Acquired Porphyria in Man and Rat due to Hexachlorobenzene Intoxication

SINCE 1956, an outbreak of cutaneous porphyria involving several thousand cases has been noted in three south-eastern provinces of Turkey[1]. Affected individuals, predominantly children and adolescents, exhibit photosensitivity with hydroa æstivale, marked porphyrinuria and hepatomegaly, but no abdominal or neurological symptoms. Epidemiological studies suggested the possibility that the disease might be related to the ingestion of wheat treated with a fungicide containing hexachlorobenzene[1,2]. Since direct verification of this possibility by field investigation has not been obtained[1], and since the available toxicological information on hexachlorobenzene is conflicting[3], an attempt was made to produce hexachlorobenzene porphyria in rats.

Adult male Sprague–Dawley rats were fed *ad lib.* ground 'Purina Laboratory Chow' containing 0·2 per cent hexachlorobenzene. Urinary and fæcal excretion of porphyrins and porphyrin precursors were determined periodically[4], and tissue porphyrins[5] and liver catalase[6] were measured in rats killed while porphyric.

Of a total of 33 rats started on the experimental diet, 13 died within the first month, exhibiting terminal tremor, ataxia, weakness, and paralysis, without evidence of major disturbance in porphyrin metabolism. In the remaining 20 rats, a significant increase in urinary excretion of porphyrins and porphyrin precursors was first noted after 2 to 8 weeks of hexachlorobenzene administration (Fig. 1). Peak excretory values per 24 hr. were as follows (normal values in parentheses): δ-amino-lævulinic acid, 1·40 mgm. (0·06 mgm.[7]); porphobilinogen, 16·96 mgm. (0·01 mgm.[7]); uroporphyrin, 0·360 mgm. (trace[8]); coproporphyrin, 0·211 mgm. (0·016 mgm.[8]). Slight to moderate increases in fæcal excretion of copro- and proto-porphyrin were also noted. From 200 ml. of rat urine, 55 mgm. of crystalline porphobilinogen were obtained[9].

In rats in which hexachlorobenzene administration was discontinued shortly after these peak excretory values had been approximated, the disturbance in porphyrin metabolism was rapidly reversed with return to normal excretion values within a week. However, maintenance of high levels of porphyrin excretion by continued feeding of hexachlorobenzene for two to three weeks resulted in an apparently irreversible porphyric state, in which marked porphyrinuria continued in spite of cessation of drug administration (Fig. 1). These animals died with the neurological complications described above.

Hepatomegaly was common in porphyric rats. Histological studies revealed liver cell degeneration, most prominent around central veins, and increased size and number of Kupffer cells. Chemical analysis of liver tissue showed the following results, per 100 gm. wet tissue (normal values in parentheses): uroporphyrin, 0·4–0·5 mgm. (trace[8]); copro- and proto-porphyrin, 0·05–0·15 mgm. (0·01–0·02 mgm.[8]); porphobilinogen demonstrable[5] in aqueous extract of liver tissue. No significant reduction in liver catalase activity was found.

In the blood, concentrations of hæmoglobin, copro- and proto-porphyrin were normal, while uroporphyrin was not detectable. At autopsy, intense red fluorescence was observed in the cortex of long bones, but not in the marrow.

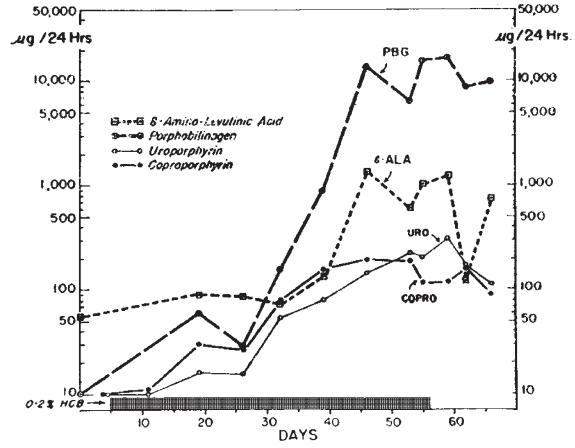

Fig. 1. Urinary excretion of porphyrins and porphyrin precursors in a 350-gm. male rat fed hexachlorobenzene. The rat died on the 68th day of the experiment, that is, 63 days after the start of the hexachlorobenzene administration and 12 days after the toxin had been withdrawn

These results demonstrate that in the rat chronic ingestion of hexachlorobenzene may indeed result in a profound disturbance in porphyrin metabolism, characterized by increased amounts of porphyrins and porphyrin precursors in the liver and excreta, with histological evidence of hepatocellular degeneration. These findings support the suggestion[1], derived on the basis of epidemiological data, that hexachlorobenzene ingestion is the cause of the recent outbreak of porphyria in Turkey. This experimental result is of particular interest in that, hitherto, human porphyria was assumed to be genetically determined, because conclusive evidence for the existence of a purely acquired form of this disease has been lacking. The widespread appearance of porphyria among three genetically distinct populations in south-eastern Turkey—domestic Turks, Kurds and Turks repatriated after several centuries of residence in the Balkans—makes its dependence on an inherited abnormality extremely unlikely.

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