The Clinical Chemistry of Variegate Porphyria With Special Reference to the Identification of a New Plasma-Marker Porphyrin

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A. Introduction

South Africa has the unenviable distinction of having the highest incidence in the world of variegate porphyria (VP) (South African genetic porphyria) (8), with an estimated incidence of approximately 9000 affected persons. How this remarkable situation has come about has been fully documented by Dean (5) in his monograph, which makes it clear that virtually all South African variegate prophyrics are descendants of a daughter of a marriage that took place at the Cape in 1688 and all are, therefore, members of one huge family. We have investigated one of the four main lines of descent that, as is shown in Figure 1, extends over ten generations and conforms to the pattern of an autosomal dominantly inherited disorder of high expressivity and penetrance. The designation 'variegate,' which was first applied by Barnes and Dean (1) aptly described the various forms that the disease assumes. They are summarized with their percentage incidence in Table 1.

As the title indicates, the first objective of this paper is to provide an account of the biochemical features of VP, but in view of the inordinately high local incidence of alcohol-associated SP and the clinically indistinguishable cutaneous manifestations of these two disorders, it is appropriate to consider the biochemical features of SP pari passu with those of VP. The second objective is to consider briefly two poorly appreciated aspects of VP, namely the profound electrolyte and uremic disorder of the acute VP attack and the nature and diagnostic significance of the fecal porphyrin peptides (porphyrin X). The main objective, however, is to give a brief report of a new ultrasensitive method of erythrocyte and especially of plasma porphyrin analysis that has led to the discovery of the consistent presence in the plasma of VP patients of a new hitherto undescribed 'marker' porphyrin.

B. The Clinical Chemistry of VP

We have investigated the clinical chemistry not only of VP but also of SP as well as the other porphyrias by both solvent extraction and thin layer chromatographic (TLC) analytic techniques.

I. Solvent Extraction Analysis

The simplified scheme of the porphyrin biosynthesis shown in Figure 2 includes the byproducts that are amenable to quantitative analysis.

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Simplified inheritance line of porphyria variegata
(from 1688-1973)

Fig. 1. One of the four lines of descent of VP in South Africa. With permission:

Table 1. Percentage (%) incidence of the different presentations of VP

<table>
<thead>
<tr>
<th>Mode of involvement</th>
<th>%</th>
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<tbody>
<tr>
<td>Cutaneous involvement (total)</td>
<td>89</td>
</tr>
<tr>
<td>Cutaneous involvement only</td>
<td>54</td>
</tr>
<tr>
<td>Acute attacks (total)</td>
<td>65</td>
</tr>
<tr>
<td>Acute attacks only</td>
<td>11</td>
</tr>
</tbody>
</table>

Thus δ-aminolevulinic acid (ALA) and porphobilinogen (PBG) are readily determined by the resin column techniques of Mauzerall and Granick (30), while the porphyrins - uroporphyrin (uro), coproporphyrin (copro), and protoporphyrin (proto), which are oxidation products of their respective porphyrinogen intermediates - are easily determined by solvent extraction (SE) analytic techniques, such as the method of Rimington and Sveinsson (36) for urinary uro and copro, and the method of Holti et al. (26) for fecal copro and proto. The quantitative determination of all of the above-mentioned intermediates constitute the minimum requirements for the proper biochemical evaluation of VP. Data drawn from a study completed in 1963 (10) made it possible to characterize the diagnostically distinctive patterns of porphyrin excretion of VP and SP shown in Figure 3. These findings were substantiated in a later report (21) of our accumulated experience, which confirmed a markedly increased fecal proto to be the hallmark of VP, with proto usually exceeding copro. This has held good in all cases of VP except in the rare instances of intercurrent liver disease,