

Porphyria in Sweden

S. THUNELL, Y. FLODERUS, A. HENRICHSON, P. HARPER

Porphyria Centre Sweden, Division of Inherited Metabolic Diseases, Department of Laboratory Medicine, Karolinska Institute and Karolinska University Hospital, Stockholm, Sweden

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Summary

In a brief survey the work of Swedish porphyrinologists through time is presented, from the organic chemist Jakob Berzelius 1840 to the molecular biologists of today. The building up in Stockholm of a Swedish national competence centre for porphyria is touched upon and the emergence of a computerized national register on the porphyria gene carriers in the country described. Figures for the prevalences of the seven different forms of porphyria diagnosed in Sweden are given. The geographical distribution of gene mutation spectra is shown for the most frequent form, acute intermittent porphyria. The organisation at Porphyria Centre Sweden of its diagnostic and consultative services is described, as is the decentralized model for porphyria care applied in the form of a clinical network covering the long and sparsely populated country. The ideas and activities of the Swedish Porphyria Patients' Association are presented. Its focus on protection-by-information of the porphyria gene carrier against maltreatment in health service contacts, and against other exposures to environmental threats to his or her health, is discussed. The combined efforts of the national porphyria centre and the patients' association have resulted in early and accurate diagnosis of most of the porphyria gene carriers in the country. The information to the carriers and to the health service regarding the mechanisms of the diseases and the importance of avoiding exposure to disease triggering environmental factors have greatly reduced porphyric morbidity. In the case of the acute porphyrias, by this programme and after the introduction of heme arginate in the therapy, mortality in the acute phase has become extremely rare in Sweden. In contrast, probably due to greater awareness of the high risk for liver cancer in acute porphyrias the number of hepatoma cases diagnosed has increased. The current research activities at the Porphyria Centre which aim at finding ways to substitute the mutated gene in acute intermittent porphyria for an undamaged one, or to substitute the enzyme deficiency by administration of exogenously produced enzyme, are mentioned, as is the work to establish a reliable drug porphyrinogenicity prediction model for evidence based drug counselling.

Key words

Porphyria review • Swedish porphyria • Prevalence • Mutations • History • Centre • Prevention • Patients' association
• Patient register • Diagnostic service • Consulting services • Laboratory

.....There were some cases that more than others aroused my curiosity and interest, since their violent acute abdominal pains again and again prompted surgical intervention which never resulted in a diagnosis. So was the case with the pale housewife who one day fell ill in severe pains. When I arrived she lay in her bed agonized and twisting, agitated and in confusion. But I could not find any fault with her body. After a few difficult days her crisis was over and she continued her work as usual. But there came new attacks and my suspicions were directed to virtually all internal

organs in her body. She was sent to hospital and its specialists, she was x-rayed, operated and treated. One time her appendix was removed, the other the gall bladder, and a third time a renal calculus was suspected. But no changes pointing to any specific disease were found. In this way she passed her life a number of years, but her tranquility of mind was disturbed by the recurrent attacks of pain and perhaps even more by anxiety about what kind of illness ravaged in her body. Her strength fell off, her pulse grew rapid even if her heart was healthy. Her gait became tottering, her hands fumbling and her mind nervous, irritable, gloomy and anxious. I was sometimes called to her and sat at her bedside talking with her, supposing and comforting, pondering and prescribing – the latter rather into the blue.

Another women went through the same history of suffering. Whenever I choose I can see before me her distorted features where she lay there in exceptional pain but otherwise obviously healthy without any temperature and without abdominal tenderness or muscular defence. I remember her gradual decay, her hopelessness when she in spite of the many journeys to the hospital never could get her health back between the attacks, her increasing nervousness and so the tottering gait, the ascending paralysis, the sloppy hands, the rigid facial expression, and finally the resignation when she after a final try had again been sent home from hospital without any other diagnosis than – only nervousness. Now she had not any attacks anymore, she just deteriorated and got more and more dependent on help from her surroundings. At last she stayed silent and immovable in her bed, tired of living and probably welcoming death when he one late afternoon came in disguise of a respiratory paralysis.

Which was this curious disease that ravaged in case after case? I phoned a colleague who had helped in her care. Respiratory paralysis pointed to some kind of organic nerve disease, but which? We talked for a long time without coming up with any ideas.

The next morning he phoned me back. "I have not been able to let her go from my thoughts. Can it be porphyrinuria?".....

Einar Wallquist: from the chapter "Arv" (Inheritance) in: "Få mans land" (A land of few) (Wallquist 1939).

Acute porphyria - from intoxication to genetically transmitted disease

In 1922, at the age of 26 Einar Wallquist (1896-1985) took up the position as a district medical officer in the isolated Arjeplog area in the most northern part of Sweden, hundreds of kilometres from colleagues and hospitals. During his first years as a mountain-doctor he met many cases of a frightful and puzzling condition, locally well known and referred to as *the Red-disease* on grounds of the red urine of the affected individuals, or *the Family-disease* due to its appearance within certain kindreds. This neurological affection with red urine, which he finally found the diagnosis for with the help of his colleague Arthur Engel, had in the last decade of the nineteenth century been observed in certain luckless psychiatric patients that had been administered the then new hypnotic sulphonal. In 1891 the Swedish chemist Olof Hammarsten (Hammarsten 1892) crystallized the red pigment which two years before had been observed by Stokvis in urine from sulphonal treated patients (Stokvis 1889). He could thus confirm Stockvis' opinion that the red colour was due to a substance with spectral

characteristics very much like - but not identical to - the iron-free hematin prepared in the late 1830s by the likewise Swedish chemist Jacob Berzelius by treating blood with sulphuric acid (Berzelius 1840), which had been described by Thudichum as a "purple substance that fluoresced with a splendid blood-red colour" (Thudichum 1867), and for which Hoppe-Seyler introduced the magic term Hämatorporphyrin (Hoppe-Seyler 1871; With 1980). The sulphonal-precipitated disease was thus – somewhat erroneously - termed *hematorporphyrinuria*, and in Sweden caution was very soon recommended in the use of the drug (Westermark 1892).

By and by the disease was also observed in patients not given the drug, or the sister-drug trional, and two forms of the disease were thought to be recognized – one toxic and one genuine. By aid of parish registers in the North of Sweden Engel and Wallquist could, however, in 1935 provide evidence of the "hematorporphyrinuria" as a hereditary disease, nineteen cases in 9 different families with the disorder being found to have a common ancestor born in 1701 (Engel *et al.* 1935).

Mapping of porphyria in Sweden

Already as a student of medicine Jan Waldenström's interest was caught by a colourless chromogen that turned red in Ehrlich's aldehyde reaction. With the help of chromatographic techniques he had worked out when he as a Rockefeller stipendiate had visited Hans Fischer's laboratory in Munchen, he could identify the chromogen in urine from patients with acute porphyria as a dipyrrole, the monoform of which he named *porphobilinogen*. He also showed that it could condense, forming the not previously described ring tetrapyrrole III-isomer of uroporphyrinogen, which as well presents in the urine from the patients (Waldenström 1939). Aware of the dominant nature of the genetic predisposition in acute porphyria and using urinary porphobilinogen as a marker for the carrier state, he conducted extensive family investigations in the northern area of Sweden. It is told that Waldenström and his coworker Arthur Engel skiing through the vast countryside, could identify farmsteads of interest by aid of the red urine spots in the snow beside the houses. In 1937 only 41 cases of acute porphyria had previously been described in the international literature. In his thesis this year Jan Waldenström gave case reports of further 101 cases (Waldenström 1937), and for several years the form of acute porphyria in question, acute intermittent porphyria was named *Swedish porphyria* (Waldenström 1957).

Thirty years later, in 1967, Lennart Wetterberg presented his doctoral thesis on the incidence of acute porphyria in a psychiatric clientele (Wetterberg 1967), where he further penetrated and enlarged the number of families diagnosed with the disorder. At that time about 120 AIP-families with around 600 affected members, of whom about half were still living, were recognized in Sweden.

Several cases of so called porphyria cutanea tarda symptomatica and hereditaria were reported in 1963 by Birgitta Haeger-Aronsen together with cases of variegata porphyria (Haeger-Aronsen 1963). She also described four families with erythropoietic protoporphyria (Haeger-Aronsen and Krook 1965) and one large family with hereditary coproporphyria (Haeger-Aronsen *et al.* 1968).

During the following years the large material of acute porphyria was further worked up into families by pharmacologist Anna-Lisa Mouchard, herself a member of a porphyria kindred.

When a reliable diagnosis of the gene carriers became a possibility, initially with the advent of enzymatic methods but later above all by aid of gene analysis, the register was considerably enlarged through the high diagnostic output of Porphyria Centre Sweden in Stockholm. Methods were developed for the diagnosis of the carrier conditions of all forms of porphyria represented in the country. Today the results of biochemical and gene analyses from in total 1400 porphyria gene carriers and from a large number of non-carriers within or outside their families, are stored in a databank. The development and maintenance of this is handled by the Porphyria Centre under sponsoring by the Stockholm county council. Due to the centralized organisation in Sweden for porphyria diagnosis and monitoring and dependent on an established national network for the care of the porphyric patients (*below*), the computerized register at the Porphyria Centre now covers at least 95 per cent of the porphyria gene carriers in the country. The numbers of carriers presently diagnosed with the different forms of porphyria are given in Table 1.

Porphyria gene mutation spectra in Sweden

With the advent of molecular biologic tools the task of carrier assessment became an easier one and in the final years of the 1980s we started the mapping of the AIP mutations in the country. Until now we have found 41 different disease-associated mutations in the *HMBS*-gene, covering about 1000 individuals. As shown in Figure 1 in spite of being extremely sparsely populated, the northern part of Sweden is inhabited by about half the number of AIP-gene carriers in the country. It is also noted that the 593G>A (W198X) mutation, even if found also in other parts of Sweden greatly dominates in the northern region. This distribution pattern is explained by a founder effect, the mutation originating in the family traced backwards in time by Engel and Wallquist (*above*) and at an early stage centred in the village of Arjeplog in Lappland. Due to a combination of high nativity, non-migratory habits of the inhabitants and relatively propitious living-conditions helping to lower infant mortality, the mutation became well preserved locally in the population. Only by and by it migrated along the larger Norrland rivers down to the coast of the Baltic Sea and from there on southwards to the rest of Sweden. The mutation is also represented in northern Norway, evidently having transversed the watershed-mountains between the two Scandinavian countries. This train of

Table 1. Most of the mutations behind the different forms of porphyria in Sweden are identified as well as the respective prevalence.

Porphyria	Number of carriers identified	Approximate prevalence	Number of identified mutations	Non-identified mutations in affected individuals	References
<i>Aminolevulinate dehydratase-deficiency</i>	1 compound heterozygous 1 heterozygous	1:5 millions	3	-	(Plewinska <i>et al.</i> 1991), (Akagi <i>et al.</i> 1999)
<i>Acute intermittent porphyria</i>	≈ 1000	1:10 000	41	1	(Lee and Anvret 1991; Lundin <i>et al.</i> 1997; Floderus <i>et al.</i> 2002)
<i>Congenital erythropoietic porphyria</i>	1 homozygous	1:10 millions	1	-	(Floderus <i>et al.</i> abstract Helsinki 1995), Desnick (personal communication)
<i>Familial porphyria cutanea tarda</i>	115	-	6	-	(Harper <i>et al.</i> 2004)
<i>Hepato-erythropoietic porphyria</i>	1 compound heterozygous	1:10 millions	1	1	(Stenberg and With 1982) [#] , de Verneuil (personal communication)
<i>Hereditary coproporphyria</i>	47	1: 200 000	6	Several	(Wiman <i>et al.</i> 2002) and Porphyria Centre Sweden
<i>Variagate porphyria</i>	75	1: 100 000	16	Several	(Wiman <i>et al.</i> 2003b) and Porphyria Centre Sweden
<i>Erythropoietic protoporphyria</i>	48	1: 200 000	16 and all have also the splice site modulator IVS3-48C	Several	(Wiman <i>et al.</i> 2003a) and Porphyria Centre Sweden

[#]The case was first described as congenital erythropoietic porphyria but later changed to hepato-erythropoietic porphyria. Erythrocyte uroporphyrinogen decarboxylase activity is below 10 % of normal.

events is reflected in the prevalence of AIP being 1:50 in the village of Arjeplog, 1:1000 in the northernmost county of Sweden, as contrasted to 1:10 000 in the country as a whole (Floderus *et al.* 2002). As remarked by Christer Andersson *et al.* 2000 (Andersson *et al.* 2000), the W198X mutation seems to be associated with a greater clinical penetrance than other AIP mutations. Most of the Swedish mutations behind variegate porphyria, hereditary coproporphyria and erythropoietic protoporphyria are today identified, as are the gene damages behind our single cases of ALAD-deficiency and congenital erythropoietic porphyria, respectively (Table 1). The prevalences in Sweden of the different forms of porphyria are given as well.

The emergence of a national porphyria laboratory

In the late 1970s the clinical biochemical laboratory at St Göran Hospital in Stockholm, where Stig Thunell was head of the department, was asked by the clinicians to extend the porphyria diagnostic menu beyond the ion exchange chromatography of porphobilinogen (PBG) and 5-aminolevulinic acid (ALA), and solvent partition of porphyrins into the fractions uro- and coproporphyrins, then available. This became the start of a national centre for porphyria diagnostic, still at work. High performance liquid chromatography (HPLC) techniques set in work at the

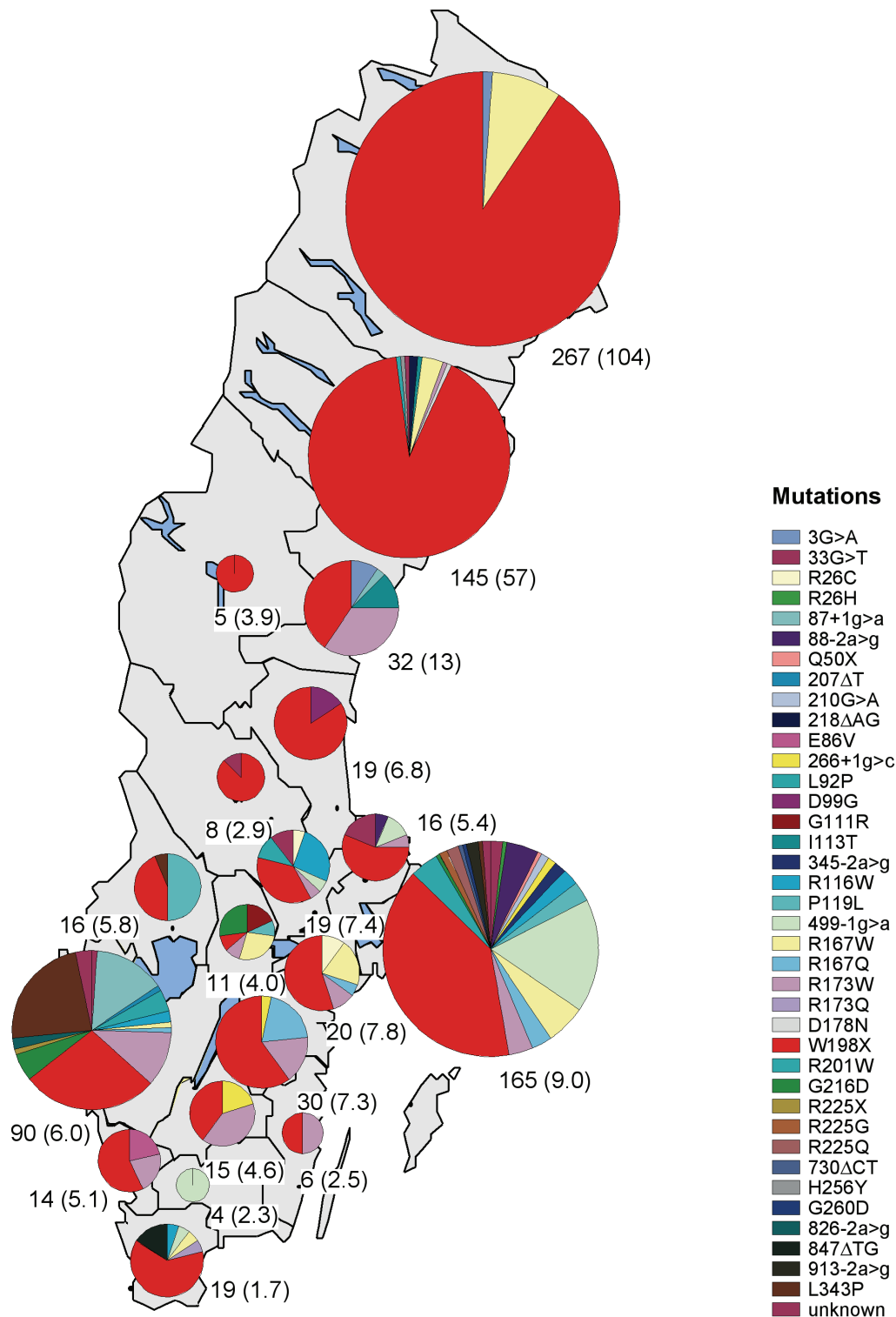


Fig. 1. The distribution (no of carriers) and frequencies (no per 100.000 inhabitants) of mutations in the *HMBSD* gene causing AIP in the different counties in Sweden. Reprinted from Floderus, Y, Shoolingin-Jordan, PM, Harper, P, "Acute Intermittent porphyria in Sweden. Molecular, functional and clinical consequences of some new mutations found in the porphobilinogen deaminase gene", *Clinical Genetics* 2002; 62: 288-297 with permission from Blackwell Munksgaard.

laboratory by Ann Henrichson soon enabled quantitation of the different porphyrin moieties in urine, stool and blood, making possible a firm biochemical diagnosis and assessment of current activity in all the seven forms of

porphyria, provided the patients were in clinically manifest phase of the disorders.

A reliable carrier detection, useful also in children, however, had to await the implementation of

methods for detection of the enzyme deficiencies behind the clinical syndromes. At that time many requests for diagnostic help regarded the carrier condition of AIP. Naturally, the first new analysis to be adopted therefore was erythrocyte porphobilinogen deaminase activity (Erc-PBGD), for which a method already was in use by professor Wetterberg in his studies at the psychiatric department of the hospital. Not any longer having to depend on the only about 30 per cent sensitivity of urinary PBG-excretion in the diagnosis of an adult carrier state of AIP and zero per cent sensitivity in a carrier before onset of puberty, was felt to be a major achievement. However, the overlap of Erc-PBGD activity between AIP-carriers and non-carriers impaired the diagnostic accuracy of the analysis, a choice of a cut-off level that included 85 per cent of the carriers being connected with a specificity of only 80-85 per cent (Lannfelt 1990; Andersson *et al.* 1995). With underdiagnosis of about 15 per cent, the determination of Erc-PBGD was still not ideal for AIP carrier detection, and the analytical grey-zone joining carriers and non-carriers showed to be the reason for diagnostic failure in too many cases – in a few patients unfortunately with fatal outcome.

In the end of the 1980s the progress in molecular biology provided much longed-for tools for *HMBS* gene analysis (Grandchamp *et al.* 1989). Since then all the different porphyria populations in Sweden have been thoroughly mapped with regard to their mutation spectra, a program supervised by Ylva Floderus, allowing carrier detection with virtually a 100 per cent reliability in most individual cases. With the help of the porphyria register it is now generally possible to directly select the proper specific mutation assay to be applied in the investigation at hand.

Since 1996 the laboratory at Porphyria Centre Sweden is certified by SWEDAC (Swedish Board for Accreditation and Conformity Assessment).

Centralized diagnostic service

Yearly, about 1400 requests from all parts of the country for diagnostic help are handled by the laboratory, between 5 to 12 separate analyses performed in each case by employing different combinations of the about 20 methods implemented, not including the different gene analytical procedures in use. The analyses available are presented on the homepage of Porphyria Centre Sweden (<http://www.karolinska.se/porfyri>) where also instruction

for sample collection, handling and sending are found. Requests for specified analyses are not paid regard to, and the use of a standardized request form is encouraged. In every case the physicians at the laboratory select the analytical menu that in the most cost-effective way will elucidate the diagnostic problem at hand. Most frequently the questions regard carrier states of the different forms of porphyria, assessment whether symptoms observed are due to porphyria or not, monitoring the carriers for accompanying diseases or for porphyrinogenic side effects due to drug exposure, or follow up of specific treatment. The analytical figures produced are reported together with reference values and with the laboratory physician's comment relating to the diagnostic question asked. The department of the ordering doctor is charged for the investigation by a sum corresponding to the prime cost of the work, all components from the rent for the premises to the analytical work and the physician's time being included in the sum.

Consulting services

In 1990 dr Pauline Harper, clinical chemist and PhD, joined the staff, she was initially responsible for the paediatric section of the mother clinical-biochemical laboratory, but to an increasing extent became involved in the porphyria work. The laboratory service to the doctors more and more frequently became accompanied by consultations in diagnostic problems, or regarding the way to handle the symptomatic patient, drugs to chose and to avoid in the acute porphyrias, prophylactic measures to undertake, or how monitoring for accompanying diseases could be accomplished, etc. About 600 such consultations are yearly given without charge, and in 1998 the Porphyria Centre Sweden was appointed by the National Health Board to constitute the national competence centre for porphyria in the country. As an aid to doctors in charge of carriers of porphyria, rationales for diagnostic intervention in all the common forms have been published (Thunell 2000; Thunell and Harper 2000; Thunell *et al.* 2000a; Thunell *et al.* 2000b).

Clinical network

Many carriers of porphyria are in great need for a steady and continuous contact with a doctor experienced within the field and with personal knowledge of the patient. In Sweden there are two clinical centres for porphyria care. One focused on AIP is situated the

university town of Umeå in the heart of the "AIP country" in the north of Sweden, and managed by dr Christer Andersson. The other specialized clinical unit, which takes on all forms of porphyria, acute as well as cutaneous, is a part of the Porphyria Centre Sweden established at the department of medicine at Södersjukhuset in Stockholm, head dr Dan EH Andersson.

A request, hard to meet in a long and sparsely populated country like Sweden with its long ways to specialized centres, is local accessibility of qualified assets for porphyria care. During the years, however, we have been able to localize clinicians in different parts of the country, which are interested in porphyria and willing to handle porphyria patients within the region advised by us or the patients' association to take contact for treatment or control. Staff meetings at the hospitals, organized from the Porphyria Centre, with information and planning programs provide a basis for the network.

A porphyria patients' association

During her adolescent years Anna-Lisa Mouchard (1914-2005) had to observe the progress of the extremely painful porphyric disease in her AIP-carrier mother. The experience made her start the Swedish Porphyria Patients' Association in 1976 and together with professor Lennart Wetterberg she formulated the key idea for its activity. Aware of the environmental threats to the carrier of a gene for acute porphyria and of the notorious ignorance among doctors (at that time, at least) of the existence of such, they focused the program on efforts to give patients as well as health care services information on the disease. A thorough knowledge of the pathogenetic mechanisms of the acute porphyric disease and of how it may become triggered, aimed at giving the carriers protection against erroneous exposure to porphyrinogenic agents in the daily life, as well as against medical maltreatment. A first step was to construct lists of drugs to be avoided and being useful, respectively. Its twenty examples of each category of substances initially included, were based on the results of an international inquiry by Lennart Wetterberg (Wetterberg 1976) and has since with the help of the Porphyria Centre been followed by nine further editions. The 2005 edition of *Drugs in Acute Porphyria* contains classifications of all around 1000 drugs and combination of drugs in the Swedish Pharmacopeia. A new feature is that the rationale for each classification is elucidated by theoretical models fetched

from the current pathophysiological paradigm for acute porphyria and from the most recent pharmacokinetic models for drug metabolism in humans (below). Also, a scheme for prediction of the individual susceptibility of the carrier to porphyrinogenic by-effects of drugs is given, which will make well founded precautions possible in the case there is need for prescription of a potentially dangerous drug. The classification system proposed has been internationally adopted and is the basis e.g. for the Canadian drug list and for the list put forward by the European Porphyria Initiative (<http://www.porphyria-europe.org/>).

Brochures with advice on how to live with a porphyria disposition without getting the symptoms of the disease have been produced for all the heterozygous forms of the porphyrias, i.e. the three acute porphyrias, porphyria cutanea tarda and erythropoietic protoporphyria, and is distributed to the members of the Swedish Porphyria Patients' Association and to the health services on request. The effects on morbidity and mortality of the preventive program have been remarkable. The upcome of heme replacement therapy in the late seventies, which was later improved in Finland to heme arginate, has as well been of great importance in these achievements.

Research

The major scientific achievements of Hammarsten, Wallquist, Waldenström, Haeger-Aronsen and Wetterberg have been touched upon above, as have the contributions of the molecular geneticists that have mapped the mutations in the Swedish porphyria population (Table 1).

The epidemiological studies on acute intermittent porphyria conducted by Christer Andersson in the heart of "Porphyria land" in the north of Sweden (Andersson 1997) has significantly expanded our knowledge of the socio-medical consequences of the disease. They have also put into focus the earlier largely overlooked, severe and frequent, late-complications of AIP in the form of renal disease (Andersson and Lithner 1994) and liver cancer (Andersson *et al.* 1996). Their findings have prompted recommendations of yearly investigations of blood pressure and kidney function and scanning for liver tumour, in carriers above middle-age with a history of porphyric manifestations earlier in life (Thunell *et al.* 2000a). The latter routine results in the detection within the aged AIP-population in Sweden of

cases of hepatoma every year and has made possible early and successful intervention.

Presently an evidence-based system for drug porphyrinogenicity prediction is being implemented (Thunell et al. to be published). It is based on the current paradigm for activation of the acute porphyrias by induction of the rate-limiting enzyme in the array of reactions harbouring the deficient enzyme in the acute porphyrias, i.e. the heme-synthetic chain. This model is combined with the recent advances regarding the role of nuclear DNA-binding proteins in the initiation of transcription of heme-based drug-metabolizing enzymes.

Lately conditions affecting the outcome of porphyria cutanea tarda in Sweden have been established (Harper *et al.* 2004; Linde *et al.* 2005). Pauline Harper and her coworkers are also engaged in two projects for treatment of AIP, where one aims at finding ways to annul in carriers of AIP the effect of the disease-producing mutation by substituting the enzyme that has become deficient (Johansson *et al.* 2003; Sardh 2003) and the other to substitute the mutated allele by an undamaged one in an AIP animal model (Johansson *et al.* 2004).

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Reprint requests

Stig Thunell, Porphyria Centre Sweden, CMMS C2 71, Karolinska University Hospital Huddinge, SE-141 86 Stockholm, Sweden. E-mail: stig.thunell@karolinska.se