Suid-Afrikaanse Tydskrif vir Geneeskunde : South African Medical Journal

Kaapstad, 24 Junie 1961 Deel 35 No 25 Volume 35 Cape Town, 24 June 1961

THE TURKISH EPIDEMIC OF PORPHYRIA

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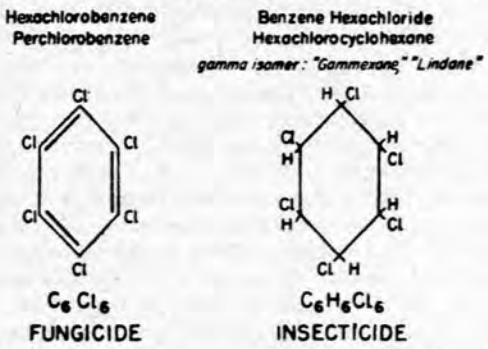
In 1955 Dr. Cihad Cam, who is the Director of the skin clinic in Diyarbakir in Eastern Turkey, found that he was seeing a large number of children with sores and blisters on the face and on the back of their hands. These children had dark pigmented skins and great hairiness of their faces. The urine of the children was reddish-brown in colour and when Dr. Cam examined the urine in ultraviolet light, using a Wood's filter, it gave a brilliant red fluorescence. He realized these children had porphyria. He had not seen children with porphyria before 1955, but in that year and in each subsequent year he saw many hundreds of affected children[1,2] (Fig. 1).

This epidemic aroused great interest and concern in Turkey. Children were admitted for further study under the care of Dr. Joseph Wray to the Hacettepe Children's Hospital in Ankara and also to a hospital in Istanbul. Prof. Cecil Watson of Minneapolis, renowned for his porphyria research, sent one of his outstanding research assistants to assist in the biochemical investigation of the children, and Dr. Rudi Schmid, an American expert on porphyria, visited Turkey and made a report on the epidemic.[3]

The Rôle of Hexachlorobenzene

Dr. Cam, who had taken the dietary history of hundreds of children with porphyria, had made a startling discovery. The peasants in the Eastern part of Turkey are extremely poor and their staple diet is bread. However, it is not possible to obtain good wheat crops unless the seed wheat is treated with a fungicide. In particular, the seed wheat was destroyed by the fungus *Tilletia tritici*. In the past the seed wheat had been treated with mercurous and mercuric chloride which was not very effective against the fungus. In 1954 some of the seed wheat was treated for the first time with 0·2% 'chloroble' or 'surmesan A' which contains the fungicide hexachlorobenzene. This fungicide must not be confused with the insecticide benzene hexachloride:



Chemical Structures of Hexachlorobenzene and Benzene Hexachloride.

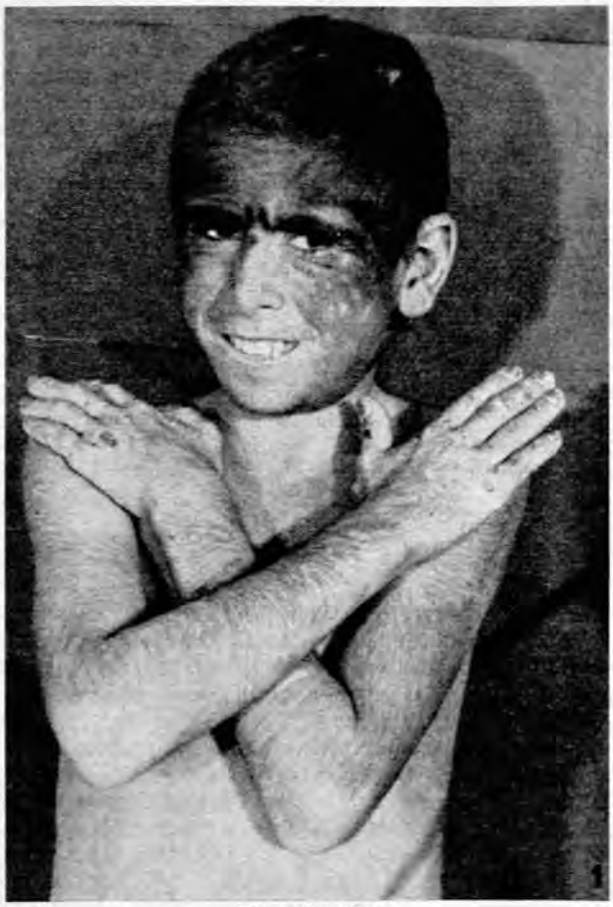


Fig. 1 See text

The hexachlorobenzene-treated seed wheat was first issued in 1954 in the Urfa Province, and in that year the first cases of porphyria appeared in that Province. In 1955 the treated wheat was also issued in the Provinces of Diyarbakir and Mardin. Dr. Cam found the affected children had been eating bread made from the wheat which had been issued to the peasants for planting; he quite rightly suspected that the seed wheat was responsible for the epidemic.

The announcement of his views caused a considerable outcry in the newspapers. The matter was complicated because the Ministry of Agriculture believed, with good reason, that unless the wheat was treated with the hexachlorobenzene the crops would be very poor. The Health Ministry, on the other hand, wished to stop the use of the new fungicide. The problem has not yet been resolved and the hexachlorobenzene-treated wheat is still issued, with due warning that it should

not be eaten. Nevertheless much of the wheat is still milled into flour and every year many hundreds of the children develop the symptoms of porphyria. Dr. Cam estimates that about 5,000 children have serious symptoms of porphyria and no doubt many thousands more are mildly affected.

Forms of Cutaneous Porphyria

Three forms of cutaneous porphyria have already been described: 1. A very rare form of porphyria, which causes cutaneous symptoms in infancy, is known as congenital, or erythropoietic porphyria; less than 70 cases have been described in the world literature. This rare disorder is inherited as a Mendelian recessive character, it is associated with anaemia and an enlarged spleen, and the porphyrin production is in the bone marrow. 2. In South Africa many Afrikaners are affected by an inherited form of porphyria that often causes blistering of the exposed skin and some increased pigmentation and hairiness in adults, but seldom in children. This is a Mendelian dominant form of porphyria, porphyria variegata; all the South African cases trace back to one ancestor who married at the Cape in 1688.[4,5]

3. A cutaneous form of porphyria which is not inherited, and which causes similar cutaneous symptoms in middle life, porphyria cutanea tarda, or symptomatic cutaneous porphyria, is also found sporadically. It is often associated with the excessive use of alcohol. This symptomatic type of porphyria is frequently seen in the Bantu, especially if they are accustomed to drinking an excessive amount of the native drink, skokiaan.[6]

The Turkish Epidemic

I visited Turkey in 1960 to see the affected children. Unlike congenital porphyria the symptoms did not start in infancy. The Turkish children developed much greater pigmentation of the skin and hairiness of the face than occurred either in porphyria variegata or in the sporadic cases of symptomatic porphyria in adults. In the villages, several members of the same family were frequently affected. They are called the 'monkey children' by the peasants because of the pigmentation and hairiness of the face. Besides blisters and sores on their hands and faces and the dark pigmentation and hairiness, these children usually had enlarged livers, and liver-function tests showed marked impairment of liver function. They did not have splenomegaly and were usually not anaemic. They were generally undersized and had apparently been undernourished before they developed porphyria. Their dark-red or brown urine contained great quantities of porphyrin, but no increase of the porphyrin precursor, porphobilinogen. There was little or no increase in the porphyrin excretion in the faeces. Analysis of the urine and stool porphyrin gave results very similar to those found in the Bantu cases of cutaneous porphyria.[7,8]

Most of the children with cutaneous symptoms were aged between 5 and 15. In some affected families, babies at their mother's breast developed pigmented patches on the skin rather like a ringworm or fungus infection. These babies did not have a sensitive skin that abraded or blistered, nor did they excrete increased quantities of porphyrin in the urine. No fungus has been recovered from their skin lesions, which are not at all like cutaneous porphyria. It is possible that some of the hexachlorobenzene is absorbed *via* the mother's milk and that in babies it causes a direct skin reaction.

This epidemic is particularly tragic because the children who were first affected in 1956 are still affected today, although they have not eaten bread made from wheat treated with the fungicide since the diagnosis was made. Their sores tend to heal during the winter months and break out again during the summer months, and some of these children have now contractures of their hands and some have osteomyelitis of the bones of the hands and atrophy of the terminal digits. Others have marked scarring of the face. The children who have been treated in hospital on a high-protein diet still show symptoms although they have improved. It appears that once the liver has been so damaged that there is serious disturbance in the porphyrin metabolism, improvement is possible, but relapse occurs very easily and in many cases symptoms persist.

Dr. Schmid has fed rats with the fungicide-treated wheat and they also developed cutaneous porphyria and excreted large amounts of uroporphyrin and coproporphyrin in the urine. The children in the Turkish epidemic did not develop abdominal pain or neurological symptoms, such as occurs in acute porphyria variegata or intermittent acute porphyria, and they did not excrete porphobilinogen in the urine—the porphyrin precursor that is found in the urine in intermittent acute porphyria and in porphyria variegata during an acute attack. In fact the syndrome affecting the children in Turkey is very similar to that affecting the Bantu of South Africa and the sporadic cases of porphyria cutanea tarda, except that children are affected and not adults, and the pigmentation of the skin and the hirsutism is greater than has been seen before—a truly remarkable phenomenon.

The difficulty in distinguishing between the treated and untreated grain makes it hard to discover how much of the seed grain is used for food. It is also difficult to find out how long the patient has been eating the toxic wheat. However, except for a few sporadic cases, all the children have been affected in the Provinces of Diyarbakir, Mardin and Urfa. Most of the wheat has been sold in the country areas and the affected children are mainly from the villages and farms and not from the towns.

It appears likely that the symptoms of cutaneous porphyria are so severe in these children because they already suffered from malnutrition, in particular shortage of sufficient protein, and, as a result, had poor liver function. The Ministry of Agriculture considers that it is not feasible to stop the distribution of the hexachlorobenzene-treated seed wheat on account of the danger of famine. However, it appears to be extremely difficult to prevent the wheat from reaching the merchants and millers. No effective measures have yet been found to stop the epidemic. My suggestion was that the seed wheat should be stained with a dye, perhaps methylene blue, and a small proportion of it crushed. Then, if it was used for making flour, the dye would pass into the flour and would colour the bread. If this was done the wheat would be easy to trace and it would not be possible to use the wheat for making bread by mistake. It is most important that urgent action should be taken because otherwise, in the affected provinces, a large number of the future generation are going to be permanently handicapped.

COMMENT

Poverty and ignorance is the root of the problem. The peasants in Eastern Turkey are living on a diet which is

extremely low in protein, the children usually getting no meat and very little milk. The protein of the diet could be increased cheaply and effectively by adding protein to the flour that is used for making bread. For instance, soya-bean protein and protein from fish which is readily available from the coastal areas. The fortified flour could then be sold to the very poor Turkish and Kurdish peasants in Eastern Turkey.

The Bantu of Africa also eat a diet which is lacking in sufficient protein. The Government of South Africa has done a great deal to counteract protein deficiency in the Bantu by adding protein to wholemeal flour. This can apparently be done very economically. If these measures of fortifying the flour with protein are also carried out in Turkey, there should be a very great improvement in the general health of the population, particularly of the children. Improved nutrition would aid the recovery of the thousands of children who are already affected by toxic porphyria, and improve the general health of the population as a whole. These measures could be undertaken with the assistance of the Turkish Government and perhaps help from the United States or the United Nations.

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