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PORPHYRIA VARIEGATA, A DISEASE OF KINGS*

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Porphyria has long been of interest to the clinician, the biochemist and the geneticist In recent years, it has also become the domain of students of history and popular mythology In 1964 Illis made the suggestion that the werwolves of ancient and medieval times, men who had allegedly been transformed into wolves, were sufferers from congential porphyria [1] Disfigured by mutilating skin lesions and often mentally disturbed, they were only too likely to inspire fear and give rise to superstitious beliefs "The red teeth, the passage of red urine, the nocturnal wanderings, the mutilation of face and hands, the deranged behavior what could these suggest to a primitive, fear-ridden and relatively isolated community?"[1]

Perhaps more important is the recent assertion by two British physicians that several members of the Royal Houses of England and Prussia were afflicted with porphyria variegata, a mixed form of hepatic porphyria [2 3] This disorder, described by Dean and Barnes, is particularly common in South Africa where its incidence has been estimated at 3 to 1,000 or 8,000 in the whole population Dean has shown that all cases in South Africa can be traced back over 9 to 13 generations to a Dutch couple who emigrated to the Cape of Good Hope in 1685-8 [4] It may be that before the advent of barbiturates and sulphonamides, the condition was harmless and perhaps even advantageous, affected subjects being more emotional and tending to have larger families [4]

Porphyria variegata is inherited as an autosomal Mendelian dominant and may cause acute symptoms, cutaneous manifestations or both Porphobilinogen may be absent from the urine in between attacks, but an increase in fecal porphyrin is invariable and serves as a valuable screening procedure

Research into the medical history of the Royal Houses of Stuart, Hanover and Prussia was first prompted by the recognition that the mental and physical illness of King George III may have been a classic case of porphyria [5]

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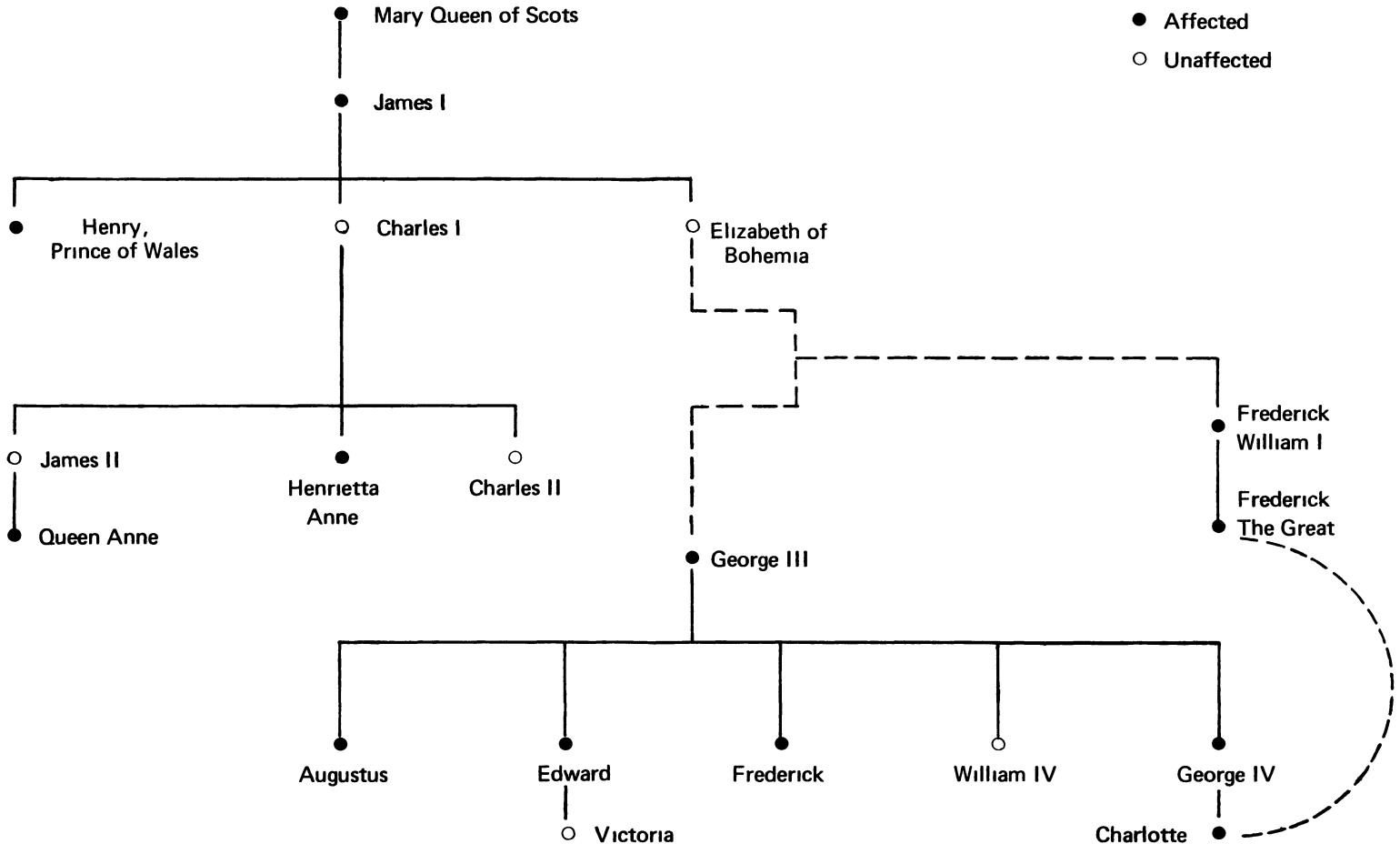
PORPHYRIA IN THE ROYAL FAMILIES (after Macalpine, et al [6])



Much information has been gleaned from recently discovered manuscripts and the story makes fascinating reading [6] It begins with Mary Queen of Scots, who suffered all her life from "hysteria" and bouts of abdominal colic Her son, King James I of England, had attacks of pain, weakness, red urine, ("like Alicante wine") and exhibited skin sensitivity to sunlight He died following an acute episode, so suddenly that foul play was suspected His son, Henry Frederick, Prince of Wales, died after a similar attack and was also thought to have been poisoned From James I, porphyria may have been passed down to Henrietta Anne, daughter of Charles I who died unexpectedly after a short illness characterized by excruciating abdominal pain, and to Queen Anne, daughter of James II, who suffered all her life from "flying gout" and died in coma at the age of 49 [6]

From the daughter of James I, porphyria may have been transmitted to the House of Hanover and hence to Frederick I of Prussia and to his son Frederick II the Great, who suffered all his life from attacks of pain, vomiting and paralysis Through the Hanoverian dynasty, the disease apparently came down to King George III of England whose recurrent attacks of madness were accompanied by physical symptoms highly suggestive of porphyria, including the passage of red urine The reign of George III was punctuated by momentous events such as the American and French revolutions His illness precipitated the Regency crisis of 1788 and shaped the course of constitutional monarchy in Britain Historians have already commented on the effects and importance of this diagnosis on the interpretation of history [7]

In addition porphyria may have affected the sister of George III, who died from acute ascending paralysis, and four of the King's sons, including George IV, whose apparent irresponsibility now has to be viewed in the light of this diagnosis, and Edward, Duke of Kent who however did not transmit the gene to his daughter Victoria Porphyria may have also been responsible for the national tragedy of 1817, when Princess Charlotte Augusta of Wales, daughter of George IV died in childbirth with an infant, leaving England temporarily without an apparent heir to the throne and threatening the Royal House of Hanover with extinction [6]

Retrospective diagnosis in historical figures are subject to controversy and uncertainty, as illustrated by the cases of Alexander, Napoleon or Mozart However the authors have supported their thesis by establishing a diagnosis of porphyria in two living members of the German branch of the House of Hanover [6] While further evidence may be forthcoming in the future, several experts have already presented objections, based on clinical or genetic grounds Dean regards porphyria variegata as a benign condition, unlikely to cause severe symptoms unless precipitated by modern drugs such

as barbiturates and sulphonamides [8] Though the last word on this subject has not yet been written, one is led to reflect that here is another disease which may have often and profoundly changed the course of history, for in the words of Gibbons, "an acrimonious humour falling on a single fibre of one man may prevent or suspend the misery of nations "[9]

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