The response to extracts of normal urine is fairly wide, but the drop in eosinophil count, after the equivalent of 12 hours' urine from "normal" hospital patients, is usually between 20 and 60% under the conditions we have used, the mean for a small group being 46%. This is equivalent to about 10 μ g. of cortisone a day. Such a figure is considerably lower than has been found by other methods (Venning *et al.*, 1946), and a considerably higher amount has actually been isolated from

normal urine (Schneider, 1950). Our own low results may be due to the method of preparation of the extract and to other factors. At present, therefore, we do not attach significance to the absolute figure, but stress rather the value of the method for comparative purposes and for following changes under various conditions.

In contrast to the normal urines, ten extracts of urine from four cases of Addison's disease showed much lower average activity. Seven of these had no activity, and only two had activity as great as the normal. These two active extracts were both derived from a patient whose Addison's disease was clinically mild and who had active pulmonary tuberculosis. The mean drop for all ten extracts in this group was 10%. Five extracts from three cases of panhypopituitarism gave no significant drop in the eosinophil count. A pooled extract derived from five patients all eight months pregnant gave eosinophil depressions in six mice equivalent to about 25 μ g. of cortisone a day, a figure more than twice that found in normal urine. Another pooled extract of urine excreted during A.C.T.H. administration was tested at several dose levels and gave a response equivalent to 120 μ g. a day. Similarly, an extract from the urine of a woman with advanced adrenal cortical carcinoma with metastases, and associated with many features of Cushing's syndrome, was tried in 12-, 6-, and 3-hour doses, and indicated an excretion of about 40 μ g. a day, or about four times the normal average.

Several specimens of blood have been tested, a different method of extraction being necessary. Two 20-ml. samples of venous blood showed no activity, but in two of three 20-ml. samples of arterial blood slight activity was suggested. Much further trial is required before this difference can be regarded as significant.

Comment and Conclusions

The method proposed has been found a useful and practical one for detecting cortisone-like activity in urine extracts. Its applicability to blood is uncertain. Preliminary results with the method show activity in normal urine extracts and a raised excretion in late pregnancy, during A.C.T.H. administration, and in a case of adrenal cortical carcinoma. The cortisone-like activity was absent from the urine of most cases of Addison's disease and from three cases of hypopituitarism.

Further work is needed before the method can become established as a reliable one for quantitative assay. When expressed in terms of cortisone acetate the activity found in normal urine and in late pregnancy is lower than was found by Venning *et al.*, using the glycogen storage method. The cause of this discrepancy is being investigated.

Since this work has been completed observations on similar lines have been reported by Rosenberg and Lewis (1950).

My thanks are due to the Medical Research Council for a generous gift of cortisone acetate, and to Miss Xenia Boysen for technical assistance in the preparation of extracts and in the eosinophil counts.

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ADDENDUM.—Further work at present in progress indicates that the nature of the solvent has a large effect on the rate of absorption of cortisone and, therefore, on the eosinophil depression resulting from a given dose. The responses shown in the first three columns of the chart were obtained with cortisone acetate in saline suspension. When, however, the injected cortisone acetate is dissolved in a volume of 20% propylene glycol equal to that used for our urine extracts a much smaller eosinophil drop occurs. The responses to our normal urine extracts, when compared with cortisone acetate injected under identical conditions, are then equivalent to daily cortisone outputs averaging 50 μ g. The cortisone equivalent of other extracts is correspondingly increased, and these then become comparable to those found by Venning *et al.*

UNUSUAL AURAE IN TWO CASES OF EPILEPSY IN CHILDHOOD

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The term "aura," in relation to seizures, was introduced into medicine in A.D. 100 by Pelops, the instructor of Galen, although the Corpus Hippocratica (see the book *De Morbo Sacro*) witnesses that premonitory subjective symptoms ushering in seizures were not unknown to earlier Greek physicians. The first attempt at systematic description of such seizure prodromata was that made by Aretaeus of Cappadocia early in the second century A.D. Since his account the varieties of epileptic aura that have been described are legion. In more recent times they have been the subject of detailed study and classical account by Hughlings Jackson (1931-2), Gowers (1901, 1907), Penfield and Gage (1933), Penfield and Erickson (1941), and Kinnier Wilson (1941).

This communication describes two cases of epilepsy in childhood which are notable for the unusual nature of the pre-ictal phenomena. Such phenomena are of interest because they probably represent the initial expression of the epileptic discharge, and as such are pertinent to the problems of cerebral localization of function.

Case 1

A girl aged 6 was referred to Dr. W. Ritchie Russell by Dr. O'Connell, complaining of frequent seizures since the age of 2½ years. The child was the product of a normal pregnancy and labour, and is the second in the family; the other child is perfectly normal. There was no family history of seizures on either side or of earlier infantile convulsions. There were no complaints other than the seizures.

Description of Typical Seizure

All the seizures have been of the same type, and have not varied in character over the past 3½ years. They usually occur early in the morning just after the child awakes. There is no preliminary cry, but after a few minutes' profuse salivation she suddenly vomits without any preliminary abdominal discomfort. Every seizure is ushered in by this unheralded vomiting, and it is not until after this that the real ictus begins: she is quite conscious during the vomiting phase, but has no memory of it after the seizure. The child has no warning of the onset of a seizure until this sudden unexpected vomiting, which has therefore come to constitute for her an epileptic aura.

After the vomiting her eyes turn upwards, and at this stage she loses consciousness, continuing to salivate profusely. Her mother describes the remainder of the seizure as consisting of slight twitching of the whole body, following upon a mildly opisthotonic phase. Urinary incontinence has occurred on a number of occasions, and sometimes the child has bitten her tongue. There is no post-ictal drowsiness.

These seizures have occurred about five or six times a year, and do not seem to be increasing in frequency. The child is right-handed. There are no abnormal physical signs in any system, the fundi are normal, and the visual fields are full. The child is very intelligent, with a good school record, though rather shy and at times excitable.

E.E.G. Studies (Fig. 1)

Electroencephalographic examination reveals a relatively stable occipital alpha rhythm at 10 cycles per second. It is rather better developed than one would expect at this age. It is of lower voltage on the left than on the right, and responds briskly to photic stimulation. Its average voltage is 60 to 70 microvolts in the occipital leads. Some lower voltage activity at 10 c./s. is also visible in the paracentral and frontal leads. During the resting record there are paroxysmal runs of slow activity in all leads, made up of mingled 4- and 6-c./s. waves, with an average voltage of 50 μ V in the precentral leads and 80 μ V in the frontal leads. This slow activity is bilaterally synchronous and symmetrical. Hyperventilation for one minute shows that the electrical activity of the cortex is markedly unstable, as there is considerable increase in the 4-c./s. waves on both sides of the brain. In places in the frontal leads there are short paroxysms of atypical wave-and-spike formations at 3 c./s. The post-hyperventilation record shows some persistence of this abnormality beyond the usual period. There are no focal disturbances.

Case 2

A boy aged 11 was referred to Dr. W. Ritchie Russell by Dr. D. Harris, having had about 50 seizures during the preceding year. There were no other complaints. All of the seizures occurred early in the morning, after he woke up screaming. He has had several further seizures since he first presented himself for examination, and all have the same chronology.

FIG. 1.—E.E.G. showing portion of a typical paroxysm in Case 1, immediately after hyperventilation for one minute. Calibration is indicated in the lower right-hand corner of each record. The origin of the discharges is indicated by the diagrams on the left.

Description of Typical Seizure

Each attack begins in the night or early morning with a loud scream, followed by a mild tonic phase, most pronounced in the arms and hands, together with turning of the head and eyes to the right. He then becomes unconscious, and shakes all his limbs, at the same time making unintelligible noises, with grimacing and smacking of the lips.

The interesting feature of this history is the child's precise description of the aura which precedes these attacks. Just before he screams he has an organized visual hallucinatory aura (see Fig. 2), in which he sees hundreds of objects

FIG. 2.—Drawing, elaborated from sketches made by Case 2, of an example of his reduplicative hallucinatory aura, representing the door of his bedroom as it appears immediately before a seizure.

ranged behind one another in a line receding from him into the distance and towards the right of his visual field. These objects always consist of some article of furniture or other object at which he is gazing at the time the fit begins, and he sees them only when the room is not absolutely dark. In complete darkness there is no visual aura whatever. The objects appear smaller than their normal size, as if they are far away, but each seems larger than the one in front of it. He describes the sensation as seeming as if the objects were seen in a number of mirrors many times reflected. There are no subjective olfactory or gustatory concomitants. His mother had a normal pregnancy and confinement at his birth, and he had no early infantile convulsions. There is no history of seizures on either side of the family. Physical examination discloses no abnormalities, the fundi are normal, and the visual fields are full. The child is extremely intelligent, bright, and co-operative, although somewhat wilful.

E.E.G. Studies (Fig. 3)

Electroencephalographic examination discloses an unstable alpha rhythm with a mean frequency of 9 to 10 c./s. and an average voltage of 25 to 30 μ V, a little higher on the right than on the left. In the resting record there are short paroxysmal bursts of 4 c./s., 60- to 80- μ V slow waves, synchronous on both sides of the brain, but of somewhat higher voltage on the right.

FIG. 3.—E.E.G. showing a typical dysrhythmic paroxysm in Case 2, immediately after hyperventilation for one minute. Calibration is indicated in the lower right-hand corner of each record. The origin of the discharges is indicated by the diagrams on the left.

Hyperventilation for one minute reveals marked electrical instability, with the rapid appearance of 80- to 100- μ V 4-c./s. activity on both sides of the brain, including the temporal regions. During this period the patient usually becomes pale, and looks and feels as if he were going to have a seizure, but no such seizure is clinically apparent, although the typical aura is generally present. During the post-hyperventilation period paroxysmal bursts of 4-c./s. activity persist for several minutes.

Discussion

Case 1

The occurrence of unheralded vomiting as an introductory feature of an epileptic seizure is extremely rare, although various forms of abdominal disturbance (Vining, 1922; Watts and Frazier, 1935; Moore, 1944, 1945; Marchand and de Ajuriaguerra, 1948) are common, especially in children, in whom they may occur in up to 14% of cases (Patrick and Levy, 1924).

Sir William Gowers, in his Hughlings Jackson Lecture in 1907, mentions a case of a female child whose rightsided Jacksonian seizures were marked by vomiting in the initial phases of the seizure, but this did not occur until after the patient had lost consciousness. In earlier reports (Gowers, 1901) he had described three adult cases whose epileptic aura seems similar to that of the present case. One was a case with a vertiginous aura, in which nausea and vomiting preceded each major seizure. Another was a case in which minor seizures were preceded by extreme nausea as an aura, so that the patient took out his handkerchief on each occasion, expecting to vomit. The third case was one in which an aura of nausea was followed by vomiting before the fit began: later this aura was replaced by pre-ictal sialorrhoea and spitting, a fact which may be related to the marked salivation reported in the present case. These cases resemble earlier descriptions by Féré (1891, 1894) and Lemoine (1898). More recently Gram (1948) has reported the case of a child with episodes of vomiting accompanied by dysrhythmic episodes in the E.E.G.

In recent years Wilder Penfield (1949) and Wilder Penfield and Erickson (1941) have demonstrated that electrical exploration of the insula will often produce on the operating table a characteristic epigastric aura in patients who experience such sensations as an essential part of their seizures. It has also been suggested that such stimulation (Davey, 1949) may produce movements of the gut, intussusception, and occasionally vomiting. But, as Penfield has pointed out, effortless vomiting may occur after electrical stimulation of a wide variety of cortical areas.

Of interest to the present discussion, however, is a case noted by Penfield and Erickson (1941), in which a boy experienced a swimming sensation in the head, followed by a strong desire to vomit, as an introductory phase of his seizures. This sequence of events was found to be reproducible on the operating table by electrical stimulation of an area of softening in the left temporal lobe.

In this first case there was no evidence, either clinical or electroencephalographic, of focal disturbances related to the insula or temporal lobe; although in view of current physiological knowledge, principally that deriving from the studies of Penfield and his colleagues (Penfield and Gage, 1933; Penfield and Erickson, 1941), one might have expected to find an epileptogenic focus in the region of one or other fronto-temporal regions.

Case 2

The occurrence of organized visual hallucinations as an introductory epileptic phenomenon has also been well known since the time of Hughlings Jackson, and has been commented on by numerous writers. But the detailed description of the aura given by this young boy, and his sketches of some examples (Fig. 2), illustrate pre-ictal hallucinations of a type which has not often been recorded.

The only example of what might be called reduplicative imagery which I have been able to discover in the literature is a case mentioned by Kinnier Wilson (1941) in which 12 men arranged in a line were seen as a hallucination immediately preceding a grand-mal convulsion. Micropsia has been reported often enough (see Marchand and de Ajuriaguerra, 1948); and Gowers (1901) described several cases in which a visual aura consisted of an organized panorama seen in the far

distance. But there seems to be no case in the literature in which receding reduplicated images have been seen.

Another unusual feature is that the images are multiplications of objects actually seen—in the absence of illumination there are no hallucinatory phenomena. As these seizures were also characterized by turning of the head and eyes to the right and smacking of the lips, a left temporo-frontal focus was sought. It is generally considered that the occurrence of organized visual hallucinations indicates a disturbance in one or other temporal lobe, usually in the dominant hemisphere; and Penfield and Erickson (1941) and Marchand and de Ajuriaguerra (1948) classify seizures characterized thereby in the group of so-called "psychical seizures." In the present case, however, no clinical or electroencephalographic evidence of such a lesion could be found.

Conclusion

These two children have electroencephalographic records and clinical histories which suggest that they are suffering from a paroxysmal cerebral dysrhythmia of non-focal type. In each case the seizures are ushered in by unusual introductory phenomena, which, on current physiological grounds, might be expected to be related to disturbance in the anterior temporal lobe or island of Reil, but in which no evidence of such dysfunction can be found. It seems that these are cases of "idiopathic" epilepsy with unusual auras, and as such have responded to treatment with phenobarbitone, with disappearance of seizures over the past year, during which time they have been under regular supervision.

My thanks are due to Dr. W. Ritchie Russell for permission to report these cases from his clinic, to Miss F. M. Taylor for carrying out the electroencephalographic examinations, and to Miss A. Arnott for working up the patient's drawings.

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Arguing that blood does not normally clot in the vessels because of the chemical nature of the endothelial lining of the vascular system, which is probably an acidic polysaccharide such as mucoitin, Drs. Lovelock and Porterfield have prepared (see *Nature*, January 6, p. 39) an artificial surface with a similar high negative (anionic) charge. They show that polystyrene tubes after a brief treatment with sulphuric acid are much better than untreated tubes and very much better than glass-ware in holding blood both fluid and free of clots.

SIXTH-NERVE PALSY AFTER LUMBAR PUNCTURE AND SPINAL ANALGESIA

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Palsy of the sixth cranial nerve following spinal analgesia has been reported regularly since soon after the introduction of this method of pain relief, and it is perhaps a reflection on anaesthetists that most of the communications on this subject come from ophthalmologists. The incidence of the complication is difficult to determine. Mild degrees of abducens paralysis probably pass unnoticed or unheeded; and although the highest figure given, 1% of all spinal analgesics, by Terrien (1923) is considerable, it is possible that the figure should be considerably greater.

Paralysis of the various cranial nerves, except the first and tenth, has been reported, but there is general agreement that the sixth is most often involved. The lesion is discussed by many, including Mühsam (1906), Babcock (1913), Tovell (1933), Fairclough (1945), Steinberg and Bishop (1946), Rose and Pritzker (1947), Azambuja (1947), and Parke (1948).

Aetiology

The sequence of events is remarkably constant. The paralysis is not noticed until 3 to 21 days after the spinal analgesia, but it is preceded by a period during which the patient complains of severe headache and perhaps dizziness, nausea, stiff neck, photophobia, and diplopia. The delay in onset of the palsy has given rise to many theories about its causation, none of which is subject to proof. They may be summarized as follows:

1. *Mechanical*.—A rise in intracranial pressure causes a "coning" of the brain through the foramen magnum so that the sixth nerve (see Diagram), anchored between its entry into the cavernous sinus and its attachment to the pons, is stretched over the apex of the petrous portion of the temporal bone (Fairclough, 1945).

Diagram showing course of the sixth nerve. (After Wolff.)