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Pointers

"Insanity" of George III: Drawing on a number of contemporary records, Dr. Ida Macalpine and Dr. Richard Hunter conclude that George III suffered from acute intermittent porphyria (p. 65). Leader on this page.

Mineral Metabolism in Mania: Dr. Alec Coppen and his colleagues find significantly increased amounts of residual sodium (intracellular and a small amount of bone sodium) and body fat in patients with mania (p. 71).

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Complications of Temporal Arteritis: Letter from Dr. B. T. Horton (p. 105).

Occupational Dermatitis: "The Industrial Injuries Act needs completely rethinking and redrafting" claims Dr. Lucy Turner in her letter (p. 106).

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A Royal Case of Porphyria?

The art of retrospective diagnosis provides an outlet for intellectual curiosity, though unlike palaeopathology it lacks the material evidence from which that science is enabled to draw its conclusions. It has perforce to rely on documentation, a case history in a medical memoir or journal, accompanied sometimes by a post-mortem report, or on descriptions in letters and diaries of lay persons who knew and observed the subject in life. The more distinguished the patient the more numerous are such references likely to be, and there is no gainsaying the fact that, human nature being what it is, our curiosity is aroused by the infirmities of a Caesar or a Napoleon and the part they may have played in the history of our civilization.

The illness of George III had a potent influence on English politics at the close of the eighteenth and beginning of the nineteenth centuries, and it is unusually well documented. The King was attended by several distinguished physicians, including the Willises, Baillie, Heberden, Baker, and Halford, whose reports and surmises on the illness are available. In addition, the Privy Council of the day required and received from his medical attendants periodic reports on the King's health. These are guarded and cautious and show the difficulties under which medical diagnosis suffered before the introduction of modern aids. One of the most valuable records is the day-to-day account by Sir Henry Halford of the illness from October 1811 to January 1812.

Dr. Ida Macalpine and Dr. Richard Hunter have drawn upon this material, including four primary sources for the first time, to make a clinical reassessment of King George III's "insanity" and have been led to the conclusion that his was "a classic case of porphyria." The evidence has been marshalled in a compelling manner and certainly requires very careful consideration. It is set out in their article at page 65 of the *B.M.J.* this week.

Acute intermittent porphyria is notoriously protean in its manifestations,[1] which adds to the difficulty of its diagnosis even at the present day. It is a genetically determined metabolic disturbance, transmitted as a Mendelian dominant character, and follows a chronic course, interrupted by periods of exacerbation of varying intensity and duration. It most frequently becomes manifest in the second or third decade of life. Biochemically it is characterized by the urinary excretion of excessive amounts of porphobilinogen, a porphyrin precursor, and of porphyrins. Porphobilinogen is colourless but is converted spontaneously into pigments with a red to deep purple colour. Urine passed during an attack may darken rapidly on standing and assume the colour even of a permanganate solution.

The symptoms and signs have been discussed by A. Goldberg and C. Rimington.[2] The triad of abdominal pain, vomiting, and constipation[3] predominates, but muscular pain, tachycardia, and some psychological disturbance ranging from emotional instability to gross psychosis are

almost invariable accompaniments. During severe attacks more severe interference with the nervous system may result in extensive paralysis, dysphagia, and aphonia.[2 4] Recovery, as the attack subsides, may be surprisingly rapid, but often leaves considerable muscular wasting.

The picture presented to us of George III's illness shows many of these features. Thus, starting at the age of 24, it followed a chronic course with four or five major and numerous minor episodes. Exacerbations were characterized by severe abdominal colic, constipation, painful muscular weakness, tachycardia, hoarseness, paraesthesia, hyperaesthesia, and mental disturbance, and they left him wasted, weak, and aged. Epileptiform convulsions have often been reported in cases of porphyria, as have diplopia and nystagmus.[4 5] These last two symptoms were in fact noted during the King's last illness. His mental disturbance, to which his physicians paid such attention, resembled that often seen in acute porphyria, ranging as it did from insomnia, emotional lability, delusions, and hallucinations to delirium and convulsions. Notwithstanding the severity of such episodes, recovery was rapid ; " the suddenness of opposite changes has been frequent and most remarkable," wrote Greville. This feature, so impressive in the patient with acute intermittent porphyria, frankly puzzled King George's physicians, whose debate was whether he suffered from " delirium " or " insanity." His case was unique. " Faith, 'twould seem as if the madman were the sanest here ! "[6] The similarity to acute intermittent porphyria would seem already to be impressive, but Drs. Macalpine and Hunter can even refer to the recorded discolouration of King George III's urine during his attacks. He was said to have passed " bloody water " during 16 hours, of which " no tinge " remained the following day. On another occasion " the water is of a deeper colour—and leaves a pale blue ring upon the glass near the upper surface." The usual description of the urine in acute porphyria is like port wine, but purple discolouration can also occur.

Finally there is the hereditary aspect. Acute intermittent porphyria is a familial disease, and thus overt or latent cases may be expected among relatives. George III was one of nine sibs, three of whom died in their teens. His younger sister, Caroline Matilda, died at the age of 24 after one week's illness, which followed two similar but milder attacks. The description of this illness given by Drs. Macalpine and Hunter is in every way compatible with a fulminating attack of acute intermittent porphyria and greatly strengthens their thesis about the King's malady.

It would be interesting to know more about the other members of the House of Hanover. George III, father of 15 children, was succeeded by his eldest son (George IV), who survived his only legitimate child, Charlotte. The crown then passed to the third son of George III, William, who died in 1837 and was succeeded by Victoria, daughter of Edward, the fourth son of George III. Drs. Macalpine and Hunter point out that research into the medical histories of the numerous members of the House of Hanover, many of whom lived abroad, would be a major undertaking, but the excellence of their present study and the high degree of probability which must be accorded to their inference support a hope that they may be persuaded to add yet another chapter to complete this fascinating medical history.

[1] Waldenström, J., *Acta med. scand.*, 1937, Suppl. 82.
[2] Goldberg, A., and Rimington, C., *Diseases of Porphyrin Metabolism*, 1962. Springfield, U.S.A.
[3] Günther, H., *Ergebn. allg. Path. path. Anat.*, 1922, **20**, 608.
[4] Goldberg, A., *Quart. J. Med.*, 1959, **28**, 183.
[5] Gibson, J. B., and Goldberg, A., *J. Path. Bact.*, 1956, **71**, 495.
[6] Hardy, T., *The Dynasts*, Pt. 2, Act 6, Sc. 5, 1925. London.

Aetiology of Intracranial Aneurysms

After H. M. Turnbull's pioneer observations[1] in 1914 it became widely assumed that " berry " aneurysms on the intracranial arteries are of congenital origin. When in 1930 W. D. Forbus[2] showed that many of them arise at points of arterial branching and in fact at sites where there are defects in the medial muscular coat of the artery this theory gained further support. But it did not explain why rupture of an aneurysm, though occurring occasionally in children and young adults, is commoner after the age of 40. Furthermore, Forbus[2] found defects of the media in many cerebral vessels and in other arteries which yet showed no evidence of aneurysmal formation. In 1940 L. E. Glynn[3] confirmed this observation and pointed out that even when the medial coat is defective the internal elastic lamina alone can withstand very high pressures.

It was R. Carmichael[4] in 1950 who suggested that formation of an aneurysm depends on a combination of two factors: there must be a defect in the media or some other congenital anomaly, but superimposed on it there must also be a lesion of the internal elastic lamina at the same site. He suggested that this second lesion is usually due to early atheroma. The subsequent investigations of T. Crawford[5 6] confirmed that atherosclerosis is an important causative factor and also suggested that many aneurysms show a steady increase in size. Moreover, the importance of atherosclerosis in this connexion is evident from the rarity of intracranial aneurysms in animals ; only three examples are on record—in a colt,[7] a llama,[8] and a chimpanzee.[9] Atheroma is uncommon in the cerebral vessels of mammals and birds, though it has been found in the aorta and coronary arteries of pigs,[10 11] rabbits, hares, chinchillas, and parrots,[12] and in primates.[13] On the other hand medial defects in intracranial vessels have been found in the dog, horse, cow, and rabbit.[14–16]

In an attempt to clarify further their aetiology and natural history G. H. du Boulay[17] has recently reported a careful analysis of the size and shape of 252 intracranial aneurysms which were seen by angiography in 197 patients. Many patients had more than one angiogram, and hence changes in the shape and size of the aneurysms could be recorded. The findings in these 197 patients (71 male, 125 female, 1 unrecorded) were compared with those in 100 consecutive patients investigated for intracranial neoplasm. He found arterial irregularity or narrowing due to atherosclerosis in the carotid tree in 64 (35%) of 180 patients in the group with aneurysm, whereas only 16% of the 100 patients with intracranial neoplasm (who were of comparable age) showed similar changes.

Du Boulay[17] also examined the circle of Willis of 32 mammals and 128 birds, in none of which was an aneurysm found. Only in one circle was there evidence of macroscopic