Book Reviews

PORPHYRIA—A ROYAL MALADY*

An Essay Review by

W. H. McMENEMEY

FARMER GEORGE was a mad king, and so we lost the American colonies: such in brief is the recollection of what the man-in-the-street garnered at school. It is remarkable that so little attention has been paid to the nature of George III's malady, and it is a sad reflection on British medical historians that during the 200 years that have elapsed since his first overt attack of illness, there have been only two serious studies on this subject, both of them by Americans. Ray (1855) believed that the disorder was recurrent mania although he found no account of earlier symptoms suggestive of an ill-balanced mind in either the illustrious but notably abstemious patient or in members of his family. Guttmacher (1941) accepted the diagnosis of manic-depressive psychosis put forward by Jelliffe (1931) invoking, on the then fashionable basis of psychopathology, self-blame, indecision and frustration on the part of the king as the underlying reasons for the symptoms. Yet, as is clear from the concise and well-documented account by Doctors Macalpine and Hunter, the contemporary opinion of courtier-physicians, and 'mad-doctors' alike with few exceptions, the disorder of the mind was of the 'consequential' rather than the 'original' type, that is to say, it was presumed to be the result of bodily disease and was not just plain lunacy. For instance Rowley (1790), a commentator of the time, postulated the existence of 'some prevailing irritating acrimony' as a cause of the mental symptoms in the illness which occurred in the winter of 1788–9 while Pargeter (1790) seems to have been of the opinion that the royal patient was suffering from a form of delirium: Addington (1788) wondered how a diagnosis of mania could be justified in the absence of any preceding phase of melancholia. Doctors R. D. Willis and William Heberden junior, who were in attendance in the last prolonged phase of the illness, commented respectively upon his 'bodily indisposition' and 'his peculiarity of constitution'. Sir Henry Halford was surely right when he said that there was no exact precedent for the king's disease: this is possibly still true today.

The evidence of the astute Fanny Burney can be invoked by those who believe that the king suffered from a confusional state. In the early phases of the illness in 1788 she reported that he had 'broken forth into positive delirium' when at dinner (19 October). He spoke to her in a hoarse voice and 'in a manner so uncommon that a high fever alone could account for it' (25 October). On 3 November she was anxious because 'he is better and worse so frequently'. She observed that he had had an attack of gout 'on the road' and that 'there is something unmistakably alarming in his smallest indisposition'. But when, on 2 February 1789, shortly before his recovery,

**Porphyria—A Royal Malady* (Articles by Ida Macalpine, Richard Hunter, C. Rimington, John Brooke, and Abe Goldberg, originally published in the *British Medical Journal*.) London, British Medical Association, 1968, pp. vii, 68, illus., 12*s.* 6*d.*

she was chased by his royal majesty in the gardens of Kew hotly followed by Dr. Francis Willis, his son John and their attendants, her description of the encounter is compatible with the diagnosis advanced by Ray. She noted his volubility, his evident delight at meeting someone he knew and with whom he could converse, that lack of inhibition which allowed him to embrace her (evidently not recognized by the doctors as other than usual practice!) and 'a look still of wildness in his eyes'. She commented upon his state of 'physical intoxication' and the fact that the doctors evidently thought him 'too elated'. On the other hand Thackeray's colourful description of the pathetic king in the long final phase of his illness, culled no doubt from many sources and written thirty-five years after the patient's death, read like late paraphrenia. Yet it appears from the authors' precis of this last illness that there were frequent changes in his mood and that he continued to suffer many attacks of physical intoxication with pain. The mind of this unfortunate soul had to contend with blindness and deafness as well as porphyria.

It was left to the authors and Professor Rimington to investigate the nature of the disease which in a Mendelian dominant mode seems to have bedevilled the lives of several unfortunate members of the royal families of Stuart, Hanover and Prussia, and to recognize the common pattern of porphyria in one of its forms. But when the news of their discovery became known to the medical world, the first reaction was one of disbelief. A cyclothymic form of mental deviation to explain the temperament and eccentricities according to George III and the constitutional issue raised by them had for too long been engrained in the minds of the profession. Doctors in mental hospitals confessed to never having seen a case of porphyric encephalopathy and many doubted if an anomaly of porphyrin metabolism manifesting itself only periodically and briefly could produce a confusional state lasting months, let alone years. In the correspondence columns of the *British Medical Journal* the implication of some critics was that the authors were premature in advancing their surmise. Biochemical evidence of the anomaly in two descendants was regarded as equivocal. The conclusions which emerged from this correspondence were clear, firstly that porphyria was a disease still too little known to the profession but that these authors had succeeded in a dramatic way in bringing it to our notice; and secondly, convincing though their evidence may have appeared, further support for their hypothesis was desirable. But absolute certainty in historical pathology can seldom be reached and we must accept the evidence presented by research writers, unless we mistrust their selection of records, their deductions or perhaps their sources of information. In this instance, one can hardly doubt the findings of these renowned and experienced historians and one must admire their enterprise in seeking new sources of information, including Sir Theodore de Mayerne's fortunately extant notes on the illness of James I and Henry, Prince of Wales. They have very skilfully presented their case for the diagnosis of porphyria to be considered in these families and many will feel that they have succeeded. In retrospect however, one feels that it would have been easier for the authors had they had the opportunity to elaborate on their theory, putting forward arguments against as well as for it. Perhaps biochemical investigation of other descendants may give firmer support to the diagnosis.

The psychiatric features of acute intermittent porphyria are important. They were

known to Günther (1912) and many since his day have commented upon their importance in the differential diagnosis of confusional psychoses. Goldberg and Rimington (1962) found that 58 per cent of patients afflicted with this disorder of metabolism had mental symptoms during the attacks and 12 per cent had been admitted to mental hospitals. Waldenström (1939) was under the impression that schizophrenia and manic-depressive psychosis might be relatively common in the families of patients with this disease but this is not borne out by the more comprehensive studies of Wetterberg (1967) who supports the view that there is probably a mental syndrome associated with acute intermittent porphyria. He maintains that porphyria should always be considered as the basis of a psychosis when the degree of depression is no more than slight to moderate, when there are transitional states of confusion, when visual hallucinations are frequent and when there are neurological signs. This well fits in with descriptions of the king's mental illness and were he alive today he would be an immediate candidate for a Watson-Schwartz and a Mauzerall and Granick test. But in spite of the frequency of mental symptoms in this disease and their variety, instances in which they have persisted for any length of time seem to be very few. In this respect the malady suffered by George III in the last ten years of his life is most unusual. Neuropathological studies have been mostly confined to peripheral nerves but changes have been noted in the brains of some persons who in life have been the victims of this disorder. They have included small foci of demyelination in the white matter and areas of ischaemia. The latter could be attributable to complicating factors such as hypertension and cerebrovascular disease, both of which could be expected in a person who survived with the malady to the age of eighty-two. Unless such lesions were in 'silent' areas of the brain, pareses of a permanent nature would be expected and from the accounts of George III's final long illness it is not clear that he had them. Alterations have been noted however in many types of nerve cells in the nervous systems of porphyrics and it is these that cumulatively, together with scattered demyelinating lesions in the brain, could account for the specific type of mental illness which some authorities recognize in this disease. Perlroth and his colleagues (1966) have found important changes in the supraoptic and paraventricular nuclei and in the median eminence of one case which, if confirmed in others, would open up an entirely new line of approach to this problem of porphyric encephalopathy.

Today our sympathies, belated though they be, are surely with the kindly monarch whose treatment as a patient was characterized by such contrasting anomalies as that rigid observance of Court protocol on the one hand, which so stupidly forbade the attending physicians from questioning their patient, and on the other hand, a regimen of treatment by restraint severe enough to cause eminent physicians not in regular attendance to lodge a protest with the Archbishop of Canterbury.

The past ravages of this hapless enzymal defect alleged to have been wrought within some of the royal families of Europe—it will come as a surprise to some to learn that Frederick II of Prussia was probably another victim—are summarized carefully, but the reader, if persuaded to accept the diagnosis, is often left in doubt as to the real cause of death. For instance, did George III have organic disease of the brain in the last ten years of his life, and if so what was its nature? If a brain such as his were to become available for study today it would cause considerable interest quite

apart from any light it might throw on this historical personage. When the unfortunate Princess Charlotte died suddenly in 1817 at the age of seventeen after giving birth to a dead child, may she not have had an amnotic fluid embolism as well as a porphyric trait? There are references to short fatal illnesses in several individuals mentioned in the monograph which the authors assume are the result of porphyria: but these patients lived at times when shigella and other acute infections were not so rare as today, when colic, stone and gout were commonplace and when diagnosis was rendered more difficult by the fact that hypochrondriasis was the proud privilege of the indulgent rich. The authors' challenge surely warrants an appraisal by someone of present-day porphyria as a cause of unexpected death. It is of the greatest good fortune if, as is claimed, this inherited anomaly of pigment metabolism largely died out with the families of George III and IV, because the fertility of the daughter of the apparently tainted Duke of Kent sufficed to refurnish the thrones of Europe with healthy stock.

The historical implications of 'the Royal Malady', reviewed by John Brooke, include such important issues as the decline of the influence of the Court and the transfer of power to the Cabinet during the illness of George III, the constitutional crises raised by the king's illness and the death of Princess Charlotte, and the growth of republicanism during the Regency and the reign of George IV.

It is uncertain and indeed unlikely that a healthy and resolute king—not given to a periodic surfeit of 8-amino-laevulinic acid synthetase—would have succeeded for long in keeping the American colonies within the growing empire but such matters are so speculative as to be unhelpful. The question of blame for their loss is another matter and Dr. Brooke shows how, once the question of insanity was raised, all facets of the king's life prior to and after that time became distorted against him.

In the minds of the public, there is no doubt that until recent times insanity was regarded as an inborn evil rather than a misfortune. Disease of the body, it was thought, might be caused by miasma, contagion, 'virus' and poison and this was not necessarily the patient's fault; but a derangement of the mind was a completely incomprehensible phenomenon. Humoral pathologists could offer little rational explanation and the cellular pathologists who followed, none at all. It is understandable that ignorant country folk clung to and fostered the old ideas of witchcraft, evil spirits and sorcery; and in a country so essentially rural, old ideas were notoriously slow in dying. Therefore there was sympathy for a sick man but not for a madman, whose mind was deemed to be corrupted and for this he must take the blame. Because he was out of touch with reality, rivals, enemies, and even relatives could use him to their own advantages; he could serve as an excuse for all sorts of misfortune. So it seems to have been with this 'much maligned ruler' (Namier, 1952) whom even psychopathologists of recent years found reasons to despise.

Although George III was sufficiently troubled by his illness in 1765 to suggest that provision should be made for establishing a Regency should his health at some time necessitate it, it seems clear that this friendly and popular king had no mental symptoms until the year 1788, some years after the American colonists had gone their own way. Indeed he seems to have been a relatively well, if misguided, man for the twenty-two years following the minor attack in the spring of 1766. The new appraisal by

Dr. Brooke serves well to reveal him in a more just and favourable light than that presented by many earlier and more recent writers. The message for medical historians is clear when he writes 'Strangely the diagnosis of porphyria which exonerates George III from so much speculative psychologizing brings him nearer to us as a human being'. An important function of the doctor historian is to see that justice is done to individuals who lived at a time when they themselves could not benefit from the medical knowledge of today and who may well have done their best while suffering bodily misfortunes and dreadful attendant pains.

Claude Bernard et les Problèmes de son Temps, by JOSEPH SCHILLER, Paris, Les Éditions du Cèdre, 1967, pp. 230, port., no price stated.

The monumental figure of Claude Bernard still remains tantalisingly shrouded in mists of mystery; for Claude Bernard fell into no clear-cut category. He was so truly an original that merely to label him 'scientist' rather than 'philosopher' does not do justice to his picture. The two ways in which clarification of Bernard's elusive greatness can be attained consist either of studying the details of his works, or of elucidating the contemporary context within which and upon which he worked. This latter is Dr. Joseph Schiller's method of exposition.

In this book Dr. Schiller brilliantly describes Bernard's position in the spheres of contemporary science and philosophy. The work is not a biography. A skeleton of biographical fact is given in a brief sketch at the beginning, supplemented by an equally brief outline of Bernard's most important works. Full appreciation of the discussions that follow is therefore enriched if the reader has some knowledge of Bernard's life such as is to be found in Olmsted's well-known biography.

In his first chapter Dr. Schiller defines Bernard's attitude to vivisection. Summarizing its history from Galen onwards, he draws attention to the interesting fact that vivisection before Bernard had paid its greatest dividends in knowledge of the transport systems of the body, of the vessels and nerves. In the case of the nervous system this is because, 'The nervous system is the most anatomical of physiological systems, and its comprehension has no need of physics or chemistry'. The work of Charles Bell and Bernard's great protagonist, Magendie, provided a case in point. Thus when Bernard wrote, 'Always pursue the idea that the physical or chemical phenomena of the organism are dominated by the nervous system;' he was expressing the spirit of his day and at the same time accounting for the fact that between 1843 and 1849 he produced thirteen communications on the physiology of the nervous system, all based on the results of experimental vivisection. It is a measure of Claude Bernard's genius that as a result of his deliberations on methods of research he reversed this traditional position and succeeded in turning chemistry itself into a method of 'vivisection without mutilation' through his experimental use of poisons such as curare. 'This action of poisons', he wrote, 'permits us to achieve a kind of infinitely delicate vivisection since it allows us to localise the phenomena of life'. It was by his manipulations of this chemical instrument of vivisection that he localized the neuro-muscular junction, and discovered glycogenesis in the liver.