EDITORIAL

AN OUTBREAK OF TOXIC PORPHYRIA IN SOUTHEASTERN TURKEY

In the summer of 1956, several patients appeared in the province of Diyarbakır in southeastern Turkey exhibiting a symptom complex never seen before. Very soon the disease was labelled as "the black sore" by the patients and the local people. The chief clinical manifestations observed included marked photosensitivity of the skin, resulting in severe blistering, scarring and mutilation of exposed parts of the body, often complicated by severe secondary infection of the blisters. In addition, patients noted hypertrichosis, hyperpigmentation, weight loss, weakness and the excretion of red urine.

In the summer of 1957 a larger group of patients appeared with the symptoms, in 1958 they numbered in the hundreds, especially during the summer months, and in 1959 new cases continued to appear in considerable numbers. As recently as January of 1960 sporadic new cases were still appearing. The exact number of patients so affected is not known, but estimates by local physicians range between 3000 and 5000. These patients are concentrated in the towns and villages of the province of Diyarbakır and two adjacent provinces, Mardin and Urfa. There we find that individuals from all walks of life, from the urban centers, smaller towns and even fairly remote villages are involved.

Dr. Cihat Çam, a dermatologist practicing in this part of Turkey, first recognised the disease as a form of porphyria.[1] Beginning in the fall of 1958, we were given an opportunity to study ten children suffering from the disease at the Research Institute of Child Health of Ankara University. Recently, more patients have been admitted to the Children's Hospital of this Institute for further study. Credit goes to Dr. Joe D. Wray for arousing keen interest in this problem at the Hacettepe Children's Hospital, and to Dr. Vedat Sezer of our staff for his painstaking work during a three month survey in the southeastern district.

Our hospital studies revealed liver enlargement with tenderness and evidence of mild malfunction, arthritic changes of the interphalangeal joints which have the x-ray appearance of rheumatoid arthritis, and emaciation with marked growth retardation in many child-

ren. Qualitative and quantitative analyses of porphyria excretion in the urine demonstrate markedly increased excretion of uro-and coproporphyrins, but practically no porphobilinogen. Although fecal coproporphyrin is definitely increased in these cases, it is far from the magnitude experienced by Dr. Dean in his South African patients.[2]

Dr. Sezer's survey of 300 patients revealed that 90% of the patients were under the age of 20, while 70% were between the ages of 6 and 15. In this series there were 190 males and 110 females. All of them showed porphyrinuria and all or most of the findings described above. 80% of the children were below the third percentile for their age in height and weight.

How can we relate this picture to known forms of porphyria? In the congenital or erythropoietic form symptoms appear very early in life and the most important features are photosensitivity, porphyrinuria and a hemolytic anemia. Here there seems clearly to be an hereditary basis for the disease, in spite of its rarity, and this is true of the next group, the so-called acute intermittent porphyria. A large series of patients with this form of the disease has been reported from Sweden, where accurate family records leave little doubt of the genetic factors. The distinguishing features of this form are its onset in older age groups–at puberty or later–abdominal colic, neurologic symptoms and the excretion in abnormal quantities of the porphyrin precursors delta-aminolevulinic acid and porphobilinogen.

The so-called mixed porphyria seen in South Africa has also a hereditary basis. Over 600 people with a somewhat different form of the disease may be traced back to one Boer couple who were married in South Africa in 1688. Another significant group of cases, usually reported in small numbers, present with symptomatic porphyria which seems to have been precipitated by a toxic insult to an already diseased liver. Frequently, the pre-existing liver disease is alcoholic cirrhosis and the insulting toxin a member of the barbiturate family. In all of these latter forms of the disease the metabolic disturbance seems to be in the liver, rather than in the marrow as in the congenital form, and a genetic basis is either present or cannot be ruled out. In the present disease the hereditary factor does not exist. The disease was unknown five years ago. While the basic population of the region is stable and has been there for centuries, there are several communities made up of Turkish Moslem individuals who, as refugees from

Yugoslavia and Bulgaria, were settled in the area by the Turkish government since 1950. The incidence of the disease in this group is comparable to that in the native population.

There remains the question of purely toxic porphyria. Dr. Cihat Çam was the first to suggest that seed wheat, treated with hexachlorobenzene (C_6Cl_6) because of its fungicidal effect, had been consumed rather widely in the area during recent years, and might be involved.[1] Initial surveys indicated that everyone with the disease had eaten this wheat in variable quantities and for varying lengths of time prior to onset of symptoms, although by no means all of the people consuming the wheat had developed the disease. A striking and important point is the fact that persistence of symptoms seems to bear no relation to known consumption of the wheat. Clinical manifestations of the disease persist in individuals who have not knowingly consumed the wheat for as long as two years.

Although the role of hexachlorobenzene remains to be proved, no other potential cause has appeared and this toxin seems clearly incriminated by the evidence at hand. This is a region in which patterns of living, food habits and the environment have changed little in centuries. So far hexachlorobenzene treated wheat is the only new factor in the area which could possibly account for the problem, and its use in that region preceded by only a few months the appearance of the disease. Although precise statistics are unobtainable, evidence suggests that the increase in the number of cases is related to an increase in the number of people eating the wheat. It has also been established that, while wheat similarly treated has been used in a number of other regions of the country, it has generally been used for the purpose for which it was intended—as seed. This, again, is in contrast to the southeastern provinces in question where it was certainly consumed on a wide scale, especially during 1956-1958. In 1932 Duesberg reported a fatal case of porphyria in a man who had been addicted to Sedormid and barbiturates. Schmid and Schwarz showed clearly in 1952 that Sedormid will produce porphyria in rabbits and that the biochemical injury seems to occur in the liver.[3] Dr. Rudi Schmid has recently observed that addition of 0.2% hexachlorobenzene to Purina laboratory chow produces urinary excretion of large amounts of uroporphyrin and coproporphyrin and, after prolonged exposure, of porphobilinogen.[4]

In the present outbreak of porphyria we have little doubt that the etiology is toxic and that the agent is hexachlorobenzene. It seems

likely that longstanding malnutrition, as evidenced by severe growth retardation, with accompanying liver injury, is a predisposing factor.

Much work remains to be done. We have undertaken a more comprehensive epidemiologic survey and hope to be able to study the fecal and urinary porphyrin excretion of a group of patients over a period of at least a year in hopes of learning something more about seasonal and individual variations in this disease. Other studies are planned in order to clarify the role of hexachlorobenzene.

İHSAN DOĞRAMACI, M.D.

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