PHENYLKETONURIA

A REVIEW AND A REPORT OF THE PATHOLOGICAL FINDINGS IN FOUR CASES

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PHENYLKETONURIA is an inborn error of metabolism characterized by excretion of phenylpyruvic acid in the urine and usually by severe mental defect and certain bodily features of which dilution of pigment is the most noticeable.

Følling first described the disorder in 1934 and since then the primary metabolic abnormality has been identified as an inability to oxidize phenylalanine to tyrosine (Jervis, 1947) due to the liver enzyme, which normally catalyses this reaction, being inactive (Jervis, 1953; Wallace, Moldave and Meister, 1957; Mitoma, Auld and Udenfriend, 1957). Although a precise correlation between the clinical, biochemical and neuropathological aspects of the condition is not yet possible, we felt it worth while to review the present position in an attempt to define the gaps in knowledge which continue to hinder such a correlation.

PATHOGENESIS

Estimations of the incidence of phenylketonuria vary, but probably about 0·6 per cent. of the institutionalized defectives and 4 per 100,000 of the general population are phenylketonuric (Jervis, 1937, 1954; Munro, 1947). However, the condition may be rare in certain races, and only isolated cases have been reported in Jews (Cohen and Kozinn, 1949) and Negroes (Ferriera-Fernandes, 1950).

Analysis of data in large series of patients has indicated that the condition is caused by the action of a single autosomal recessive gene (Jervis, 1938; Følling, Mohr and Ruud, 1944; Munro, 1947). Phenylketonuria occurs only in persons who are homozygous for this condition when the disorder invariably develops. The heterozygote is clinically normal and phenylpyruvic acid is not excreted in the urine. However, the presence of the single abnormal gene usually results in some defect of the enzyme activity, the heterozygotes showing a diminished capacity to metabolize large doses of phenylalanine. Thus, a phenylalanine tolerance test in these individuals tends to exhibit abnormally high and persistent blood levels of the amino-acid, presumably caused by a decreased phenylalanine hydroxylase activity (Hsia, Driscoll, Troll and Knox, 1956; Hsia, Paine and Driscoll, 1957; Hsia, 1958).

The primary abnormality in phenylketonuria is an inability to hydroxylate phenylalanine to tyrosine. Normally there are three components involved in this enzyme system, a non-protein co-factor, a stable fraction widely dispersed

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throughout the body and an unstable fraction found only in the liver. It is this latter fraction which is lacking in phenylketonuria (Wallace, Moldave and Meister, 1957; Mitoma, Auld and Udenfriend, 1957; Kaufman, 1958).

As a result of this primary defect abnormalities occur which may be immediate or remote. As an immediate consequence of the block in hydroxylation, the concentration of phenylalanine in the blood plasma rises from normal levels of about 0·5–1·5 mg./100 ml. to values ranging from 20–60 mg./100 ml. and a similar rise occurs also in the C.S.F. (Jervis, Block, Bolling and Kanze, 1940; Borek, Brecher, Jervis and Waelsch, 1950; Knox and Hsia, 1957). Phenylalanine appears also in the urine together with phenylpyruvic acid, phenyllactic acid and the conjugate of phenylacetic acid, phenylacetylglutamine. Typical urinary excretion values for these substances are, in mg./100 ml.: phenylalanine 38, phenylpyruvic acid 50, phenyllactic acid 51 and phenylacetylglutamine 53 (Woolf, 1951). p-Hydroxyphenyllactic acid and p-hydroxyphenylacetic acid (Boscott and Bickel, 1953) are probably formed from the parent compound by non-specific hydroxylation (Dalgliesh, 1954). o-Hydroxyphenylacetic acid is also found in the urine (Armstrong, Shaw and Robinson, 1955; Boscott and Kirman, 1955). It is thought that the block of the normal hydroxylation in the para position allows the subsidiary process of o-hydroxylation to occur (Armstrong and Shaw, 1955), though it has been suggested that phenylpyruvic acid is the precursor (Tashian, 1959).

However, it is doubtful whether any of these substances are the immediate cause of the mental defect. Certainly there is no correlation between the concentrations of phenylalanine or its metabolites and the degree of mental deficiency (Borek, Brecher, Jervis and Waelsch, 1950; Jervis, 1950, 1952; Armstrong, Shaw and Robinson, 1955); the phenylalanine content of protein, as judged by its estimation in haemoglobin, is normal (Allen and Schroeder, 1957) and there is no good evidence that the abnormal metabolites of phenylalanine found in phenylketonuria are themselves toxic to the brain in the amounts occurring *in vivo*. One group of workers suggests that o-tyramine, which might be formed via o-tyrosine, could be toxic and cause mental defect (Mitoma, Posner, Bogdanski and Udenfriend, 1957). If this were so, a monoamine oxidase inhibitor, such as iproniazid, might be expected to cause a deterioration in phenylketonurics, by retarding the inactivation of o-tyramine. However, a 6-months controlled trial of iproniazid in 8 phenylketonurics, in which the drug was given to counteract the deficiency of adrenaline, noradrenaline or 5HT, revealed no evidence of deterioration either clinically, electroencephalographically or by intelligence testing (Kirman, Pare, Sandler and Stacey, 1959).

Secondly, there are the remote consequences of the block in phenylalanine metabolism. A theoretical deficiency of tyrosine will not account for the mental deficiency. The body does not rely on the formation of tyrosine from phenylalanine as tyrosine is a normal component of the diet. In fact the blood levels of tyrosine are fairly normal, as judged by the results of the phenylalanine-tyrosine ratio when compared with the simple phenylalanine tolerance test (Hsia, Driscoll, Troll and Knox, 1956; Hsia, Paine and Driscoll, 1957; Hsia, 1958). However, the excessive concentrations of phenylalanine in the blood may have an inhibitory effect on tyrosinase, the enzyme which metabolizes tyrosine, and so it is possible that there is a deficiency of substances along this pathway, stemming from such an inhibition (Fig. 1) (Dancis and Balis, 1955; Bickis, Kennedy and Quastel, 1957; Miyamoto and Fitzpatrick, 1957). Cowie (1951a) was the first to try the effect of feeding tyrosine and others have repeated

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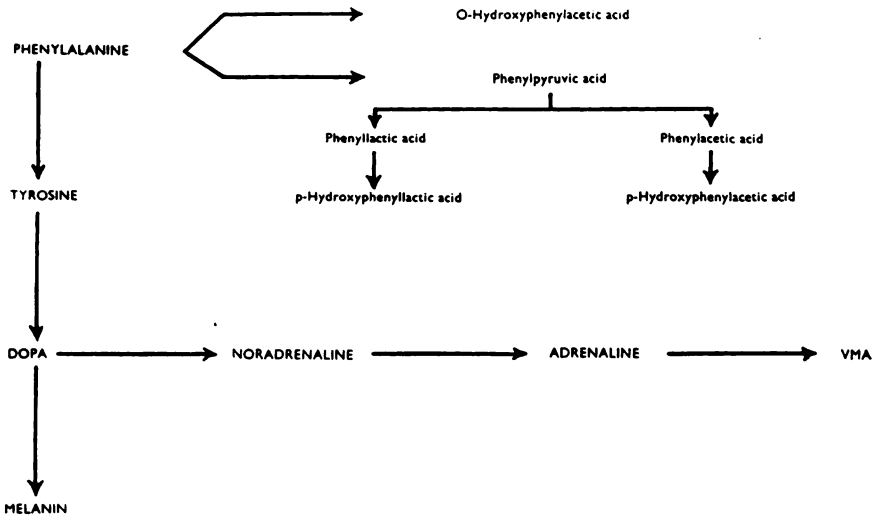


FIG. 1.—The normal pathway of phenylalanine metabolism and some of the abnormal metabolites of the amino-acid, found in the urine in phenylketonuria.

the experiment (Snyderman, Norton and Holt, 1955). The hair may become darker and so presumably the additional tyrosine increases melanin formation, but it has no effect on intelligence. The hair darkening which occurs with a phenylalanine-restricted diet may be due to lessening of the inhibition of tyrosinase consequent on the reduction of phenylalanine in the blood (see below).

It is likely that there is a deficiency of adrenaline and noradrenaline formation in phenylketonuria. Weil-Malherbe (1955) has demonstrated a deficiency of a substance with the biochemical characteristics of adrenaline in blood platelets from phenylketonurics; Cawte (1954, 1957) has found an abnormal sensitivity of the blood pressure response to injections of adrenaline and Armstrong (1958) a decreased output of 3-methoxy-4-hydroxy-mandelic acid (VMA), one of the main end-products of adrenaline and noradrenaline metabolism (Armstrong, McMillan and Shaw, 1957) in a small number of affected children he investigated. These abnormalities can again be traced back to the specific defect of phenylalanine hydroxylation, because the abnormal metabolites of phenylalanine have been shown, *in vitro*, to inhibit the enzyme responsible for decarboxylating 3,4-dihydroxy-phenylalanine (DOPA), (Fellman, 1956), which is the precursor of noradrenaline and adrenaline (Fig. 1). As catechol amines probably play an essential part in normal brain functioning, this may well be of importance in relation to the mental deficiency.

The demonstration by Armstrong and Robinson (1954) of indolelactic acid in the urine, suggested an abnormality of tryptophan metabolism in phenylketonuria. Following this lead, Pare, Sandler and Stacey (1957) showed that phenylketonurics had a deficiency of 5-hydroxytryptamine (5HT) in the blood and a similar deficiency of 5-hydroxyindoleacetic acid (5HIAA) which is the end product of 5HT metabolism, in the urine, when compared with normal controls and with mental defectives of the same age and in the same hospital. This finding has now been repeated in a larger series (Pare, Sandler and Stacey, 1959) and the low output of 5HIAA confirmed by independent workers (Berendes, Anderson, Ziegler and Ruttenberg, 1958; Baldridge,

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Borofsky, Baird, Reichle and Bullock, 1959). Such a deficiency of 5-hydroxyindoles might be due to a defect in hydroxylation of tryptophan, similar to that of phenylalanine (Pare, Sandler and Stacey, 1957). However, an alternative explanation may rest in an inhibition of 5-hydroxytryptophan (5HTP) decarboxylase, the enzyme responsible for the production of 5HT from its precursor 5HTP (Fig. 2). Thus Davison and Sandler (1958) have shown that

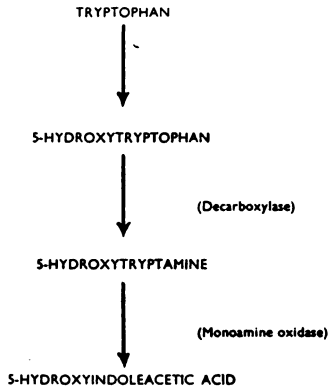


FIG. 2.—Illustrating the production of 5-hydroxytryptamine by the decarboxylation of 5-hydroxytryptophan, and its inactivation by monoamine oxidase and ultimate excretion in the urine as 5-hydroxyindoleacetic acid.

phenylpyruvic acid, phenylacetic acid and phenyllactic acid inhibit 5HTP decarboxylase *in vitro* and phenylacetic acid, at least, has a similar action *in vivo* (Davison, Ruthven and Sandler, 1959; Sandler and Close, 1959; Sandler, Davies and Rimington, 1959). Such a decreased 5HTP decarboxylase activity has been demonstrated in phenylketonuria by Pare, Sandler and Stacey (1958). They also showed that the 5-hydroxyindole deficiency could be corrected by reducing the concentrations of aromatic metabolites of phenylalanine by a phenylalanine-restricted diet (Pare, Sandler and Stacey, 1958; Baldridge, Borofsky, Baird, Reichle and Bullock, 1959). Since 5HT is thought to be of importance in normal brain functioning, this deficiency may also be a factor in relation to the mental defect. That it is not the only factor, however, is suggested both by the absence of a correlation between intelligence and 5-hydroxyindole values in blood or urine (Pare, Sandler and Stacey, 1959) and by the lack of any improvement in I.Q. following treatment designed to increase brain concentrations of 5HT (Kirman, Pare, Sandler and Stacey, 1958).

Finally there is the possibility that phenylalanine metabolites inhibit the formation of γ-aminobutyric acid (Hanson, 1958) which is again thought to be important in normal brain functioning (Elliott, 1959; Tower, 1959). Other biologically active amines, as yet little investigated, may also be involved.

To summarize, it seems likely that the mental defect in phenylketonuria is caused by the indirect action of aromatic metabolites of phenylalanine, acting on various enzyme systems and resulting in a deficiency of certain substances essential to normal brain functioning (Pare, Sandler and Stacey, 1959). Such inhibitory mechanisms acting on tyrosinase, DOPA decarboxylase, 5HTP decarboxylase and possibly glutamic acid decarboxylase, have been described.

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Clinical

It is probable that the maternal liver protects the foetus adequately during intra-uterine life and that the phenylketonuric child is normal at birth. The plasma phenylalanine increases in concentration during the first few weeks of life but phenylpyruvic acid may not appear in the urine until after the fifth week (Armstrong and Binkley, 1956). Woolf and his associates conclude that the child is mentally normal at birth, deterioration ensuing rapidly over the first few weeks or months of life (Woolf, Griffiths, Moncrieff, Coates and Dillistone, 1958). The evidence for this view is necessarily tenuous, relying as it does on the assessment of the motor reactions of the new-born child and comparing it with the wider interests and abilities attained as the child gets older. However, further evidence as to the occurrence of intellectual deterioration and possibly irreversible brain damage, can be drawn from the results obtained with a phenylalanine-restricted diet when treatment is started in the first few months of life (Woolf, Griffiths, Moncrieff, Coates and Dillistone, 1958) (see below). It is certain that after 2–3 years, most untreated phenylketonurics are of idiot level and remain at a nearly stationary mental age (Paine, 1957), while some authorities believe that further deterioration may continue over a long period.

There is a wide variation in attainment of normal childhood milestones but, on average, phenylketonurics will sit at 12–15 months and walk at 2½ years (Paine, 1957). About half the cases never learn to talk (Knox and Hsia, 1957). However, about one per cent. of cases have an I.Q. above 70 (Table I) and occasional cases have been reported with normal or near-normal intelligence (Cowie, 1951b; Cowie and Brandon, 1958; Low, Armstrong and Carlisle, 1956; Coates, Norman and Woolf, 1957; Hsia, Knox and Paine, 1957). Such cases have been reviewed by Hsia, Knox and Paine (1957), who have shown that the I.Q. cannot be accounted for by such possibilities as partial chemical blockage, mild variants of the gene or the patient being a heterozygote. Thus the reason for the wide variation in intelligence remains unexplained.

Table I

Distribution of I.Q. in 330 Phenylketonurics (Jervis, 1954)

I.Q.	Below 10	11–20	21–30	31–40	41–50	51–60	61–70	Above 70
Number ..	122	88	41	34	31	7	4	3
Per cent. ..	37	26	12	10	9	2	1	0·9

The general physical development is relatively unimpaired and phenylketonurics stand out among other children of comparable mental level by their lack of gross physical defects. However, a general dwarfing and a slightly reduced head circumference are not uncommon, especially in the most defective children, and epicanthic folds, widely spaced incisor teeth, pes planus and partial syndactyly of the toes may also occur (Jervis, 1937; Penrose, 1946; Cowie, 1951a; Paine, 1957). Phenylketonurics tend to have fairer hair than their normal siblings (Cowie and Penrose, 1951) and lighter coloured eyes (Berg and Stern, 1958). The skin is usually soft, smooth and fine in texture and between 20–30 per cent. patients show a tendency to dermatitis (Cowie, 1951a and b; Knox and Hsia, 1957; Paine, 1957). This may range from severe eczemoid lesions to mild eruptions, or only a dry, rough or scaly skin. The lesions occur especially on wet or exposed parts of the body and may be simply

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the result of an increased sensitivity of the skin to the trauma habitually sustained by a defective child (Knox and Hsia, 1957). It is noteworthy that phenylketonurics tan in response to sun or ultraviolet lights and histochemical studies of excised irradiated skin have shown that the pigment activity of the melanocytes is normal (Hassel and Brunsting, 1959).

Neurological examination reveals no abnormality in phenylketonurics with higher levels of intelligence, but, as the mental defect becomes more pronounced, features suggestive of "extrapyramidal" abnormality become apparent. Jervis (1937) claims that about two-thirds of the most severely defective cases have neurological signs. These include a stooped posture, muscular hypertonicity with hyperactive reflexes, tremor of the outstretched hands or digital mannerisms such as flicking, twiddling or pill-rolling movements (Cowie, 1951a; Hilliard and Kirman, 1957; Paine, 1957), though these signs are quite unspecific. Spasticity or pyramidal signs are uncommon, though Cowie (1951a) reported 3 patients with extensor plantar responses. Epilepsy is a common feature in phenylketonuria, occurring in 25 per cent. of 418 patients in whom this symptom was looked for (Jervis, 1954). As with other neurological abnormalities, epilepsy is commoner in the more severely defective cases. Thus, in one series, 26 out of 78 (33 per cent.) patients with an I.Q. of less than 25 had a history of fits, compared with only 2 out of 28 (7 per cent.) patients with an I.Q. of over 25 (Paine, 1957). The seizures usually start before the age of 2 years and may cease spontaneously in later childhood. They are usually infrequent, but are often difficult to control by ordinary anticonvulsant drugs (Wright and Tarjan, 1957).

Electroencephalography reveals an abnormality in the majority of cases whether or not the patient has overt epilepsy. The commonest is a non-specific generalized epileptic activity (Gibbs and Gibbs, 1941; Pond, 1959), but hypsarrhythmia, spike and wave formation and non-specific low-voltage activity are not uncommon (Paine, 1957; Low, Bosma and Armstrong, 1957).

Cerebral arteriovenous oxygen studies suggest that cerebral metabolism is reduced in phenylketonurics (Himwich and Fazekas, 1940, 1944).

Diagnosis is made by adding a 5 per cent. solution of ferric chloride, preferably acidified, to urine. When 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 reaction is positive in all phenylketonurics after about the fifth week in life unless on a reduced phenylalanine diet. The diagnosis can be confirmed by chromatographic examination of the urine.

Treatment

Obviously the most rational therapy is to reduce the concentrations of the phenylalanine metabolites which directly, or more probably indirectly, are thought to cause the mental defect. All dietary proteins are about equally rich in phenylalanine and a suitable diet can therefore be devised only by supplying the bulk of the nitrogen as a mixture of amino-acids, the cost of which would be prohibitive. However, protein hydrolysates can be freed from phenylalanine, tyrosine and tryptophan by passing through a column of charcoal. A casein acid hydrolysate, made phenylalanine-free in this way and with tyrosine and tryptophan, minerals and vitamins added, was suggested by Woolf as a suitable dietary treatment for phenylketonuria. Such a diet was first fed to a phenylketonuric by Bickel, Gerrard and Hickmans (1953) who reported marked

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improvement in the child's mental condition. Since then numerous reports on the efficacy of this regime have appeared (Woolf, Griffiths and Moncrieff, 1954; Woolf, Griffiths and Moncrieff, 1955; Woolf, Griffiths, Moncrieff, Coates and Dillistone, 1958; Armstrong and Tyler, 1955; Blainey and Gulliford, 1956; Horner and Streamer, 1956; Hsia, Knox, Quinn and Paine, 1958; Brimblecombe, Stoneman and Maliphant, 1959). The biochemical abnormalities characteristic of phenylketonuria disappear within a few weeks depending on the degree of phenylalanine restriction (Woolf, Griffiths and Moncrieff, 1955; Pare, Sandler and Stacey, 1958). The clinical signs likewise improve in the first few months. Skin lesions clear up and in most patients new-grown hair is darker (Armstrong and Tyler, 1955; Woolf, Griffiths and Moncrieff, 1955). Perhaps the most convincing evidence of improvement is the decrease in number or the complete cessation of epileptic fits and the disappearance of abnormal patterns in the electroencephalogram, relapse occurring as soon as the diet is withdrawn (Bickel, Gerrard and Hickmans, 1953; Armstrong and Tyler, 1955; Woolf, Griffiths and Moncrieff, 1955; Woolf, Griffiths, Moncrieff, Coates and Dillistone, 1958; Horner and Streamer, 1956; Low, Bosma and Armstrong, 1957).

Taken as a whole the reports strongly suggest that the diet benefits the mental defect in phenylketonuria. In a child of idiot level, this benefit rarely amounts to more than an alleviation of a still severe mental defect and any improvement occurs slowly over a period of months or years, in contrast to the rapid disappearance of other signs. However, Woolf and his associates believe that, by starting the diet sufficiently early in life, severe mental deficiency can be prevented and a relatively high I.Q. maintained (Woolf, Griffiths, Moncrieff, Coates and Dillistone, 1958). These authors maintain that improvement can only be expected in children under the age of 2 years, though treatment is worth while up to the age of 4 years in brighter children with an I.Q. of 40 or over. They suggest that after a certain period, irreversible brain damage occurs. Taking into account the fact that only one per cent. of untreated phenylketonurics have an I.Q. over 70, their results in patients treated early in life are suggestive. These results, compared with those when treatment was started later, add substance to the suggestion of the development of irreversible brain damage.

If this is so, early treatment is essential. When phenylketonuria is suspected at birth, because of a family history, the urine should be tested at weekly intervals for the first two months of life, after which time, if the ferric chloride test is negative, the parents can be reassured that the child is not phenylketonuric. A simplified, yet reliable, test has recently been developed whereby a strip of reagent-impregnated paper, folded in a wet nappy, gives an immediate colour reaction if phenylpyruvic acid is present ("Phenistix", Ames, Co.). It has been suggested that these might be used to screen all babies at three weeks of age (Woolf, Griffiths, Moncrieff, Coates and Dillistone, 1958). However, since only about 4 per 100,000 babies are phenylketonuric, the expense in both time and money would be considerable. Certainly all babies who are slow to develop should be so tested.

The practical difficulties of treatment with a phenylalanine-restricted diet are substantial. For the treatment to succeed, the blood levels of phenylalanine must be kept within normal limits. Lack of phenylalanine results in the child failing to grow (Berry, Sutherland, Guest and Umbarger, 1958; Hsia, Knox, Quinn and Paine, 1958; Woolf, Griffiths, Moncrieff, Coates and Dillistone, 1958), excess, in failure of mental development. The parents must be fully

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co-operative and the treatment controlled by serial assessments of phenylalanine in the blood. This is important, as phenylpyruvic acid does not appear in the urine until the concentration of phenylalanine in the blood exceeds 15 mg./100 ml. (Armstrong and Tyler, 1955). Occasionally the introduction of a phenylalanine-restricted diet results in the child going into status epilepticus; a similar state of affairs may occur if, for any reason, the diet has to be stopped.

Where treatment with a phenylalanine-restricted diet is not possible, an attempt may be made to increase the brain concentrations of such amines as 5-hydroxytryptamine and noradrenaline, the formation of which is thought to be inhibited in phenylketonuria (see above). Kirman and his associates suggest that this could be achieved by treating affected children with iproniazid (Pare *et al.*, 1959). This substance inhibits monoamine oxidase, the enzyme responsible for much of the further metabolism of monoamines (Fig. 2) (Blaschko, 1954), and it has been shown, in animals, to increase the brain concentrations of both catechol amines and 5-hydroxytryptamine (Spector, Prockop, Shore and Brodie, 1958).

PATHOLOGY

We were able to trace neuropathological reports of only 20 phenylketonuric cases (Table II) and some of these are exceedingly brief. The brain was stated to be normal in only 3 cases (Cases 2, 3 and 4), but it is possible that other workers, feeling uncertain of the findings, have refrained from publishing their case material. Observations based on unpublished material and lacking enough detail for inclusion in Table II (Jervis, 1954; Norman, 1958) will be mentioned below.

Reduction in the weight of the brain is the commonest and most certain of the recorded anomalies. Taking as normal the brain weights presented by Copoletta and Wolbach (1933), those in Table II are under 90 per cent. in 8, and over 90 per cent. in 2, instances. The weight is not stated in 8 cases and the age not given in 2. Moreover, one of the 2 brains weighing over 90 per cent. of the average (Case 14) is stated by the author to have been "heavy" on account of accumulation of fluid, since its "substance, particularly the white matter, was strikingly underdeveloped", while four of the brains of unstated weight (Cases 6, 7, 8 and 9) were reported to have weighed about two-thirds of the normal. It is also noteworthy that none of the brains exceeded the average weight for the age, and although available information is not sufficiently precise for statistical treatment, there is no doubt that the brains of phenylketonuric patients are mostly small, and this is in keeping with the early observations of Jervis (1937), who found slight microcephaly in 14 of his 18 patients subjected to anthropological measurement. Encephalograms were made in 11 of his cases and several of these presented moderate ventricular dilatation and diffuse increase of subarachnoid air.

The second common anomaly is pallor of myelin staining, present in 7, and absent in 10, of the cases. Of the 3 remaining ones, one (Case 19) is not fully described, one (Case 9) showed absence of myelinated nerve fibres only in the centre of the optic chiasma, the seat of a singular "honeycomb" degeneration, and another (Case 15) presented focal demyelination with fibrous gliosis, thought to be ictal in origin, in one of the occipital lobes. Most of the authors reporting defective myelination interpreted it as evidence of retardation rather than degeneration or atrophy of the myelin, speculating upon its relation to the known biochemical disturbance. It is not easy, however, to be certain

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TABLE II

Serial No.	Source	Original Case No.	Age and Sex	Main Clinical Features	Brain Weight Over Average Normal for Age	Main Somatic Findings at Autopsy	Main Neuropathological Findings	Comments
1	Penrose (1939)		9 years M	Epileptic idiot.	1,167 / 1,275	Genital infantilism. Broncho-pneumonia. Hydro-nephrosis. Caseous mesenteric gland.	Brain soft and oedematous with a simple pattern of convolutions. Several tense swellings, 0·5–1 cm., present on trunks of both vagi and smaller ones on most of their branches. Phrenic nerves also slightly affected. Similar nodules in region of pudendal and near coeliac plexus. Irregular focal hypertrophy of some nerves in the left arm and left sciatic nerve. Histologically, regarded as neurofibromatosis.	
2	Coquet, Myle, Nyssen and Bogaert (1944)		12 years F	Marked mental retardation. Multiple skin eruptions. Terminal pyrexia of obscure origin.		Pulmonary oedema. Fatty change in the liver. Phagocytosis of pigment in the spleen.	Findings thought to be negative. The only abnormality found was a small zone of necrosis in the frontal lobe and slight proliferation of the oligo- and macroglia in the centrum semiovale.	
3	Josephy (1948)	a.		Idiot.	1,200	Tuberculosis.	No abnormality found.	Very incomplete reports.
4	*Ibid.*	b.		Idiot.	1,200	Tuberculosis.	No abnormality found.	
5	Alvord, Stevenson, Vogel and Engle (1950)	1	16 months M	Epilepsy and low-grade mental retardation. Chronic eczema, many intermittent infections and anaemia. Terminal bronchopneumonia. One sister (Case 2 below) also phenylketonuria.	650 / 1,010	Oedema and ulceration of scalp. Bronchopneumonia.	Lack of myelin in optic nerves and tracts. Absence of myelin in cortico-spinal tracts. Pallor of myelin-staining in many parts of the occipital lobe, medial longitudinal bundle, brachium conjunctivum, medial lemniscus, commissure of the inferior colliculi and inferior quadrigeminal brachium, middle cerebellar peduncles and transverse pontine fibres. Cervical cord almost entirely devoid of myelin. Spinal nerve roots myelinated but pale, with better staining in sacral cord. Incomplete myelination of the 8th cranial nerve. Only traces of myelin in the cauda equina. Perivascular and pericellular oedema. Increase of fat around blood-vessels and in the white matter of the pre-central gyrus with astrocytic proliferation. Faint staining of neurones. Depletion of Purkinje cells.	Autopsy performed 53 hours after death and some of the appearances may possibly be due to autolysis.

Serial No.	Source	Original Case No.	Age and Sex	Main Clinical Features	Brain Weight Over Average Normal for Age	Main Somatic Findings at Autopsy	Main Neuropathological Findings	Comments
6	*Ibid.*	2	5½ years F	Chronic eczema, marked mental retardation, epilepsy. Measles followed by hyper-pyrexia and death. Sibling of Case 1, above		Bilateral interstitial pneumonia.	Brain and spinal cord developed normally. Pallor of myelin with astrocytic proliferation in the optic nerves. Loss of nerve cells and myelin in the paracentral lobule. A little fat around blood-vessels. Loss of Purkinje cells. Pallor of myelin in posterior and antero-lateral columns of the spinal cord and in the cauda equina.	
7	*Ibid.*	3	67 years			Carcinoma of the thyroid and lipomatosis of the skin.	Neuroglia preparations showed a definite increase in astrocytes. Increase of fat about blood vessels.	Previously seen by Dr. R. M. Stewart who reported paucity of nerve cells and glial excess in the cerebral cortex.
8	*Ibid.*	4	54 years				Normal myelin staining with gliosis of the cortex and optic chiasma. Increase of fat about blood-vessels.	
9	*Ibid.*	5	33 years M	Microcephalic idiot.			Normal myelin staining. Astrocytes and microglial proliferation in the cerebral cortex. Increase of fat about blood vessels. "Honeycomb" appearance of optic chiasma with gliosis and a marked loss of myelinated fibres in centre of the optic nerve.	Half of the brain, with cerebellum, weighed 470 g.
10	Larson (1950)	4	20 years F	Idiot.	1,110/1,191	Perforated peptic ulcer.	Cytoarchitectonic anomalies, particularly in area 6 with increased cellular density in fifth and sixth laminae. A few malformed and misplaced cells in the cerebral cortex.	Very brief and incomplete reports.
11	*Ibid.*	5	21 years F	Idiot.	1,000/1,350	Pulmonary and abdominal tuberculosis.	"Sparse and banal changes of type common in brains of idiots."	
12	Sander (1951) also Klein (1946)		20 years M	Epileptic fit at 1½ years. Microcephalic idiocy with hypogenitalism and dwarfing.	1,070/1,450	Miliary tuberculosis. Increased amount fibrous tissue in the middle and posterior lobes of the pituitary.	Slight hemiatrophy of the brain. "Hyalinization" and irregularity in the outlines of the lumina of blood-vessels with "état criblé" most marked in the lenticular, subthalamic and red nuclei, and in the substantia nigra. Some perivascular loss of cells. Reduction in the number of Purkinje cells and loss of fibres in the inferior olives.	

Table continued overleaf

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TABLE II—*continued*

Serial No.	Source	Original Case No.	Age and Sex	Main Clinical Features	Brain Weight Over Average Normal for Age	Main Somatic Findings at Autopsy	Main Neuropathological Findings	Comments
13	Benda (1952), also Mautner and Quinn (1949) (Case 20)	1	21 years F	Idiot with exaggerated knee jerks and undeveloped lobules of the ear	1,135 / 1,350	Fibrous tuberculosis. Degeneration of eosinophil cells in the anterior and absence of cells in the posterior pituitary. Arachnodactyly. Thick calvarium.	Marked degeneration with vacuolation of the central white matter of the brain. Perivascular fibrosis with some hyalinization of some blood vessels. Degeneration of white matter in external capsule, claustrum and the centre of the temporal lobe. Demyelination of the fronto-pontine fibres. Amyloid and myelin bodies present in the globus pallidus. Lack of myelin in the centrum and folia of the cerebellum. Degeneration of the reticular substance of the medulla and the granular layer of the cerebellum.	
14	*Ibid.* Case 22 of Mautner and Quinn (1949)	2	21 years M	Idiot with attacks of "nodding and shaking" and of momentary loss of consciousness. Two siblings probably had phenylketonuria.	1,360 / 1,450	Pulmonary tuberculosis. Chronic hepatitis.	Degeneration of white matter as in Case 1 above. The centrum semiovale is small and grey in the myelin preparations. The digital white matter is very thin. Demyelination of the cerebellum and fronto-pontine fibres. Paucity of cortical nerve cells. The spinal cord is small, narrow and under-developed. Amyloid metachromatic bodies in the white matter of the spinal cord.	The author observed that the "heavy" weight of the brain must have been due to accumulation of fluid, since the substance, particularly the white matter, was strikingly under-developed.
15	Corsellis (1953)	R.C.	25 years F	Epileptic idiot with slight spasticity of lower limbs and clumsiness and inco-ordination of voluntary movements. Absence of ear lobules. Obscure terminal pyrexial illness. Two siblings were also phenylketonuric.	1,175 / 1,350	Mild myocardial and hepatic degeneration. Skull cap unusually thick.	Retrograde degeneration or pellagra-like change in Betz cells and neurones of striatum, mamillary bodies, reticular substance, many pontine cells, nucleus ambiguous, dorsal nucleus of the vagus, cuneate nucleus, and a few anterior horn cells of the cervical and thoracic segments of the spinal cord. Marginal gliosis of the cerebral cortex. Walls of perforating blood-vessels prominent showing some hyalination. Patches of demyelination and heavy gliosis in right occipital lobe. Slight paucity of cells in the Sommer sector of the hippocampus. Small amount of pigment in the substantia nigra. Slight focal meningeal haemorrhage over cerebellum with subjacent necrosis.	

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Serial No.	Source	Original Case No.	Age and Sex	Main Clinical Features	Brain Weight Over Average Normal for Age	Main Somatic Findings at Autopsy	Main Neuropathological Findings	Comments
16	Leoni (1953)		20 years M	Mental retardation and paralysis following attack of meningo-encephalitis in early infancy. Flexion contractures of lower limbs. Craniofacial asymmetry.		Single kidney and adrenal. Hepatomegaly. Bronchopneumonia.	Small occipital lobes and abnormal shape of posterior horn of the lateral ventricles. Cytoarchitectonic anomaly of area 4. Some focal pallor of myelin staining and cellular loss in the cerebral cortex and corpus striatum.	
17	Bonfiglio (1954)	Case II	7 years M	Mental retardation with epilepsy commencing at 10 months, lasting a year, and not recurring since.	1,060 / 1,263	Adhesive pericarditis and pulmonary tuberculosis.	Thickening of the meninges. Atrophy and loss of nerve cells, particularly in the anterior portion of the brain, Betz cells being particularly affected. Astrocytic proliferation in the transitional zone between grey and white matter. Hypertrophy of some blood vessels. Increase of oligodendrocytes in the white matter. Myelin normal. Some loss of Purkinje cells.	
18	Scholz (1957)		23 months F	Severe mental deficiency with terminal epilepsy. Pulmonary tuberculosis.	825 / 1,064	Primary T.B. complex. Anaemic areas in kidneys and heart. Enlargement and fatty change of liver.	Anomaly of nuclear chromatin in nerve cells consisting of pallor of nucleolus and dispersion of dark particles of chromatin throughout nucleus. Peripheral chromatolysis. This change is found in about half of the cortical pyramidal cells, in most of the thalamic neurones, corpus striatum, and to a lesser extent in the Purkinje cells and vegetative centres. Retardation of myelination in the centrum semiovale, anterior commissure, internal capsule, pontocerebellar fibres, central zone of corticopontine fibres, the hila and periphery of the superior olives, lateral columns of the spinal cord and Helweg's tract. Fibrous gliosis of the cerebrum and cerebellum increasing caudad.	The author considers that the state of myelination is that of a normal 5-month old child.
19	Fellman (1958)		14 years				Hypopigmentation of the substantia nigra and locus caeruleus.	Full neuropathological report to follow.
20	Poser and Bogaert (1959)		18 years M	Mental defective with I.Q. = 30. Severe intractable epilepsy with frequent status epilepticus.		Lobular and aspiration pneumonia.	A few foci of necrosis, possibly ictal in origin. Areas of pallor of myelin-staining with fibrous gliosis in centrum semiovale, corpus callosum, periventricular white matter, cerebellar white matter, hilum of dentate nucleus and optic tracts. More severe lesions in arcuate fibres of the inferior olives, olivo-cerebellar and vestibular tracts and in the dorso-lateral portion of the medulla.	

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about pallor of myelin staining if it is slight and unaccompanied by evidence of myelin breakdown or other reactive change. It is true that some of the authors have also reported a certain amount of associated glial proliferation, but this again may be somewhat subjective. Among the comments not tabulated here Jervis (1954) mentions that he examined 5 cases for histological evidence of myelin change. In three, all adults, no demyelination was found; in the fourth, a boy aged 3, there was some paleness of myelin in the temporal region. The fifth presented a curious and probably fortuitous association with Schilder's disease which commenced at the age of 25. Pallor of myelin in the celloidin-embedded material of one of his cases was found by Norman but the myelin stained normally in frozen Kulschitzky-Pal sections.

Phenylketonuria seems to be rarely associated with frank neural or somatic malformation. Peripheral neurofibromatosis was present in Case 1, and a single kidney in Case 16, the latter case showing also smallness of occipital lobes with abnormal shape of the posterior horns of the lateral ventricles. The occurrence of micropolygyria in one of his unpublished cases is mentioned by Norman.

A pellagra-like retrograde neuronal change was reported in one instance (Case 15) and a neuronal nuclear anomaly in another (Case 18). Hypopigmentation of the substantia nigra and locus caeruleus was described in Case 19, but it is difficult to be sure of its significance without comparison with an adequate number of normal controls. It is noteworthy in this connection that the substantia nigra and locus caeruleus are normally pigmented in albinos (Foley and Baxter, 1958) and the pigment is probably not formed, as in the skin, by the tyrosine-tyrosinase system.

The apparent inconstancy of the morphological changes is in contrast to the persistent biochemical disturbance and this has been commented upon by some of the authors (Peters, 1958). Poser and Bogaert (1959) relate this to the wide difference in the level of intelligence known to occur in phenylpyruvic cases. However, it is difficult to accept this interpretation since few, if any, pathological reports of the higher-grade phenylketonuric patients have been published and all the cases listed in Table II appear to be of idiot or imbecile range of mentality.

It is somewhat strange that more attention has not been given in the past to the one constant and certain feature of phenylketonuria, viz., the tendency to microcephaly and micrencephaly.

As a basis for further discussion, we present below the clinical and pathological findings in 4 cases of phenylketonuria which have come to autopsy at the Fountain Hospital. Three were admitted for inclusion in a clinical trial with 5-hydroxytryptophan (Kirman, Pare, Sandler and Stacey, unpublished). The fourth (Case 1 below), had been studied earlier.

The histological methods employed were similar in all cases. After prolonged fixation in formol saline, representative blocks of all cerebral lobes, basal ganglia, optic nerves, brain-stem and spinal cord were embedded in celloidin and in paraffin. The celloidin sections were stained with cresyl violet, Heidenhain's haematoxylin and the Adams method for myelin (Adams, 1959), haematoxylin and Van Gieson, by the Holzer method for fibrous glia, and with phosphotungstic acid and haematoxylin. Paraffin sections were stained with haematoxylin and eosin and Van Gieson. Frozen sections were treated by the Herxheimer method for fat, the Holzer method, the del Río-Hortega's method for astrocytes, Penfield's modification of del Río-Hortega's method for microglia and the original as well as the Gros modification of Bielschowsky's

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method for neurofibrils. Blocks of somatic tissue were embedded in paraffin and treated by the customary histological techniques. All neural material was compared with tissue of normal controls of approximately the same age, treated in a similar way. Blocks of the brains were also sent to Dr. G. H. Sloane-Stanley for a chemical estimation of myelin by the galactose method. It is hoped to publish the results of this investigation later.

Case I. D.G.O.

Two maternal cousins of this boy were certified mental defectives but a very careful enquiry by Dr. Renwick elicited no proved cases of phenylketonuria in the family. There is no consanguinity in the family. The patient's one older brother has a cleft palate.

His father was 34 and mother 26 years old at the time of the patient's birth, which took place at full term after a normal pregnancy. Early infancy was uneventful, but by the 6th month he was noticed to be slow and lethargic, and this was at first attributed to fatness. On account of weight and helplessness he became increasingly a burden at home and was admitted to the Fountain Hospital at 4½ years. His weight then was 19 kg. with height—96·2 cm., and head circumference—51·8 cm. He was fair and blue-eyed. Other tests were non-contributory. There was a circumoral salivary rash and some roughening of the skin over the extremities. All tendon jerks appeared to be normal.

He was a large placid child who would seize objects and put them to his mouth without curiosity or manipulation. He could stand but not walk unaided, had no sphincter control and was unable to eat solid food. He could follow a rattle with his eyes and reach for it when left by himself, but showed little other spontaneous activity, sitting about all day, gurgling, and opening and closing his fists aimlessly. His developmental age on the Vineland Maturity Scale was 9 months, and he was considered to be of idiot level. The urine of this case was positive for phenylpyruvic acid in a single test done on the ward, which unfortunately was not repeated.

He died from broncho-pneumonia a month after admission.

Pathological Findings

The brain weighed 1,360 g. and showed no macroscopic abnormality. Histologically, no definite abnormality was seen in any part of the central nervous system.

Less certain changes included the following: slight diffuse deficiency in the number of cortical neurons was possibly present in many areas including the Sommer sector of the hippocampus. Some of the remaining cells showed shrinkage and many "ghost" forms were also present. Indistinctly demarcated areas of pallor in myelin staining of both celloidin embedded and frozen sections of the kind described in some of the previously reported cases of phenylketonuria were present in the centrum semiovale (Fig. 3). Similar appearances could be produced in the control material and the significance of the findings seems thus uncertain. The cerebellar white matter showed comparable pallor of myelin staining, and there was possible slight loss of Purkinje cells. Individual myelin sheaths and axis cylinders in the "pale" areas showed no abnormality of staining when viewed under high magnification. The long fibre tracts in the brain-stem and spinal cord also stained normally for myelin but showed considerable vacuolation of interstitial tissue (Fig. 4). No fibrous gliosis or glial hyperplasia was demonstrable anywhere by the Holzer and the silver impregnation methods.

A few of the cells in the substantia nigra showed early slight pigmentation, and this was more marked in the locus caeruleus. Comparison with control material showed no appreciable retardation in the degree of this pigmentation.

The only significant abnormality outside the nervous system was broncho-pneumonia, the lungs showing foci of alveolar consolidation and of lobular collapse. The following other organs were examined histologically: the heart, skeletal muscle, thyroid, kidney, small intestine, thymus, adrenals, pituitary

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and the testis. The liver showed a moderate amount of fatty change, more marked in the centre of the lobules. Other organs were normal.

Case II. J.P.

This boy was the third child of a mother aged 27 and father 28 at his birth. The 2 older siblings are normal. A younger sibling was expected in 1958 but no details about his state of health are as yet available.

The patient was a full-term baby, born at home and weighing 2·8 kg. Pregnancy was quite normal and, although the birth was said to be precipitate, there was no obvious evidence in the immediate neonatal period of damage having occurred to the child. Slowness of development became apparent at 9 months and phenylketonuria was diagnosed at 13 months. The paediatrician observed at that time that he was quiet and passive, making no response to examination. He did not reach for objects and took no interest in toys placed before him. He would not turn his head towards noises or lights; could not sit up or hold up his head consistently. Phenylalanine-free diet brought with it a somewhat doubtful improvement.

He was admitted at 19 months to the Fountain Hospital, for inclusion in a trial of 5-hydroxytryptophan (Kirman, Pare, Sandler and Stacey, unpublished).

The psychologist (Mrs. L. Mundy) assessed his mental age on the Griffith Mental Development Scale as 19 weeks with an I.Q. of 23. He appeared thus to be of low imbecile level, and showed little variation in the various developmental aspects, though that of speech was the lowest. Physically, he was a pale, delicate, fairly well-nourished baby. His head circumference measured 16¾ inches (41·8 cm.) (normal 48·8 with S.D. $\pm$1·1), so that he was well within the microcephalic range. The anterior fontanelle could not be palpated. He was unable to walk, stand or sit up, but could lift his head off the pillow, smiled occasionally and seemed pleased when given attention. He did not reach for objects but clenched a pencil when it was placed in his hand. His muscle tone was low, but no focal neurological signs could be elicited. The EEG report (Dr. D. A. Pond) reads: "One grain of 'seconal' produced a satisfactory sleep record. The barbiturate fast activity is not prominent but the slow rhythms are regular and symmetrical."

Estimations of serum 5-hydroxytryptamine and 5-hydroxyindoleacetic acid in early morning urine showed values of 190 ng./ml. (1 ng.$=10^{-9}$ g.) and 4·2 mg./g. creatinine respectively.

A few months after admission, the patient developed diarrhoea, from which he recovered. This recurred again when he was 2 years old in a more severe form and he died a week later.

Pathological Findings

The brain weighed 737 g., the average normal for this age being 1,064 g. It presented no external abnormality. The coronal blocks of the cerebrum showed possible slight diminution in the amount of white matter. Transverse sections through the subcerebral formations were macroscopically normal.

The unequivocal histological abnormalities in this case consisted of diffuse fibrous gliosis of the white matter of the centrum semiovale (Fig. 5), and a small focus of post-necrotic scarring in the cerebellum (Fig. 6).

The diffuse cerebral gliosis was easily seen on naked-eye examination of the histological preparations, presenting as a dense network of glial fibres on higher magnification (Fig. 7). This density was uniform centrally, showing some accentuation in the juxta-cortical areas. The cells concerned were mostly fibrillary astrocytes. The number of swollen-bodied cells or of microglia was not increased. There was also no discernible pallor of myelin in the appropriately stained sections, or evidence of past or continued myelin degeneration in the form of sudanophil debris or structural abnormality of myelin sheaths. A small number of fat-containing compound granular corpuscles was present, however, around a few of the blood vessels.

The areas of cerebellar scarring were situated superficially on two adjoining folia of the uvula and pyramid, the affected tissue showing atrophy of the molecular and Purkinje cell layers with astrocytic replacement.

The less certain findings were as follows: glial cells showed a slight increase in the molecular layer of the cerebral cortex, and there was a possible loss of neurons in layer III, particularly of the frontal lobes. Slight neuronal loss was also present in the Sommer sector of the hippocampus. Some gliosis with an

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excess of syncytial astrocytes was present around the ventricles, especially the fourth. There was excess of fibrous glia in the grey matter at all levels of the spinal cord.

Although histological evidence of past or present myelin degeneration was lacking in the gliosed centrum semiovale, naked-eye comparison of the section with normal controls suggested that the total amount of the white matter was somewhat deficient.

As in the controls, no pigmentation could be detected in the substantia nigra and locus caeruleus.

Other Organs. The lungs showed areas of bilateral basal collapse, more marked on the left side. Areas of collapse were also present in the right upper lobe. Veins draining the lower parts of both kidneys showed ante-mortem thrombosis and the tissue drained by them was greatly congested. The testes were in the inguinal canals. The pituitary weighed 0·17 g. and the thyroid 1·5 g.

The following organs were examined histologically: kidneys, small intestine, eyes, heart, spleen, liver, lung, pancreas, dural sinus, bone-marrow, adrenal, testes, thymus, thyroid and pituitary.

The *eyes* showed no detectable reduction of pigment in the retina, choroid or posterior layers of the iris. There was, however, lack of pigmented chromatophores in the iridial stroma. The *adrenals* presented a sharp contrast between the lipoid-rich zona glomerulosa and the rest of the cortex. The *kidneys* showed considerable congestion with recent ante-mortem thrombosis of some of the renal veins. In the *lungs* there was some suppurative bronchiolitis and early bronchopneumonia, together with widespread complete and incomplete pulmonary collapse. Other organs showed no noteworthy change.

Case III. B.N.

There is no family history of mental or neurological disease apart from fits during the childhood of one paternal uncle which did not recur in later life. The mother's first pregnancy resulted in a miscarriage. The oldest living child has cerebral palsy but not phenylketonuria; the next child is normal, and the patient was the third of the liveborn children. The father was 27 and mother 23 years old at the birth of the patient. After a normal pregnancy, the baby was born spontaneously by the vertex at the 37th week of gestation. His birth weight was 3 kg. and his condition during and after birth was considered normal.

His normal development was retarded; at 11 months he was still unable to sit up on his own. At 1 year he could hold up his head and at that time began having epileptiform fits. He was thought to be deaf. Phenylketonuria was diagnosed at 13 months. The head circumference at 15 months measured 43·9 cm., the average normal for the age being 48·8 cm. with S.D. $\pm$1·1. Thus he was grossly microcephalic. He had an iron deficiency anaemia with Hb of 75 per cent. (Haldane). He was having then many petit mal attacks, and the EEG report was as follows: "slow waves and occasional spikes were recorded from both hemispheres. The slow waves had a frequency of 3 per second. The abnormalities were diffuse, no one region being the predominant generator." His motor development quotient was 34.

The child was admitted at 15 months to the Fountain Hospital for trial with 5-hydroxytryptophan.

In the first month of his stay at this hospital, he had 5 petit mal attacks but none occurred later. His mental age was assessed at 15½ weeks, with an I.Q. of 20 on the Griffiths Mental Development Scale. No abnormality was seen on ophthalmological examination. The jaw-jerk was brisk and there was no facial weakness. A blink reflex was present to very loud noise, with no response to other sounds. The tongue showed occasional quivering and central bunching. The upper limbs were flaccid on passive movement with, however, marked briskness of tendon jerks; occasionally both arms were outstretched with the hands clenched and the arms exhibited a rapid "shivery" tremor. The abdominal reflexes were absent. The lower limbs were held in abduction at the hips and moderate flexion at the knees. They were immobile in comparison with the arms, and hypotonic. The tendon jerks were present and equal, and the plantar responses were flexor. The muscles seemed wasted beneath the fat. Placing and supporting reactions were absent in upper and lower limbs.

An EEG done a month after admission under chloral hydrate (Dr. D. A. Pond) showed symmetrical fast and slow activity and there were in addition low voltage spikes and spike

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and wave complexes seen independently on the right and left sides. The amplitude of all activity was much larger in the posterior than the frontal area.

At the same time, the child developed diarrhoea which lasted 3 weeks. No pathogens were isolated from several specimens of the stool.

There were 63 mg. 5-hydroxytryptamine/ml. serum and 1·8 mg. 5-hydroxyindoleacetic acid/g. creatinine in early morning urine.

A blood count raken 2 months after admission showed Hb—10·2 g./100 ml. (69 per cent.) C. The W.B.C. were 10,800/c.mm.

Five months after admission, the diarrhoea recurred. Pathogens were again not found in the stool but, in spite of treatment, the patient died a week after the onset of the symptoms.

Pathological Findings

The C.N.S. The head circumference at post-mortem was 45·4 cm., the average normal for the age being 49·6 cm. with S.D.$=\pm 1\cdot 2$.

The complete brain weighed 871 g., with the cerebellum together with the brain-stem weighing 120 g. (The average normal for the age is 1,050 g.)

The superficial veins were greatly congested and an area of terminal subarachnoid haemorrhage, $2\cdot 5\times 1$ cm., was present over the right inferior frontal gyrus. All ventricles were moderately dilated, and the floor of the 3rd ventricle was thin. Coronal blocks of the cerebrum showed slight reduction in the thickness of the corpus callosum and the centrum semiovale.

Histological preparations presented on naked-eye examination generalized diffuse fibrous gliosis of the cerebral and cerebellar white matter. Higher magnification showed an increase of fibrous astrocytes with a dense network of glial fibres. There was, however, no unequivocal evidence of corresponding loss of myelin. The white matter stained normally in most areas and myelin sheaths showed no evidence of past or continued degeneration, but, as mentioned above, the total amount of white matter was probably smaller than normal. In addition, a few small foci of definite myelin loss (Fig. 8) with astrocytic replacement were seen in the white matter of the frontal lobe.

Less certain histological abnormalities were as follows: the thickness of the cerebral cortex seemed reduced in some areas, particularly at the bottom of the sulci, and there was some neuronal paucity in the superficial cortical laminae. Perivascular cellular loss was also present in the cerebral grey matter (Fig. 9). The molecular layer showed some glial hyperplasia and a curious feature was microglial proliferation in layer 2 of the fusiform gyrus (Fig. 10). A lesser degree of microglial excess could also be seen in the superficial layers of many other cortical areas. A few ependymal granulations were present in the posterior horns of the lateral ventricles. There was some marginal and periventricular fibrous gliosis of the brain and brain-stem and syncytial astrocytes were present for some distance around the ventricles in the periventricular grey matter. The only abnormality in the spinal cord was fibrous gliosis without apparent parenchymal loss in the anterior horns of the grey matter. The Bergmann glia were increased in the cerebellum, some Purkinje cells had disappeared, and a few showed "homogenizing cell change" (Fig. 11).

Neutral fat was present in only a few compound granular corpuscles around some of the blood vessels.

The substantia nigra and locus caeruleus were unpigmented.

Somatic Organs. The trachea and main bronchi contained purulent secretion, and pleural adhesions were present over the right lower lobe. Yellowish, gritty particles of gravel were present in the renal pelves. The teeth were carious. The jejunum and colon were somewhat indurated and leathery in consistency, and the intestinal mucosa showed areas of congestion and possible inflammation. The pituitary weighed 0·15 g. and the thyroid 1·75 g.

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The following organs were examined histologically: eyes, spleen, small and large intestine, adrenals, pituitary, bone-marrow, pancreas, thyroid, salivary gland, thymus, liver, lungs and testes.

The *eyes* showed no apparent lack of retinal or choroidal pigment. The posterior layers of the iris were likewise well pigmented, but there was no pigment in the chromatophores of the iridial stroma. The *lipoid-rich* zona glomerulosa of *the adrenals* was sharply demarcated from the sub-joining lipoid-poor cortex (Fig. 12). The *liver* showed diffuse fatty change, somewhat accentuated towards the lobular periphery. There was marked increase in the amount of submucosal tissue in the small and large intestine. It formed a dense layer, equalling in places the thickness of the muscularis and consisting of sparsely cellular cylindrical structures (Fig. 13). The material stained slightly more bluish with haematoxylin than the usual collagen, giving in some areas the appearance of almost cartilaginous hyaline tissue. It was fuchsinophil with the Van Gieson stain. The innermost parts of the intestinal mucosa were necrotic and denuded in some places. Most of the *pulmonary tissue* examined showed collapse with purulent bronchiolitis and early bronchopneumonia. Some areas showed ante-mortem thrombosis of the pulmonary veins with intense capillary engorgement. The only histological change in the kidneys was the presence of a few partially calcified casts in the collecting tubules.

Case IV. H.H.

The patient was the issue of the last of four pregnancies, the first of which had ended in miscarriage. One of the two living siblings suffers from pulmonary tuberculosis. The family is free from mental defect, phenylketonuria or consanguinity.

In the fifth month of the patient's gestation, the mother was found to have pulmonary tuberculosis; in addition there was said to be a threatened abortion at 3–4 months. However, the pregnancy proceeded to term, the birth was normal and the baby weighed 2·8 kg. General retardation of his development became obvious at 7 months and he is said to have had epilepsy. Phenylketonuria was diagnosed on admission to hospital at 10 months, and an EEG taken at that time was said to be typical of myoclonic epilepsy. The fits were said to be controlled by "Diamox"—250 mg. b.d. He was started on a phenylalanine-restricted diet but it was difficult to get him to eat it; his weight remained stationary and after 2 months, in spite of some improvement in his mental state, the diet was discontinued.

At one year he was admitted to the Fountain Hospital for inclusion in the clinical trial of 5-hydroxytryptophan, but had not received this substance prior to death.

At the time of admission, he was described as a blond, rather pale child with broad, widely-spaced upper incisor teeth. His skull was slightly asymmetrical and the head circumference measured 44·7 cm., the average normal for the age being 47·1 cm. with S.D. $\pm$1·3. He showed slight hypotonia but no other neurological signs. "Diamox" was discontinued but no epileptic fits recurred. Several EEG records (Dr. D. A. Pond) showed symmetrical high voltage delta activity and low voltage fast activity, regarded as normal for age and drug effects. The serum total proteins measured 7·2 g./100 ml. and lipids 625 mg./100 ml. (Dr. J. Stern), these values being within the normal range.

Estimation of 5-hydroxytryptamine in the serum and 5-hydroxyindoleacetic acid in the early morning urine gave values of 140 ng./ml. and 1·4 mg./g. creatinine respectively.

His intelligence was estimated carefully on several occasions. Early after admission he was thought to be of imbecile level and no significant change was observed when the progress was last assessed some 6 months later.

He had recurrent attacks of respiratory and intestinal infection during his stay in hospital, succumbing to one of these at 1 year 8 months.

Pathological Findings

The brain weighed 870 g., the average normal for the age being 1,050 g. The right cerebral hemisphere projected slightly forward in keeping with the contours of the skull, but there was no gyral abnormality. The coronal blocks of the cerebrum and transverse sections of the brain-stem and spinal cord were also macroscopically normal.

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The only certain histological abnormality was slight or moderate fibrous gliosis of the white matter in the frontal and temporal lobes.

Less certain findings consisted of the following: slight pallor of myelin staining was present in the temporal lobes and the lower portion of the external capsule. Elsewhere myelin stained normally, but the total amount of the white matter in the centrum semiovale was probably reduced. Subpial fibrous gliosis was widespread over the cerebral cortex and periventricular gliosis was present around the ventricles, particularly the 4th, where many syncytial hyperplastic astrocytes ("Gliarasen") were situated in the periventricular grey matter external to the zone of fibrous gliosis (Fig. 14). Slight deficiency in the numbers of cortical neurones was present in many cerebral areas (Fig. 15). The white and grey matter of the brain-stem presented considerable vacuolation, but there was no excess of neutral fat or other evidence of past or continued degeneration of myelin.

Cells in the substantia nigra and locus caeruleus showed no pigmentation, but this was also the case in the control material. Some fibrous gliosis was present in the grey matter of the spinal cord.

Other Organs. The lungs showed basal congestion with a narrow rim of marginal collapse and a few small areas of lobular collapse. The pituitary weighed 0·3 g., and the thyroid 2·7 g.

The following organs were examined histologically: spleen, kidney, testes, salivary glands, small intestine, thyroid, thymus, adrenals, heart, lungs, 3 parathyroids and bone-marrow.

The *lungs* showed areas of collapse and a variable amount of oedema. The mucosal epithelium of the *small intestine* was partially denuded and the lymphoid tissue of the Peyer's patches was oedematous. Follicles at the periphery of the *thyroid* gland contained colloid; centrally, they were devoid of it, the tissue consisting of solidly arranged cells filling the lobules. The amount of fatty tissue in the *parathyroids* was possibly excessive. Their glandular parenchyma was formed entirely by "chief" cells without any acidophil or "wasserhelle" elements. Granular and hyaline casts were present in the collecting tubules of the *kidney*, which also showed some desquamation of the epithelium. The zona glomerulosa of the adrenals contained much lipoid and was sharply demarcated from the subjoining zona fasciculata and reticularis which had little lipoid. Other organs showed no noteworthy change.

Discussion

Save for Case I, whose phenylketonuria was perhaps doubtful, all brains in this series showed some micrencephaly weighing 69 per cent. of the average normal in Case II and 83 per cent. in Cases III and IV. Case III showed in addition moderate ventricular dilatation.

The presence of defective myelination, as shown by pallor of myelin staining, is more doubtful. There was slight pallor of the temporal lobe and external capsule in Case IV, and a few small foci of demyelination were present in the frontal lobe of Case III. Defective myelination could neither be confirmed or excluded in other areas or cases. On the other hand, all the 3 micrencephalic brains showed diffuse fibrous gliosis of the white matter of the centrum semiovale and its digital extensions with probable reduction in the total bulk of the white matter. It is possible therefore that in cases showing no definite pallor, individual normally-staining fibres had been condensed to normal proximity with each other by the associated scarring. The concomitant slight

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paucity of nerve cells and absence of gross myelin breakdown suggest that the change had involved entire neurons or areas and that the pathogenetic process is not selectively myelinoclastic.

Diffuse gliosis of the white matter with little or no apparent loss of myelin is common in low-grade mental defectives, particularly if they are micrencephalic. It was first described by Freeman (1927) in 4 cases of microcephaly Meyer and Cook (1937) were also impressed by its frequency in the brains of 22 mental defectives examined by them. In a later study, Meyer and Jones (1939) found it in 10 out of 15 cases of mongolism. The condition is therefore non-specific, signifying, possibly, the result of different processes ending in non-development or disappearance of neurons and their axons with condensation of the remaining ones.

Pending further study, these changes must be regarded as inconstant in phenylketonuria, However, some of the brains in Table II may well have shown similar changes, and this applies particularly to Cases 3, 18 and 20. Only the use of identical methods by different workers could ensure verification of their frequency.

It is not yet possible to determine the time of onset of the morphological changes. Micrencephaly does not necessarily imply prenatal onset; the head circumference of many microcephalic children is within normal limits at birth, and this may be so in phenylketonuria. Rarity of associated neural or somatic malformations in this condition also suggests that the morphological changes do not commence in early gestation. Biochemical evidence (Armstrong and Binkley, 1956) certainly suggests that the baby is normal at birth and this is supported by the clinical picture (see above). That irreversible changes of a diffuse gliotic type associated with micrencephaly do develop, however, is also in line with clinical experience, especially when it comes to treatment. Generally speaking, a phenylalanine-restricted diet is most likely to be effective when started in the first few months of life but may be worth trying up to the age of 3 or 4 years if the I.Q. is 40 or higher (Woolf, Griffiths, Moncrieff, Coates and Dillistone, 1958). Children over this age, especially if they have an I.Q. of less than 20, are unlikely to receive much benefit from dietary treatment. It would appear that, following separation from the mother and the protection which her liver affords, changes occur in the phenylketonuric's brain which not only prevent the normal development of intelligence, but which rapidly become irreversible in the absence of effective treatment. Thus, the morphological considerations do not preclude arrest or reversibility of pathogenesis, but rather emphasize the need for early and effective treatment. Efforts should be made to find a simpler and more reliable treatment based on further biochemical studies.

SUMMARY

. Following a general review of the literature, the neuropathological features of four phenylketonuric cases are presented. Micrencephaly and fibrous gliosis of the white matter were the main findings, but slight pallor of myelin staining was also demonstrated in two of the cases.

The neuropathological, clinical and biochemical findings in phenylketonuria are compatible with the view that irreversible changes occur in the brain, but may only develop postnatally. This emphasizes the need for early and effective treatment.

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