q. remains in the mid-eighties, whereas her sister scores over 100. Seen together there seems little to choose between them, except the interesting point that the *affected* child is in fact a little taller and heavier than her normal sister, and her hair is darker. She takes her special food to school. This has been made possible through the closest co-operation by the education authority. She is also lucky in having an intelligent mother.

Low-phenylalanine Diet

At the time of the appearance of the above report on the Great Ormond Street series, a pessimistic comment appeared in the *British Medical Journal* (1958) in which it was stated: "It seems unfortunately to be the case that by the time phenylpyruvic amentia is established a low-phenylalanine diet is likely to raise a child's mental rating only from idiot to imbecile level." Early testing of the urine, now being carried out in many areas as a routine procedure, makes it possible to start treatment at an early stage. Even if diagnosis is made later, the situation is not always so hopeless as is implied by the quotation. For example, here is a summary of a case quoted in replying to the *British Medical Journal* comment (Moncrieff, 1958).

A boy aged 9 months had been attending the Hospital for Sick Children for eczema, and was referred because of backwardness. He was found to be a case of phenylketonuria. Our colleague, Mr. Stephen Coates, made his G.Q. on the Griffiths scale only 30 with a wide scatter—almost at the idiot level. The child was in hospital for six weeks to establish treatment, and then managed continuously and successfully at home. Six months after discharge his G.Q. was 55, and at the age of 2½ years it had reached 64, with some indication of levelling out at this point. He should be able to attend a school for the educationally subnormal.

Horner and Streamer (1959) reported the cases of three children in the United States of America treated from early infancy. After 3½, 2¼, and 1 year respectively "the patterns of mental and motor activity are considered to be normal." Hsia *et al.* (1958) in Boston, however, also took a pessimistic line in their report, but their patients were mostly older subjects, and even they admitted possible beneficial effects in four young patients. Blainey and Gulliford (1956) reported clear evidence in two Birmingham patients of acceleration in the rate of development as shown by mental testing, although in one this was not maintained owing to inadequate dietary control at home.

Even if the intelligence is not raised to a satisfactory level the affected children on a low-phenylalanine diet are much more manageable, losing a troublesome restlessness. Fits, if present, cease and eczema clears up. Many parents have asked to be allowed to continue treatment even when it was clear that little or no success was being obtained in raising the intelligence level.

Early Detection and its Difficulties

However, it must in fairness be stated that spectacularly good results are not yet generally found when treatment is started after early infancy, but better results are hoped for those infants in whom the phenylketonuria is discovered at a very early date and treatment is instituted at once. In certain of the older children—for example, detected in the second year of life because of backwardness—there may be a rise of the general intelligence level from, say, 30 to 45, and there the improvement ends. In one case—that of a child with a very conscientious mother and without any evidence of relapse because of failure in giving the special diet—the intelligence level, which had risen to 45, actually dropped back under treatment over the last few years and is now stationary at 30. Similar and even greater and more accelerated falls in the I.Q. have occurred when the special diet has been stopped. One feature of the I.Q. levels which is difficult to explain is that there is a wide variation in the initial level found in children of approximately the same age. There is no clear connexion between the degree of mental retardation and the level of phenylalanine in the blood at the time of examination.

Perhaps not enough attention has yet been paid to the time of taking blood for examination in relation to meals and possible variations throughout the day in

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the untreated child. The effect of infection and fever on blood levels of phenylalanine was strikingly shown recently in the following case:

A boy aged 3 years had been diagnosed at the age of 14 months and a low-phenylalanine diet instituted and maintained. He had good parents and his blood phenylalanine level had been on the whole satisfactory. He was admitted to hospital for reassessment and partly for social reasons. The urine was negative for phenylpyruvic acid and the blood level for phenylalanine was satisfactory. After a week he developed tonsillitis and fever. Phenylpyruvic acid appeared in the urine and the level of phenylalanine in the blood rose to 15 mg./100 ml. No change was made in his diet, and after a few days the blood and urine reverted to normal.

It may, however, even be that, as in cretinism, there is more than one genetic fault present. It is well recognized that some cretins, diagnosed early and treated successfully as judged by physical standards, fail to achieve a corresponding standard in their mental rating. But as in cretins treatment must be attempted, so in phenylketonurics there is as yet no means of ascertaining whether or not treatment is likely to be successful unless it is tried. Some criteria in this respect were discussed in our last report (Woolf *et al.*, 1958).

Early detection and treatment have presented certain special difficulties. *False negatives* may arise when the urine is not fresh, especially when it has been allowed to stand in a warm atmosphere, since phenylpyruvic acid is easily destroyed. A little chlorbutol or merthiolate should be placed in the specimen bottle to act as a preservative and the specimen kept as cool as possible. The urine should not be acidified if the ferric chloride test is used. When "phenistix" test strips are used they must be quickly dipped in and out of the urine, for the reagents are leached out after a second or two (Gibbs and Woolf, 1959). When there is already an affected subject in a family, the urine of a new baby must be tested frequently in the first six weeks of life before it can be assumed that this child is clear of the disorder. (Serum phenylalanine should also be estimated in all cases of doubt.) Clearly it is a more serious error to achieve a false negative in testing for possible phenylketonuria than the opposite. *False positives* certainly occur, and Gibbs and Woolf (1959) give a valuable list of the sort of reactions found with ferric chloride and with "phenistix" when various substances were added to normal urine. Hudson and Ireland (1959) have also discussed certain aspects of fallacies in the testing for phenylketonuria. Anyone planning a programme for routine testing of the urines of infants should study these two papers carefully.

We see no reason at present to depart from the original conclusion made by our group that a routine test at 3 weeks is the best programme except for babies born into a family in which the possibility of phenylketonuria is present—for example, affected sibs or other relatives. Only a very small proportion of infants with phenylketonuria give a positive test until after the third week, and the administrative difficulties of a double test at present appear to outweigh the advantages.

Dietetic Problems

The "treatment" of young babies presents problems concerned with maintaining growth on a low-phenylalanine diet. The twin referred to above had a stormy passage in the early months, but no special alterations were made to the standard diet and it was maintained throughout. She is now, as already stated, slightly ahead physically of the twin sister. But in a subsequent case the troubles were more serious, and we have been in correspondence with Professor D. B. Macdonald, of Perth, Western Australia, about his difficulties with a young baby.

This child, who had an older affected sibling, was found to develop phenylketonuria at the age of 3 weeks. A low-phenylalanine diet was started, but after 11 weeks there had been no increase in weight. All the necessary supplements (vitamins and minerals) were added with no success, and at the age of 4½ months the child was put on to a whole-milk mixture. There was an immediate gain in weight and the level of phenylalanine in the blood rose and phenylketonuria recurred. After one month the whole milk was gradually reduced and a low-phenylalanine preparation substituted. The blood phenylalanine was reduced to zero and the diet then adjusted to keep this at a low level. The child continued to gain weight satisfactorily and intelligence-testing at the age of 8½ months did not indicate any serious damage, especially in light of the severe physical illness.

A recent experience at Great Ormond Street has also indicated the difficulty of getting satisfactory growth in the early months on a low-phenylalanine diet, and, incidentally, the question of "cure."

A female baby was referred to the Hospital for Sick Children, Great Ormond Street, at the age of 4 weeks because a week previously, on a routine testing of her urine arranged by the local health authorities, a positive reaction to ferric chloride, indicating the presence of phenylketones, had been obtained. This test, by the health visitor, was confirmed on two subsequent occasions by an assistant county medical officer of health. The parents were unrelated, there was no history of any relevant disorder in the family, and there were three elder children of the marriage, one girl and two boys, all normal. The baby had been breast-fed for a few days only and then given dried milk. Her birth weight was 7 lb. (3,175 g.), and on admission at 4 weeks she weighed 8 lb. 13¼ oz. (4,005 g.). Physically she appeared normal in every way. An intelligence test by Mr. Stephen Coates at the age of 6 weeks gave, on the Griffiths mental development scale, a general quotient of 102. Testing of the urine in the ward, with ferric chloride, gave a positive reaction for phenylketone. Laboratory testing gave only a slight colour change with ferric chloride and a negative reaction with the phenistix method. However, the blood phenylalanine level was found to be moderately raised (about 10 mg./100 ml.), and it was decided that at this early age she would probably become worse with more definite reactions in the urine as the phenylalanine in the blood rose.

It was therefore decided to institute dietetic treatment, and after our experience with older children for the most part we placed the baby on a phenylalanine-free diet. At first the feeds were taken fairly well, although the child developed some restlessness. After about a week the phenylalanine level in the blood had decreased but was still raised (about 5 mg./100 ml.). After another week no phenylalanine was detected in the blood. The weight remained stationary. An electroencephalogram at this time (Dr. G. Pampiglione) showed a moderate but definite abnormality, with multifocal discharges of a kind often seen in young patients with phenylketonuria. Milk (2 oz.—57 ml.) was now added daily, but three days later the blood phenylalanine level had risen and the milk was reduced to 1½ oz. (42.5 ml.). The weight rose slowly, but the child was more restless and vaguely unsatisfactory, and a skin eruption appeared on the chin and cheeks. Three weeks later the blood level of phenylalanine was normal. Extra vitamin B was given intramuscularly and the child was transferred to the hospital's country branch at Tadworth. Extra liver extract resulted in an exacerbation of the skin lesion. The child developed tonsillitis, enlarged cervical glands, and some areas of bronchiolitis.

A visiting medical officer thought the skin lesions resembled those of porphyria, and they were now more

extensive. The blood showed a raised phenylalanine level again and the vitamin intake was carefully revised; the question of whether or not the rash could be due to phenobarbitone was raised. There was some regurgitation of watery fluid and a slight increase in the looseness of the stools. There had been virtually no gain in weight for three weeks, and the child was returned to Great Ormond Street. The blood phenylalanine level was still raised and the daily milk intake was reduced to 1 oz. (28.5 ml.). The skin lesions were extensive and unusual. Skin swabs showed pyogenic organisms and no thrush (which had been suggested as a cause). One of us (A. M.) thought they resembled lesions he had seen in Africa in severe cases of kwashiorkor, which led to a consideration of the amino-acid content of the diet (see below). Our colleague, Dr. E. J. Moynahan, who helped us considerably in dealing with the skin condition, was also of the same opinion—namely, that the rash was essentially due to animo-acid deficiency.

Meanwhile the weight continued to drop. The phenylalanine level in the blood had again become normal. The child's condition was, however, deteriorating, and it was decided to abandon the low-phenylalanine diet, at any rate for a period. A half-cream dried milk was started and within a few days the improvement was dramatic. The child took the feeds willingly, gained weight, and the skin lesions, which had resisted several varieties of local treatment, cleared within a few days. A week after the diet had been changed the blood phenylalanine level was still normal. A week later it was slightly raised (6 mg./100 ml.), and after a further week it was back to normal. The urine remained free of phenylpyruvic acid. The child, now aged 5 months, was again tested by Mr. Coates, who found a G.Q. of 83. The child was sent home. A fortnight later the baby had gained over 1 lb. (450 g.) since discharge and seemed flourishing. A month later, now going on to a mixed diet, she had a normal phenylalanine level in the blood, and the urine amino-acid pattern was reported as at the top limit of normal. Further examinations were as follows: April 11, 1960 (aged 10 months): Blood, normal level of phenylalanine; urine, no phenylpyruvic acid, June 2 (aged nearly 1 year): Blood, phenylalanine level, 4.7 mg./100 ml. (this was performed by a new method—L-amino-acid oxidase (Wilkinson, 1961)—in which the normal is 2 mg./100 ml.); urine, no phenylpyruvic acid.

A second electroencephalogram (Dr. G. Pampiglione) showed some improvement on the previous record made at the age of 3 months, but was still abnormal. A third intelligence test (Mr. S. Coates) gave a G.Q. of 103, so that she had regained her original level. It was decided at this stage to keep her on ordinary food and watch her progress, especially as regards her blood phenylalanine level. At 14 months the blood phenylalanine level was normal and she weighed 24 lb. (10.9 kg.).

Comparison of Amino-acid Composition of Diets and Breast Milk (Figures Indicate mg./100 ml., as the "L" Form, which is Either Found or Calculated)

Amino-acid	Hydrolysed Casein Low-phenylalanine Diets		Synthetic Amino-acid Diets (Kwashiorkor) (Hansen *et al.*, 1956)		Human Breast Milk (Clements, 1956)	Bovine Serum Product §
	1 Berry *et al.* (1958)	2 Minafen‡	3 950 mg.	4 1,300 mg.	5 900 mg.	6 1,200 mg.
Aspartic acid	100		66	91	62	135
*Threonine	70	100	39	54	38	89
Serine	110		36	50	43	89
Proline	200		83	114	56	78
Glutamic acid	288		179	247	150	147
Glycine	80		17	24		60
Alanine	94		33	45	20	73
*Valine	140	120	58	80	41	89
*Methionine	10	40	13	18	18	14
Isoleucine	174	100	62	86	47	34
*Leucine		160	92	127	128	101
†Tyrosine	Added	Added (100)	50	69	45	91
*Phenylalanine	Trace	Trace	32	44	47	Trace
*Lysine	170	200	91	125	54	110
*Histidine	5	20	28	39	17	30
*Arginine	28	40	42	58	37	66
*Tryptophan	Added	Added (25)	12	16	17	13
Cystine	5	2	8	11		

* Normally essential amino-acids.
† Probably becomes essential in phenylketonuria.
‡ Data on "minafen" supplied by the manufacturers, Allen & Hanburys Ltd., London.
§ Data on "albumaid XP" supplied by the manufacturers, Powell & Scholefield Ltd., Liverpool.

Supplements to Diet

Since the rearing of young infants who have an impaired tolerance for phenylalanine has been difficult in some instances, it is clear that a careful review is required of the detailed composition of the diet and the supplements supplied during the rapid growth period of the first few months of life. The normal baby doubles its birth weight in five months, and relatively small deficiencies in essential amino-acids and vitamins may produce defects in growth at this age and not necessarily later on. We are at present reviewing the situation with special reference to vitamin-B supplements. The source of amino-acids in the diet is casein hydrolysate that has had phenylalanine removed as completely as possible. Tyrosine and tryptophan, which are removed at the same time, have to be replaced.

The accompanying Table shows two casein hydrolysate diets (columns 1 and 2) and an average breast milk (column 5). The figures for the amino-acid composition are either those found as the L form or calculated in part where the D and L forms were present. Each diet has been adjusted to contain between 900 and 1,300 mg. of amino-acids per 100 ml., as would be found in breast milk appropriate for the age of the infants under consideration. Columns 3 and 4 show figures for the synthetic mixture of amino-acids used by Hansen *et al.* (1956) in the treatment of kwashiorkor. Column 6 shows the analysis of an alternative source of low-phenylalanine diet—hydrolysed bovine serum protein. Apart from the phenylalanine content,* the amino-acid composition of these various diets does not suggest that any important differences are present. The possible use of a low-phenylalanine product other than casein is being explored and the questions of palatableness and cost need careful scrutiny.

The unusual infant whose case is described above failed to thrive, had a marked skin lesion, and was seriously ill on the low-phenylalanine casein hydrolysate diet. It recovered rapidly when a half-cream dried milk was substituted. The low-phenylalanine diet has been adequate for the growth of most of the affected infants. The phenylalanine content of the diet is adjusted by the addition of milk so that it is just sufficient for growth and yet not too great for the infant's impaired metabolism. Individual variations in amino-acid requirements do occur, and this may be the explanation of the dietary difficulties met with in this infant. The phenylalanine requirements of both normal infants and those showing phenylketonuria have been studied by Snyderman *et al.* (1955) and Paine and Hsia (1957).

Individual variations in requirements may cause difficulties. Thus, Berry *et al.* (1958), when examining the dietary requirements of phenylketonuric children fed on low-phenylalanine casein hydrolysate diets, noted one patient with a tyrosine deficiency which was associated with a raised serum phenylalanine level. The patient became irritable. Raising the tyrosine intake

*Since this paper was written, at Dr. Barbara Clayton's suggestion, we have been looking at the nature of the fat present in the special phenylalanine-free foods available. The type of fat added differs appreciably, and it may be that in the young baby the fatty-acid intake needs careful attention.

reversed these changes. It was suggested that tyrosine had become an essential amino-acid when phenylalanine hydroxylation was deficient and that the raised serum phenylalanine levels were due to tissue-protein breakdown. Methionine deficiency caused amino-aciduria and hyperlipaemia. This was corrected by an increased intake of L-methionine and cystine. Similarly, histidine deficiency was associated with amino-aciduria. The deficiencies appeared in different patients on similar diets.

Points in Amino-acid Metabolism

A further point to be considered is that other abnormal aspects of amino-acid metabolism are also found in children with phenylketonuria, the exact significance of which in relation to mental retardation still requires further investigation. Pare *et al.* (1957, 1958, 1959), in London, have discussed associated disorders of tryptophan metabolism, and there is a growing literature on the subject in the U.S.A. The relationship of this to growth difficulties in early life requires elucidation.

It may be that variations in the present regime will be achieved. Geisler and Ströder (1958) have reported that large quantities of fructose (up to 6 g./kg. body weight) raised phenylalanine tolerance, reducing the phenylketonuria present in a normal diet. We repeated this on two children with phenylketonuria, but failed to find any reduction in blood phenylalanine levels (Moncrieff and Wilkinson, 1960).

Can Dietary Restrictions be Relaxed?

The question of whether or not phenylketonuric subjects will require dietetic treatment for life can be settled only after a much longer period of time. Ethical considerations might forbid a relaxation of diet for a trial period, although in an older subject—for example, after physical growth has ceased or even when it is estimated that brain growth has ceased—a period of six months on a normal diet with careful intellectual assessment followed by a return to a low-phenylalanine diet, if necessary, might be justified. The case referred to previously, where apparent " recovery " has occurred, raised the question of a possible late appearance of the necessary enzyme for the hydroxylation of phenylalanine to tyrosine.

It is the labile fraction of phenylalanine hydroxylase which is absent from the livers of patients showing phenylketonuria. This fraction is absent from the livers of foetal animals, but it has been shown by Kenney and Kretchmer (1959) to appear in the livers of rats one or two days after birth, and to reach adult levels one to ten days later. A few observations suggest that there is a deficiency in the enzyme in the livers of premature infants. Several abnormal situations might occur, therefore, if the development of this enzyme proceeded abnormally in early infancy. The enzyme might be absent from the patient's liver at birth and remain deficient during later life, as is probably the case in infants showing phenylketonuria associated with oligophrenia. The enzyme might be absent or low in concentration at birth and develop to normal levels after a variable time. Such infants should present the picture we have described, and their serum phenylalanine levels should return completely to normal later on normal diets. The enzyme might be low in concentration at birth and remain low for a considerable period.

The liver would be unable to meet the increased need of the early growth period for the phenylalanine–tyrosine conversion, and a phenylketonuria would result. The serum phenylalanine levels would not return to normal while this relative insufficiency of enzyme existed, when the patient was taking a normal diet. Alternatively, the enzyme might be present in normal concentrations in the infant's liver but the energy requirements of the reaction might not be met. Whatever the explanation may be, it is clear that some infants are born with a decreased tolerance for dietary phenylalanine. The serum levels of phenylalanine rise and a phenylketonuria follows. Later the infants can tolerate increasing amounts of phenylalanine in their diet. Another speculation might be on the lines of the development of alternative pathways, so to speak. Claims for the apparent failure of any mental retardation to appear in older subjects after relaxation of diet have not been generally accepted and need confirmation. For that reason they will not be further discussed.

Carriers

The detection of heterozygote carriers of the affected gene in phenylketonurics is clearly of importance in relation to prevention by genetic counselling. Healthy relations of affected children would well merit investigation as regards their phenylalanine tolerance. However, the subject is not without difficulties. A loading dose of phenylalanine is costly (about £7), and the methods of estimating blood phenylalanine levels still show a varying degree of experimental error. When using a specific method for diagnosis or for control of treatment some measure of *local* laboratory accuracy is achieved which is sufficient for these purposes. However, for demonstrating a decreased tolerance for phenylalanine in carriers more accurate methods are required, and further investigation in this aspect of the subject is proceeding.* By present methods the parents of phenylketonurics, with some exceptions, are positive as regards a lowered tolerance, and so are approximately two-thirds of the sibs.

The possibility of the experimental production of phenylketonuria is worthy of mention. Workers at the University of Wisconsin have reported the effect of adding phenylalanine and tyrosine to the normal diet of rats, with a rise in the fasting levels of these substances (Auerbach *et al.*, 1958). Waisman and Wang, at the 1959 annual meeting of the American Pediatric Society, reported further experimental feeding of a similar type in dogs and monkeys. The results in the former appeared to have been disappointing, but in monkeys, as recorded in more detail by Waisman *et al.* (1959), it was possible to produce long and sustained raised phenylalanine plasma levels with the excretion of phenylpyruvic acid in the urine. Tests for motor and discriminatory performance and other psychological investigations are proceeding. A further report on this aspect was given by Waisman and Harlow at the 1960 meeting of the American Pediatric Society, and this will no doubt be published. Suggested inferiority in the " intellectual " development, and in two monkeys major epilepsy with fits at long intervals, developed. This experimentally produced disorder will facilitate metabolic experiments not possible in human subjects.

*We are indebted to Dr. L. I. Woolf for a memorandum on the subject of carriers.

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.

We are indebted to our clinical colleagues at the Hospital for Sick Children, Great Ormond Street, for permission to use their cases, and to Dr. Barbara Clayton. Dr. G. Pampiglione has taken electroencephalograms when required, and Mr. Stephen Coates has continued to be of most valuable help with intelligence-testing. Dr. L. I. Woolf, who was a member of our original team, is now in Oxford, but continues to help with advice and criticism. Some of the work was supported by the Research Committee of the Hospital for Sick Children. We also thank numerous other friends and colleagues on both sides of the Atlantic who have supplied references and discussed matters personally.

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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.