leprosum has been suspected but not proved to be the cause of nephritic changes. Recently Drutz and Gutman have published a detailed study on the specific relation of glomerulonephritis to type 2 reaction in lepromatous leprosy,[19] and our findings are in accordance with their conclusions and those of others[20 21] on the role of immune-complex deposition in glomerular basement membranes and capillary walls. The occurrence of bacilli in relation to the juxtaglomerular apparatus must be rather unusual, and though bacilli have been found in necropsy studies, and also in biopsy specimens,[22] kidney parenchyma is not usually invaded in this disease. The common association of cryoglobulinaemia with lepromatous leprosy has been described,[23] and our finding of IgG and IgM in both glomeruli and the cryoglobulin suggests that they share a part in the pathogenesis of this glomerulonephritis. To our knowledge there are no published data relating the incidence of proteinuria or glomerulonephritis to that of serum cryoglobulins in leprosy, though this association has often been noted in other diseases. In conclusion the inverse relation between skin and joint manifestations in this syndrome seems to be worth further investigation, as are the effects of renal involvement on the prognosis for patients with lepromatous leprosy in reaction.

We thank Dr. A. G. S. Hill, director of the Oxford Regional Rheumatism Research Unit at Stoke Mandeville Hospital, for permission to report this case and for helpful advice in preparation, and Dr. R. J. W. Rees of the National Institute for Medical Research, Mill Hill, London NW7 1AA, for data on concentrations and morphology of leprosy bacilli in biopsy specimens and nasal mucus. A. C. McDougall is supported by grants from the Medical Research Council and the British Leprosy Relief Association.

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Erythropoietic Uroporphyria of Gunther First Presenting at 58 Years with Positive Family Studies

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British Medical Journal, 1975, **3**, 621-623

Summary

Erythropoietic uroporphyria of Gunther was seen in a 58-year-old man who presented with photosensitivity, haemolytic anaemia, and classical laboratory findings. Family studies showed five asymptomatic relatives with erythrocyte uroporphyrin concentrations in the probable latent heterozygote range.

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Introduction

After the demonstration of defects in both bone marrow and liver in erythropoietic protoporphyria[1] three major divisions of the porphyrias have been described—namely, the erythropoietic, erythrohepatic, and hepatic types.[2] The erythropoietic group is the rarest of the porphyrias. Only two cases of erythropoietic coproporphyria and 70 authentic cases of congenital erythropoietic uroporphyria (Gunther's disease) have been recorded.[3] In 1962 Goldberg *et al.*[4] wrote of the latter condition, "all cases in whom a definitive statement was made regarding age of onset presented in childhood and no patient has survived to middle age." In 1965, however, a Bantu man was reported whose first manifestations occurred when he was 55.[5] Of all recorded cases of Gunther's disease, the man we describe here is the first in Australia, the ninth with associated thrombocytopenia, and the oldest at initial presentation.

Case Report, Methods and Results

The patient, an Australian man with British forebears, presented to a dermatological outpatient clinic in March 1965 aged 58 years. He had a three-month history of recurrent blistering of the skin of the face, scalp, and hands on exposure to the sun, plus intermittent red or dark urine. He had never been thus afflicted before. He admitted to a moderate daily intake of alcohol, but was not on any medication. There was no family history compatible with porphyria. He was married with no children. Physical examination showed a hairy man with blistering of the face, scalp, and hands. Mild facial hypertrichosis

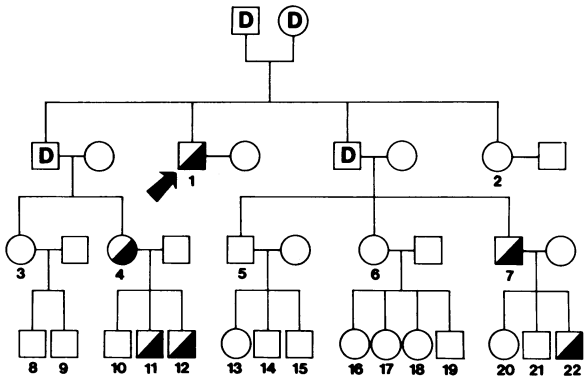
was present. He had been edentulous since the age of 45 years and his teeth had never been discoloured. The liver and spleen were not palpable and there was no peripheral evidence of chronic liver disease. His urine was "port-wine" in colour and negative for bilirubin, excess urobilinogen, and porphobilinogen, but it contained gross excesses of porphyrins (2256 nmol (1880 μg) of uroporphyrin and 6·43 μmol (4200 μg) of coproporphyrin per 24 hours) as did his faeces. Porphyria cutanea tarda was diagnosed.

In June 1965, three months after his initial presentation, he was admitted to hospital because of a severe spontaneous epistaxis lasting 24 hours. Episodes of blistering and discoloured urine had continued. His blood picture was grossly abnormal and included a haemoglobin of 8·3 g/dl, a reticulocytosis of 10·4%, a platelet count of 28×10^9/l, and 60 nucleated red blood cells per 100 white blood cells. Special haematological investigations (to be reported elsewhere) showed both haemolysis and ineffective erythropoiesis.

SPECIAL PORPHYRIN STUDIES

Because of the combination of a porphyria and haematological abnormality a detailed porphyrin investigation was performed in 1971. The results are shown in table I. Individual porphyrins were separated by electrophoresis,[6] and isomer type was determined by lutidine paper chromatography[7] and confirmed by melting point for urinary uroporphyrin and faecal coproporphyrin. In addition 50-140 erythrocytes per low power field showed prolonged fluorescence under ultraviolet light. The fluorescence varied in intensity, in many instances being very bright and, though some fading did occur, was still marked in many cells after 15 minutes. A few normoblasts in bone marrow smears also fluoresced under ultraviolet light, but fluorescence was transient, persisting for only one or two minutes. The blood lead concentration was normal at 0·24 μmol/l (5 μg/100 ml) of red cells (reference range <1·9 μmol/l (<40 μg/100 ml)).

Urine and red blood cells were sought in 1974 from 21 relatives and obtained in 16 cases (see fig.) in an attempt to distinguish whether this man's condition was familial or had arisen spontaneously as a result of a mutation. Total porphyrins in urine were estimated spectroscopically after conversion to the esters. Results ranged from 15 μg/l to 290 μg/l. Two samples with results on the upper limit of normal (270 and 290 μg/l) were examined qualitatively by electrophoresis of the free porphyrins and showed a normal composition, being mainly coproporphyrin. No red cells fluoresced under ultraviolet light. For the estimation of uroporphyrin in lysates of red blood cells heptacarboxylic porphyrin (20 ng) was added to 2-ml samples as an internal standard and esters of the mixed porphyrins were isolated without any attempt to make the isolation quantitative. The esters were separated on thin-layer chromatographic plates and the spectrophotometric signals of the uroporphyrin and heptacarboxylic porphyrin were compared to those from a mixture of equal amounts of the two porphyrins. The results are given in table II.



Pedigree of family of patient studied (no. 1). □ = Male. O = Female. D = Deceased. Shaded symbols = Probable heterozygotes.

TABLE I—*Results of Porphyrin Analyses*

Analysis (and Reference Range)*	Results
Urine	
D-Aminolaevulate (μmol/24 h; trace—45·8)	38·9
Porphobilinogen (μmol/24 h; trace—8·8)	10·6
Uroporphyrin (octacarboxyl) (nmol/24 h; 12-60 mainly isomer III)	9240 (95% isomer I, melting point 286°C)
Heptacarboxyl (nmol/24 h)	679·5
Hexacarboxyl (nmol/24 h)	162
Pentacarboxyl (nmol/24 h)	715
Coproporphyrin (tetracarboxyl)	1652 (95% isomer I)
Heptacarboxyl: uroporphyrin	1 : 14·4
Faeces (nmol/g dry weight)	
Coproporphyrin (7·7-77)	2050 (95% isomer I, melting point 254°C)
Protoporphyrin (8·9-133·5)	195·8 (as dicarboxylic porphyrins)
Erythrocytes (nmol/l packed cells)	
Uroporphyrin (trace)	2179
Coproporphyrin (0-31)	994·5
Protoporphyrin (178-890)	178
Serum (nmol/l)	
Uroporphyrin (trace)	180·6
Coproporphyrin (trace)	137·7

*As adopted by the biochemical research laboratory of the Institute of Medical Research, Royal North Shore Hospital, Sydney, New South Wales.

Conversion: SI to Traditional Units: D-Aminolaevulate: 1 nmol/24 h ≈ 0·13 mg/24 h. Porphobilinogen: 1 μmol/24 h ≈ 0·23 mg/24 h. Uroporphyrin: 1 nmol/24 h ≈ 0·83 μg/24 h; 1 nmol/l ≈ 0·083 μg/100 ml. Heptacarboxyl: 1 nmol/24 h ≈ 0·79 μg/24 h. Hexacarboxyl: 1 nmol/24 h ≈ 0·74 μg/24 h. Pentacarboxyl: 1 nmol/24 h ≈ 0·69 μg/24 h. Coproporphyrin: 1 nmol/24 h ≈ 0·65 μg/24 h; 1 nmol/l ≈ 0·065 μg/100 ml. Protoporphyrin: 1 nmol/g ≈ 0·56 μg/g; 1 nmol/l ≈ 0·056 μg/100 ml.

Discussion

Gunther's erythropoietic porphyria presents classically during the first few years of life with severe photosensitivity, haemolytic anaemia, red teeth, and red urine and death occurs usually at an early age. Photosensitivity has, however, been recorded in every type of porphyria except the acute intermittent form. In our case photosensitivity accompanied by haemolytic anaemia and increased excretion of porphyrins in urine and faeces plus the presence of fluorocytes was a combination specific for erythropoietic uroporphyria of Gunther. More sophisticated analyses of the porphyrin content of the urine, faeces, and erythrocytes were entirely consistent with this diagnosis (table I).

The haematological abnormalities in this case were, apart from the thrombocytopenia, those commonly described in Gunther's disease.[3] Thrombocytopenia has been recorded in only eight other cases of erythropoietic uroporphyria[5 8-13] though hypersplenism is present in about 80% of cases. Unlike the Bantu patient[5] our patient experienced a rise in the platelet count to normal after the institution of prednisolone at a maintenance dose of 10 mg/day.

Gunther's disease is thought to be inherited as a Mendelian autosomal recessive,[3] and our patient and the Bantu man[5] may both have been heterozygotes and their disease may have manifested itself only late in life due to other unrecognized

TABLE II—*Age, Sex, and Erythrocyte Uroporphyrin Levels in Relatives (shown in fig.)*

Pedigree position:	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22
Age and sex	67 M.	52 F.	46 F.	30 F.	40 M.	35 F.	32 M.	23 M.	21 M.	10 M.	9 M.	2 M.	12 F.	9 M.	7 M.	14 F.	12 F.	8 F.	5 M.	8 M.	6 M.	2 M.
Erythrocyte Uroporphyrin (nmol/l R.B.C.)	2179	22·9	24·1	44·6*	N.T.	16·9	33·7*	21·7	N.T.	24·1	55·4*	93·9*	N.T.	N.T.	N.T.	18·1	26·5	18·1	12·0	19·3	20·5	38·6*

*Probable latent heterozygotes.
N.T. = Not tested due to unavailability of specimens.
Conversion: SI to Traditional Units—Uroporphyrin: 1 nmol/l ≈ 0·083 μg/100 ml.

factors. That neither patient had discoloured teeth supports this theory. Discolouration of teeth occurs only if excess uroporphyrin is present when the dentine of the permanent teeth is being laid down and hence will not occur when the disease is of late onset.[4]

There was no positive history of photosensitivity in other members of the family. A diagnostic concentration for erythrocyte uroporphyrin in latent heterozygotes for Gunther's disease must remain in doubt till more families are studied. In three family studies concentrations ranging from 48 to 1324 nmol/l (4-110 μg/100 ml) of red cells have been found in presumed heterozygotes, whereas normal family members showed only a trace.[14 15] One of us (W.H.L.) has found erythrocyte uroporphyrin concentrations of 36 and 30 nmol/l (3·0 and 2·5 μg/100 ml) of red cells in the parents (presumed heterozygotes) of a very recently discovered second Australian patient and 51 nmol/l (4·2 μg/100 ml) in a sister. Thus, we provisionally accept a concentration of at least 30 nmol/l (2·5 μg/100 ml) of red cells as being consistent with the heterozygote state. On this criterion five of our patient's relatives would be latent heterozygotes, as were presumably his two deceased brothers. These results support a familial nature to this man's porphyria and thus future studies of the descendants of five uncles and six aunts of the patient would be worthwhile.

We thank Dr. D. Deller, formerly of the Department of Medicine, Royal Adelaide Hospital, for permission to publish data on this case.

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ADDENDUM: Since this report was prepared the patient died with bronchopneumonia, and a poorly differentiated squamous cell carcinoma of the lung was found at necropsy. It is of interest that one brother also had a carcinoma of lung, and the other died with a myocardial infarct.

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Effect of Lithium on Hypothalamic-Pituitary-Thyroid Function in Patients with Affective Disorders

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British Medical Journal, 1975, 3, 623-626

Summary

Hypothalamic-pituitary-thyroid (H.P.T.) function was assessed in 17 patients on maintenance doses of lithium carbonate for a mean period of 21 months (range 1-67 months) and by serial studies on four patients from the start of lithium treatment for a maximum of six months. An exaggerated thyrotrophin (TSH) response to intravenous thyrotrophin-releasing hormone (TRH) occurred in 14 of the 17 patients on maintenance treatment, though basal TSH levels were raised in only three. Two of the three patients were clinically and biochemically hypothyroid and showed a delayed recovery of normal H.P.T. function after lithium was stopped. There were no significant differences in thyroid hormone or basal TSH levels between the euthyroid lithium-treated patients and a group of controls. In all four patients studied serially an exaggerated TSH response to TRH developed soon after starting lithium and persisted throughout the period of observation. Basal TSH levels increased in two of the four patients within the first two weeks of treatment but no consistent trend was found in total thyroxine and total triiodothyronine levels. We suggest that the exaggerated TSH response to TRH is due mainly to the well established direct effects of lithium on the thyroid.

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Introduction

Lithium treatment is occasionally associated with the development of goitre and frank hypothyroidism,[1-4] which is thought to be due to the direct inhibitory action of lithium on thyroid hormone secretion with a compensatory increase in thyrotrophin (TSH) levels.[5-10] There is no general agreement, however, on the effect of lithium on thyroid hormone levels in clinically euthyroid patients. Some workers have reported a significant reduction in the levels of protein-bound iodine and total thyroxine (T-4) and triiodothyronine (T-3), whereas others have found no significant changes[5 7-13] The effect of lithium on basal TSH levels also remains in doubt.[6-9] Thus to establish in more detail the nature and frequency of lithium-induced abnormalities of hypothalamic-pituitary-thyroid (H.P.T.) function we have carried out tests with thyrotrophin-releasing hormone (TRH) on lithium-treated patients, since the response