THE SKIN AND DISORDERED PORPHYRIN METABOLISM*

BY

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The difficult subject of disordered porphyrin metabolism is bedevilled by a riot of names which have been created to try to distinguish one disorder from another. To add to the confusion the same name, porphyria cutanea tarda, has been used in different senses by different workers. It is therefore clearly necessary to define the criteria by which the types of disorder are distinguished. The classification has been improved, notably by Waldenström (1957), whose scheme I have followed. It should be remembered that the inherited types of disorder are almost certainly separate diseases and represent what Garrod (1923) called inborn errors of metabolism, but that the acquired group, which Waldenström calls porphyria cutanea tarda symptomatica, must still be regarded as a syndrome.

Classification

The two most clearly defined types of porphyria are the congenital and acute intermittent. In *congenital porphyria* there is, according to Watson *et al.* (1951), an inherent defect in the bone-marrow leading to the continuous production of porphyrins, which are excreted in the urine and faeces from a very early age. Apart from the pink or red urine which the subjects void, the disorder is noticed on account of the skin changes, which are confined to the habitually exposed parts, which renew their activity every summer, and which finally lead to severe mutilations. The general health is little affected, but the expectation of life is somewhat diminished. The disease runs a quiet, unremitting course and is probably inherited in a recessive manner.

By contrast, *acute intermittent porphyria* is a disease whose victims are liable to fulminating attacks of a catastrophic nature, including violent abdominal pain, complete constipation, paralyses, mania, and often death. The abnormal metabolites excreted in the urine are the precursors porphobilinogen (Waldenström, 1937) and δ -aminolaevulinic acid (Haeger, 1958). The inheritance is dominant (Waldenström, 1956), and examination of the urine of some apparently healthy members of affected families shows that they pass porphobilinogen (PBG) and δ -aminolaevulinic acid (ALA) without, as yet, having any symptom—a phenomenon described as latency. The skin is affected in only a few cases, and then by no more than an increase in pigmentation.

Protocoproporphyria, or porphyria cutanea tarda hereditaria, resembles acute intermittent porphyria in that its subjects are liable to similar though usually less severe attacks of abdominal pain, neuropathy, or psychosis, its inheritance is dominant (Tio and Leijnse, 1958; Holt *et al.*, 1958), and latency exists. It differs in three main respects. Firstly, porphyrin, chiefly proto- and copro-, is excreted predominantly in the

faeces, except during exacerbations, when the urinary excretion rises at the expense of the faecal (Gray *et al.*, 1948; Macgregor *et al.*, 1952; Wells and Rimington, 1953; Calvert and Rimington, 1953; Holt *et al.*, 1958). Secondly, PBG and ALA are passed, if at all, only in small amount and are most likely to be found at the height of the attack. Thirdly, the skin is conspicuously affected in some cases.

The last type of disorder, *porphyria cutanea tarda symptomatica*, is regarded as acquired, begins in middle life, and is rare in women except among the Bantu (Barnes, 1955), in whom it is commoner in women than in men. The clinical picture is of a seasonal blistering eruption on the exposed parts. Liver disorder, often attributed to the toxic effects of alcohol, but sometimes to supposed nutritional deficiency as in the Bantu, and exceptionally to porphyrin-producing liver tumours (Hamminga, 1951; Tio *et al.*, 1957; Waldenström, 1957), may be the cause of the trouble, but alcoholic bouts can precipitate exacerbations in protocoproporphyria, and since the skin changes can be identical in both diseases every effort should be made to exclude protocoproporphyria before labelling a case as porphyria cutanea tarda symptomatica.

The main distinguishing criteria of the porphyrin disorders are summarized in Table I.

TABLE I.—Summary of Distinguishing Criteria of Porphyrin Disorders

	Porphyria			
	Con- genital	Acute Inter- mittent	Proto- copro	Cutanea Tarda Sympto- matica
Heredity	Prob. recess	Dom.	Dom.	—
Main route of excretion	Urine	Urine	Faeces	Urine
PBG and ALA	—	+	+	—
Presumed site of defect	Bone- marrow	Liver	Liver	Liver
Abdominal pain, neuro- pathy, psychosis	—	Very severe	Less severe	—

Here I must digress to discuss some of the other names and in particular porphyria cutanea tarda, which has been used in two senses. The name originated with Waldenström (1937), who used it to describe cases of porphyria with skin manifestations of late onset as compared with those of congenital porphyria. He has now subdivided porphyria cutanea tarda into hereditary and symptomatic types, the former being synonymous with protocoproporphyria (Waldenström, 1957), which I prefer. The sense in which Brunsting (1954) uses porphyria cutanea tarda is equivalent to the clinical aspects of Waldenström's symptomatic type, whereas Rimington uses it as identical with protocoproporphyria.

Within any family group the possible clinical forms of protocoproporphyria are of four types: (1) latent; (2) with skin lesions only; (3) with skin lesions accompanied by abdominal pain, neuropathy, or psychosis; and (4) with abdominal pain, neuropathy, or psychosis only. From a *clinical* point of view the type with skin lesions only can be identical with porphyria cutanea tarda symptomatica, and the type with abdominal pain, neuropathy, or psychosis only can be identical with acute intermittent porphyria. Therefore, so long as a clinical classification is adopted confusion is bound to arise. The situation is further complicated by the use of the term "mixed" for cases in which there are skin manifestations accompanying what is clinically an attack of acute intermittent porphyria. It is probable

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that these mixed cases are in reality examples of protocoproporphyria. The possible clinical forms of protocoproporphyria are summarized in Table II.

TABLE II.—Possible Clinical Forms of Protocoproporphyria

Manifestation in Individual	Possible Clinical Confusion with	N. American Name
None (latent)	—	—
Skin only	P.c. tarda sympt.	P.c. tarda
Skin + abdominal pain, neuropathy, psychosis	—	Mixed
Abdominal pain, neuropathy, psychosis	Acute i.p.	Acute i.p.

In this connexion there has been one very beautifully worked out family group of porphyrics (Dean and Barnes, 1955) who have so far been difficult to classify. The family are the offspring of an early settler in South Africa who arrived from Holland in 1713. Dean and Barnes traced all the 434 living descendants of the third son of the patriarch's great-grandson. The clinical features of this family group exactly correspond with the possible clinical forms of protocoproporphyria, with a tendency for men to have the skin lesions only, and women to have abdominal pain, neuropathy, or psychosis only, their often lethal attacks usually being precipitated by taking barbiturates. Dean and Barnes, who originally felt that they were dealing with acute intermittent porphyria, later (Dean and Barnes, 1959) compared their cases with some of Waldenström's Swedish cases of acute intermittent porphyria and concluded that the diseases are different. Dean and Barnes's cases behave, in fact, exactly like cases of protocoproporphyria from a biochemical point of view. They suggest calling their cases variegate porphyria, which is far less ugly than protocoproporphyria, and has much to recommend it from the clinical standpoint, since the disease varies so much in its manifestations in the family as a whole. I agree in rejecting porphyria cutanea tarda hereditaria on the grounds that in some individuals the skin is never affected, and in those who are affected the skin lesions are seldom late in appearance.

The conception of porphyria cutanea tarda symptomatologica includes those cases originally described as chronic cutaneous porphyria by Szodoray and Sümegi (1944), as bullous and erosive porphyria of the adult by Borda and Campins (1950), as cutaneous porphyria of the adult by Bolgert *et al.* (1953), and as actinic-traumatic bullous dermatosis by Tappeiner and Tirschek (1953).

Types of Skin Changes

So much for the rather difficult matter of classification. My object has been to review the skin changes which occur in the different types of disordered porphyrin metabolism, and the study which follows has been founded on a consideration of cases of porphyria with skin lesions culled from the literature. When it came to assigning cases to types of disorder according to the criteria already described I was in the immediate difficulty that, with few exceptions—for example, Calvy *et al.* (1951)—the families of cases had not been studied nor had the faecal excretion of porphyrin. It was therefore only possible, in general, to assign to protocoproporphyria cases which had definite abdominal, paralytic, or psychotic symptoms. No doubt one or two patients have been included thereby whose symptoms happened to have perfectly ordinary causes. On the other hand, it is inevitable that some will not

have been included in protocoproporphyria who really belong there on account of the manifestations of their disease being confined to the skin up to the time of their description.

Since the object was to relate the types of disordered metabolism to the skin changes observed, the cutaneous manifestations were not considered in any way in typing the cases. The inevitable result was a remainder group which contained neither obvious congenita nor obvious protocoproporphyria cases, but which could be expected to contain cases of porphyria cutanea tarda symptomatologica as well as incomplete cases of protocoproporphyria, and possibly late cases of congenita as well.

There were 85 cases altogether (Table III), and the skin lesions of all types of porphyria had in common their occurrence on the habitually exposed parts.

TABLE III.—Occurrence of Skin Lesions on Exposed Parts

	Totals	Exposed Parts
Porphyria congenita ..	16	16
Protocoproporphyria ..	40	39
Remainder ..	29	29

That light is essential for the production of the lesions is certain, both because of their distribution and because protection from light prevents their occurrence. Nevertheless, the skin is seldom photosensitive in any obvious sense, for it is unusual to be able to produce lesions experimentally by the use of light, and it seems that prolonged and repeated exposure is necessary as a rule to produce them naturally. This matter is discussed further after the morphology of the skin lesions has been considered.

The skin of the porphyric can be altered in three main ways, apart from pigmentary changes: (1) *blistering*; (2) *mutilating scarring*, and (3) any one or any combination of the triad of *oedema*, *erythema*, and *vesiculation*, hereafter called the O.E.V. reaction.

The blistering tendency resembles epidermolysis bullosa in that the lesions are provoked by such minor activities as bed-making or tying up a parcel, and they usually appear without preceding erythema. It differs in that the feet are spared in shod persons and that sunlight provokes blistering, but it is usual for blistering to be worse in the summer rather than after a particular exposure, unless this has been an exceptionally severe one. It appears that repeated exposures to light in requisite dosage damage the skin, which damage is manifested not only by an epidermolysis-bullosa-like syndrome but also by easy rubbing off of the skin, easy bruising, and delayed healing of the ulcers which follow blistering. The cutaneous vessels share in this damage, with the result that subjection of the skin to an erythema dose of light for the normal individual produces little or no reaction in the porphyric, the wealing effect of histamine is much diminished (Holti *et al.*, 1958), and the histology of the blisters shows virtually no inflammatory reaction. The blisters are followed by superficial scars, milia, and pigmentary changes—usually a blanching of the scar and darkening of the surrounding skin.

The mutilations develop after a long time on the basis of the blistering tendency. The nose and ears are eaten away as in lupus vulgaris, the scalp is scarred, the corneae are scarred, the nails of the fingers dystrophic or shed, the fingers fixed in a claw-like deformity, and the terminal phalanges lost. The old name for this hideous picture was apt—*pemphigus leprosus*.

The O.E.V. reaction is less common than blistering. The oedema is sometimes sudden and severe and imitates angioneurotic oedema. The addition of erythema, and the malaise which often accompanies this type of reaction, suggests erysipelas, and the occurrence of vesiculation a severe contact eczema.

The distribution of these three types of reaction among the three groups of cases shows that the blistering tendency is common to all but not universal in protocoproporphyruria as it is in the other groups (Table IV). Mutilating scarring is typical of congenita

TABLE IV.—Incidence of Main Types of Change

	Total	Blistering	Mutilation	O.E.V.
Porphyria congenita ..	16	16	9	1
Protocoproporphyruria ..	40	30	1	27
Remainder ..	29	29	1	6

and the O.E.V. reaction of protocoproporphyruria, with a few in the remainder group. It seems likely that the reaction of O.E.V. is confined to protocoproporphyruria and that the cases in the remainder group that exhibit it are *formes frustes*, the real nature of which would be revealed by fuller investigation; but this suggestion must await further study. Some cases of protocoproporphyruria have never exhibited it, and its presence does not preclude the blistering tendency, for both patterns of reaction can occur in the same patient during the course of the disease.

Exposure to Light in Relation to Skin Lesions

If one now considers the relationship between exposure to light and the production of skin lesions, two patterns emerge. On the one hand, there are aestival recurrences of blistering activity where the variable factor seems to be the quality of light, for in climates where the sun is strong all the year round the blistering activity never ceases (Findlay and Barnes, 1950). On the other hand, there are sporadic bursts of activity in the skin, related to a particular exposure to light, not necessarily a severe one, in which the variable factor seems to be the activity of the disease, and these are typical of protocoproporphyruria, and of the O.E.V. reaction in particular. The O.E.V. pattern of reaction is the one which is sometimes obviously photosensitive, and it is the one displayed by the majority of patients who have developed experimental lesions, notably the brother and sister described by Wells and Rimington (1953) and by Magnus *et al.* (1959).

On comparison of cases showing the O.E.V. pattern of reaction with all others (Table V) it is seen that the former are less likely to display seasonal activity and more likely to show sporadic activity in the skin, an obvious relationship between exposure to light and the

TABLE V.—Relation of Skin Lesions to Light Exposure

	Total	Seasonal	Sporadic	Obvious Relationship	Experimental Hyper-sensitivity
O.E.V. ..	34	12	14	25	10
Others ..	51	36	6	14	2

TABLE VI.—Patterns of Reaction to Light

Pattern of Reaction	The Variable	The Stimulus
Seasonal blistering	Quality of light	Summer
O.E.V.	Activity of disease	A specific exposure

occurrence of skin lesions, and a demonstrable hyper-sensitivity of the skin to light. The two patterns of reaction are summarized in Table VI.

I have shown that patients reacting with O.E.V. are prone to sporadic outbursts of activity in their skin due to enhanced photosensitivity, and that the O.E.V. pattern of reaction is typical of protocoproporphyruria. This type of porphyria is known to undergo variations in its activity, and I have already mentioned that during exacerbations urinary porphyrin excretion is increased at the expense of faecal, presumably by some impediment to biliary excretion. It seems possible that the increased sensitivity associated with the O.E.V. pattern of reaction could be due to increase of porphyrin in the blood and tissues, and this suggestion is supported by the far greater incidence of jaundice among O.E.V. reactors (Table VII).

TABLE VII.—Incidence of Jaundice

	Total	Jaundice
O.E.V. ..	34	11
Others ..	51	2

Magnus *et al.* (1959) have shown that the oedema reaction is due to the presence of porphyrins, and Wells and Rimington (1953) found that the superficial blood-vessels in the dermis are severely affected in histological sections from the oedema reaction, and they and others have described purpura after sufficient exposure. Finally, the historical experiment of Meyer-Betz (1913), who injected haematoporphyrin into his own vein and became an oedema reactor for over two months, is consistent with the idea that the O.E.V. pattern of reaction is due to an increase in blood and tissue porphyrins. This is not the whole story, because some cases of protocoproporphyruria never develop the O.E.V. reaction, even though they are jaundiced—for example, Macgregor *et al.* (1952)—and I wonder whether the type of porphyrin may be important or the presence of porphyrin precursor, such as porphyrinogen, which is strongly catalysed by light.

When the activity of the disease abates the patients lose their capacity for reacting by O.E.V. For example, Thomas's (1950), patient, who sat in the open under an overcast sky in August, 1948, and reacted briskly, was able to bathe in the sea and wear short-sleeved dresses with impunity by 1954 (personal communication). This patient's exposure seems to have precipitated an exacerbation of the disease as well as the O.E.V. reaction, and in many reports there is the suggestion that exposure to light increases the production of porphyrins. For example, in the case described by Calvy *et al.* (1951) the patient knew from experience that exposure to the sun made him feel ill and made his urine darker, and he had arranged his life accordingly. Incidentally their paper described what must be protocoproporphyruria in three generations, and the histories of the affected members cover all the clinical forms of the disease.

I would like now to describe briefly the other skin manifestations. Hypertrichosis is common in congenital porphyria, especially in females, but seems less frequent in the other types. The scalp hair sometimes darkens as the disease develops. Increased pigmentation occurs in all types of disorder; it is often blotchy and resembles chloasma, is sometimes diffuse, and, very rarely, Addisonian. It reaches its most dramatic degree

when the features, and occasionally the sclerae, are suffused with a coppery, fiery, or cyanotic tinge. Bolgert *et al.* (1953) make a special mention of blotchy pigmentation of the temples in porphyria cutanea tarda symptomatica. In porphyria congenita the teeth erupt pink or purple, and they tend to turn brown.

There are a whole range of changes which imitate other dermatoses, such as acne necrotica, colloid milium, scleroderma, lichenification, and hydroa aestivale. In this connexion it seems likely that cases of hydroa aestivale in which porphyrinuria has been reported have been really cases of porphyria. There seems to be a general tendency in protocoproporphyria for the skin to itch and to develop erythematous lesions followed by vesicles and then crusts, which are often black with blood. Healing of these lesions is more rapid than it is in the lesions associated with seasonal blistering. A warty change or hyperkeratosis of the exposed parts occurs, the skin often looks thickened and coarse, and the normal markings are exaggerated.

Conclusion

My main theme has been that there are, apart from pigmentary disturbance, three major ways in which the skin can be altered in the subjects of disordered porphyrin metabolism. They are blistering, mutilating scarring, and the reaction of oedema, erythema, and vesiculation (O.E.V.). No skin changes occur in acute intermittent porphyria except an increase of pigment. The blistering tendency is common to all other types, mutilation is typical of congenital porphyria, and the O.E.V. reaction of protocoproporphyria. The O.E.V. reaction differs from the blistering tendency in that the former depends upon a temporary greatly increased sensitivity to light, probably brought about by an increase of porphyrins, or porphyrin precursors, in blood and tissues, and the latter depends upon the seasonal quality of light. It seems probable that the skin changes which occur in protocoproporphyria cover a much wider range than those in porphyria congenita and porphyria cutanea tarda symptomatica, but the position can be clarified only when the routine investigation of all cases includes study of faecal porphyrin excretion in the patient and his family.

For the purposes of this paper I have borrowed freely from the work of other people and have contributed no more than a reappraisal of their material. Four of the cases included here have been observed personally, and are as yet unpublished; the remainder I have met only in print. To them, and their physicians, I owe a great debt. Finally, I must acknowledge the most generous help from Professor C. Rimington.

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