Figure 1 The appearances of echinocytes or ‘burr cells’ (top and bottom left) and acanthocytes (top and bottom right) on light and electron microscopy. Echinocytes and acanthocytes are easily confused on routine inspection of a blood film.
INTRODUCTION
Acanthocytes, from the Greek ‘acantha’ meaning thorn, are red blood cells with irregular thorn-like projections. They are easily confused with ‘echinocytes’ also known as ‘burr cells’, which occur in liver disease, uraemia and following splenectomy. Echinocytes have more regular projections and a broader base than acanthocytes (Fig. 1). Acanthocytes are not normally present in peripheral blood. Their detection requires careful, sometimes repeated, examination of blood smears. They are principally associated with three rare but fascinating neurological syndromes: choreoacanthocytosis, the McLeod syndrome and hypo- and abeta-lipoproteinaemia (Fig. 2).

AN ILLUSTRATIVE CASE
A 50-year-old unemployed man, who had been abnormally fidgety ever since childhood, was referred to the psychiatric services because of impulsive and disinhibited behaviour, for example going naked into his back garden and talking loudly to himself in public. He had been sleeping poorly. Furthermore, his wife reported that he had been hoarding ‘junk’ in his house for many years. He had been sacked from his work as a chef about 10 years before because he had become too disorganized to cope. He was an only child and there was no relevant family history.

Examination revealed lack of insight into his difficulties, an inappropriately jocular manner, choreoathetosis, borderline wasting of the muscles of his lower legs and areflexia. Neuropsychological assessment did not indicate any impairment of general intelligence but suggested ‘subcortical or frontal lobe dysfunction’. CT scan of the brain was reported to be normal (though in retrospect showed caudateatrophy). A wide range of other investigations, including genetic testing for Huntington’s disease, gave normal results, except for a mention of ‘burr cells’ on a blood film and elevation of serum ALT to 168 U/L (10–40) with a normal gamma GT result. A diagnosis of ‘frontal lobe dementia’ was suggested.

However, repeated examination of blood films 3 years after his first presentation revealed the presence of acanthocytes. Creatine kinase was raised at 1350 U/L (24–161), with LDH raised at 1139 U/L (208–508). Subsequent blood grouping demonstrated the McLeod phenotype with weak expression of Kell group antigens (see below). The diagnosis was confirmed by genetic testing. Levels of apolipoprotein B were normal. The final diagnosis was neuroacanthocytosis due to the McLeod syndrome. His behavioural disturbance has progressed, requiring compulsory detention under the Mental Health Act.
wasting and weakness in some cases. True myopathy is confined to the McLeod syndrome in which a cardiomyopathy, seen in around two thirds of patients, is a common cause of death.

- Splenomegaly and hepatomegaly can occur.
- The McLeod syndrome is distinguished by the presence of a generally well-compensated haemolytic anaemia, and weak expression of Kell antigens on red blood cells: the Kell group of erythrocyte antigens is the third most important blood group system after the ABO and rhesus systems.

Neuroimaging reveals abnormalities in the basal ganglia in both conditions, with atrophy and signal change affecting the caudate, putamen and globus pallidus. SPECT and PET scanning indicate reduction of blood flow, glucose utilization and dopamine-receptor binding in the striatum.

Post-mortem studies confirm the impression that these disorders target the basal ganglia, and provide no evidence for direct involvement of the cerebral cortex.

The affected genes have now been identified. Choreoacanthocytosis is an autosomal recessive condition, while the McLeod syndrome is X-linked. The gene implicated in the former, on chromosome 9, codes for a protein known as "chorein", which is expressed widely in human tissues. The numerous mutations described in the chorein gene may cause acanthocytosis by affecting the passage of proteins into the red cell membrane. The mechanism by which neurones are lost from the basal ganglia is unknown, but likely to be due to a local effect of the gene in the striatum rather than to red cell acanthocytosis per se. In the McLeod syndrome the affected gene, XK, on the X chromosome, codes for the XK protein which anchors Kell antigens in the red cell membrane. Local expression of the gene in brain, nerve and muscle, rather than red cell acanthocytosis per se, probably accounts for the neurological manifestations.

Hypo- and abeta-lipoproteinaemia
Abeta-lipoproteinaemia is characterized by a spinocerebellar syndrome, fat malabsorption, and acanthocytosis in the peripheral blood (Rampoldi et al. 2002). The neurological features include progressive peripheral neuropathy with dorsal column sensory loss, cerebellar signs and retinitis pigmentosa. Fat malabsorption is
suggested by failure to thrive and steatorrhea. Triglyceride and cholesterol levels, and levels of fat-soluble vitamins, are very low. Serum apolipoprotein B is absent. Onset is usually in childhood but can occur in young adults. Though rare, it is important to recognise the condition because neurological deterioration can be prevented by treatment with Vitamin E. Hypo-abeta-lipoproteinaemia has a similar though more variable and generally milder phenotype, but a distinct mode of inheritance and genetic basis. The neurological features also respond to Vitamin E.

Abeta-lipoproteinaemia is an autosomal recessive disorder (Rampoldi et al. 2002). It is caused by mutations in a gene on chromosome 4q22–24 that codes for ‘MTP’, a microsomal triglyceride transfer protein. Hypo-beta-lipoproteinaemia is an autosomal codominant condition generally caused by mutations of the apolipoprotein B gene itself on chromosome 2p23–24: heterozygotes are usually asymptomatic. The acanthocytosis associated with both disorders is thought to be due to an abnormal lipid composition which lowers the fluidity of the red cell membrane.

OTHER NEUROLOGICAL DISORDERS ASSOCIATED WITH RED CELL ACANTHOCYTOSIS
Several other, even rarer, neurological disorders have been associated with acanthocytosis (Rampoldi et al. 2002). These include a recently described autosomal dominant disorder associated with chorea, dementia, parkinsonism, acanthocytosis and ubiquitin-positive cortical inclusion bodies (Walker et al. 2002); some cases of Hallevorden-Spatz disease, which is now known to be due to mutations in the panthothenate kinase gene; and the HARP syndrome (hypo-prebeta-lipoproteinaemia, acanthocytosis, retinitis pigmentosa, pallidal degeneration).

AND SO?
These syndromes are all uncommon, though of course significant to those who suffer from them. Chorea-acanthocytosis and the McLeod syndrome are mimics of Huntington’s disease; abeta- and hypo-beta-lipoproteinaemia are treatable inherited disorders. Diagnosis requires a diligent hunt for acanthocytes by a forewarned and interested haematologist. This family of disorders illustrates the extraordinarily rapid progress of neurogenetics, which has brought order to a confusing area of neurology by identifying almost all the responsible genes within the last decade, although a good deal more work is required to trace every link in the chain from gene to behaviour. These conditions defy the misleading distinctions we all tend to draw between psychiatric, neurological and general medical disorders. In a similar vein, they highlight the complex functions of the basal ganglia: the caudate, putamen and globus pallidus contribute to cognitive and behavioural as well as to motor processes (Cummings 1993). Besides chorea, dystonia and parkinsonism, striatal pathology is apt to give rise to personality change, depression, mania, obsessive-compulsive disorder and subcortical dementia.

CONCLUSIONS
- Acanthocytes are very easily confused with echinocytes (burr cells) in the peripheral blood – haematologists need to be asked specifically to distinguish them.
- Acanthocytes are associated with a number of rare neurological disorders, particularly choreoacanthocytosis, McLeod syndrome and hypo and abeta-lipoproteinaemia.
- Hypo- and abeta-lipoproteinaemia respond to vitamin E.
- McLeod syndrome and choreoacanthocytosis are easily confused with other disorders such as Huntington’s disease and have genetic implications for affected families.
- Disorders of the basal ganglia – the primary site of pathology in choreoacanthocytosis and McLeod syndrome – can present with cognitive and psychiatric symptoms and signs, as well as with motor features.

REFERENCES