PORPHYRIA AND PHOTOSensitivity

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With Plates 4 to 9

Introduction

The purpose of this paper is to appraise the clinical, biochemical, and histo-
logical picture of three types of porphyria with photosensitivity of the skin.
Experimental data from photobiological and simple pharmacological studies
are also presented.

The porphyrias considered here are all relatively common: erythropoietic
protoporphyria; porphyria cutanea tarda (Cutaneous Hepatic Porphyria);
variegate porphyria (South African Genetic Porphyria).

Congenital porphyria (Gunther's Disease) is excluded from present considera-
tion because it is rare; acute intermittent porphyria because it is not associated
with photosensitivity; and erythropoietic coproporphyria (Heilmeyer and
Cлоттен, 1964) because we have no experience of this disease.

The salient features of the three conditions represented in this survey may
be outlined as follows.

In erythropoietic protoporphyria (EPP) photosensitivity is for practical
purposes the only symptom. It usually starts within the first one or two years
of life and there is often evidence of inheritance, apparently by dominant
transmission. The urine contains normal amounts of porphyrin, but the stool
porphyrin may be raised. The red-cell protoporphyrin is markedly increased
and sometimes the coproporphyrin also, and protoporphyrin may be present
in the plasma.

In porphyria cutanea tarda (PCT) symptoms usually develop during adult
life and are generally cutaneous only. There has been some lack of unanimity
about the definition of this type of cutaneous hepatic porphyria due, in part, to
its confusion with variegate ('mixed') porphyria and in part through doubt as
to whether or not a genetic predisposition underlies the tendency for cutaneous
porphyria to develop in certain clinical circumstances, for example, in some,
but not all, cases of chronic alcoholism. Waldenström, who originally introduced
the term 'porphyria cutanea tarda' in 1937, revised his concept of this group
in 1957 and subdivided it into (a) porphyria cutanea tarda symptomatica and
(b) porphyria cutanea tarda hereditaria or protocoproporphyria.

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In subgroup (a) there is usually evidence of hepatic injury due to alcoholism, infection, drugs or chemicals (Rimington, 1964), although a precipitating cause may often be difficult to identify. Typically, the excretion of urinary uroporphyrin is greatly raised, that of coproporphyrin to a lesser extent. Herbert (1966) has suggested adoption of the term 'Secondary hepatic porphyria' in place of porphyria cutanea tarda symptomatica, a suggestion which has much to recommend it.

Subgroup (b) comprises cases of porphyria with evidence of genetic transmission and cutaneous symptoms. This type is probably different from variegate porphyria.

Variegate porphyria (VP) is commonest by far among the white population of South Africa. It is a hereditary disease with dominant transmission manifesting itself about puberty. Cutaneous symptoms, similar to those in PCT, occur in the same family and often in the same individual together with neuropathy, psychoses, or abdominal symptoms similar to those seen in acute intermittent porphyria. Attacks are commonly precipitated by barbiturates. The urinary porphyrins, porphobilinogen and δ-aminolaevulic acid excretion are markedly raised during attacks. Red-cell porphyrins are always normal.

The present survey of 35 patients includes 17 cases of EPP, 16 of PCT, and two of VP. Some have been described before; thus, of the EPP patients, Cases 1 and 2 were briefly reported under another diagnosis by Calnan and Shuster (1962) and under the present diagnosis by Cripps, Calnan, Senter, and Pegum (1964), who also briefly reported our Cases 4 and 5; Cases 1, 2, 3, 4, and 10 were also reported with regard to liver pathology and skin fluorescence by Cripps and Scheuer (1965) and by Cripps, Hawgood, and Magnus (1966); Case 7 was mentioned briefly without a final diagnosis by Sir Archibald Gray (1926) and was later studied by Gray, Kulczycka, Nicholson, Magnus, and Rimington (1964); Cases 12, 13, and 14 were originally reported by Holti, Magnus, and Rimington (1963); Case 15 was described by Magnus, Jarrett, Frankerd, and Rimington (1961). Of the patients with PCT, Cases 10 and 11 were first described by Wells and Rimington (1953) and later by Magnus, Porter, and Rimington (1959). PCT Case 1 has also been reported recently by Copeman, Cripps, and Summerly (1966), being Case 2 of their paper. Beer (1965) described at length PCT Case 12. A special study of the biochemical situation in the two cases of VP is the subject of a preliminary report by Rimington and Lockwood (1966).

Clinical Features

Erythropoietic Protoporphyria

Of our 17 patients, 10 were familial (four different families). All patients present a quite distinctive clinical picture. Of the acute manifestations the most constant symptom is burning and stinging of skin exposed to the sun, either directly or sometimes through window glass or even through thin clothes. The length of exposure necessary may be a few minutes or as long as an hour. The burning, which may be mild or very severe, starts either during exposure
or an hour or so later and lasts from several hours to several days. Although this often very unpleasant symptom may be the only acute manifestation, most patients also develop erythema or swelling of the skin, or both. Erythema comes on during or soon after exposure; swelling appears within a few hours of the onset of burning and can last, in a severe attack, up to three weeks. The degree of swelling varies from a slight *peau d’orange* to something resembling severe angioneurotic oedema; it is sometimes paler than normal skin, sometimes slightly red or blue. A less common acute manifestation is urticaria, when weals, which soon become confluent, develop a few minutes after exposure and last about half-an-hour. In children purpura, vesicles, occasional haemorrhagic bullae, and later scabs and crusted patches, seem to follow sunlight exposure. Purpura occurred also in four of our patients, one of them an adult.

The chronic skin lesions present between acute attacks are often not obvious and unless looked for carefully may easily be missed. They are manifested in a varying degree of thickening and scarring of skin most exposed to sunlight, together in some patients with a slight violaceous erythema. Areas frequently affected are the front of the nose, cheeks, back of the hand between thumb and index finger and dorsum of the finger joints, especially that of the second and third metacarpophalangeal and proximal interphalangeal joints. Very small pits and shallow pock-like or short linear scars are sometimes seen on the cheeks. Linear scars may also be seen on the dorsum of the hands and feet.

Although for all practical purposes this is a dermatological disease, it is to be noted that two of our patients had undergone operations for gall stones at a relatively early age. These were *Case 4*, in which porphyrin analysis of the stones showed a high concentration of protoporphyrin (Cripps and Scheuer, 1965), and *Case 15* (Magnus, Jarrett, Prankerd, and Rimington, 1961). Haeger-Aronsen (1963) has also noted cholelithiasis in one of her EPP cases when the patient was about 28 years old; Lynch and Miedler (1965) also reported cholecystectomies in three patients, all males, aged 23, 35, and 38.

A full list of references to published cases of EPP is given by Rimington and Cripps (1965) and a review of 20 cases in the literature by Lynch and Miedler (1965) who also report on four related patients of their own. Wiskemann and Wehrmann (1965) in a valuable paper report on 11 patients in five different families; however, it must be noted that several of their cases had a red-cell coproporphyrin concentration, as well as protoporphyrin, that was very greatly increased. Other more recent reports are given by Gasser-Wolf (1965) from Switzerland of seven cases, by Findlay, Scott, and Cripps (1966) from South Africa of six cases, by Suurmond (1965) from Holland of three cases, by Schwarz, Schwarz-Speck, and Sulser (1965) from Switzerland of three cases, and by Connelly and Creutzfeldt (1965) from Australia of two cases. Lynch and Miedler (1965) from the U.S.A. also refer to seven further American cases of Peterka, as yet unpublished. Among a number of single case reports of EPP are those of Sweeney, Dowdle, and Saunders (1963) from South Africa and Tronnier (1965) from Germany. Other known cases in the Netherlands, Canada, England, Scotland, Spain, and Japan remain unpublished at the time of writing.
Illustrative Cases from the present Material

**EPP Case 1.** Female aged 21. Attacks of redness and swelling, appearing three to four hours after the start of an exposure and continuing for several days, had been liable to occur since the age of four years, but even as a baby she had cried when brought into strong sunlight. Up to the age of 10, blisters on her nose seemed to appear a few days after exposure and were followed by crusts. Strong sunlight, even through window glass, still provokes an unpleasant burning sensation but this is now not followed by blisters.

On examination there was a violaceous erythema of the face and circumoral pallor, thickening of the cheeks and fine pits together with small irregular nasal scars. Slight thickening of the skin over the metacarpophalangeal and proximal interphalangeal joints was apparent on close scrutiny. Her voice was husky, but laryngoscopy was normal.

The red-cell protoporphyrin concentration was markedly raised, that of coproporphyrin to a lesser degree. Stool protoporphyrin was usually moderately raised though on occasion this had been insufficient to be detectable by a qualitative screening test. The urinary porphyrin was in the normal range (see Table I). Examined with a fluorescence microscope with mercury-vapour source and filter combination transmitting 400 m/μ but not red light, the erythrocytes (diluted about 1 in 4 in 0.8 per cent. saline) showed the red fluorescence characteristic of porphyrin. Fluorescence was transient and lasted usually less than 20 seconds; this was in contrast to the stable fluorescence in Günther's Disease due to uroporphyrin in the red cells. With an iodine-quartz tungsten lamp, fluorescence microscopy of the red cells in EPP may give fluorescence for up to two minutes (Cripps, Hawgood, and Magnus, 1966).

In a biopsy from the cheek, the epidermis was hyperkeratotic and acanthotic, with elongated, pointed rete ridges. In the upper dermis faintly eosinophilic amorphous material was present in large amount round capillaries, especially where the papillae were widened. The capillary lumina were increased in number and some unidentified cells were seen around the vessel walls. Clinically normal skin from the dorsum of the hand showed essentially the same changes but to a lesser degree. Nothing abnormal was found in the skin of the elbow and back.

Tests on the skin of the back with monochromatic radiation showed normal erythema reactions to wavelengths in the 'sunburn' region (i.e. around 300 m/μ). All other wavelengths were negative, in particular 400 m/μ. This was confirmed on three different occasions. However, it was found that if the skin was warmed immediately prior to irradiation, an erythematos response could be provoked with 400 m/μ. These tests were unaccompanied by subjective sensations.

**EPP Case 5.** Male aged 11. From the age of nine months this boy had cried if he was in the sun; later he complained that it brought on a stinging sensation. Sunlight through window glass had also brought this on. From two years old he had also developed swelling, crusting, and scabbing of exposed areas, sometimes with haemorrhagic bullae. He had usually had only one bad attack a year.

On examination scabs had occurred on the cheeks, ears, and nose; there were now shallow pits below and lateral to the eyes and diffuse superficial scarring of the nose (see Plate 4, Fig. 1). The dorsal skin of the second and third metacarpophalangeal joints was thickened and violaceous in colour. His voice was not hoarse.

The red-blood cells showed markedly raised protoporphyrin and coproporphyrin. These porphyrins could also be detected in the plasma. Stool
protoporphyrin was considerably raised but stool coproporphyrin and urinary
porphyrins were within the normal range (see Table I). Microscopically, the
red cells showed transient red fluorescence indicative of porphyrin. This
fluorescence lasted some seconds.

A biopsy from thickened dorsal skin of the metacarpophalangeal joint of
the index finger showed normal epidermis, apart from elongation of the rete
ridges. A large amount of amorphous perivascular material was seen in and
immediately beneath the widened dermal papillae and some unidentified cells
were present around the papillary capillaries.

Monochromatic irradiation of the skin with 400 m\(\mu\) gave an immediate
erithema response followed by delayed oedema. Exposure to the latter wave-
length was sometimes associated with mild sensations of pricking. The oedema
reaction sometimes seemed to be better provoked if the skin were slightly
warmed before irradiation. Immediate erythema responses were also provoked
by 500 and 600 m\(\mu\). Tests employing other wavelengths, including those
causing sunburn, were normal.

**EPP Case 10.** Male aged 45. For as far back as he can remember, this man
has had burning, followed by swelling of the face, hands, and neck, precipitated
by exposure to sunlight even through window glass, and occasionally through
thin clothing. At least 13 other members of his family have proven EPP. The
genealogy of this large family is to be described (Donaldson and Donaldson,
1966).

On examination the face was slightly violaceous and the skin over the
second and third metacarpophalangeal and proximal interphalangeal joints
was thickened and violaceous. His voice was not hoarse.

The red-cell protoporphyrin and coproporphyrin were considerably raised,
as was the stool protoporphyrin. The urine was in the normal range (see Table
I). The red cells also showed a transient but typical red fluorescence due to
porphyrin.

Two biopsies were made. In the first from violaceous skin over the dorsum
of the hand, where the epidermis appeared normal, the capillary loops of the
dermal papillae were thickened and strongly PAS positive. A second biopsy
from clinically normal skin of the thigh showed no abnormality.

Monochromatic irradiation tests showed normal reactions to sunburn wave-
lengths, but from 380 to 600 m\(\mu\) there was an immediate erythema which
persisted; at 400 m\(\mu\) this was followed by delayed oedema. Irradiation at
the latter wavelength was often accompanied by a burning or itching sensation.

**Porphyria Cutanea Tarda**

In our 16 cases of this disease, two were brother and sister (Cases 10 and 11).
Case 8 also had a sister with porphyria not included in this series; both are
alcoholics. Other patients who undoubtedly suffered from alcoholism were
Cases 1, 4, 9, 13, 14, 15, and 16.

The acute manifestations of photosensitivity were, as judged by the history,
much less striking than in EPP. In only two PCT patients (Cases 10 and 11),
discomfort followed by urtication or swelling of skin commonly followed exposure
to sunlight. In the remaining 14 patients there was seldom a very clear-cut
history suggesting photosensitivity. The acute skin lesions are well known,
e.g. erythema, vesicles, and bullae, the latter being sometimes haemorrhagic.
In our patients these appeared usually during sunny weather and on exposed
areas of skin such as scalp, face, neck, and backs of forearms and hands and were followed by erosions, crusts, scabs, and scars.

The chronic skin lesions are also well known; they include milia, scarring, hirsuties, and pigmentation, and occasionally changes resembling scleroderma. Our patients showed all these changes in various degree, except that none had sclerodermatous changes. Exposed skin of patients with PCT is highly susceptible to trivial trauma, and this was demonstrable in most of our patients.

Illustrative Cases

**PCT Case 1.** Male aged 73. This man first developed blisters at the age of 72 on his face, neck, hands, and feet while in Spain. These symptoms started during the summer about a year before he was first seen by us. He was an alcoholic and was being treated with stilboestrol for carcinoma of prostate. There was no family history of photosensitivity, and he himself could not give a clear account connecting the development of his skin lesions with exposure to the sun.

On examination large bullae were present on the neck and the backs of the hands, and the finger nails were loose and white. The liver was enlarged. Faecal protoporphyrin and urinary uroporphyrin were greatly raised (see Table I). Red-cell porphyrin concentrations were normal, but measurable quantities of uroporphyrin were detected in the plasma on occasion. Fluorescence microscopy of the red cells was negative.

A section of a biopsy from the dorsum of the hand, stained with haematoxylin and eosin, showed no abnormalities and in particular no perivascular amorphous material. However, a faint reaction for lipid in the region of the papillary capillaries occurred in fresh frozen sections stained with Sudan Black B.

Monochromatic irradiation gave normal results with 300 m$\mu$ and neighbouring wavelengths. On the other hand, a most striking urticarial reaction was obtained in the spectral regions 350–425 and 500–600 m$\mu$. This was unaccompanied by subjective sensations. Reactivity was maximal at 400 m$\mu$. He was not a very good witness and frequently got muddled in giving his history, presumably due to his alcoholism, so that it was difficult to know how much weight to give to his denial of having urticaria or subjective sensations in the skin provoked by sunlight.

**PCT Case 4.** Male aged 68. This man had had blisters on the back of both hands and crusted lesions on the scalp for the past nine months. No relation between blistering and sunlight had been noted, nor any particular susceptibility to erythema following exposure to sunlight. He was a heavy drinker in the past but claimed that he now drank only in moderation. He had syphilitic aortitis. There was no family history of photosensitivity.

On examination crusts and scars were present on the scalp and hands, and the face was scaly. The backs of the fingers and hands also showed haemorrhagic blisters and milia. There was erythema of the palms. An erythematous crusted rash was seen on the lower half of both legs together with gross pitting oedema of the feet. The liver was enlarged and there were signs of aortic incompetence and of mild congestive heart failure.

The urine showed greatly raised urinary uroporphyrin excretion, the coproporphyrin also being increased (see Table I). Faecal porphyrin was within the normal range as was the concentration of porphyrins in the blood. Porphyrin fluorescence was not seen in the blood by fluorescence microscopy.
A section from a biopsy from the scarred dorsum of the hand, stained with haematoxylin and eosin, was normal. But with PAS the papillary vessels appeared thickened and contrasted with the normal appearance of the vessels in a biopsy from the chest.

Tests with monochromatic radiation gave immediate erythema reactions, readily obtained with short exposures to 400 m\(\mu\) radiation and to a lesser extent to 500–600 m\(\mu\). Tests at the sunburn wavelengths were normal.

**Variegate Porphyria**

This condition has been well described by Eales (1963) and Dean (1963). However, no detailed accounts of the skin photosensitivity seem to have been made and our present purpose is to emphasize certain points about this symptom in the history. Our two patients were brother and sister; at least eight other members of the family were affected. In both of our patients it was highly probable that the porphyria was aggravated and thereby the symptoms of photosensitivity provoked by drugs.

**VP Case 1.** Male aged 21. About four months before investigation he had been severely ill with abdominal pain, porphobilinogenuria, and later jaundice. Chlorpromazine and quinalbarbital had been taken in small quantities a few months previously. During the following summer, porphyrin metabolism gradually improved and, apart from the episode mentioned below, there was no evidence of photosensitivity.

His one and only attack of photosensitivity had occurred as a burning feeling of the skin on one side of the face, the side to the sun, which came on in the spring during a fine day on the English south coast. The burning lasted for about an hour after exposure had finished. There was no erythema or other kind of objective reaction.

Monochromatic irradiation tests, done soon after photosensitivity had been first noted, showed a wealing reaction to 400, 500, and 600 m\(\mu\); the threshold dose at 400 m\(\mu\) was the smallest. 300 m\(\mu\) radiation gave normal results. Repeated about two months later, the monochromator tests showed less-marked photosensitivity, and at this time he could sunbathe with impunity. Apart from his having developed, especially in the hands, increased skin susceptibility to mechanical trauma, he had had no other skin lesions attributable to porphyria (see Plate 4, Fig. 2).

Histology of this case in haematoxylin- and eosin-stained sections appeared normal. With the PAS stain, papillary capillaries were thickened and Sudan Black B revealed lipid in their walls.

**VP Case 2.** Female aged 19. She had noted symptoms of photosensitivity for about four months. These came on some three months after taking a few tablets of an oestriadiol preparation. On several occasions in the spring and summer the sun had produced a burning sensation of the exposed skin. On one occasion, whilst she was lying in the sun, a burning sensation had developed in the lower limbs, even though these were clothed in linen trousers; uncovered skin was also affected by this burning sensation. On changing her clothes about three hours later, erythema was noted in the previously trouser-clad area, as well as on exposed skin. Tests with monochromatic irradiation, which were done on one occasion only, gave essentially the same results as in her brother, i.e. a wealing response maximal at 400 m\(\mu\).
### Table I

**Porphyrin Findings in Urine, Stool, and Blood**

<table>
<thead>
<tr>
<th>EPP</th>
<th>Case 1 Sister of Case 2</th>
<th>2 Sister of Case 1</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7 Twin brother of Case 9 and father of Case 8</th>
<th>8 Daughter of Case 7</th>
<th>9 Twin sister of Case 7</th>
<th>10 Brother of Case 11</th>
<th>11 Brother of Case 10</th>
<th>12 Sister of Case 13</th>
<th>13 Sister of Case 12</th>
<th>14 Mother of Cases 12, 13</th>
<th>15</th>
<th>16</th>
<th>17</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urine [μg/day]</td>
<td>35-4</td>
<td>40-6</td>
<td>10-9</td>
<td>10-9</td>
<td>18-6</td>
<td>18-6</td>
<td>21-5</td>
<td>0</td>
<td>3</td>
<td>50-0</td>
<td>119</td>
<td>72-6</td>
<td>69-6</td>
<td>72-9</td>
<td>0</td>
<td>3</td>
<td>5</td>
</tr>
<tr>
<td>Stool [μg/g dry weight]</td>
<td>100-5</td>
<td>57-5</td>
<td>380</td>
<td>132</td>
<td>1,156</td>
<td>1,156</td>
<td>1,095</td>
<td>610</td>
<td>333</td>
<td>1,000</td>
<td>3,400</td>
<td>1,820</td>
<td>734</td>
<td>1,195</td>
<td>1,030</td>
<td>620</td>
<td>75</td>
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<tr>
<td>Red Blood Cells [μg/100 ml packed cells]</td>
<td>619</td>
<td>745</td>
<td>7-5</td>
<td>7-9</td>
<td>1,105</td>
<td>1,105</td>
<td>6-37</td>
<td>22-7</td>
<td>3-0</td>
<td>5-5</td>
<td>12-3</td>
<td>5-5</td>
<td>4-11</td>
<td>7-7</td>
<td>2-0</td>
<td>2-0</td>
<td>0-6</td>
</tr>
<tr>
<td>Plasma [μg/100 ml]</td>
<td>2-0</td>
<td>2-8</td>
<td>5-5</td>
<td>6-3</td>
<td>0-87</td>
<td>0-6</td>
<td>0-3</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>7-4</td>
<td>N</td>
<td>N</td>
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</tr>
<tr>
<td>VP</td>
<td>Brother of Case 8</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>1,000*</td>
<td>1,000 *</td>
<td>1,000</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>42-7</td>
<td>1-7</td>
<td>0</td>
</tr>
<tr>
<td>Case 1 Brother</td>
<td>7,950</td>
<td>3,640</td>
<td>65</td>
<td>45</td>
<td>320</td>
<td>320</td>
<td>Below 50-0</td>
<td>Much inextractable porphyrin</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>Much inextractable porphyrin</td>
<td>12</td>
<td>11</td>
<td>4</td>
</tr>
<tr>
<td>and</td>
<td>7,000</td>
<td>3,640</td>
<td>65</td>
<td>45</td>
<td>320</td>
<td>320</td>
<td>Below 50-0</td>
<td>Much inextractable porphyrin</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>Much inextractable porphyrin</td>
<td>12</td>
<td>11</td>
<td>4</td>
</tr>
<tr>
<td>Case 2 Sister</td>
<td>100-5</td>
<td>57-5</td>
<td>380</td>
<td>132</td>
<td>1,156</td>
<td>1,156</td>
<td>1,095</td>
<td>610</td>
<td>333</td>
<td>1,000</td>
<td>3,400</td>
<td>1,820</td>
<td>734</td>
<td>1,195</td>
<td>1,030</td>
<td>620</td>
<td>75</td>
</tr>
<tr>
<td>Case 3 Sister</td>
<td>100-5</td>
<td>57-5</td>
<td>380</td>
<td>132</td>
<td>1,156</td>
<td>1,156</td>
<td>1,095</td>
<td>610</td>
<td>333</td>
<td>1,000</td>
<td>3,400</td>
<td>1,820</td>
<td>734</td>
<td>1,195</td>
<td>1,030</td>
<td>620</td>
<td>75</td>
</tr>
</tbody>
</table>

**Biochemical Features**

The three types of porphyria under consideration display fairly distinct and different patterns of porphyrin distribution and excretion (Rimington, 1964). Thus only in EPP are erythrocyte porphyrin levels abnormal and in this disease, in contradistinction to PCT and VP, urinary porphyrins are always within the normal range. The urinary pattern in symptomatic PCT is characterized by relatively large amounts of uroporphyrin. The intensity of the biochemical disturbance is subject to fluctuation in all types of porphyria, and it
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is therefore more appropriate to speak of porphyrin patterns rather than of absolute values; this applies particularly to plasma porphyrins.

There is some difference of opinion concerning the acceptable normal levels of porphyrin excretion. This is mainly due to the effects of race and dietary habit upon faecal porphyrin excretion in particular, in the populations studied; differences in technique may be a contributory factor. It is well established that a part of the total protoporphyrin of the stool arises from degradation of haem compounds by micro-organisms in the gut; a diet rich in meat produces a correspondingly large contribution from this source. Ideally, excretion should be measured on a haem-free diet but even so some porphyrin will still arise from biosynthesis by the bacteria themselves. Eales, Levey, and Sweeney (1966) have recently tabulated the figures for normal faecal porphyrin excretion found by six groups of workers. The differences between the means are not serious; a higher upper limit of the range for protoporphyrin is found by the South African workers.

Calculation of the arithmetic means from all six groups of investigators gives a value for coproporphyrin of 8 \( \mu \text{g.} / \text{g.} \) and for protoporphyrin of 21 \( \mu \text{g.} / \text{g.} \) dry weight respectively. A similar calculation affords figures for mean urinary coproporphyrin of 90 \( \mu \text{g.} / 24 \text{ hours} \) and uroporphyrin 9 \( \mu \text{g.} / 24 \text{ hours} \). Mean urinary excretion levels of 8-aminolaevulic acid and of porphobilinogen are accepted as being about 2·5 and 1·5 mg./day with upper normal limits of about 4·5 and 2·0 mg./day respectively.

As normal values for red cell porphyrins, we have taken the following ranges due to Wranne (1960): protoporphyrin 16–52 and coproporphyrin 0·5–2·3 \( \mu \text{g.} / 100 \text{ ml.} \) cells respectively.

Erythropoietic Protoporphyria

A constant finding in this condition is a raised protoporphyrin content of the erythrocytes; levels as high as 2,000 to 4,000 \( \mu \text{g.} / 100 \text{ ml. packed cells} \) are not uncommon. Erythrocyte coproporphyrin is also usually raised but uroporphyrin is not significantly increased, a feature which distinguishes EPP sharply from Günther’s Porphyria congenita, in which uroporphyrin (series I) excess dominates the picture. A few cases of a type of erythropoietic porphyria, erythropoietic coproporphyrina, have recently been reported by Heilmeyer and Clotten (1964) in which it is the coproporphyrin of the red cells rather than protoporphyrin as in EPP which is most markedly increased.

Blood plasma in EPP usually contains detectable quantities of protoporphyrin (see Table I) but no uroporphyrin. Urinary excretion of porphyrins is normal. Faecal protoporphyrin and coproporphyrin are usually raised, often greatly raised, but some cases have been reported in which faecal porphyrin excretion was not above normal (Haeger-Aronsen, 1963; Redeker and Bryan, 1964). There may be a tendency in some affected individuals for the disease and the abnormal biochemical signs to ‘burn themselves out’ in later life. A clinical history must always be taken into consideration, therefore, as well as biochemical analyses when screening a family for affected members.
Illustrative Cases

EPP Case 15. Male aged 35. Erythrocyte protoporphyrin and coproporphyrin were both considerably raised and on occasions plasma protoporphyrin was as high as 70 µg./100 ml. Stool protoporphyrin and coproporphyrin were both raised (see Table I), but urinary porphyrins were normal.

EPP Case 6. Male aged 17. This man's total stool porphyrin was 72 µg./g. dry wt., a figure which is only very moderately raised, yet protoporphyrin was readily demonstrable in his plasma (6-8 µg./ml.). His erythrocyte porphyrins were above normal but were not so greatly raised as in other cases.

EPP Case 14. Female aged 48. This woman has a slightly but consistently raised stool protoporphyrin excretion; this is her only biochemical abnormality. She is the mother of EPP Cases 12 and 13, both of whom have severe photosensitivity and marked biochemical abnormalities typical of this condition. The mother herself has always been entirely symptom free. It is suggested that her case is a forme fruste.

Porphyria Cutanea Tarda Symptomatica

The cases we have here designated as porphyria cutanea tarda symptomatica have mostly been associated with chronic alcoholism. The same pattern of porphyrin excretion as in the chronic alcoholic may be seen in the absence of alcoholism in some individuals who have suffered liver injury due to causes such as infective hepatitis, administration of hepatotoxic drugs, or accidental poisoning. Characteristic in this pattern of porphyrin excretion is the much greater increase of uroporphyrin than of coproporphyrin in the urine. Stool coproporphyrin and protoporphyrin are generally both raised. Red-cell porphyrins are normal but uroporphyrin may be present in the plasma.

Illustrative Cases

PCT Case 1. Male aged 73. The urine contained over 4-5 mg. of uroporphyrin and 0-5 mg. of coproporphyrin per day; stool porphyrins were also greatly raised; erythrocyte porphyrins were normal but in the plasma 10-6 µg. of uroporphyrin was found per 100 ml. accompanied by traces of protoporphyrin and coproporphyrin.

PCT Case 13. Male aged 48. The same pattern of raised urinary uroporphyrin was found but in this case stool porphyrins were only a little over normal.

Porphyria Cutanea Tarda Hereditaria

Among our cases is a small number with cutaneous symptoms and evidence of genetic transmission of their disease but with apparently no abdominal or nervous symptoms such as are found in variegate porphyria. Their erythrocyte porphyrins are normal but porphyrin may be found in detectable quantities in the plasma. Faecal protoporphyrin and coproporphyrin are invariably greatly raised. Urinary coproporphyrin is usually high, but the uroporphyrin is not increased to the extent it is in PCT symptomatica.
Illustrative Cases

PCT Case 10. Male aged 45. This man excreted over 1.5 mg. of porphyrin/g. dry wt. of stool and 1.5 mg./l. of coproporphyrin in his urine. The urinary uroporphyrin has never been significantly raised. Blood porphyrins were normal.

PCT Case 11. Female aged 37, sister of Case 10. The biochemical disturbance was less intense in this woman but followed the same general pattern as in her brother. The blood protoporphyrin was marginally increased.

Variegate Porphyria

In this disease symptoms may occur in the same individual which are at times similar to those of acute intermittent porphyria (abdominal pain, constipation, neurological disturbances) and at others similar to those of PCT (cutaneous symptoms). The biochemical picture changes in the same way, acute attacks being accompanied by porphobilinogenuria and the 'cutaneous phase' by raised stool and urinary porphyrins. Uroporphyrin is never raised to the extent that it is in PCT. Erythrocyte porphyrins are normal but porphyrin may be detectable in the plasma.

Recent investigation by one of us (C. R.) of the two cases VP Cases 1 and 2 and of another family with this condition has revealed the presence in the excreta of considerable quantities of an unusual hydrophilic porphyrin (Rimington and Lockwood, 1966). The present report will be confined, however, to the pattern presented by the familiar porphyrins.

Red-cell porphyrins are normal but during exacerbations porphyrin is detectable in the plasma. There is a well-marked reciprocity in the route of excretion of porphyrin. Thus during phases of remission faecal protoporphyrin and coproporphyrin are high whilst urinary porphyrins are only moderately increased. During exacerbation, the porphyrin levels in the stool fall, even to normal levels, whilst coproporphyrin in the urine rises and to some extent uroporphyrin also and these may be accompanied by considerable quantities of porphobilinogen.

Illustrative cases

VP Case 1. Male aged 21. This patient belongs to a family in which one death from porphyria has already occurred. He was observed during an exacerbation brought on by the taking of barbiturates and then continuously until remission was established. During the acute phase his urine contained a considerable quantity of porphobilinogen (138 mg./l.) and very large amounts of coproporphyrin and uroporphyrin while the faecal porphyrin levels were only moderately greater than normal (see first set of values in Table I). His plasma at this time exhibited intense red fluorescence but the porphyrin was found to be inextractable. By the time he had come into clinical remission, the urinary porphyrin had dropped and porphobilinogen became normal but the faecal porphyrin had increased, illustrating reciprocity in route of excretion (Rimington, 1962 and 1963; Waldenström, 1957; Goldberg and Rimington, 1964). His plasma was also less fluorescent (see second set of values in Table I).

Biochemical examination showed the presence of unusual porphyrins characterized by high water solubility but insolubility in ether; they differed
chemically from uroporphyrin or porphyrins intermediate between uroporphyrin and coproporphyrin (Rimington and Lockwood, 1966). Throughout his illness no abnormality was found in the porphyrins of his red cells.

**VP Case 2.** Female aged 19. This girl was a sister of VP Case 1. She had been followed biochemically during two exacerbations separated by a period of remission. The picture of porphyrin distribution and excretion which she presented was essentially similar to that of her brother although less opportunity occurred to demonstrate reciprocity in the route of porphyrin excretion. She appeared to be very sensitive to oestrogens which were almost certainly responsible for precipitation of her first exacerbation. In her plasma, protoporphyrin was found at a level of 7.4 µg./100 ml.; her blood-cell porphyrins were normal. She also excreted the unusual hydrophilic porphyrins detected in her brother’s urine and faeces.

**Photobiological Features**

To demonstrate abnormal skin photosensitivity, a high output irradiation monochromator (Magnus, Porter, McCree, Moreland, and Wright, 1959) was used and 29 of our 35 patients with porphyria were so investigated. Each narrow wave-band was studied in turn using a number of exposures of increasing length; thus the approximate threshold dose could be estimated for any skin...
response at each spectral region. Data obtained in this way must however be treated with caution and the inaccuracies inherent in action spectroscopy, as this procedure is called, have been pointed out by Magnus (1964).

In porphyria patients such responses are seen at the 400 mμ region and, to a lesser extent, in the band 500–600 mμ. This corresponds well with the absorption spectrum of porphyrin and is to be contrasted with the action spectrum of normal sunburn in which peak activity is in the shorter UV wavelengths (see Fig. 3). The reactions in the skin of a porphyric patient may be subjective only, a burning, pricking, or scalding sensation felt during irradiation and for about half an hour afterwards; or it may be an objective response. Types of objective response are as follows: (a) immediate erythema, temporary, lasting 15 to 60 minutes or prolonged for up to 36 to 72 hours. The erythema is confined to the skin area irradiated. (b) delayed erythema, where there is a latent period of a few hours. Reaction persists for one to three days and is quite strictly confined to the irradiated skin site. (c) weal and flare, indistinguishable from the triple response, the erythema spreading out several centimetres beyond the irradiated skin site but the weal being confined to this site. Sometimes the weal is not associated with significant flare. (d) delayed oedema, a swelling pinker than, or more or less the same colour as, normal skin. It becomes apparent two to six hours after exposure and lasts from six hours to seven days. It has occasionally been associated with purpura. (e) bullous response, preceded for a day or so by the delayed oedema reaction (d).

With our irradiation monochrometers normal persons do not often produce erythema reactions to wavelengths longer than about 330 mμ, if the dose is such that can be given within a practical time, e.g. 15 minutes, the longest exposure used on patients. With exposures of about an hour and a half it is occasionally possible to produce erythema with wavelengths longer than 330 mμ in normal persons though we have only succeeded on one occasion with 400 mμ.

Illustrative Cases of Abnormal Skin Reactions to Monochromatic Irradiation

Wealing response

PCT Case 1. 300 mμ irradiation gave a delayed erythema, i.e. a normal sunburn reaction, the threshold dose being about 1.7×10^4 μW. sec./cm.²; though the normal range is wide, this is a high threshold if the normal mean is taken to be about 2.5×10^4 μW. sec./cm.² (Rottier and van der Leun, 1960; Rottier, 1962). The wavelengths 320 to 360 mμ gave no erythema, nor did 450, 700, and 800 mμ, in the visible spectrum. On the other hand, 380 and 425 mμ gave just perceptible urticarial reactions with large doses, viz. 6.8 and 10.2×10^4 μW. sec./cm.² respectively. Similarly threshold wealing at 500 and 600 mμ occurred with 8.2 and 23.6×10^4 μW. sec./cm.² respectively. The most reactive wavelength was 400 mμ, which with large doses produced an immediate erythema followed by a weal with a flare; the weal sometimes showed small pseudopods. The threshold dose for wealing at 400 mμ was about 3×10^4 μW. sec./cm.², that is smaller than at 380, 425, 500, and 600 mμ. Immediate pigmentation reactions were frequently seen at most wavelengths between 340 and 500 mμ inclusive. A plot of the action spectrum for wealing is shown in Fig. 4. This should be compared with Fig. 3 which shows the normal pattern of
erythema curve for sunburn and the absorption spectrum of protoporphyrin. The absorption spectra of uroporphyrin and coproporphyrin are similar.

Wealing responses to essentially similar wavelengths were seen in other patients; these were EPP Case 15 and PCT Cases 8, 11, and 13. VP Cases 1 and 2 also showed wealing at 400, 500, and 600 mμ but full action spectra were not determined. Only EPP Case 15 and PCT Case 11 noted urticaria from exposure to the sun and both had earlier been diagnosed as cases of idiopathic solar urticaria. PCT Case 11 had originally showed the delayed oedema reaction, more recently the triple response; on one occasion she had shown purpura and an haemorrhagic bulla to monochromatic light (see Magnus, Porter, and Rimington, 1959).

\[4\text{Or}^\sim\text{Delayed erythema}\]
\[3\text{Or}^\sim\text{Weal}\]
\[3\text{Or}^\sim\text{No reactions}\]
\[3\text{Or}^\sim\text{Reactions}\]

Wave length; mμ

300 400 500 600 700

Reactivity: log units

Fig. 4. Action spectrum for the normal sunburn response (delayed erythema) and that for wealing reaction of triple response in porphyria cutanea tarda Case 1. Note maximal reactivity for wealing at 400 mμ and lesser reactivity at 500 to 600 mμ, corresponding to absorption spectrum of porphyrin, cf. Curve B in Fig. 3.

Delayed oedema response

EPP Case 10. The wavelengths 250 to 340 mμ gave delayed erythema reactions that were essentially within normal limits, though the threshold doses were somewhat high, e.g. 1·6 \times 10^8 μW. sec/cm.² at 300 mμ. But at 400 mμ a delayed oedema response occurred; the threshold was about 3·3 \times 10^8 μW. sec/cm.². This reaction, which was preceded by erythema, appeared about six to eight hours after exposure and lasted about eight to 12 hours. A plot of the spectral reactivity for persistent erythema found in this man is shown in Fig. 5. At 400 mμ the threshold for erythema and for delayed oedema were the same.

Other patients showing similar erythema reactivity and with the delayed oedema response are EPP Cases 3, 4, 5, 10, 11, and 12 and PCT Cases 10 and 11. EPP Case 3 sometimes showed purpura as well. It has already been noted that PCT Case 11 originally showed the delayed oedema reaction, sometimes with purpura.

Erythema reaction only

A number of patients showed this, including EPP Cases 7, 13, 16, and 17 and PCT Cases 3, 4, 6, 7, 9, 14, 15, and 16. The shape of the action spectrum
was essentially the same as that shown in Figs. 4 and 5, though not all of them were studied as fully. EPP Case 16 showed maximal reactivity for erythema at 410 rather than 400 m\(\mu\). Two other EPP patients had maximal reactivity between 390 and 425 m\(\mu\) with no clear peak at 400 m\(\mu\).

**Negative reaction**

This occurred in three instances, in EPP Cases 1, 2, and 8. In EPP Case 1, irradiation with 400 m\(\mu\) alone was usually negative, though occasionally transient immediate erythema occurred. If irradiation was done after prior warming of the skin a definite persistent erythema reaction was produced. The skin was warmed for about five minutes by placing a hot water bottle against it; this produced a temporary heat erythema which had vanished by the time irradiation with the monochromator was completed. Unfortunately a proper study of the skin temperature could not be undertaken at that time.

The whole procedure, i.e. irradiation of warmed skin with 400 m\(\mu\) was repeated on a normal subject with a negative result. Unfortunately EPP Cases 2 and 8, who also were negative to monochromatic 400 m\(\mu\) radiation, were not available for test in this way.

**Variable response**

EPP Case 5 readily gave erythema reactions with 400, 500, and 600 m\(\mu\). The wavelength 400 m\(\mu\) also gave a well-marked delayed oedema reaction if the skin was heated prior to irradiation. This reaction could also be provoked without prior skin warming, but the response was then generally weak and not always reproducible.

It was frequently impossible to repeat the monochromator tests on an individual patient after intervals of months or years. However, this was done in a few instances, namely on EPP Cases 7 and 15, PCT Case 11, and VP Case 1; they all showed variability in reactivity. EPP Case 7 was negative on a first
occasion, although the diagnosis was known; repeated some months later results similar to those in Fig. 5 were produced. In EPP Case 15 a rise and fall in skin photosensitivity paralleled similar changes in the severity of the porphyrin metabolism (Magnus, Jarrett, Frankerd, and Rimington, 1961). Correlation between a fall of photosensitivity at 400 μm and a reduction in severity of the biochemical disorder also occurred in VP Case I.

**Histology**

The results of full histological and histochemical studies of the skin in various kinds of porphyria, in polymorphic light eruption, and other dermatological conditions associated with solar exposure are given in detail by Ryan (1966). Here we are concerned only with porphyria.

**Histology of Erythropoietic Protoporphyria**

Eight patients were studied and all showed a characteristic picture in exposed skin; covered skin, on the other hand, was normal. In sections stained with haematoxylin and eosin there was sometimes hyperkeratosis and acanthosis and the rete ridges were elongated, narrow, and pointed; or the epidermis might be entirely normal. The main abnormality was in the upper dermis where amorphous material lay in and around the capillary walls. When present in large quantities, this substance widened the papillae. This change was only found in skin exposed to the sun but was present even where there was no sign of clinical abnormality. The papillary vessels appeared tortuous, and endothelial proliferation was sometimes seen. In some sections the capillaries were surrounded by cells which could not be identified with certainty (see Plate 6, Fig. 6).

The amorphous material was strongly PAS positive and with this method its distribution could not be seen much more clearly than in sections stained with haematoxylin and eosin. In biopsies from exposed but clinically normal skin, the PAS-positive material closely followed the capillaries and was almost entirely in the dermal papillae (Plate 6, Fig. 7). Skin showing clinical changes had greater amounts of this substance (Plate 6, Fig. 8).

**Histochemistry of the amorphous material**

The PAS-positive material is not glycogen as the staining is unaltered by diastase. Nor is it lipid as it is not removed by hot pyridine, and the staining is not prevented by bromination. On the other hand, the PAS staining is inhibited by acetylation but restored by alkaline hydrolysis. This suggests that the PAS staining is due to 1:2 glycol groups, which may be present in a carbohydrate-protein complex, i.e. neutral mucopolysaccharide, mucoprotein, or glycoprotein (Leblond, Glegg, and Eidinger, 1957).

The results of staining fresh frozen sections with toluidine blue and alcian blue at pH 2·0 suggest, in addition, the presence of traces of acid mucopolysaccharide in the amorphous material, but not in all biopsies.

Lipid is present in the amorphous material in all cases. This is readily demonstrated in unfixed frozen sections stained with Sudan IV or Sudan Black B. In
One case a stronger result was obtained by using formol-calcium fixed post-chromed tissue (Plate 6, Fig. 9). In some cases lipid closely follows the capillary walls, in others it is distributed unevenly throughout the amorphous material. Tryptophan is detectable with the dimethylaminobenzaldehyde nitrite test (Adams, 1957). The blue colour of the amorphous material contrasts well with the negative normal surrounding collagen (Plate 7, Fig. 10).

Collagen, reticulin, and elastic fibres are few in number or absent in the amorphous areas, and there is no solar elastosis. Mallory's phosphotungstic acid haematoxylin method for fibrin and the methyl violet, congo red, and thioflavin T stains for amyloid are also negative.

It should be noted that in six biopsies examined from exposed skin, fresh frozen sections did not show primary porphyrin fluorescence.

**Histology of Porphyria Cutanea Tarda**

Eleven patients were examined. In exposed skin, bullae were present in five biopsies and were subepidermal in four, intraepidermal in one. The subepidermal bullae showed festooning of the base as described by Bolgert, Canivet, and Le Sourd (1953). None of the patients with PCT had solar elastosis. Only one patient showed amorphous material to the same extent as obtained in EPP; this was Case 10 with the hereditary type of PCT, the patient previously described by Wells and Rimington (1953). The histochemistry of the amorphous material was precisely the same as in EPP. Of the remaining 10 patients studied, five had thickened intensely PAS-positive vessel walls. Lipid closely followed the capillary walls; this was demonstrated in three of these five biopsies when stained with Sudan IV and Sudan Black B, and also in two others who gave a normal appearance with PAS. These changes were never as extensive as in EPP. The remaining three patients showed no histochemical abnormality. Biopsies from clothed skin were all normal (see Plates 8 and 9, Figs. 11 and 12).

**Histology of Variegate Porphyria**

In the exposed skin the walls of the papillary capillaries appeared thickened when stained with PAS, and gave a strongly positive result for lipid. The clothed skin was normal. Only one case was examined.

**Pharmacological Tests**

A few patients had simple pharmacological tests with a view to elucidating the mechanism of the skin reactions provoked by light. These were all patients who had consistent responses from monochromatic radiation. The following procedures were used:

- Antihistamines were used to block histamine release in the skin.
- Compound 48/80 was used to deplete the skin of histamine.
- Acetyl salicylic acid was given to block so-called 'slow reacting substance'.
Chloroquin, 100 mg. b.d. for seven days up to the day of testing, was given to see if it reduced the response to radiation as seems to occur in the polymorphic light eruption. Prednisone was used for its anti-inflammatory action. Tests were also done on four patients to see if the reaction was reduced if the skin was hypoxaemic. In one of these an attempt was also made to increase the oxygen tension of the skin.

The results of these tests are summarized in Table II.

**Table II**

**Results of Pharmacological Tests on Monochromatic Radiation Lesions**

<table>
<thead>
<tr>
<th>EPP Cases</th>
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<tbody>
<tr>
<td>No. 3. Usual reaction to radiation, 400 mμ</td>
<td></td>
</tr>
<tr>
<td>Tests: Chlorpheniramine maleate</td>
<td></td>
</tr>
<tr>
<td>Prednisone</td>
<td></td>
</tr>
<tr>
<td>No. 10. Usual reaction to radiation</td>
<td></td>
</tr>
<tr>
<td>Tests: Chlorpheniramine maleate</td>
<td></td>
</tr>
<tr>
<td>Acetyl salicylic acid</td>
<td></td>
</tr>
<tr>
<td>Prednisone</td>
<td></td>
</tr>
<tr>
<td>48/80</td>
<td></td>
</tr>
<tr>
<td>No. 11. Usual reaction to radiation, 400 mμ</td>
<td></td>
</tr>
<tr>
<td>Tests: Cyproheptadine HCl</td>
<td></td>
</tr>
<tr>
<td>Acetyl salicylic acid</td>
<td></td>
</tr>
<tr>
<td>48/80</td>
<td></td>
</tr>
<tr>
<td>Chloroquin</td>
<td></td>
</tr>
<tr>
<td>No. 15. Usual reaction to radiation, 400 mμ</td>
<td></td>
</tr>
<tr>
<td>Test: Mepyramine maleate</td>
<td></td>
</tr>
<tr>
<td>No. 16. Usual reaction to radiation, 400 or 600 mμ</td>
<td></td>
</tr>
<tr>
<td>Tests: Cyproheptadine HCl</td>
<td></td>
</tr>
<tr>
<td>48/80</td>
<td></td>
</tr>
<tr>
<td>Hypoxaemia</td>
<td></td>
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<tr>
<td>Hyperoxaemia</td>
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<tr>
<td>Chloroquin</td>
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<table>
<thead>
<tr>
<th>PCT Cases</th>
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</thead>
<tbody>
<tr>
<td>No. 1. Usual reaction to radiation, 400 mμ</td>
<td></td>
</tr>
<tr>
<td>Tests: Chlorpheniramine maleate</td>
<td></td>
</tr>
<tr>
<td>Prednisone</td>
<td></td>
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<tr>
<td>Acetyl salicylic acid</td>
<td></td>
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<tr>
<td>Hypoxaemia</td>
<td></td>
</tr>
<tr>
<td>Chloroquin</td>
<td></td>
</tr>
</tbody>
</table>

Immediate erythema persisting for about 2 days; oedema appearing 4-6 hours after irradiation.

Reduced weal from intradermal histamine; 400 mμ reactions unchanged.

Immediate erythema lasting about 1 hour with 400 to 600 mμ; oedema appearing 6-8 hours after irradiation with 400 mμ only.

Immediate erythema lasting about 1 hour; oedema appearing 3-4 hours after irradiation.

Reduced control histamine weal; 400 mμ and 500 mμ reactions unchanged.

Immediate erythema followed by weal and flare.

Immediate erythema persisting up to 3 days.

Reduced control histamine weal; 400 mμ and 500 mμ reactions unchanged.

Immediate erythema followed by weal and flare; delayed erythema appearing 6-12 hours later.

Reduced control histamine weal; weal and flare to 400 mμ and 600 mμ prevented but immediate and delayed erythema unaffected.

All reactions to 400 mμ unchanged.

Reduced control histamine weal; weal and flare to 400 mμ and 600 mμ prevented but immediate and delayed erythema unaffected.

All reactions to 400 mμ unchanged.

Reduced all reactions, weal and flare markedly.

Reactions to 400 mμ unchanged.
No. 3. Usual reaction to radiation, 400 mJ

Test: Cyproheptadine HCl

Immediate erythema followed by weal and flare; delayed erythema appearing 6–18 hours later.

Reduced control histamine weal; immediate erythema, weal, and flare to 400 mJ prevented, but delayed erythema unchanged.

No. 8. Usual reaction to radiation, 400 or 500 mJ

Tests: 1. Chlorpheniramine maleate
2. Hypoxaemia
3. Acetyl salicylic acid
4. Prednisone
5. Chloroquin

Immediate erythema followed by weal without significant flare; sometimes persistent erythema present next day.

Reduced control histamine weal; weal to 400 mJ and 500 mJ prevented.

Immediate erythema, weal, and delayed erythema to 400 mJ prevented.

Reactions to 400 mJ and 500 mJ unchanged.

Reactions to 400 mJ and 500 mJ unchanged.

No. 11. Usual reaction to radiation, 400 mJ

Test: Mepyramine maleate

Morphology various, at time of testing was immediate erythema followed by weal and flare.

Wealing possibly reduced slightly, control test to intradermal histamine not done.

No. 13. Usual reaction to radiation, 400 mJ

Tests: 1. Cyproheptadine HCl
2. 48/80
3. Hypoxaemia
4. Chloroquin

Immediate erythema, weal, and flare, then usually erythema persisting for about 2 days.

Reduced control histamine weal; weal and flare to 400 mJ prevented, no effect on immediate and delayed erythema.

Weal and flare to 400 mJ prevented, no effect on other reactions.

All reactions greatly reduced.

Reactions to 400 mJ unchanged.

**Antihistamines and Compound 48/80.**

First a dose of 400 mJ radiation was given; this was about three times the threshold for wealing as previously determined. Immediately afterwards 0.1 ml saline containing 0.1 mg histamine acid phosphate was injected intradermally into the mid-volar forearm. About 10 minutes later the area of the weal on the forearm was measured by tracing it on to graph paper. When this was done intramuscular antihistamine was given; this was usually 10 mg. of chlorpheniramine maleate or 10–20 mg. of cyproheptadine HCl. Two hours later the irradiation on the back and the intradermal histamine on the forearm were repeated. The latter was repeated so as to be sure that the antihistamine was working. Antihistamines were also tried on three patients with delayed oedema and one with erythema only.

Compound 48/80 was injected intracutaneously into the back, four injections of 0.1 mg each being given at the angles of a 2-cm. square of skin. The injections led to a large area of erythema and wealing which had settled 18 hours later. The area enclosing the four injection sites was then irradiated and control exposures made on untreated skin at a symmetrical site.

In EPP Case 15 and PCT Case 11 mepyramine maleate was given orally 100 mg. t.d.s. for three days and the irradiations then repeated.

**Acetyl salicylic acid.** This was given to four patients who showed either a weal or a delayed oedema response. Control exposures were made with several different doses of 400 mJ radiation, and were then repeated immediately after the last of four oral doses (each of 1.3 g.) of acetyl salicylic acid, given at hourly intervals.
**Corticosteroid.** Prednisone, 30 mg. daily for three days, was given to four patients; two of these had an immediate erythema and delayed oedema, the other two a triple response to irradiation. The threshold for these responses to light, as found the day before starting the prednisone, was compared with that during the last day of the course.

**The effect of oxygen.** In three patients (EPP Case 16; PCT Cases 1 and 13) a sphygmomanometer cuff (kept well above systolic pressure) was placed around the upper arm for 10 minutes immediately before irradiation, kept in place during the exposure and removed immediately afterwards. A dose sufficient to give a well-marked reaction, as found by previous tests, was given. In a fourth patient (PCT Case 8) a piece of 3 mm. thick plate glass was pressed firmly against the skin, so as to cause complete blanching. This was done by making the patient lean against the glass which was placed over the exit of the monochromator, the shutter being closed. After 10 minutes the shutter was opened and the exposure made with the glass still in position. The exposure time was slightly increased to take account of a minor degree of absorption by the glass (as found by prior spectrophotometric measurements).

In EPP Case 16 an attempt at raising the oxygen tension of the skin was made by getting the patient to breathe through a face mask. Pure oxygen was run through the mask at a rate of 12 litres per minute for 15 minutes before irradiation and was continued throughout the time the exposure was made.

**Results**

These are seen in Table II. Although not completely consistent, the results suggest that where a wealing response occurs this is due to histamine release. The only other tentative conclusion one can come to is that oxygen, or at least an intact blood-flow, appears to be necessary for the production of the lesion. Hypoxaemia appears to reduce or abolish all responses to light which is consistent with oxygen being associated with the early stages of the photochemical reaction.

**Differential Diagnosis**

Of the three porphyrias under consideration, EPP is that which is least well known and most often wrongly diagnosed. PCT and VP can pose diagnostic difficulties but they are not new problems and have been well treated elsewhere. With EPP the three most common errors have been to mistake it for polymorphic light eruption, lipid proteinosis, or psychoneurosis.

1. **Polymorphic light eruption**

A typical history in a case of EPP is unmistakable but it is sometimes difficult to separate it from polymorphic light eruption. In our experience, patients with the latter condition seldom complain of symptoms during or an hour or so after exposure; they do not commonly have symptoms from sunlight through window glass or clothes. However, we believe that all patients with photosensitivity should have urine, stool, and blood examined for porphyrins, preferably by quantitative analysis. The red cells may also be examined by
fluorescence microscopy for the red fluorescence of porphyrins, which in the case of EPP is transient, or screened by a qualitative biochemical test (Rimington and Cripps, 1965). Two patients in our series were wrongly diagnosed as polymorphic light eruption because these tests were not done when they were first seen. This error is especially liable to occur if the urine alone is examined for porphyrins, the normal value found in EPP being wrongly thought to exclude all types of porphyria. In addition, according to our experience, PAS-positive material is not observed histologically around the papillary capillaries in polymorphic light eruption.

High concentrations of red-cell protoporphyrin may be encountered in certain anaemias and in lead poisoning, but these conditions would hardly be confused with EPP on clinical grounds.

It seems probable that some of the cases reported in the older literature under the title of *hydroa aestivale* and *vacciniforme*, especially where the urine was stated to contain no excess porphyrin, were examples of EPP.

2. Lipoid proteinosis

The chronic skin changes in EPP resemble those seen in lipoid proteinosis. In the past this has led to a wrong diagnosis of lipoid proteinosis in many patients who really had EPP. For example, in this country Calnan and Shuster (1962) presented two patients at the Royal Society of Medicine as cases of lipoid proteinosis. These were later found to have EPP and are Cases 1 and 2 in the present paper. EPP Case 3 was also given an initial diagnosis of lipoid proteinosis. In South Africa, Scott and Findlay (1960), in their paper on lipoid proteinosis, included several patients who were later found to have EPP (Findlay, Scott, and Cripps, 1966). The latter authors also describe cases of VP with skin changes resembling lipoid proteinosis. Heyl (1963) also described cases of 'light-sensitive lipoid proteinosis with burning flesh syndrome' that really had EPP. Lipoid proteinosis or *hyalinosis cutis et mucosae* was described by Urbach and Wiethe in 1929 and is characterized clinically by a curious waxy thickening of the skin with scarring and warty excrescences. Histologically there is hyaline infiltration of the skin and mucous membranes. Amongst other peculiar clinical features may be mentioned hoarseness, which is an early and prominent symptom due to involvement of the mucous membrane of the larynx.

**Points of similarity between EPP and lipoid proteinosis**

Both show thickening and scarring of light-exposed areas. These chronic clinical changes are much more marked in EPP patients living in sunny countries, e.g. in South Africa (Findlay, Scott, and Cripps, 1966) than in this country where, as we have seen, lesions may be very slight or even absent. Both diseases may be familial. In both also there is PAS-positive hyaline material in the dermis which stains for carbohydrate, lipid, and protein. In both diseases no excess of porphyrins in the urine is to be expected.

**Points of distinction between EPP and lipoid proteinosis**

**Clinical features.** No mucosal changes have been reported in EPP; in lipoid
proteinosis mucosal changes are always present and symptoms referable to these, especially hoarseness due to laryngeal lesions. In EPP lesions are strictly confined to light-exposed areas; in lipoid proteinosis clothed skin may also be affected. The very characteristic lesions in lipoid proteinosis, where the free border of the eyelids shows 'beading', have not been reported in EPP. Lipoid proteinosis often shows radiological opacities in the region of the hippocampus, occasionally macular degeneration and absence of lateral incisors; none of these has been seen in EPP.

Histology. In EPP, PAS-positive amorphous material is found only in light-exposed areas of skin; in lipoid proteinosis it is also present in clothed skin and in mucous membranes. In EPP, PAS staining is always most marked in the upper part of the dermis and is found only around blood-vessels; in lipoid proteinosis it lies at all depths in the dermis and is found not only around capillaries, but also around appendages and in masses bearing no obvious relation to these structures.

Biochemistry. In all patients with EPP, the red-cell protoporphyrin concentration is increased (Table I). Although the stool porphyrins are also usually abnormal in EPP, they may be normal or only slightly raised (Haeger-Aronsen, 1963; Redeker and Bryan, 1964). The urinary porphyrin levels have always been normal, except in one of our patients (EPP Case 11) where there was a slight increase in uroporphyrin excretion. Quantitative studies on the blood, urine, and stools of proven cases of lipoid proteinosis with mucous membrane lesions are normal (Findlay, Scott, and Cripps, 1966).

3. Psychoneurosis

In some patients with EPP the only manifestation of an acute attack is an intolerable burning sensation. The chronic skin changes are often slight, at least in this country, and very easily missed (cf. the different picture in South Africa as shown by Findlay, Scott, and Cripps, 1966). This paucity of skin lesions, with the sometimes apparently hysterical behaviour resulting from the burning sensation, has led to some patients with EPP being wrongly diagnosed as psychoneurotic. This occurred in EPP Case 6 when he complained of intolerable burning while standing on parade in the sun when he was at school. EPP Case 7 was diagnosed as an hyster and attended psychiatrists for several years. This mistake was made because test irradiation with a therapeutic mercury-vapour arc in a physiotherapy department failed to provoke his symptoms; such a result is only to be expected since the appropriate wavelengths for activating porphyrin are only feebly represented in this source. The diagnosis of psychoneurosis extended to the parents of one patient with this disease when he was a child (EPP Case 5). Here the patient's mother was told that it was her emotional response which made her baby cry after exposure to sunlight and that there was nothing physically wrong with him.

A wrong diagnosis of psychoneurosis may also be made in cases of PCT, as in Case 12 who was thought for many years to be suffering from neurotic excoriations until her stool and urine porphyrins were examined (Beer, 1965).
Discussion

That photosensitivity in the diseases we now group together as porphyria is associated with the presence of porphyrins appears to have been first postulated by McCall Anderson (1898). This notion was further developed by Hausmann (1908) and Ehrmann (1909). Subsequently, the view was treated with reserve, on the grounds of lack of evidence (Brunsting, Brugsh, and O'Leary, 1939; Blum, 1964; Clare, 1956), in spite of the unambiguous self-experiment of Meyer-Betz (1913). Alternative suggestions were that the photosensitivity had an allergic basis (Burckhardt, 1958), or that it was a so-called Koebner or isomorphic response, the susceptibility to mechanical trauma being related to the 'physical trauma' due to light.

All porphyrins show well-marked absorption spectra. In a neutral solvent there is typically a system of four discrete absorption bands extending from 500 to 650 m\(\mu\) in the visible region, the intensities of which increase as one passes towards shorter wavelengths. A narrow band of much greater intensity of absorption occurs at about 400 to 410 m\(\mu\); this is the so-called Soret band (see Fig. 3, curve \(B\)).

The earliest evidence of photosensitivity in porphyria being associated with a specific waveband in the incident illumination was given by Urbach and Bloch (1934), who exposed a patient with PCT to filtered sunlight. Their results suggested that it was not the short UV wavelengths that cause normal sunburn that were active in porphyria. Next Riemerschmid and Quin (1941), in detailed absorption filter studies, showed that the limits of the action spectrum for skin photosensitivity corresponded closely to the absorption spectrum of the porphyrin. This was shown in Geeldikkop, a disorder of sheep associated with photosensitization, in which the photosensitizer is the porphyrin phylloerythrin, a breakdown product of dietary chlorophyll (Rimington and Quin, 1934). Studies on action spectra were then extended to human porphyria in cases of PCT and Günther's Disease by Wiskemann and Wulf (1959), in PCT by Magnus, Porter, and Rimington (1959), in EPP by Magnus, Jarrett, Prankerd, and Rimington (1961) and Holti, Magnus, and Rimington (1963), and in VP by Gordon (1964). Our present survey extends and confirms these findings. These are that the same wavelengths that are absorbed by the porphyrin molecule are those that cause lesions in the porphyric patient. This is in accordance with the Grotthus-Draper Law which states that only those wavelengths which are absorbed by a substance can excite it chemically.

If the original idea that photosensitivity in porphyria was due to porphyrin in the skin has been revived, our further knowledge of the mechanism remains fragmentary. It can, however, be said with confidence that light of wavelengths specifically absorbed by porphyrins may provoke reactions in the skin much in the same way as does natural sunlight.

The absorption of light energy by a photosensitizer can be taken to result in the production of an excited state (Blum, 1964) which is usually of very short duration. The excess energy may be dissipated by ionization, by fluorescence,
by transfer of energy to another molecular species, or by entry of the excited molecule into a direct chemical reaction. In the case of photosensitization reactions, there is evidence that in some instances oxygen plays a role (Blum, Watrous, and West, 1935; Oster, Bellin, Kimball, and Schrader, 1959; Slater and Riley, 1966; Allison, Magnus, and Young, 1966; the present investigation), suggesting that an essential part of the process may be the formation of oxygen-containing free radicals of the peroxo type. Such radicals are readily formed by the interaction of molecular oxygen and many other free radical systems (Wallenberg, 1957). If this view is correct, such an event would be harmful to the cells in which the reaction occurred, for example, epidermal cells. Lipid peroxidation, a process involving such radicals, is known to have a powerfully damaging action on lipid-rich structures, such as the many types of membrane system present in cells (Desai and Tappel, 1963; Hoffsten, Hunter, Gebicki, and Weinstein, 1962; Hochstein and Ernster, 1964).

Evidence has been accumulating that lysosomes, sub-cellular particles with lipid-rich membranes, may take part in the manifestations of photosensitivity (Allison and Young, 1964; Slater and Riley, 1965, 1966; Allison, Magnus, and Young, 1966). The first-named authors found uroporphyrin I to be taken up by lysosomes in cultures of rhesus monkey kidney cells. Slater and Riley (1966) demonstrated in rat-tail epidermis not only the disruption of lysosomes by the combined action of light and the chlorophyll porphyrin phylloerythrin, but also their protection if certain substances known to be free-radical scavengers were added to the system. Allison, Magnus, and Young (1966) found that the action spectrum for lysosome damage in tissue culture cells, pretreated with porphyrin, corresponded both with the absorption spectrum of porphyrin and the action spectrum for skin lesions in patients with porphyria. They also showed that oxygen was necessary for this damage. Tappel, Sawant, & Shibko (1963) have clearly shown that free radicals, induced by a variety of methods, cause rupture of a purified preparation of rat-liver lysosomes.

Lysosomes contain a variety of hydrolytic enzymes from which the remainder of the cell is protected by the integrity of the impermeable lysosomal membrane. Should this become damaged, the enzymes escape into the cytoplasm causing consequent damage and eventually the death of the cell. We feel that there is much to support the hypothesis that in light-sensitive porphyrias, porphyrins function in the presence of light as initiators of free radical (chain) reactions the free radicals then causing disruption of intracellular membrane systems such as those of the lysosomes, no doubt by a process of lipid peroxidation, with consequent liberation of damaging enzyme systems.

Release of lysosomal enzymes may play some part in the production of mediators which bring about the final pathological response in the skin. Our own pharmacological results, as those of others (e.g. Feldberg, 1953), point to histamine as being one such mediator in photosensitization due to porphyrins; where the response to light is urticarial it may be blocked by antihistamines. Our studies do not elucidate the mechanism of the delayed oedema or other types of reaction.
It seems possible that repeated photochemical reactions causing vascular effects might eventually lead to the histological changes seen around the papillary capillaries. These could result from direct action on the vessels, as wavelengths of 400-600 m\(\mu\) penetrate the skin well (Kirby-Smith, Blum, and Grady, 1942) or from action on dermal components such as, for example, mast cells; finally, the effect might be an indirect one via the epidermis. The delayed oedema response in porphyria might belong to the latter category, the latent period being the time required for some mediator substance of high molecular weight to diffuse from the epidermis to the dermal vessels. The facilitation of the response which we observed by warming the skin in some patients could perhaps be explained by more rapid diffusion of a mediator at the higher temperature, or by accelerated enzymatic action, or by both; the free radical generating mechanism is not temperature dependent. (The experiments of Lipson and Baldes (1960) are of interest in this connexion.) The burning sensation produced so rapidly by light in EPP and occasionally in PCT and VP might be brought on by a direct action of light on porphyrin situated near epidermal or sub-epidermal sensory nerves.

It may be asked whether natural sunlight of the appropriate wavelength is of sufficient intensity to bring on the phenomena provoked by monochromatic radiation. An average dose to produce a weal or the delayed oedema reaction is about \(3 \times 10^8 \mu\text{W. sec./cm.}^2\) at 400 m\(\mu\); is there enough of this wavelength in ordinary sunlight to provoke a skin lesion in a porphyric patient within an hour or so? Unfortunately, there are very few published records of the spectral distribution of energy from the sun in absolute units; the most appropriate seem to be those published by Stair, Johnston, and Bagg (1954) who recorded values of solar energy from 299 to 535 m\(\mu\) at an altitude of 9,200 feet in New Mexico. Caution must be exercised in arguing from these data, but calculations made from them, nevertheless, suggest that the sun emits enough energy at 400 and 500 m\(\mu\). Even if a patient were not to receive enough energy on a single occasion to produce an acute lesion in the skin, it is possible that smaller doses could be summated and lead to the chronic effects, such as those seen by histological examination.

It must be pointed out that in the three diseases we have been discussing the end result is very similar, namely, that photosensitivity is present in the skin to the same spectral wavebands in all three, in spite of wide differences in the basic biochemical abnormality in each. It is quite impossible to differentiate clearly between these three porphyrin disorders by action spectroscopy of the skin alone. However, some types of abnormal morphological reaction were found to be commoner in certain types of porphyria than in others, e.g. urticarial responses occurred in five PCT patients and in both those with VP, but only in one with EPP. The delayed oedema response, on the other hand, was most frequent in EPP. The histological changes in and around capillary walls are much the most striking in EPP, but occur also in PCT and VP.

Where an accurate clinical history of acute photosensitivity is obtainable, this is often highly characteristic; an observant patient will note subjective
symptoms, or even the provocation of an acute skin response, from sunlight through window glass or thin clothing. In the United Kingdom a sunlight effect of this kind is most unlikely to be due to short ultraviolet radiation in the 300 mμ region for it is extremely unusual for such wavelengths to penetrate ordinary window glass or thin clothing in sufficient amount to cause any response in the skin. Longwave ultraviolet radiation and visible light can, however, do so, as evidenced by skin photosensitivity provoked through clothing by 8-methoxypsoralen where the active wavelengths lie around 380 mμ, i.e. bordering the visible spectrum (Buck, Magnus, and Porter, 1960). Since porphyria is probably the commonest cause of photosensitivity to visible light in man, such observations submitted by the patient constitute a useful diagnostic pointer.

We are grateful to our clinical colleagues, too many to thank individually, for allowing us to investigate patients under their care and to the patients themselves for cooperating.

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Summary

A survey has been made of 35 patients with porphyria and skin photosensitivity. They comprise 17 cases of erythropoietic protoporphyria (EPP), 16 of porphyria cutanea tarda (PCT), and two of variegate porphyria (VP)

Consideration is given to the clinical picture, the diagnostic clinical chemistry, and histological changes in the skin. A description is given of photobiological examination, carried out on 29 patients. Some simple pharmacological tests were also performed. The differential diagnosis of EPP is discussed.

Patients with EPP often gave a distinctive clinical history, highly suggestive of sensitivity to sunlight, and sometimes allowing the diagnosis to be made correctly on these grounds alone. On the other hand, the clinical changes in skin were frequently slight and very easily overlooked. These mild clinical lesions are in marked contrast with the histological changes, which are obvious even in skin appearing clinically normal. The essential abnormalities are PAS-positive amorphous material and lipid found in the distribution of the upper dermal capillaries. For a firm diagnosis of EPP, however, biochemical studies are essential, the characteristic feature being a large increase in the concentration of erythrocyte protoporphyrin. The red cells may show transient fluorescence indicative of porphyrin by fluorescence microscopy. Stool porphyrin levels are usually but not always raised, urinary porphyrins, on the other hand, are always normal.
Fig. 1. Close-up of nose of erythropoietic protoporphyria Case 5 to show superficial scarring. The small dark flecks are freckles.

Fig. 2. Abrasions of finger from minor trauma in variegated porphyria Case 1.
Fig. 6. Erythropoietic protoporphyria, Case 3; from thickened skin over knuckle. Haematoxylin and eosin, x 50. Note increased cellularity of upper dermis.

Fig. 7. Erythropoietic protoporphyria, Case 10; from clinically normal skin on dorsum of hand. Unfixed frozen section stained with PAS, x 80. Note PAS staining associated with papillary capillaries.
Fig. 8. Erythropoietic protoporphyria, Case 2; from thickened skin on dorsum of hand. Paraffin section stained with PAS and light green, × 85. PAS-positive material associated with capillaries in upper dermis.

Fig. 9. Erythropoietic protoporphyria, Case 7; from thickened skin over knuckle. Formol-calcium fixed postchromed section stained with Sudan Black B, ×85. Shows lipid in upper dermis.
Fig. 10. Erythropoietic protoporphyria, Case 6; from thickened skin of index finger. Stained by DMAB nitrite method, × 112. Shows tryptophan associated with capillaries in dermal papillae.
Patients with PCT of the symptomatic type, generally associated with alcoholism, may not give a distinct clinical history suggestive of photosensitivity. On the other hand, the clinical signs in the skin are usually characteristic. The histological changes in sun-exposed skin, apart from bullae, are generally slighter than in EPP. The biochemical diagnosis of symptomatic PCT is made on a greatly increased excretion of urinary uroporphyrin. The red-cell porphyrins are normal, though occasionally the plasma may contain detectable porphyrin.

Two patients with PCT of the hereditary type gave a history and showed clinical and histological features similar to EPP. Urinary coproporphyrin and faecal porphyrins were raised.

The two patients with VP gave a history which was highly suggestive of photosensitivity and similar to that obtained in EPP. The histological abnormalities were similar to those in PCT. The biochemical picture shows interesting features which are discussed.

From photobiological studies, using a high intensity irradiation monochromator, it is possible to show that the skin of nearly all these patients reacts to visible light at the 400 m/region and to a lesser degree to the band 500 to 600 m/.

Such an action spectrum corresponds well with the absorption spectrum of porphyrins. Experimental lesions similar to those provoked by natural sunlight were often produced. Erythema reactions, the classical triple response, or a delayed oedema reaction were obtained.

Simple pharmacological tests were done to see if the reaction to monochromatic irradiation could be modified with a view to identifying the mediators of the lesions due to light. Evidence was produced that histamine may be one of the mediators responsible for the pathological reaction in the skin. The cause of the erythema and delayed oedema reactions was not ascertained.

In regard to the mechanism of the photosensitivity, it is suggested that porphyrins in the skin, possibly located in or near lysosomes, are chemically activated by light of the wavelengths most strongly absorbed by the porphyrin molecule. The presence of oxygen appears to play a part in subsequent reactions leading to injury of the lysosomal membrane and consequent cellular damage.

The reactions in the skin to monochromatic radiation and also to some extent the histological changes are similar in all the three porphyria conditions considered, despite markedly different biochemical features.

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Fig. 11. Porphyria cutanea tarda, Case 8, from temple. Paraffin section stained with PAS and haematoxylin, x120. Shows subepidermal bulla and slight thickening of papillary capillaries.
Fig. 12. Porphyria cutanea tarda, Case 12; from extensor aspect of forearm. Unfixed frozen section stained with Sudan Black B, x 64. Shows lipid in distribution of papillary capillary.
PORPHYRIA AND PHOTOSENSITIVITY