Nyhan-Lesch Syndrome and Juvenile Gout (Two Cases)

Rodney Bluestone[1] MB MRCP
(for Professor E G L Bywaters FRCP
and L P J Holt MRCP)
(*Department of Medicine,
Royal Postgraduate Medical School, London*)

Case 1 T T, boy aged 5

History: Premature vertex delivery. Birth weight 4 lb 6 oz (1·98 kg). Neonatal jaundice. Obviously backward at 1 year and started tongue and lip biting and nose clawing; required splinting to control.

On examination: Unable to sit or feed unaided; incontinent; strong tendency to self-mutilation (Fig 1). Central nervous system normal; skull circumference 47 cm. Blood pressure 100/60.

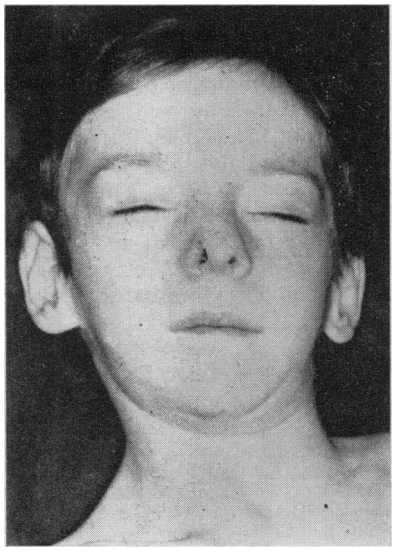


Fig 1 **Case 1** *Areas of self-mutilation on lower lip and nares*

Investigations: IQ educationally subnormal. Blood urea 60 mg/100 ml. Urine sterile. Serum uric acid 9 mg/100 ml. Basal urinary uric acid 559, oxypurines 31, total 590 mg/24 h; on allopurinol, urinary uric acid 163, oxypurines 480, total 643 mg/24 h (Dr J T Scott). Enzyme studies (Dr J E Seegmiller) showed gross deficiency of hypoxanthine guanine phosphoribosyltransferase (HGPR). Family studies not possible.

Comment: Classical Nyhan-Lesch syndrome of mental deficiency, compulsive self-destruction, hyperuricæmia and renal failure. Subsequent studies confirm HGPR deficiency.

[1]Present address: School of Medicine, Center for the Health Sciences, Los Angeles, California 90024

Case 2 A R, man aged 24
Refuse collector

History: Normal school – 'a bit backward'. Aged 12: started grand mal epilepsy. Aged 16–18: confined to colony; treated with phenobarbitone and phenytoin with good control of fits. Aged 15: tophaceous gout with severe recurrent arthritis uncontrolled by probenecid and colchicine.

On examination: Numerous tophi ears, elbows, hands (Fig 2). Blood pressure 110/70. Central nervous system normal.

Investigations: IQ (full scale) 74. Blood urea 40 mg/100 ml. Creatinine clearance 23 ml/min. Urine sterile. Urinary protein 400 mg/24 h. Intravenous pyelogram showed calyceal clubbing. Hb 10·8 g/100 ml. Serum folate 3 ng/ml. Marrow megaloblastic. Serum uric acid 15·5 mg/100 ml. Basal urinary uric acid 711, oxypurines 162,

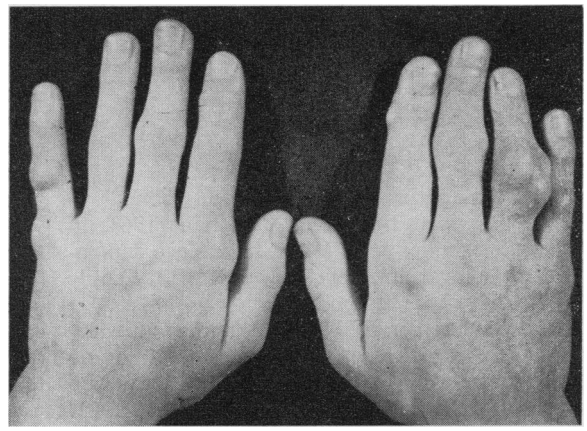


Fig 2 **Case 2** *Gouty tophi on hands*

total 873 mg/24 h; on allopurinol, urinary uric acid 183, oxypurine 749, total 932 mg/24 h (Dr J T Scott). Enzyme studies (Dr J E Seegmiller) showed partial deficiency of HGPR to about 0·5–1·0% of normal levels.

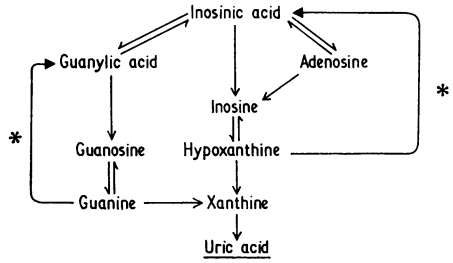
Family studies: no abnormality found in father, mother or 2 sisters.

Treatment: Hyperuricæmia and gout controlled by allopurinol 400 mg/day. Megaloblastic anæmia responded to oral folic acid with no increased frequency of fits.

Comment: Juvenile tophaceous gout in a patient with near-complete HGPR deficiency and mild cerebral disorder. Coincidental folate-deficiency anæmia.

Discussion

It is likely that both patients exhibit features of the same metabolic disorder. Both have a deficiency in their tissues of the enzyme hypoxanthine guanine phosphoribosyltransferase (HGPR) and, as illustrated in Fig 3, showing the final stages of the purine metabolic cycle, such a deficiency will result in overproduction of uric acid. Xanthine oxidase inhibition with allopurinol suppresses this overproduction as effectively as in primary gout, but leaves the total (i.e. uric acid+oxypurine) purine excretion about the same, in contrast to normal gout where up to one-third of normal purine excretion is abolished by allopurinol.



* Site of action of hypoxanthine guanine phosphoribosyltransferase in uric acid cycle.

Fig 3 *Final stages of purine metabolic cycle. (After Seegmiller* et al. *1967)*

The first patient is in all respects similar to those described by Lesch & Nyhan (1964) in whom Seegmiller *et al.* (1967) have since demonstrated an invariable deficiency of HGPR. Family studies have not been possible.

Case 2 has survived to adulthood with only mild cerebral disease, tophaceous gout but no known tendency to self-mutilation. There is no hyperuricæmia, mental abnormality or HGPR deficiency in his immediate family. He has a similar metabolic abnormality to the first patient and Seegmiller (1968, personal communication) has made observations on other adults presenting in this manner.

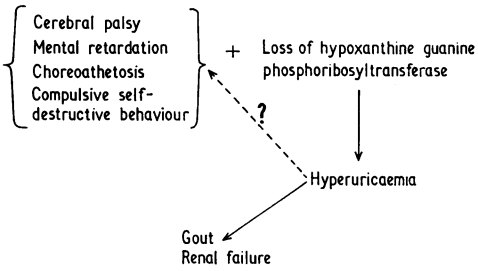


Fig 4 *Characterization of Nyhan-Lesch syndrome (sex-linked, familial disease)*

Clearly much is still to be learned of the metabolic defects and their mode of inheritance. But it does look as if a disease pattern exists presenting in childhood in gross form (Nyhan-Lesch syndrome), and amongst populations of adult subjects with mental abnormalities, epilepsy, hyperuricæmia or gout, in its milder form.

Fig 4 summarizes the known cardinal features of our patients' disease. What relation the enzyme deficiency or hyperuricæmia has to the cerebral disorder is problematical; and whether there are other abnormalities of enzymes concerned in purine metabolism in this disorder is as yet unanswered.

Acknowledgment: I am grateful to Dr Jack Rubie and Dr E M Belton for permission to report Case 1.

REFERENCES

Lesch M & Nyhan W L (1964) *Amer. J. Med.* 36, 561
Seegmiller J E, Rosenbloom F M & Kelley W N (1967) *Science* 155, 1682