Copper deficiency is an increasingly reported but under-recognised cause of blood dyscrasias and neurological dysfunction. It can present to the neurologist as a myeloneuropathy that resembles subacute combined degeneration of the cord both clinically and radiologically. We describe a patient who presented initially to the haematologists with a myelodysplastic syndrome but went on to develop a myeloneuropathy triggering the recognition of copper deficiency as the unifying diagnosis. Copper supplementation completely reversed the haematological disorder and stopped his neurological deterioration.

**Case report**
A 69-year-old retired clergyman, who had undergone a partial gastrectomy for a duodenal ulcer in the 1960s, presented in late 2004 to his GP with fatigue. He was found to have a normocytic anaemia (Hb 7.7g/dl, MCV 88.5fl) and leukaopenia (white cell count 1.1*10^9/l) in the presence of a normal platelet count and normal B12, folate and ferritin levels. He was referred to the haematologists at his local hospital where a bone marrow biopsy showed dyserythropoiesis with vacuolated erythroid precursors, left shift of granulopoiesis, and normal megalakaryocytes. Perl’s stain demonstrated normal iron stores and ring sideroblasts. A diagnosis of myelodysplastic syndrome was made.

He was managed supportively over the next 18 months with recurrent red cell transfusions, as required. His white cell count remained low, with neutrophils never exceeding 0.9*10^9/l (Figure 1).

His white cell count remained low, though the red cells were now macrocytic (MCV 103fl). B12 and folate levels were again normal. ESR was 74. CSF was acellular with a protein of 0.4g/l and no detectable oligoclonal bands. Antinuclear antibodies, antineuronal antibodies and serology for syphilis and human T-cell lymphoma viruses. CSF was acellular with a protein of 0.4g/l and no detectable oligoclonal bands.

Further neurological deterioration occurred over the next 6 months. By this time, the patient’s numbness had ascended to the level of the mid-chest and to the elbows. He complained of feeling increasingly unsteady on his feet, and was having frequent falls, particularly at night. He was only able to mobilise a few steps with assistance. His sphincter function remained normal.

On examination, tone in the upper limbs was normal. In the lower limbs, tone was markedly increased with sustained clonus at both ankles. There was mild power loss (MRC 4–4) in all limbs in a pyramidal distribution. Upper limb reflexes were diminished, while lower limb reflexes were pathologically brisk with bilateral extensor plantar responses. Sensation to light touch and pin prick was diminished up to the waist, with a fl ank-sparing extension to a level of T5, and in a glove pattern up to the elbows. Vibration sense was absent to the sternum. Proprioception was markedly impaired to the proximal interphalangeal joints in the upper limbs, and to the ankles in the lower limbs. There was pseudoseptale thetkis and sensory ataxia. He was able to stand only with support.

The patient was admitted to the regional neurosciences centre for further investigation. Haemoglobin and white cell count remained low, though the red cells were now macrocytic (MCV 103fl), B12 and folate levels were again normal. ESR was 74. CSF was acellular but contained mildly high protein levels at 0.53g/l. Nerve conduction studies showed normal amplitudes, conduction velocities and distal latencies. MRI brain was normal, however MRI of the spinal cord now showed a longitudinally extensive high T2 signal lesion in the dorsal cord (Figure 2).

The clinical and radiological findings were reminiscent of subacute combined degeneration of the cord, and although B12 levels had been repeatedly normal, functional B12 deficiency was considered possible and...
B12 replacement was initiated. Concurrently, a literature search using the terms ‘subacute combined degeneration’ and ‘myelodysplasia’ led to case reports of copper deficiency. The patient’s copper and caeruloplasmin levels were found to be undetectable, thus confirming a copper deficiency state. Zinc levels were slightly high at 24µmol/l (normal 9-19).

Copper oral supplementation equivalent to 8mg of elemental copper per day resulted in prompt haematological recovery (Figure 1) and cessation of neurological deterioration, but without functional improvement to date (now eight months into therapy).

Discussion
Copper is a micronutrient essential to the function of nervous system and bone marrow as a prosthetic group in many key enzymes, including cytochrome oxidase (respiratory chain), superoxide dismutase (antioxidant defence), dopamine β-hydroxylase (catecholamine synthesis) and methionine synthase (folate metabolism). It is contained in many common foodstuffs including meat, fish, nuts, seeds and legumes, and pure dietary deficiency is rare. Absorption occurs in the stomach and proximal duodenum. While the bulk of absorbed copper is excreted into the bile, a small proportion is incorporated into caeruloplasmin for transport to extrhepatic tissues.

Despite the recognition of copper deficiency as a cause of anaemia and neutropenia for over 30 years,1 there is still limited awareness of copper deficiency as a cause of cytopenias. The anaemia is most commonly macrocytic, but may be normocytic or microcytic. Thrombocytopenia is rare.2 Bone marrow assessment often shows morphological characteristics suggestive of myelodysplastic syndrome, such as ring sideroblasts and nuclear maturation changes of erythroid and myeloid precursors. As a rare and poorly recognised cause of sideroblastic myelodysplastic syndrome, copper deficiency is not listed as a differential in many current haematology textbooks3 and the neurologist seeking such cases may be the first to make the connection.

The commonest neurological manifestation of acquired copper deficiency is a myeloneuropathy with sensory ataxia. Spinal cord MRI typically shows increased T2 signal in the dorsal cord.4 The syndrome is thus clinically and radiologically similar to subacute combined degeneration of the cord seen with vitamin B12 deficiency, and both conditions may potentially coexist.5 Copper deficiency myelopathy was first described in 2001,6 and a total of 36 cases have been reported to date.7,8 It predominantly affects females (F:M 3.6:1), with age at presentation ranging from 36 to 78 years. The most frequent cause is previous upper gastrointestinal surgical procedures with implications in almost half the cases.7,9 Whilst the majority of these cases had a remote history of partial gastrectomy for peptic ulcer disease, three of them occurred following bariatric gastric surgery. The increasing use of such bariatric interventions may leave a growing number of patients at risk of copper deficiency in the future.

Further causes include malabsorption7 and zinc overload.10-14 Despite hyperzincaemia, no external source of excess zinc may be evident. Zinc induces the expression of the intracellular chelator metallothionein in enterocytes. Copper has a higher affinity for metallothionein than zinc, and thus displaces zinc from metallothionein. Copper remains bound in the enterocytes which are then sloughed into the lumen and eliminated (a mechanism exploited when using zinc as a treatment for Wilson’s disease). Despite adequate investigation, approximately 25% of cases remain idiopathic.1

Treatment involves stopping any excessive zinc intake, and administering copper supplements. No studies have addressed the most appropriate dose, route and duration of supplementation. Several previous cases were treated with oral supplements equivalent to 2mg of elemental copper per day. A relapse was reported with this dose in a patient with a past history of gastric surgery,1 and we therefore opted for a higher dose. Although deficiency is usually due to impaired absorption, oral supplementation is effective, and is more practical than parenteral supplements.

Haematological abnormalities resolve rapidly and completely, while the neurological decline can usually only be halted but not reversed. Where neurological recovery occurs, it tends to be limited to a subjective improvement in sensory symptoms.10

Conclusion
Copper deficiency represents a rare but treatable cause of neurological disability, which should be considered in individuals presenting with undiagnosed myelopathy. The coexistence of haematological abnormalities and a history of gastric surgery may suggest the diagnosis.

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References