Thirty-six children received a further injection at 24 hours, and 26 of these showed an adequate concentration at 48 hours. Twenty-three were given a third injection at 48 hours, and 19 of these gave a level of over 0.03 u./ml. at 72 hours. The children presenting a low level after a second injection were not always those having a low level at 24 hours.

No patient showed a general reaction to the injection. In one child there was a localized swelling at the site of injection which resolved in two days.

Discussion

This study was confined to the investigation of serum penicillin levels, and no attempt was made to relate clinical change to the concentrations obtained. We have assumed that a minimum bacteriostatic serum level of 0.03 u./ml. is required. Although this level is that most generally accepted, the minimal penicillin level approved in some studies of procaine penicillin varies from 0.1 u./ml. (Carson *et al.*, 1949) to 0.01 u./ml. (Hewitt *et al.*, 1948); the direct comparison of results is therefore difficult.

The results that we have obtained are very similar to those reported in adults—i.e., that penicillin is present in the blood stream in significant amounts in approximately half of the cases 24 hours after an injection of procaine penicillin in arachis oil (see Table I).

A difference in 24-hour serum levels between ambulatory patients and in-patients was seen in our cases. These groups are small, but when considered with the cases described by Boger *et al.* (1948) they yield results which are just significant and indicate a more rapid absorption and excretion in ambulant cases. This point is important, as this preparation is most likely to be used in ambulant patients.

The results of Carson *et al.* (1949) differ a little from ours. The dose of penicillin that they gave to their children was approximately twice that given in the present series. Although they noted no exact correlation between serum penicillin titres and the amount of penicillin administered, the levels maintained at 24 hours were higher than ours, whereas the levels they obtained during the first six hours after injection were lower. This discrepancy may be due to the use of a penicillin preparation of a different particulate size.

By greatly increasing the dose of procaine penicillin it may be possible to attain a reliable 24-hour serum penicillin level. Higher doses have not been given in this series, because of the bulk of the injection, the possible toxic effects of absorbed procaine, and the inhibitory action on sulphonamides of procaine hydrolysed to para-amino benzoic acid (Carson *et al.*, 1949).

We conclude that procaine penicillin, owing to the variation of the 24-hour serum penicillin levels seen in this series and those of others, is not suitable for once-daily injection.

Preliminary trials with a procaine penicillin preparation containing aluminium stearate indicate that it may maintain more reliable blood levels.

Summary

The serum penicillin concentration after the intramuscular injection of procaine penicillin in arachis oil has been followed in 50 children.

Procaine penicillin was absorbed rapidly, but the penicillin titre in the blood after 24 hours was extremely variable.

Procaine penicillin in arachis oil is not an ideal preparation for the administration of penicillin by once-daily injection in children.

In-patients in this investigation were under the care of Professor R. S. Illingworth. We would also like to thank Dr. S. Doxiadis, of the Department of Child Health, and Professor E. J. Wayne, of the Department of Pharmacology, University of Sheffield, for the interest they have taken in this investigation.

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ACUTE PORPHYRIA AND ASSOCIATED ELECTROLYTE CHANGES

BY

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The porphyrias are attracting increasing interest in Britain, though most of the work on the subject still appears in Scandinavian and American literature. The history of the porphyrias is reviewed by Nesbitt (1944).

Acute and latent porphyria are different phases of one disease, a chronic disorder of pyrrole metabolism which is sometimes familial. The aetiology remains unknown. Barbiturates, often cited as precipitating factors of the acute phase, seem to have been given following the onset of clinical manifestations in most cases. Symptoms usually appear between the ages of 20 and 45. The chemistry and reactions of the porphyrins have been reviewed by Dobriner and Rhoads (1940), Prunty (1946), Jørgensen and With (1947), and Discombe (1948).

The case of acute porphyria here presented showed most of the classical features of the disease. The presence of testicular atrophy, not previously reported, may be coincidental. Some cases may show only some of these features, and urinary discoloration may be inconspicuous, so that only increasing awareness of the condition and of the tests described by Discombe will lead to early and more frequent diagnosis.

Chronic porphyria and porphyrinuria, distinctly separate entities from acute porphyria, are respectively described by Mason, Courville, and Ziskind (1933) and by Rimington (1943).

Case History

A man aged 20 was admitted to a Royal Naval hospital on Nov. 14, 1947, with abdominal pain of four days' duration. His father had suffered from bouts of abdominal pain for several years and died at the age of 43 after a "cold" appendectomy. His mother, two brothers, and a stepbrother by the same mother were well. Their urine showed no porphobilinogen or spectroscopic evidence of porphyrins. His alcohol consumption was negligible, and there was no evidence that he had taken drugs at any time.

He had been quite well until June, 1947, when he complained of periumbilical pain, vomiting, and constipation, and two days later (June 11) he was admitted to hospital. Mild symptoms continued for two weeks. The day after admission his pulse rate rose to 90–100. It remained so for three weeks and then fell to 85–90. The only findings were a mild anaemia

and achlorhydria. He was symptom-free on discharge on July 25.

Apart from the loss of some 10 lb. (4.5 kg.) in weight he remained well until Nov. 11, when he was admitted on the fourth day of this illness. He complained of constant aching pain in the lower abdomen. He had vomited thrice and had obstinate constipation. The temperature was 97.4° F. (36.3° C.) and pulse 80. He looked thin and ill. The sclerotics had an unusual brownish tint, not due to bilirubinaemia. There was no pigmentation of the skin. He had generalized abdominal tenderness and considerable borborygmi. The testicles were small, measuring about 2 cm. in their long diameter. No other abnormality was noted. The temperature remained normal throughout the illness.

On the sixth day his pulse was 80. He was restless at night and was found sleep-walking. The next two days his pulse was 80-100 and the blood pressure 140/90. He was very miserable, lying curled up and complaining of his pain. All tendon-jerks were found to be sluggish. On the ninth day, after being delirious during the night, he had hallucinations. Acute porphyria was at this time first considered as a diagnosis on the combination of abdominal and nervous symptoms. The urine was macroscopically normal, but no chemical tests were done. The nightly administration of pentobarbitone ("nembutal") was stopped. On the 10th and 11th days his pulse was 90-120 and the blood pressure 115/85. Delirium and hallucinations continued, but pain had subsided. The urine on the 11th day had a pinkish tinge.

Examination with a Hartridge reversion spectroscope showed no definite absorption bands (but had a thick layer been used as recommended by Chandler, Harrison, and Rimington (1939) a positive result might have been obtained). The porphobilinogen test was not done. A psychiatrist diagnosed schizophrenia and advised transfer to a psychiatric hospital. This was done, but as it was still considered that the diagnosis was acute porphyria urine was kept for further examination. In three days this became dark brown in colour, and spectroscopy showed the absorption bands of acid porphyrin.

He was brought back to the general ward on the 16th day. He was mentally clear, and had noticed weakness of the arms, with difficulty in sitting up, for the previous two days. The urine appeared normal when passed. The pulse was 80-120 and the blood pressure 120/80. There was only flickering contraction of deltoid and pectoralis major muscles, with slight weakness of all the arm muscles. Biceps-jerks were absent. Flexion of the spine was very weak. On the 20th day the knee- and ankle-jerks were absent and there was some weakness of the legs.

Between the 22nd and 24th days he was again restless and delirious. Impaired pain sensation was found on the inside of the thighs. His condition was critical between the 24th and 28th days, and his pulse rate rose to 140. Thereafter there was very gradual improvement. By the 36th day he was mentally alert, there was some increase in power in arms and legs, the knee and ankle reflexes were normal, and no sensory changes were found. The pulse was still 110-135. By the 55th day the pulse was 85-100 and the blood pressure 115/80.

In the 10th week there was transient nausea and abdominal pain and a phase of hypotension; the blood pressure was 95/70. By the 17th week there was still considerable weakness of the deltoids, and the pulse rate ranged between 85 and 100. During the 21st week he had another attack of abdominal pain lasting about a week. Twenty-six weeks after the onset he was gaining weight and his arms were improving in strength.

Porphobilinogen and porphyrins were found in the urine throughout the period following diagnosis. Detailed examination of the porphyrins was not undertaken.

Subsequent History.—On July 3, 1948, he was admitted to hospital under the care of Dr. G. A. Emmerson with a recurrence of abdominal pain and severe insomnia. Hypertension and tachycardia were present and low serum sodium and chlorides were recorded. His abdominal pain gradually subsided, but the pulse rate rose to 110-130. On July 14 he complained of hoarseness. Phonation appeared to be weak, and there was weakness of extension of the right wrist. He died

suddenly and unexpectedly on the morning of July 16. No barbiturates had been administered.

Post-mortem examination showed pulmonary oedema and some bronchopneumonia and a flabby, thin myocardium. The testicles were not examined. Dr. F. T. G. Prunty reported on some of the tissues sent for examination. The lungs showed bronchopneumonia. There was some old and active tuberculosis in a tracheo-bronchial lymph gland. The liver showed early central necrosis in some lobules, and the liver cells contained brownish pigment granules not yet identified. The kidneys contained epithelial debris in some capsular spaces and there was capillary congestion. The convoluted tubules were the site of cloudy swelling, and in some places atrophy and pyknosis of nuclei had occurred. The adrenals were greatly hypertrophied, and the cells of the fasciculata in places gave evidence of lipid depletion.

Investigations.—Body weight: 13th day, 104 lb. (47.2 kg.); 27th day, 91 lb. (41.3 kg.); 40th day, 88 lb. (39.9 kg.); 75th day, 89 lb. (40.4 kg.); 110th day, 92 lb. (41.7 kg.). Urinary creatinine: 5th to 7th weeks, 0.5-1.4 g. per 24 hours. Urinary creatine: 42nd day, *nil*. Wassermann reaction negative. Fourth week: Serum bilirubin less than 0.5 mg. per 100 ml.; cephalin flocculation and Takata-Ara reaction negative; alkaline phosphatase, 3.8 King-Armstrong units. Quick's intravenous hippuric acid test: (30th day) excretion, 0.78 g. hippuric acid (as sodium benzoate); (107th day) excretion, 0.97 g. hippuric acid. Serum proteins (42nd day), 7.6 g.—albumin 5.3 g., globulin 2.3 g. Glucose-tolerance test (35th day): fasting, 74 mg.; $\frac{1}{2}$ hour, 110 mg.; 1 hour, 158 mg.; $1\frac{1}{2}$ hours, 146 mg.; 2 hours, 128 mg. per 100 ml. White blood count, 7,900-14,000 per c.mm. Red blood cells:—9th day: red cells, 4,790,000; Hb, 12.6 g.; 17th day: red cells, 4,670,000; Hb, 12.7 g.; P.C.V., 46/100; M.C.V., 98.5 μ ; M.C.D., 7.4 μ . 42nd day: red cells, 5,130,000; Hb, 14 g.; P.C.V., 50/100. 79th day: red cells, 4,600,000; Hb, 12.6 g.; P.C.V., 46/100; M.C.V., 100 μ . Electrocardiograms showed left axis deviation and very low T waves in leads I and CR4.

Electrolyte and Renal Function Changes in Acute Porphyria

The occurrence in acute porphyria of low serum sodium and chloride was described by Abrahams, Gavey, and MacLagan (1947) and Linder (1947). They also noted that despite low serum levels the urine still contained considerable quantities of chlorides. Both suggested that there was adrenal insufficiency.

In the present case low serum sodium and chloride levels were confirmed. The patient was placed on a special diet with a varied chloride intake. Desoxycortone acetate and adrenal cortical extract were given in addition for two periods. During the investigation there was no vomiting, diarrhoea, or excessive sweating. The urinary excretion of chloride was estimated daily and the serum levels were estimated at intervals (see Table). Sodium balance might have been of greater value, but chloride estimations taxed laboratory facilities considerably less.

It was found that the chloride output was directly proportional to the intake, and that cortical extract and desoxycortone acetate had no effect on this. During the first period of administration the patient's condition was deteriorating, and during the second period spontaneous improvement had already started. During both periods there was a rise in serum sodium, but this seemed to be part of a gradual rise that took place throughout the period of observation rather than an effect of drug administration. Chloride levels showed considerably less change throughout. Potassium had fallen before the administration of desoxycortone acetate, and the initial high level may have been produced by increased tissue breakdown, as there was a pronounced loss in weight at this time. Dehydration was not obvious clinically, and red-cell estimations suggested its presence about the 42nd day only. The alkali reserve was normal throughout. These findings indicate that

Table showing Chloride Estimations and Serum Levels

Day:	17	18	19	20	21	22	23	24	25	26	27	28	39	47	53	57	64	71	79	107
Fluid intake (litres) ..		2.50	2.35	2.55	2.27	1.48	3.10	2.30	3.10	2.45	1.94	1.94								
Urine vol. (litres) ..	1.01	1.13	1.65	1.90	1.88	1.64	?	2.02	1.82	2.15	?	2.10								
Chloride intake (as g. NaCl)	2.75	4.10	4.75	14.5	16.0	11.3	20.5	14.0	18.0	16.5	12.4	12.3		10+						
Urine Cl (as g. NaCl) ..	3.8	4.4	4.75	6.5	10.5	12.4	?	19.3	17.8	15.6	?	20.6								
Serum (mg. per 100 ml.)																				
Na ..		225					230					244		265	280	282	280	320	330	325
K ..		25					20					19.4		21.4	21.6			20.0	18.2	
Ca ..		7.5					8.1							9.8	10.0	10.0		9.8	10.0	
Cl as NaCl ..		495		505			495					495	500	490	515	495	495	520	528	490
HCO ₃ as vol. CO ₂ ..		69		72			69					73		65	72	74		65.5	67	
PO ₄ ..												4.4		4.0	4.05			3.96	3.65	
Urea ..		50		52			43					43	46	39	26		28	68	32	38
Pulse range ..	120 80	110 90	110 98	110 98	120 115	120 100	120 105	140 110	140 120	135 110	135 120	125 115	120 105	110 100	100 90	95 85	110 100	90 80	105 95	100 85
Blood pressure ..		120 80		135 110		135 110		125 95	120 90	125 95	115 85	120 95	120 85	120 80	125 90	115 80	105 70	110 80	110 80	

23rd to 27th days: 10 mg. of desoxycortone acetate were given by injection daily. 48th to 53rd days: 10 mg. of desoxycortone acetate plus 5 ml. cortin B.P.C. were given daily. A total of 500 mg. of pantothenic acid was given intramuscularly between the 57th and 70th days.

adrenal deficiency played no part in the production of the electrolyte picture. This is in harmony with the post-mortem findings, which suggested adrenal overactivity rather than underactivity.

Broch (1945), in a varied collection of conditions, found similar electrolyte changes without any appreciable response to salt therapy. He could find no harmful effect attributable to the electrolyte changes in themselves, and warned of the danger of giving intravenous saline, in the absence of dehydration, in an attempt to correct the electrolyte levels.

Oliguria and a moderately raised blood urea are very often found in acute porphyria and are usually attributed to circulatory disturbance. Albuminuria occurs in the minority and is usually slight. It was absent throughout in the present case. Water balance and serum-urea levels are shown in the Table.

The urea clearance test on the 58th day showed 60% of average normal function in the first hour and 62.5% in the second hour, on the 78th day 64% and 56%, and on the 107th day 58% and 51%. Thus in this case there was evidence of relatively persistent renal disorder. The findings suggest that attention should be directed to the kidneys for the explanation of the alteration in serum electrolytes. That the kidneys are responsible is perhaps further supported by the findings in a recently observed case, not yet fully investigated, in which only minor changes in serum electrolytes were found and renal function appeared to be normal.

Pantothenic Acid Deficiency and Porphyria

Liver and vitamin B have been recommended for acute porphyria, but little improvement attributable to their administration has been recorded.

Pantothenic-acid deficiency in animals results in failure to grow, porphyrin deposits on whiskers, gastro-intestinal symptoms, tachycardia, prostration, neurological changes, and coma, associated with low blood chloride and raised urea. Post mortem there is myelin degeneration of the nervous system, degeneration of the liver, adrenal cortical exhaustion, and renal tubular degeneration (Deane and McKibbin, 1946). No defect in sodium conservation is revealed (McQueeney, Ashburn, Daft, and Faulkner, 1947). In this state there is at least superficial resemblance to acute porphyria. Further, it was shown that pantothenic acid will reduce or abolish porphyrin excretion produced by drugs (Hoesch, 1947). Its effect in acute porphyria was not studied.

In the present case 500 mg. of pantothenic acid was given by intramuscular injection between the 57th and 70th days. There was no appreciable change in the rate of clinical

improvement or in the pulse and blood pressure. It was not practicable to assess the quantitative excretion of porphyrins, but the depth of colour produced in the porphobilinogen test, though of little value in assessing quantitative excretion, showed no appreciable variation. Between the 64th and 71st days the sodium level, previously steady, rose from 280 to 320 mg., and this level was maintained. There was a temporary rise in urea (see Table).

Thus the only evidence of a beneficial effect from pantothenic acid was given by the serum sodium level. Whether this was therapeutic or coincidental can be assessed only by its trial earlier in a crisis. That a deficiency of the vitamin is a factor in precipitating a crisis seems unlikely.

The conclusions arrived at are: (1) that the changes in serum electrolyte levels in acute porphyria are not dependent on adrenal cortical deficiency but are probably due to renal damage; (2) that pantothenic acid, reported as beneficial in chemically induced porphyrinuria, is of doubtful value in acute porphyria, though further trial is advisable. I realize that conclusions drawn from the investigation of a single case may require modification with further experience.

Summary

A classical case of acute porphyria is presented. The previous finding of low serum sodium and chloride is confirmed, and it is shown that these are not due to adrenal deficiency but are probably dependent on renal damage.

The relationship between pantothenic acid and porphyria is discussed and observations during pantothenic acid therapy are described.

I am indebted to the Medical Director-General of the Navy and to Surgeon Captain J. G. Holmes, Royal Navy, for permission to publish this case, and to Surgeon Commander H. J. Bennett, Dr. G. A. Emmerson, and Dr. F. T. G. Prunty for use of their findings. I wish to thank Dr. Philip Hamill and Dr. A. J. Shillitoe for advice and criticism in the preparation of this paper, and, above all, Sick-Berth Petty Officer J. G. Scott for his valuable laboratory work.

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