PHENYLPYRUVIC OLIGOPHRENIA.

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" The study of phenylpyruvic amentia may throw light on the whole problem of mental deficiency."—JERVIS.

PHENYLPYRUVIC oligophrenia is a syndrome in which mental deficiency is accompanied by the excretion of phenylpyruvic acid in the urine.

It was first described by Föllings (1934), who made observations on 10 cases discovered in a survey of 430 mental defectives in Norway. In the next year Penrose described 2 cases in England (Penrose, 1935*a*). Jervis (1939) discovered as many as 200 cases in a large-scale survey of the 20,300 inmates of fourteen State Institutions in America. In Switzerland, Brugger (1942) found 2 cases and Morel (1944) found a third. In France, Rhein and Stoeber (1936) discovered 7 cases, and Turpin and Duchene (1945) discovered one certain case and one possible case which circumstances did not permit them to examine. In subsequent years numerous authors have written upon the subject of phenylpyruvic oligophrenia.

The syndrome was originally denoted by Föllings (1934) as imbecilitas phenylpyrouvica. Jervis (1937*b*) suggested the name phenylpyruvic oligophrenia. This is a good term, since patients suffering from the disease have been found in all grades of mental deficiency; moreover, it incorporates both the aspects of biochemical error and mental defect, which are essential components of the syndrome. Penrose referred to the condition as phenylpyruvic amentia in his first two papers on the subject (Penrose, 1935*a* and *b*), but later used the name phenylketonuria, which emphasizes the biochemical nature of the abnormality and brings the nomenclature into line with that of other comparable abnormalities, such as alkaptonuria and cystinuria.

INCIDENCE.

Jervis (1939) estimated the incidence of phenylpyruvic oligophrenia as being from 3·0 to 0·5 per cent. of mental defectives. Brugger (1942) made a survey of 1,634 mental defectives in Switzerland and found the positive colour reaction given in phenylpyruvic oligophrenia in only 2 cases. Munro (1947) found 30 phenylpyruvic oligophrenics among 2,457 institutional idiots and imbeciles in Britain. He estimated, basing his calculation on the assumption that the incidence of imbeciles and idiots in the general population is 0·17 per cent., that the incidence of phenylpyruvic oligophrenia in the general population would be approximately 4 per 100,000; and on a basis of 40 million population, that there should be about 1,600 cases of the condition in Britain.

The present writer made a survey at the Fountain Hospital, London, of 553 mental defectives of all grades, consisting of females of all ages and males up to the age of 15 years. Fifteen cases of phenylpyruvic oligophrenia were discovered. An investigation into the family histories of the patients led to

the discovery of 2 more patients in other institutions suffering from the disease.

As regards sex distribution, Jervis, in 1937, stated that the excess of female over male cases seemed well established; 30 of his series of 50 cases of phenylpyruvic oligophrenia were female (Jervis, 1937*b*). Penrose (1949) stated that phenylketonuria has been ascertained more frequently in males than in females, his observation being based on data obtained in the intervening years since the statement made by Jervis. He suggests that this sex distribution may arise simply because females are healthier and live longer than males. Of the 15 cases of phenylpyruvic oligophrenia at the Fountain Hospital, 10 are female. In this instance the preponderance of females may be explained by the fact that there are females of all ages in the Fountain Hospital, whereas there are no males over the age of 15 years. No female patients over the age of 21 years at the Fountain Hospital were, however, found to be phenylketonuric.

Mental Level.

Jervis (1937*b*), using Stanford-Binet tests, gave the distribution of intelligence quotients for 45 cases as being 71 per cent. idiots with an intelligence quotient below 20, and 29 per cent. imbeciles with an intelligence quotient between 20 and 50. Penrose (1946) gives the distribution of cases on the scale of mental level as being some 60 per cent. of idiot grade, 30 per cent. imbeciles, and 10 per cent. of higher grade.

Of the 15 phenylpyruvic oligophrenics of the present series, 12 are idiots, 2 are imbeciles and 1 is of remarkably high intelligence in view of his condition, being in the dull-and-backward range. The percentage of idiots in the present series of cases is therefore high, being 80 per cent.

Clinical Picture.

The clinical features of phenylpyruvic oligophrenia are usually well marked.

The patient is in nearly every case fair-haired and fair-skinned, with light blue eyes. The exhibition of dilution of hair colour in phenylpyruvic oligophrenia in comparison with siblings and other members of the family is well illustrated by the case of Turpin *et al.* (1945), in which the patient was strikingly blond, although occurring in a family of darkly-pigmented people of Spanish descent. Jervis (1937*b*) quotes a similar case of an ash-blonde phenylketonuric patient in a Sicilian family, where all the other members for several generations were dark-haired.

The skin is soft, smooth and fine in texture. Bates (1938) observes the tendency towards marked dermatographia. Föllings (1934) and Jervis (1937*b*) remark upon frequent occurrence of eczema amongst the patients, and Penrose (1946) states that the skin, which may show pigmented patches, is unduly subject to dermatitis, and that hyperidrosis is commonly a feature. There is frequently cyanosis of the hands and feet, due to poor peripheral circulation.

The general physical development is symmetrical and harmonious. Föllings (1934) states that the majority of his first 10 cases had remarkably broad shoulders. Jervis (1937*b*) obtained anthropometric details from 18 patients,

in which only the craniometric data showed deviation from normal, the patients being considered as slightly microcephalic. Penrose (1946) and Frazier (1947) remark upon dwarfing of stature. Penrose (1946) remarks upon the reduction of head measurement as compared with normal. The stance is typical in the majority of cases, the patient standing with hips and knees flexed, in an attitude described by Delay *et al.* (1948) as " pithecoid."

The gait is stiff, short-stepped and on a broad base, with decreased associated movements. Frazier (1947) describes occasional retro- and anteropulsion. Kyphosis is described as being a common feature by nearly all writers, although Lepow (1944) considers this as secondary to the stooping posture.

Phenylpyruvic oligophrenics are usually free from gross physical deformities. Penrose (1935*a*) describes partial syndactyly in one case between the second and third toes. He also mentions that the incisor teeth are characteristically widely spaced (Penrose, 1946). Larcomb (1939) reported that congenital deafness had not been found in cases of phenylpyruvic oligophrenia, nor has it been reported since.

Bates (1938) described retinoscopy in 3 cases. He mentions a poor choriocapillaris, small vessels and a pale optic nerve. One case showed peripheral arrangement of pigment in an irregular fashion.

Hypertonicity of the limbs is a feature. Jervis (1937*b*) detected an increase in muscular tone in 70 per cent. of his cases and at times obtained cogwheel movements by passive movement of the upper extremities.

The reflexes are very brisk. Penrose (1946) maintains that all reflexes are accentuated, whilst Frazier (1947) describes increased response in the deep reflexes only. These signs have been interpreted by most authors as being referable to the extrapyramidal system. Delay *et al.* (1947) state that there is never a positive Babinski response.

Epileptic fits were observed by Jervis (1937*b*) in 21 per cent. of cases. Penrose (1946) states that these occur in the early years of patients who are severely mentally affected, and he has not known them to occur in phenylpyruvic oligophrenics over the age of ten years.

The patients tend to be hyperkinetic and to show stereotyped digital mannerisms (Penrose, 1946). These are especially a feature in patients of idiot grade. They may be pill-rolling or flicking in character, and are often intricate but performed rapidly and delicately. Such mannerisms in phenylpyruvic oligophrenics are described in detail by Delay *et al.* (1948) and are mentioned by Penrose (1946), Frazier (1947) and Jervis (1937*b*).

Delay and his co-workers (1947) concluded that on the whole patients with phenylpyruvic oligophrenia are apathetic and even stuporose, and frequently show echolalia and echopraxia. Penrose (1949) observes that sometimes isolated symptoms that form part of the characteristic picture of schizophrenia are seen in phenylketonuric patients. These symptoms include catatonia, outbursts of violence and stereotypy. Penrose points out that their psychiatric significance is difficult to determine ; they may be signs of psychosis, but alternatively may merely represent modes of reaction of an infantile nature ; implying that instinctual and emotional development has been retarded along with intellectual development.

Detection of Phenylpyruvic Acid in the Urine.

Föllings originally discovered the condition of phenylpyruvic oligophrenia by adding a 5 per cent. solution of ferric chloride to the urine. Where phenylpyruvic acid is present a characteristic olive green coloration is produced which develops several seconds after the addition of the ferric chloride solution, quickly reaches a maximum intensity, and fades in 15 minutes to half an hour. This test was used by the present writer in the survey of the 553 patients at the Fountain Hospital.

Penrose (1946) suggests neutralization of alkaline urine with dilute sulphuric acid before the test, and the present writer used 2 per cent. sulphuric acid, and on other occasions 2 per cent. acetic acid, for this purpose.

Several confirmatory tests have been devised to demonstrate the presence of phenylpyruvic acid in urine. Delay *et al.* (1946) describe the development of an intense green coloration on the addition of ammoniacal ferric alum to the urine. This is the basis of a method for the quantitative estimation of phenylpyruvic acid described by Polonowski *et al.* (1947). Delay *et al.* (1946) also describe a test where the development of an orange coloration occurs when picric acid is added to the alkalinized urine. Penrose and Quastel (1937) describe the preparation of the dinitrophenylhydrazone of phenylpyruvic acid. This is the basis of their method for the quantitative estimation of phenylpyruvic acid in urine.

Summary of Findings in the Present Series of Cases.

Fourteen of the patients in the present series each showed a number of the characteristics described by previous writers as being typical in phenylpyruvic oligophrenia.

The most common of these characteristics, seen in all 15 of the patients of the present series, was the wide spacing of the incisor teeth. In 10 cases the superficial and deep reflexes were very brisk. Nine were subject to eczema and dermatitis. Eight showed evidence of a poor peripheral circulation. Eight had slightly reduced head measurements as compared with normal (see Table I).

In six cases there was a history of epilepsy. Six were kyphotic. Five walked in the manner described by previous writers as being typical in phenylpyruvic oligophrenia, with short, quick steps on a broad base, with decreased associated movements. Four showed the " pithecoid " stance with flexion at knees and hips. Four had stereotyped digital mannerisms. Three had minor pigmentary anomalies, consisting in two cases of pigmented moles and in the third of a " café au lait " birthmark. In three, thinning of the retinal pigmentation was observed, but this was within normal limits for children as blond as the patients in which it occurred. Hyperidrosis was observed in only two patients, and dermatographia was seen in only two.

Although it has been stated that a positive Babinski response is never found in phenylpyruvic oligophrenia, (Delay *et al.*, 1947), the plantar responses were plantar-extensor in three cases ; each of these patients was subject to epilepsy.

TABLE I.

Patient	Age (years).	Sex.	Head circumference in inches.
Pauline P—	4 +	Female	19·0
Francis W—	6 +	Male	20·2
Carol B—	6 +	Female	18·7
Frances T—	7 +	Female	19·0
John R—	7 +	Male	21·0
Georgina H—	8 +	Female	19·7
Brian C—	8 +	Male	20·2
Margaret W—	9 +	Female	21·0
Alan J—	9 +	Male	20·2
Arthur P—	12 +	Male	20·7
Iris S—	12 +	Female	20·0
Derek T—	14 +	Male	21·5
Lilian B—	18 +	Female	19·0
Pamela P—	20 +	,,	21·0
Joan S—	21 +	,,	20·0

In addition to the characteristics that have been described as typical in phenylpyruvic oligophrenia by former authors, the present writer has observed others occurring with frequency. Twelve of her patients had pes planus, which was usually very severe ; in some cases the patient bearing weight on the inner borders of the feet and walking with the soles everted. The 12 patients in which this was observed comprised all those of the series who were able to stand and walk.

In 5 of the patients there was a wide gap between the first and second toes. On close inspection, in each of these patients there was a very mild degree of syndactyly between the roots of the second and third toes, which probably caused the second toe to be drawn laterally, thus widening the first interdigital cleft. Penrose (1935*a*) mentions partial syndactyly between the second and third toes in a phenylpyruvic oligophrenic patient, but does not describe a widening of the first interdigital cleft.

In 10 of the patients the upper jaw was prominent and had the appearance of overhanging the lower jaw, and caused the teeth to protrude. The present writer believes that this expansion and prognathos of the maxilla is the factor causing the wide-spacing of the incisor teeth in patients suffering from phenylpyruvic oligophrenia.

In one patient a palpable and slightly enlarged liver was observed.

Fourteen of the patients in the present series were fair-skinned. Their irides were light in colour. Their hair was either red or fair, the darkest hair being medium brown in colour. The hair-colour of the patients and that of their parents and siblings was analysed by means of spectrophotometry and a relative dilution of hair colour in the case of the patients in comparison with that of the other members of their families was consistently demonstrable (Penrose and Cowie, 1951).

The fifteenth patient, John R—, however, had dark brown hair and olive skin,

and his irides were almost black. Moreover, the only characteristic he possessed beside the excretion of phenylpyruvic acid, described by former writers as being typical in phenylpyruvic oligophrenia, was wide-spacing of the incisors. His level of intelligence was in the dull-and-backward grade, and on the basis of this finding alone his case is unique, since no other case of phenylpyruvic oligophrenia has been reported in which the level of intelligence, as revealed by psychometry, has been so high (Cowie, 1951). His output of phenylpyruvic acid was low, being only half a gramme daily. The usual finding is that approximately 1 gm. of phenylpyruvic acid is excreted daily in urine by phenylketonuric patients (Penrose, 1946), and the findings of the present writer, who carried out quantitative estimations on the urine of all 15 patients in her series, are in accordance with this average figure.

Table IV shows the distribution of the characteristic features found in the 15 cases of the series.

The Genetics of Phenylpyruvic Oligophrenia.

The high familial incidence of phenylpyruvic oligophrenia, i.e. its occurrence in sibs of the same fraternity, points to the probability of a genetic mechanism.

Penrose (1935*b*) made the first publication concerned with the inheritance of phenylpyruvic amentia. In this paper he gave a pedigree consisting of five generations, demonstrating the mode of action of a rare recessive gene in a consanguineous family. This gene, he postulated, was responsible for the appearance of phenylketonuria in the family. In the same paper, Penrose advanced the hypothesis that the gene for phenylketonuria is not completely recessive, but that it exerts an influence upon the heterozygotes, predisposing them to mental breakdown. The heterozygotes in the family concerned showed a marked tendency to develop insanity at the involutional period of life.

Jervis (1937), in his introductory study of 50 cases of phenylpyruvic oligophrenia, made a critical examination of the anamnestic data, and concluded that such exogenous agencies as maternal health, birth trauma, syphilis, infectious disease or endocrine disturbance could be excluded as aetiological factors in the production of phenylpyruvic oligophrenia. He pointed out, moreover, that the family incidence of the condition suggested that a genetic mechanism is of significance, and subsequent statistical elaboration and critical analysis of the figures provided by his material afforded justification for regarding the condition as determined by a single recessive gene.

A later paper by Jervis (1939) was devoted to the study of the influence of heredity on phenylpyruvic oligophrenia. His material consisted of 200 patients grouped in 125 families, and he showed that factual data proved that the conditions ran in families. Many environmental factors were considered, and the conclusion was reached that without exception the data indicated the improbability that factors due to the external environment play a significant role in the causation of the disease. Various genetic possibilities for the production of phenylpyruvic oligophrenia were then considered, including the action of a single dominant gene, of two complementary dominant genes, of sex-linked genes and of a recessive autosomal gene. In connection with the latter, the ratios of affected to normal children, the rate of consanguinity among

parents and the distribution of the condition among ascendant and collateral relatives of affected individuals were all studied. The findings were all consistent with the quantitative requirements of the theory of monomeric recessivity, and indicated that the disease is determined by an autosomal recessive gene.

To these considerations a suggestion for practical application was added; the parents of affected children should be discouraged from having other children, since, according to the laws of inheritance, one-quarter of these would be affected, and one-half would be carriers, and consanguineous marriages amongst members of affected families should be particularly avoided.

As the gene producing phenylpyruvic oligophrenia is rare and recessive, the incidence of consanguinity in families where the condition is found might be expected to be high, especially in regions such as Switzerland, where only three cases have been reported, two by Brugger (1942) and one by Morel (1944). Morel traced the pedigree of his case back to the year 1660 to show there was no consanguinity. Pichot, Delay and Bertagna (1944) also traced the genealogical tree of their patient back to 1780 over seven generations, to exclude the incidence of consanguinity. In the 125 families in the series of Jervis (1939) the parents of only 7 families were cousins. In the case described by Delay, Pichot, Desgrez and Delbarre (1946) the father and mother were first cousins. Munro (1947) estimates the incidence of parental consanguinity in phenylpyruvic oligophrenia as being approximately 10 per cent., using a method of calculation depending upon the concept of gene frequency in the population.

Examination of data relating to the family histories of the 15 patients of the present series reveals evidence supporting the belief that the condition is due to a recessive gene. There is no consanguinity of the parents of any of the patients. In 9 cases the urine of both parents, and in 1 case the urine of the widowed mother, was tested and found to contain no phenylpyruvic acid, nor did these parents show any signs of mental deficiency. The remaining three pairs of parents could not be traced at the time this work was being carried out, but family histories taken previously state that none of these parents was mentally deficient.

Familial incidence is shown in the present series. In two of the families concerned there are a brother and a sister, both affected, with no normal siblings.

In the sibship of which the phenylketonuric patient Derek T— is a member, it has been confirmed that at least one other sibling suffers from phenylpyruvic oligophrenia, and it is believed to be very likely that a third sibling, now dead, was also phenylketonuric. There are 5 normal siblings in the sibship.

Another family, of whom Carol B— is a member, is of interest. The brother of the patient's father is also phenylketonuric. If the theory of inheritance by a recessive gene is accepted, then both of the paternal grandparents as well as both of the parents of Carol B— must have been heterozygotes for phenylpyruvic oligophrenia.

In the case of only one parent in the group is there evidence of any mental disturbance. This parent is a highly distractable and excitable individual of manic-depressive type, but he has not yet shown true insanity or mental

breakdown, which tend to appear in heterozygotes according to Penrose (1935*b*). He has not, however, yet reached the involutional period of life in which mental breakdown is most likely to occur according to the observations of Penrose.

Genetic Linkages.

Phenylpyruvic oligophrenia is a clear-cut biological condition, and such a sharply segregated characteristic, not very common in human biology, facilitates genetical studies. Penrose (1941) pointed out that the material provided by cases of phenylpyruvic oligophrenia is particularly suitable for use in the search for possible linkages on the autosomal part of the human chromosome map.

Munro, Penrose and Taylor (1939) collected data concerning 25 families in England, and observed that there was a suggestion of genetic linkage between the ABO blood agglutinogen allelomorph series and the gene for phenylpyruvic oligophrenia, but the scarcity of material permitted only tentative conclusions to be drawn. Penrose (1941) put on record data obtained from a Canadian family in which there were two phenylketonuric patients. Further data are provided by Penrose (1945), who studied ABO groupings of another Canadian family, and by Munro (1947) who obtained material including ABO and MN blood groupings from families in which there is phenylpyruvic oligophrenia. The statistical significance of the suggestion of linkage is doubtful where there is yet a relatively small number of families. Penrose (1945) points out that should further investigation continue to support the suggestion of linkage between phenylpyruvic oligophrenia and the ABO agglutinogens, the result will be of great theoretical interest although the linkage is not close enough to enable the blood types by themselves to be used as markers in identifying carriers of the condition.

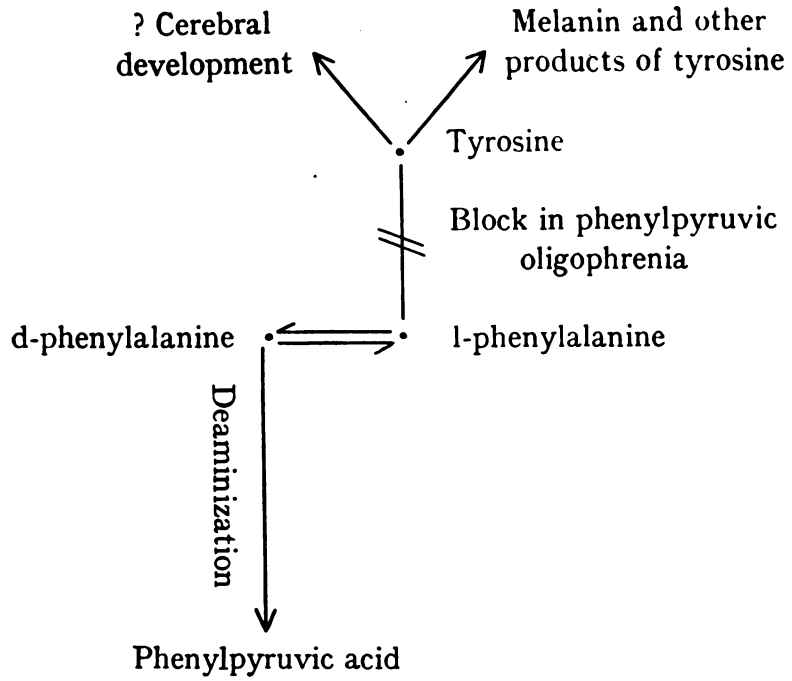
Study of the blood grouping was made in 8 of the families of which patients in the present series were members. Besides the ABO and MN groups, S, P, Lewis, Kell, Lutheran and Rhesus groupings were studied, and in one family the Duffy grouping was used. The findings are given in Table II. In Families 2, 5 and 7, where there are two affected siblings in each sibship, there is no evidence against linkage between phenylpyruvic oligophrenia and the ABO, MN, S, Lewis and Lutheran agglutinogens. In Family 7 the differences in the Rhesus, P, and Kell groupings of the phenylketonuric siblings, suggest that there is no genetic linkage between these agglutinogens and phenylpyruvic oligophrenia.

The Biochemistry of Phenylpyruvic Oligophrenia.

The fundamental biochemical error in phenylpyruvic oligophrenia is a disturbance in the metabolism of phenylalanine.

It is believed that in the normal individual, phenylalanine, in the laevo form, is converted to tyrosine, but that there is a block in this process in the phenylketonuric patient. In him, phenylalanine in the dextro form is deaminized, presumably in the kidney, to phenylpyruvic acid, which is excreted in the urine.

The biochemical picture in phenylpyruvic oligophrenia may thus be shown diagrammatically as follows :



Experimental evidence of many workers throws light on the metabolism of phenylalanine in the normal individual and in the phenylketonuric patient.

In Dakin's classical experiment it was shown that *in vitro* phenylalanine is converted to phenylpyruvic acid in the presence of kidney slices. Upon this evidence he based his hypothesis that the normal pathway of metabolism of phenylalanine passed through phenylpyruvic acid, the conversion being effected by oxidative deaminization.

Embden and Baldes (1913) put forward the hypothesis that the normal pathway of catabolism of phenylalanine was through tyrosine, the first step being a nuclear oxidation in the para position. This was supported by the fact that perfusion of the liver with dl-phenylalanine led to the production of tyrosine.

Föllings (1934) originally suggested that two biochemical lesions may exist in phenylpyruvic oligophrenia ; first, a pathological oxidative deaminization, transforming phenylalanine to phenylpyruvic acid, occurring only in the phenylketonuric individual ; and, secondly, a disturbance in the breakdown of the phenylpyruvic acid thus formed, since in the normal individual ingestion of this acid leads to rapid breakdown rather than to urinary excretion. Experiments carried out by Penrose and Quastel (1937) in which phenylpyruvic acid was fed to both phenylketonuric patients and to normal individuals, supported this belief that phenylpyruvic acid is metabolized with greater difficulty in the phenylketonuric patient than in the normal subject.

TABLE II.

Family.	Member.	ABO.	MN.	S.	Rh.	P.	K.	Le.	Lu.	Fy.
1	Father	A_2	N	+	rr	+	–	–	–	..
	Mother	A_1	MM	–	rr	+	–	–	–	..
	Patient, J. S—	A_1	MN	+	rr	+	–	–	–	..
	Sister	A_1	MN	–	rr	+	–	–	–	..
2	Father	O	MN	+	R_1R^1	+	–	–	–	..
	Mother	O	M	+	rr	+	–	–	–	..
	Sister, H. F—	O	MN	+	R_1r	+	–	–	–	..
	Sister, J. T—	O	MN	+	R^1r	+	–	–	–	..
	Patient, L. T—	O	MN	+	R^1r	+	–	–	–	..
	Sister, Jo. T—	O	MN	+	R_1r	+	–	–	–	..
	Patient, D. T—	O	MN	+	rr	+	–	–	–	..
	Sister, P. T—	O	M	+	R_1r	+	–	–	–	..
3	Mother	A_1	NN	+	R_1R_2	+	–	+	–	..
	Patient, G. H—	A_1	NN	+	R_1R_2	+	–	–	–	..
	Sister	A_1	NN	+	R_1R_2	+	–	–	–	..
4	Father	O	MN	–	$R_1^wR_1$	+	–	–	–	..
	Mother	B	MM	+	R_1r	–	–	–	–	..
	Brother, P. C—	O	MN	–	$R_1^wR_1$	+	–	–	–	..
	Sister, P. C—	O	MN	–	$R_1^wR_1$	+	–	–	–	..
	Patient, B. C—	O	MM	–	R_1^wr	+	–	–	–	..
	Brother, A. C—	O	MN	–	R_1r	+	–	–	–	..
	Brother, C. C—	B	M	+	$R_1^wR_1$	+	–	–	–	..
5	Father	O	NN	–	rr	–	–	–	–	..
	Mother	B	NN	–	rr	–	–	–	–	..
	Patient, P. P—	O	NN	–	rr	–	–	–	–	..
	Patient, A. P—	O	NN	–	rr	–	–	–	–	..
6	Father	BO	M	+	R_1r	+	–	..	–	–
	Mother	A_1B	N	–	rr	+	–	..	–	+
	Sister, S. J—	A_1O	MN	–	R_1r	+	–	..	–	+
	Patient, A. J—	A_1B	MN	–	R_1r	+	–	..	–	+
	Brother, D. J—	A_1O	MN	–	rr	+	–	..	–	+
	Brother, B. J—	B	MN	–	R_1r	+	..	..	–	..
7	Father	A_1B	N	–	R_1r	–	+	..	–	..
	Mother	A_1B	N	–	R_1R_1	+	–	..	–	..
	Patient, M. W—	A_1B	N	–	R_1r	–	+	–	–	..
	Patient, F. W—	A_1B	N	–	R_1R_1	+	–	–	–	..
8	Mother	O	MN	+	R_2	+	–	..	–	..
	Sister	A_1	MN	+	R_2	+	–	..	–	..
	Patient, J. R—	A_1	MN	+	R_2r	–	–	+	–	..

Penrose and Quastel (1937) also studied the effects of feeding phenylalanine to phenylketonuric and to non-phenylketonuric individuals. They found that in phenylpyruvic oligophrenia only part of the phenylalanine ingested appears as phenylpyruvic acid. They showed also that the phenylketonuric patient has almost as great difficulty in metabolizing l-phenylalanine as d-phenylalanine. The non-phenylketonuric subject, on the other hand, apparently metabolizes l-phenylalanine with greater ease than either the racemic or d-forms, and both optically active forms are metabolized less completely in the phenylketonuric patient than in the normal individual.

Penrose (1937) believed that phenylalanine catabolism could follow two pathways, the main pathway passing through phenylpyruvic acid, and a subsidiary pathway passing through tyrosine. Jervis and his co-workers (1940), after carrying out metabolic studies with phenylalanine, postulated that these two pathways were reversed in importance. They believed that the main pathway passed through tyrosine, and that the pathway of metabolism passing via phenylpyruvic acid was accessorial.

If one accepted the classical conception of Dakin that phenylalanine is

normally catabolized to phenylpyruvic acid, the disturbance in phenylpyruvic oligophrenia would seem to be a fault in the catabolism by which phenylpyruvic acid is disposed of in the body.

If one agreed with Embden and Baldes (1913) that phenylalanine is normally metabolized by way of tyrosine, phenylpyruvic acid would seem to be an abnormal metabolite produced by an abnormal method of metabolism, the transformation of phenylalanine to tyrosine being blocked. Further evidence of phenylalanine being metabolized to tyrosine and its derivatives was afforded by an observation by Medes (1932), who found that in a case of tyrosinosis the urinary output of Millon-reacting substances increased after the ingestion of phenylalanine.

New light was thrown on the problem when Jervis (1940) and his co-workers examined the blood and cerebrospinal fluid of phenylketonuric patients. Their findings excluded the presence of appreciable amounts of phenylpyruvic acid in these body fluids, although the phenylalanine content was high. It was on the basis of these findings that Jervis reversed his belief in the relative importance of the two possible pathways of metabolism of phenylalanine which he formerly held (Jervis, 1937). He now concluded that the essential biochemical characteristic of the disease consisted of an inability of phenylketonuric subjects to dispose of phenylalanine at a normal rate rather than in the failure to break down phenylpyruvic acid. He considered the presence of phenylpyruvic acid in the urine as an incidental phenomenon resulting from the deaminization of a portion of the blood-phenylalanine by kidney tissue. He considered the formation of phenylpyruvic acid in the kidney as representing an alternative pathway in the catabolism of phenylalanine, this route being available when the normal pathway is blocked. He now believed the normal route of phenylalanine catabolism to be through tyrosine, and not through phenylpyruvic acid. In support of this belief he gave evidence of studies in alcaptonuria, where it was shown that both phenylalanine and tyrosine caused an increase in the elimination of homogentisic acid; he quoted the experimental evidence of Embden and Baldes (1913), and of Medes (1932). He also described experiments with tissue slices indicating that phenylpyruvic acid fails to give acetoacetic acid under conditions in which phenylalanine and tyrosine yield this compound. Other evidence quoted of the close metabolic relationship between tyrosine and phenylalanine was provided by studies on experimental alcaptonuria, and by the finding of l-p-hydroxyphenyllactic acid in the urine of vitamin C deficient premature infants following the ingestion of either phenylalanine or tyrosine.

It is upon the conclusions drawn by Jervis and his co-workers (1940) from their fundamental experiments, that is based the conception now held of the biochemistry of phenylpyruvic oligophrenia as outlined above in diagrammatic form.

The relationship of the biochemical error in phenylpyruvic oligophrenia to mental deficiency is not yet fully understood, but one may conjecture that the deficiency of tyrosine or of its products or of the enzyme system required for the metabolism of phenylalanine to tyrosine may in some way impair cerebral development or function. On the other hand, the accumulation of excessive

phenylalanine in the tissues of phenylketonuric patients as demonstrated by Jervis and his co-workers (1940) may act as a toxic factor, inducing mental deficiency. To investigate the possible toxic effects of excessive phenylalanine it would be interesting to feed phenylketonuric patients with a diet entirely free from phenylalanine. This has, however, great practical difficulties. Alternatively, the feeding of massive doses of phenylalanine to experimental animals might throw light upon the matter, but again difficulties would arise in recognizing any signs appearing in an experimental animal comparable to those seen in phenylpyruvic oligophrenia in man.

The biochemical error seems compatible with the physical signs of lack of pigmentation of skin and irides and of dilution of hair-colour, if one accepts the deficiency of tyrosine available from phenylalanine in these patients, tyrosine being a precursor of the pigment melanin, although it must be borne in mind that tyrosine is available directly from the diet, and that the deficiency is therefore not a total one. This is supported by the evidence obtained by Block *et al.* (1940), who showed that the tyrosine contents of serum from phenylketonuric and from normal individuals were approximately the same, being 4·3 per cent. in the former and 4·1 per cent. in the latter.

There is no evidence at present against the possibility of an enzyme deficiency in phenylpyruvic oligophrenia, and Penrose (1949) postulates the lack of some enzyme capable of splitting and utilizing the laevo-phenylalanine. Himwich and Fazekas (1940) supposed that the low level of mental activity in patients suffering from phenylpyruvic oligophrenia might be attributed to diminished rate of oxidation. By examination of the blood from the internal carotid artery and internal jugular vein they established that there was a diminution in cerebral oxidation in patients suffering from phenylpyruvic oligophrenia. They stated that such a diminution may be due to the lack of oxidative enzyme, a defect similar to that which prevents the oxidation of phenylalanine. They also demonstrated, however, a similar diminution in the cerebral oxidation of mongols, and there is no evidence to prove that this phenomenon is not common in mental defectives generally.

Several authors have commented upon the possibility of enzyme deficiency in phenylpyruvic oligophrenia.

Pichot *et al.* (1947) postulated a possible disturbance in the enzymes in the kidney, since feeding with either dextro or laevo forms of phenylalanine leads to increased output of phenylpyruvic acid in the phenylketonuric patient, but phenylketonuria is stimulated only by ingestion of the dextro form in the normal individual.

Jervis (1937*b*) observed that there was excellent ground to assume that the oxidation of a single product of metabolism may be impaired without affecting the capacity of the body to oxidize other substances, since it appears that oxidizing agents bear a special relation to the substance undergoing change, and that such a specificity seems to exist for the catalysts involved in the oxidation of phenylalanine. In another paper Jervis (1937*a*) again asserts that it may be safely assumed that an enzyme deficiency is at fault in phenylpyruvic oligophrenia, stating that the nature of the enzyme system responsible for the breakdown of phenylalanine had been worked out by Bernstein.

Pichot, Delay and Bertagna (1949) carried out experiments to determine whether an enzyme, phenylalanine-oxidase, exists in the circulating blood, conjecturing that the congenital absence of such an enzyme could be the fundamental disturbance in phenylpyruvic oligophrenia. They studied the urinary elimination of phenylpyruvic acid in cases in which exsanguino-transfusions had been performed. The result was completely negative. The enzyme, however, may well exist in some other organ or tissue than the blood, although there is no report to date of further quest along these lines.

The present writer hopes that future liver-biopsy to be carried out upon the phenylketonuric patients of her series will provide material for an experiment on the following lines.

From the findings of Embden and Baldes (1913) it is assumed that conversion of phenylalanine to tyrosine can take place in the liver in the non-phenylketonuric individual. The liver tissue removed at biopsy from the phenylketonuric patients would be placed, immediately following removal, in a physiological solution containing phenylalanine. Liver tissue obtained from non-phenylketonuric individuals at biopsy would be treated in the same way. A study would be made of the behaviour of the liver tissue from the phenylketonuric and non-phenylketonuric subjects with respect to the production of tyrosine. Decreased production of tyrosine in the case of the liver obtained from the patients suffering from phenylpyruvic oligophrenia would point to the metabolic error being seated in the liver in this condition.

Blood Chemistry in Phenylpyruvic Oligophrenia.

Investigation into the blood chemistry of the patients of the present series was carried out. The results are given in Table III.

The increased reflexes and tendency towards hypertonicity often found in phenylpyruvic oligophrenia and seen in some of the present patients, suggested that these manifestations might have been due to a low level of serum calcium. Investigations showed, however, that this was not the case. The serum calcium and phosphorus levels were within normal limits in each of the 15 cases.

Table III.

Name.	Age.	Serum calcium mg.%	Serum Phosphorus mg. %.	Alkaline Phosphates K units.	Cholesterol. Total mg. %.	Free mg. %.	Ester mg. %.	Free/Ester.
Lilian B—	18 yrs. 8 mths.	9·1	4·1	12	165	53	112	1/2·2
Carol B—	6 ,, 9 ,,	9·3	4·7	13	196	50	146	1/2·9
Brian C—	8 ,, 11 ,,	9·6	5·0	19	189	41	148	1/3·6
Georgina H—	8 ,, 4 ,,	9·7	4·5	13	177	41	136	1/3·3
Alan J—	9 ,, 9 ,,	9·7	4·2	10·5	225	65	160	1/2·5
Arthur P—	12 ,, 2 ,,	10·2	5·3	17·5	225	90	135	1/1·5
Pauline P—	4 ,, 6 ,,	10·1	5·3	13	225	65	160	1/2·5
Pamela P—	20 ,, 2 ,,	10·8	4·0	8·5	135	45	90	1/2·0
John R—	7 ,, 9 ,,	10·0	4·9	13	188	40	148	1/3·7
Joan S—	21 ,, 9 ,,	9·4	3·6	9	200	51	149	1/2·9
Iris S—	12 ,, 9 ,,	10·3	5·0	15·5	177	41	136	1/3·3
Derek T—	14 ,, 10 ,,	10·6	4·9	22·7	142	35	107	1/3·0
Frances T—	7 ,, 8 ,,	10·1	5·2	26	165	56	109	1/1·9
Francis W—	6 ,, 5 ,,	9·9	4·9	15	118	32	86	1/2·7
Margaret W—	10 ,, 1 ,,	9·6	4·5	14	212	59	153	1/2·6

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TABLE IV.

	Carol B—	Lilian B—	Brian C—	Georgina H—	Alan J—	Arthur P—	Pauline P—	Pamela P—	John R—	Iris S—	Joan S—	Derek T—	Frances T—	Francis W—	Margaret W—
Fair hair and fair skin	+	+	+	+	+	+	+	+	..	+	+	+	+	+	+
Blue irides	+	+	+	+	+	+	+	+	..	+	+	+	+	+	+
Widely-spaced incisors	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Brisk reflexes	+	+	..	+	+	..	..	+	..	+	+	+	..	+	+
Tendency to dermatitis	..	+	..	+	+	..	+	+	..	+	+	..	..	+	+
Poor peripheral circulation	+	+	+	+	..	..	+	..	..	..	..	..	+	+	+
History of epilepsy	+	..	..	+	..	..	+	..	..	..	+	+	..	..	+
Kyphosis	..	+	..	+	..	..	..	+	..	..	+	+	..	..	+
Characteristic gait	..	+	..	+	..	..	..	+	..	+	+	..	..	..	..
Pithecoid stance	..	+	..	+	..	..	..	+	..	..	+	..	..	..	..
Digital mannerisms	..	+	..	..	..	..	..	+	..	..	+	..	..	+	..
Pigmentary anomalies of skin	..	..	..	..	..	..	+	+	..	..	+	..	..	..	..
Thinning of retinal pigment	+	..	..	..	..	..	+	..	..	..	..	..	..	+	..
Dermatographia	..	..	..	..	..	..	+	..	..	..	..	+	..	..	..
Hyperidrosis	..	..	..	..	..	..	..	+	+	..	..	..	..	..	..
Pes planus	..	+	+	+	+	+	..	+	+	+	+	+	..	+	+
Partial syndactyly of toes	..	+	+	..	..	..	..	..	+	+	+	..	..	..	..
Prognathos of maxilla	..	+	+	+	+	+	+	+	..	+	+	+	..	..	..
Palpable liver	..	..	..	..	..	..	..	..	..	..	..	..	..	+	..
Idiot	+	+	+	+	+	..	+	+	..	+	+	..	+	+	+
Imbecile	..	..	..	..	..	+	..	..	..	..	..	+	..	..	..
Dull and backward	..	..	..	..	..	..	..	..	+	..	..	..	..	..	..

Values for blood cholesterol were obtained, and in each case these were within normal limits. This provides additional evidence in favour of the belief that there is no dysfunction of the thyroid in phenylpyruvic oligophrenia.

THE PATHOLOGY OF PHENYLPYRUVIC OLIGOPHRENIA.

Until the time of writing, only two post-mortem examinations upon phenylpyruvic oligophrenics have been reported in publications, and a third post-mortem examination, the report of which has not yet been published, was performed at the Middlesex Colony in July, 1949. The writer was present at this event and observed the macroscopic appearances. The histological findings have not yet been made known.

The body was that of a small woman aged 25. The organs, including heart, liver, spleen and kidneys were all correspondingly small. The brain weighed 2½ lb. and showed no macroscopic defect. There was a marked kyphosis and lumbar lordosis. The hair was slatey fair, and the irides were pale bluish-grey. The hands were in a "main en griffe" position, with hyperextension at the metacarpo-phalangeal joints, and it was stated that this was a characteristic of the patient during life. The liver lobules were well-defined on examination by the naked eye. The liver was leathery to feel. There was a small amount of pus in the upper calyx of the left kidney. When 5 per cent. ferric chloride solution was dropped onto the cut surface of the kidney the tubules gave a dark green coloration. No colour reaction was produced when ferric chloride solution was dropped on the cut surface of the liver or spleen. There were calcified lymph nodes in the mesentery. No abnormalities were

observed by the naked eye in the peripheral nerves. The macroscopic appearance of the thyroid was normal. The cause of death was established as pneumonia.

The patient was reported to have been of idiot grade, being unable to walk, bed-ridden, doubly incontinent and unable to speak or to do anything for herself. Her sister, who died as a child at the Fountain Hospital in 1925, was a fair-haired idiot with light grey eyes and widely-spaced incisor teeth. She died following an attack of jaundice. She was classified as an imbecile of no specific type, but was almost certainly suffering from phenylpyruvic oligophrenia. Apart from the case of her sister, whose post-mortem findings are described above, there was reported to be no case of mental deficiency or insanity in the family history, and the parents were not consanguineous.

The two post-mortem reports have been published by Penrose (1939) and by Coquet *et al.* (1944).

Penrose's case was that of a male idiot, aged 9 years and 7 months ; bronchopneumonia was found in both lungs. The most striking feature of the post-mortem examination was the finding of several tense swellings, up to 1 cm. in diameter on the trunks of both vagi, and smaller ones on nearly all their branches. The phrenic nerves, medial brachial cutaneous, ulnar, median, musculospiral and sciatic nerves were also affected, and there were multiple small nodules of a similar kind near the pudendal and coeliac plexuses. When cut through, some fluid could be expressed with difficulty from the swelling, but neither the nerve nor the fluid gave a colour with ferric chloride. Microscopically the appearances in sections of the sciatic nerve were indistinguishable from those found in some cases of neurofibromatosis, with a decreased amount of interstitial connective tissue and loss of myelin in many of the nerve fibres. The localized swellings appeared mainly due to presence of fluid which had infiltrated a network of nerve fibres. The brain was soft and oedematous, the nerve cells of the cortex being widely spaced and the connective tissue of the grey matter loosely packed. The liver was not studied. Penrose points out that the swellings on the nerves may be related to changes observed in progressive hypertrophic polyneuritis which have been attributed to the action of toxins, and suggests that the swellings and hypertrophy of peripheral nerves in this case may have been due to a toxic action of phenylpyruvic acid, and that the association between metabolic abnormality and cerebral oedema may have a parallel explanation.

In the post-mortem examination reported by Coquet *et al.* (1944), perilobular fatty degeneration was found in the liver, and there was stasis in the intra-trabecular capillaries. There was liquefaction of the pyramidal cells of the cerebral cortex in layers II, III and IV. There was a small zone of necrosis in the white matter of the frontal lobe. The interstitial tissue of the thyroid was said to be "rich in nuclei." No abnormality of the peripheral nerves was discovered.

In addition to the definite pathological evidence mentioned above, the post-mortem report is available of a female idiot, Gladys T—, who died at the Fountain Hospital in 1941, aged 18½. Her case has already been described, together with those of her brothers, Derek T— and Leslie T—, who are both

phenylketonuric. It is almost certain that Gladys T— herself suffered from phenylpyruvic oligophrenia. The patient was said to be very obese when she died. Patches of broncho-pneumonia were found in both lungs. Apart from this the only abnormal findings recorded were that the heart was flabby with infiltration of fat, and that the liver, weighing 3 lb. 3 oz. was enlarged and light-coloured, with infiltrated fat throughout. The brain showed no macroscopic abnormality and weighed 2 lb. 4 oz.

The Liver in Phenylpyruvic Oligophrenia.

There are certain indications that the liver may be the seat of the metabolic error in phenylpyruvic oligophrenia.

It has been shown that the fundamental biochemical disturbance underlying the condition is an inability of the patient to dispose of phenylalanine at a normal rate (Jervis, 1940). Jervis (1947) demonstrated an increase of a tyrosine-like substance in the blood of rabbits, following intravenous administration of phenylalanine. This indicated that the conversion of phenylalanine was not due to changes occurring in the intestinal tract. The experimental evidence of Embden and Baldes (1913), who found tyrosine in the perfusion fluid after perfusing the liver with phenylalanine, is in favour of the liver as being an organ in which the metabolism of phenylalanine takes place. Coquet, Myle *et al.* (1944) describe pathological changes in the liver in a post-mortem report on a phenylketonuric patient.

Urine from 8 of the phenylketonuric patients was examined by means of chromatography and was found to contain a high level of taurine, sarcosine and "Substance A." An increase in the urinary output of these three substances has been observed on occasions during or shortly after gastro-enteritis with liver involvement. The identity of "Substance A" is unknown, but it is known to be a nitrogen-containing compound.

Delay, Pichot *et al.* (1947) draw attention to the extrapyramidal signs and choreoathetotic movements seen in Kinnier-Wilson's disease, in the pseudosclerosis of Westphal-Strümpell and in phenylpyruvic oligophrenia. Delay and his co-workers point out that it is interesting to compare the hepatic lesions in the former two diseases with the pathological findings of Myle, Coquet *et al.* (1944). Delay *et al.* (1947) carried out a galactose tolerance test upon one patient suffering from phenylpyruvic oligophrenia. The result of the test was similar to that found in acute hepatitis.

The present writer carried out galactose tolerance tests for liver function on 12 patients of her series (Cowie, 1950).

Intravenous galactose tests were also performed on 8 of the phenylketonuric patients. The method used was on the same lines as that of King and Aitken (1940).

Galactose was administered, either orally or intravenously, to a fasting patient, in amounts varying according to the bodyweight. The blood-level of galactose in the subsequent two hours was assessed at half-hourly intervals.

The results obtained are given in Table V. The galactose was administered orally in 6 cases. This method was preferred, since the galactose after absorption from the gut passes directly into the portal vein.

TABLE V.

Patient.	Galactose. gm.	Route.	Blood galactose, mg. per cent. 0 hrs.	½ hr.	1 hr.	1½ hrs.	2 hrs.	Liver dysfunction.
B. C—	50	Oral	0	7	7	33	8	−
F. W—	25	,,	0	90	48	40	..	+
I. S—	25	,,	0	0	0	0	0	−
	50	I.V.	0	57	0	..	0	−
M. W—	25	Oral	0	6	20	20	..	±
D. T—	50	I.V.	0	77	33	5	2	−
A. J—	35	Oral	0	30	72	63	6	+
C. B—	25	,,	0	12	36	81	72	++
P. Ph—	50	I.V.	0	15	0	..	0	−

In 3 cases strongly positive results were obtained, indicative of liver dysfunction Each of these cases gave results within normal limits when tested previously by the galactosuria method. A fourth case gave weakly positive results, possibly indicative of slight liver dysfunction.

The finding of abnormality of structure in the living liver would add much weight to the hypothesis wherein the liver is cited as being the possible seat of metabolic disturbance in phenylpyruvic oligophrenia.

Liver biopsy was carried out on two of the patients of the present series. The writer selected the patient Francis W— for biopsy because his liver edge was palpable half an inch below the right costal margin, and there was corresponding liver dullness. The liver biopsy was made through a 2-in. incision and a small wedge was removed. The report of the examination of the material by Dr. Martin Bodian is as follows :

"*Naked eye examination.*—The specimen comprised a small wedge of hepatic tissue taken from one margin of the organ. It was a light cream colour and showed some areas of congestion.

"*Microscopy.*—Chronic inflammatory cell infiltration of the larger portal tracts and slight thickening of the connective tissues of the central vein are present, and these serve to accentuate slightly the lobular architecture of the organ. The reticulin pattern is within normal limits, but the network of strands is rather thicker and more prominent than usual, and shows moderate condensation on the surface of the portal tracts. The hepatic cells are of normal form in some fields, while in others they display a shrunken appearance. The latter zones are most obvious around some portal tracts, but are also present elsewhere. A sprinkling of binucleated liver cells can be found. Glycogen storage appears to be adequate, and there is a fine diffuse fatty change, most marked in the peripheral parts of the lobules. Sudanophilic material also occurs in the intimal region of an artery and in the wall of another structure—probably a vein. There is no retention of bile."

The second biopsy was carried out on the phenylketonuric patient, Carol B—. The report by Dr. Martin Bodian runs as follows :

" Microscopical examination of the liver biopsy revealed no striking abnormality. The cells were normal, the reticulin framework was normal, the glycogen content was normal. There was a slight excess of fine and medium-sized fat globules dispersed fairly equally throughout the lobules."

Neither biopsy revealed any gross abnormality. This is in keeping with the negative findings of the induced galactosuria liver function tests. The fine diffuse fatty change in the periphery of the lobules in Francis W—'s case, and the slight excess of fine and medium fat globules in the lobules of Carol B— are interesting findings in view of the post-mortem findings in the liver by Myle, Coquet *et al.* (1944).

The Basal Metabolic Rate in Phenylpyruvic Oligophrenia.

Reports of the depression of the basal metabolic rate in phenylketonuria were published in France on two occasions (Delay *et al.*, 1947; 1948). In both instances the basal metabolic rate was depressed to — 27 per cent. The writers state that the true level may have been even lower than this, since the restlessness of such patients tends to give a higher result than would a recording of their truly basal metabolic rate.

Himwich and Fazekas (1940) found depression of cerebral metabolism in 15 cases of phenylpyruvic oligophrenia, using a method in which the oxygen content was measured in blood flowing to and from the brain. Such a lowering of cerebral metabolism may have been due to a general lowering of metabolism in the body.

Estimations of the basal metabolic rate were attempted in the cases of all of the 15 patients of the present series. In 12 cases no reliable results were obtained owing to the complete lack of co-operation of the idiot patients.

Derek T—, of imbecile grade, co-operated fairly well. On occasions where he was most co-operative, basal metabolic rates of + 23 per cent., + 24 per cent., + 26 per cent. and + 29 per cent. were obtained, but on all occasions he breathed more deeply than usually, and his pulmonary ventilation was high, being 7–10 litres per minute. His respiratory quotient was correspondingly high, varying from 1·06 to 1·17, this being accounted for by his increased effort of breathing, increased oxygen consumption and increased CO_2 removal. It cannot be stated that the results obtained in this case are significantly altered, since on no occasion did the patient relax completely, and the metabolism was therefore not truly basal.

Arthur P—, a phenylketonuric imbecile, was more co-operative than the idiot patients, but tended to be restless and frequently rejected the mouthpiece of the apparatus, causing leakage. Very few reliable figures were obtained, but his basal metabolic rate was probably slightly higher than normal, and his respiratory quotient was calculated as being 0·84.

John R—, of dull-and-backward mental grade, was very co-operative, when he had overcome some initial apprehension. The results obtained in his case are reliable. The pulmonary ventilation varied from 4·8 litres to 5·6 litres per minute on different occasions. The respiratory quotient was 0·81, 0·76 and 0·70 on different days. The basal metabolic rate was estimated as being + 13 per cent., + 12 per cent., + 15 per cent. and + 13 per cent. on different days. The depression of the respiratory quotient in this patient and in the case of Arthur P— may indicate preferential fat metabolism.

The hyperidrosis, hyperkinesis and exaggerated reflexes found in phenylpyruvic oligophrenia may suggest that hyperthyroidism is a possible component of the syndrome, although enlargement of the thyroid gland and other thyrotoxic signs are not features in any of the cases in the present series, nor are they reported in literature relating to the subject. An elevation of the basal metabolic rate fits in with this hypothesis.

On the other hand, since phenylalanine and tyrosine are raw materials required for the ultimate production of thyroxine, one might postulate a hypothyroidism in phenylpyruvic oligophrenia, although there is no clinical evidence

of this apart from the findings of Delay and his co-workers mentioned above. One of the patients of the present series was falsely diagnosed as a cretin at eight months of age and was treated with thyroxine for nine years, and his sister, also falsely diagnosed as a cretin, was treated with thyroxine from nine weeks to one year of age, and the condition of both of these patients has remained unaltered since the cessation of thyroid treatment. Studies of the blood cholesterol in patients of the present series provided no evidence of thyroid dysfunction.

All the figures obtained by the present writer indicate that the basal metabolic rate is increased in phenylpyruvic oligophrenia. This is in direct contradiction to the findings of Delay and his co-workers.

The Output of Phenylpyruvic Acid.

The urinary excretion of phenylpyruvic acid in phenylpyruvic oligophrenia is usually approximately 1 gm. daily (Penrose, 1946). The patient described by Coquet, Myle *et al.* (1944) excreted 2 gm. of the acid per litre of urine.

The present writer carried out quantitative estimations of the phenylpyruvic acid in the urine of the patients of the present series. The method used for the estimation of phenylpyruvic acid was that of Penrose and Quastel (1937). This method depends upon the formation of 2:4 dinitrophenylhydrazone in standard alkali solution, the resulting colour being compared with standard colours obtained with known amounts of phenylpyruvic acid. The results obtained are shown in Table VI.

Table VI.

Name.	Average daily output of phenylpyruvic acid (gm.).	Mental level.
John R—	0·5	Dull and backward
Derek T—	1·0	Imbecile
Lilian B—	1·0	Idiot
Arthur P—	1·1	Imbecile
Pauline P—	1·1	Idiot
Francis W—	1·3	,,
Georgina H—	1·4	,,
Carol B—	1·5	,,
Frances T—	1·8	,,
Pamela P—	1·8	,,
Margaret W—	1·9	,,
Joan S—	2·2	,,
Iris S—	2·3	,,
Brian C—	2·5	,,
Alan J—	2·9	,,

It is noteworthy that the phenylpyruvic acid output of the dull-and-backward patient should be so remarkably low. The number of patients in the series is too small for a conclusion to be drawn as to a correlation between the

amount of phenylpyruvic acid excreted and the mental level of the patient, but it is suggestive that the three patients of higher mental grade should be amongst those who excrete the least phenylpyruvic acid in the group.

In chromatography of the urine of the patients, although the urine of the dull-and-backward patient, John R—, was found to conform in other ways to the picture produced by the other phenylketonuric patients, the phenylalanine present, although excessive, was approximately only one-half of that excreted in the urine of the other phenylketonurics. This finding, together with the results of the quantitative estimations of the urinary excretion of phenylpyruvic acid in this patient, is in accordance with the view that the amount of phenylpyruvic acid excreted is an index of the amount of phenylalanine which is failing to be metabolized normally by the patient. It seems that John R— can metabolize phenylalanine at least twice as easily as any member of the series. His case indicates that phenylpyruvic oligophrenia does not follow an " all-or-none " rule ; the metabolic error may be present in patients in varying degrees.

Electroencephalography in Phenylpyruvic Oligophrenia.

Kreezer (1937) studied the electroencephalography of 8 phenylketonuric patients. He found a relatively high percentage of regular sequences made up of alpha waves of high amplitude and low frequency. The frequency averaged about nine waves per second, compared with an average of ten waves per second in the normal individual.

Kreezer stated that the low frequency found among phenylketonurics was of interest in the light of the fact that in phenylpyruvic oligophrenia there might be a diminished rate of oxidation due to lack of appropriate oxidizing enzymes. He quoted evidence that various factors, such as blood sugar, body temperature and basal metabolic rate, which might be presumed to correlate with rate of oxidation of brain cells, had a significant effect on the frequency of alpha waves, and that variation in these factors which might be expected to reduce the rate of oxidation in the brain cells led to reduction in alpha frequency. The reduced frequency of alpha waves in phenylpyruvic oligophrenia would therefore support the belief in reduced cerebral oxidation, probably due to a deficiency of essential enzymes.

Later, Kreezer (1939), after investigating the electroencephalography of various types of defectives and observing that abnormally slow occipital alpha rhythm was a common finding in low-grade cases, came to the conclusion that this dysrhythmia could be attributed to general immature cerebral organization.

Gibbs and Gibbs (1941) studied the electroencephalograms of 8 phenylketonuric patients. They found that even where there was no history of epilepsy, the records were similar to those commonly found in the case of epileptic patients during inter-seizure periods. They showed bursts of low frequency usually seen best in the parietal leads.

Jervis (1937*b*) writes that from examination of the electroencephalogram in phenylpyruvic oligophrenia, it appears that the extrapyramidal signs

commonly found may be referred simply to cortical atrophy, particularly of the frontal lobe.

Delay *et al.* (1947) report the electroencephalography of a phenylketonuric case, the interpretation of which was rendered difficult owing to the appearance of numerous rapid waves produced by the restlessness of the patient.

Delay *et al.* (1948) reported another electroencephalogram of a phenylketonuric child. This was a normal tracing. It was made when the patient was at rest.

Pichot *et al.* (1949) report a normal electroencephalogram, made on a female phenylketonuric imbecile, aged 17, at rest, the alpha-rhythm being twelve cycles per second.

Electroencephalograms were carried out on 13 of the phenylketonuric patients of the present series, and on 22 of their relatives, 2 of whom also suffered from phenylpyruvic oligophrenia.

Consideration was given to the possible relationship between epilepsy and phenylpyruvic oligophrenia.

Of the present series of cases 6 were epileptic. Of these 3 had epileptic electroencephalograms, 2 had normal or doubtful records, and 1 had no recording made. Of the electroencephalograms of the 9 patients without epilepsy, 7 were normal or doubtful, 1 was of epileptic type and in 1 case a satisfactory record was not obtainable. Of the 6 cases with epilepsy 1 had a parent with an epileptoid electroencephalogram with the presence of bursts of fast and slow activity. Of the 9 cases without epilepsy 1 also had a parent with an epileptoid electroencephalogram. From the data it seems that phenylpyruvic oligophrenia may be genetically independent of and unrelated to epilepsy, but epilepsy may be related to phenylpyruvic oligophrenia inasmuch that it appears as part of the clinical picture in a number of cases, as it often does in non-phenylketonuric mentally defective patients.

One of the purposes for carrying out electroencephalography on the relatives of the patients was to find whether abnormalities existed in the records obtained in the case of heterozygotes for phenylpyruvic oligophrenia. In the case of two parents, neither of whom showed any clinical signs of epilepsy, the electroencephalograms were epileptoid in character. Abnormalities were seen in only one other parent's record, where the abnormal findings were due to a previous history of brain abscess and operation.

A third point of interest in connection with the electroencephalography is the possible relationship between the abnormality of the record and the mental level of the patient. Such a relationship does not appear to exist. The dull-and-backward patient had a mildly abnormal electroencephalogram. Of the 2 imbeciles 1 had a normal record and 1 had an abnormal one. Of the 7 idiots without epilepsy all the records were doubtful or abnormal.

The records of the epileptics showed gross abnormalities which were probably related to the epilepsy rather than to phenylpyruvic oligophrenia. Leaving these records aside, the records of the non-epileptic patients tended to resemble each other in frequently being of low voltage and showing traces of rhythm on the alpha, beta and theta bands with little difference in the rhythmical patterns between the different parts of the brain, and poor rhythmical co-ordination between one area and another.

The electroencephalograms of the patients of the present series did not reveal any evidence as to a possible site of maximal disturbance in the brain in phenylpyruvic oligophrenia. Dr. D. A. Pond, who kindly carried out the electroencephalography, states that the abnormality in the electroencephalograms of these patients does not easily fit into any simple concept of the effect of the biochemical abnormality and that the records are not like those that one might expect in simple developmental retardation, nor in the case of a normal brain in a state of chronic chemical intoxication, although this is perhaps more likely than the former.

Tyrosine-feeding in Phenylpyruvic Oligophrenia.

Jervis (1937*b*) fed a phenylketonuric patient with 10 gm. of tyrosine, the diet being protein-free. He observed that the output of phenylpyruvic acid was not increased.

Penrose and Quastel (1937) fed tyrosine to two phenylketonuric patients. They found that administration of tyrosine did not consistently result in any increase in the excretion of phenylpyruvic acid. They found also that it was impossible to induce phenylketonuria in any control patients by feeding tyrosine. The findings seemed to indicate that in phenylpyruvic oligophrenia tyrosine is probably normally metabolized.

Three patients of the present series have been fed over a period of 16 weeks with 20 gm. of l-tyrosine daily to each patient. The tyrosine was administered in the diet of the patients. Quantitative estimations, for the assessment of phenylpyruvic acid in the urine, were carried out weekly during the experimental period. Three of the other phenylketonuric patients, corresponding as closely as possible to the tyrosine-feeders in age, sex and mental level, were chosen as controls, the patients being paired as follows :

	Receiving tyrosine.	Control patient.
(1)	John R—.	Arthur P—.
(2)	Lilian B—.	Joan S—.
(3)	Brian C—.	Alan J—.

During the experimental period the 6 patients concerned were kept under close observation for any change in their physical signs, behaviour or mental level.

At the end of the first week of the experiment, 24-hour specimens of urine were collected from the six patients. The method of Penrose and Quastel was used in each case to estimate the content of phenylpyruvic acid. In the case of the patients being fed with tyrosine, the readings obtained by this method were markedly increased, the value in one case being over four times as great as that obtained before the administration of tyrosine ; whereas the readings obtained from the urine of the control patients remained at their original levels.

Throughout the experimental period of 16 weeks, these values remained raised in the cases of the patients receiving tyrosine, and at the levels originally obtained in the control patients with little fluctuation. These results are given in Table VII.

TABLE VII.

Name.	Average 24-hr. output of phenylpyruvic acid prior to tyrosine feeding (gm.).	Weekly readings obtained during the period of tyrosine-feeding using the method of Penrose and Quastel for the estimation of phenylpyruvic acid (gm.).														
		1st	2nd	3rd	4th	5th	6th	7th	8th	9th	10th	11th	12th	13th	14th	15th	16th
*John R—	0·5	0·8	0·8	1·0	1·4	1·2	1·0	1·0	1·0	1·6	1·3	1·0	1·1	1·0	0·9	1·0	1·0
Arthur P—	1·1	1·2	1·0	1·2	1·5	1·3	1·1	1·0	1·4	1·0	1·2	1·2	0·9	1·0	1·1	1·2	1·0
*Lilian B—	1·0	4·3	4·8	4·9	5·2	3·8	2·7	2·4	3·4	3·3	4·7	4·0	3·8	3·5	3·8	4·0	3·5
Joan S—	2·2	1·8	2·0	1·9	1·2	2·2	1·9	1·6	2·4	2·2	2·0	2·0	2·4	2·2	1·9	2·0	2·3
*Brian C—	2·5	3·3	3·5	4·0	4·2	3·7	3·0	3·2	3·8	3·6	4·4	3·6	3·6	3·2	3·4	3·4	3·8
Alan J—	2·9	2·8	2·5	2·9	2·4	2·4	2·6	2·5	2·7	2·9	3·0	2·8	2·5	2·8	2·9	2·7	2·4

* Tyrosine-fed patients.

The increased readings obtained in the cases of the patients being fed with tyrosine was due to the excretion of parahydroxyphenylpyruvic acid, this compound giving very similar chemical reactions, including the reaction with 2:4 dinitrophenylhydrazine, as does phenylpyruvic acid itself.

The mechanism of oxidation of tyrosine to parahydroxyphenylpyruvic acid occurs in the non-phenylketonuric individual. This was well illustrated by the feeding of 20 gm. of l-tyrosine daily to a non-phenylketonuric patient over a period of ten days. At the end of this time his urine gave an intense colour reaction with 5 per cent. ferric chloride solution. This was instantaneous on addition of the ferric chloride to the urine, and produced a very deep blue-green coloration which faded rapidly. The reaction differed slightly from the reaction between ferric chloride and phenylpyruvic acid ; in the case of phenylpyruvic acid the colour takes several seconds to develop, is less blue, and takes about half an hour to fade. The urine gave a reaction with 2:4 dinitrophenylhydrazine similar to that produced by phenylpyruvic acid. The urine gave a positive Millon reaction and a positive Briggs reaction. These two reactions are given by parahydroxyphenylpyruvic acid, but not with phenylpyruvic acid.

The present writer, who is non-phenylketonuric, took 20 gm. of l-tyrosine by mouth daily for three days. This did not lead to the urinary excretion of any substance giving reactions with $FeCl_3$ or 2:4 dinitrophenylhydrazine. It seems that a latent period of several days occurs before parahydroxyphenylpyruvic acid appears in the urine.

The finding that both phenylketonuric and non-phenylketonuric individuals metabolize tyrosine in the same way, by oxidation to parahydroxyphenylpyruvic acid, is in accordance with the conception that the block in metabolism occurs in phenylpyruvic oligophrenia at the stage of conversion of phenylalanine to tyrosine, and that the metabolism of tyrosine can proceed unimpaired.

During the period of the tyrosine feeding experiment it was observed that the two idiot patients receiving tyrosine, Lilian B— and Brian C—, became more active and hyperkinetic, and appeared to take more notice of their surroundings than formerly. This was not observed in the control patients, nor in the case of the dull-and-backward patient, John B—, who received tyrosine.

Eight weeks after the experiment was started, psychological testing was carried out on the patients concerned. In every case except one the mental level remained unchanged. In the case of one patient, however, Alan J—, who was not receiving tyrosine, there was reported to be " a slight increase on the previous assessment of his developmental level as estimated on the Vineland Social Maturity Scale."

At the end of the period of the experiment, 16 weeks after it was started, the following findings were made :

On examination of the three tyrosine-fed patients and their controls, no change in physical signs was observed. The head measurements were the same as those obtained prior to the experiment. The heights and weights of the 6 patients at the beginning and end of the experiment are given in Table VIII. The youngest patient of the 6, John R—, who received tyrosine, gained the most weight during the period of the experiment. Weight was lost by only one of the 6 patients, Lilian B—, who also received tyrosine. Two tyrosine-fed patients, Brian C— and John R—, and one control patient, Arthur P—, showed small increases in height. Growth, as assessed by measurements of height and weight, appeared to be independent of the feeding of tyrosine.

TABLE VIII.

Name.	Age at beginning of tyrosine feeding experiment.		Weight at beginning of tyrosine feeding experiment.		Weight at end of tyrosine feeding experiment.		Height at beginning of tyrosine feeding experiment.		Height at end of tyrosine feeding experiment.	
	yrs.	mths.	st.	lb.	st.	lb.	ft.	in.	ft.	in.
*Lilian B—	18	8	4	2	3	13¾	4	3½	4	3½
Joan S—	21	9	7	4	7	5½	4	8½	4	8½
*Brian C—	9	0	3	13	3	13½	4	1	4	1½
Alan J—	9	10	3	5	3	7¼	3	11	3	11
*John R—	7	9	3	12	4	1	4	1¼	4	2
Arthur P—	12	4	5	1½	5	2	4	7½	4	8

* Tyrosine-fed patients.

Electroencephalography was repeated on the patients at the end of the experiment. According to the records obtained it appeared that the feeding of tyrosine had not promoted cerebral maturation. There was evidence that some maturation had occurred in one of the control patients. The only new positive finding in the tyrosine-fed patients was seen in the case of the dull-and-backward patient, John R—, where epileptoid features, not previously found, were observed. It cannot, however, be assumed that these features were previously absent and were induced by the feeding of tyrosine. It is more likely that they were in a latent phase during the recording of the previous electroencephalogram, but it is not impossible that they were brought into evidence by an activating effect of the tyrosine.

At the end of the experimental period psychometry was repeated, using the same battery of tests as previously, except, to obviate the learning factor, in the case of the Stanford-Binet/Terman-Merrill Revision used for the two higher-grade patients, where Form L was substituted for Form M, which was previously used. The tests used included the Vineland Social Maturity Scale for the idiot patients ; Stanford-Binet, Porteus Mazes, Goodenough " drawing-of-a-man " test ; and Raven's Matrices for the higher-grade patients. In no case was there any significant change recorded since the previous assessment at the beginning and middle of the experiment.

Prior to the performance of this experiment tyrosine had only been fed to phenylketonuric patients over short periods and in small quantities (Jervis,

1937*b*; Penrose and Quastel, 1937). This experiment has served to show that no apparent therapeutic effect is produced in patients suffering from phenylpyruvic oligophrenia when tyrosine is fed in larger quantities and over a period of four months. It appears that after the human organism has developed for years in the "internal environment" of phenylpyruvic oligophrenia, no amelioration of the mental condition or physical signs can be brought about by the administration of tyrosine. Hope lies, however, in the case of the newborn phenylketonuric child. The youngest patient of the present series fed with tyrosine was already seven years and nine months old at the beginning of the experiment. Phenylpyruvic acid is not sought in the urine of infants as a routine measure; the discovery of phenylpyruvic oligophrenia is made, and then but occasionally, when the child has reached an age at which signs of mental defect show themselves. By this time the damage is done. The writer feels that every effort should be made towards an early diagnosis of the condition by a simple chemical test, so that possible therapeutic methods may have every chance of fair trial.

Summary

Fifteen cases of phenylpyruvic oligophrenia were discovered at the Fountain Hospital, London. Examination of family histories led to the discovery of two more phenylketonuric patients in other institutions, not previously diagnosed as suffering from phenylpyruvic oligophrenia. On physical examination of the patients, observations of certain characteristics were made which had not before been described in the literature dealing with phenylpyruvic oligophrenia. The family histories were studied with reference to the mode of inheritance of the condition, and the search for a genetic linkage between the human serological types, previously limited to a study of the ABO and MN, groups, was extended to include investigation into the Lewis, Kell, Lutheran, S, P, Duffy and Rhesus groupings. The possible role of the thyroid in phenylpyruvic oligophrenia was discussed, and in this connection investigations into the basal metabolic rate and the blood chemistry of the patients were made. The blood chemistry findings also threw light on the problem as to whether the increased muscle tone of the patients was due to a low serum calcium level. The dilution of hair colour was measured by an objective method of evaluation. The possible role of the liver in phenylpyruvic oligophrenia was considered, both the structure and function of this organ being studied. Quantitative estimations of the output of phenylpyruvic acid were carried out, with a view to discovering whether there was any correlation between the amount of phenylpyruvic acid excreted and the severity of the mental defect. Electroencephalography of the patients and their relatives was carried out, with a purpose of finding whether abnormalities existed in the brain potentials of heterozygotes for phenylpyruvic oligophrenia; to find, if possible by this method, the site of maximal disturbance in the brains of the patients; and to establish whether any relationship existed between the mental level and abnormality of electroencephalogram. Electroencephalography was also used, together with psychological testing, quantitative analysis of the urine, and observations and measurements concerned with the physical state of the patients, to provide base-lines

for an experiment in tyrosine-feeding. The results obtained within the limits of this experiment were negative, but it is hoped that tyrosine-feeding will in the future be tried in the case of newly-born phenylketonuric infants.

Phenylpyruvic oligophrenia stands alone as being a condition in which a specific metabolic error is accompanied by mental defect. It is a clear-cut biological entity in itself, but at the same time is a complex study which is approached through the avenues of psychological and clinical medicine, biochemistry and genetics. The ultimate problem it presents is the nature of the relationship between the metabolic disturbance and the mental state.

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