

LA PETITE SIMULATRICE: THE STORY OF THE CHESTER PORPHYRIA *

G.R. Youngs

My interest in porphyria started in 1980 with an unpleasant outpatient consultation at the Chester Royal Infirmary.¹ The mother of my patient, a 16 year old girl, quickly surmised that I had never seen a case of porphyria and accused me of being as ignorant of the condition as all the other local hospital and general practitioners. Four years earlier her husband, aged 38, and her son, aged 17, had died of the condition within six months of each other. Eleven of her husband's cousins had died, nine of them under the age of 40 years or less. Stung by her condemnation I resolved to study the family. A picture slowly emerged of the medical misfortunes of a remarkable kindred suffering from an inherited disease which hoodwinked medical practitioners in Chester for several decades. With hindsight, it is easy to spot the delayed or inaccurate diagnoses leading to inappropriate management over the years and to the issuing of incorrect death certificates.

The family is remarkable for its size. The index person, a salmon fisherman on the River Dee which runs through Chester, married in 1888 and spawned 10 children, 38 grandchildren, and 106 great-grandchildren, so that there are now (1998) over 350 descendants. Only three of the 38 grandchildren left Chester and most of their offspring still live locally, thus creating an ideal crucible for study of a disease that is inherited as a Mendelian dominant.²

What is porphyria?

The evocative name 'porphyria' derives from the port-wine coloured urine³ passed during a relapse by those with the condition. The disease has enjoyed a certain notoriety since being labelled '*The Royal Malady*'⁴ as a postulated explanation for George III's bizarre psychiatric behaviour, abdominal pain and coloured urine. The theory was embroidered in Alan Bennett's play (and subsequent film) *The Madness of King George III*,⁵ although students of porphyria were mortified to find that the script describes the royal urine as blue.⁶ Porphyrins are pigments probably contemporaneous in evolution with the emergence of life itself for they are 'what makes blood red and grass green'.⁷

* Based on a paper delivered to the Liverpool Medical History Society on 30 October 1997.

¹ Chester Royal Infirmary, 1755-1996.

² A parent carrying a dominant gene will pass it to approximately half of his or her offspring.

³ Porphuros: Greek for 'purple'.

⁴ I. Macalpine and R. Hunter, "The "insanity" of King George III: a classic case of porphyria', *Brit.Med.J.*; 1966, 65-71; I. Macalpine, R. Hunter and C. Rimington, 'Porphyria in the Royal Houses of Stuart, Hanover and Prussia. A follow up study of George III's illness', *Brit.Med.J.*, 1968, 7-18.

⁵ A. Bennett, *The Madness of King George III* (London: Faber & Faber, 1992).

⁶ W.N. Arnold, "King George III's urine — an indigo blue'. *Lancet*. 1996, 1811-13.

⁷ A. Goldberg, "Historical introduction to the porphyrias', in *Dobson's complaint: the story of the Chester Porphyria*, ed. by G.R. Youngs (London: Royal College of Physicians, 1998), pp. 1-6.

The disease porphyria is an inherited inborn error of metabolism due to a deficiency of an enzyme needed for the synthesis of haem, the iron-based pigment in haemoglobin (the substance in red blood cells which acts as a 'carrier' of oxygen).⁸ The symptoms of porphyria are protean and often bizarre, frequently mimicking more common conditions. The disease is rare and many general and hospital practitioners may never see a case. This led Waldenström, the 'father' of clinical porphyria to describe the disease as *la petite simulatrice*⁹ as opposed to syphilis 'the big simulator'. He noted that several young women, posthumously shown by family studies to have porphyria, had died in Swedish Lapland after being labelled 'hysterical'.

As my patient's mother correctly surmised, I was totally unversed in the ramifications of the porphyria diseases. I had had difficulties swotting up the biochemical complexities before examinations and any knowledge gained was ephemeral. Nevertheless I was captivated by the mother's tale of the high mortality rate in her late husband's family from such seemingly disparate causes as respiratory paralysis,¹⁰ accelerated high blood pressure (hypertension) leading to strokes and renal failure, inexplicable death after abdominal surgery for 'appendicitis'¹¹ or after admission with psychiatric illness to the County Mental Hospital. The true cause of these maladies was often unrecognised by the victims' medical advisers. Patients often received scant explanation or sympathy and hysteria was suspected in some; thus there existed a climate of resentment and despair in family members, whilst others denied that the 'taint' affected their line despite obvious evidence to the contrary.

My Palestinian registrar researches the family and finds that a Yugoslavian and a South African junior doctor did likewise 17 and 26 years before

I resolved to document the family and their ailments, and thus porphyria became my hobby within medicine. In this detective quest I was greatly helped by my medical registrar of 1980, Mohammed Qadiri, a Palestinian who qualified in Baghdad. It was only later that the earlier remarkable role of two other 'foreign' junior doctors became apparent.

Qadiri spent his evenings driving around Chester calling on members of the kindred in order to construct a family tree.¹² Often his directions were vague: 'look for the brown mini parked outside the house towards the end of the street', or 'try the butcher's shop two streets along'. He quickly learned that the family was large (38 cousins); more amazingly he learned that he was not the first 'foreign doctor' to knock on doors unannounced seeking personal and medical information, some of which aroused unhappy memories and sometimes hostile emotions. Qadiri became aware of mistrust of the medical profession and some family

⁸ There are several types of porphyria, each dependent on the deficiency of a particular enzyme. The clinical features vary. The Chester porphyria is a type of acute hepatic porphyria and appears to be biochemically and genetically unique.

⁹ J. Waldenström, 'Neurological symptoms caused by so-called acute porphyria', *Acta Psychiatrica et Neurologica*, 14(1939), 375-79.

¹⁰ Respiratory paralysis caused by progressive damage to the nerve supply to the musculature somewhat akin to that found in poliomyelitis.

¹¹ Abdominal pain is the commonest porphyric symptom due to malfunctioning of the nerve fibres transmitting pain.

¹² M.R. Qadiri, S.E. Church, K.E.L. McColl, M.R. Moore and G.R. Youngs, 'Chester porphyria: a clinical study of a new form of porphyria', *Brit.Med.J.*, 1986, 455-59.

members declined to co-operate. His fortitude overcame this unpromising scenario, doubtless helped by the unforeseen blessing that the foreign doctor who had preceded him was held in high esteem and remembered with affection.

Dr Zorka Bekerus

Zorka Bekerus was a Yugoslavian anaesthetic registrar who worked in Chester between 1963 and 1965. At Barrowmore Hospital¹³ she was anaesthetising a patient for the removal of nasal polyps. He collapsed post-operatively and the next day the house surgeon told Bekerus that the patient's urine was red. By chance, Bekerus had recently attended a lecture in Liverpool delivered by the late Professor John Dundee as part of the Mersey Region junior anaesthetists training programme under the aegis of Professor Cecil Gray. The speaker described the great danger of a barbiturate anaesthetic precipitating a porphyric crisis which could be fatal.¹⁴ This phenomenon, first described in 1938 by Waldenström, perhaps because of the lull in medical communication occasioned by World War II was not widely appreciated.

Bekerus surmised that her patient had suffered a porphyric crisis and proved this by finding abnormal pigment (porphobilinogen) in the urine.¹⁵ Intrigued, she embarked on a large family study. She visited numerous families in their homes and collected repeated urine and stool samples.¹⁶ She constructed a family tree and wrote copious pen-pictures of family members, particularly emphasising their porphyric symptoms which were often exacerbated by the unwitting prescription of barbiturates by family and hospital practitioners (*Figure 1*).

Ward or Department <u>3</u>		Patient's Unit No.
PHYSICIAN OR SURGEON <u>R. E. C. NASH</u>		
NAME		
Date	Dose and Route	Prescriber
<u>22/11/66</u>		<u>Sodium amobarbital 200 mg</u>
		<u>every evening R.C.P.</u>
<u>1/12/67</u>		<u>had 1/2 tablet after meals</u>
<u>5/1/67</u>		<u>5mg of 1/2 Nactal 1/2</u>

1: Drug prescription chart (1966-67) showing barbiturate prescr

¹³ Opened as a tuberculosis sanatorium in 1921 and closed in 1982.

¹⁴ J.W. Dundee, W.M.C. McCleery and G. McLoughlin, "The hazard of thiopental anaesthesia in porphyria'. *Anaesthesia and Analgesia - Current Researches*, 41(1962), 567-74.

¹⁵ Bekerus's patient died in 1969, aged 40, of the long-term complications of porphyria, hypertension and renal failure, an outcome not at that time recognised in medical literature but amply demonstrated by the Chester porphyria family.

¹⁶ Z.Bekerus, "Complications after nasal polypectomy: a family tree is constructed', in *Dobson's complaint*, pp. 59-65.

Figure 1: Drug prescription chart (1966-67) showing barbiturate prescription written in both apothecaries' and metric notation.

In Bekerus's study period (mid-1940s to 1960s) barbiturates were widely prescribed for conditions such as insomnia, anxiety, epilepsy, hypertension, as well as being used for anaesthesia.

The family remembers Bekerus with affection, for they sought counsel from her to help them endure the often tragic morbidity and mortality due to the porphyria many suffered. Her pen picture of one family is particularly poignant: four brothers died between 1941 and 1953 at the ages of 16, 18, 21 and 29. Their respective death certificates recorded nephritis, myotonia atrophica, operation (appendicitis) and malignant hypertension. With hindsight we can be sure that all these death certificates were incomplete, and that the brothers died of the complications of porphyria: respectively, renal damage, paralysis due to damaged nerve supply to the muscles, a barbiturate anaesthetic for abdominal pain (which was probably porphyric pain and not appendicitis), and accelerated hypertension.

By the time Qadiri and I began our enquiries in 1980, the trail pioneered by Bekerus had become indistinct. Several general practitioners in Chester had patients with porphyria but no hospital clinician maintained a register or sustained interest. It took me nine years to trace Bekerus to the United States for I did not realise she had kept in touch with her old professor of anaesthetics, Cecil Gray.¹⁷ Only in 1989 did I have the joy of receiving her manuscripts. They were never published although she had won the 1965 Registrar Prize at the Royal Society of Medicine (London) for a presentation at a meeting there.

Dr A.G. Shaper

Meanwhile my own researches in the 1980s resurrected yet another 'foreign' junior doctor who had preceded us all. To him must be given the accolade of the first diagnosis of porphyria in the Chester family. Dr Andrew Shaper was in 1954 neurology registrar at Clatterbridge Hospital, 10 miles from Chester.¹⁸ He had qualified in Cape Town and had been a medical student on the firm of Professor Lennox Eales who had an international reputation in porphyria.¹⁹ Shaper diagnosed porphyria in a woman of 23 years transferred to Clatterbridge Hospital from the County Mental Hospital in Chester because of the development of complete paralysis of her limbs. Two months before, she

¹⁷ Professor Cecil Gray attended the meeting at which this present paper was delivered and enlightened the author and entranced the audience with his revelation that Dr Bekerus had a substantial address in New York and that they communicated frequently. [Ed.].

¹⁸ Shaper was registrar to the late Dr R.R. Hughes, neurologist to the Royal Southern Hospital, Liverpool, and Clatterbridge Hospital, Wirral. He was subsequently to become Professor of Epidemiology at the Royal Free Hospital, London.

¹⁹ South Africa has the highest concentration of patients with porphyria in the world. They all descend from a Dutch orphan girl sent out to the Cape in 1688. This remarkable story can be read in a classical monograph, G. Dean, *The porphyries, a story of inheritance and environment* (London: Pitman Books, 1963).

had been admitted to Chester City Hospital²⁰ with abdominal pains, accelerated hypertension and, later, epileptic seizures. Circumstantial evidence suggests that she was treated with barbiturates both for the epilepsy and hypertension. Her urine was a 'funny brown red colour'. She then became confused and disorientated. The visiting psychiatrist diagnosed a 'depressive state with schizophrenic symptoms'. She was duly transferred to the County Mental Hospital in Chester where, unsurprisingly, she was prescribed more barbiturate (phenobarbitone). She developed a profound paralysis and so was transferred to the neurologists' care at Clatterbridge Hospital. Shaper examined her, recorded her admission and pronounced her to have porphyria. She was to remain in hospital eight months recovering from her paralysis. Nurses at both Chester City Hospital and the County Mental Hospital are documented as having labelled the woman a hysteric — 'there is nothing wrong with J.B., only her bowels'.

Porphyria complicated her subsequent pregnancies and quite early in my own researches I discovered that these events had been published by the then obstetric registrar, C.R. Porteous.²¹ Neither he nor I realised until 1995 (when I first made contact with Shaper) that Shaper had beaten him to it.²² Bekerus makes no mention of either publication. Shaper remembers the case well more than 40 years after his pioneering diagnosis.²³

The impact of porphyria on the kindred

I have briefly described Shaper's and Bekerus's index cases, but what impact has porphyria had on the kindred as a whole? The original index person and his wife had ten children born between 1890 and 1911 who reached adulthood and died between 1938 and 1982 (*Figure 2*). We have the death certificates of all of them and porphyria is recorded as a cause of death in only the one sibling in whom Bekerus had found porphyria-positive urine in 1963. That porphyria contributed to the deaths of any remaining siblings is circumstantial but we know seven of the ten must have carried the gene (assuming paternity to be as declared on the birth certificates) because their children had porphyria.

²⁰ Chester City Hospital, 1877-1992.

²¹ C.R. Porteous, "A case of porphyria complicated by pregnancy". *Journal of Obstetrics & Gynaecology*, 70(1963), 311-14.

²² A.G. Shaper, 'Porphyria in Africa', *Central African Journal of Medicine*, 4(1958), 411-20.

²³ Shaper's patient died aged 46 in 1978 of a cerebellar haemorrhage doubtless due to her longstanding hypertension (now known to be a long-term complication of porphyria).

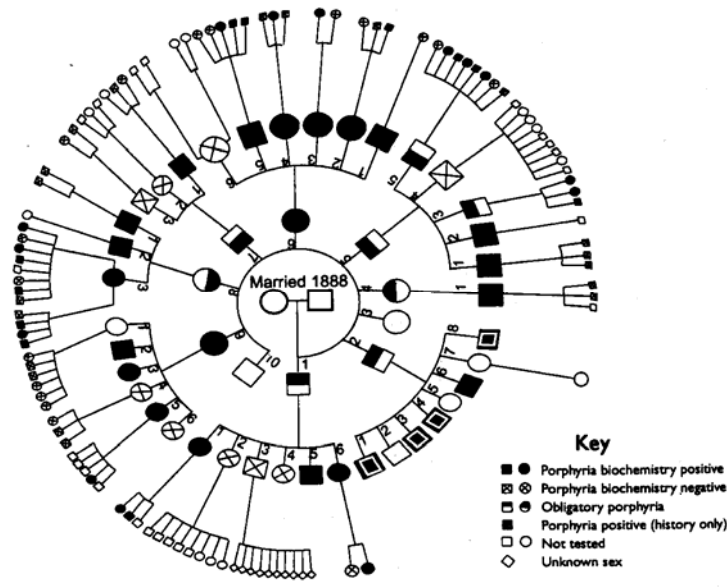


Figure 2: The Chester porphyria pedigree (1998)

Eight (seven porphyric) of these original children produced a total of 38 grandchildren and our studies show that 25 (66%) of these carried the porphyria gene.²⁴ Of the others, nine are porphyria-negative and four have not been tested. Not all suffered porphyric symptoms because asymptomatic carriage of the gene (latent porphyria) is seen in all porphyria families. But why did at least 66% of the grandchildren carry the gene when Mendelian law suggests a probability of 25%? This could have arisen by chance but there is the remote possibility that all ten of the original children carried the porphyria gene. This would only be likely if the original index parents were homozygous for porphyria — that is, if either of them had received a porphyria gene from both parents, perhaps because of intra-kindred breeding or incest. This is an intriguing thought because, as we shall see later, the original index person (the father) was illegitimate.

Twenty-one of the 38 grandchildren have died, ten below the age of 50. Table 1 shows the excess death rate (17/25) in the porphyria subjects; only one non-porphyric member has died. One of the fascinations of this study is that only six of the 21 death certificates mention porphyria:

Table 1: Excess mortality in porphyria positive compared with porphyria negative grandchildren

Porphyria positive	Porphyria negative	Unknown	Total
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²⁴ *Dobson's Complaint* (1998) records 24 grandchildren as carrying the gene. Since then information has been received from Tasmania that a cousin who died aged 30 in 1956 had porphyria diagnosed six weeks before dying post-operatively of 'appendicitis'.

Living	8	8	1	17
Deceased	17	1	3	21
All subjects	25	9	4	38

Retrospective study of the casenotes (often not available as general practitioners' and most hospital casenotes are destroyed 5 years after death) or of the death certificates themselves show that certification was incorrect or incomplete in many cases. The following case histories of two brothers show that they, like other of their cousins, died of the complications of porphyria with the cause unrecognised.

Case 1

A driver salesman of an ice-cream van died age 30 in 1953 in Chester City Hospital. His death certificate recorded pneumonia, paralysis and peripheral neuritis. He had been admitted to hospital with abdominal pain thought to be due to peptic ulcer. He had an odd personality and used to drink vinegar. Bekerus records that he was treated with barbiturates. Porphyria was not suspected but in retrospect we know he was porphyric because his children have been tested positive.

Case 2

His brother, an unemployed taxi driver, died age 50 in 1982 in Chester City Hospital. He was admitted to the County Mental Hospital in 1981 after being found at home lying on the floor, conscious but neglected. He was treated with tricyclic antidepressants, and began to hear voices commanding him to clean the toilets. He developed bizarre behaviour, licking urine from the floor. Subsequently, he developed an epileptic fit, meningism, papilloedema and coma. He was transferred to the Chester City Hospital but died two days later without a clinical diagnosis. Necropsy showed no intercranial abnormality. His death certificate recorded acute heart failure, atherosclerosis, and bronchitis. Porphyria was not suspected and it was only as a result of the present study that I am sure this was a porphyric death. His children have subsequently been tested and some of them are positive for porphyria.

Reading these case histories it is not difficult to imagine the anguish and frustration experienced by members of the kindred over the middle decades of this century. Their medical advisers were diagnostically perplexed, thus creating a recipe for inappropriate management, misunderstanding and a suspicion of hysteria or malingering. The doctors' performance was further tarnished in the eyes of their patients by a lack of awareness of the long-term sequelae of porphyria — chronic hypertension and renal

failure — little reported in the literature but common in porphyric members of the Chester kindred.²⁵

The 106 members of the next generation born between 1940 and 1972 were obviously reared in an unpromising cradle, so how have they fared? Two have died of porphyria. One was the brother of the 16 year old girl I met in outpatients whose mother's condemnation inspired this study. He died aged 17 after a 13 day stay in hospital, having presented with abdominal pain and red urine later complicated by paralysis. His illness was recognised to be porphyria (his aunt was Shaper's index case and his father had died of porphyria six months earlier); nevertheless there was thought to be an emotional element to his illness and he died of respiratory paralysis 12 hours after receiving a placebo injection of sterile water.

The suspicion of hysteria on the part of the medical and nursing profession runs like a thread connecting the illnesses of many family members. The most senior great-grandchild, born in 1940, has recently retired from the administrative staff of the Countess of Chester Hospital. She remembers being admitted with abdominal pain to Chester Royal Infirmary at the age of 19. As is usually the case with porphyric pain, standard physical examination and investigations were unrevealing; it was suggested to her that her imagination had been stimulated by watching the early television soap opera, 'Emergency Ward 10'. Some of the emotions aroused in patients' carers are picturesquely summarised by Kark:²⁶

The vicious acerbity of the conduct of porphyrinuric termagants makes it difficult at times to treat them on a medical ward. Nurses dislike caring for them. They are a troublesome group of patients and kindle feelings of hatred and aggression in the most urbane physicians.

Family members with porphyric symptoms present to five different hospital departments

There is little need in this mainly historical paper to document the numerous symptoms and syndromes suffered by family members over the decades. As the title suggests, they were protean but appropriate to no one hospital specialist, and so members presented to different departments. Of the 25 porphyric grandchildren, 22 were symptomatic and three latent. The 22 presented with their porphyric illnesses as follows:²⁷

Table 2: Specialists consulted by family members with porphyric symptoms

²⁵ S.E. Church, K.E.L. McColl, M.R. Moore and G.R. Youngs. 'Hypertension and renal impairment as complications of acute porphyria', *Nephrology, Dialysis, Transplantation*, 7(1992), 986-90.

²⁶ R.M. Kark, 'Clinical aspects of the major porphyriopathies', *Medical Clinics of North America*, 39(1955), 11-30.

²⁷ Seven subjects (including Shaper's index case) appear under more than one heading if they presented to different departments on separate occasions or if the complication of their porphyric crisis necessitated transfer to another department.

General Physicians:	14	hypertension, stroke, paralysis, renal failure,
General surgeons:	5	abdominal pain
Obstetricians/Gynecologists:	3	paralysis in pregnancy, hypertension
Psychiatrists:	6	all admitted to County Mental Hospital
Ear, nose & throat surgeons:	2	porphyric crisis after surgery for nasal polyps

Eight of the 38 grandchildren with psychiatric morbidity are known to have had treatment with barbiturates and six had admissions to the County Mental Hospital. Two of these died shortly after discharge. In their parents' generation two of the ten siblings had admission to the County Mental Hospital where one died age 40. The death certificate records influenzal pneumonia, perhaps a euphemism for 'diagnosis unknown'. The siblings' grandmother (the mother-in-law of the original salmon fisherman) was admitted to the County Mental Hospital in 1878 at the age of 43 with 'melancholia due to drink'. This proved to be a terminal illness and her death certificate records 'disease of the heart and kidneys'.

The frequent psychiatric attendances made by family members together with a high prevalence of epilepsy have been a cause of shame to many of their kin and is one reason why some have denied that the porphyria taint affects their line. The psychiatric manifestations in our family and an assessment of their current status are more fully described elsewhere,²⁸ as is the hypertension and renal failure,²⁶ metabolic upset²⁹ and the prevalence of asthma and nasal polyps.³⁰

Quarrelsome salmon fishermen on the River Dee

Mention must be made of the social history of the family, researched by Andrew McDonagh (my medical registrar in 1987) and a local historian Terry Kavanagh.³¹ The family were salmon fishermen (Figure 3) and the impecuniosity consequent on large families, together with the variable profits of fishing, probably played their part in the frequent mention of family members in the annals of justice, faithfully recorded in the Chester Chronicle. Thus in 1821 the great-grandparents of the index person were arraigned for assault after retrieving a fishing net from a bailiff,³² and in 1853 their son was charged with illegally trammelling a net in the river and threatening to kill or do

²⁸ R. Chitty and G.R. Youngs, 'Psychiatric morbidity in the kindred', in *Dobson's Complaint*, pp. 151-67.

²⁹ D. Chew, S.E. Church and G.R. Youngs, 'Hyponatraemia frequently complicates acute porphyric crises', in *Dobson's Complaint*, pp. 137-42.

³⁰ T. Toma, J. Evans, J. Sayer and G.R. Youngs, 'Asthma and atopy in the kindred: a surrogate marker for Chester porphyria', in *Dobson's Complaint*, pp. 143-50.

³¹ A.G. McDonagh and T. Kavanagh, 'The Chester porphyria: notes on the social history of the Dobson family', in *Dobson's Complaint*, pp. 37-45.

³² Chester Chronicle, 7 December 1821.

violent injury to a fisherwoman if she dared to trammel her line before him.³³ The family lived with other fisherfolk in Stye Lane, now Greenway Street, near the old Dee Bridge, an area described thus in 1854:³⁴

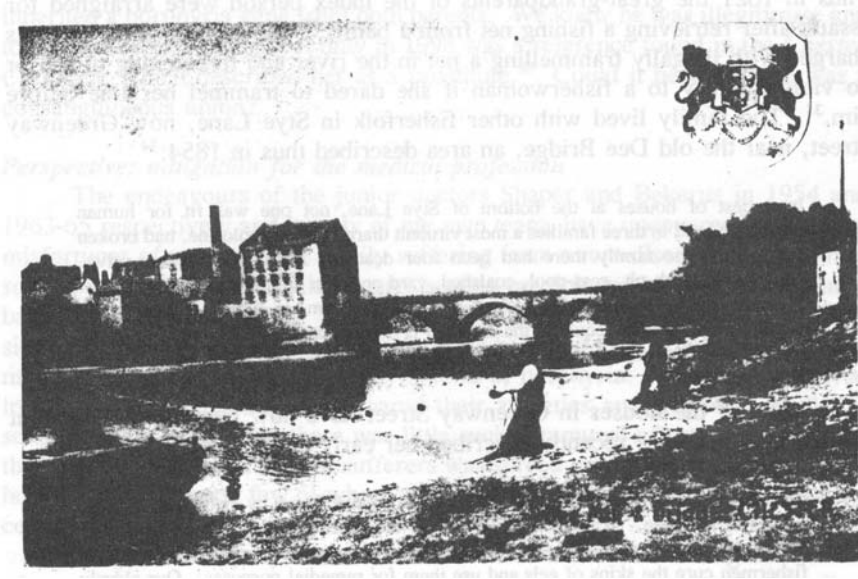


Figure 3: Chester from Handbridge showing use of draft net between old Dee Bridge and the weir. Greenway Street is a quarter of a mile downstream. Salmon are caught by a draft or trammel net. The former is used on the upper stretches of the tidal River Dee opposite Greenway Street. A fisherman stays on the bank with the net end while a second rows the boat in a wide circle across the river, paying out the net until he returns to the bank a short distance downstream. Trammel netting is unique to the Dee estuary. The boat rows across the flow of the tide shooting the net which forms a vertical wall. The boat and net drift with the tide, the boat being manoeuvred by oar to keep the net across the tidal flow. In 1979 a full-time net fisherman could expect to catch 70-100 fish a year.

In a nest of houses at the bottom of Stye Lane, not one was fit for human habitation, and in three families a most virulent diarrhoea, or cholera, had broken out and in one family there had been four deaths. There was neither privy, convenience, ash-pit, cess-pool, coalshed, yard or water supply attached to any of these houses, and the cubic feet of space in a room, in which at least seven persons slept, was not equal to the required prison cell space for one person, in the model prisons of this country.

Most of the houses in Greenway Street have now been demolished but Elizabeth Hughes has recently described her early days there:³⁵

³³ *Ibid.*, 9 July 1853.

³⁴ *Ibid.*, 23 September 1854.

³⁵ Writing in a local amenity magazine. *Friends of the Meadows*, Newsletter No. 32, February 1997.

The fishermen in those days earned their entire livelihood by fishing the turbid waters of the Dee. We practically lived on the succulent Dee salmon and other varieties of fish such as flukes and slimy eels, which we call 'snigs'. Some of the fishermen cure the skins of eels and use them for remedial purposes. Our elderly neighbours wore them under scarves around their necks as poultices for sore throats, and they swore that they worked a treat.

Although none of the sons of the index person became a fisherman, salmon fishing continues on the Dee and licences are advertised in the *Chester Chronicle* annually.

The great-grandfather of the index person (born in 1776) 'perished at sea under melancholy circumstances in 1835'.³⁶ His great-grandson, who married the mother of the Chester kindred in 1888 and sired the family which is the subject of this study, died in 1932: 'formerly a fisherman the funeral procession of in accordance with local custom, passed over both Dee Bridges on the way to the cemetery on Monday'.³⁷ As mentioned earlier, he may have inherited a porphyria gene from both parents. We knew he was illegitimate and took his mother's name, but only in 1998 was a reference found in the *Chester Chronicle* which described her as a prostitute.³⁸ Could it be that there was a consanguineous union?

Perspective: mitigation for the medical profession

The endeavours of the junior doctors Shaper and Bekerus in 1954 and 1963-65 respectively and latterly of my own team, have uncovered the medical misfortunes of a remarkable family suffering from a rare disease which mimics several more common conditions and is often precipitated by drug (particularly barbiturate) administration. The family were only too well aware of their plight since 21 cousins were dead by 1995, twelve had died under the age of 50, and many of those still living had had symptoms of porphyria. Nearly all still lived in Chester and obviously they shared their anxieties and sorrows. Sadly, it seemed to the family that there was little such communal effort being made by their medical advisers; care of sufferers was spread over numerous general and hospital practitioners, few of whom were well versed in the complexities of the condition.

I hope our enquiry has uncovered some factors which mitigate this tale of woe. Firstly, the clinical aspects of the porphyrias were accurately described only immediately before the Second World War in fairly obscure journals. Porphyria was thus not in the medical school curriculum of many of the early medical advisers of our family and the concept of 'continuing medical education' was as yet unborn. Moreover, the porphyrias are rare diseases and many physicians will not see a case in the whole of their career. Above all, our family's experience demonstrates the dangers posed by a rare disease

³⁶ Chester Chronicle, 13 March 1835.

³⁷ *Ibid.*, 10 December 1932.

³⁸ *Ibid.*, 8 June 1861.

masquerading as a more common ailment — abdominal pain, psychiatric disturbance or neuritis. So diverse are the clinical presentations that porphyria does not fit comfortably into any one specialty, curriculum or text book; instead we find rather brief mention of it in the textbooks of gastroenterology, haematology, psychiatry, and inborn errors of metabolism. There is no national or international clinical porphyria society or journal.

With increasing social mobility (so that society now drives genes rather than vice versa) the opportunities for repeating a study such as this in the future may be few and far between.³⁹ It is salutary that much of the pioneer work was done by junior doctors: they were in post only one or two years, yet they alone often provided succour to the family members — a bond which was then broken as they moved on to another hospital in another town.

We also have to contend with changing medical practice. When I was a medical student at the London Hospital in 1963 I had to test all my patients' urine samples, as did King George III's medical adviser, Sir Henry Hallford.⁴⁰ Medical students and qualified hospital clinicians no longer do this and so would miss the port-wine colour of porphyric urine.

The organisation of medical care in Chester also explains the delay in defining the enigma. It is to be expected that the primary care of the family was divided between different general practices, but for most of this century our city of 80,000 inhabitants with its catchment area of 220,000 people had hospitals on four separate sites — each with its own radiological department and three with operating theatres. Care was thus compartmentalised and fragmented and joint academic activities were rare. Only in 1996 were we amalgamated on the Countess of Chester Hospital site. This diversity of sites is, of course, a heritage found in many British cities and county towns and reflects their varying origins: philanthropic (Chester Royal Infirmary), municipal poor law institution (Chester City Hospital), lunatic asylum (County Mental Hospital) or rurally sequestered tuberculosis sanatorium (Barrowmore Hospital).

There is still no reliable test for porphyria, and sadly no treatment. We provide subjects with a list (published in the British National Formulary) of drugs to avoid. Thankfully, over the last ten years serious complications of the disease in our Chester family have become vanishingly rare — a phenomenon also noticed in South Africa⁴¹ — and this happenstance is difficult to understand. Hopefully some of this good news is due to better recognition, documentation and education that this study has fostered.

The first mention of the practice of medicine in Chester dates from nearly two thousand years ago⁴² and I am fortunate to have been able to continue this tradition and

³⁹ The Chester porphyria kindred is the second largest to be reported in the United Kingdom.

⁴⁰ Arnold.

⁴¹ Personal communication from Robert Hift, Groote Schuur Hospital, Capetown.

⁴² V. Nutton, 'A Greek doctor at Chester', *Journal of the Chester Archaeological Society*, 55(1968), 9-15.

record some curiosities of the medical care of a large Chester family over the last several decades.

ACKNOWLEDGEMENTS

This work would not have been possible without the co-operation of medical colleagues in Chester both in primary and secondary care. The major contribution of junior hospital doctors is evident in the text. Local historian, Terry Kavanagh, discovered numerous references to the family in the local press. The biochemical⁴³ and genetic complexities⁴⁴ of Chester porphyria, not described in the text, were unravelled by colleagues in Glasgow: Kenneth McColl, Michael Moore and Michael O'Connor. A study such as this cannot be conducted without perfect medical secretaries: Maureen Willetts (1974-89) and Kathy Kusinski (1989 to date).

Finally, I am grateful to the family members themselves for their cooperation over many years and for providing samples for biochemical tests and information permitting construction of the family tree.

⁴³ K.E.L. McColl, G.G. Thompson, M.R. Moore, A. Goldberg, *et al.*. 'Chester porphyria: biochemical studies of a new form of acute porphyria'. *Lancet*, 1985, ii. 796-99; S.E.Church, 'Chester porphyria' (unpublished MD thesis. Faculty of Medicine, University of Liverpool, 1986).

⁴⁴ B. Norton, W.G. Lanyon, M.R. Moore, M. Porteous, *et al.*, 'Evidence for involvement of a second genetic locus on chromosome 11q in porphyrin metabolism', *Human Genetics*, 91(1993), 576-78; B.Norton, 'A genetic study of Chester porphyria' (unpublished MD thesis. Faculty of Medicine, University of Liverpool, 1993).