be reduced by an increase in concentration of the drops, but a striking difference was noted in the case of inclusion bodies. Of the 16 cases of inclusion bodies treated by penicillin, 2,500 units per ml., nine gave an unsatisfactory response, while only four out of 15 failed to respond when the concentration was increased to 10,000 units per ml. Only one of the five cases with diphtheroids treated by systemic injection gave an unsatisfactory response; there were three cases with unsatisfactory response out of a total of 17 with inclusion bodies.

3. The poor responses and relapses recorded in this series are to be understood in a relative sense. A total failure to respond to penicillin treatment has not been observed, and in no case has penicillin treatment failed to influence the condition sufficiently to remove all anxiety within a matter of hours, or less. The optimum mode of use of penicillin is still to be determined, though even now the results obtainable are as great an advance on those of the sulphonamides as these in turn were over the classical methods of treatment.

I am indebted to Drs. Olga Bloom, Joan Haythorne, Joan Jenkins, J. Kennedy, R. E. O'Neal, K. B. Redmond, and C. Taylor for their help while they were residents at White Oak Hospital. I am also obliged to the matron and to Sister Condon and her staff for their loyal collaboration. To Dr. H. M. Walker, Dr. J. Ungar, Mr. J. T. Marsh, M.P.S., and Mr. W. A. Woodard, M.P.S., of Messrs. Glaxo Laboratories, Ltd., I am indebted for the supply of pure penicillin and much help in the preparation of oily suspensions and ointments.

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A FATAL CASE OF ACUTE PORPHYRIA WITH UNUSUAL FEATURES

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The following case is worthy of record because of the difficulty in diagnosis and the possible relationship to drug therapy. The type of porphyrin was also atypical, and there were signs suggestive of adrenal insufficiency.

Case Report

A woman teacher aged 34 was admitted to hospital on the 9th day of a febrile illness which began with hoarseness and intermittent severe pains and weakness in all limbs. Except for appendicectomy some years ago and sinusitis a month before, she had been active and well until the onset of the present illness. She was an only child of parents, now dead, of whom she knew little. The limb pains subsided in two days, but on the 6th day she had lower abdominal pain with slight tenderness in the right lumbar area. No relief was obtained from an enema. A second was given with some success, but soon the abdominal pain increased with vomiting. Morphine, 1/4 gr. (16 mg.), had been given a few hours before admission.

On admission she was drowsy. The temperature was 100.5° F. (38.05° C.), the pulse 120, and the respirations 28. Pallor was evident but her general nutrition was good. The tongue was furred and dry. Slight tenderness was elicited in the right iliac fossa and hypogastrium. Rectal examination was negative. The lungs and heart were normal except for an exocardiac murmur at the mitral area. The blood pressure was 120/80. The central nervous system was normal, though the tendon reflexes were sluggish. The urine—specific gravity 1020—was red, evidently from admixture with menstrual blood; albumin was present, sugar absent. Pus and *B. coli*

were found in a catheter specimen. She had no frequency of micturition, but the urinary findings, coupled with abdominal tenderness, suggested pyelo-cystitis. On the 11th day sulphamezathine was given, 2 g. at once followed by 1 g. four-hourly, together with potassium citrate, 30 gr. (2 g.) four-hourly. The temperature fell to normal after 24 hours, she felt and looked better, and the dose of sulphamezathine was reduced to 1 g. thrice daily. She received "soneryl," 1½ gr. (0.1 g.), and tab. codein. co. on several occasions.

On the 12th day of the disease there was mental confusion, with marked nocturnal restlessness and recurrence of severe pain and tenderness in the hypogastrium. Similar symptoms were present during the following night, and on the 15th day she had a fit, during which she bit and chewed her tongue. Her temperature was 98° F. (36.7° C.), pulse 104, and blood pressure 130/80. She could with difficulty be roused. Sulphamezathine was suspended after a total of 20 g. had been given, and potassium citrate was also stopped, half-normal saline being administered by mouth on account of suspected salt deficiency. Improvement rapidly followed and she became coherent and co-operative. The tongue was much swollen; cervical adenitis was present, and for this penicillin, 30,000 units three-hourly, was given intramuscularly. The abdomen was distended but not tender. The knee-jerks were sluggish, but other tendon reflexes were normal and weakness or sensory loss was not apparent. A skiagram of the chest and abdomen was normal. The C.S.F. showed: a pressure of 114 mm. of fluid, with less than 1 cell per c.mm.; protein 25 mg. per 100 ml.; globulin nil; colloidal gold test, 000000. A blood count showed: white cells, 30,000 per c.mm. (polymorphs, 89%; lymphocytes, 10%; eosinophils, 1%); plasma chlorides, 416 mg. per 100 ml.; serum sodium, 253 mg. per 100 ml.; urea, 25 mg. per 100 ml.; alkali reserve, 64 vols. CO₂ %. On the 17th day the blood chemistry was: chlorides, 470 mg.; sodium, 272 mg.; potassium, 14.9 mg.; alkali reserve, 61 vols. CO₂ %. It is of interest to note that the urine contained chlorides in spite of the low plasma chloride level.

On the 18th day porphyrin was discovered in the urine. Some general clinical improvement was apparent: the blood pressure was 110/80. The knee-jerks were now absent, but the ankle-jerks remained brisk and there was no weakness of the legs. Complaint was made of numbness of the lower abdomen, buttocks, and thighs, and objectively there was some loss of sensation to cotton-wool over the abdomen, but pin-prick was felt normally here and elsewhere. No postural or vibratory loss was noted at any time during the illness. Blood culture was negative. The white cells numbered 11,550 per c.mm. (polymorphs 80%). The urine contained a few pus cells only, and culture was sterile.

20th Day.—There was sudden deterioration during the preceding night. Her temperature was 101.5° F. (38.6° C.), and pulse 130; there were abdominal and limb pains, and mental confusion with phobias and delusions; a toxic appearance; a false rigor; and loss of all limb reflexes. The right kidney was palpable and tender and the exocardiac murmur was more pronounced. Half-strength saline was administered by mouth. Blood chemistry: chlorides, 494 mg.; sodium, 298 mg.; potassium, 14.7 mg.; urea, 24 mg.; calcium, 9.1 mg.

21st Day.—The temperature was 101° F. (38.3° C.) and the pulse 110. She was cyanosed and drowsy but co-operative. Diminished movement and breath sounds at the right base were believed to be due to a high diaphragm, as shown by a skiagram. The right kidney was tender.

22nd Day.—She was less cyanosed and more rational and co-operative. Temperature had fallen to 99° F. (37.2° C.). Examination revealed the following: weak abduction of shoulders; weakness of extensors of wrist and fingers; tendon jerks absent but sensation normal; weakness of legs, especially quadriceps; ankle- and knee-jerks absent but no more pain; abdominal reflexes absent; plantar reflexes flexor; analgesia to pin-prick over lower limbs and lower trunk, and anaesthesia to cotton-wool over trunk.

23rd Day.—Kaolin, 1/2 oz. (14 g.) three-hourly, was administered in the hope of its adsorbing porphyrin. On sternal puncture no abnormal cells were seen, but the marrow was very active, with a high count of neutral polymorphs and large

numbers of reticulocytes; 88% of normoblasts showed a cytoplasmic reticulum—a possible source of porphyrins. Ultra-violet light, applied to the skin and to the teeth, showed no fluorescence.

25th Day.—Now felt and looked well. Ankle-jerks brisk, but knee-jerks still absent. No sensory loss; no urinary symptoms or signs; B.P. 120/80.

31st Day.—She had gradually improved during the past few days, but her temperature was 100° F. (37.8° C.), for which no explanation was forthcoming; in particular there were no urinary symptoms or signs. The urinary output was good—3 to 5 pints (1.7 to 2.8 litres) per 24 hours. She received soneryl, 1½ gr. (0.1 g.), nightly until the 32nd and 33rd days, when "nembatal," 1½ gr. (0.1 g.), was given each night.

35th Day.—The patient complained of nausea with vomiting on one occasion, but she was able to sit up unaided. There was moderate weakness of the limbs, mainly proximal, but no demonstrable weakness at the ankles. The ankle-jerks had become sluggish once more and the knee-jerks were still absent. The upper-limb and the abdominal reflexes were not obtained. Though she was febrile—temperature 99° F. (37.2° C.) and pulse 116—the clinical impression was favourable. A few hours later she complained of an intolerable desire to bite her tongue, and she did so while lapsing into semi-consciousness, which deepened during the night.

36th Day.—At 6.30 a.m. chewing movements recurred and she remained comatose, with dilated but active pupils which showed hippus. The plantar reflexes were flexor. The pulse quickened to 140; the blood pressure fell to 80/60, and by 6 p.m. was 75/50. Her clinical state now suggested adrenal failure, especially in view of the blood chemistry, tachycardia, and hypotension. Serum sodium 248 mg.; potassium 18.8 mg.; urea 41 mg.; alkali reserve 60 vol. CO₂ %; chlorides 380 mg. Treatment by intravenous "eucortone" and 1.8% saline was given.

38th Day.—During the next 36 hours she received 4½ pints (2.6 litres) of double-strength saline and a total of 50 ml. of eucortone. After 16 hours' treatment the blood pressure began to rise a little to 80/55, and she very gradually improved and could be roused to answer "Yes" and "No." The highest blood pressure was 90/60 after 36 hours. Blood urea, 127 mg.; plasma chlorides, 576 mg.; blood sugar, 123 mg. Urine: albumin present, alkaline. *B. coli* present.

42nd Day.—Unable to cough (diaphragmatic paralysis), but intercostal muscles active. Voice weak, otherwise normal. Neck muscles unable to support head. Hand movements slight. Incontinent. Temperature 100° F. (37.8° C.), pulse 150/60. Blood urea, 277 mg.; chlorides, 680 mg.; alkali reserve, 57 vols. CO₂ %.

43rd Day.—Patient was cyanosed, with difficult respiration. She was put into an artificial respirator on account of intercostal and diaphragmatic paralysis. B.P. 75/60.

45th Day.—There was progressive paralysis of trunk and limbs but no cranial nerve paralysis; she was semi-conscious until death.

Post-mortem Examination (abstract)

The external appearances were not remarkable. The positive findings were: striking bluish-black discoloration of both rectus abdominis muscles, a few streaks in the psoas, and dark flecks on the parietal and visceral peritoneum of the lower abdomen and great omentum; distended discoloured sigmoid and rectum, containing greasy faeces. The liver was normal in appearance and weighed 51 oz. (1.45 kg.). The engorged kidneys were normal in size, the capsule stripped easily, and the right showed mild dilatation of the pelvis and pyelonephritis. There were purulent cystitis, oedema of mucosa obstructing the right ureteric orifice, and right hydro-ureter. The adrenals were normal. The right ovary contained a dermoid cyst with pale hair; other abdominal viscera were normal. The thyroid was atrophic, weighing only 9 g. No thymus was found. The lungs showed no effusion. The right lower lobe was almost completely consolidated, and section revealed a chequered pattern with alternating dark-red and dark-grey patches. The left lower lobe showed patchy collapse. The heart showed mild brown atrophy and slight irregularity of the mitral valve. The aorta was hypoplastic, with a diameter of only 1.5 cm.

at the level of the coeliac axis. No coarctation was present. The brain and spinal cord were normal.

Red fluorescence under ultra-violet light was seen in specimens of costal cartilages which showed concentric rings, in sternal marrow, in the blackened portions of the rectus abdominis, in the posterior cusp of the mitral valve, in the septal endocardium, in the small intestine, in the medulla of the kidneys, and to a slight extent also in the adrenal glands.

Histology.—Detailed examination of the central nervous system disclosed nothing abnormal except vacuolation of the anterior horn cells. Some excess of lipid pigment was present in ganglionic cells of the sympathetic, as well as oedema between nerve fibres and perineural sheaths and mild degeneration in the myelin sheaths. The lower lobe of the right lung showed infarcts at least one week old surrounded by supervening bronchopneumonia. Arterial thrombi were present, but otherwise no disease of the vessels was found. The liver showed mild fatty degeneration; the right kidney was in a state of low-grade pyelonephritis, there was complete necrosis of the whole thickness of the wall of the rectum, with only scanty leucocytic infiltration; and the adrenals exhibited slight degenerative changes, more marked in the deeper cortex. Microscopy of the other organs revealed nothing of importance.

Chemical Findings

The initial observation of porphyria was made by spectroscopic examination of a faintly pink specimen of urine on the 18th day of the disease. The two-banded spectrum of a metallo-porphyrin complex was easily seen in a 1½-in. (1.27-cm.) layer, the wavelengths being 577 and 541 mμ (Hartridge reversion spectroscopy). On treatment with concentrated HCl the acid porphyrin spectrum was obtained (594 and 551 mμ) and after neutralization with sodium acetate all the porphyrin was readily extractable by ether, giving a four-banded spectrum (623, 597, 575, 569 mμ). These wavelengths correspond closely to those given by Chandler, Harrison and Rimington (1939) for coproporphyrin derivatives measured with the same type of instrument. Subsequent specimens were collected into Winchester containing HCl as preservative. It was noted that they were often normal in colour when passed but darkened to a reddish brown on standing.

The total daily urine porphyrin excretion, estimated by the method of Rimington (1943) on eleven 24-hourly specimens, is shown in the accompanying Chart. It will be seen that the

Chart showing total daily urine porphyrin excretion.

values fall between 4.7 and 12.5 mg. per day (normal up to 0.1 mg.), with some suggestion of a fall during the period of kaolin administration. No marked increase was noted at the onset of the fatal termination, but collection of complete 24-hour specimens became impossible at this time. The faecal excretion of coproporphyrin was determined fluorimetrically on a pooled 10-day specimen of stool collected from the 22nd to the 32nd day of the disease, and gave an average value of 50 mg. per day (normal up to 0.3 mg.). In this estimation the stool was first dried with acetone and then extracted with a mixture of ethyl acetate 10 parts to acetic acid 1 part. Extraction from ether into 0.25% w/v HCl was used to avoid the inclusion of protoporphyrin and deuteroporphyrin, which were present in small amounts.

Qualitative examination of the porphyrins by the methods of Dobriner (1937), supplemented by chromatography on alumina,

showed that the urine porphyrins consisted of about 99% of coproporphyrin III (methyl ester, melting point 142°C ., remelt 177°C .), and 1% of coproporphyrin I (methyl ester, melting point 254°C . corrected), with only traces of uroporphyrin. The stool coproporphyrin consisted of approximately 55% of coproporphyrin III (methyl ester, melting point 144°C ., remelt 177°C .) and 45% of a coproporphyrin whose methyl ester melted at 163°C . This porphyrin could not be identified with any previously described, and is being further investigated.

The low serum sodium, potassium, and chloride levels and the terminal uraemia have been referred to above. The urinary 17-ketosteroid excretion was estimated on the 36th day of the disease and gave a normal result (12 mg. per 24 hours). The lead content of a 24-hour urine specimen was also within normal limits (0.11 mg. per litre). Liver function tests gave normal results—that is, serum bilirubin, 0.8 mg. per 100 ml.; serum alkaline phosphatase, 12 units; thymol turbidity test and serum colloidal gold reaction, negative.

Discussion

The principal difficulty in the diagnosis of porphyria lies in the comparative rarity of the condition, which therefore tends to be overlooked; in the present case the diagnosis was made more or less accidentally on the 18th day of the disease while the urine was being examined for another purpose. It would seem to be advisable to look specifically for porphyrinuria in any case of obscure abdominal pain associated with constipation, especially if accompanied by mental or neurological symptoms. The literature on porphyria will not be considered here in detail as it has been well reviewed by Chandler, Harrison, and Rimington (1939), Dobriner and Rhoads (1940), and Welcker (1945).

With regard to aetiology, the post-mortem finding of a hypoplastic aorta and an ovarian dermoid suggests the possibility of an inherited defect, but no useful family history was obtainable. The relationship of the porphyrin to drugs is by no means clear in this case. Porphyrinuria due to drugs (with the exception of the sulphonal group) usually produces less than 1 mg. per day of urinary *coproporphyrin* without symptoms directly attributable to the porphyrinuria except in lead-poisoning (Dobriner and Rhoads, 1940; Rimington and Hemmings, 1938). Acute idiopathic porphyria, on the other hand, usually produces an excretion of many milligrams of *uroporphyrin* per day with typical symptoms, and the porphyria of sulphonal poisoning is closely similar (Dobriner and Rhoads, 1940). The present case is therefore different from both these types, as there was a heavy excretion of *coproporphyrin* with typical symptomatology. It seems likely that the porphyria preceded the administration of any of the various drugs used, but the red colour of the urine noted on the ninth and tenth days of the disease was ascribed to menstrual blood, and no tests for porphyrin were made at this time.

The possibility of lead-poisoning seems to be ruled out by the normal urinary lead values and the absence of any history of exposure to lead. This case therefore appears to be intermediate between the drug porphyrinurias on the one hand and acute idiopathic porphyria on the other, having certain features in common with both groups.

In retrospect there is a distinct suggestion that the condition was aggravated by some of the drugs used, and the fatal termination followed closely on the administration of "nembutal," given to control the marked nocturnal restlessness. In this connexion the advice of Waldenström (1940) to restrict sedative drugs to opiates in this condition needs renewed emphasis, and it may perhaps be worth while to give the following list of drugs which are known to produce porphyrinuria and which should be particularly avoided. These are: sulphonal, trional, sulphonamides, bar-

biturates, arsenicals, alcohol, phosphorus, selenium, and lead (Dobriner and Rhoads, 1939). Kaolin was given in full doses for twelve days in an attempt to immobilize the porphyrin in the bowel, *in-vitro* experiments having shown that the urinary porphyrin in this case was well absorbed by kaolin. There was some clinical improvement, with a slight fall in urinary porphyrin excretion during this period, but the effect was not very definite. However, this line of treatment might be worth a trial in other cases.

The low serum sodium and chloride values found on three occasions are of interest, as these estimations do not appear to have been carried out previously in cases of porphyria. These changes were associated with tachycardia, hypotension, and collapse, and suggested adrenal involvement; but large doses of eucortone and sodium chloride failed to avert the fatal outcome, and no significant lesions were found in the adrenals at necropsy. During the exacerbations the resemblance to adrenal failure was, however, a striking feature, and the possibility of a purely functional adrenal disturbance should be considered as a contributory cause of death in porphyria. In this connexion it may be mentioned that the exact cause of death is not obvious in this condition, and that respiratory paralysis may not be the sole explanation in cases where efficient mechanical respiration is available.

Summary

The case is reported of a woman aged 34 who suffered from an illness lasting six weeks, characterized by four main exacerbations. The principal symptoms were fever, limb pain, weakness, abdominal pain, constipation, mental confusion, and epileptiform attacks. A urinary infection was present, and there were two episodes suggesting adrenal involvement. Death was preceded by progressive polyneuritis and respiratory failure.

The urine contained from 4.7 to 12 mg. of coproporphyrin a day, which was mainly coproporphyrin III. The stools also contained an excess of coproporphyrin III and an unidentified coproporphyrin.

The dangers of administration of certain drugs in this condition are discussed.

We are indebted to Dr. Alan Morgan for the necropsy findings, to Dr. J. G. Humble for the haematological details, and to Prof. C. R. Rimington for a sample of pure coproporphyrin I methyl ester. Mr. V. R. Wheatley gave valuable technical assistance.

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Practical Physiological Chemistry (twelfth edition), by Philip B. Hawk, Ph.D., Bernard L. Oser, Ph.D., and William H. Summerson, Ph.D. (J. and A. Churchill; 50s.), requires no introduction to British readers, but during the ten years that have elapsed since the last edition great advances have been made in biochemistry. The authors have produced a well-balanced, up-to-date, and comprehensive book without increasing the size unduly. They achieved more than the title suggests. There is a sound theoretical discussion of the subject matter of each chapter, followed by illustrative practical procedures, including a wealth of useful technical detail. New material includes accounts of electrophoresis, the use of isotopes and antibiotics, and metabolic antagonists. The chapter on vitamins has been extensively revised and expanded. The sections dealing with blood and urine analysis and energy metabolism are particularly useful to the clinical biochemist, for they include well-chosen descriptions of modern analytical techniques. The interpretations of pathological findings are brief but useful. The authors have wisely deleted obsolete material and included a chapter describing in detail the principles of colorimetry and photometry. This work will continue to retain its place in the laboratory as a practical manual and in the library as a valuable reference book.