The sites of primary disturbance to be considered in Cushing's syndrome are the adrenals, the pituitary, and the hypothalamus (Jailer and Longson, 1957). In this patient, though there is no direct evidence of primary lesions in the adrenals or pituitary, there is some indication that a hypothalamic disorder may be present, as disturbances at this site occur not uncommonly as sequelae of encephalitis.

In addition, variations in endocrine function, particularly adrenal over-activity, including Cushing's syndrome, have been attributed to hypothalamic disorders (Heinbecker, 1944; Wilkins, 1950; Rey *et al.*, 1957). Cyclical variations in hypothalamic activity are well known in animals (Zuckerman, 1954) and may be seen in patients with post-encephalitic Parkinsonism. Furthermore, in hypothalamic disorders psychological factors often influence the course of the disease, and it would seem that this type of stress may have occurred in the present case prior to the onset of each relapse, although in this patient and in the only similar case (Anderson and Haymaker, 1944) the relapses had a definite seasonal incidence. There seems to be little doubt, however, that in the present case a definite remission had been induced by giving cortisone, even though spontaneous improvement had been noticed at this time of the year during previous relapses.

Two further features of this case deserve comment. Firstly, it has been reported that Cushing's syndrome may occur during salicylate therapy (Cochran *et al.*, 1950), and, as moderate doses of aspirin were given to this patient during her initial symptoms in 1954, it was then suggested that salicylates may have been responsible. However, the subsequent course of her disease makes this unlikely. Secondly, a less well known clinical feature of Cushing's syndrome which this case illustrates is the occurrence in the early stages of renal calculi (Albright, 1943; Soffer *et al.*, 1955).

Summary

An unusual example of Cushing's syndrome demonstrating several spontaneous remissions is reported, along with a brief review of the literature on such cases.

We thank Dr. E. Wyn Jones for permission to publish a report on the above patient.

ADDENDUM

After the completion of the above report the patient remained well until July, 1960, when she experienced a further attack of Cushing's syndrome. About this time she also fell and injured her right leg.

In October she was readmitted to hospital as an acute abdominal emergency. At laparotomy, generalized peritonitis due to diverticulitis of the pelvic colon was found, and a transverse colostomy was performed. At this time she still showed all the clinical features of Cushing's syndrome, and a 24-hour specimen of urine contained 64 mg. of 17-keto-steroids and 94 mg. of 17-ketogenic steroids, and her serum electrolytes revealed a hypokalaemic alkalosis.

Her immediate post-operative progress was satisfactory, but on the tenth post-operative day she became hypotensive and died.

At necropsy there was a generalized peritonitis with fibrinous adhesions and a loculated pelvic abscess containing about 500 ml. of pus. The pelvic colon contained diverticula with some diverticulitis. The lungs showed bronchopneumonia, with abscess formation in the left lower lobe. The kidneys were somewhat fibrotic and small abscesses were present at the bases of some of the pyramids. The

adrenals were uniformly enlarged to about twice the normal dimensions, the left weighing 12.2 g. and the right 14.7 g. The cortex was thickened and showed bright yellow radial streaks. The pituitary was macroscopically normal and weighed 0.72 g. The thyroid, parathyroids, ovaries, and pancreas also appeared normal. No thymic tissue was recognized. The brain was macroscopically normal and the substantia nigra well pigmented. The head of the right femur was destroyed and the hip-joint contained 20–30 ml. of turbid yellowish fluid.

Microscopical Examination.—The adrenals were of normal architecture, but the cortical cells contained only small amounts of lipid. The pituitary basophils showed well-marked hyaline changes. No adenomata of the pituitary or adrenals were found. The thyroid, parathyroids, pancreas, and ovaries were histologically normal. Sections of the hypothalamus and mid-brain revealed no obvious abnormality. The lungs showed bronchopneumonia and early abscess formation.

We thank Professor H. L. Sheehan for the post-mortem report and histological studies.

REFERENCES

- Albright, F. (1943). *Harvey Lectures, 1942–43*, 38, 123.
 Anderson, E., and Haymaker, W. (1944). *J. ment. nerv. Dis.*, 99, 511.
 Cochran, J. B., Watson, R. D., and Reid, J. (1950). *Brit. med. J.*, 2, 1411.
 Crooke, P. C. (1958). *Ciba Foundation Colloquia on Endocrinology*, 12, 149.
 Cushing, H. (1932). *Bull. Johns Hopk. Hosp.*, 50, 137.
 Heinbecker, P. (1944). *Medicine (Baltimore)*, 23, 225.
 Jailer, J. W., and Longson, D. (1957). *Biochemical Disorders in Human Disease*, edited by R. H. S. Thompson and E. J. King, Chapter 7. Churchill, London.
 Knowlton, A. I. (1953). *Bull. N.Y. Acad. Med.*, 29, 441.
 Luft, R. (1958). *Ciba Foundation Colloquia on Endocrinology*, 12, 116.
 Plotz, C. M., Knowlton, A. I., and Ragan, C. (1952). *Amer. J. Med.*, 13, 597.
 Rey, J. H., Nicholson-Bailey, U., and Trappl, A. (1957). *Brit. med. J.*, 2, 843.
 Rowntree, D. W., and Kay, W. W. (1952). *J. ment. Sci.*, 98, 100.
 Soffer, L. J., Eisenberg, J., Iannaccone, A., and Gabrilove, J. L. (1955). *Ciba Foundation Colloquia on Endocrinology*, 8, 487.
 Sosman, M. C. (1949). *Amer. J. Roentgenol.*, 62, 1.
 Thompson, K. W., and Eisenhardt, L. (1943). *J. clin. Endocr.*, 3, 445.
 Wilkins, L. (1950). *Diagnosis and Treatment of Endocrine Disorders in Childhood*. Thomas, Illinois, U.S.A.
 Zuckerman, S. (1954). *Lancet*, 1, 739.

Medical Memoranda

Imipramine Overdosage—Report of a Fatal Case

Imipramine ("tofranil") is being increasingly used in psychiatric practice. It was introduced into this country in 1959 and has been found to be most useful in depression, particularly when this is endogenous. In a recent trial in this country (Ball and Kiloh, 1959), 74% of cases of endogenous depression showed a good result on imipramine compared with 54% on iproniazid; in addition, 59% of cases of reactive depression did well. The authors concluded that it is worth trying either iproniazid or imipramine in most cases of endogenous depression before trying electric convulsion therapy. Other reports show comparable results, and a large number of patients must now be taking the drug. Side-effects include dryness of the mouth, sweating, dizzy feelings, drowsiness, and nausea. In addition, English (1959) first drew attention to a coarse, often violent, tremor occurring in patients on imipramine. Foster and

Lancaster (1959) confirmed this finding in a group of their own patients, some of whom sustained injuries while taking the drug.

Only two cases of overdosage have been reported. Moll (1959) described the case of a woman aged 21 who took 100 tablets. In spite of gastric lavage, she became stuporous 75 minutes after taking the drug. Salient clinical features were rapid, stertorous respiration, restlessness on stimulation, ataxia, widely dilated pupils with slight but brisk response to light, very brisk but equal reflexes, and extensor plantar responses. There was a typical tonic-clonic grand-mal convulsion lasting 5 to 10 seconds. The patient returned to normal over the course of 36 hours. During recovery her temperature was 99.4° F. (37.4° C.). In the other case (Lancaster and Foster, 1959), a woman of 29 took 1,500 mg. After eight hours of apparently normal sleep she awoke agitated and with gross involuntary movements of limbs and neck. There was increased tone, but reflexes and plantar responses were normal. The temperature was 99.6° F. (37.6° C.). Recovery was complete in about three days, although she remained rather depressed.

CASE REPORT

A woman aged 24 was admitted to hospital as an emergency case on March 14, 1960, at 12.5 a.m. Three months previously it was discovered that she had been taking phenmetrazine ("preludin") for about two years as a stimulant. Since that time she had been under psychiatric care and had been treated with various drugs—chlorpromazine, phenelzine ("nardil"), and, more recently, imipramine, the last having been prescribed three days before. Thirty-six hours before admission she complained of perspiration and slight headache; these persisted until the day of admission. In the evening she went for a walk with her father and complained that the sweatiness and headache were worse, but she was able to complete the walk, and arrived home at about 9 p.m. She said she felt rather sleepy, and was left alone in a room for about 15 minutes, during which time, her parents admit, she had access to her supply of tablets. By the time they returned to the room she was complaining of increased headache, was very drowsy, and, in addition, there were spontaneous jerking movements. Her doctor, when called, found impaired consciousness with extreme restlessness, but the thing which impressed him most was her temperature, which was 106° F. (41.1° C.) (site not named), and he referred her to hospital.

On admission she had an axillary temperature of 106.6° F. (41.4° C.), which soon rose to 109.6° F. (43.1° C.). She was unconscious with rapid, stertorous, but regular respiration. Fundi were normal. Upper lids were half closed; the pupils were widely dilated, with no reaction to light. Jaws were tightly closed. All four limbs showed marked hypertonia in extension and the fists were clenched. There were occasional clonic contractions of the forearms. Reflexes were unobtainable owing to hypertonicity, and plantar responses were extensor. There was no response to painful stimuli. After cooling with iced sheets and a fan, the temperature fell to 106° F. (41.1° C.). However, she died suddenly less than an hour after arriving at hospital.

The immediate diagnosis presented a problem. Three conditions were considered—pontine haemorrhage, acute encephalitis, and poisoning by an unknown drug. The first was regarded as unlikely because of the gradual onset and the state of the pupils. There seemed no way of differentiating the other two conditions. However, a careful comparison of the number of imipramine tablets prescribed with those remaining showed a discrepancy of at least 25, allowing for usual dosage over the previous three days.

Post-mortem Examination.—There was profound engorgement, with cyanosis and petechiae, in the heart, lungs, and liver. In the heart there was terminal dilatation, and in the

bronchial tree some excess of mucus. The brain and meninges showed no macroscopic change—notably of encephalitis. The stomach contained a medium-sized food residue, with no pill or capsule separable. In summary, the necropsy findings were those of a drug overdose, and microscopy elicited no further facts. **Analysis:** Tests for aspirin, barbiturate, the amphetamine group, and vegetable alkaloids were negative. The delicate yellow-after-blue tint characteristic of imipramine was obtained from stomach and upper-bowel content, but not from minced liver. It was concluded that the cause of death was hyperpyrexia and central respiratory failure due to imipramine. There was therefore clinical and pathological evidence that the patient died from a drug overdose, and that imipramine was the drug concerned.

COMMENT

The most striking clinical feature was the hyperpyrexia. The axillary temperature reached 109.6° F. (43.1° C.), and it is likely that the body temperature was even higher. Chlorpromazine, which is chemically related to imipramine, is well known for its effect on temperature regulation, and Sigg (1959) stated that this effect occurs but is less marked with imipramine. Domenjoz and Theobald (1959) found that intraperitoneal imipramine produced a fall in temperature in rats, but they did not comment on the environmental temperature. Increase in motor activity is well recognized as an effect in animals (Domenjoz and Theobald, 1959), and also convulsions can be produced or increased (Domenjoz and Theobald, 1959; Van Meter, Owens, and Himwich, 1959). In man the coarse tremor both at rest and on purposive movement have been previously mentioned (English, 1959; Foster and Lancaster, 1959), and it has been noted that convulsions may be induced in epileptics (Kuhn, 1959). In the two cases previously reported, involuntary movements and hypertonia were present and in one there was a type of convulsion.

In the present case there was extreme restlessness followed by hypertonia and convulsive movements. All these factors would tend to raise the temperature in the presence of an impairment of temperature regulation. In addition, the extreme pallor noted in Lancaster and Foster's and the present cases suggests extreme vasoconstriction, which would act in the same direction.

It is doubtful if any measures could have saved the life of this young woman. However, in further cases, in addition to making attempts to lower the temperature, it would be reasonable to diminish the excess muscular activity with a muscle-relaxant drug. This would necessitate assisted respiration via intubation or tracheotomy.

I thank Lord Evans for permission to publish the case, and H.M. Coroner, Mr. A. Gordon Davies, and Dr. Keith Simpson for permission to report the post-mortem findings. I am grateful to the medical department of Geigy Pharmaceutical Limited for much helpful advice.

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REFERENCES

- Ball, J. R. B., and Kiloh, L. G. (1959). *Brit. med. J.*, **2**, 1052.
- Domenjoz, R., and Theobald, W. (1959). *Arch. int. pharmacodyn.*, **120**, 450.
- English, H. L. (1959). *Lancet*, **1**, 1231.
- Foster, A. R., and Lancaster, N. P. (1959). *Brit. med. J.*, **2**, 1452.
- Kuhn, R. (1959). Quoted by Van Meter *et al.* (1959).
- Lancaster, N. P., and Foster, A. R. (1959). *Brit. med. J.*, **2**, 1458.
- Moll, A. E. (1959). *Canad. psychiat. Ass. J.*, **4**, Special Suppl. S. 64.
- Sigg, E. B. (1959). *Ibid.*, Special Suppl. **4**, S. 75.
- Van Meter, W. G., Owens, H. F., and Himwich, H. E. (1959). *Ibid.*, Special Suppl. **4**, S. 113.