

HEXACHLOROBENZENE AS A CAUSE OF PORPHYRIA TURCICA

Joe D. Wray. M.D.,* Yunus Müftü, M.D.,**

and Ihsan Doğramacı, M.D.***

Dr. Cihat Çam, Director of the Dermatologic Clinic in Diyarbakir State Hospital, was the first to suggest that seed wheat, treated with hexachlorobenzene (C_6Cl_6) for its fungicidal effect, might be involved in the etiology of the cutaneous porphyria seen in southeastern Turkey.¹

When Dr. Çam first began to suspect a toxic etiology he knew that he was dealing with a relatively stable population, whose pattern of life was equally stable. It was apparent that any substance to be considered as the toxic agent must have been widely available in the region to people in all walks of life and its availability must have coincided in time with the appearance of the disease. When, in his search for something which would meet these two essential conditions, he learned that chemically treated wheat distributed for planting had been consumed in the area, it was reasonable to suspect it. When he began to question the patients with porphyria about their consumption of this wheat they reported, without exception, that they had indeed eaten it. Not everyone who had eaten the wheat had the disease, but everyone who had the disease had eaten the wheat.

It was thus the initial deduction of Dr. Çam which led to the suspicion of hexachlorobenzene as the causative agent. Neither his own subsequent investigations nor those of a number of others, including our own, have revealed any other reasonable possibility. The conviction that hexachlorobenzene is the only possible agent can only be arrived at by way of an understanding of a number of facts about the region and the population. For those not familiar with these, it is essential to describe certain of them in some detail.

From the Department of Pediatrics of Ankara University Hacettepe Medical Center and Hacettepe Children's Hospital.

* Associate in Pediatrics (Present address: Apartado Aereo 6555, Cali, Colombia, S.A.).

** Assistant in Pediatrics.

*** Professor of Pediatrics and Chairman of the Department.

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In the first place, it must be understood that wheat is the main dietary staple of the average family in this region, as it is almost everywhere in Turkey, in both urban and rural areas. Farmers usually consume wheat which they have grown themselves, townspeople must, of course, purchase their wheat. In either case, the wheat is eaten in bread made of rather coarse flour, or as *bulgur*, a national dish which consists almost entirely of cracked whole wheat.

Secondly, the provinces which constitute the focus of the epidemic are similar in most significant respects to many others in Turkey in which the disease has not been a problem. They are by no means unique in regard to climatic or topographic conditions, racial or ethnic derivation of the population, the basic life habits of the people, or their general economic situation. Nor are they the only provinces in which hexachlorobenzene - containing compounds were used in preparing seed wheat.

The provinces in question *are* unique, however, in that they are the only provinces in which widespread human consumption of hexachlorobenzene treated wheat is known to have occurred. How this came about can be understood by piecing together bits of information and deserves to be examined carefully.

In fairness to everyone concerned — those who distributed the wheat and those who ultimately consumed it — it must be remembered clearly that the treated wheat was never intended for human consumption. Hexachlorobenzene was used for the sole purpose of preventing damage by a crop-destroying fungus, and thereby improving the farmer's yield. Beyond this, it must be emphatically stated that from the time of its first use, and for at least a year thereafter — i. e. during at least two distribution seasons — no one knew or even suspected the toxic nature of hexachlorobenzene.

Various plant diseases plague wheat growers the world around. Fungus infestations are among the most common, producing a variety of «rusts» or «smuts,» which cause a great deal of damage to crops and consequent economic loss. In southeastern Turkey a species of the fungus *Tilletia* causes a form of wheat smut and is responsible for serious losses. The spores of the fungus adhere to the wheat grains; when these are planted and germinate the spores do likewise. As the plant grows toward maturity, mycelia of the fungus grow inside it, biding their time, so to speak, until the new seeds mature. When those grains of wheat which are not directly destroyed by the fungus mature some of them are consumed and

others, implanted with spores for the next generation of *Tilletia*, are reserved for planting.

This cycle can be prevented by dusting seed wheat with hexachlorobenzene, which prevents germination of the fungus spores without affecting the wheat itself. Two western European products, «Chlorable» and «Surmesan,» containing 10 per cent hexachlorobenzene, have been used for this purpose in Turkey in addition to other nonhexachlorobenzene - containing products. In the routine seed treatment, 20 Gm. of the commercial products is mixed with 100 Kg. of wheat.

It is of interest that until 1954 the pesticides used by the Ministry of Agriculture were Agresan, Graminen, Gerasan, Anticaris and Tritisan but not Chlorable or Surmesan.² In the year 1954 the latter two fungicides were used for the first time and in table 1 the quantities of Chlorable and Surmesan used in eight provinces of southeastern Turkey are listed. It can be seen from this table that practically none of these two products has been used since 1959 and no *new* cases of porphyria have been diagnosed since the beginning of 1960.

Why, was hexachlorobenzene treated wheat consumed in these provinces on a rather wide scale? The answer to this must be synthesized from information obtained from a variety of sources including agricultural and health officials in the region, and from farmers, merchants and townspeople. From the best information available, it seems clear that several factors were involved, varying from time to time and place to place. One of these was simply that there were occasional shortages of wheat in some localities, due to poor crops or for other reasons, and the only wheat available for human consumption was treated wheat. In other instances, according to reliable sources, speculators obtained the wheat from the government at the low price which had been established to encourage the farmers to use a better quality seed stock. Instead of planting it, they sold it at the regular market price which was substantially higher than the government price.

Finally, and probably most important in terms of the number of people involved, reliable information indicates that in the fall of 1954, seed wheat shipments into this region were delayed. Farmers, growing desperate as the planting season slipped by, bought up the local supplies of wheat to plant. When the seed wheat finally arrived, it replaced that which had been planted and was consumed by great numbers of people. During the spring and summer of 1955 sporadic

TABLE 1

KILOGRAMS OF CHLORABLE AND SURMESAN USED IN EIGHT PROVINCES IN SOUTHEASTERN TURKEY FROM 1954 TO 1961

			Chlorable	Surmesan
Elazığ	Before	1954	—	—
	1954 —	1955	—	780
	1956 —	1957	150	2977
	1958 —	1959	—	165
	1960 —	1961	—	—
Tunceli	Before	1954	—	—
	1954 —	1955	—	—
	1956 —	1957	—	—
	1958 —	1959	354	—
	1960 —	1961	—	—
Muş	Before	1954	—	—
	1954 —	1955	2896	—
	1956 —	1957	—	—
	1958 —	1959	2051	726
	1960 —	1961	—	—
Siirt	Before	1954	—	—
	1954 —	1955	300	1734
	1956 —	1957	—	2948
	1958 —	1959	1860	—
	1960 —	1961	—	—
Urfa	Before	1954	—	—
	1954 —	1955	1018	8231
	1956 —	1957	—	24094
	1958 —	1959	—	—
	1960 —	1961	—	—
Diyarbakir	Before	1954	—	—
	1954 —	1955	—	2340
	1956 —	1957	—	7199
	1958 —	1959	660	900
	1960 —	1961	—	—
Malatya	Before	1954	—	—
	1954 —	1955	6874	3165
	1956 —	1957	1004	3364
	1958 —	1959	201	709
	1960 —	1961	—	—
Mardin	Before	1954	—	—
	1954 —	1955	8806	831
	1956 —	1957	8166	11145
	1958 —	1959	1900	—
	1960 —	1961	50	—

cases of porphyria had already begun to appear; but they began to appear in large numbers in the summer of 1956 and again in 1957 following this exposure. Many of Dr. Çam's original cases were in this group and, fortunately, their histories of exposure were clear-cut.

Many people did not believe that hexachlorobenzene treated wheat could be harmful because all the members of their families had eaten it for months without any deleterious effect. This was the reason why so many continued to eat HCB treated wheat for several months in spite of the fact that its relation to the «new disease» or «black sore,» as the disease was locally termed, had become known. On the other hand some patients claimed that they had eaten this type of wheat only once, while visiting friends in other villages.

Our survey bears out satisfactorily the original deductions of Dr. Çam. Our specific data, considered in the light of general information obtained at the same time, suggest that all persons with the disease, knowingly or unknowingly, consumed hexachlorobenzene treated wheat at some time prior to the onset of their symptoms. Furthermore, neither our field investigators who spent months in the region nor other members of the staff who made shorter visits, were able to uncover evidence on which to base a proposal that some other etiologic factor should seriously be considered as a primary precipitating cause.

Investigations of the toxicity of hexachlorobenzene, using laboratory animals, have been reported and provide convincing supplementary evidence. Kantemir³ found that rabbits fed hexachlorobenzene developed skin lesions and showed increased urinary porphyrin excretion as judged by semi-quantitative methods. Experimental porphyria has also been produced in animals by other investigators.^{4,5,6} All this leaves little reason to doubt that the immediate causative agent in the Turkish type of porphyria (porphyria turcica) is hexachlorobenzene.

Summary

An outbreak of cutaneous porphyria in southeastern Turkey is traced to the ingestion of hexachlorobenzene treated wheat by the victims.

The fact that seed wheat, treated with two commercial products containing hexachlorobenzene, was introduced into the region for

the first time just prior to the outbreak of the disease is established. The reasons for the consumption of seed wheat by the local population are explored at length. Field studies, in which it was determined that everyone who developed the disease had eaten treated wheat, are reported, and it is further stated that no evidence was uncovered by the field investigators to indicate that any other etiologic factor could seriously be considered as the primary precipitating cause of this type of porphyria.

In view of these facts, and the laboratory demonstration of the toxicity of hexachlorobenzene, it is concluded that the immediate precipitating agent in the Turkish type of porphyria (porphyria turcica) is hexachlorobenzene.

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