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CLINICAL ARTICLES

PORPHYRIA AND PHOTOSENSITIVITY

By

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The porphyrias may be described as metabolic disorder where excess porphyrins are produced. Photosensitivity of the skin (and eyes sometimes) occurs when these substances become deposited in these organs. The porphyrins are of course intermediate products of the biosynthetic pathway of haems such as haemoglobin, myoglobin. catalase, the cytocromes, etc. In passing, one can mention that cobalamin (Vitamin B 12) and chlorophyll, are also porphyrins, containing cobalt and magnesium respectively instead of iron as in the haems.

In the human the porphyrins normally formed during haem biosynthesis are uroporphyrins III, coproporphyrins III and protoporphyrins IX, in that order. See Fig. 1. A very small or negligible amount of uro–and coproporphyrin of Isomer

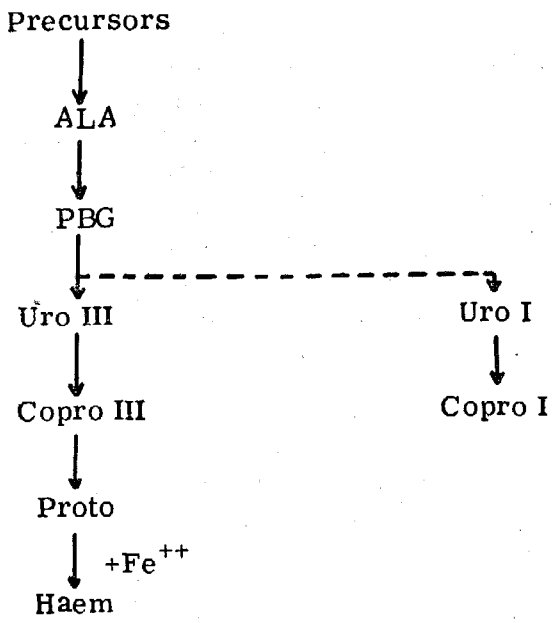

Fig. 1. Simplified scheme illustrating probably normal biosynthetic pathway for porphyrins and haem. See text for details. (From Magnus, I. A. & Wood, M. (1971) Trans. St. John Hosp. Derm. Soc., **in the press,** by kind permission of the Editor)

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I series is also normally formed,but has no physiological role. Precursors to the true porphyrins in the biosynthetic pathway are delta-aminolaevulic acid (ALA) and porphobilinogen (PBG). Small quantities of these porphyrins and their precursors are normally excreted in the urine and stool. All are formed enzymatically and ALA production is controlled by the important enzyme delta-aminolaevulic acid synthetase (ALA-S), which seems to control the overall rate of porphyrin production. There is evidence that, in most of the natural poryhyrias, and in some experimental porphyrias in animals, this enzyme is overactive. There is also some evidence of faults in other enzyme systems in certain of the clinical porphyrin syndromes, but much work remains to be done to substantiate and clarify this.

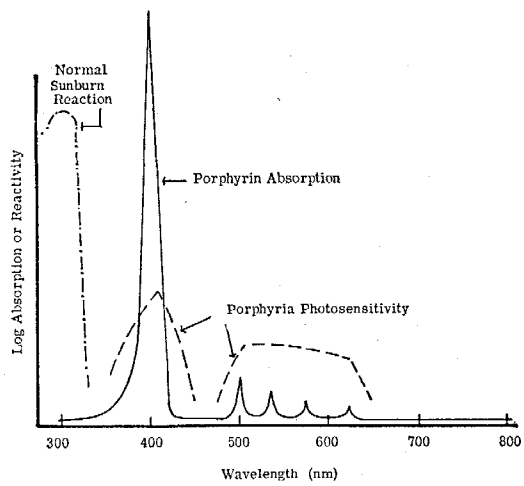
The human porphyrias may be divided into two groups depending on whether the major pathology appears to be in the liver or in the bone marrow The *erythropoietic* porphyrias include the generally very severe Gunther's Disease, for which in India there is a special interest, as there seems to be more patients with this disease in this coutry than anywhere else in the world. The less severe but still potentially mortal erythropoietic protoporphyria, on the other hand, is much commoner in European stock and as yet has not been seen in Indians. The *hepatic porphyrias*, especially the clinical picture known as *porphyria cutanea tarda* (PCT), is relatively common all over the world and India is no exception. However India again has made an interesting contribution to this condition. PCT normally only starts in middle or late adult life, but Indian patients starting the disease in childhood are well known (Bhutani,1971). PCT is commonly associated with alcoholism, less often with other hepatoxic substances, rarely with virus hepatitis. It may presumably arise as a complication of infective hepatitis, or something similar, when it occurs in young patients. *Porphyria variegata* (VP) is more or less world wide in distribution and a very common hepatic porphyria in the South African of European origin. This may be conveniently considered clinically as a combination of the cutaneous features of PCT and the systemic episodes of *acute intermittent porphyria* (AIP). This last disease, AIP, is, of course, not associated with cutaneous symptoms. But it is important that our medical and surgical colleagues be encouraged to let us dermatologists see their AIP cases so that VP can be properly excluded. A classfication of the porphyrias is shown in Table I and the clinical features of some of the more important diseases of interest to dermatologists are summarized in Table II to V. It is worth particularly emphasising that all the porphyrias are serious conditions and that this also applies to EPP, where the cutaneous lesions are so slight, but where nevertheless cholelithiasis may be a complication and a fatal outcome from cirrhosis occur.

The obvious basis for explaining photosensitivity in the skin in porphyria would be to blame it on porphyrins and to their being present in the skin. Porpyhrins are well known photosensitizers of the "photodynamic" type, that is to say they are oxidative photosensitizers with which one reactant is molecular oxygen. The

substrate oxidized can be of great variety, including biological materials such as amino acids, lipids, DNA, proteins. Or micro-organisms, such as bacteria, or cells in tissue cultures may also be used (Allison et al., 1966).

It can now be shown that, for porphyric photosensitivity to occur, the substrate, be it skin or whatever, the sensitizing wavelengths of light must contain wavelengths that the porphyrin molecule absorbs. This can be shown to be chiefly at about 400nm (violet light) and to a lesser extent at about 500 to 600nm (green-yellow light). Ultraviolet light and in particular normal sunburn radiation (around 300nm) are not absorbed and, as it will be seen, play no part in the specific photosensitization process. Fig. 2 shows the kind of action spectrum, the

Fig. 2. The approximate normal **action** spectrum (_____) for sunburn, showing peak near 300nm. The **absorption** spectrum of prophyrin (continuous line) showing chief peak at 400nm. A typical **action** spectrum (_____) for skin photosensitivity in a porphyric patient, showing major sensitivity at 400nm, lesser at 500-600nm. The prophyric patient also shows the normal reaction at 300nm. (Figure by kind permission of the Honorary Editors of the Proc. Roy. Soc. Med. (1968) **61**, 197.)



wavelengths active, that can be expected in the skin. Similar results are found with tissue culture treated with porphyrin (Allison et al., 1966).

The next point to make is that photosensitization by porphyrins is an oxidative process requiring the presence of molecular oxygen. This can be shown readily enough in the use of tissue cultures to which traces of porphyrin are added and then irradiated with 400nm light. It can also be shown that porphyric skin lesions due to light require oxygenated blood to be flowing in the skin during irradiation, if a lesion is to be provoked This is done by showing that there is no response in porphyric skin if it is hypoxaemic, e.g. by constricting the arm with a tourniquet during irradiation with 400nm.

I would like next to turn briefly to the treatment of some of the porphyrias; here dermatologists have made a special contribution. This is in the treatment of PCT by repeated venesection, first introduced by Ippen (1961). How this treatment

works is not clear, but that it is effective is abundantly so. Biochemical and clinical remissions may be obtained for as long as a year in many instances. Another promising line of treatment has been developed by dermatologists working with a bacteriologist; they have obtained encouraging results with an oral light screen, beta-carotenoid (Mathews-Roth et al., 1970). This substance screens rather well against 400nm radiation and the usually slight orange tint imparted to the skin by it is quite acceptable in the white skinned and would presumably be even less detectable in the Indians. It is worth noting that porphyric photosensitivity is not helped by the usual sunscreen preparations that absorb in the normal sunburn range around 300nm. This is to be expected. It is also worth noting that the built-in solar screen that the Indian skin has, melanin, is not so very effective against 400nm radition, as in porphyria, as it is against 300nm radiation, as in sunburn.

Many problems still remain in understanding the porphyrias. This is especially so in elucidating the details of the metabolic pathways in the disease mechanisms. Progress has been somewhat slow in this difficult field. Much also needs to be known about the dermatological features and mechanisms of the porphyrias. For instance we know nothing about the mechanism of hirsutes or of the increased susceptibility towards minor mechanical trauma that are such common symptoms. There is much room for further work.

CLASSIFICATION OF THE PORPHYRIAS

Erythropoietic :
1. Congenital (erythropoietic) Porphyria *or* Günther's Disease.
2. Erythropoietic Protoporphyria (EPP).
3. Erythropoietic Coproporphyria

Hepatic :
1. *Acute intermittent Porphyria* (Swedish)
2. Porphyria cutanea tarda (PCT) } hereditary
3. *Variegate Porphyria* (South African Genetic)
4. Toxic or symptomatic
5. Hereditary Coproporphyria.

CONGENITAL (ERYTHROPOIETIC) PORPHYRIA OR GUNTHER'S DISEASE

Onset : infancy or early childhood.

Transmission : recessive.

Symptoms : very severe photosensitivity, hirsutism, pigmentory changes haemolytic anaemia, splenomegaly erytrodontia.

Laboratory Diagnosis : RBC : uro, copro and proto raised; persistent fluorescence on microscopy.

Stool : uro, copro and proto greatly raised.
Urine : uro and copro greatly raised;

N. B. : Isomers I and III found in all situations.

ERYTHROPOIETIC PROTOPORPHYRIA

Onset : early childhood.

Transmission : probably dominant.

Symptoms : mild to moderate photosensitivity, cholelithiasis & liver failure.

Laboratory Diagnosis : RBC : proto high; transient fluorescence on microscopy.

Stool : proto usually raised.

Urine : normal.

Liver function : only impaired terminally.

Liver biopsy : excess porphyrin and portal cirrhosis.

PORPHYRIA CUTANEA TARDA

Onset : adult life

Transmission : rarely familial

Symptoms : skin fragility, hirsutes, pigmentary changes, photosensitivity moderate or absent.
exacerbated by : alcohol, oestrogens, chloroquin.

Laboratory Diagnosis : RBC : normal; no fluorescence on microscopy.

Urine : uro very high, copro raised.

Stool : variable porphyrins sometimes raised in remission.

Liver function ; usually abnormal.

Liver biopsy : excess porphyrin, portal ciarhosis.

VARIEGATE PORPHYRIA

Onset : early adult life.

Transmission : dominant.

Sympmtoms : acute episodes, precipitated by sulphonamides, barbiturates etc. other symptoms as for PCT.

Laboratory Diagnosis : RBC : normal; no fluorescence on microscopy.

Urine : porphyrins variable, PBG and ALA raised in acute episodes.

Stool : proto and copro raised.

Liver function : normal

Liver biopsy : excess porphyrin

REFERENCES

ALLISON, A. C., MAGNUS, I. A. and YOUNG, M. R. (1966) Role of lysosomes and of cell membranes in photosensitization. Nature (Lond') **209, 874.**

BHUTANI, L. K (1971)personal communication.

IPPEN, H. (1961) Allgemeinsymptome der spaten Hautporphyrie (Porphyria cutanea tarda) als Hinweise für deren Behandlung. Dtsch Med Wschr. **86,** 127.

MATHEWS-ROTH, M. M., PATHAK, M. A , FITZPATRICK T. B., HARBER, L. C. and KASS, E. H. (1970) Beta-carotene as a photoprotective agent in erythropoietic protoporphyria New Engl. J. med., **282** 1231.