suggests that the discrimination analysis precedes arousal as manifested by the K.

The responses which are obtained may occur in various relationships in time to the auditory signal. It may occur as: (1) An on effect, (2) during the signal, (3) an off effect, (4) several seconds after the signal has ceased.

It is found that the time when the response is seen in relation to the signal is a function of the loudness of the signal above the auditory threshold and the depth of sleep. It is easier to elicit the responses in the light stages of sleep.

Taylor (1962*a*, *b*) has shown that the psychophysical laws which govern audiological testing of hearing in the conscious state also apply in the sleep state. The one difference is that the methods of arriving at auditory thresholds in the sleep state have to involve greater changes of intensity at each step. This adds supportive evidence to the suggestion that the K complex is the electrical evidence of a crude perceptive mechanism.

The method of testing has been shown to be of great use in children when the diagnosis of auditory problems presents difficulties. A series of three different groups have presented data as to the possible usefulness of auditory testing under sleep:

(1) Peripherally deaf children (i.e. children with lesions of cochlea or cochlear nuclei).
(2) Children with language disorders.
(3) Children suffering from athetosis.

The series included children from the first year of life.

Results

In the peripherally deaf, the waking and sleep responses correlate closely, whereas in the second group, unless there was a concomitant peripheral loss, the sleep responses were obtained to very quiet sounds.

The athetoid children were found to be divided into two groups. Those who had language disorders and those who had a more peripheral type of lesion and responded as peripherally deaf children.

The sleep EEG was shown to be valuable as a prognostic guide to the likely eventual responsiveness in the conscious state.

REFERENCES

Davis H, Davis P A, Loomis A L, Harvey E N & Hobart G (1939) *J. Neurophysiol.* **2**, 500

Oswald I, Taylor A M & Treisman M (1961) In: Ciba Foundation Symposium on the Nature of Sleep. Ed. G E W Wolstenholme & M O'Connor. London; p 343

Roth M, Shaw J & Green J (1956) *Electroenceph. clin. Neurophysiol.* **8**, 385

Taylor I G (1962*a*) MD Thesis, Manchester

(1962*b*) *Spastics Quart.* **2**, 37

Homocystinuria

by G M Komrower MB FRCP
and V K Wilson MSc
(*Mental Retardation Research Unit, Royal Manchester Children's Hospital*)

Among the increasing number of errors of amino-acid metabolism associated with mental retardation, the condition of homocystinuria has recently been described (Carson & Neill 1962, Waisman *et al.* 1962, 1963, Carson *et al.* 1963). The first case identified in the Royal Manchester Children's Hospital is described below.

CASE HISTORY

J W, female, born 2.2.54

History: The only child of two intelligent parents. Born by vaginal delivery at 36 weeks, weighing 5 lb 13 oz. Apparently progressed well, talking at 12 months and walking at 14 months. She was a hyperactive infant who did not sleep well, but was a lively, active child with good co-ordination until 4½ years of age. At that time she had the first immunization against poliomyelitis (Salk vaccine) and within forty-eight hours she had a generalized convulsion. When she recovered consciousness she had lost control of her legs and it was a fortnight before she was walking satisfactorily. The description of her movements at the time suggests ataxia, and this condition recurred following the second immunization when in addition she became hysterical, talked incessantly and said that she could not see anybody. She became quite violent and was admitted to a local hospital where a detailed neurological investigation, including Myodil ventriculography, was carried out. She was discharged with a diagnosis of encephalitis.

Following this illness her condition deteriorated with impaired co-ordination, clumsy slow movements and a refusal to speak when in public. Her shyness has precluded her from learning anything at school and her teachers have made repeated reference to the rigidity of her muscles and her refusal to speak other than '—sss' for 'yes'.

Several unsatisfactory attempts had been made to estimate her IQ. She never scored more than 50 although it was felt that this did not represent the true level of her intelligence.

First seen in January 1962. Her parents stated that she was reserved and backward at school, she walked badly and had poor co-ordination of all limbs. She had not had a convulsion since her admission to hospital in 1958. More recently she had been seen by an ophthalmologist who said she had a high degree of myopia in both eyes and also bilateral dislocation of the lenses. Appetite

good. Bowel and bladder control normal. Sleep normal.

Family history: Father: many attacks of hay fever and asthma. Mother: good health. No history of convulsions. No other member of the family has had any allergic upset. One case of mental and physical retardation (D M, nephew of the patient's mother); probably due to cerebral birth trauma. No Irish or Scottish ancestry.

Examination: Height 48 in. (average for girl of 7 years 5 months). Weight 47 lb (average for girl of 6 years). Strikingly fair, with high colour of skin over malar bones; irides pigmented; the fair hair, which was coarse, broke very readily. Obviously myopic; it was impossible to see the fundi properly.

The examination was difficult as the child did what she was told but very slowly and refused to speak during the examination (she never spoke at any of the consultations held during the next twelve months). As a result sensory examination and co-ordination testing were very difficult.

Muscle development was poor, and the child was very flat-footed, walking like Charlie Chaplin. No disorder of heart, lungs or abdomen, but peripheral circulation was poor. Full movements of eyes, no nystagmus, no involvement of facial nerves, tongue or auditory nerve. Fingers long with thickening at interphalangeal joints. All tendon reflexes depressed; indifferent finger-nose co-ordination. Leg co-ordination was very difficult to test; it was impossible to abduct the hips satisfactorily due to increased tone in the legs. The mother said that this inability to relax had been very apparent but had improved over the past two or three months. She also said that the child spoke quite well and had a good vocabulary; this has been confirmed by tape recordings of her speech made while she was playing at home.

Investigations: Hb 90%. WBC 17,800 (polys. 77%, lymphos. 19%, monos. 4%).

X-rays: Hands long and delicate-looking, but do not qualify as arachnodactyly. Slight increase over normal metatarsophalangeal joint spaces in hands and feet. The distribution of the metaphyseal anomalies is symmetrical in the lower limbs and at the wrists, but not elsewhere in the upper limbs.

Urine chromatogram, medium square: Cysteic acid (9), serine (6), glycine (8), taurine (8), threonine (6), alanine (7), glutamine (7), valine (4), leucine (4), amino-isobutyric acid (6), histidine (5), methyl histidine (5). Urine amino-nitrogen 170 mg/24 h. Total nitrogen 4,357 mg/24 h. Marked amino-aciduria.

CSF normal. EEG within normal limits for age.

We had considerable reservation about the 'cystine' spot on the urine chromatogram and on more detailed examination by Dr D Cusworth, University College Hospital, this was found to be homocystine.

Further studies: Serum calcium 10·5, phosphorus 4·6 mg/100 ml, alkaline phosphatase 10 K-A units. Total serum proteins 6·3, albumin 4·1, globulin 2·2g/100ml. Liver function tests normal. EEG normal. Both homocystine and homocysteine were present in the blood (35% of the total in the free -SH form). Urine from both parents gave normal chromatograms.

Cousin, DM: Urine examination: Spot tests all negative. No ultraviolet bands. Large square: Cysteic acid (2), serine (5), glycine (5), glutamine (6), alanine (5), threonine (4), histidine (3), tyrosine (2). Slight amino-aciduria.

May 3, 1963: Operation performed on right eye for removal of lens which was now dislocating forward with evidence of increasing intraocular tension.

May 4, 1963: The child seemed in reasonably satisfactory condition although her colour had deteriorated slightly.

May 5, 1963: Died suddenly at 4.30 a.m. At autopsy a pulmonary embolus was found with an ante-mortem thrombus in the tributaries of the right femoral vein. This is a very uncommon finding in children.

Homocysteine, from which homocystine is produced, is an intermediate substance in the conversion of methionine to cystathionine and thence to cysteine. In this case homocystine was found in the blood and urine on all occasions, the mechanism of the urinary excretion being an 'overflow' one (Cusworth 1963, personal communication): Detailed studies (Carson *et al.* 1963) indicate a reduced ability to metabolize methionine following a loading test with L-methionine, with high renal clearances of this amino acid but with only slight increases in homocystine excretion. At the present time it is not possible to indicate the exact mechanism of the metabolic block or the way in which the widespread tissue upset is produced.

REFERENCES

Carson N A, Cusworth D C, Dent C E, Field C M B, Neill D W & Westall R G (1963) *Arch. Dis. Childh.* **38, 425**
Carson N A J & Neill D W (1962) *Arch. Dis. Childh.* **37, 505**
Waisman H A, Gerritsen T, Vaughan J G & Kaveggia E (1962) *Biochem. biophys. Res. Commun.* **9, 493**
(1963) Communication to annual meeting of Amer. Pediat. Soc. May 3–4, 1963

The following paper was also read:

Acquired Carbohydrase Deficiencies
Dr A Holzel

The following exhibits were shown:

(1) **Fatal Cases of Hæmorrhagic and Necrotic Enteritis**
(2) **Chromogenic Mycobacteria in Lymphadenitis**
(3) **Fluorescent Microscopy in the Diagnosis of Bacterial Infections**
Dr H B Marsden

Chromatography of Glycinuria, Homocystinuria, Argininosuccinic Aciduria and 'R' Disease, a Disease of Abnormal Tryptophan Metabolism
Miss V K Wilson
and Dr G M Komrower

Letterer-Siwe Disease
Dr J K Steward and Dr A Holzel

Brain Biopsy in the Diagnosis of Progressive Cerebral Defect
Dr L L R White

Estimation of Total Body Water and Extracellular Fluid by a Single Injection Method
Mr K Dixon

Defective Coagulation and the Effect of Vitamin K in the Newborn, Studied by the Thrombotest Method
Dr E O'Brien

Respiratory Syncytial Virus Infection
Dr L L R White and Dr J O'H Tobin

Meeting January 25 1963

The following papers were read on the subject of **Growth Disorders in Childhood:**

Methodology
Dr J M Tanner

Biochemical Investigation of Dwarfism
Dr Barbara Clayton

Treatment of Dwarfism
Professor A Prader (*Zürich*)