None of the results recorded in these papers would have led to a misclassification of obstructive jaundice as non-obstructive. Maclagan refers to the tendency towards positive flocculation reactions in cases of rheumatoid arthritis and heart failure even in the absence of jaundice, and states that the possibility that these diseases may be complications in cases of jaundice should be borne in mind. It would seem possible that an alkaline phosphatase of below 15 units might be found early in a case of minimal jaundice due to stone, but the chance of mistaking surgical obstruction for liver disease seems to be slight.

The present series is too small for any final conclusions to be drawn on whether the routine inclusion of tests for urobilinogen and derangement of the serum protein would make for a significant improvement in diagnostic precision. These tests pointed to the correct diagnosis in the four cases in which phosphatase and thymol findings were anomalous, but this might not occur again. No misleading results were obtained from these tests, but a larger series might not show the same freedom from fallacy. In the present series one case of carcinoma of the pancreas showed amounts of urobilinogen which, while not sufficient to be classified as strongly positive, caused serious consideration to be given to a diagnosis of chronic hepatitis in spite of a high phosphatase and negative thymol. Acute cholecystitis complicating obstruction due to stone could clearly give rise to large quantities of urobilinogen. A normal or slightly raised globulin with a low albumin can occur in cases of obstruction (Sherlock, 1946). These are changes in the same direction, but not to the same degree as the changes observed in hepatitis and cirrhosis.

Summary

The use of the diagnostic criteria of Maclagan is illustrated in a series of 70 cases of jaundice.

Four cases gave anomalous results, and these are discussed.

The use of routine tests for urobilinogen and for derangement of the serum proteins to give increased diagnostic precision is considered.

My thanks are due to Professor C. H. Gray for advice and criticism, to my colleagues at Townleys Hospital for access to their cases and advice, and to Mr. J. M. Ellice for carrying out many of the tests.

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The July number of *Marriage Guidance*, the monthly bulletin of the National Marriage Guidance Council, contains a brief report on the work done in 1949. For the first time all affiliated marriage-guidance councils were asked to submit returns of their year's work, and 67 replied. They showed a total of 6,540 married couples helped, and 1,076 engaged couples prepared for marriage. Forty-five of the councils attempted to classify their remedial work, and reported 1,096 successful cases, 679 unsuccessful, and 1,327 unknown, doubtful, or pending, though accurate classification is at present very difficult or impossible. There were 249 counsellors, 50 of whom have passed the national selection procedure and completed their training.

ACUTE IDIOPATHIC PORPHYRIA REPORT OF TWO CASES

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Porphyria may occur as a congenital condition, with red urine, pink teeth, and hydroa aestivale, or as an acute disease, either idiopathic or toxic, or it may be produced by drugs such as sulphonal, methylsulphonol, and others. We are concerned here with the acute idiopathic variety. We have recently encountered three examples, and two of them are recorded. Had Case 1 been admitted during the later stages of her paralysis the diagnosis would probably not have been made, as the urine had then lost its colour. Case 2 came under her doctor's care for hallucinatory psychosis, porphyria being diagnosed only on her death-bed some weeks later, and in this patient previous bouts of "gastric ulcer" may well have been episodes of relapsing porphyria. The testing of urine for porphyrins with ultra-violet light is simple, and porphyria may explain puzzling cases of polyneuritis, Landry's ascending paralysis, psychosis, and acute abdominal pain.

Acute porphyria with nervous complications was first described by Ranking and Pardington (1890). Günther (1911) recorded 14 cases, and Waldenström (1937) 103 Swedish cases. The biochemistry has been defined by Fischer and Zerweck (1924), Rimington (1939), Dobriner and Rhoads (1940), Turner (1937), and others, and the pathology has been reviewed by Denny-Brown and Sciarra (1945).

Case 1

A woman aged 51 was seen in consultation with Dr. W. A. Whitehouse Parkes, of Sutton Coldfield, on April 7, 1948, and was at once admitted to hospital. For six weeks she had been complaining of sharp central abdominal pain, passing through to the back, associated with aching in her limbs, fatigue, and intractable insomnia. Three weeks before admission her urine had become dark red in colour and nephritis had been suspected; a week later she had a slight transient sore throat. There was no significant previous history, nor was there any exposure to lead, sulphonal, or antipyretics.

On examination she was seen to be very ill, drowsy, disorientated, and confused, and had difficulty in answering questions. The skin had a brownish pigmentation and the conjunctivae were injected. The tongue was dry and coated. There was no tenderness in the abdomen,

FIG. 1.—Case 1. Showing myasthenic appearance of the facies due to bilateral facial palsy. The patient was instructed to close her eyes. This appearance is also present during sleep.

rigidity, or undue distension. Examination of her central nervous system revealed no abnormality apart from her confused state. The urine was a dark burgundy colour and contained occasional casts; spectroscopic examination gave absorption bands for porphyrin, thus establishing the diagnosis of porphyria.

During the next 48 hours the drowsiness and confusion increased, and on April 9 she became irrational and endeavoured to climb out of bed. Twelve hours later her mental condition had improved, but she complained of some numbness below the waist. There was extensive weakness of lower motor neurone type involving all limbs and the trunk. The weakness affected the right side of the body more than the left, and the proximal limb segments more than the distal. Her biceps, triceps, and deltoids were particularly weak. Bilateral facial weakness of lower motor neurone type caused difficulty in closing the eyes, and gave her face a myasthenic appearance (Fig. 1). Ocular movements were normal; there was no difficulty in swallowing or in speech, and no palatal weakness. Screening of the chest showed diminished movement of the left cupola of the diaphragm. She was unable to raise her head and shoulders from the pillow or her legs from the bed. Despite the numbness of which she complained at the onset, all forms of sensation were unimpaired. For the next three days she had retention of urine. Her blood pressure was 150/100 mm. The electrocardiogram showed no abnormality.

Biochemical Findings.—Examination of the faeces on June 2 showed: coproporphyrin, 3.5 mg. in 24 hours; and protoporphyrin, 1.6 mg. On June 16 it showed: coproporphyrin, 2 mg.; protoporphyrin, 0.5 mg. Uroporphyrin was absent on both occasions. The urinary porphyrin content was estimated

FIG. 2.—Case 1. Total daily output of porphyrin.

from April 14, 1948. The figures are shown in Fig. 2. The values given are those of total porphyrin, as efforts to obtain crystalline material were unsuccessful.

The estimations shown in Fig. 2 have been made by fluorometric comparison with a standard solution of porphyrin supplied by Professor C. Rimington. The

values obtained by this method are considerably lower than those which might be expected when using the method of Sveinsson, Rimington, and Barnes (1949), but they are published because they give a comparative value of the daily excretion.

The wavelengths of the absorption bands are given in Table I. At all times there was a quantity of pigment which was not fluorescent, particularly when the urine was infected. This was later shown by Mr. Garfield Thomas to have the absorption bands of indolylacetic acid. Spectroscopic examination of the patient's serum showed no abnormal absorption bands.

TABLE I

	No. of Bands	Wavelength in Angstrom Units	Solvent	Dodds's Figures Compared	Solvent
Faecal protoporphyrin	2 (or 3)	{ 5995 5535	5% HCl	6000 5540 (5740)	
Urinary coproporphyrin	3	{ 5920 5710 5480	1% HCl	5920 5700 5480	20% HCl
Faecal coproporphyrin	3	{ 5953 5705 5435		5920 5700 5480	
Urinary uroporphyrin	3	{ 5959 5732 5520	5% HCl	5960 5770 5530	20% HCl

The urine contained granular casts. The cerebrospinal fluid had a high initial pressure of 280 mm., the cytology and protein content were normal, and no fluorescent substance could be demonstrated in it on examination by ultra-violet light.

Apart from the demonstration of these abnormal pigments in the urine and stool there was found to be a raised blood urea and a slightly raised serum total cholesterol. Serum potassium estimations were made, as it was felt that this predominantly motor weakness might be connected with a low value of serum potassium, but these were found to be consistently normal. The pathological and biochemical findings are summarized in Table II.

TABLE II

Date	White Cell Count	Blood Urea (mg./100 ml.)	Serum Total Cholesterol (mg./100 ml.)	Serum Potassium (mg./100 ml.)
8/4/48	5,600 (53% P., 42-7% L., 0-7% E., 0-3% B., 3% M.)	98	—	—
12/4/48	8,500	—	—	—
18/4/48	—	57	450	—
20/4/48	—	42	400	20
28/4/48	11,000	37	464	21
6/7/48	—	—	—	21.6

Serum albumin, 4 g./100 ml. Serum globulin, 2 g./100 ml.

Transillumination of the hands showed no loss of translucency of the metacarpal bones or phalanges when compared with those of a normal control. Exposure to an erythema dose of ultra-violet light disclosed no abnormal sensitivity.

Progress

Oral nicotinic acid and thiamin did not appear to influence the slow improvement; nor did neostigmine and quinine administered at different times produce any effect on the facial weakness. On April 29 there was a temporary return of bladder function, though on May 2 the patient was again unable to pass urine without the administration of carbachol. A *Bacterium coli* infection of the urine developed, and this was treated with sulphacetamide. The power of the grip had returned by May 4, the ability to close her eyes normally by May 10, and the power had begun to return in her biceps and triceps by May 11. On May 12 screening of the chest showed the diaphragm to be moving. By May 22 she had recovered enough power in the legs to walk a few steps with assistance, and was able to walk unaided by May 31.

One year later, on May 31, 1949, it was found that her urine had been free from discoloration and a specimen no longer fluoresced with ultra-violet light. There was still weakness of the extensor muscles of the legs, and a slight residual weakness of extension of the right wrist and fingers. Although there was no longer a demonstrable weakness of the muscles of her shoulder girdle or face, she complained of aching in these muscles after use. She was seen again on February 14, 1950, when there had been no further abdominal complaints, bladder disturbance, or weakness. The urine had been free from discoloration. There was some pain in the transverse arches of the feet which appeared to be due to pes planus, and occasional cramp-like pains in the muscles, chiefly in the thighs and upper arms. There was no demonstrable weakness of trunk, limbs, or face, her gait being normal. She could rise from the lying position without assistance and get up from a chair without difficulty.

Specimens of urine of the patient's three sisters and son (aged 19) had been found to be normal.

Case 2

A woman aged 74 was seen by us in her home in consultation with Dr. R. E. Wilkinson, of Bromsgrove, on December 12, 1949. Eight weeks previously she had begun to pass urine which was red in colour, and a week later her doctor had been called in because she had had visual hallucinations of objects flying around the room, or people coming and sitting on her bed and pinning her down. The only abnormal finding was a

blood pressure of 220/120, and on moving her to another bedroom the symptoms subsided. After five weeks she had an attack of bronchitis unaccompanied by pyrexia, and a week later she developed lower abdominal pain, associated with vomiting. For 10 days she had become increasingly weak, and during the previous 48 hours she had not made any movement of her arms or legs, her eyes had remained half-open when she slept, and there was dysphasia and complete retention of urine. She had had recurrent attacks of abdominal pain, attributed to a gastric ulcer, for many years.

On examination the patient was listless and apathetic, replying to questions in a low voice. Although comprehension was dull she was able to recognize people and respond to instructions. There was a bilateral facial weakness of lower motor neurone type causing difficult closure of the eyes. Beyond a feeble attempt to grip with both hands, the arms showed a complete flaccid paralysis. Her legs were also completely paralysed and no reflexes could be obtained. Her tongue was protruded a little to the right and there was difficulty in swallowing, but the palate moved normally. The bladder was painlessly distended almost to the umbilicus. There was no sensory loss.

The patient was catheterized and 640 ml. of burgundy-coloured urine withdrawn for examination. She was considered to be too ill to be transferred to the hospital. She died next day, and permission could not be obtained for a necropsy.

Biochemical Findings.—A portion of the urine specimen collected was forwarded to Professor C. Rimington, who reported as follows: "Coproporphyrin, 2.1 mg. per litre; uroporphyrin, 103.9 mg. per litre. Even allowing for the fact that the urine is a very concentrated specimen, these are enormous quantities even for acute porphyria. There seems to be little doubt about the nature of the condition from the chemical point of view."

Porphyryns were not found in the urine of the patient's grandchild.

Discussion

Aetiology.—Most authorities regard the condition as being not so much due to abnormality of the breakdown of blood pigments as to an anabolic abnormality of synthesis. This idea is supported by the occurrence of large amounts of porphyrin in foetal serum, bone marrow, and meconium. The only undisputed aetiological factors are familial incidence, which may persist through three generations, and the transmission of the disease as a Mendelian dominant.

Age and Sex Incidence.—Waldenström (1937) found that symptoms usually appeared between the ages of 21 and 25, and most deaths occurred between 26 and 30. Only one case over 61 was recorded, so that our second case, at the age of 74, must be one of the oldest patients on record. In Waldenström's (1937) series 65% were women.

Pathology.—The pathological changes described have been nerve-cell degeneration in the anterior horns of the spinal cord and, to a less extent, the posterior horns, associated with chromatolysis, eccentricity of the nucleus, lipid pigment accumulation, and vacuolation (Bostroem, 1920; Courcoux *et al.*, 1929; Mason *et al.*, 1933). In cases in which paralysis has been brief there might be no demonstrable change in the nerves (Löffler, 1919; Rothman, 1926; Borst and Königsdörffer, 1929), otherwise a patchy demyelination most marked in the nerves of the lower extremities was usual (Mason *et al.*, 1933). Demyelination in the spinal cord has been described by Courcoux only as a marginal demyelination of the antero-lateral tract of the lumbar cord. The cerebral glia may be laden with pigment (Grünwald, 1922), the oligodendroglia swollen, and the Purkinje cells of the cerebellum chromatolysed, or there may be a diffuse oedema of the brain (Eichler, 1932). Denny-Brown and Sciarra found gaps in the myelin in the

nodes of Ranvier similar to nerve segments rendered ischaemic by pressure. Mason *et al.* (1933) and Palmer (1940) found scattered but constant lymphocytic infiltration. The pathogenesis of the disease is quite obscure.

Symptomatology and Signs.—The initial symptoms are severe cramp-like pains in the central abdomen accompanied by the passage of red-coloured urine. There ensues a widespread paralysis of the lower motor neurone type, often accompanied by a confusional state with delirium and hallucinations. Abdominal symptoms and porphyrin excretion may lessen before the neurological symptoms occur. In Case 1 the patient had lost her abdominal pain and became markedly disorientated before the onset of paralytic symptoms, which were heralded by a feeling of numbness below the waist. Paralysis may include bulbar muscles, intercostal muscles, diaphragm, or face. The distribution of the muscle weakness is that of a neuromyelitis rather than a peripheral neuritis, and proximal limb segments may be involved in excess of the distal. Both our cases showed bilateral facial palsy, which lent to the face a rather characteristic myasthenic appearance during sleep. Case 1 also showed a paresis of the right cupola of the diaphragm on screening. Oliguria is often observed, and when coupled with the findings of casts and red urine may lead to an erroneous diagnosis of acute nephritis. Death may take place from the results of bulbar or intercostal paralysis.

Differential Diagnosis.—Other conditions which cause extensive motor paralysis are acute ascending paralysis of Landry's type, diphtheria, poliomyelitis, acute infective polyneuritis, and botulism. It has been pointed out by Grünwald that many cases of ascending motor paralysis are really undiagnosed porphyric neuromyelitis. Diphtheria produces a toxic polyneuritis which is very similar in type in that bulbar, facial, or diaphragmatic involvement may occur, and intercostal paralysis may cause death. It is interesting, when considering this, to note that *Corynebacterium diphtheriae* produces porphyrin in bouillon culture (Coulter and Stone, 1931). Lead poisoning is a condition which may be associated with a motor paralysis and porphyrinuria. Botulism is not often mentioned in the differential diagnosis, but is a condition in which bulbar paralysis may ensue after a gastro-intestinal upset. The symptomatic porphyria due to sulphonal or methylsulphonol—known as acute toxic porphyria—is very difficult to separate clinically from acute idiopathic porphyria.

Treatment.—There is no evidence that treatment has any effect on the disease.

Prognosis.—The mortality is given as being over 50% in the first attack (Mason *et al.*, 1933). Waldenström's mortality among the cases with the fully developed clinical picture was very much higher, for out of 46 cases 40 died and 1 committed suicide, and all 3 cases with nervous but no abdominal symptoms died. The lowest mortality was in the purely abdominal group: 4 out of 24 died; the others recovered (Waldenström, 1937).

Summary

Two cases of acute idiopathic porphyria with abdominal, mental, and polyneuritic symptoms are described. The polyneuritis was accompanied in both cases by a bilateral facial palsy and painless urinary retention, and in one case by a diaphragmatic weakness.

We should like to thank Mr. Garfield Thomas, of the Department of Biochemistry at the Queen Elizabeth Hospital, for his careful investigations of the pigments of the urine and stool, and Professor C. Rimington for his investigation of the urine of the second case, for a supply of porphyrin which was used as a standard for the estimations of Case 1, and for his kindly criticisms.

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POLIOMYELITIS AND IMMUNIZATION AGAINST WHOOPING-COUGH AND DIPHTHERIA

BY

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Following upon the reports of McCloskey (1950), Martin (1950), and Geffen (1950), we searched the records of our cases of poliomyelitis admitted to the Park Hospital during the years 1947–9 for evidence of any relationship between the onset of poliomyelitis and recent immunization. We found that two cases of paralysis of the arm occurring within three weeks of an immunizing injection in the same arm had been specially noted in the case records in 1947, but after that no further cases had been observed until July, 1949, when a more acute awareness of the problem began to develop in London. One of us (H. S. B.) reported five such cases in the annual report of the hospital for 1949. We were, however, somewhat surprised to discover no fewer than seven further cases by systematic search of the records and by following up clues with letters of inquiry to parents and public immunization clinics. This made a total of at least 14 (12.6%) such cases, all of them children under 5 years of age, among 111 paralytic poliomyelitis cases of all ages admitted during the period (Table I). Confirmation of the facts regarding date, site, and nature of the immunizing injection was obtained in practically all cases from the immunization clinics. No instance was observed of any relationship between immunization and non-paralytic poliomyelitis.

It is not our purpose to make any estimate of the statistical significance of our data. This has been done on a more adequate scale by Bradford Hill (1950). But, while we merely record the data observed in one hospital,

it is pertinent to mention two facts. First, the incidence of poliomyelitis in England and Wales, including London, in 1947 and 1949 was the highest on record, but was much lower in 1948 (18 and 14 per 100,000 population in 1947 and 1949 and 4 per 100,000 in 1948). Secondly, the number of young children immunized against diphtheria and whooping-cough was at a high and increasing level during these three years. There can be little doubt that there would be frequent overlapping of these occurrences, and that many children would be likely to be immunized at a time when they were actually infected with the poliomyelitis virus, although showing no clinical signs of it.

TABLE I.—Paralytic Poliomyelitis: Admissions and Deaths

	1947	1948	1949	Total
Cases admitted	40	12	59	111
Deaths ..	2	0	6	8

Table II shows the preponderance of lower-limb paralysis in the group who were not immunized or who were immunized over six months prior to onset of poliomyelitis, and

TABLE II.—Incidence of Paralysis in Upper (U) and Lower Limbs (L) in Relation to Immunization History

	1947		1948		1949		Total	
	U	L	U	L	U	L	U	L
No immunization history ..	7	9	3	1	7	12	17	22
Not immunized or immunized over 6 months before	7	15	2	4	11	24	20	43
Immunized within 2 months:								
(a) Total ..	5	0	3	1	4	2	12	3
(b) Inoculated limb ..	5	0	3	1	4	1	12	2

the preponderance, on the contrary, of upper-limb paralysis in the group who were immunized within two months of onset of poliomyelitis. This latter group with one exception consisted of cases in which the same "double event" occurred; namely (1) inoculation for whooping-cough, diphtheria, or both combined; and (2) within two months of one of the injections in the course, the onset of poliomyelitis with paralysis of a practically uniform pattern in the same limb. In the upper limb it was the muscles of the shoulder-girdle (deltoid, spinati, and pectorals) and the biceps and triceps which were invariably the first to be paralysed, and were often the only muscles seriously paralysed, although weakness was not uncommon also in the neighbouring muscles of the trunk and forearm. Occasionally the other arm was also, but less extensively, affected, and in one case the paralysis starting in the inoculated arm rapidly became general and was fatal. In the lower limb the pattern was similar. The muscles of the inoculated buttock and thigh were the earliest and most seriously affected, the paralysis being restricted to the inoculated limb in nine cases, and spreading also to neighbouring muscles in five cases. Where neighbouring muscles were affected, in both upper and lower limbs, there was usually considerable return of function in them within three months, but not in the muscles first paralysed—namely, those of shoulder-girdle and upper arm, or buttock and thigh. There was no particular grouping of the cases in time or in place—for example, in association with any particular clinic, instruments, or batch of prophylactic.

The preponderance of upper-limb paralysis in those immunized within two months suggests the influence of the inoculation in determining the site of paralysis, since inoculations in London are much more frequently done in the arm than in the leg. The only exception in this group was a child of 10 months who, eleven days after a first injection of diphtheria alum-precipitated toxoid in