# PORPHYRIA — THE ACUTE ATTACK*

## AN ANALYSIS OF 80 CASES

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### INTRODUCTION

The clinical and biochemical findings in cases of acute porphyria have been reported sporadically for many years, but there are surprisingly few comprehensive analyses of large series.[1-3] The acute attacks in both Waldenstrom's and Goldberg's series were presumably due to pyrroloporphyria[4] (Swedish genetic porphyria). Similar acute attacks, however, also occur in cases of protocoproporphyria (South African genetic porphyria). Differentiation of these two conditions may be difficult, since both are inherited as Mendelian dominant traits. In both, uroporphyrinuria occurs, and porphobilinogenuria is a prominent and important diagnostic feature of both conditions during the acute attack. However, cutaneous involvement, although not invariable, is common in protocoproporphyria, and is not a feature of the Swedish type. Furthermore, there is increased faecal excretion of copro- and protoporphyrins in protocoproporphyria, while this is normal or only slightly raised in Swedish porphyria.

The purpose of this report is to present the findings during the acute attacks in a series of 80 patients, most of whom had protocoproporphyria. Seven patients with pyrroloporphyria are included in the analysis, since the

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same clinical features characterize the acute attack in that condition.

### CLINICAL FEATURES

The 80 patients (25 males and 55 females) were made up of 62 White, 16 Coloured and 2 Bantu patients. The family history was positive in 52 of these patients.

These patients have had 107 attacks; 17 had more than one attack (11 had 2, 4 had 3, 1 had 4, and 1 had 6 attacks). The ages at which the first attacks occurred are shown in Table I.

TABLE I. AGE OF PATIENTS AT FIRST ATTACK

| *Age (years)* | *Male* | *Female* | *Total* |
|---|---|---|---|
| 11—20 | 3 | 5 | 8 |
| 21—30 | 7 | 13 | 20 |
| 31—40 | 8 | 20 | 28 |
| 41—50 | 5 | 11 | 16 |
| 51—60 | 1 | 3 | 4 |
| 61+ | 1 | 3 | 4 |
| | 25 | 55 | 80 |

Over 80% of the attacks occurred during the third, fourth and fifth decades, the peak incidence being in the fourth decade. The youngest patient was 17 years old and the oldest patient 77 years.

The majority (51 patients) had cutaneous involvement. In most this had preceded the acute attack by many years. The characteristic increased fragility of the sun-exposed skin, the production of abrasions and bullae as a result of trivial trauma, and the subsequent scarring, were usually unmistakable. In some patients, however, increased fragility was the sole cutaneous manifestation and the scarring was minimal or absent.[5]

Where acute attacks occurred without cutaneous involvement, a family history of increased cutaneous fragility and/or the finding of increased faecal porphyrins established the diagnosis as one of protocoproporphyria. Of the 29 patients who had acute attacks without skin involvement, 7 had Swedish porphyria, and in all but 9 of the remaining 22 information was sufficient to establish the diagnosis as one of protocoproporphyria. All of these except 1 were South African born.

### PRECIPITATING FACTORS

In some of the attacks the operation of a single precipitating factor appeared likely, but in many instances multiple factors had to be considered. These included drugs (notably the barbiturates and the sulpha drugs), over-indulgence in alcohol, the effects of anaesthesia and operative procedures, infections, and mental stress.

The administration of a barbiturate in close relationship to the onset of the attack figured prominently. This was so in 47 of the 107 attacks. Phenobarbitone and thiopentone had been used most frequently, followed by butobarbitone, quinalbarbitone, pentobarbitone and amylobarbitone. In 12 of the 47 instances more than 1 barbiturate had been administered. Unidentified sleeping tablets and analgesics had been taken in a further 14 attacks. It should be noted that 2 patients with epilepsy had received phenobarbitone continuously for many months before the development of the acute attack.

Furthermore, in many instances symptoms had preceded the administration of the drug. Thus, while thiopentone anaesthesia may have played a part in the genesis of the acute attack in 18 patients, in only 8 of these was abdominal pain *not* already present. In this group of 8 the indications for operation were: severe menorrhagia in 3, and in the other 5 the following conditions — pelvic infection, recto-vaginal fistula, tonsillitis, torn medial meniscus of the knee, and varicose veins. In the remaining 10 patients in whom abdominal pain preceded the operative or investigative procedure in which thiopentone anaesthesia was used, appendicectomy was performed in 4, laparotomy in 3, hysterectomy in 1, and gastrectomy in 1, and cystoscopy was carried out in 1. In only 1 of the 18 patients was there no neurological or psychiatric involvement. The development of the neurological syndrome correlated more closely with the administration of thiopentone. Of these 18 patients, 12 had undergone operations previously without ill effects, although in 6 thiopentone had been used.

A further 25 patients had undergone operations (more than 1 operation in some cases) months or years before their admission to this hospital (appendicectomy in 12, hysterectomy in 3, dental clearance in 2, varicose-vein ligation in 2, and tonsillectomy in 2; in the remaining cases, laparotomy, myomectomy, dilatation and curettage, bone graft, tendon suture, and drainage of osteitis). Seven definitely, and 4 probably, had received thiopentone previously. Four patients had had a stormy postoperative convalescence, possibly from mild attacks of acute porphyria. One fatal attack followed dental extraction under local anaesthesia with subsequent sulpha-drug therapy. One patient, with a history of 2 severe acute attacks 6 years previously, underwent dilatation and curettage under thiopentone anaesthesia subsequently at another hospital without ill effect. Sulpha drugs alone and over-indulgence in alcohol each preceded attacks on 6 occasions.

Many of the above patients had infections in addition, but in 11 infections alone, usually of the respiratory tract, were present. While in 4 mental stress and great anxiety were major factors, in 18 no precipitating factor could be invoked. Three patients were pregnant and in 5 instances the attack occurred postpartum within 2 months of delivery. In several of the female patients attacks occurred premenstrually.

### SYMPTOMS AND SIGNS

Abdominal and nervous manifestations occurred together in 68 attacks, abdominal alone in 33, and nervous alone in 6. The incidence of various symptoms and signs is depicted in Tables II and III.

#### *Symptoms*

Characteristically, the acute attack commences with cramp-like abdominal pain which is frequently described as deep-seated. It may be located in any quadrant and often radiates to the back, into the thighs and less often to the chest. The pain is usually continuous, but fluctuates in intensity and at times may be extremely colicky. When it is severe, the patient pleads for injections and in a vain

TABLE II. SYMPTOMS

| Symptom | % of attacks in which present |
|---|---|
| Abdominal pain | 90 |
| Vomiting | 80 |
| Constipation | 80 |
| Pain in limbs | 51 |
| Pain in back | 50 |
| Confusional state | 32 |
| Severe confusion plus hallucinations | 18 |
| Increased frequency of micturition | 31 |
| Dysuria | 28 |
| Abnormal behaviour and personality change | 23 |
| Epileptic seizures | 12 |
| Status epilepticus | 2 |
| Diarrhoea | 8 |
| Stupor | 7 |
| Coma | 6 |
| Amaurosis | 3 |

effort to gain relief adopts unusual positions. Abdominal pain is the commonest presenting symptom and is present at some stage in 90% of cases, but there is frequently a striking discrepancy between the patient's complaint of intolerable pain and his ability to discuss it freely — often with a facile smile! This leads the unwary to make a diagnosis of hysteria. Constipation, nausea and vomiting are common. Vomiting frequently occurs repeatedly and constipation is extreme, periods of 7 days or more without bowel action being common, thus simulating intestinal obstruction. An increased frequency of micturition and dysuria occurs in about one-quarter of the patients. Severe aching pains in the limbs are present in about half the patients and this usually heralds the advent of neurological involvement.

*Signs*

On physical examination at this stage over 80% show a well-marked sinus tachycardia — usually 120 beats per minute or more. An elevated temperature is much less common. Temporary hypertension of moderate grade occurs in about half the patients; only in one instance was hypertensive encephalopathy encountered. Hypotension is rare. Great motor restlessness is usually evident, signs of dehydration are often prominent and sweating is sometimes extreme. There is a characteristic lability or mood imbalance with alternation between withdrawal and overt anxiety or apprehension which in some cases amounts to irrational fear.

TABLE III. SIGNS

| Sign | % of attacks in which present |
|---|---|
| Tachycardia | 83 |
| Hypertension | 55* |
| Motor neuropathy | 53 |
| Mild | 19 |
| Severe | 34 |
| Pyrexia | 38 |
| ECG abnormality | 23** |
| Leucocytosis > 12,000 | 20 |
| Bulbar involvement | 18 |
| Objective sensory loss | 15 |
| Cranial-nerve involvement | 9 |
| Proteinuria | 8 |
| Hepatomegaly (> 2 fingers) | 5*** |

Nystagmus occurred in 3 patients, and serratus anterior paralysis in 1.
*There were 8% with established hypertension.
**Other than tachycardia.
***Including patients with congestive heart failure, Hodgkin's disease, and myelosclerosis.

The abdomen may be scaphoid, but distension sometimes occurs. While tenderness on palpation is frequently noted, there is no rigidity or rebound tenderness and visible peristalsis is not seen. Despite these findings cases are commonly misdiagnosed as acute surgical emergencies, and the scars of previous operations testify to this. X-ray of the abdomen at this stage will usually show some segmental dilatation of small or large gut, commonly at the splenic flexure, and areas of spasm may also occur.

Oliguria is common and the urine may be dark in colour, the degree being variable and commonly increasing with standing. Anaemia is rare, the haemoglobin being less than 12 G. per 100 ml. in only 10% of cases. A leucocytosis exceeding 12,000 white blood cells per c.mm. was found in 20%, and the erythrocyte sedimentation rate exceeded 20 mm. per hour in 24% of the patients.

*Progress*

In many patients these symptoms and abnormal signs subside rapidly over the course of 1 - 3 weeks, with complete recovery. Fig. 1 illustrates the rapid resolution in such a patient. In other patients, however, a variable time after the onset of abdominal pain (usually a few days) neurological and/or neuropsychiatric symptoms appear.

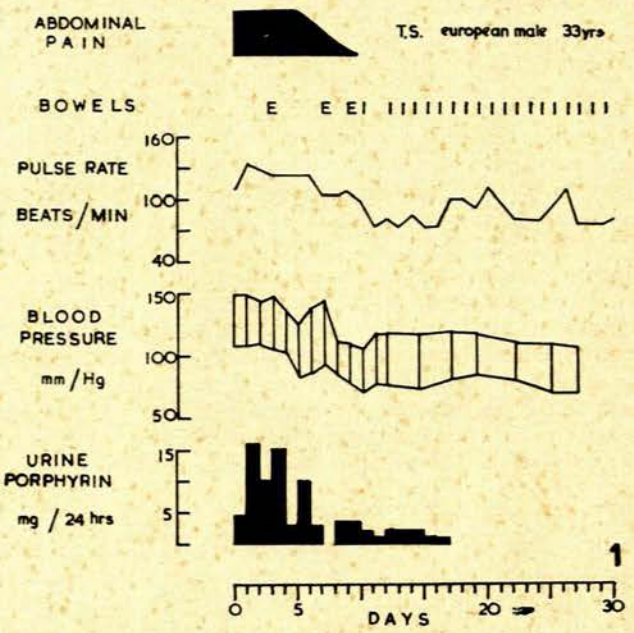



*Fig. 1.* Showing the spontaneous subsidence of an acute attack (E=enema, |=bowel action).

*Nervous Manifestations*

Frankly abnormal behaviour is present in about a fifth of the patients. The earlier mood imbalance, emotionalism, querulousness, apprehension, and irrational fears are replaced, in about one-third of the patients, by graver signs of a severe confusional state. Hallucinations which may be visual and/or auditory occur in half of these. Stupor

or a frankly maniacal state necessitating forcible restraint has occasionally been seen, and sometimes epileptiform seizures may dominate the picture.

*Motor Neuropathy*

The complaint of severe aching pain in the limbs precedes the development of the commonest neurological manifestation — motor neuropathy. This almost invariably takes the form of a lower-motor-neurone paralysis, not necessarily starting in the lower limbs. Usually, all 4 limbs are involved. Motor weakness, flaccidity and loss of tendon reflexes are followed by severe muscular wasting, which may be extreme. The severe form has been misnamed an ascending paralysis of the Landry type. The muscular weakness suggests a neuromyelitis in its distribution rather than a peripheral neuritis, the proximal muscles being more grossly affected than the distal. The degree of involvement need not be symmetrical, and occasionally distal involvement is more pronounced. Sphincter disturbances are not uncommon. Mild attacks show only slight but definite weakness and fleeting areflexia. Some tendon jerks may be hyperactive, but a Babinski reflex is very rare.

The cranial nerves are involved in about 10% of cases. The 3rd, 4th, 5th, 6th and 7th cranial nerves have all been affected. Amaurosis was present in 3 patients, but apart from questionable arterial spasm, retinal and optic-nerve changes are never seen. Subjective sensory loss or paraesthesiae are frequent, but objective loss is uncommon and is often patchy and irregular, and does not conform to a segmental distribution.

Paralysis and areflexia may regress rapidly, but not infrequently the early development of bulbar symptoms, such as dysphagia and dysphonia, indicate a far graver situation. Diaphragmatic and intercostal paralysis complete the picture. Although at this stage chances of recovery are slender, skilled and devoted care may yet avert death and permit eventual recovery, which in most cases is complete.

Tremor of the limbs, great restlessness, and insomnia are common findings and, when accompanied by tachycardia and sweating, thyrotoxicosis may be simulated. Prolonged galactorrhoea occurred in 2 patients.

OTHER INVESTIGATIONS

The cerebrospinal fluid (CSF) was examined during 23 attacks and, excluding a grossly abnormal CSF resulting from a subarachnoid haemorrhage, was within normal limits in all except 1 patient. The 1 abnormal CSF showed a slight elevation of the protein to 60 mg. per 100 ml. and a trace of globulin. Electroencephalograms were carried out in 13 patients. Abnormal slow activity was noted in 3, and persistent low-voltage fast activity in 3 others.

Electrocardiographs were done in 44 attacks. In 26 there was a pronounced sinus tachycardia. In 10 the praecordial T waves were flattened and in a further 4 they were inverted. Premature beats and auricular fibrillation were each observed on 2 occasions. In only 1 instance could severe paroxysmal auricular fibrillation be attributed to the porphyric state.

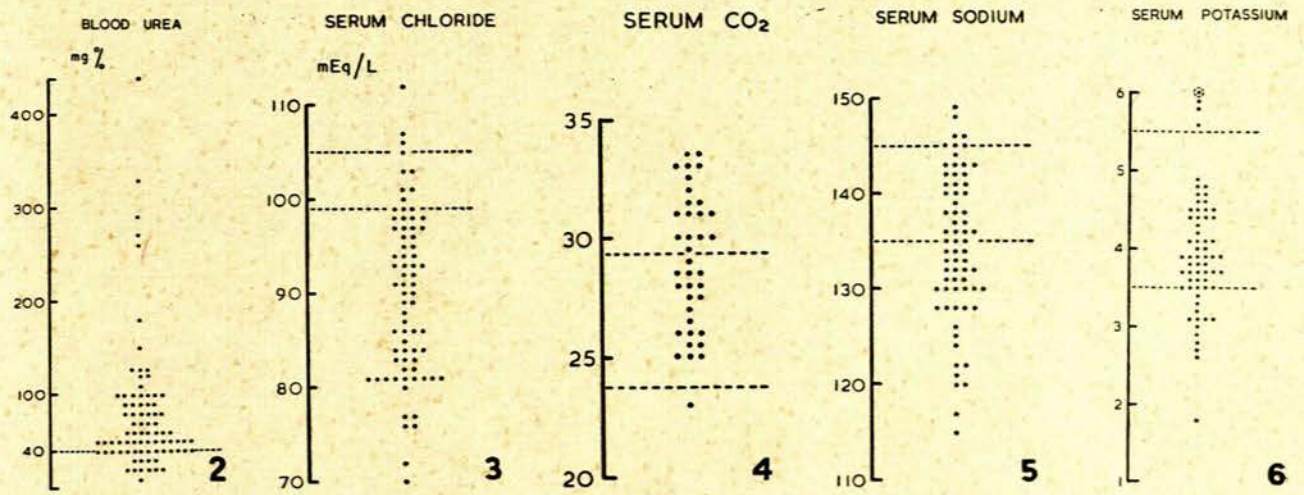
The chest was X-rayed in 45 patients. Pneumonia or pneumonitis was noted 3 times, uraemic lung and atelectasis twice. One patient had healing tuberculosis, and an enlarged left ventricle was noted in 2 others.

A straight X-ray of the abdomen or a barium-meal examination was carried out in 28 patients. Distension of the bowel was noted frequently — most often in the region of the splenic flexure of the colon.

*Routine Chemistry*

*Blood urea.* Blood-urea determinations were carried out in 81 attacks (Fig. 2). Azotaemia was a marked feature. In over two-thirds of the patients the peak urea concentration exceeded 50 mg. per 100 ml. and was more than 100 mg. per 100 ml. in one-quarter. Of the 5 patients with blood-urea levels over 200 mg. per 100 ml., 3 died, 1 recovered with conservative therapy, and 1 needed haemodialysis.

*Serum electrolytes.* Before treatment, the serum electrolytes showed major aberrations. Hypochloraemia was the most frequent finding (Fig. 3). The serum chloride was below 90 mEq./l. in 50% of the patients and could be as low as 70 mEq./l. Alkalosis was frequently associated (Fig. 4). Surprisingly, hyponatraemia was often encountered, the serum sodium being 130 mEq./l. or less in 30% of attacks (Fig. 5). Hypokalaemia (3 mEq./l. or less) occurred in 29% of cases (Fig. 6). Hyperkalaemia was very infrequent. Serum magnesium




The blood-urea level is the maximum value and the electrolyte levels the initial values in each patient. The normal limits are shown by horizontal lines.

*Fig. 2.* A blood-urea level of 100 mg. per 100 ml. or above occurs in approximately 25% of cases.
*Fig. 3.* Hypochloraemia is the commonest electrolyte abnormality.
*Fig. 4.* Alkalosis is frequent.
*Fig. 5.* Hyponatraemia is not as frequent as hypochloraemia, but it may be gross.
*Fig. 6.* Moderate hypokalaemia occurs. (The ringed figure represents a value of 6·8 mEq. per litre.)

was slightly reduced in 3 of 5 patients. Serum calcium was estimated in 22 attacks and was below 9·5 mg. per 100 ml. in 5. Serum inorganic phosphate was elevated in 2 uraemic patients and serum alkaline phosphatase was normal.

*Renal function.* Despite the azotaemia, signs of renal damage were rare. Proteinuria was present in 8% of patients, but in all except 1 patient with previous nephritis, it was mild (trace to +). Apart from the patients with urinary infection, the urinary sediment was normal. Occasionally granular casts were found. The filtration rate, as represented by creatinine clearance, varied in 10 patients from normal to moderately severe reduction (115 - 30 ml. per minute).

*'Liver-function tests'.* Thymol turbidity was normal in all but 1 of 57 attacks, while zinc turbidity was abnormal (> 12 units) in 3 of 29 attacks. The serum bilirubin was elevated above 1 mg. per 100 ml. in 8 patients, ranging between 1·5 and 3·5 mg. per 100 ml. in 5, while in 1 it was 6·2 mg. per 100 ml. (fatal Hodgkin's disease). The serum globulin exceeded 3·5 G. per 100 ml. in 8% of patients.

*Excretion of Porphyrins and their Precursors*

In the earlier cases (up to 1956) biochemical investigation during the acute attack was limited to the qualitative test for porphobilinogen and the serial determination of the total urinary porphyrin. The total porphyrin concentration at the height of the attack varied from 172·0 to 3·8 mg. per l. Faecal porphyrin estimations were subsequently made in many of these cases in remission and found to be high. With the development of suitable methods,[6] quantitative determinations of urinary delta-aminolaevulinic acid (ALA) and porphobilinogen (PBG) became possible, and these have been carried out in 20 patients (in addition to uro- and coproporphyrin determinations). On admission, in cases of protocoproporphyria, high values of urinary ALA, PBG and porphyrins were found, and these usually returned rapidly to normal within the course of several days or 1 - 2 weeks (Fig. 7). In the patients with pyrroloporphyria, similar increases in urinary ALA and PBG were found during the attack, but an increased excretion continued during remission although at a considerably lower level (Fig. 8). The faecal copro- and protoporphyrins were markedly elevated in the South African genetic cases — both during and after the acute attack. The total faecal porphyrin concentration in 24 patients varied from 208 to 2,055 μg. per G. dry weight (mean 1,038 ± 576).

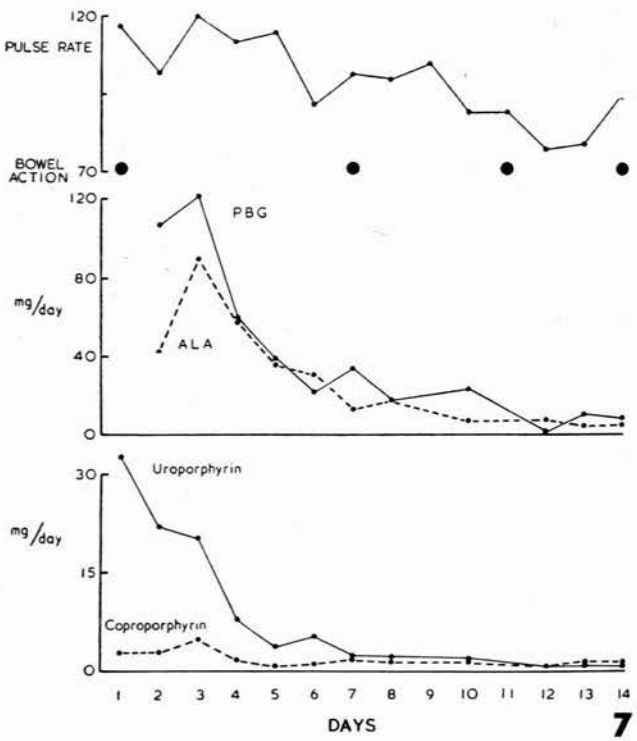



*Fig. 7.* Showing the rapid subsidence of an acute attack in a White female (family history positive, cutaneous fragility demonstrable, faecal porphyrin increased — coproporphyrin 105, protoporphyrin 217, and total porphyrin 322 mg. per G. dry weight). Note that PBG and ALA were within normal limits on discharge.

STAY IN HOSPITAL

Most patients were in hospital for less than a month. Of the 39 who spent 1 month or more in hospital, 19 stayed between 1 and 2 months, 12 for varying periods up to 6 months, and 8 for 6 months or more. Among these 8 patients was 1 who spent 28 months in hospital, the only one who stayed for more than 1 year. Eight of the 39 patients still had residual weakness on discharge and this appeared to be permanent in 3 of them.

MORTALITY

Of the 80 patients in this series, 25 are dead. Four died outside the hospital (2 as a result of accidents, 1 reputedly as a result of a heart attack, and 1 in diabetic coma with postmortem changes compatible with acute pancreatitis). After excluding these 4 patients, the mortality was 26%. Age and mortality in the acute attacks are shown in Table IV. In 13, death was attributable solely to the porphyria; all these patients had quadriplegia and bulbar paralysis. Three died suddenly of cardiac arrest, and 3 were admitted moribund and died within 24 hours. No death occurred in the acute attack after the third week. In the remaining 8, porphyria may have contributed to the death. In 6 patients the nervous system was involved, and 2 of them

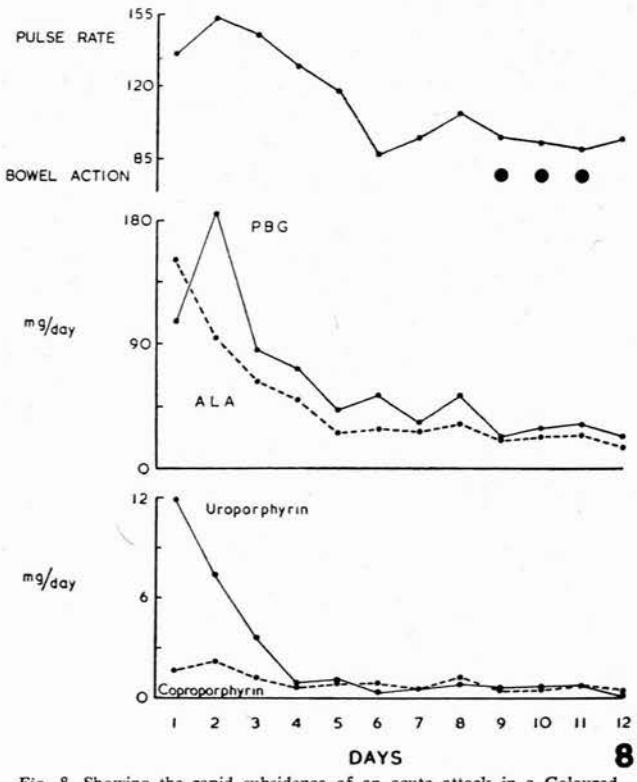



*Fig. 8.* Showing the rapid subsidence of an acute attack in a Coloured female (family history positive, no cutaneous involvement, faecal porphyrin normal — coproporphyrin 24, protoporphyrin 20, and total porphyrin 44 mg. per G. dry weight). Note that PBG and ALA remained elevated after the acute attack, and at follow-up the qualitative PBG remained positive.

TABLE IV. AGE AND MORTALITY* IN ACUTE ATTACKS

| Age (years) | All cases | | | Cause of death | |
|---|---|---|---|---|---|
| | Male | Female | Total | Porphyria alone | Porphyria contributing |
| 11-20 .. | 1 | — | 1 | — | 1 |
| 21-30 .. | 1 | 5 | 6 | 6 | — |
| 31-40 .. | 5 | 4 | 9 | 6 | 3 |
| 41-50 .. | 1 | 2 | 3 | 1 | 2 |
| 51-60 .. | — | 1 | 1 | — | 1 |
| 61-70 .. | — | 1 | 1 | — | 1 |
| Total .. | 8 | 13 | 21 | 13 | 8 |

*Four others died from unrelated causes outside the hospital.

were recovering from their paralysis when a complication caused sudden death (pulmonary embolism, and peritonitis with bacteriogenic shock). In the remaining 6 fatal cases the associated disease was in itself a sufficient cause for death. These conditions were Hodgkin's disease, hypertensive heart failure and pulmonary embolism, nephritis with uraemia, myelosclerosis, pneumonia, and subarachnoid haemorrhage.

## MANAGEMENT

Attention was directed to the following:

1. Skilled nursing with full anti-infective precautions in a darkened side room.
2. Close medical supervision with appropriate biochemical investigations — often required daily.
3. Prompt and judicious correction of fluid and electrolyte abnormalities and the use of the artificial kidney if necessary.
4. Maintenance of nutrition.
5. Symptomatic treatment with drugs, including treatment of complicating infection.
6. Assisted respiration with a mechanical respirator when indicated.
7. Physiotherapy during recovery and rehabilitation.

Skilled nursing was extremely important and required full 24-hour cover in severe cases. Firm but sympathetic handling and frequent reassurance was important. Isolation with full anti-infective precautions was essential in patients with severe neurological involvement. With the advent of diaphragmatic paralysis some form of assisted respiration became necessary. In the earlier cases a tank respirator was employed, but more recently tracheotomy and intermittent positive-pressure respiration with a mechanical respirator has been used.

Correction of the hypochloraemia and alkalosis was easily achieved by the judicious infusion of normal saline. Haemodialysis may be necessary when oliguric renal failure with uraemia is severe.

There is no specific therapy, and treatment is directed at the control of symptoms:

1. *Alleviation of pain.* Control of pain was difficult, necessitating hypnotics (pethidine, 'physeptone', morphine, and hyoscine) in 59 of the attacks. Analgesics, especially aspirin, phenacetin and codeine, were required in 22 cases.

2. *Control of restlessness and insomnia* necessitated one of the following — paraldehyde in 23, chloral hydrate in 13, chlorpromazine in 31, promazine in 10, and trifluopromazine in 3.

3. *Control of fits.* The above drugs and 'epanutin' have been used.

4. *Control of infection.* The prophylactic use of antibiotics was avoided, but antibiotics were not withheld in treating established infection. Chlortetracycline, chloramphenicol, nitrofurantoin, isonicotinic acid hydrazide, kanamycin, penicillin, and oxytetracycline have all been used without ill effect. The sulpha drugs were avoided. The use of an indwelling catheter was unfortunately unavoidable in patients with retention, but it was withdrawn as soon as possible.

5. *Recommended therapeutic procedures.* Many claims have been made for the therapeutic effectiveness of a variety of drugs. It must be remembered that spontaneous remissions are frequent and very often rapid and complete — hence reports of therapeutic success must be treated with scepticism.

*Steroids.* In 25 attacks steroids were administered; 12 received prednisone, 11 cortisone, 1 dexamethazone and 1 ACTH. In some an apparent beneficial effect was seen (Fig. 9), but in others treatment was without effect or

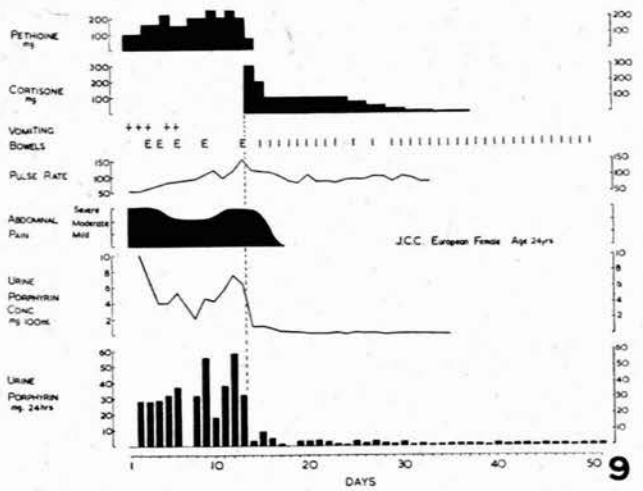



*Fig. 9.* Showing an apparent response to treatment with cortisone (E=enema, |=bowel action).

undoubted deterioration occurred (Fig. 10). Four of the prednisone- and 5 of the cortisone-treated patients died. The only patient treated with ACTH showed rapid deterioration with respiratory paralysis and died despite the use of a tank respirator.

## DISCUSSION

It is of interest to compare the clinical findings of Waldenstrom,[1] Goldberg,[2] and Markovitz[3] with our own (Table V). Apart from the fundamental differences of the frequent presence of increased cutaneous fragility and the high faecal porphyrin excretion in the South African cases, there is close general correspondence in the clinical findings during the acute attack. However, there are discrepancies.

Five of Waldenstrom's patients had symptoms before the age of 15 years. As in Goldberg's series, the main incidence was between 20 and 30 years. None of our

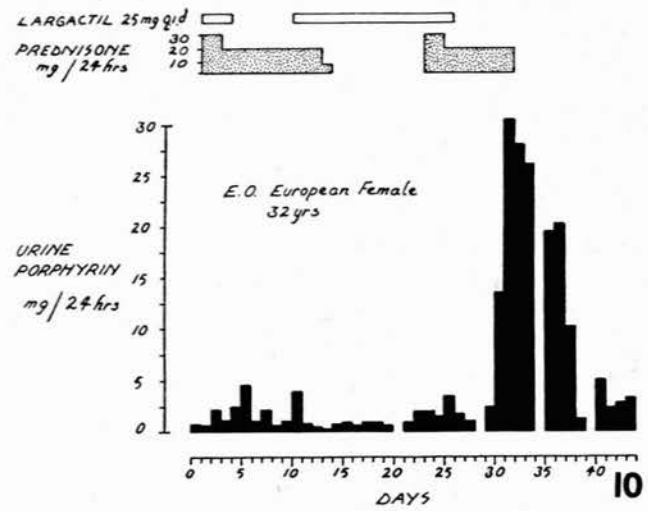



*Fig. 10.* Showing that an acute attack began during the second course of prednisone in this patient.

TABLE V. CLINICAL FEATURES IN THE ACUTE ATTACK—A COMPARISON OF PERCENTAGE INCIDENCE

| | *Walden-strom*[1] (*233*) % | *Gold-berg*[2] (*50*) % | *Marko-vitz*[3] (*69*) % | *This series* (*80*)* % |
|---|---|---|---|---|
| Males .. .. | 40 | 38 | 39 | 30 |
| Females .. .. | 60 | 62 | 61 | 70 |
| Abdominal pain .. | 85 | 94 | 95 | 90 |
| Vomiting .. .. | 59 | 78 | 52 | 80 |
| Mental changes .. | 55** | 56 | 80*** | 55 |
| Constipation .. | 48 | 74 | 46 | 80 |
| Paralysis .. .. | 42 | 68 | 72 | 53 |
| Hypertension .. | 40 | 56 | 49 | 55 |
| Pyrexia .. .. | 37 | 14 | 36 | 38 |
| Tachycardia .. | 28 | 64 | 51 | 83 |
| Seizures .. .. | 10 | 18 | — | 12 |
| Sensory loss .. | 9 | 38 | 24 | 15 |
| Diarrhoea .. .. | 9 | 12 | 11 | 8 |
| Azotaemia .. .. | 9 | ? | 67 | 69 |
| Proteinuria .. | 9 | 14 | — | 8 |
| Leucocytosis .. | 7 | 24 | 48 | 20 |
| Amaurosis .. .. | 4 | 3 | — | 3 |
| Cranial nerves .. | ? | 29 | 51 | 9 |
| ECG abnormalities | ? | 44 | 47 | 23 |

*Bracketed figures refer to the number of patients in each series, but in the present series 107 attacks were analysed.
**Delirium + hysteria + apathy.
***Includes epileptiform seizures.

patients was below 17 years of age and the peak incidence was in the 4th decade. The sex distribution was very similar, there being rather more females in our series.

Only 28% of Waldenstrom's patients were reported as having tachycardia. This is at variance with the findings of the others. Markovitz noted an incidence of 51%, but observed that in many of his patients the pulse rate was not recorded and that tachycardia was probably more frequent. In our series it was present in no less than 83% of patients. It should be noted that the pulse rate may be normal on admission, only to rise some days later. The tachycardia, which is almost invariably a sinus tachycardia, is an excellent index of activity and is an important guide to the progress of the patient. Although it is usually maintained at a level of 110 beats a minute, it may rise to 150 or more. In some there is considerable lability of the pulse rate. Our practice has been to keep patients at rest in bed until the tachycardia settles. In some instances the tachycardia is attributable to the accompanying pyrexia. In its absence other possible causes of the tachycardia are vagus neuropathy (nucleus or nerve) or cardiomyopathy. The electrocardiographic (ECG) changes are usually non-specific flattening of the T waves or, less frequently, actual inversion. Similar changes were noted by Goldberg and Markovitz. Although ECG findings are not incompatible with a cardiomyopathy, the alterations are usually transient and of the kind which are associated with a disturbance in the electrolyte metabolism. Sudden cardiac arrest does occur, but a frankly hypokalaemic picture with prolonged QT interval and U waves was only noted once.

Another striking discrepancy is the infrequency of azotaemia (9%) in Waldenstrom's series. Goldberg, too, mentioned only 3 patients with an increased blood-urea level. This is probably due to the infrequency of investigation, since no less than 69% of our patients* and 67% of Markovitz's had azotaemia. Although this was mild in most cases, over 25% of our patients had blood-urea levels exceeding 100 mg. per 100 ml.

Furthermore, the aberrations in the mineral metabolism in this series are striking — Goldberg also found abnormalities in 6 of 8 patients who were investigated. Hypochloraemia was the most frequent finding. Hyponatraemia, hypokalaemia and alkalosis were often present. Hypochloraemia and co-existent hyponatraemia in acute porphyria were first reported independently in 1947 by Abrahams *et al.*[7] and by one of us.[8] At that time these changes were attributed to functional adrenal insufficiency. In only 1 of the 2 patients with hypochloraemia (described by one of us[8]) was vomiting present and, furthermore, alkalosis was absent in both. Both patients failed to conserve chloride and the response to salt and cortical extract in the first case seemed to support the diagnosis of adrenal insufficiency. However, hypertension and not hypotension is likely to be found in the acute attack. Generalized pigmentation is often absent and in only 1 of 8 patients whom we tested was there a poor eosinopenic response to the injection of ACTH. Davies[9] reported a lack of response to DCA and the postmortem finding of adrenal hyperplasia. He noted the frequency of oliguria and azotaemia in the acute attack and felt that this, with the moderately depressed urea clearance, was evidence of persistent renal disorder. Prunty[10] also found no evidence of adrenal disorder, but found changes suggestive of acute tubular necrosis in 2 of his patients.

Frank tubular necrosis is rare. Proteinuria, too, is uncommon. The finding of hyponatraemia may reasonably be attributed to the sodium loss induced by azotaemia. Calvert and Rimington[11] found no evidence of abnormality of renal or adrenal function in their 26-year-old patient with persistent hyponatraemia, but at the onset, at least, azotaemia was present. The common finding of azotaemia is attributable firstly to acute renal circulatory insufficiency, the result of dehydration, and secondly to the profound catabolic processes that occur in acute porphyria with neurological involvement. The hypochloraemia,

* Blood urea exceeding 50 mg. per 100 ml.

hypokalaemia and alkalosis can readily be explained on the basis of vomiting coupled with a deficient intake of electrolytes, but co-existent hyponatraemia cannot be explained on this basis. Profuse and persistent sweating, however, may be present. This was of an extreme degree in 3 patients.

It is not surprising that certain patients with electrolyte depletion will benefit from the administration of ACTH and the steroids, particularly when, in addition, depletion is corrected. Yet another factor is the euphoria induced by steroids, which may improve appetite and fluid intake. In the early phases a case could be made for the use of steroids, but it does not usually affect porphyrin output or established neurological disorder and may, in fact, as we have shown, be associated with a relapse. In the absence of renal circulatory insufficiency possible explanations of persistent hyponatraemia include the depletion syndrome which Moore *et al.*[12] described in severely ill patients, and renal sodium loss with hyponatraemia from the 'inappropriate secretion of antidiuretic hormone'[13,14] which may well accompany the porphyric encephalopathy. Further detailed studies are required.

In most of the patients with South African genetic porphyria, the high ALA and PBG excretions returned rapidly to normal, but in a few these remained slightly elevated — about 6 mg. per day of ALA and 2 - 5 mg. per day of PBG — for longer periods before becoming normal. Three patients, whom we regarded as Swedish porphyrics, continued to excrete 20+ mg. of PBG per day for months after the acute phase. This continued excretion is a feature which Dean and Barnes[15] have stressed as characteristic of the Swedish type. We are well aware of Watson's[16] statement that PBG may diminish remarkably and at times disappear completely. It is possible that some of these cases were examples of protocoproporphyria with the temporary pyrrole disturbance of the acute phase.

It is well known that delay in applying the qualitative test for porphobilinogen may be responsible for a negative report. Watson *et al.*,[17] however, have recently reviewed the question of urinary porphobilinogen and other Ehrlich reactors and have noted that the Ehrlich reaction might disappear in a few hours and yet quantitative determination might show it to be present. We, too, have found, on rare occasions, elevated values of urinary PBG (and of ALA) by the Mauzerall-Granick method when the qualitative test for PBG was negative or only faintly positive. It is of interest that Waldenstrom himself first described intermittent excretors of PBG in 1937,[18] but 20 years later stated that it was probable that such patients would become much rarer when they could be examined with the aid of modern refined techniques for the demonstration of PBG and ALA.

*Precipitating Factors*

Attacks have been associated with the administration of many drugs, especially the barbiturates. Thiopentone and phenobarbitone are incriminated most frequently, but amylbarbitone, butobarbitone, pentobarbitone and quinalbarbitone have all been under suspicion. In addition to phenobarbitone, Watson[16] listed sulphonal, trional, 'sedormid', 'phanodorm',* ergot preparations and chloroquine. We would add sulpha drugs and alcohol to this list.

* Cyclobarbital.

While there appears to be general agreement concerning the possible adverse effects of barbiturates, there is by no means a constant relationship between the taking of a drug and the development of the attack. There are unequivocal instances of continued administration before the development of an acute attack. While Dean has stressed the role of thiopentone anaesthesia in the genesis of the acute attack,[19] surprisingly enough Goldberg, among others, does not even mention it. Porphyrics have undergone thiopentone anaesthesia on more than one occasion without ill effect both before and after an acute attack. In many of our patients acute symptoms were already present at the time of the administration of the barbiturate. In agreement with Goldberg it is believed that there is a better correlation between the administration of a barbiturate during the attack and the development of the neurological syndrome.

The relationship between the menses, pregnancy, and the acute attack is uncertain. In a few of the female patients, as Goldberg has also observed, the attack started in the premenstrual phase, but Watson has reported cyclic pain coming on with the mid-menstrual period. Other cases occur after the menopause. The propensity of women to take drugs in the premenstrual phase must not be overlooked. Only 3 of our patients were pregnant and in 2 there were other possible causes. More striking was the onset in the postpartum phase (5 patients) also observed by Watson and Goldberg. Here again the question of drug administration is to be considered. There is no definite evidence that relapse is due to pregnancy or delivery. Most porphyrics have normal pregnancies.

Acute alcoholic bouts, mental stress, and infection are other possible precipitating factors. In many cases multiple factors are present.

*Management*

It is worth emphasizing that the successful management of porphyria turns very much on the question of skilled nursing, the strict application of anti-infective precautions and the availability of experienced staff and biochemical facilities. Patients with respiratory failure require the use of tracheotomy and intermittent positive-pressure respiration, and sometimes the artificial kidney may be life-saving. Most important is the prompt transfer of patients with severe paralysis (quadriplegia) to a specialized centre. Deterioration with bulbar involvement can occur with alarming speed and any delay jeopardizes the patient's chance of survival.

Barbiturates must be avoided and reliance placed on chloral hydrate and paraldehyde. The morphine derivatives and pethidine appear to be safe in patients with severe pain, although prolonged use raises the danger of addiction. Chlorpromazine and promazine have been very useful in treating patients with a purely abdominal presentation, as well as those with nervous-system involvement. The usual dose has been 25 - 50 mg. 6-hourly, although higher doses of promazine have been used in patients with porphyric encephalopathy. The control of seizures is very important since they materially increase the chances of a fatal outcome. Epanutin has been used successfully to this end. Hypertension is usually not of a grade to warrant any treatment.

In the early phases, provided severe uraemia is absent, a case can be made for the use of the steroids, but their effect is unpredictable. In some an apparent prompt improvement occurs, in most there is no change, and in a few there is undoubted aggravation. Watson strongly recommended their administration as early as possible. Courses of treatment with cortisone acetate (or one of the other steroids) should be short and not exceed 10 days, commencing with 200 mg. for 2 days, then 100 mg. for 2 days, and reducing by 25 mg. every 2nd day.

There is as yet no specific therapy for the condition. A host of drugs has been advocated. Evaluation of therapy is particularly difficult since remissions are not only frequent, but abrupt and complete. Improvement may occur despite therapy! Thus reports of the beneficial effect of treatment with chelating agents,[20] adenosine monophosphate,[21] and cytochrome,[22] must be treated with the greatest reserve. In one of our recent cases dramatic improvement appeared to coincide with the administration of adenosine monophosphate, but scrutiny of the biochemical data showed that the high values of ALA and PBG had in fact already diminished before the treatment began. The serial *daily* determination of the porphyrins and their precursors is essential in making any evaluation.

With our present mode of management the mortality in the acute attack has been of the order of 25%, an improvement on the 58% mortality reported by Markovitz and the 52% reported by Waldenstrom,[18] although some of this improvement may be attributed to earlier recognition and the possible inclusion of milder cases.


## SUMMARY

The chemical and biochemical findings during 107 acute attacks in 80 porphyric patients are analysed. Apart from the routine biochemistry, daily excretion of ALA and PBG as well as the porphyrins has been investigated in many cases. The management, including the use of steroids, is presented.

Comparison with 3 other large series shows close general correspondence in the clinical features, but notable biochemical findings in this series were azotaemia, hypochloraemia and alkalosis. The genesis of these aberrations as well as the not uncommon hyponatraemia are discussed.

While there is no specific therapy, the importance of skilled management at a hospital centre with adequate biochemical and other ancillary facilities is stressed. Prompt transfer of a seriously ill patient to such a centre is essential.



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## REFERENCES


1. Waldenstrom, J. (1957): Amer. J. Med., **22,** 785.
2. Goldberg, A. (1959): Quart. J. Med. (new series), **28,** 183.
3. Markovitz, M. (1954): Ann. Intern. Med., **41,** 1170.
4. Eales, L. (1961): Ann. Rev. Med., **12,** 251.
5. *Idem* (1960): S. Afr. J. Lab. Clin. Med., **6,** 63.
6. Mauzerall, D. and Granick, S. (1956): J. Biol. Chem., **219,** 435.
7. Abrahams, A., Gavey, C. J. and McLagan, N. F. (1947): Brit. Med. J., **2,** 327.
8. Linder, G. C. (1947): Lancet, **2,** 649.
9. Davies, D. (1949): Brit. Med. J., **1,** 846.
10. Prunty, F. T. G. (1949): J. Clin. Invest., **28,** 690.
11. Calvert, R. J. and Rimington, C. (1953): Brit. Med. J., **2,** 1133.
12. Moore, F. D., McMurray, J. D., Parker, H. V. and Magnus, I. C. (1956): Metabolism, **5,** 447.
13. Schwartz, W. B., Bennet, W., Curelop, S. and Bartter, F. C. (1957): Amer. J. Med., **23,** 527.
14. Schwartz, W. B., Bassel, D. and Bartter, F. C. (1960): New Engl. J. Med., **262,** 743
15. Dean, G. and Barnes, H. D. (1959): S. Afr. Med. J., **33,** 246.
16. Watson, C. *in* Duncan, G. G. ed. (1959): *Diseases of Metabolism,* 4th ed., p. 682. Philadelphia: Saunders.
17. Watson, C. J., Bossenmaier, I. and Cardinal, R. (1961): J. Amer. Med. Assoc., **175,** 1087.
18. Waldenstrom, J. (1937): Acta. med. scand., suppl. 82.
19. Dean, G. (1956): S. Afr. Med. J., **30,** 377.
20. Peters, H. A. (1956): Dis. Nerv. Syst., **17,** 2.
21. Gajdos, A. and Gajdos-Torok, M. (1961): Lancet, **2,** 175.
22. Riederer, J. (1961): Med. Klin., **56,** 96.