Industrially Acquired Porphyria

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Twenty-nine patients working in a chemical factory engaged in the manufacture of 2,4-dichlorophenol (2,4-D) and 2,4,5-trichlorophenol (2,4,5-T) exhibiting features of chloracne were studied for the presence of porphyria cutanea tarda. In 11 cases urinary uroporphyrins were elevated.

Two of these patients who showed evidence of acquired porphyria with chloracne were hospitalized. The features of chloracne as well as the clinical and laboratory features of acquired porphyria have been discussed. There appeared to be an etiologic but not quantitative relationship between the chloracne in workers engaged in the manufacture of 2,4-D and 2,4,5-T and porphyria cutanea tarda of the acquired type. It is our feeling that either the finished chemicals or some intermediate are responsible for both diseases.

Since Waldenström first implied that porphyria cutanea tarda might be acquired, a growing number of chemicals have been implicated in the pathogenesis of this disease. These chemicals have included alcohol, sedatives, fungicides, etc.[1-18] While treating a severe outbreak of chloracne in a factory which manufactures 2,4-D and 2,4,5-T, a number of workers were noted to have hyperpigmentation, hirsutism, fragility of the skin and vesiculobullous eruptions on exposed areas of skin, together with cutaneous findings of chloracne. Investigation revealed evidence of porphyria cutanea tarda of varying degrees of severity in 11 out of 29 workers investigated. Porphyria cutanea tarda has never before been described as related to chloracne, nor has it been ascribed to industrial exposure in the United States. This outbreak is therefore of interest in adding more evidence to the growing concept that porphyria cutanea tarda may be an acquired disease occurring after various insults to the liver. Three cases were studied in detail.

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Report of Cases

CASE 1.—A 48-year-old white male who was employed at the factory for three years as a chemical operator. His work brought him into intimate contact with the suspected chemicals. His past history included two attacks of biliary colic prior to 1953. He was never a heavy user of alcohol. A diagnosis of cholecystitis had been made and a cholecystectomy was performed early in 1953. After this he came to work at the factory in question. In 1956 he began to notice some darkening of his skin and suffered right upper quadrant pain. A diagnosis of common duct obstruction was made, and this patient was operated on again in January of 1956. An unsuccessful attempt was made to probe the common duct, and no further operative procedure was done. During the postoperative course, this man received 2 gm of barbiturates. The patient stated that his urine had turned "the color of Coca-Cola" at least one year prior to the second operation. That spring, an eruption of bullae appeared on the face, ears, and hands. These lesions could be produced either by exposure to the sun or

Fig 1.—Crusted bullae and atrophic scars on the dorsal surface of the hands.

Fig 2 (Case 3).—Illustrates hirsutism of the eyelids and lateral surface of the forehead.

by pressure. In addition to the vesicular eruption, the patient noted progressive darkening of his skin and marked hirsutism, especially over the temples. Inspection of the urine revealed a Coca-Cola coloration and, under the Wood's light, a brilliant red fluorescence. The exact laboratory data on this patient are no longer available except for the presence of quantitatively markedly increased excretion of urinary porphyrins including uroporphyrins, coproporphyrins, and porphobilinogen.

This man is now alive and well and apparently is suffering minimal if any symptoms of porphyria cutanea tarda. His present job does not entail the use of any chemicals. He has failed to present himself for further testing.

Case 2.—This is a 60-year-old white male who has been employed in the factory for seven years as a welder. In the course of his work, which consisted of welding tanks and pipes, he was brought into frequent and prolonged contact with chemicals. He was admitted to the Newark Beth Israel Hospital for investigation. He stated that three months prior to admission, he had noted an increased darkening of the skin, thickening of the eyebrows, and a darkening and reddening of his urine. His family history and his past medical history were unrevealing, except for moderately heavy alcohol intake for some years.

Physical examination revealed numerous comedones and small epidermoid cysts and furuncles of

the face, chest, and shoulders. There was intense grayish-brown hyperpigmentation with a purplish tint on the exposed surfaces of the face, neck, chest, and hands and moderate hypertrichosis of the temples. The scalp hair showed a lusterless, dull silver color change. The liver edge was palpable about 3 cm below the right costal margin and was smooth and nontender. The remainder of the physical examination was within normal limits. A casual urine specimen revealed a strong tea color with a deep fluorescence, reddish, under the Wood's light.

Laboratory studies revealed increased urinary uroporphyrin, coproporphyrin, and urobilinogen excretion. There was no demonstrable porphobilinogen. The feces showed increased uroporphyrins and coproporphyrins. All porphyrin determinations were qualitative and done by the Watson-Schwartz method. Other significant findings included an elevated serum glutamic oxaloacetic transaminase ranging between 41 and 51 units on five different days. Serum glutamic pyruvic transaminase on corresponding days ranged between 53 and 64 units. The sulfobromophthalein retention was 6% in 30 minutes. The erythrocyte sedimentation rate (Westergren) was 24 mm in the first hour. All other studies, which included complete blood count, bleeding and clotting time, urinalysis, glucose tolerance test, serum bilirubin, blood urea nitrogen, total proteins, albumin-globulin ratio, serum cholesterol, alkaline phosphatase, cephalin flocculation, and thymol turbidity, serum electrolytes, and CO_2 combining power, as well as serological tests for syphilis were all within normal limits. Electrocardiograms and chest x-rays were normal. A liver biopsy was performed and the specimen immersed in isotonic saline. It fluoresced intensely under the Wood's light. The red pigment diffused out into the saline, so that the entire tube fluoresced. The microscopic examination of the liver specimen revealed parenchymal cell regeneration and hemofuscin deposition. A skin biopsy from clinically hyperpigmented postauricular skin showed a normal epidermis except for the dermoepidermal border, where there was a striking deposition of brown granular pigment. In addition, there was mild infiltrate of small round cells in the dermis. No sebaceous glands were visible in the sections. Shortly after discharge from the hospital in June, 1963, the patient was treated for a chronic trichophytosis of the feet with griseofulvin 0.5 gm twice daily. About four days after the onset of this treatment, a severe vesiculobullous eruption on the dorsal surface of the hands appeared. The griseofulvin was stopped, but the eruption progressed for another two weeks. Healing time was very prolonged, and at present, residual atrophic scarring is visible on both hands (Fig 1). In the scars occasional milia are seen.

Summary of Data for 25 Workers Whose Urine Was Tested for Porphyrins

Patient	Chloracne*	Hyperpigmentation	Hirsutism	Urine Coproporphyrins	Chemical† Contact	Skin Fragility
1	Severe	Mild	Moderate	Pos.	Moderate	Pos.
2	Mild	None	None	None	Severe	Neg.
3	"	Mild	"	"	"	"
4‡	Severe	"	Mild	"	"	Pos.
5	Mild	None	"	Pos.	"	"
6	"	"	None	None	Moderate	Neg.
7	"	Mild	"	Pos.	Moderate	"
8	Severe	Moderate	Severe	None	"	"
9	"	Mild	Mild	"	"	"
10	Moderate	Moderate	Moderate	"	Severe	"
11	Severe	"	"	"	Moderate	"
12	None	None	None	"	Severe	"
13	"	"	"	"	"	"
14	"	"	"	Pos.	Moderate	"
15	Moderate	Mild	Moderate	None	"	Pos.
16	"	Moderate	Marked	"	Severe	"
17	Mild	Mild	None	"	Mild	Neg.
18	Moderate	Moderate	Marked	"	"	"
19	Severe	Marked	None	Pos.	"	"
20	Mild	Mild	Moderate	Pos.	"	"
21	None	None	None	None	"	"
22	"	"	"	"	"	"
23	Mild	"	"	"	"	"
24	None	"	"	"	"	"
25	"	"	"	Pos.	"	"
26	"	"	"	Pos.	"	"

* Severity of chloracne is judged on the presence of comedones, epidermoid cysts, and furuncles and pustules.
† The extent of exposure is difficult to truely judge because of such variables as personal hygiene and work habits.
‡ Brief period of unemployment.

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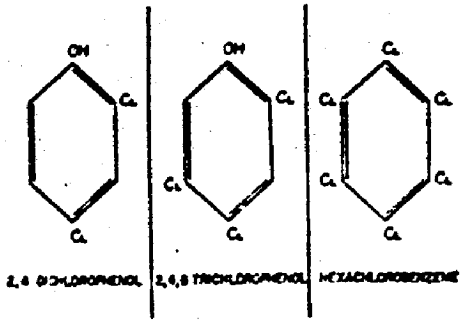

Fig 3.—Comparison of structural formulae of weed killer manufactured and fungicide responsible for acquired porphyria cutanea tarda. Note the similarities.

Case 3.—This is a 48-year-old white male employed at the factory for eight years mixing batches of chemicals. During the past two years, he had developed hyperpigmentation of the exposed skin of the face and hands. There was marked hirsutism which involved the temples. The dull silvery tint of the hair was visible. He stated that in the past he had had episodes of blistering of the exposed skin. He also had noticed that his urine was dark on voiding. His family history was noncontributory. The physical examination revealed an intense hyperpigmentation of the face, neck, and hands. There was severe hirsutism involving the eyelids, eyebrows, and lateral aspects of the forehead (Fig 2). Comedones and small epidermoid cysts were very prominent, and there were numerous furuncles scattered over the entire body. The remainder of the physical examination was within normal limits except for prolapsed hemorrhoids. The following laboratory studies were within normal limits: complete blood cell count, urinalysis, bleeding and clotting time, prothrombin time, blood glucose tolerance test, urea nitrogen, cholesterol, bilirubin, alkaline phosphatase, total protein and albumin-globulin ratio, cephalin flocculation, thymol turbidity, serum electrolytes including sodium, potassium, chlorides, CO_2 combining power, calcium, and phosphorus. The serum glutamic oxaloacetic transaminase on five successive days ranged between 39 and 56 units while the serum glutamic pyruvic transaminase on corresponding days ranged between 47 and 72 units. The sulfobromophthalein retention was 8% in 30 minutes. The electrocardiogram was normal. The chest x-ray revealed a diffuse nodular infiltration of both lungs due to pneumoconiosis. This was consistent with the patient's history of having worked a number of years as a coal miner. The plain film of the abdomen was negative. The urine revealed a positive Watson-Schwartz test. The urine failed to fluoresce under the Wood's light. The erythrocyte sedimentation rate (Westergren) was 24 mm in the first hour.

A liver biopsy was performed and the specimen immersed in saline. Under the Wood's light the specimen and saline in which it was immersed fluoresced faintly. On microscopic examination, the liver biopsy showed evidence of liver cell regeneration and hemofuscin deposition. A skin biopsy showed brown granular pigmentation at the basal margin of the epidermis. There was a mild chronic inflammatory infiltrate scattered through the dermis. No sebaceous glands were visible in the sections.

Since this man's chloracne has been so severe, he had been removed from contact with chemicals two years prior to his admission to the hospital. This probably was responsible for the failure to prove qualitative chemical evidence of porphyrins in the urine. It also may indicate that acquired porphyria cutanea tarda is reversible.

Screening Tests

Twenty-six additional men working at this chemical factory were studied on an ambulatory basis. In addition to routine urinalysis, each urine specimen was tested for uroporphyrin by the Watson-Schwartz method. Eight out of the 26 manifested significantly increased excretion of urinary uroporphyrins by the Watson-Schwartz method. If the three cases described in the case reports above are added, this is a total of 11 cases of porphyria cutanea tarda of varying degrees of severity out of 29 patients tested, or 37+% (Table).

Comment

Hyperpigmentation in these workers was limited to the sun-exposed areas of the head, neck, and hands. It was more frequently observed in the Negro patients involved. The degree of hyperpigmentation was roughly proportional to the severity of the chloracne. The hyperpigmentation varies from mild redness in extremely fair individuals to dark gray intense dusky bronzing of the skin. The degree of hirsutism was also proportional to the severity of the chloracne. This too was quite variable in degree but always involved the temples between the lateral half of the eyebrow and the temporal hair of the scalp. The hirsutism in a few cases, notably case 3, extended beyond this and involved both the upper and lower eyelids. The hair was of approximately the same texture and density as that of the eyebrows.

The occupational environment of these men consists of a group of basic chemicals including acetic acid, phenol, monochloracetic acid and sodium hydroxide, plus the finished products 2,4-D and 2,4,5-T as well as many unknown intermediary products. It is known that one of the intermediaries is a highly volatile chlorinated phenolic ether which contains six chlorine atoms. This particular compound, because of its volatility, is strongly suspected of being a possible causal agent. Porphyria has been described in many cases as a result of ingestion of hexachlorbenzene,[2,3] chemically a closely related compound (Fig 3). This would lend support to the concept that porphyria cutanea tarda is not necessarily genetically produced, unless the genetic defect is an extremely common one.

An analysis of the table of the 26 surveyed workers (Table 4) reveals: the severity of chloracne does not usually correspond to the degree of exposure to chemicals (patients 1, 8, 11, 19 or patients 2, 3, 5, 10, 12, 13, 16). The severity of porphyria does not usually correspond to the degree of chemical exposure (patients 7, 20, 25, 26 or patients 2, 3, 4, 10, 12, 13, 16). The severity of chloracne does not usually correspond to the presence of porphyria (patients 1, 4, 8, 11, or patients 5, 20, 25, 26). Therefore it would appear that there is some individual susceptibility to these diseases. It has been observed in general that: (1) Patients with adolescent acne tend to get worse chloracne; (2) Possibly previous liver damage (alcoholism, etc) predisposes to porphyria. Also there must be in these cases some etiologic relationship between chloracne and porphyria since a relatively large number of both diseases began to appear and have persisted at the same time.

On the basis of the elevated transaminase levels and the histological signs of liver cell regeneration in the liver biopsies, it may be assumed that the basis of the disturbed porphyrin metabolism is a hepatotoxic effect of one or more of the chemicals in this factory environment. The synergistic roles of other known liver toxins such as alcohol and barbiturates, or griseofulvin (1 case), cannot be overlooked.

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