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This Week's Citation Classic®

De Matteis F & Rimington C. Disturbance of porphyrin metabolism caused by griseofulvin in mice. *Brit. J. Dermatol.* 75:91-104, 1963.
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A marked disturbance of porphyrin metabolism in mice follows administration of griseofulvin in the diet. The disorder is characterized primarily by accumulation of protoporphyrin in the liver but, after a few days of treatment, increased protoporphyrin is also found in the circulating red blood cells. [The *SCI*® indicates that this paper has been cited in over 125 publications.]

A Model of Porphyrin

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We were first alerted to the possibility that griseofulvin might cause a disorder of porphyrin metabolism by the experiments of Weston Hurst and G.E. Paget.[1] They showed that mice given griseofulvin for long periods of time developed hepatomata and biliary cirrhosis, with deposition of a brown pigment in their intrahepatic biliary system. Preliminary experiments indicated that the pigment was mainly protoporphyrin, and this set us investigating the effect of griseofulvin in more detail. Our work showed that orally administered griseofulvin caused, within 24 hours, massive faecal excretion of protoporphyrin: The observed picture indicated a porphyria of hepatic type, with liver accumulation of protoporphyrin as the most characteristic feature. However, we were surprised to find that, after several days of treatment, a marked increase in protoporphyrin was also seen in the peripheral red blood cells, a mixed hepatic-erythropoietic distribution reminiscent of that seen in erythropoietic protoporphyria of man. By employing [2 —^{14}C]-glycine as a precursor of protoporphyrin *in vivo*, we showed that the vast majority of faecal and hepatic protoporphyrin must have originated in the liver through a marked increase in its rate of synthesis, but the source of the erythrocyte protoporphyrin was not determined. In a subsequent paper,[2] increased faecal and erythrocyte protoporphyrin was also found in patients given griseofulvin for treatment of fungal infection, although the increases were only small and a possible role of the tinea infection itself could not be excluded.

One of us (FDeM) has maintained a vivid recollection of those experiments to this day for more than one reason. It was his first investigation carried out after leaving clinical medicine for experimental research in toxicology, and it was during that period that Dr. Jennifer Wildy, a young biochemist working in the department, became his wife. Personal recollections aside, those were the days when increased porphyrin biosynthesis and porphyrin underutilization were still debated as alternative mechanisms for porphyrin accumulation in porphyria, before the importance of induction of ALA-synthase[3] and of ferrochelatase inhibition[4] came to be appreciated and the role of *N*-methyl protoporphyrin in inhibiting ferrochelatase was discovered.[5] We now know that griseofulvin and similarly acting drugs convert the haem of cytochrome P-450 into *N*-methyl protoporphyrin,[6] a powerful inhibitor of ferrochelatase; the inhibition of this enzyme is then responsible for a block in the metabolism of protoporphyrin, while the secondary, compensatory, stimulation of ALA- synthase leads to marked accumulation of protoporphyrin. Porphyria, therefore, results from a combination of increased biosynthesis and underutilization of porphyrins.

There are two main reasons that have contributed, in our opinion, to this paper being cited. First, it provided some of the original findings on which the more recent advances in mechanisms have been based. Secondly, it offered for the first time a partial experimental model for the erythropoietic protoporphyria of man, so that disorders of liver structure and symptoms of photosensitivity, which are shared by the two conditions, could be investigated experimentally. An additional reason may have been the association, after griseofulvin feeding to mice, of porphyria and liver cancer.

1. **Hurst E W & Paget G E.** Protoporphyrin, cirrhosis and hepatomata in the livers of mice given griseofulvin. *Brit. J. Dermatol.* 75:105-12, 1963. (Cited 80 times.)
2. **Rimington C, Morgan P N, Nicholls K, Everall J D & Davies R R.** Griseofulvin administration and porphyrin metabolism. *Lancet* 2:318-22, 1963. (Cited 100 times.)
3. **Granick S.** The induction *in vivo* of the synthesis of δ-aminolevulinic acid synthetase in chemical porphyria: a response to certain drugs, sex hormones and foreign chemicals. *J. Biol. Chem.* 241:1359-75, 1966. (Cited 755 times.)
4. **Lochhead A C, Dagg J H & Goldberg A.** Experimental griseofulvin porphyria in adult and foetal mice. *Brit. J. Dermatol.* 79:96-102, 1967. (Cited 15 times.)
5. **De Matteis F & Gibbs A H.** Drug-induced conversion of liver haem into modified porphyrins. *Biochem. J.* 187:285-8, 1980. (Cited 35 times.)
6. **De Matteis F, Gibbs A H & Holley A E.** Occurrence and biological properties of *N*- methyl protoporphyrin. *Ann. NY Acad. Sci.* 514:30-40, 1987. (Cited 5 times.)

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