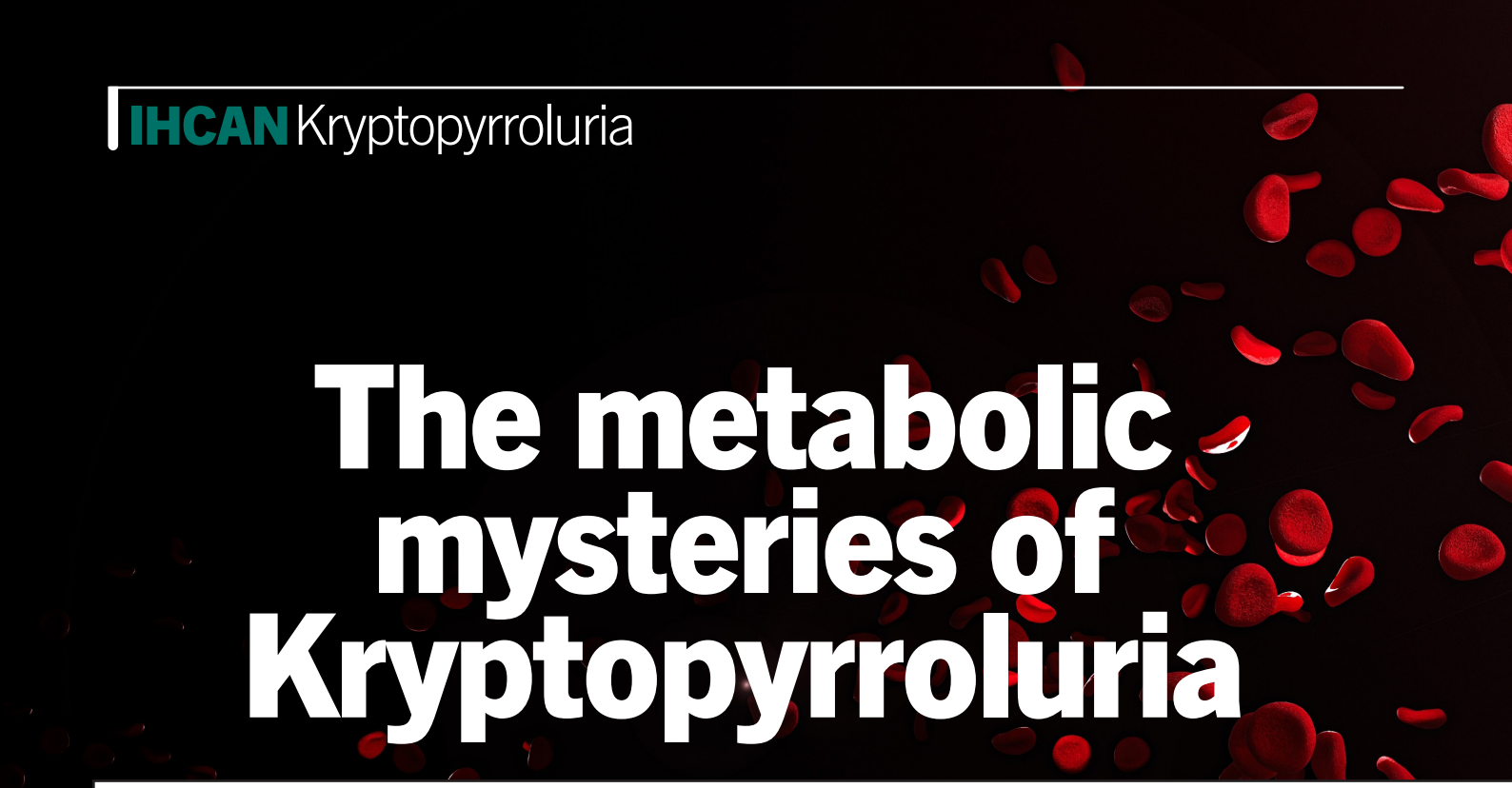


The metabolic mysteries of Kryptopyrroluria

Practically unknown in the UK, Kryptopyrroluria can be a hidden cause of nutrient deficiencies and an unsuspected complicating factor in conditions such as Lyme disease and heavy metal toxicity. **GILIAN CROWTHER**, Director of Research at the Academy of Nutritional Medicine, explains.

Kryptopyrroluria (KPU) is a metabolic disorder that revolves around a glitch in the production and breakdown of haem, the iron-containing part of haemoglobin.

Pyrroles are the "scaffolding" holding together porphyrins, and porphyrins form the ring-like structure that holds iron in the centre of haem.

"Krypto" means "hidden" in Greek: the pyrroles are hidden because they cannot easily be detected, and "uria" means excreted in the urine.

This byproduct of haemoglobin synthesis - 2,4 dimethyl-3-ethylpyrrole - commonly binds to B6 and then to zinc, building an insoluble complex that is flushed out instead of being properly utilised. As Dr Dietrich Klinghardt, MD, PhD, once put it, sufferers are "peeing out an improperly synthesised haem molecule".

This condition was discovered back in the early 1960s when Drs Abram Hoffer, Donald Irvine and Carl Pfeiffer detected a compound in the urine of psychiatric patients that Hoffer termed the "Mauve Factor" due to its appearance on the chromatograms used in its analysis. (1)

Dr Pfeiffer found that a considerable proportion of patients labelled schizophrenic were suffering from KPU, and that targeted support of their broken metabolic pathways could often relieve the condition. A quotation from his 1988 book *Nutrition and Mental Illness* (2) reads: "Approximately 15-30% of 'schizophrenics' have pyroluria".

(Various different terms have been used over the years: "The Mauve Factor", Malvaria, Pyrroluria, Pyroluria, KPU (Kryptopyrroluria) and HPU (Hemopyrrollactamuria); HPU is characterised by a disorder in the production of haem, KPU by a disorder in the breakdown of haem: the physiological outcomes and therapeutic approaches are the same.)

KPU is still practically unknown in the UK after more than six decades, but a large body of expertise has grown around it, particularly in Germany. There appears to be both a primary and a secondary form. The primary form - thought to be genetic - is said to manifest as the excessive production of pyrroles that are excreted in urine (3), rather than the normal quantity eliminated in the stool, as is usual in the turnover of haem. The secondary form is acquired, and greatly increases under stress - whether physiological or psychological, particularly in chronic conditions.

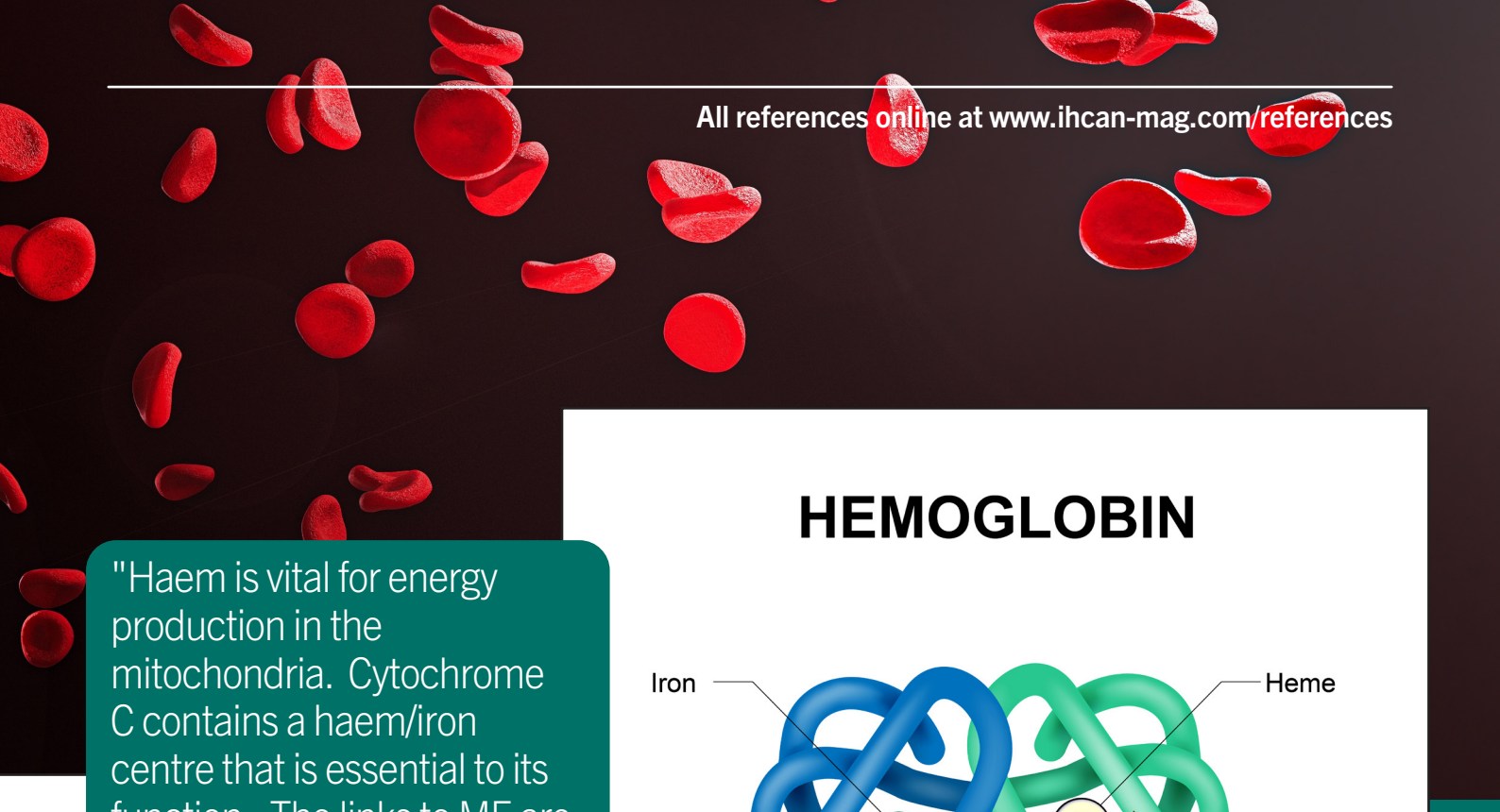
To quote from a seminal 2017 article by Dr Klinghardt and Scott Forsgren (4): "Dr. Klinghardt has found the incidence of KPU in Lyme disease to be 80% or higher; in patients with heavy metal toxicity (lead, mercury, aluminium, cadmium, and others) over 75%; and in children with autism over 80%". (5)

It is worth noting the numbers involved, just to get a sense of the potential scale of the issue. One typical red blood cell contains about 270 million haemoglobin molecules, each carrying four haem groups, each with four pyrroles (6). The calculations reveal that just one erythrocyte contains over 4 billion pyrroles - while we produce 2-3 million red blood cells every second, or should do (7). A metabolic catastrophe in the making if this goes wrong...

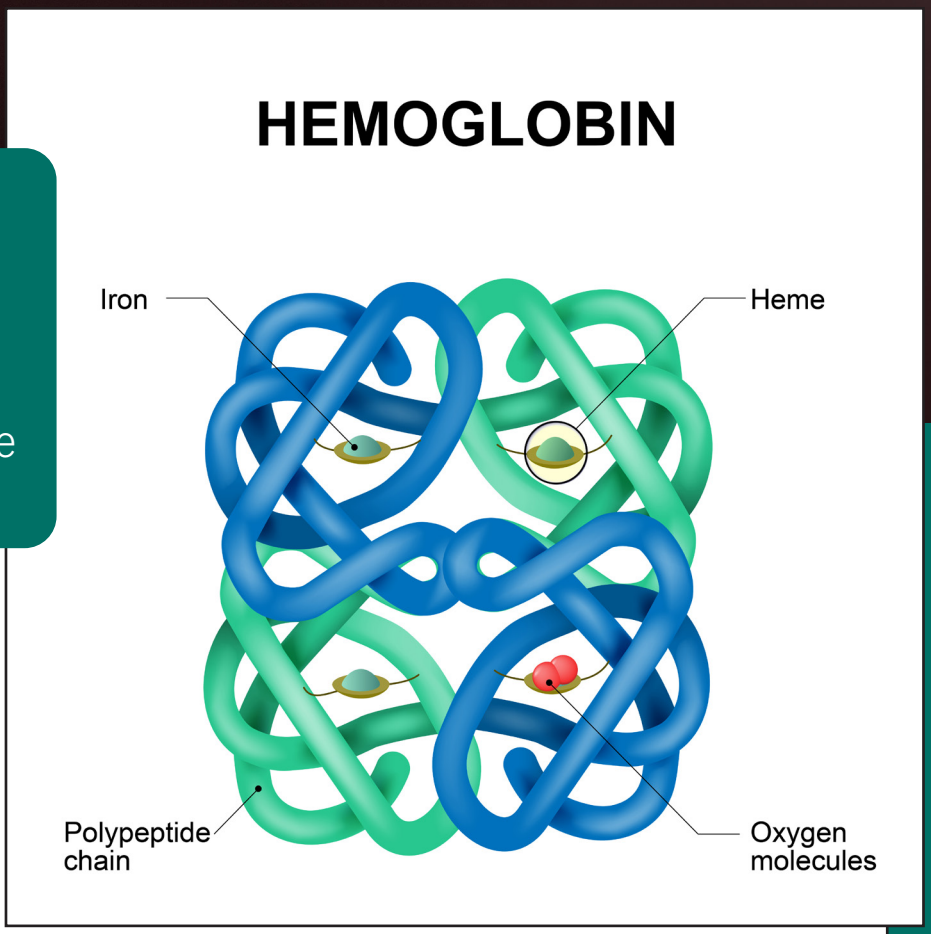
Two-pronged ramifications

The ramifications of KPU are significant along two key axes. First is the loss of nutrients due to the aberrant pyrroles. The either excessive or dysregulated pyrroles lead to the loss of important nutrients - mainly B6 and zinc, as mentioned. Their deficiency can impair the metabolism of other nutrients. To take omega-6 as an example: every step in the downstream pathway of alpha-linolenic and linoleic acid - whether delta-6- or delta-5-desaturase, or elongase - requires B6 (the first two need zinc as well), and the desaturases tend to give preference to the omega-3 pathway (8), hence the O6 deficiency when the pathway is anyway under pressure. Deficiencies of manganese, biotin, chromium and, more rarely, magnesium and even calcium have also been reported.

The second axis is the improper formation of haem. Why? B6 is essential for the first step in haem synthesis, aminolevulinic acid synthase: "Haem biosynthesis starts in mitochondria with the condensation of succinyl Co-A from the citric acid cycle and an amino acid glycine. They combine to produce a key haem intermediate, 5'-aminolevulinic acid (ALA) in mitochondria catalysed by the



"Haem is vital for energy production in the mitochondria. Cytochrome C contains a haem/iron centre that is essential to its function...The links to ME are starkly evident".



pyridoxal phosphate-requiring (vitamin B6) enzyme, aminolevulinic acid synthase (ALAS). This reaction is the rate-limiting step in the pathway" (9). With the loss of B6, haem production will be compromised in an ever-growing vicious cycle. Plus the pyrroles that hold haem together are failing in their function anyway, in the most common acquired form, which will impair haem production.

Consequences of axis 1: B6 and zinc deficiency

So what does it mean to be depleted of these specific nutrients? Let's take the prime ones: B6 and zinc (and sometimes manganese) being flushed out with the pyrroles.

• **Physical appearance:** Excessive pyrrole excretion via the kidneys may be reflected in dark rings around the eyes, eyes sunk deep into their sockets; zinc deficiency can lead to soft gums, striae on the skin similar to stretch marks, white spots on the nails (leukodynia), sometimes hair loss, acne, eczema, dandruff, and poor dental enamel (10).

• **Neurological issues**, often labelled psychiatric: Memory and concentration difficulties, problems with short-term memory, "brain fog", poor dream recall (B6 dependent), low mood, fear, panic attacks, withdrawal from social activities, hallucinations, apparent schizophrenia/psychosis, perhaps ADHD. Lack of B6 and zinc metabolism can all contribute by causing low serotonin, adrenalin and dopamine levels. Animal experiments have also shown that injecting rats, cats and guinea pigs with free pyrroles leads to severe neurological disorders (11).

• **Thyroid disorders:** hypothyroidism/Hashimoto's thyroiditis, because tyrosine is key for the thyroid, and zinc deficiency can lead to hypochlorhydria, stymieing the breakdown of protein in the stomach. And "B6 and its derivative, pyridoxal 5'-phosphate (PLP), are essential to over 100 enzymes mostly involved in protein metabolism" (12)

• **Immune disorders:** as antibodies are formed from amino acids, the production of which will be impaired by the same factors as just mentioned.

• **Collagen/connective tissue disorders:** "Yes pyroluria can be a factor in many tendon and joint issues (and ankle/wrist/thumb) pains as it affects all types of collagen. Zinc, B6, EPO and manganese are all needed" (Dr Trudi Scott: https://www.everywomanover29.com/blog/pyroluria-questionnaire-from-the-antianxiety-food-solution/).

Cartilage consists of collagenous connective tissue, which requires all three KPU suspects - B6, Zn, and Mn. Manganese is especially essential for the synthesis of hyaluronic acid, glucosaminoglycans and chondroitin sulphate. It has even been suggested that KPU could be connected with Ehlers Danlos Syndrome (EDS), as hyperextension of the joints (hEDS) can be due to manganese deficiency. Osteocytes also require B6, Zn and Mn (as well as Mg and vitamin D).

• **GI disorders:** Protein maldigestion can arise due to lack of Zn for HCl, and aversion to meat because the conversion of muscle protein to our own protein is B6-dependent.

• **Histamine issues/exacerbation of MCAS**, because diamine oxidase (needed to break down histamine) requires the cofactors B6 and zinc.

• **Hypoglycaemia**: The conversion of protein and carbohydrate stores into glucose (gluconeogenesis) is B6-dependent.

Dr Dietrich Klinghardt discusses "Kryptopyrroluria (Pyroluria) - Lyme Induced Autism": watch at https://www.youtube.com/watch?v=THZhANfFnyY

• **Reproduction issues**: B6 and zinc are vital for fertility. PCOS, a leading cause of infertility, is complicated by Zn and B6 deficiency. Oogenesis is reliant upon zinc, as are spermatogenesis and foetal development.
• **Methylation issues**: the synthesis of B12 can be impaired because aminolevulinic acid derived from ALAS (a pathway broken in the vicious cycle, see above) is also the universal precursor molecule involved in tetrapyrrole synthesis, and B12 is a tetrapyrrole. B12 deficiency in turn has consequences for the methylation cycle (as well as numerous neurological sequelae).

Consequences of axis 2: Haem depletion

As if the above wasn't enough, we need to consider the implications of throttled haem production.
• **Oxygen deficiency:** without haem you can't make haemoglobin, which means the erythrocytes are impaired in their ability to carry iron for transferring oxygen to the tissues. Of course this will not be a global issue, but the reduction is likely to cause a degree of hypoxia, and can eventually result in anaemia.
• **Energy:** closely linked to this, haem is vital for energy production in the mitochondria. Cytochrome C contains a haem/iron centre that is essential to its function. During the electron transport process, this haem iron interconverts between the Fe3+ and Fe2+ oxidation states, which allows electrons to be accepted and donated - without which the electrons can't reach ATP synthase to create mitochondrial ATP, our key energy currency. The links to ME are starkly evident.
• **Apoptosis:** this is vital for cell recycling and sloughing off cancerous cells. Cytochrome C is also crucial for triggering apoptosis via the protein P57. If the action of cytochrome C is disabled, apoptosis will be impaired too.
• **Detoxification:** Cytochrome P450 detoxification enzymes, crucial for Phase I detoxification, all have haem at their centre and cannot work without it, so every form of detoxification will be impaired. Environmental toxins build up as a result, medications cannot be properly metabolised and intolerances build up. One possible result: multiple chemical sensitivity (MCS).
• **Myoglobin** contains a haem group, so this protein in the cardiac and skeletal muscles will be weakened, contributing to musculoskeletal symptoms, pelvic instability, and joint pain.

This is not the full picture, as haem exists in every single cell in the body (13), but gives an impression of KPU's broad potential reach into many familiar disorders. Especially since the resultant oxygen/ATP deficiency will inevitably have a knock-on effect on mitochondrial function, which is so firmly intertwined with every aspect of health (14).

Is copper a huge missing piece in the puzzle?

The usual therapies, as we will see in part two, usually focus on repleting the nutrients known to be most frequently lost in the urine unmetabolised – supraphysiological doses of B6, zinc and other supportive cofactors. But could there be a deeper underlying cause? A missing puzzle piece that has led to the upset metabolism in the first place?

It has long been considered that the likely cause of pyrroluria in both primary and secondary KPU could be a defect in haem metabolism in the inner mitochondrial membrane (15). It was mentioned at the outset that there are six enzymatic steps in haem metabolism. Three lie in the mitochondria. And the last is ferrochelatase. Ferrochelatase is copper-dependent, a fact identified by Wagner and Tephly as far back as 1975 (16) and further corroborated by Prof Bruce Ames et al in 2005: "Today we know that copper stimulates the activity of ferrochelatase" (17). Some of the excellent German literature (18), as well as more recently the detailed research around copper of the Root Cause Protocol (19), posit that a deficit in bioavailable copper may have disabled ferrochelatase.

This would certainly explain the failure to synthesise haem properly in the mitochondria, leading to the disuse of pyrroles and the resulting KPU cascade.

In the "Therapeutic approaches" section next month we will discuss the therapeutic approaches often recommended for this complex condition and look at how to address a lack of bioavailable Cu, the importance of which has already been examined in *IHCAN* in October 2024 and January 2025. IHCAN

About the author

GILIAN CROWTHER, MA (Oxon), FBANT, mANP, mNNA, CNHC reg., is a fully qualified Nutritional Therapist and Naturopath specialising in complex multisystem disorders. Her key focus is on infectious pathologies and mitochondrial dysfunction.

She studied complementary therapy in Germany for many years before completing her training in the UK. She has been a senior member of the Academy of Nutritional Medicine (www.aonm.org) since 2010, and is their Director of Research. She is a committee member of the General Naturopathic Council (GNC) as well as the British Society for Ecological Medicine (BSEM).

Gilian has featured in *IHCAN* mag before, spoken at an IHCAN Summit, and was runner-up for the "Outstanding Contribution to the Community" Award in 2018.