In six cases E.E.G. studies were carried out to ascertain if the phenomena described by Roth as occurring in the electric shock treatment of depression would occur. The change was seen in one case out of six, and at the point when a striking clinical improvement occurred in a woman suffering from obsessional illness.

With this unpromising material it was possible to obtain a much closer emotional rapport than by using other forms of abreaction. The patients would show great emotion, and discuss previously repressed material relating to their conflicts in the frankest manner and with great emotion. In some cases the patients were able to free themselves from antisocial sexual habits of a criminal character.

In cases in which horrific war experiences had been a causal factor the patient relived the incident with marked emotional expression of fear and rage. A strong abreaction was of favourable prognostic significance.

Thirty-eight (76%) patients stated that they had received immediate emotional relief from the treatment. Twenty-five (50%) have shown an improvement lasting from six months to two years. Illustrative cases are given.

The treatment has been found valuable in conjunction with psychotherapy in treating chronic cases of neurosis and behaviour disorder, and may be superior to other methods of abreactive therapy.

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ACUTE PORPHYRIA

EXPERIMENTAL TREATMENT WITH A.C.T.H.

BY

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In the past two decades the clinical study of the porphyrias has received growing attention. The aetiology of these diseases, however, remains obscure and their treatment symptomatic. It was perhaps inevitable that a new therapeutic agent, such as A.C.T.H., would be tried in the treatment of this puzzling group of diseases, particularly as it has been suggested that there may be some connexion with hypofunction of the adrenals. Myerson (1951) and Oltman and Friedman (1951) did not find A.C.T.H. of value in this condition.

This paper reviews the clinical features of two cases of acute idiopathic porphyria, in one of which a course of A.C.T.H. was given.

Case 1

A man aged 28 was admitted to the Western Infirmary, Glasgow, on February 21, 1946, suffering from severe abdominal pain; he gave a history of four previous attacks of abdominal and limb pain. His first bout was in September, 1944, when he was serving in the Royal Air Force, and his condition was diagnosed in an R.A.F. hospital as idiopathic porphyria. He had been a coal-miner before joining the R.A.F., and had had no previous ill-health. There was no family history suggestive of porphyria.

Since February 21, 1946, six further attacks were observed in the Western Infirmary, and he was admitted on numerous occasions to Ayr County Hospital. Dr. R. Hill is publishing observations made on this case while under his care in the latter hospital. Some episodes of porphyria were characterized by abdominal pain only, but several showed both colicky pain and polyneuritis. They varied in duration from a few days to a month.

A typical bout observed in the Western Infirmary and beginning on September 22, 1946, had the following features. While in apparently good health, the patient noticed that his urine became darker in colour. Within a few hours generalized abdominal pain developed; the pain was continuous and was punctuated by frequent bouts of colic of great severity. At this stage the abdomen was as rigid as in a case of perforated peptic ulcer. He was constipated and his urine became scanty and reddish black in colour. A persistent tachycardia up to 150 a minute was present, and the blood pressure rose to 170/130 (his normal blood pressure was 120/90). Within one week the abdominal pain subsided and was succeeded by pain in the thighs, with marked spasm of the abductors and hamstrings. The pain spread to involve the muscles of all four limbs, which showed hypotonicity, pronounced wasting, and diminished tendon reflexes. No loss of vibration or tactile sense was noted, but the muscles were very tender. This polyneuritic phase lasted three weeks. The pain gradually lessened during the final week, and this was accompanied by reduction in the intensity of the urinary coloration. Convalescence was rapid when the pain subsided.

During the acute stages of a few attacks mental confusion and hallucinations were noted. Staphylococcal skin infections were common, and in one episode bronchopneumonia developed (September 10, 1948). The patient stated that during his attacks he tended to become "blue in the face." Body weight fell by about 30 lb. (13.6 kg.) during each attack, but weekly records failed to demonstrate any weight loss before the onset of pain.

Investigations.—Repeated clinical and laboratory investigations were carried out during the attacks, and the following abnormalities were found: (1) The patient continuously excreted uroporphyrins, almost entirely the Series III isomer, with a marked rise in excretion during acute attacks. The isomer type was established by partial decarboxylation and separation of the resulting mixture of coproporphyrins. (2) The plasma chlorides fell to levels around 0.52 g.% (as NaCl) during attacks. (3) Liver-function tests showed some impairment of hippuric acid synthesis.

Treatment of the acute attacks by intravenous calcium gluconate, by saline and glucose-saline, or by the injection of whole adrenal extracts ("eucortone"), of D.C.A., and of B-group vitamins produced no significant improvement. The symptomatic treatment of pain required large doses of morphine-type drugs over long periods.

At the time of writing the patient's condition is satisfactory, though his urinary porphyrin excretion is still above normal and includes uroporphyrin. Recently the episodes have consisted of mild attacks of abdominal discomfort of a few hours' duration, occurring every three to four months. The attacks are adequately controlled by minor analgesics, and he is able to work as a storeman.

Case 2

A single woman aged 21, a whisky-bond worker, was admitted to the Western Infirmary, Glasgow, on January 19, 1951, because of lower abdominal pain, nausea, vomiting, and constipation of two days' duration. The pain was constantly present, but became more severe and colicky at times. She had been normally active and healthy until two months before her admission to hospital, but since then her mother thought she looked "thinner in the face" and was not so active as previously. So far as could be ascertained she had taken no drugs in the past few months. There was nothing of note in the family history.

On admission the patient was anxious, was crying, and was in great pain. A noteworthy feature was that her lips, ear-lobes, and finger extremities were cyanosed and remained cyanosed for about three to four days. Her temperature was 100.2° F. (37.9° C.), pulse rate 140, blood pressure 150/115, and white blood count 8,200 per c.mm. General physical examination revealed no abnormal signs except some slight generalized abdominal tenderness. There was no rigidity of the anterior abdominal wall.

On the day after admission her abdominal pain remained very severe and she was still vomiting. It was noted that her urine was rose-brown in colour, and gave the spectrum characteristic of porphyrin. The reaction of the urine to Ehrlich's aldehyde reagent was strongly positive. The pain continued for two days, then diminished greatly in severity as she began to menstruate on January 22, 1951. For the next month she had little abdominal pain, but complained of shooting pains in the medial aspect of both thighs. She was up and about the ward, her blood pressure had returned to normal (115/80), and her urine was clear.

On February 19, about one month after her admission and just before her expected period, she started a prolonged and severe attack with almost constant abdominal pain, and with tachycardia, amenorrhoea, and the passage of red-brown urine. In this phase, lasting about six weeks, she lost 28 lb. (12.7 kg.) in weight. There was marked and progressive mental deterioration. She often screamed and shouted in the ward, had visual hallucinations, and threatened suicide. In order to provide relief she was given, on different occasions, opiates, chloral hydrate, paraldehyde, nicotinamide, diphenhydramine hydrochloride ("benadryl") methylene blue, kaolin, and intravenous calcium gluconate. With the exception of the opiates, chloral hydrate, and paraldehyde, these drugs did not seem to benefit her.

By March 27 her general condition had become very poor. She was weak, hypotensive (B.P. 70/54), somewhat dehydrated, and still in agony with abdominal pain. Up to this time she had required large doses of sedatives, and this aggravated the dehydration. She was given 1½ pints (850 ml.) of normal saline by a subcutaneous drip (using hyaluronidase, 9 mg.) and began a course of A.C.T.H. A daily dosage of 50 mg. was given for one week, in six-hourly injections of 12.5 mg. intramuscularly. Her general condition improved within one or two days, and her blood pressure rose to 120/100. She required less sedatives, and thus was able to drink more, and the urinary output improved. She became euphoric and excited at times and began to sing to the other patients. Her physical condition improved slowly, and, although she still passed reddish urine and was still depressed and unstable, she was allowed home on April 19. Three months later she was free from pain, had put on weight, and had almost returned to her normal mental state.

Investigations

Blood examination resulted as follows: Hb, 11.4 g.%; red cells, 4,280,000 per c.mm.; P.C.V., 43%; M.C.V., 100 μ^3 ; M.C.H.C., 27%; white cells, 7,400 per c.mm. (neutrophil polymorphs 80%, lymphocytes 17%, eosinophils 2%, basophils 1%); reticulocyte count less than 1%; icteric index, 3 units; E.S.R. (Westergren), one hour 4 mm., two hours 7 mm. Film showed no abnormality. The blood picture showed no change on repeated examinations during

her stay in hospital. The Coombs test and red-cell fragility test were normal. Repeated estimations of serum sodium and chlorides before, during, and after A.C.T.H. administration were normal. Alkaline phosphatase was 7 King-Armstrong units; cephalin flocculation and colloidal gold tests were negative; total plasma protein 6.85 g.% (albumin 4.57 g.%, globulin 2 g.%, fibrinogen 0.28 g.%); non-protein nitrogen, 36 mg. per 100 ml.; blood urea, 34 mg. per 100 ml.; van den Bergh reaction, negative; blood cholesterol, 165 mg. per 100 ml. The electrocardiogram and the x-ray film of the chest were normal.

The adrenaline-eosinophil test (Recant *et al.*, 1950) was carried out on two occasions. On March 19 the eosinophil count changed merely from 248 to 246 per c.mm. four hours after the subcutaneous administration of 5 minims (0.3 ml.) of 1:1,000 adrenaline hydrochloride. This was repeated three days later and showed a drop from 181 to 137 per c.mm. four hours after the subcutaneous injection of 7 minims (0.42 ml.) of 1:1,000 adrenaline. After A.C.T.H. was given on March 27 her eosinophil count fell from 147 per c.mm. to zero in four hours.

The urine contained uroporphyrin, mainly of Series III. An amyl alcoholic extract of the urine was very fluorescent under ultra-violet light. Quantitative estimations of the total daily urinary uroporphyrin excretion before, during, and after A.C.T.H. therapy were carried out after preliminary heating of the urine at pH 4.8 as described by Grieg *et al.* (1950). The results were as follows (see Graph):

Comment

These two cases conform to the usual clinical picture of acute idiopathic porphyria. In Case 1 there were numerous episodes over a period of seven years, and in the second case two attacks occurred in three months. Thus the condition is often a subacute or chronic one, though it may appear acutely in its presenting phase.

The age of onset—22 years in Case 1 and 21 years in Case 2—is typical of this disorder, which usually begins in the third decade. In both cases the presenting features were acute colicky abdominal pain associated with tachycardia and hypertension. Definite board-like rigidity occurred in Case 1 but not in Case 2. Grossfeld (1951) and Chandler *et al.* (1939) reported cases in which the abdominal signs were such that laparotomy was performed.

Pain in the limbs occurred in both patients, but manifest neurological signs were present only in Case 1. In this case mild mental confusion and hallucinations occurred during acute attacks. In Case 2, on the other hand, there was a pronounced toxic psychosis; the patient's personality completely changed and only returned nearly to normal several months after the acute attack had settled.

During the acute phases weight loss was noted in both patients, but records taken in Case 1 failed to demonstrate the pre-episodic fall stressed by Discombe and D'Silva (1945).

Cyanosis of the extremities, and especially of the lips, was striking in Case 2, while Case 1 was described as becoming "blue in the face" during attacks. Similar cyanosis has been described by Turner (1938). Venous blood from Case 2, examined during this cyanosed phase, did not contain methaemoglobin, and a short course of methylene blue, given empirically, had no apparent clinical effect.

The dramatic fluorescence, under ultra-violet light, of urine containing porphyrins encouraged us to examine the skin of Case 2 under that light. Interest was aroused when tiny pin-points of intense rose-pink fluorescence were found on the naso-labial folds and on the anterior and posterior surfaces of the patient's chest. A few days later, however, it was found that the application of the proprietary talcum powder used by the patient produced similar fluorescence in a normal control. Abrahams *et al.* (1947) also failed to find skin fluorescence in their case of acute porphyria.

It is well known that a clinical state of hypotension with low serum sodium and chlorides may supervene in acute porphyria, although in some cases these changes are not observed. Abrahams *et al.* (1947) and Linder (1947) have suggested that this is due to adrenal insufficiency and have used eucortone in this phase, but without much success. On the other hand, Davies (1949) believes that these changes in electrolytes are due to renal causes. In Case 1 low serum chlorides were found, though no fall in blood pressure occurred during an attack. In Case 2, however, a profound state of peripheral circulatory failure developed, though no biochemical changes were revealed. Rawlings (1950) reported the case of a 22-year-old woman suffering from idiopathic porphyria who showed remarkable clinical improvement on becoming pregnant. The stimulus of pregnancy upon the anterior pituitary is well recognized, and Rawlings's report is also reminiscent of Hench's original observation on rheumatoid arthritis. It was felt, therefore, that a trial with A.C.T.H. was justified in Case 2.

The significance of the negative adrenaline test and the normal eosinophil response to A.C.T.H. is doubtful. According to Recant *et al.* (1950) adrenaline is a non-specific stimulator of the pituitary-adrenal axis. A positive test is said to suggest a normal response of the pituitary and adrenal glands, "but recent work has cast doubt on this interpretation" (Prunty *et al.*, 1951; Kark and Muehrcke, 1952). The normal response to A.C.T.H. in our case presumably indicates that the adrenals act in this respect normally, but our findings might suggest an anterior pituitary dysfunction. Further inference that acute porphyria is associated with endocrine changes might be drawn from the frequency with which attacks occur in the immediate premenstrual period, from the greater incidence of the disease among women, and, in our Case 2, from the patient's amenorrhoea, which has persisted for five months after the cessation of her symptoms of porphyria.

Clinically, the administration of parenteral fluid and A.C.T.H. undoubtedly improved Case 2 during her hypotensive phase. The effect of A.C.T.H. on porphyrin excretion cannot be judged on one case alone. The pronounced rise in urinary porphyrins on the third day of treatment followed by a lowered excretion during the period of A.C.T.H. treatment is of interest, but similar large fluctuations in daily porphyrin excretion have been recorded previously (Rimington, 1943); they render difficult the evaluation of any therapeutic trial. The mean daily uroporphyrin excretion during the periods immediately preceding and following the administration of A.C.T.H. were 19.6 and 14.4 mg. a day respectively. During treatment the mean figure was 31.4 mg. a day, or, if March 29 is excluded, 13.5 mg. a day. There is no indication, therefore, that the treatment with A.C.T.H. lowered the porphyrin excretion in this experiment. The drug may, however, be worthy of further trial in porphyria, especially in the so-called "adrenal

insufficiency" phase of the disease, when this is present. Further experience by two of us (C.R. and A.G.) in the treatment of other cases of porphyria with A.C.T.H. leads us to conclude that the drug does not significantly alter the uroporphyrin excretion. In one case with persistently lowered serum chlorides (approximately 400 mg. per 100 ml., expressed as NaCl), unresponsive to added oral salt or parenteral normal saline, the administration of A.C.T.H. brought about a prompt and sustained restoration of the normal level (approximately 560 mg. per 100 ml.).

The presence of a toxic psychosis was considered as a possible contraindication to A.C.T.H. treatment. Towards the end of the week's course the patient became rather euphoric and excitable, and it was perhaps fortunate in this respect that A.C.T.H. was discontinued after seven days.

Sedation and the relief of pain in this condition present important and difficult problems. In both our cases opiates were used in large doses without any resultant addiction.

The prognosis is generally regarded as poor. Nesbitt (1944) remarks that the immediate mortality may be as high as 80 to 90% in acute episodes showing neurological manifestations. Happily, both our patients are now in good health. Case 1 is carrying on a useful job, and has recently been married. Case 2 is free from pain, is putting on weight, and has almost recovered her previous mental stability, five months after the cessation of her symptoms.

Summary

Two cases of acute idiopathic porphyria are described. One of them was treated with A.C.T.H. for a period of one week, but without any significant lowering of the mean daily uroporphyrin excretion.

The clinical manifestations and certain factors in diagnosis and treatment are discussed.

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Opening a conference on housing research in South Africa on November 17, the Minister of Health and Social Welfare, Dr. K. Bremer, said that housing in Africa had become an urgent problem. Increasing urban native populations now urgently required houses of a new standard. Estimated requirements for native housing were 350,000 dwelling units over the next 10 years at a cost of approximately £100m. Europeans also needed houses. The problem was not unique to South Africa, and most countries in Africa were experiencing similar difficulties. The National Building Research Institute was studying the problems, including how to reduce building costs.