Medical History

Porphyria and George III

L. J. WITTS

British Medical Journal, 1972, 4, 479–480

Practitioners of medicine are often interested in biography, if only because each of their case records is in some sense a biography. John Brooke's life of King George III[1] is of special interest, both because of the change in the esteem in which the king is held, as a result of the researches of Namier and others over the last 50 years, and because of the problems still present about the nature of the mental illness or illnesses from which he suffered in his later years. The most important sources of information about these illnesses—the journals of the Willises who attended the king in his several attacks and the diary of Sir George Baker, the first physician to be called in 1788—have only recently become available.

George III was the first of the Hanoverian kings who could truly say, "Born and educated in this country I glory in the name of Britain." Oddly enough, the evidence is conflicting whether he said Britain or Briton. He came to the throne in 1760 at the early age of 22 and reigned till his death in 1819. He was educated privately and deprived of the company of young people of his own age, so that he was at first shy and unduly influenced by his tutor, Lord Bute—an unfortunate event, as Bute lacked administrative ability and parliamentary experience. George, therefore, made mistakes in his early years, but it is now abundantly clear that he was a man of unusual ability and common sense. During his reign the principles of constitutional monarchy and cabinet government were firmly established, to the envy of all Europe, and largely as a result of the king's shrewd judgement of the rights, duties, and limitations of his office. The American rebellion would have been better handled if ministers had taken his advice and in the end American independence was a blessing in disguise.

Cultivated Tastes

The man who achieved all this was no simpleton. When he cried, "Was there ever such stuff as great part of Shakespeare?" he was only echoing what Ben Jonson had said before him. In fact, he collected books from an early age and at his death his library contained about 65,000 books and 450 manuscripts. It was eventually presented to the British Museum and became the nucleus of the national library. He loved music, especially that of Handel, and was a regular attender at the opera and at the concerts of the Ancient Music Society. He was interested in astronomy and had his own observatory at Kew, but perhaps the biggest thing he ever did was to patronize the astronomer Herschel, giving him a pension of £200 per annum and paying the cost of his new telescopes, one of them a veritable giant. Physically he was strong, he had a passion for riding and hunting, and he admired courage and endurance. He was a great countryman and followed the latest ideas on scientific farming.

Oxford
L. J. WITTS, C.B.E., M.D., F.R.C.P., Emeritus Nuffield Professor of Medicine

This was the man who has been described as psychiatry's most famous patient and about whom a fanciful picture of a weak and neurotic personality was formed in the nineteenth century. The first symptoms of the illness, which was later to give rise to the Regency Crisis, appeared a week after his 50th birthday and took the form of what George himself described as a "pretty smart bilious attack." Some weeks later he began to suffer from weakness and pains in the limbs, rambling and incoherent conversation, insomnia, and delirium at night. He clearly had an organic psychosis of a toxic or infectious type, and the illness showed the characteristic variability of symptoms, the king being sometimes completely lucid and painfully aware of the sufferings and indignities which his physicians imposed on him. He was ill from June 1788 to February 1789, and he was then completely well until his second attack in 1801. A third attack occurred in 1804, and in 1811 he became permanently disabled by blindness, senility, and mental disturbance.

The Royal Malady

The details of the king's illness and its maltreatment are fully described by John Brooke. By the end of November 1788 seven physicians had been consulted with little or no benefit. They were paid 30 guineas a visit and by the time of the king's death the total cost of his four illnesses was enormous. No diagnosis was ever agreed on, though a number of unconvincing ones were suggested at the time and later. On 8 January 1966, Ida Macalpine and Richard Hunter electrified medical historians by claiming in a paper in the *British Medical Journal* that the insanity of George III was due to attacks of acute intermittent porphyria.[2] This diagnosis was modified to porphyria variegata in their book *George III and the Mad Business*,[3] which gives a splendid and well-documented account of George III's illnesses and treatment, and the repercussions they had in the improvement of the treatment of mental disease in the nineteenth century. They believe that the porphyria gene passed directly down the royal line through nine generations from Mary Queen of Scots to George IV.

The Macalpine-Hunter thesis is so persuasively presented and argued that it has been widely accepted, but it cannot yet be said to be proved. Some of the evidence against it has been summarized by Geoffrey Dean—who has probably seen as much porphyria as anyone else in the world—in his book *The Porphyrias*.[4] He does not find the picture typical of porphyria variegata and some of the genealogical evidence is bizarre. George III sometimes passed red urine but he had renal calculi and in hereditary porphyria the urine is clear when passed and develops a reddish or brownish colour on standing. Porphyria is not a common cause of insanity and is rarely found in surveys of patients in mental hospitals. The only way of testing the hypothesis would be to show that the descendants of George III have a higher prevalence of porphyria than would be expected in the normal population and this would not be an easy thing to do. For all this, it seems likely that the diagnosis of hereditary porphyria will hold the field for the present in the absence of a credible alternative.

John Brooke wisely leaves these questions to the experts. His biography of the king has been praised by professional

historians for its accuracy and in addition it is extremely readable. It abounds in quotable phrases—"Pitt was always proof against the call of duty when he saw nothing to his own advantage;" or again, "Few people today are so naive as to equate monarchy with tyranny or republicanism with virtue." It is, indeed, an ideal book for refreshment at the end of a day's work.

References

[1] Brooke, John, *King George III*. London, Constable, 1972.
[2] Macalpine, I., and Hunter, R., *British Medical Journal*, 1966, **1**, 65.
[3] Macalpine, I., and Hunter, R., *George III and the Mad-Business*. London, Allen Lane, The Penguin Press, 1969.
[4] Dean, G., *The Porphyrias*. 2nd. edn., London, 1971.

Today's Drugs

With the help of expert contributors we print in this section notes on drugs in common use

Oxygen Therapy

British Medical Journal, 1972, **4**, 480–481

Additional inspired oxygen may be needed whenever tissue oxygenation is impaired, to allow essential metabolic reactions to occur. Inadequate tissue oxygenation implies a defect at some stage in the transport of oxygen from inspired air to the tissues—either in the lungs, the cardiovascular system, the blood, or the tissues. Thus oxygen may be required in a wide variety of conditions such as the respiratory distress syndrome, chronic bronchitis, asthma, pneumonia, cardiac infarction, shock, clostridial infections, carbon monoxide poisoning, and many more. These are considered in a comprehensive survey of oxygen therapy[1] but are beyond the scope of this article, which will be confined to the management of oxygen therapy in adult patients with cardiorespiratory disease.

The purpose of oxygen therapy is to prevent the complications attributed to hypoxaemia. These include confusion and other signs of cerebral anoxia, cardiac arrhythmias, reactive pulmonary hypertension, lactic acidosis, and tissue death. Oxygen is usually given as a temporary measure to prevent tissue hypoxia, but in no way replaces the definitive treatment of the underlying cause.

Dangers of Therapy

The most important danger from oxygen therapy is the development of carbon-dioxide narcosis in patients with ventilatory failure. The way in which oxygen is administered depends largely on whether the patient has ventilatory failure or not and this is discussed below. Other complications are rare and largely preventable. They include the risk of fire and explosion, collapse of the lung, and damage to pulmonary epithelium (which does not, however, appear to cause problems unless the inspired oxygen concentration exceeds 70%[2].)

Indications

PATIENTS WITHOUT VENTILATORY FAILURE

Ventilatory failure (CO_2 retention) is not present in most patients with cardiorespiratory disease—for example, asthma, pneumonia, pulmonary oedema, pulmonary embolism, and fibrosing alveolitis. These patients usually have a low arterial P_{O_2} and a normal or low arterial P_{CO_2}. Measurement of arterial P_{O_2} is not essential but is helpful and often reveals quite severe hypoxaemia in conditions such as asthma. Oxygen is usually given to these patients in high concentrations (uncontrolled oxygen therapy). Though most of these patients have a normal or low arterial P_{CO_2}, the iller patients will occasionally develop CO_2 retention and this can be determined only by measuring P_{CO_2}. This should be done in any asthmatic patient with an unrecordable peak flow rate and in the iller patients with pneumonia, pulmonary oedema, etc.

PATIENTS WITH VENTILATORY FAILURE

The main problems with oxygen therapy occur in patients with ventilatory failure who are depending to some extent on a hypoxic drive. This is seen particularly in patients with an acute exacerbation of chronic bronchitis. The dangers of oxygen therapy are greater and the benefits are perhaps more debatable. These patients, who have often had an arterial P_{O_2} below 60 mm Hg for many years, develop adaptive processes to improve oxygen transport. They appear to tolerate a further reduction in arterial P_{O_2} relatively well and can be managed without any oxygen therapy. Most people prefer to treat these patients with low concentrations of oxygen (controlled oxygen therapy). This usually results in a small increase in both arterial P_{O_2} and P_{CO_2}. Because these patients are on the steep part of their oxygen dissociation curve the small increase in arterial P_{O_2} will be associated with a relatively large increase in oxygen content of the blood and in the oxygen available to the tissues. The rise in P_{CO_2} is related to the increase in inspired oxygen concentration—if this is small (for example, 24%) the rise in P_{CO_2} is usually small.[2]

There are many ways of giving controlled oxygen therapy to these patients but the following procedure appears to be satisfactory. A baseline measurement of either arterial or mixed venous P_{CO_2} is made, the patient is given 24% oxygen, and P_{CO_2} is measured again after one hour. If the P_{CO_2} is less than 75 mm Hg (arterial) or 85 mm Hg (mixed venous) and if the rise in P_{CO_2} is less than 10 mm Hg it is considered safe to proceed to 28% oxygen. Further measurements of P_{CO_2} should then be made after another hour and at suitable intervals afterwards depending on the level of P_{CO_2} and the patient's condition. It is probably wise not to exceed 24% if P_{CO_2} cannot be measured regularly or if mechanical ventilation is either not available or considered unsuitable should CO_2 narcosis occur.

When patients are seen with CO_2 narcosis from high concentrations of oxygen, it is important not to withdraw the oxygen suddenly as the arterial oxygen tension will rapidly fall and if the P_{CO_2} is at narcotic levels the patient will die from anoxia. If the patient is conscious he should be vigorously encouraged to breath while the inspired oxygen concentration is slowly reduced. If he is unconscious assisted ventilation should be instituted immediately.