DIAGNOSIS OF ACUTE PORPHYRIA

BY

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Although the pattern of symptomatology in acute intermittent porphyria is recognizable with ease in retrospect or in frankly paralytic cases, it is well known that striking simulation of abdominal or neuropsychiatric disease may deceive the practitioner with no personal experience of the condition.

The disease may be described as uncommon but not rare. In Australia it is possible to arrive at an approximate estimation of its incidence. Ten cases have already been reported (Derrick, 1946, two cases; Hetzel, 1949, two cases; Saint *et al.*, 1952, six cases). Fifteen new cases were diagnosed in one year (1952-3) in Western Australia, South Australia, Victoria, and part of New South Wales, giving an approximate "standardized" incidence of 1.5 per 100,000 in adult females. Other mild cases undoubtedly pass unrecognized; but the incidence is low enough to preclude the majority of family doctors and many general physicians attending a case in the course of their professional life. Since there is evidence that the indiscriminate use of some drugs, notably barbiturates and sulphonamides, may materially worsen prognosis, it is felt that attention should be paid to early clinical recognition. Three further cases of acute porphyria are presented from this point of view.

In each case diagnosis was eventually established by the identification of porphobilinogen in the urine by means of the modified Ehrlich reaction of Watson and Schwartz (1941). Total uroporphyrin and so-called "uroporphyrin III" in 24-hour urine specimens was estimated quantitatively by methods described by Sveinsson *et al.* (1949). Urinary coproporphyrin was estimated by the method of Schwartz *et al.* (1951), using Soret absorption and corrections described by Rimington and Sveinsson (1950). The three cases were investigated in the Royal Perth Hospital between December, 1952, and May, 1953.

Case 1

Classical Acute Porphyria with Pain, Psychosis, and Neuropathy, with Death from Respiratory Paralysis

A 27-year-old married woman of Scots ancestry complained quite suddenly, in November, 1952, of nondescript pains in the legs and back, and was treated by her family doctor for "influenza." Sulphonamides and barbiturates were freely prescribed. After several weeks improvement had not occurred. She became extremely depressed and was admitted to a mental hospital, where a short course of electric convulsion treatment was given without material benefit: in fact, her condition worsened, and she was admitted to the Royal Perth Hospital in January, 1953, complaining of generalized abdominal pain of great intensity, constipation, and weakness of all limbs. For several weeks she had been vomiting intermittently, and it was clear that her nutritional status had greatly deteriorated.

Examination revealed a dehydrated woman, weeping and grimacing in consequence of severe pain, and greatly con-

fused with respect to time and space. Her temperature was 99.4° F. (37.4° C.); pulse 140; blood pressure 110/90 mm. Hg. No abnormality was detected in the heart or lungs; the abdomen, despite some pain, was lax and not tender. The cranial nerves were normal. There was profound weakness of all the muscle groups of both arms and legs and the trunk. Diaphragmatic movements appeared impaired (confirmed fluoroscopically). Her confusional state prevented a full examination of sensory function—at least, pain sensibility did not seem impaired. Loss of deep reflexes was patchy: the biceps-, knee-, and ankle-jerks could not be elicited on either side, but supinator and triceps jerks were present. Plantar reflexes were flexor. Freshly collected urine was a deep burgundy colour, darkening on standing in light.

For a day or two she appeared to improve, taking food and drinks by mouth satisfactorily. Pain was controlled with pethidine. In view of her inability to cough, penicillin and streptomycin were given to prevent respiratory infection. Five days after admission she became more confused than ever. Weakness of intercostal muscles appeared suddenly, and she was transferred to a Both respirator, in which she was fed by means of an intragastric drip. However, both temperature and pulse rose, weakness and confusion increased, and she died two days after the initiation of artificial respiration, seven days after admission to hospital, and two months after the onset of her illness.

The only abnormal finding from a variety of biochemical investigations was a fasting blood urea of 56 mg. per 100 ml. The Watson and Schwartz test on fresh urine was strongly positive.

Porphyryn Excretion.—Quantitative studies on urinary porphyrins are shown in Table I.

TABLE I.—Quantitative Studies on Urinary Porphyrin Excretion in Case 1. Significant Worsening of Symptoms Occurred on D+5 and D+6. Death Occurred on D+7

Day after Admission	Total vol. of Urine (ml.)	Total Uroporphyrin Excreted (mg./24 hrs.)	"Uroporphyrin III" Excreted		Total Coproporphyrin Excreted (mg./24 hrs.)
			Total (mg./24 hrs.)	% of Total Uroporphyrin	
+1	500	13.7	11.5	84	0.368
+5	475	9.7	8.7	90	0.667
+6	785	25.2	20.2	84	2.375

Necropsy.—Marked congestive changes were seen in both lungs. No macroscopic abnormality was seen in the adrenals, kidneys, spleen, alimentary tract, brain, or spinal cord. The liver showed on its surface, and on section, numerous irregularly distributed foci of yellow discoloration of inconstant shape, measuring up to 5 mm. in diameter. Microscopically, moderate patchy fat infiltration was seen. Microscopical sections of the myocardium showed marked disintegration of muscle fibres with loss of nuclei and striation. Patchy demyelination was seen in peripheral nerves.

Familial Studies.—There was no evidence of consanguinity in the marriages of the parents or grandparents of the patient. Urine from the majority of her close relatives—both parents, four siblings, and four children—was examined both qualitatively for porphobilinogen and quantitatively for uroporphyrin, with negative results.

Comment.—Although the significance of the tetrad of pain, polyneuritis, psychosis, and port-wine urine was apparent late in the course of her illness, it is not difficult to see how the vague onset must have seemed like an influenza illness to her family doctor, and how the association of depression with ill-localized pain later suggested hysteria. During this phase large doses of sulphonamides and barbiturates were administered empirically, and E.C.T. given; it is reasonable to suppose that they did not aid recovery.

Case 2

Acute Porphyria in an Elderly Patient with Associated Hypertension and Diabetes Mellitus

A 61-year-old married Scotswoman was admitted to the surgical wards in December, 1952, with severe epigastric pain. At 23 she had a caesarean section, and in 1944 spent a week in hospital with acute vomiting, dyspnoea, and signs of pulmonary oedema, attributed to hypertensive and coronary heart disease. For ten years she was known to have moderate hypertension (200/100) and mild diabetes well controlled by diet.

The abdominal pain was of sudden onset. It was accompanied by vomiting, was unremitting, and was felt in the upper abdomen, radiating to the back. She had not been taking drugs.

She was extremely obese. Her temperature was 98.4° F. (36.9° C.), pulse 130, blood pressure 200/130 mm. Hg. The heart was not apparently enlarged. There were no abnormal signs in the central nervous system. Some tenderness was noted in the upper left abdominal quadrant. The urine was straw-coloured; sugar and acetone were not detected at first examination.

During the ensuing week she continued to complain of abdominal pain. The urge to explore was resisted in the face of a lax abdomen, a normal plain x-ray film of the abdomen, a normal cholecystogram, and normal urinary findings. At least 4 gr. (0.26 g.) of phenobarbitone was given daily, along with pethidine.

When a specimen of urine was noticed to be of a reddish colour the Watson and Schwartz test was found to be positive. Thereafter she became confused and occasionally delirious. During the next two weeks her condition rapidly deteriorated: her limbs became paralysed; she had difficulty in swallowing, necessitating intragastric feeding; she developed a right facial paresis and paralysis of the limbs; all deep reflexes were absent; she became incontinent of both urine and faeces; her diastolic blood pressure remained persistently high (130-140 mm. Hg). Only a minimal degree of narrowing of vessels was seen in the optic fundi.

She died in a coma three and a half weeks after admission. Of the many investigations, significant positive findings included a fasting blood urea of 72 mg. per 100 ml., and a fasting blood sugar of 172 mg. per 100 ml. Electrocardiographic tracings showed a pattern of left ventricular strain.

Porphyria Excretion.—Only one specimen was examined quantitatively. It fluoresced strongly in ultra-violet light. The total porphyrin content of native urine was 10.3 mg. per litre (of which 0.4 mg. per litre was ether-soluble—coproporphyrin); after heating with N/2 HCl this increased to 21.9 mg. per litre.

Necropsy.—Congestion and signs of early bronchopneumonia were present in both lungs. The heart was not enlarged and the coronary vessels showed minimal atherosclerotic changes. The pancreas was atrophic and contained areas of recent necrosis. Fat infiltration was present in the liver. Macroscopically and microscopically the kidneys appeared to be normal.

Comment.—Manifestations of porphyria begin as a rule in the third or fourth decade of life; the late onset in this patient is worthy of comment. The 64-year-old patient of Kench *et al.* (1953) is possibly the oldest on record, but symptoms were mild in their case and had been present for many years. The localization of abdominal pain was highly suggestive of pancreatitis. This was confirmed at necropsy by the appearances of recent focal necrosis in the pancreas. The association of long-standing hypertension with porphyria inevitably gives rise to speculation. Macleod and Grant (1953) describe a case with attacks of left ventricular failure: at necropsy chronic pyelonephritis was present. Our patient probably had "essential" hypertension, which by the usual clinical and pathological

criteria seems to have been relatively benign. It is not inconceivable that the attack of pulmonary oedema she is said to have had in 1944 was due to sudden rise in blood pressure, beyond an elevated baseline, due to an episode of porphyria.

Case 3

Mild Acute Porphyria with Evidence of Pancreatitis

A 27-year-old woman of Scots ancestry was admitted in April, 1953, with a short history of generalized pain and vomiting. Six months previously she had had a similar illness diagnosed as "influenza"—but, unlike a virus infection, muscle pain had persisted three weeks. On the present occasion she complained of occipital headache, pain in the back and legs, and nausea. The urine was noted to be "dark": her family doctor was inclined to diagnose subicteric infectious hepatitis, which was endemic in the neighbourhood.

Although she looked ill the only abnormal sign was an unexplained tachycardia of 130 a minute. The liver was not enlarged and the abdomen was lax. Her blood pressure was 130/72 mm. Hg. There were no abnormal signs in the central nervous system. The urine was amber-coloured.

For a week after admission her chief complaint was of pain in the epigastrium radiating to the back, with intermittent vomiting. The Watson and Schwartz test proved to be positive. The site and radiation of pain suggested pancreatitis, which was confirmed by the finding of raised levels of serum amylase (see Table II). She was discharged, free of pain, three weeks after admission.

TABLE II.—Quantitative Studies on Porphyrin Excretion in Case 3, Related to Severity of Abdominal Pain and Serial Estimations of Serum Amylase

Day after Admission	Vol. of Urine 24 hours (ml.)	Total Uroporphyrin mg./24 hr.	Uroporphyrin III		Abdominal and Back Pain	Serum Amylase (units) (N=70-200)
			mg./24 hr.	% of Total Uroporphyrin		
+7	—	—	—	—	±	20
+8	—	—	—	—	++	—
+9	—	—	—	—	+++	228
+10	—	—	—	—	++	—
+11	990	5.76	4.30	75	+	—
+12	—	—	—	—	±	—
+13	—	—	—	—	±	—
+14	—	—	—	—	±	359
+15	910	3.39	2.95	87	—	—
+17	1,410	6.60	5.80	88	—	384
+18 & 19	1,530	2.26	2.00	87	—	—
+20 & 21	3,020	2.67	2.12	79	—	—
+22	880	1.65	1.20	73	—	—
+23	2,010	2.83	2.42	85	—	285
+85	—	—	—	—	—	50

The majority of investigations were negative, apart from the bromsulphthalein test, which showed 12% retention of dye at 30 minutes; other tests of liver function were normal.

Porphyria Excretion.—Porphobilinogen was present in all specimens examined. The daily output of total uroporphyrin varied between 1.65 and 6.60 mg., between 73 and 88% being present as uroporphyrin III (see Table II).

Comment.—This was a comparatively mild episode, probably only the second the patient had ever had. As in Case 1, the initial diffuseness of pain led to a provisional diagnosis of virus infection. Happily, sulphonamides and barbiturates were not prescribed. As in Case 2, the site of pain was compatible with a clinical diagnosis of pancreatitis, proved biochemically.

Discussion

These case records indicate how vague and misleading are the early symptoms of acute porphyria. The simulation of abdominal emergencies (Case 2) is well known; but pain may not always be confined to the abdomen (Cases 1 and 3)—"virus infection," "rheumatism," "fibrositis," and "hysteria" were the diagnostic dustbins into

which our patients had been relegated at an early stage in their illness. Too great a reliance cannot be placed on the colour of the patient's urine; early in the course of the illness of Case 3 the urine was of normal appearance. In diagnosis the Watson and Schwartz test for porphobilinogen is an extremely simple and valuable one which can be performed in any side-room; moreover, it is wholly reliable (Hammond and Welcker, 1948). It is possible that the more widespread use of this diagnostic test might bring to light many more mild cases of porphyria.

This question of early diagnosis and the diagnosis of mild cases is of more than purely academic interest. At present the disease defies comprehension, and treatment is for the most part supportive, attention being paid to nutrition, prevention of respiratory complications, and the control of pain. The supervention of profound and widespread paresis should not engender complete despair: Saint *et al.* (1952) described a case with paralysis of the diaphragm and intercostal muscles in which full recovery occurred after two weeks in a respirator. If we can do patients little positive good, there is certainly evidence that we can do positive harm. The unfavourable influence of sulphonamides and barbiturates on the natural history of the disease has been recorded too often to be ignored. Unfortunately the very symptoms with which the disease is announced—pain and psychotic behaviour—are those which often call for the empirical use of these drugs. The answer to the problem must lie in awareness of the diagnosis.

Like the understanding of the underlying metabolic anomaly, the origin of symptoms in porphyria remains obscure. There is much to support the contention of Denny-Brown and Sciarra (1945) that many of its manifestations are explicable on the basis of spasm of smooth muscle, particularly of the circular muscle of small arteries. The diffuse pathological changes seen in the central nervous system and elsewhere are highly suggestive of focal ischaemia. In this respect the variety of systemic manifestations—renal (hypertension), abdominal, neurological, myocardial—calls to mind that other disease of focal ischaemia, periarteritis nodosa. To the long list of organs involved in porphyria the pancreas must now be added, for the clinical, biochemical, and pathological evidence of mild pancreatitis in Cases 2 and 3 was wholly convincing. It is interesting in this connexion to note that pancreatic involvement sufficient to cause abnormality in the sugar-tolerance curve in periarteritis nodosa has been recorded by Middleton and McCarter (1935) and by Baker (1953).

Summary and Conclusions

A survey of the reported cases of acute porphyria in Australia indicates an approximate incidence of 1.5 per 100,000 females over the age of 15 years.

Three cases with classical biochemical findings are described in which the earliest symptoms bore little relation to the "classical" picture of the disease.

In two cases pain was entirely peripheral in distribution, and was attributed to mild infective illness. The unfolding of neuropsychiatric symptoms and signs followed the administration of barbiturates.

In two cases the abdominal pain was due to pancreatitis, proved biochemically and at necropsy.

The importance of early recognition is stressed so that the harmful influences of sulphonamides, barbiturates, electric convulsion therapy, and unnecessary surgery may be avoided. The more widespread use of the simple Watson and Schwartz test in the diagnosis of obscure abdominal and peripheral pain, hysteria, unexplained depressive states, and neuropathy is urged.

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REFERENCES

- Baker, G. A. E. (1953). *Guys Hosp. Rep.*, **102**, 265.
 Denny-Brown, D., and Sciarra, D. (1945). *Brain*, **68**, 1.
 Derrick, E. H. (1946). *Med. J. Aust.*, **1**, 241.
 Hammond, R. L., and Welcker, M. L. (1948). *J. Lab. clin. Med.*, **33**, 1254.
 Hetzel, B. S. (1949). *Med. J. Aust.*, **2**, 600.
 Kench, J. E., Ferguson, F. R., and Graveson, G. S. (1953). *Lancet*, **1**, 1072.
 Macleod, J. G., and Grant, I. W. B. (1953). *Edinb. med. J.*, **60**, 232.
 Middleton, W. S., and McCarter, J. C. (1935). *Amer. J. med. Sci.*, **190**, 291.
 Rimington, C., and Sveinsson, S. L. (1950). *Scand. J. clin. Lab. Invest.*, **2**, 209.
 Saint, E. G., Finch, E. S., and Parsons, I. (1952). *Aust. Ann. Med.*, **1**, 163.
 Schwartz, S., Zieve, L., and Watson, C. J. (1951). *J. Lab. clin. Med.*, **37**, 843.
 Sveinsson, S. L., Rimington, C., and Barnes, H. D. (1949). *Scand. J. clin. Lab. Invest.*, **1**, 1.
 Watson, C. J., and Schwartz, S. (1941). *Proc. Soc. exp. Biol.*, **47**, 393.

ACUTE PANCREATIC NECROSIS AS A CAUSE OF SUDDEN DEATH

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Acute pancreatic necrosis has long been recognized as an acute and frequently fatal abdominal catastrophe, but it does not usually figure as a cause of sudden death. Roberts *et al.* (1950), however, mentioned the possibility, and Gaskell (1942) described 10 cases of sudden death from this condition.

During the past two years five cases have been encountered in the course of post-mortem examinations carried out at the Royal Victoria Infirmary, Newcastle-upon-Tyne, all of them investigated at the request of H.M. Coroner. In the following account a short summary of the clinical history of each case is given together with descriptions limited to the state of the pancreas and adjacent organs and any other positive findings.

Case Histories

Case 1.—A public works contractor aged 48 (weight 112 kg.), an obese subject enjoying good health, was suddenly seized with acute abdominal pain. He became breathless at work, collapsed, and died instantly. A month previously he had suffered an attack of "food poisoning," with subsequent recovery. *Post-mortem Examination:*—The pancreas (weight 200 g.) was soft and swollen, and the cut surface showed diffuse areas of haemorrhage with a limited amount of fat necrosis. Histology confirmed a severe necrosis of the pancreas with abundant haemorrhage. Stomach and duodenum contained a recent meal; the mucosal surface appeared congested. The liver showed severe fatty change. The lungs were congested and very oedematous.

Case 2.—A brewer's cooper aged 62, well nourished and of good physique (weight 70 kg.), who normally enjoyed good health, suddenly complained of abdominal pain whilst at work. His colleagues saw him collapse. He lost consciousness and died instantly. *Post-mortem Examination:*—The pancreas (weight 160 g.) was dark plum-coloured and flecked with yellowish necrotic material. Histology showed a haemorrhagic necrosis of pancreatic tissue with limited fat necrosis. The stomach, duodenum, gall-bladder, and bile ducts appeared normal. The lungs were severely congested and oedematous.