The Effect of Metabolic Disorders on Brain Activity

G. PAMPIGLIONE, MD, FRCP, Physician in Charge, Department of Neurophysiology, The Hospital for Sick Children, Great Ormond Street, London

The ways in which primarily extracerebral metabolic disorders may affect brain function are of growing general medical interest even if we still know too little about the mechanisms that underlie cerebral homeostasis and electrogenesis in health and disease. However, we do know that the features of the electrical activity of the brain are largely dependent on the metabolic state of neuronal aggregates.

Over the last fifteen years the intensive care situation has forced surgeons and physicians to combine their resources in an attempt to measure rapidly changing clinical states by whatever means available. During this period the introduction of mobile equipment has made it possible to carry out EEG studies at the patient's bedside. Progress in cardiothoracic surgery, renal dialysis and organ transplantation, as well as a reappraisal of the concept of death, have given an opportunity to physicians, surgeons, anaesthetists and others, to gain first-hand experience of the use of the EEG as a measure of brain function in a rapidly varying metabolic situation. EEG studies should be considered an extension of the physical examination of the patient with electronic apparatus: such resulting physical signs are permanently recorded on either paper or tape.

The metabolic changes discussed in this article have a primary cause in the body, though mostly outside the brain. Phenomena related to the administration of exogenous substances such as drugs or anaesthetics are not considered.

RANGE OF METABOLIC EVENTS TO BE CONSIDERED

Life can be envisaged as a sequence of metabolic and biophysical events which underlie the function of various organs. In the brain a large number of events are taking place all the time and their duration may vary from less than a millisecond to seconds, hours and probably weeks, months, and years. Some groups of metabolic alterations are better known than others in relation to the concomitant alterations in the EEG (Table 1).

These metabolic alterations, commonly encountered in clinical practice, are detectable from measurements in the peripheral blood, even if the rela-

TABLE 1. Some Metabolic Changes in Clinical Practice that may be accompanied by EEG Changes

Speed of effect	Examples
1. Rapid (seconds or minutes)	Ischaemia, anoxia, voluntary hyperpnoea, acute hypoglycaemia.
2. Moderately slow (hours or few days)	Alterations of water and electrolyte balance. Hypocalcaemia in the newborn. Cardiorespiratory failure. Hepatic encephalopathy.
3. Very slow (weeks, months or years)	Nutritional stresses. Some cardiorespiratory diseases. Many endocrine disorders. Several genetically determined metabolic disorders.

tionship between brain tissue and peripheral blood content of a substance is not always direct or simple. Careful studies of patients and appropriate timing of the biochemical and EEG investigations make it possible to confirm that some metabolic derangements have a much more rapid effect on cerebral activity than others. The precise mechanisms that lead to the occurrence of both EEG and clinical changes are poorly understood, although seemingly specific names are given to conditions such as ischaemia, hypoglycaemia and hyponatraemia. Moreover, there is a great deal of individual variability in response to an altered metabolic state with apparently similar parameters.

During a metabolic upset of relatively short duration the margin of tolerance of the brain may vary considerably in response to a change in the concentration of one or other constituent of the perfusing blood (Table 2). Moreover, the margin of tolerance of the brain (as detected by the appearance of EEG alterations) may be quite different with respect to a decrease, as compared with an increase of a given substance.

We do not know why cerebral homeostasis is capable of dealing successfully with wide ranges of fluctuations in the potassium levels in the peripheral blood while either a 10 per cent fall or a 10 per cent increase in the amount of sodium, chloride, or water, may be followed in a matter of hours by substantial EEG changes. A fall in blood sugar level of the order of 50 per cent generally has a greater effect upon the EEG features than an increase of blood sugar of 100 per cent or even 200 per cent. While marked EEG changes may follow a 40 per cent reduction in serum calcium, an increase in serum calcium does not appear to affect in any gross way the EEG features or the patient's ability to carry out complex tasks.

The EEG changes related to voluntary hyperventilation have been well

TABLE 2. Margin of Tolerance of the Brain with persistence of Normal EEG features in spite of a Decrease or an Increase in some constituents of Normal Peripheral Blood

Margin of Tolerance	Decrease	Increase
Narrow (less than 10 per cent)	Water Sodium Chloride	Water ? Sodium ? Chloride
Moderate (often 10–50 per cent)	Calcium CO_2 Glucose	? Calcium
Wide (usually over 50 per cent)	Urea Potassium pH O_2	Urea Potassium Glucose pH CO_2

described in the literature and there is no need to emphasise what is already well known. The mechanism is uncertain but it seems probable that the arteriolar vasoconstriction produced by the fall in CO_2 during hyperventilation is responsible for a diminished flow of blood through the brain, and the availability of oxygen to the cerebral tissues is therefore reduced, as in ischaemia.

HYPONATRAEMIA

The EEG changes during transitory hyponatraemia following stress, and in particular after major surgical operations, have not been universally recognised. Kiloh et al. (1972) stated that alterations in plasma electrolyte levels had little or no effect on the activity of the brain. However, other authors have demonstrated a particular cycle of events with marked EEG changes accompanying hyponatraemia and hypochloridaemia following major operations with a fully reversible cycle of events over a period of 4 to 7 days (Pampiglione, 1965; Harden et al., 1968). The EEG changes and the fall in plasma sodium do not occur in the first few hours following the operation but only towards the end of the first day and become more marked in the second and third days after surgery. The EEG changes are peculiar in that there is an increase in slow components usually more obvious over the posterior than over the anterior half of the head and an overall increase in the amplitude of the traces (Fig. 1). In spite of the marked EEG changes, the patient's clinical state, and particularly his alertness, are not grossly affected.

While the effect of transitory hyponatraemia tends to be a little more marked in children than in adults, the general trend is the same and the EEG changes
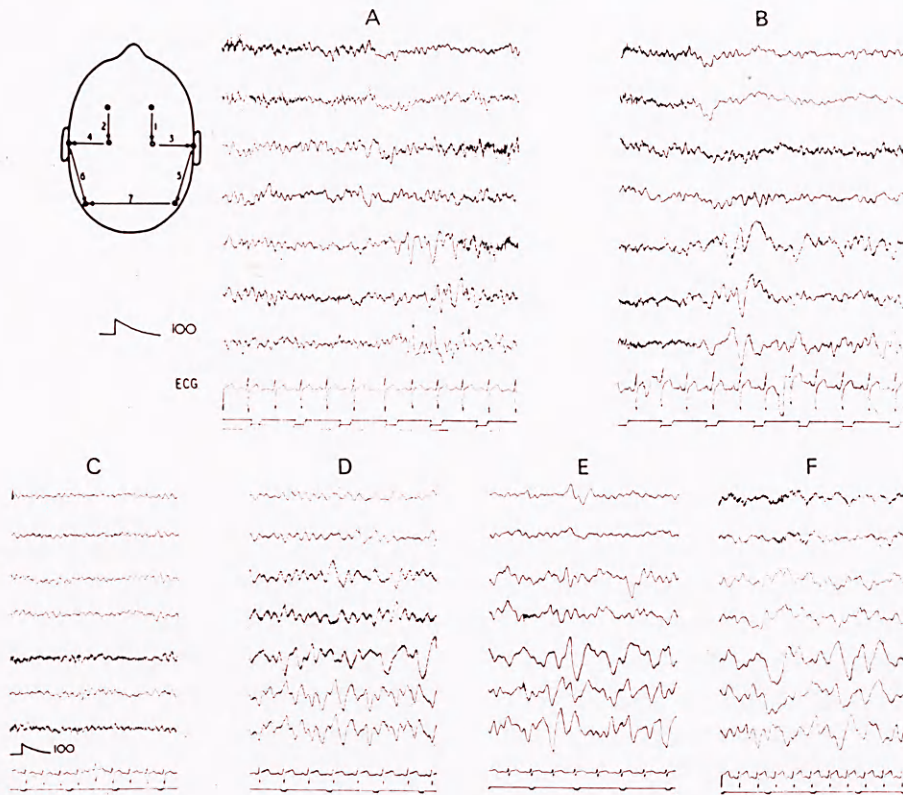
349

Fig. 1. EEG changes related to a fall in plasma sodium and chloride during the post-operative period. *A*: one day before operation (23-1-61). *B*: 10 days after operation (features similar to *A*). *C* to *F*: during the period of hyponatraemia (Na 125 Chl. 89) gradual increase in slow activity more marked in the posterior than in the anterior regions of the brain (January 24th-25th-26th-27th 1961). (Pampiglione, 1965. Courtesy of *The Lancet*.)

are rapidly and fully reversible; in contrast, for example, with the sequelae of an episode of severe cerebral ischaemia or anoxia.

In clinical practice, and particularly in the intensive care situation, it is essential to remember that between 24 and 72 hours after major surgery or after any acute trauma (not affecting the brain directly) some degree of hyponatraemia occurs. An increase in slow activity in the EEG in this situation should not be confused with the EEG changes which accompany a cerebral lesion. The postoperative hyponatraemia has been attributed by some authors solely to the water retention secondary to the altered secretion of anti-diuretic hormone but the mechanism underlying this type of hyponatraemia is obscure (*see* discussion in Harden *et al.*, 1968).

350

Whenever a primary cerebral complication is suspected during a major operation and an EEG may be required to assess the cerebral condition, it is advisable to take the EEG in the first few hours after surgery, and before the changes associated with the hyponatraemic phase begin to appear.

HYPERNATRAEMIA

An increase in plasma sodium level is more common in young babies than in adults and it is usually accompanied by some degree of dehydration. While the degree of hypernatraemia is easily measured, it is more difficult to evaluate its effects upon the brain both in the acute phase and later. Moreover, the type of therapeutic approach, with administration of isotonic or hypotonic saline, the amount of fluid given and probably also the rate of administration may complicate the course of events following what seemed to be 'a simple hypernatraemic episode'.

It is known that a high plasma sodium may be a possible cause of local alterations in vascular permeability, with the occurrence of multiple small haemorrhages in the brain and the consequent appearance of abnormal neurological phenomena including seizures. On the other hand, a rapid fall of plasma sodium as well as a rapid fall in blood urea following administration of hypotonic saline are sometimes suspected of facilitating the occurrence of seizures. In our experience a moderate acidosis or alkalosis does not seem to precipitate seizures in babies and a gradual fall in plasma sodium may perhaps even prevent the occurrence of convulsions. Probably, several compensatory systems are available to maintain normal cerebral function and we cannot be overconfident that drastic therapeutic measures might not derange a delicate homeostasis. In general, the administration of anticonvulsant drugs in an acute metabolic upset during which convulsions have occurred is of limited value.

An increase in plasma sodium is not accompanied by an increase in slow activity in the EEG in contrast with hyponatraemia but is commonly followed by an increase in sharp elements and sometimes the appearance of spikes which become prominent during clinically recognisable seizures (Fig. 2). Once the metabolic upset is corrected the EEG changes tend to disappear but sometimes patchy abnormalities of various kinds may persist, possibly due to sequelae the nature of which is not easily verifiable (Pampiglione, 1968a).

HYPOGLYCAEMIA AND HYPERGLYCAEMIA

A great deal of work has been carried out on the effect of hypoglycaemia upon the electrical activity of the brain (see early bibliography in Dawson and Greville, 1963). There is general agreement in the literature that the lower the
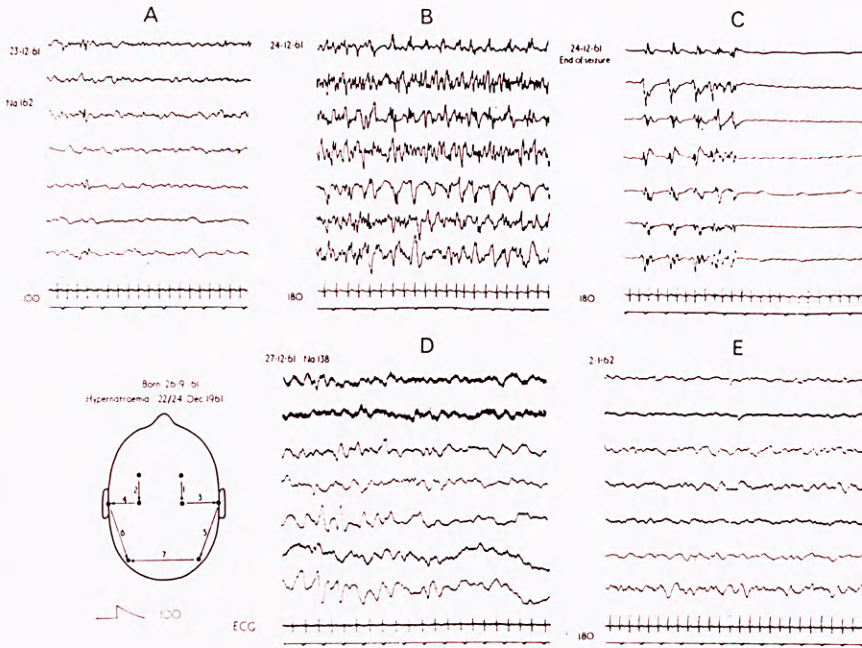
Fig. 2. EEG changes during dehydration and high plasma sodium and chloride. *A*, *B* and *C*: during acute phase (Na 162) and a seizure. *D*: 3 days later after return to normal water and electrolyte balance. *E*: 10 days after acute episode.

blood sugar level the greater the alteration in the EEG, though with considerable individual variability. The cause of hypoglycaemia, the rate of blood sugar fall, and the total duration of the episode of low blood sugar level may all influence the type, severity and duration of the EEG changes. A period of fasting with a fall in blood sugar level from 100 to 60 mg/100 ml is not accompanied in most mammals by gross EEG changes while in some individuals a similar reduction in blood sugar level may be accompanied by some degree of slowing of rhythmic activity in the EEG. The careful studies of Poiré *et al.* (1966) demonstrated the considerable individual variability in electroclinical manifestations during induced hypoglycaemia and also the individual variability of other neurophysiological measurements.

Experimentally induced hypoglycaemia in dog and pig (Pampiglione *et al.*, 1962) showed considerable variability not only in individual animals but also between these two species. Following insulin administration the changes in the electrical activity of the brain in the dog were more marked than in the pig though both were more closely related to the occurrence of some clinical events (including sweating, semi-coma, and seizures) than to the actual blood sugar
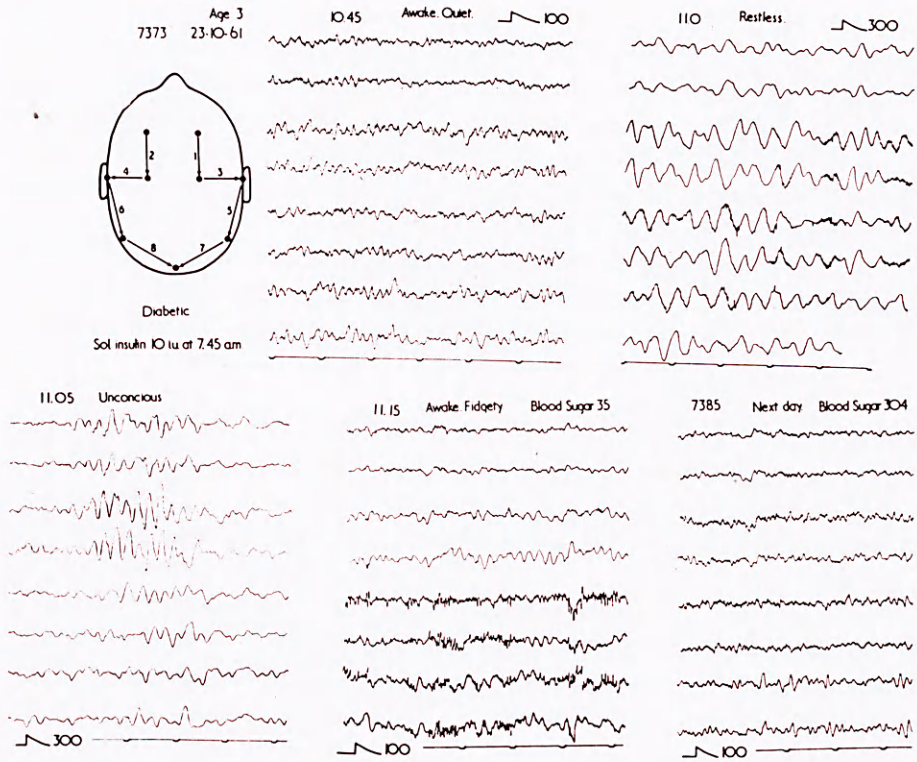
Fig. 3. EEG changes in an unstable diabetic child with hypoglycaemic episodes lasting several minutes with restlessness, sweating, stupor and coma, followed by rapid recovery. Soluble insulin 10 i.u. had been given at 7.45 a.m. The EEG is illustrated at 10.45 a.m. when the patient was well. By 11 a.m. the patient was restless at the beginning of the period of rapid hypoglycaemia with marked increase in amplitude of slow activity in the EEG. By 11.05 a.m. the patient was unconscious but by 11.15 a.m. had already regained consciousness spontaneously while the blood sugar level was still very low (35 mg/100 ml) but a great deal of the slow activity in the EEG had disappeared. The next day with a blood sugar level of 304 both the clinical state of the child and her EEG had returned to normality.

level at any time. It seems probable, therefore, that the changes in cerebral functions are more complex than would be expected from any simple relation to the degree of hypoglycaemia.

In all mammals the main EEG changes during marked hypoglycaemia consist of an increase in slow activity which may be rhythmic and of very large amplitude, particularly over the frontal lobes during pre-coma and coma (Fig. 3). There is a rapid reversibility in a matter of very few minutes once the blood sugar level is restored to usual levels for that particular individual. In patients with seizures, however, the occurrence of abnormal phenomena in the EEG may be triggered even by relatively small falls in blood sugar.

When persistently local EEG abnormalities are seen in a patient of any age following an episode of hypoglycaemia it is important to ascertain from the patient's history and from the clinical examination whether some pre-existing or intercurrent cerebral trouble might be present to which the hypoglycaemia might be only a minor concomitant. This is particularly relevant in young children or babies who may become hypoglycaemic during prolonged seizures due to a primary cerebral disorder.

In contrast to the variable but usually clear electroclinical correlations of a fall in blood sugar, an increase in blood sugar for a similar period does not appear to affect the electrical activity of the brain even if such an increase is of the order of 100 to 200 per cent.

HYPOCALCAEMIA

This type of problem is not simple, partly because of our ignorance about the precise function of calcium at neuronal level, and partly because other ill-understood metabolic events may accompany a transitory fall in serum calcium.

Hypocalcaemia is much more common in the early postnatal period than in later infancy, childhood, or adult life. The mechanisms underlying hypocalcaemia and their relationship to magnesium and protein levels, and to clinical symptoms, are largely unknown. The clinical manifestations of hypocalcaemia are predominantly peripheral in adults (tetany) and predominantly cerebral in the new born (seizures).

In a series of 20 young babies referred for EEG studies during seizures the serum calcium was found to be between 4·1 and 7·3 mg/100 ml (Pampiglione et al., 1970). These children had several EEGs during the period of hypocalcaemia and until the end of the clinical episode. The intravenous administration of calcium often appeared to correct the abnormal metabolic state with disappearance of the clinical phenomena and return to a normal EEG (Fig. 4) in some babies, though not in others. Sometimes, hypomagnesaemia and other metabolic alterations were present, requiring additional therapy. The EEG features with prolonged rhythmic discharges lasting minutes, often with variable focal distribution alternating with periods of less abnormal EEG patterns, are sufficiently characteristic to help in the differential diagnosis of possible causes of seizures in young infants. In serial EEG studies of hypocalcaemic babies, the changing features may offer information about the degree of reversibility of the cerebral trouble after administration of calcium and magnesium.

It seems probable that particular types of metabolic upsets may be defined in EEG and biochemical parameters, which differentiate them from other

Fig. 4. Large rhythmic discharges in the EEG of an 8-days-old baby with seizures and low serum calcium (5·1 mg/100 ml). Rapid clinical recovery with a normal EEG, two days later, when the serum calcium was 9·1 mg/100 ml.

conditions with apparently similar clinical manifestations. Again, a number of largely unknown individual factors make it possible for some babies to have clinically recognisable seizures with a serum calcium which is undoubtedly low but which in other children may not be accompanied by either clinical or EEG manifestations.

MALNUTRITION

In contrast with the response to acute disorders of metabolism the EEG changes in chronic malnutrition develop more slowly but may be more persistent. Malnutrition is a generic term which includes 'hypoalimentation' and also dietary imbalance, whether or not the total calorie intake is adequate, excessive, or poor. In the developing countries, particular attention has been given to the more extreme forms of marasmus and kwashiorkor, the first meaning wasting or loss of body weight while the second indicates also the presence of oedema of the tissues, changes in the colour and texture of the hair and skin, or a combination of these features. Protein-calorie deficiency indicates a particular type of malnutrition in which, when the calorie intake is low, protein may be expended as energy and thus be unavailable for anabolism.

In clinical practice most cases of human malnutrition are often difficult to classify or define because of the multiplicity of interdependent factors resulting in a complex syndrome. Diets deficient in protein and/or calories impair the utilisation of adequate quantities of other nutrients. Moreover, dietary toxins are now being considered as important factors in the development of some neurological disorders. The subject has been reviewed excellently by Platt and Stewart (1971) and Osuntokun (1972). The study of the electrical activity of

the brain in chronic malnutrition is a fascinating field for further investigations of well-documented clinical and metabolic syndromes.

In experimental work carried out on dogs and pigs (Platt *et al.*, 1965) the protein intake of the animal was lowered while supplementing the diet with carbohydrate; groups of control animals of either similar or different litters were reared on normal diets. In the pig, when the protein-calorie deficiency was severe, particularly with large carbohydrate supplements, the appetite failed, the animal became listless, and motor inco-ordination, particularly of the hind legs, became very obvious. The EEG changes did not appear until the age of two to three months on low protein/high carbohydrate diet. In general, there was a greater proportion of slow components in the EEG of the experimental animals than of controls on low protein diets; when carbohydrate was added to the diet there was a considerable decrease in fast components in the experimental animals in comparison with the controls. There was, however, a great deal of individual variability and there was no constant relationship between the type and severity of the EEG changes and the type and severity of the histological changes. In spite of the clearly recognisable EEG changes in the experimental animals, the histological changes were mostly found in the spinal cord, while the cerebral changes were either doubtful or absent.

The EEG changes in the puppies born of bitches on a low protein diet and subsequently reared on diets of low protein value were more striking than those seen in the pigs (Fig. 5). Not only was there a disruption of the normal rhythmic activity appropriate to the age of the individual dog but also the appearance of large amplitude spikes, sharp waves, and irregular slow waves reaching 2 to 5 times the normal amplitude (Pampiglione, 1963). There was no constant relationship between the severity of the EEG changes and the severity of the motor disorder which appeared in the puppies aged 6 to 8 weeks but such relationships became more obvious between 8 to 12 weeks of age.

It was interesting to notice in this experimental work that when the puppies survived after the age of 12 weeks there was a gradual improvement both in the clinical and in the EEG features in spite of the fact that the animals continued to be on diets of low protein value. It seemed that although the nutritional stress was severe and accompanied in some cases by substantial histological changes, after the age of about three months there was a tendency for spontaneous improvement, as if the animal did not have similar dietary requirements after the age of 12 to 15 weeks. At the present stage it is difficult to understand why individual differences between animals reared on similar experimental diets might have been so marked both in terms of clinical and EEG features, why some animals should develop seizures under nutritional
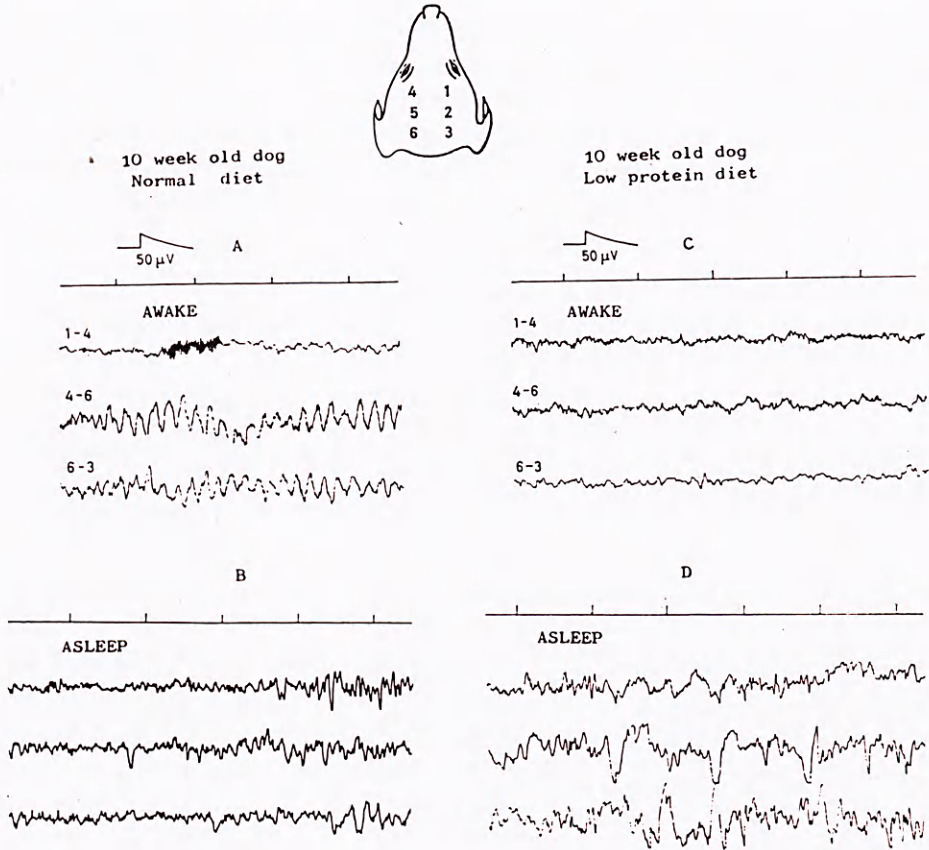
Fig. 5. A and B = control dog on normal diet (awake and asleep) born of a bitch on normal diet. C and D = dog on low protein diet before, during and after pregnancy. Note irregularity of the EEG from various areas, both during waking and sleeping states.

stresses, why the histological changes in the pig and the dog should be somewhat doubtful at cerebral level (in spite of the marked EEG changes) while histological changes in the spinal cord were so obvious.

In malnourished African children there was a high percentage of EEG abnormalities which diminished with treatment. However, EEG abnormalities could persist even long after clinical recovery from malnutrition (Nelson, 1959; Nelson and Dean, 1959; Mundy-Castle et al., 1953).

In some unpublished EEG studies at Great Ormond Street an excess of slow components, particularly over the posterior half of the two hemispheres, has been found in children with coeliac disease and such mild abnormalities improved over a period of a few months once the children were given a gluten-

free diet. This field of work is very promising, not only because of the effects of specific nutritional imbalance upon the brain but also because genetically determined intolerances to particular nutrients continue to be discovered and will form an ideal field for research. Use of the EEG as a sensitive indicator of a variety of metabolic upsets in one or other form of malnutrition should offer further ways to study relationships between nutrition and the brain.

ENCEPHALOPATHY IN LIVER FAILURE

The electrical activity of the brain is affected in a conspicuous and characteristic way in severe forms of liver failure for reasons which are poorly understood. A diffuse increase in slow activity is seen in the EEG with progressive slowing and disorganisation of the alpha rhythm which may occur over a period of a few days or even a few hours. If the patient's condition deteriorates further to pre-coma or coma, large amplitude slow and sharp components are seen, often reaching half a millivolt, and more obvious over the anterior than over the posterior half of the two hemispheres. The term triphasic waves has been used to describe some of the EEG features but this term is not universally accepted (Kiloh *et al.*, 1972).

This sequence of EEG events (Fig. 6) is seen in a particular type of fairly acute encephalopathy occurring in liver failure and often accompanied by an increase in blood ammonia. However, while an increase in ammonia in the blood and CSF may be accompanying the deterioration of the patient's clinical features, the correlation with the EEG changes is much more variable. It is interesting to note that in spite of the very marked changes both at clinical and EEG level during a given episode of hepatic encephalopathy, reversibility is strikingly rapid over a period of a day, or even hours, with appropriate neomycin therapy.
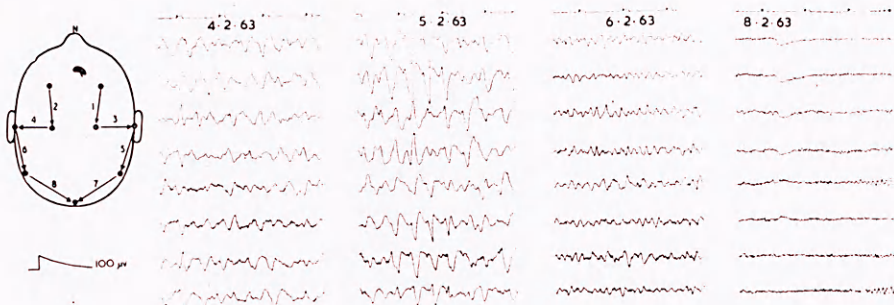

Fig. 6. EEGs taken during the pre-coma (4.2.63), coma (5.2.63), marked improvement (6.2.63) and recovery (8.2.63) of a patient aged 64 with hepatic encephalopathy.

In the same group of patients, similar EEG changes may be induced over a period of a few days by an increase in dietary protein: the changes are rapidly reversed when the diet is appropriately altered. These EEG features of hepatic encephalopathy are not seen in other conditions, although in milder forms of liver failure the changes are less specific.

In patients with known liver disease often complicated by ascites, low sodium diets may be administered and on occasions the patient appears drowsy. In these cases the different topographic distribution as well as the morphology of the EEG changes may help in the differential diagnosis (with the support of biochemical data) between hyponatraemia and hepatic encephalopathy.

GENETICALLY DETERMINED NEUROMETABOLIC DISORDERS

Studies of the EEG in patients with genetically determined metabolic disorders are relatively few. This is partly due to the fact that a large number of metabolic errors are commonly seen in young children and there is a widespread uncertainty in many centres as to the limits of normality in EEGs of babies and children. Another problem has always been the difficulty in diagnosing the disease at an early stage of its development, and of establishing the exact onset of an insidious symptomatology which may tend to vary from one case to another. Sometimes the provisional diagnosis with which the patient may first be referred for EEG investigations may be different from the final diagnosis which may be reached months later, perhaps in another hospital.

The reasons why some symptoms may appear in one patient and not in another with an apparently similar enzymatic defect are largely unknown, even when we have obtained all the detailed laboratory evidence. It may well be that the individual clinical symptomatology in genetically determined metabolic disorders is related to a coincidence of factors, and that the imbalance of enzymatic functions is perhaps more relevant than a single enzyme defect in influencing both the type of alterations in cerebral electrogenesis and the age at which particular clinical and EEG features appear in the course of the disease. It should be possible, however, in the near future to establish a multifactorial analysis of each patient's 'enzymatic profile', combined with an individual 'EEG profile' during the evolution of illnesses due to a particular inborn metabolic defect. This should make it possible to utilise the EEG in the differential diagnosis of a variety of obscure disorders of cerebral function in young children and babies, as the EEG features tend to be specific for some particular disorders.

An increasing number of genetically determined metabolic disorders are being recognised, sometimes with controversial terminology and discrepancies of classification. It seems, however, that the EEG features in proven cases have

TABLE 3. EEG Features in the Differential Diagnosis of some Genetically Determined Metabolic Disorders with 'Cellular Storage'

Disease	Rhythmic slow	Fast	Irreg. slow	Spikes (poly)	W+SP. 2/sec	Disch at slow phot.	Startle (noise)
Tay–Sachs (3–12 mths)	+	–	–	–	–	–	+++
Tay–Sachs (1–3 yrs)	–	–	++	+	–	–	++
Bielschowsky-Jansky (2½–5 yrs)	–	–	++	++	–	+++	+
Spielmeyer-Vogt (6½–12 yrs)	+	–	+	+	++	–	–
M.L.D. (1–10 yrs)	++	++	+	–	–	–	–
Glycogenoses (0–10 yrs)	±	–	–	–	–	–	–

some specificity for each verifiable disease, often with diagnostic features (Pampiglione, 1961, 1968a; Dumermuth, 1965; Pampiglione and Lehovsky, 1968; Ellingson and Schain, 1969; Kliemann et al., 1969; Mastropaolo et al., 1971; Pampiglione and Harden, 1973).

In a series of some 130 verified cases of 'storage disorders' studied at Great Ormond Street, the main EEG features to be utilised in the differential diagnosis are summarised in Table 3 (see also Fig. 7). The use of eponyms in the table is limited to those conditions that have been generally accepted in the current literature on neurometabolic disorders although some are controversial (Zeman et al., 1970; Pampiglione and Harden, 1973).

In patients with abnormal metabolism of some amino acids, only limited histological changes have been reported (Crome and Stern, 1972.) However, the EEG alterations may be quite marked in some diseases and minimal in others. This would suggest that the accumulation of some substances has more effect on cerebral electrogenesis than others (Dumermuth, 1965; Pampiglione 1961, 1968b; Sonksen et al., 1971). In untreated phenylketonuria, the EEG changes may be gross though reversible (Fig. 8) on appropriate dietary treatment. In the inadequately treated cases, the EEG alterations may be quite marked in the first two years of life with a poverty of the rhythmic activity appropriate to the child's age, an excess of irregular slow waves, sharp waves and some spikes with variable distribution and, often, an asymmetry between the activities of the two hemispheres. Between the ages of two and a half and four years there is usually a diminution in the amount of discharges but the alpha rhythm is poorly formed and mixed with an excess of irregular slow
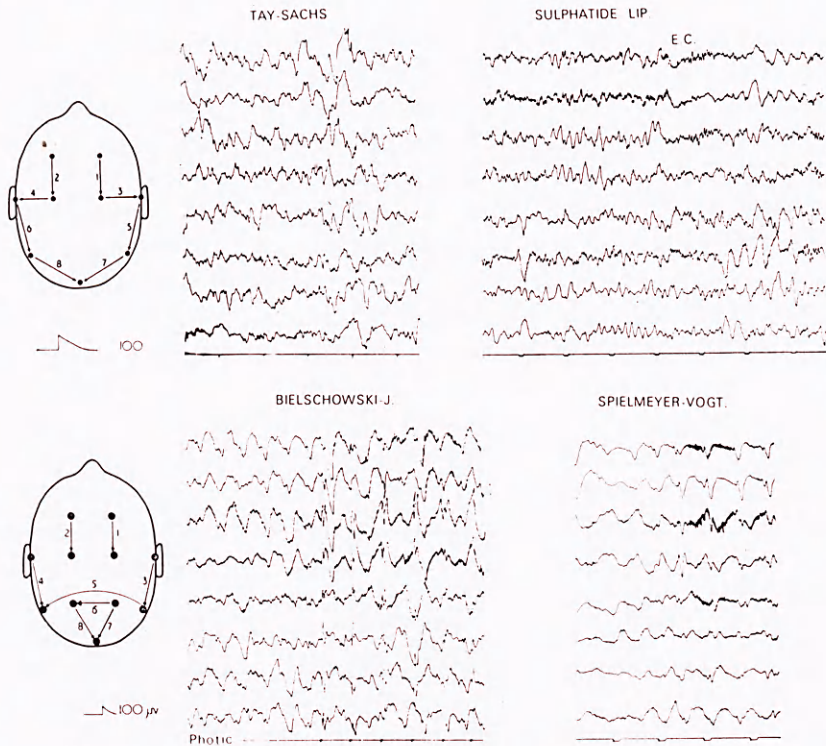
Fig. 7. EEG features in four main types of genetically determined neurometabolic disorders. Note the differences in the morphology of activity, its topographic distribution, and amplitude.

components, usually larger over the right than over the left posterior temporal region. There is also an excess of intermediate slow activity over the anterior frontal regions.

After the age of four years until adolescence there is usually a persistence of the excess of irregular slow activity in the posterior temporal regions, larger on the right than on the left side, though mostly blocked on eye opening together with the alpha rhythm; and multifocal discharges may be present. Usually at this age runs of rhythmic 6 per second waves are seen, often reaching 50–150 microvolts in the anterior third of the head on the mid-line, whether or not the patient's eyes are open. In addition, there is often an abnormal sensitivity to photic stimulation at relatively high rates of flickering. This combination of events is unusual in any other known genetically determined metabolic disorder and seems to be a specific finding in partly treated phenylketonuria. However, in patients treated at an early age with a low phenylalanine diet
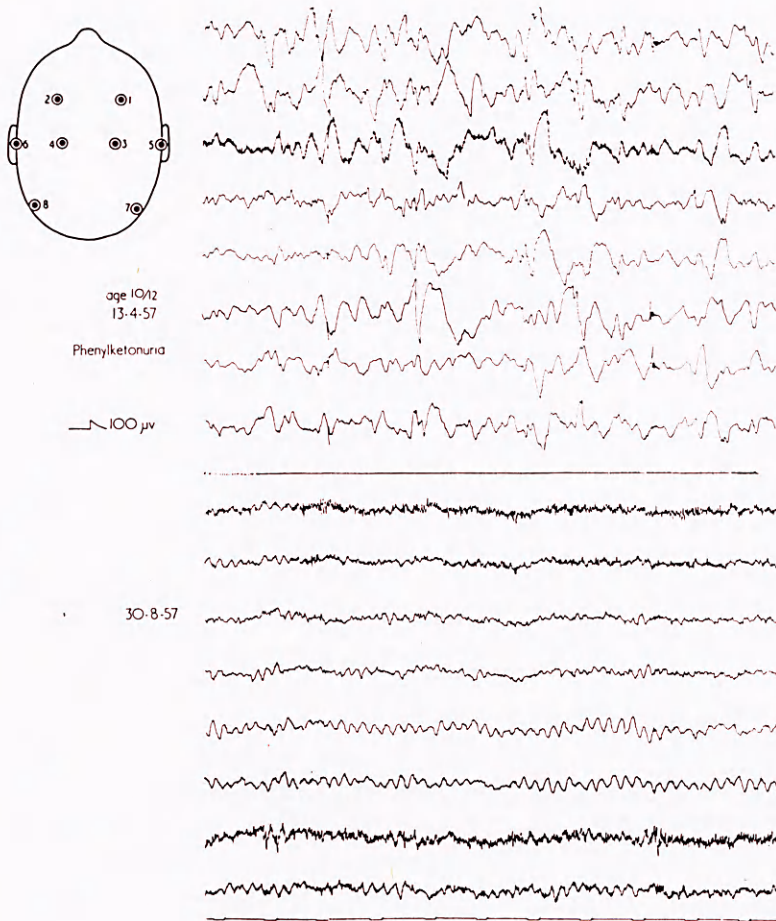
Fig. 8. Above: EEG features in an untreated 10 months' old baby with phenylke-tonuria. Below: marked improvement of the EEG on a low phenylalanine diet for 4 months (average reference montage through 0·5 MΩ).

cerebral maturation may occur at a normal pace with well-preserved rhythmic activity both in the rolandic regions and in the occipital areas after passive eye closure. In some of these patients a phenylalanine load may be accompanied within 1 to 6 hours by the appearance of substantial EEG abnormalities of the kind seen in partly untreated phenylketonuric children (Clayton *et al.*, 1966).

CONCLUSIONS

When correlations are attempted between EEG changes and metabolic events the following points must be kept in mind:

1. A sound knowledge of the range of normality of the EEG features in various age groups, whether in animals or man, is essential. Each area of the brain generates electrical signals that differ from those of other areas. A systematic approach to electrode placement on the scalp and to the utilisation of appropriate combinations of electrodes is of basic importance.

2. The electrophysiological and the biochemical studies should be strictly controlled in real time and both should be carried out on the same individuals. A statistical average of random events in different individuals can mislead.

3. The increasing importance of statistical methods of analysis in biological work has enticed many investigators into averaging out individual variations rather than emphasising individual differences, with possible loss of information.

4. Both in acute and chronic disorders of metabolism the topographic distribution of EEG changes seems to be peculiar to each group of conditions. For example, the increase in slow activity is more obvious over the anterior than over the posterior half of the head in uraemia, hypoxia, advanced hepatic encephalopathy, and severe hypoglycaemia. There is, instead, a greater amount of slow components over the posterior than over the anterior half of the two hemispheres in other disorders such as hyponatraemia, overhydration, and chronic malnutrition. Particular examples of the topographic distribution of specific EEG abnormalities may be found in some inborn errors of metabolism, as in phenylketonuria, and in some storage disorders, often with diagnostic implications, while specific morphological features may be found in the hypocalcaemia of the new born and in the semi-coma of hepatic encephalopathy.

5. The timing of electrophysiological observations must be appropriate to the group of disorders to be studied: for example, in acute metabolic upsets EEG investigations should be taken as soon as possible and repeated perhaps several times during the first 24 hours. In slowly evolving processes the investigations may be carried out at intervals of days, weeks, and months.

6. The biochemical parameters measured in peripheral blood may not necessarily parallel metabolic changes in brain tissue but usually give some indication of trends.

7. It seems probable that various compensatory systems maintain normal cerebral function during specific alterations of one or other constituent of the peripheral blood. However, the homeostatic mechanisms are not always as efficient for a decrease as for an increase of a particular blood constituent.

8. Although most clinicians are prepared to give apparently precise names to particular conditions such as hypocalcaemia, hypoglycaemia, or hypernatraemia, usually more than one factor contributes to each of these condi-

tions once cerebral homeostasis is upset and clinical and EEG abnormalities become apparent.

This article is based on a paper read at the Conference on Clinical Electroencephalography held at the Royal College of Physicians in November, 1972.

References

Clayton, B. E., Moncrieff, A. A., Pampiglione, G. and Shepherd, Jean (1966) *Archives of Disease in Childhood*, **41**, 267.

Crome, L. C. and Stern, J. (1972) *Pathology of Mental Retardation*, 2nd edn. London: Churchill.

Dawson, M. E. and Greville, G. D. (1963) In *Electroencephalography*, Chap. 5, Biochemistry, p. 147 (ed. D. Hill and G. Parr) London: Macdonald.

Dumermuth, G. (1965) *Elektroencephalografie im kindesalter*, Stuttgart: Thieme.

Ellingson, R. J. and Schain, R. J. (1969) *EEG and Clinical Neurophysiology*, **27**, 191.

Harden, Ann, Glaser, G. H. and Pampiglione, G. (1968) *British Medical Journal*, **4**, 210.

Klieman, F. A. D., Harden, Ann, and Pampiglione, G. (1969) *Developmental Medicine and Child Neurology*, **11**, 475.

Kiloh, L. G., McComas, A. J. and Osselton, J. W. (1972) *Clinical Electroencephalography*, 3rd edn., London: Butterworth.

Mastropaolo, C., Pampiglione, G. and Stephens, R. (1971) *Developmental Medicine and Child Neurology*, **13**, 20.

Mundy-Castle, A. C., McKiever, B. L. and Prinsloo, T. (1953) *EEG and Clinical Neurophysiology*, **5**, 533.

Nelson, G. K. (1959) *EEG and Clinical Neurophysiology*, **11**, 73.

Nelson, G. K. and Dean, R. F. A. (1959) *Bulletin of the World Health Organisation*, **21**, 779.

Osuntokun, B. O. (1972) *Tropical and Geographical Medicine*, **24**, 311.

Pampiglione, G. (1961) *Proceedings of the VIIth International Congress of Neurology*, Vol. I, pp. 53–63. Rome: Societa Grafica Romana.

Pampiglione, G. (1963) *Development of Cerebral Function in the Dog*. London: Butterworth.

Pampiglione, G. (1965) *Lancet*, **2**, 263.

Pampiglione, G. (1968a) In *L'Epilessia nell'Infanzia* (a symposium) Geigy: Milan.

Pampiglione, G. (1968b) In *Some Recent Advances in Inborn Errors of Metabolism* pp. 80–98 (ed. K. S. Holt and V. P. Coffey) Edinburgh: Livingstone.

Pampiglione, G., Friend, C. J. and Heard, C. R. C. (1962) *Proceedings of the Nutrition Society*, **21**, 3.

Pampiglione, G. and Harden, Ann (1973) *Journal of Neurology, Neurosurgery and Psychiatry*, **36**, 68.

Pampiglione, G., Harden, Ann, Chaloner, J. and Gumosz, M. (1970) *EEG and Clinical Neurophysiology*, **28**, 424.

Pampiglione, G. and Lehovsky, M. (1968) In *Clinical EEG of children*, pp. 287–306 (ed. P. Kellaway and I. Peterson) Stockholm: Almquist and Wiksell.

Platt, B. S., Pampiglione, G. and Stewart, R. J. C. (1965) *Developmental Medicine and Child Neurology*, **7**, 9.

Platt, B. S., and Stewart, R. J. C. (1971) *World Review of Nutrition and Dietetics*, Vol. 13, pp. 43–85, Basel: Karger.

Poiré, R., Debry, G., Cygler, B. and Beck, L. (1966) *Extraits Comptes Rendus Cougney Psychologie et Neurologie de Langue Francaise. LXIVᵉ Session*, Grenoble, Sept., pp. 730–747.

Sonksen, P. M., Cottom, D. G. and Harden, Ann (1971) *Developmental Medicine and Child Neurology*, **13**, 606.

Zeman, W., Donahue, S., Dyken, P. and Green, J. (1970) *Textbook of Clinical Neurology*, Chapter 25, Vol. 10 (ed. P. J. Winken and G. W. Bruyn) Amsterdam: North Holland Publ. Co.