eases. The factors involved in the precipitation of both of these conditions are also similar. We know now that there are several factors besides drugs which can trigger off acute attacks in both of these conditions. For example, alcohol,[6,7] infection,[4] oestrogens,[8] low caloric intake.[9] All of these factors are firmly substantiated on both clinical and experimental evidence. There are thus a group of very important provoking factors which could have been operative three or four or five hundred years ago. This is not to underrate the importance of drugs in provoking attacks in the modern age. Of 48 of my patients in whom a drug history was very carefully taken 18 had no evidence of barbiturates or any other offending drugs.[3] That is, in more than one-third of these patients other factors besides drugs were operative in producing attacks, and some of these attacks were severe.

Professor Dent's next point is his statement that the clinical manifestations were not typical of porphyria itself. There are certainly some features which are atypical—for example, the diarrhoea which is discussed occurs in about 12% of my own series of acute porphyria patients and in about 7% of Eales's variegate porphyria series.[4] But it is possible that the severe purging, then commonly practised, might have altered this aspect of the gastrointestinal pattern of the disease. Professor Dent finds that the paralysis of the patients recovered too quickly for this to be due to a true porphyric neuritis. Recovery from porphyric neuritis can certainly take many months, but what is perhaps, in my own experience, almost as common as the frank peripheral neuritis is a paresis, a weakness of limbs from which recovery can take place relatively quickly, within days or weeks.

Biochemistry

I was frankly surprised by Professor Dent's unwillingness to accept the biochemical evidence. I am certainly quite happy to accept the evidence of patient A from this source. The elevated hydrophilic porphyrin or X-porphyrin, found in case B, is of great importance; this is a technique which will undoubtedly be very useful for the detection of latent cases.

Genetics

Professor Dent's mathematical pyrotechnics on the genetic findings were most impressive. I think the authors have done well in getting two positives in the present generation. Professor Dent has shown a lack of appreciation, unusual for him, of the exceptional difficulties in obtaining specimens in this family.

Perhaps the most remarkable suggestion was that the papers in some way rendered a clinical disservice to the porphyria sufferer because they presented the disease as a serious rather than as a trivial one. There was indeed a sad reference to a patient who was "exceedingly upset when she read recent accounts of this disease." It is of course important to present a hopeful picture to the patient, and in many cases this is fully justified; but unfortunately some patients do persist in having severe attacks for many years without taking the offending drugs. Among several of my patients with porphyria who read of this work there was no one who was in any way upset. Indeed, most of them showed considerable interest and even a sneaking pride that they might have a "royal malady."—I am, etc.,

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SIR,—Professor C. E. Dent's letter (3 February, p. 311) does not raise objections to "statements" in our papers,[1,2] it merely reveals differing opinions concerning interpretation. We would like to emphasize certain points.

Severity of acute attacks of porphyria and the influence of drugs.—Many of the royal sufferers lived to old age, with long intervals between acute attacks. Barbiturates and sulphonal, to name but two comparatively recent medicaments, are well known to exacerbate or precipitate attacks of porphyria, but similar severe and even fatal attacks with neurological involvement can occur independently of their administration.[3-7] The boy of 14 described by Macgregor, Nicholas, and Rimington[8] was, in retrospect, an undoubted case of variegate porphyria. He experienced three major attacks, the last fatal, in 18 months, the only drugs given having been pethidine to control his pain and on one occasion an antibiotic for his hydroa. Calvert and Rimington[9] report a case of "mixed" (that is, variegate) porphyria in acute exacerbation in which the patient had taken no barbiturates and was a total abstainer.

Why the change in diagnosis from acute intermittent (A.I.P.) to variegate porphyria (V.P.)?—Precisely because study of a wider material showed that cutaneous manifestations of the V.P. type frequently accompanied abdominal and nervous ones in relatives of George III. Not all V.P.s have marked skin lesions, and records concerning George III's skin lesions were too meagre to be significant. The acute phases of A.I.P. and V.P. are so similar that they are not readily distinguishable without recourse to biochemical investigation of porphobilinogen and porphyrin excretion, which George III's attendants did not perform.

Urine colour.—Waldenström and Vahlquist[10] have demonstrated (with colour plate) that the colour of the urine in A.I.P. depends upon its *p*H when passed. Usually it is acid and dark, but "when the urine is made alkaline through administration of alkali to the patient there is a normal colour of the urine." Macgregor, Nicholas and Rimington[8] recorded a "deep purple" urine in their case of V.P.; at other times it was port-wine coloured or sherry coloured. James I passed urine the colour of Alicante wine.[2] The reference to blue colour in our first paper[1] states that "The water is of a deeper colour—and leaves a pale-blue ring upon the glass near the upper surface" (Willis MSS). It does *not* say the urine was blue. An acid, porphobilinogen-rich urine can leave a film or deposit of purplish porphobilin or porphobilin-like products on the walls of a container, especially white porcelain.

Living patients.—It seems rather churlish not to accept the findings of "a distinguished physician who is a recognized authority on porphyria." The reagent used was naturally the Ehrlich aldehyde reagent (Watson–Schwartz test). Stool analysis will always present difficulty in any but the hospitalized patient. England *et al.*[11] are of the opinion that for a proper assessment of 24-hour excretion of porphyrins at least a five-day collection of faeces between markers is necessary. During a recent colloquium of workers in the porphyrin field (at University College Hospital Medical School, May 1967) it was agreed that determination of porphyrin content per gramme dry weight of faeces was the most satisfactory and convenient parameter, and more reliable than a figure based on a 24-hour stool collection.

Genetics.—Our study convinces us that we are dealing with an inherited abnormality. Commenting upon the probability of porphyria having occurred randomly in Mary, Queen of Scots and in patients A and B, Professor Dent ignores evidence of the malady in the intervening 12 or 13 generations in this closely inbred line—which to our mind is inadmissible.—I am, etc.,

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Respiratory Disease and Terminology

SIR,—The B.B.C.-T.V. programme "Medicine Today—Breathlessness" (7 February) was a valuable and lucid account of the clinical background to this symptom, and generally worthy of the important contributions of the Hammersmith Hospital physicians to our understanding of respiratory sensation. However, in one respect the programme was confusing rather than clarifying. This was in the use of the terms "length-tension inappropriateness" of the respiratory muscles and "mismatch" of ventilatory variables as general concepts of the processes underlying breathlessness and dyspnoea. These terms are rapidly becoming part of medical jargon, and progress in the subject could be cloyed by their widespread use.

Unless more clearly defined and subdivided, "length-tension inappropriateness" means no more than that there is something wrong with the muscular and mechanical