

A Health Survey of Workers in a 2,4-D and 2,4,5-T Plant

With Special Attention to Chloracne,
Porphyria Cutanea Tarda, and
Psychologic Parameters

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A study of 73 male employees in a 2,4,5-T factory was made. Chloracne was found in 13 (18%) workers. Severity of chloracne correlated significantly with the presence of hyperpigmentation, hirsutism, eye irritation, and a high score on the manic scale of the Minnesota Multiphasic Personality Inventory. Chloracne was not, however, correlated significantly with job location within the plant, duration of employment, or coproporphyrin excretion. Although 11 subjects with uroporphyrinuria and at least three with overt porphyria cutanea tarda had been found in a study of the same plant six years ago, no clinical porphyria could be currently documented and only one worker had persistent uroporphyrinuria. Evidence of toxicity in other organ systems was markedly less than that reported in previous studies and could not be shown to differ from normal populations in most instances.

THE herbicides 2,4-D (2,4-dichlorophenoxyacetic acid) and 2,4,5-T (2,4,5-trichlorophenoxyacetic acid) are widely used throughout the world. Several distinct medical problems have been described in workers involved in the production of these compounds. These problems can arbitrarily be subdivided into (1) chloracne and mucous membrane irritation, (2) hepatotoxicity,

neuromuscular symptoms, psychologic alterations, and other systemic symptoms, and (3) porphyria cutanea tarda (PCT).

Chloracne and Mucous Membrane Irritation.—Chloracne (perna disease, perchloronaphthalene disease) has been described as an extremely refractory acne seen in workers involved in the production of several chlorinated aromatic compounds.^{1,2} Kimmig and Schulz^{3,4} described this dermatologic condition in workers in a 2,4,5-T factory. The condition is characterized by inclusion cysts, comedones, and pustules, with eventual scarring, and originates in the temple-zygomatic area with spread to the pinna, nape of the neck, back, upper chest, and inguinal area. Many of these patients also had blepharconjunctivitis. The investigators showed that purified 2,4,5-trichlorophenol (TCP) was not acnegenic, but that 2,3,6,7-tetrachlorodibenzodioxin (TCDD) isolated from the crude TCP reaction mixture was an extremely potent acnegenic agent when applied to rabbits' ears.⁴ The TCDD is con-

sidered an im- the only, acne production. Hepatotoxic Psychologic Al Symptoms.—In studies of wor frequently not suggestive of include anorexia pains and post; weakness in th tion.⁶⁻¹⁰ The fe tions were also and libido; ea stability; and Porphyria cutanea tarda i erally occurri which significa ally a history The syndrome sions on areas hirsutism, excor the skin, hype of red urine co of uroporphyrin but not a large levulinic acid (PBG).^{11,12} F hyperferremia c omy often rev decreases porpl In 1964, Bl of 29 workers i Many of the v had abnormal phyrins. Man without uropor perpigmentatio ty. Liver dysf pitalized patie As a follow- berg et al¹³ of workers, we re the same plan ticular emphas toxicity, and n

Submitted for publication April 27, 1970; accepted May 27.

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sidered an important, but not necessarily the only, acrogenic compound in 2,4,5-T production.

Hepatotoxicity, Neuromuscular Problems, Psychologic Alterations, and Other Systemic Symptoms.—In addition to chloracne, studies of workers in 2,4,5-T plants have frequently noted other signs and symptoms suggestive of systemic toxicity. These include anorexia and weight loss, abdominal pains and postprandial flatulence, headaches, weakness in the legs, and hepatic dysfunction.⁶⁻¹⁰ The following psychological alterations were also noted: lack of vigor, drive, and libido; easy fatigability; emotional instability; and diminished ability to learn.

Porphyria Cutanea Tarda.—Porphyria cutanea tarda is an acquired porphyria, generally occurring in men after age 40, in which significant liver dysfunction and usually a history of alcoholic abuse are found. The syndrome consists of vesiculobullous lesions on areas of the body exposed to light, hirsutism, excessive mechanical fragility of the skin, hyperpigmentation, and excretion of red urine containing an increased amount of uroporphyrin or coproporphyrin, or both, but not a large increase in urinary δ -aminolevulinic acid (ALA) or porphobilinogen (PBG).^{11,12} Frequently these patients have hyperferremia and hemosiderosis, and phlebotomy often reverses the clinical picture and decreases porphyrin excretion.^{12,14}

In 1964, Bleiberg et al¹⁵ reported studies of 29 workers in a 2,4-D and 2,4,5-T factory. Many of the workers had chloracne and 11 had abnormal excretion of urinary uroporphyrins. Many of the workers with and without uroporphyrinuria had hirsutism, hyperpigmentation, and increased skin fragility. Liver dysfunction was noted in two hospitalized patients.

As a follow-up of the observations of Bleiberg et al¹⁵ of a toxic PCT in these factory workers, we restudied all the employees in the same plant in February 1969 with particular emphasis on PCT, chloracne, hepatotoxicity, and neuropsychiatric symptoms.

Methods

All volunteers submitted to a medical history and physical examination; special emphasis was placed on occupational, smoking, drinking, and

medication histories and the detection of any neurologic or dermatologic signs and symptoms. Physical examinations were performed by three different physicians; each physician's findings were considered final and were not confirmed by a second physician.

The Minnesota Multiphasic Personality Inventory (MMPI)¹⁶ was administered to all employees in a quiet atmosphere at work supervised by management. The only exceptions were a few plant administrators who completed the inventory at home. The individual tests were scored by computer, and the mean and standard deviations were computed for each scale and compared with normative data.¹⁶ In addition, the frequencies of high and low two-point scores were determined.

Each employee, after fasting for at least three hours, was given a bottle of a beverage containing 75 gm carbohydrate (Glucola) to drink. Two hours after ingestion, a blood sample was obtained and the serum glucose and other analyses were performed in an automated clinical laboratory. In persons reporting after 135 minutes, the two-hour serum glucose was considered invalid and not included in the statistical analysis. In addition to the glucose determination, serum glutamic oxaloacetic transaminase (SGOT), lactic dehydrogenase (LDH), alkaline phosphatase, cholesterol, bilirubin, albumin, total protein, blood urea nitrogen (BUN), and hemoglobin values, and a hematocrit reading, red blood cell count, white blood cell count (WBC), serum iron value, and iron-binding capacity were disclosed for each employee.

A routine urine specimen was collected from each volunteer, the pH was adjusted to 7.0, and the specimen was frozen until porphyrin analysis. An attempt was made to shield the urine from ultraviolet light but was not entirely satisfactory in the industrial setting. In addition, each urine sample was analyzed for ALA and PBG by the method of Marver et al¹⁷ and for uroporphyrin and coproporphyrin by the method of Schlenker et al.¹⁸ The porphyrin and porphyria precursor levels were expressed per gram of creatinine.

For statistical analysis, employees were subdivided into several different groups according to location in the plant, exposure to chemicals, and educational level. All quantitative results were reported as mean \pm one standard deviation, percent of prevalence, or a correlation coefficient between two variables. Significance was determined by Student's *t*-test or χ^2 test; results reported as nonsignificant are those with the significance level (probability value) of greater than 0.05. Where distribution of

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Results

Descriptive Data.—Seventy-eight persons were studied in the plant. Five women employed in the office were excluded from the analysis. The remaining 73 employees, all men, included one part-time worker and four persons who had not worked in the plant for one to six months. The group of 73 persons was subdivided into four basic occupational subgroups: (1) administrators and technical help, 20 men including engineers, business office workers, laboratory technicians, and janitorial help, all housed in a building separated from the production area and, thus, less exposed to production chemicals; (2) supervisors, 11 foremen spending most of their time in the production area; (3) on-line personnel, 28 persons working in the production area; and (4) maintenance, 14 men with various occupations (plumbers, electricians, etc); some were confined to the maintenance shop and others were frequently in the production area.

As seen in Table 1, the average age of the 18 Negro and 55 white employees was 39.3 ± 11.1 years and the average years of schooling, 11.9 ± 2.6 years. The average duration of employment was 8.3 ± 7.6 years (Table 2). Of 64 workers questioned, 22 missed more than one day from work due to illness in the past year. The average number of days lost for 63 employees was 2.8 days per year. (This excludes one person hospitalized for almost two months with a urinary tract infection.)

Acne.—A specific dermatologic history with special emphasis on acne and porphyria was taken from all the employees and all were examined by one of us (P.P.).

The minimal acne lesion consisted of comedones and inclusion cysts in the temple-zygomatic area and the pinna of the ear. In more severe cases, cysts and comedones were accompanied by pustules on the face and ear, nape of the neck and back, and in the worst cases, the chest and inguinal area. With anatomic spread, the severity of the

lesions and the scarring was generally increased. No erythematous or edematous lesions were found, as previously reported by some investigators studying intense or massive exposures.⁶

"Active acne" was defined as the presence of cysts, comedones or pustules (but not scarring). Each of the three lesions was graded according to the severity (grade 0 to 4) in each location (five possible areas: face, neck, back, chest, and other). The severity grades for each lesion were summed over all five locations. Finally, these severity sums were totaled to produce an overall active acne score (maximal possible score: grade 4 in all five locations = 20 for each of three lesions = 60). This arbitrary rating allowed us to deal with the degree of active acne in a statistical form. Scarring was scored separately by the same system (grade 0 to 4 multiplied by five possible areas = maximal score of 20).

Twenty-five persons had an active acne score of 0 (no lesions), 35 had a score of 1 to 8 (minimal), and 13 employees had a score of 9 or greater (moderate to severe). Scarring was also a highly skewed parameter: 37 employees had a score of 0; 29 had a score of 1 to 8; and 7 had a score greater than 9. As seen in Table 3, with increasing active acne scores, the prevalence of scarring, hyperpigmentation, hirsutism, and complaints of eye irritation was greater.

Another way of expressing the same data is to convert the skewed active acne scores to a more normal distribution by logarithmic transformation (see Methods) and compare these transformed scores with other parameters by correlation coefficients. Scarring, also a skewed parameter, was similarly transformed.

Active acne was correlated with the degree of scarring ($r = 0.80$), the presence of hyperpigmentation ($r = 0.38$) and hirsutism ($r = 0.44$), and complaints about eye irritation ($r = 0.39$). All the above correlations have a significance level of $P < 0.001$. The active acne scores were not significantly correlated with the duration of employment nor with the excretion of coproporphyrins per gram of creatinine.

The occurrence of acne was not significantly greater in Negro employees than in white workers (χ^2 test). Although all six

Table 1.—Distribution, Age, and Educational Level of Employees According to Job Category

Group	No. of Employees	Age*	Years of Schooling*
Administrators,			
lab technicians,			
janitors	20	34.0 ± 12.2	13.8 ± 2.3
Supervisors	11	46.8 ± 7.4	12.7 ± 3.0
On-line personnel	28	40.1 ± 10.0	10.6 ± 1.7
Maintenance	14	39.1 ± 10.5	10.6 ± 1.8
Total plant	73	39.3 ± 11.1	11.9 ± 2.6

* Mean ± 1 SD.

Table 2.—Duration of Employment in Plant

No. of Years*	No. of Employees
0-4	33
4-8	10
9-12	1
> 13	29

* Mean ± 1 SD = 8.3 ± 7.6 years.

individuals who stated that they had had teen-age acne and who had worked in the plant for more than 14 months do presently have active acne, the prevalence of acne in this group (100%) was not statistically higher than the prevalence of acne in a group who had also worked in the plant for more than 14 months but had no history of teen-age acne (62% [$\chi^2 = 3.40$; 1 degree of freedom, $0.05 < P < 0.10$]).

The 73 male employees were subdivided into groups with respect to present work location in the plant: TCP formation, 2,4-dichlorophenol (DCP) formation, phenoxyacetic acid production, esterification, formulation and storage tanks, maintenance, supervisory, laboratory help, and administration. Often one man might work in several locations (eg, supervisors might work in both TCP and DCP production and in phenoxyacetic acid production and esterification). In these cases, each area was compared (χ^2 test) to see if the severity of the active acne of the employees might be worse in certain locations in the plant. There were no statistically significant differences, perhaps because of the small size of each group and the mobility of the workers. However, as might be expected, the maintenance men tended to have the most acne (having to clean and repair vats and pipelines) and the administrative people (housed in a separate building) tended to have the least acne.

Mucous Membrane Irritation.—Seven employees complained of itching of the eyes, 14 of frequent tearing, five of "blood-shot eyes," and seven of sties. On physical examination, however, only three (4.1%) had appreciable conjunctival injection. Twenty-three (31.5%) employees had hyperemia of the nasal mucosa and eight (10.9%) had inflammation of the buccal mucosa.

Hyperpigmentation and Hirsutism.—Hyperpigmentation, usually most prominent on the face, consisted of a grayish or brownish tone to the complexion. Hirsutism was most noticeable in the area between the outer edge of the eyebrow and the temple hair margin. Both characteristics were recorded only as being present or absent. As seen in Table 3, 16 subjects had facial hypertrichosis and 30 had hyperpigmentation. Correlation between hirsutism and increased hyperpigmentation was significant ($r = 0.25$, $P < 0.05$). As previously mentioned, hirsutism and hyperpigmentation are significantly correlated with the severity of active acne, but neither is significantly correlated with coproporphyrin excretion.

Urinary Excretion of Porphyrins and Porphyrin Precursors.—The average values of ALA, PBG, and coproporphyrin found in routine urine specimens of 72 workers in the plant are shown in Table 4 along with the normal values from the literature.¹⁷ The excretions of ALA, PBG, or coproporphyrin were not abnormally elevated. One employee, hospitalized several years ago with severe PCT, still has mild uroporphyrinuria (107 $\mu\text{g}/\text{gm}$ of creatinine). However, no overt clinical cases of porphyria were found during this study. Only four of the 11 workers with uroporphyrinuria originally described by Bleiberg et al¹² were still working in the plant. Several of the seven employees with uroporphyrinuria who had left the plant had been retested by Dr. Bleiberg before they left and had no elevation in urinary porphyrin excretion.

Several pertinent observations can be made about these urinary porphyrin values. The excretion of ALA and PBG, although not abnormally elevated, nonetheless tended to be relatively increased in the 15 maintenance men versus the other 56 workers. The coproporphyrin excretion per gram of creatinine, although again within normal limits,

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was significantly elevated in the maintenance men versus the same 56 workers (48.3 ± 14.4 vs 36.7 ± 19.6 , $P < 0.025$). Persons with higher values for coproporphyrin excretion (≥ 50 mg/gm of creatinine, $N = 15$) did not have any greater duration of employment in the plant than those with lower values (χ^2 test). There was a significant positive correlation between ALA excretion and coproporphyrin excretion ($r = 0.42$, $P < 0.001$) and between ALA excretion and age ($r = 0.42$, $P < 0.001$). There was a significant negative correlation between ALA excretion and serum bilirubin concentration ($r = -0.26$, $P < 0.05$).

Cardiovascular Findings.—Pulse rate and blood pressure recordings were taken. The average pulse was 85.1 ± 10.2 beats per minute; systolic blood pressure, 126.6 ± 12.8 mm Hg; and diastolic blood pressure, 75.4 ± 7.8 mm Hg. Only four persons had a diastolic pressure greater than 90 mm Hg. Cardiac evaluation was unremarkable except for histories of myocardial infarction in three employees.

Pulmonary Findings.—Twenty of 73 employees (27.4%) gave a history of a chronic cough, emphysema, or fairly consistent raising of early morning sputum. Of these 20 workers, 16 (80%) currently smoke cigarettes and the other four (20%) had smoked considerably in the past. In the entire plant, 42 employees (57.5%) currently smoke cigarettes and another 15 (20.6%) gave a history of smoking in the past. The group of current smokers averages 25.6 pack-years.

On physical examination 18 workers were judged to have some impairment of maximal diaphragmatic excursion. Fourteen of these currently smoke and three had smoked in the past. Eight of these 18 workers gave a history of chronic cough or frequent early morning sputum and one gave a history of asthma.

Although the incidence of chronic pulmonary disease in the plant seems to be appreciable, it cannot be attributed to any industrially related cause, as suggested by the report of Bauer⁷ because 78% of the employees now smoke or have smoked cigarettes previously.

Hepatic Function.—All serum total bilirubin values and albumin concentrations were within the normal laboratory range (Table 5

includes mean values). Two subjects had alkaline phosphatase values slightly above the normal laboratory range (18.7 and 19.0 King-Armstrong units/100 cc, respectively [normal range, 7 to 18 King-Armstrong units/100 cc]); the other liver function tests were normal. Two employees had SGOT levels elevated above the normal range (48 and 121 Karmen units/ml, respectively [normal range, 7 to 45 Karmen units/ml]), but otherwise had normal liver function tests. The employee with an SGOT value of 48 Karmen units/ml was receiving lincomycin injections at two- to four-week intervals. The SGOT value of 121 Karmen units/ml was not confirmed by a second testing, and the subject had no other evidence of liver malfunction. Six persons had palpable liver edges; five of these six findings were observed by one of the three physicians. Two of these six subjects were heavy beer drinkers (at least four cans of beer per day), and one had emphysematous lung changes with lowered diaphragm. Only one of the six subjects with a palpable liver had an abnormal liver function test, an alkaline phosphatase level of 19 King-Armstrong units/100 cc.

Gastrointestinal Results.—Several studies of 2,4,5-T workers have mentioned high prevalences of anorexia and weight loss, postprandial flatulence, nausea and vomiting, abdominal pain, and documented cases of gastritis and ulcers.^{4,6,8,10} At the time of the examination 22 workers in this plant (30%) were intermittently experiencing at least one of the following symptoms: nausea, vomiting, diarrhea, abdominal pains, or blood in the stool. Two persons in this group and four other persons had a history of "ulcers" (6 of 73 persons or 8.2%). We found no results from other industrial settings with which to compare our data.

Neurologic Findings.—Several authors have noted lower extremity weakness and fatigue in many of the patients with chloracne in 2,4,5-T factories.^{4,7} Only seven of 73 (9.6%) employees in our study complained of lower extremity fatigue or difficulty in climbing stairs. Five of these workers gave a history of arthritis in the lower extremities or heart disease with dyspnea; thus, only two (2.7%) experienced leg fatigue totally unexplained by other concomitant disease. Lower extremity weakness was not detected

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subjects had slightly above (18.7 and 19.0 μ g/ml), respectively. Armstrong's function tests as had SGOT in normal range (48 units/ml), respectively [normal range (48 units/ml)], but function tests. ST value of 48 mg/ml. Receiving lincomycin weekly intervals. Urine creatinine in normal range (100 mg/ml) and absence of liver enzymes. No palpable liver. Findings were observed by physicians. Two persons drank beer (1.5 l per day), and weight changes with one of the six persons had an abnormal alkaline phosphatase (100 units/100 cc). Several studies mentioned high weight loss, edema and vomiting documented cases. At the time of study in this plant persons experiencing symptoms: nausea, abdominal pains, or persons in this study had a history of diabetes (8.2%). We found no industrial setting. Several authors report weakness and symptoms with chloracne. Only seven of 73 persons complained of difficulty in these workers gave a lower extremities numbness; thus, only one person had total fatigue totally comitant disease. Diabetes was not detected

in the neurologic examination of any subject.

Eight workers (11%) complained of nonspecific headaches. Ten workers had decreased auditory acuity (inability to hear a watch ticking 1 cm from the ear); four of these had tympanic membrane disease. No discrimination was made between nerve or bone conduction defects. A decrease in olfactory discrimination was observed in only one employee and was most likely due to nasal obstruction. Two persons had a decreased sense of proprioception (one with history of chronic lumbar arthralgia secondary to traumatic injury to the back). In three persons, Achilles tendon reflexes were absent without other neurologic deficits (one had a two-year history of diabetes mellitus). Tremors of the hands were observed in three employees. We found no abnormalities of cranial nerves other than those noted above: no clonus, no alterations in deep tendon reflexes of musculi biceps or triceps brachii or quadriceps femoris, and no alteration in pain sensation.

Results of Other Laboratory Determinations.—Only one employee had an elevated BUN value, as shown in Table 5 (29 mg/100 ml; normal range, 6 to 24 mg/100 ml), and none had an elevated uric acid level (normal range, 3.0 to 7.9 mg/100 ml). The serum cholesterol (normal range, 133 to 294 mg/100 ml) was elevated in seven of 71 persons. There was an unexplainable elevation in the serum LDH (normal range, 50 to 160 Wacker units/ml) in 20 of 70 employees (28.6%); this may have been due to centrifuging clinical chemistry blood specimens more than two hours after sampling.

The two-hour serum glucose levels, as determined by the automated ferricyanide method for glucose determination, were judged satisfactory with 58 employees (see Methods). Six employees (10.4%) had a two-hour serum glucose value of \geq 140 mg/100 ml²⁰ after a 75-gm oral carbohydrate load (145, 148, 152, 171, 174, and 176 mg per 100 ml). The average age of these six individuals (50.6 years; range, 39 to 62)

was higher than that of the 52 individuals whose results were $<$ 140 mg/100 ml (39.3 years; range, 21 to 56). One of the six was the only known diabetic in the plant; he had a 19-year work history in the plant and a two-year history of diabetes which is currently being treated with tolbutamide. The average period of employment in this plant for the six individuals was 9.2 years, with the range being 1 to 19 years; three had minimal chloracne and one had severe chloracne. None of the six had a family history of diabetes; one was obese. The prevalence of 10.3% hyperglycemic results in this factory is consistent with a 14% prevalence figure of two-hour postglucose hyperglycemia in a random sample of a normal population in Bedford, England.²¹

Only two of 72 employees had a hemoglobin value of less than 13 gm/100 ml of blood, and 16 employees (22%) had a serum iron determination of less than 75 μ g/100 ml. The mean serum iron value was 97 ± 32 μ g/100 ml and only two employees had a value of 160 μ g/100 ml or greater. The average value for saturation of the iron-binding capacity was $27.4\% \pm 9.0\%$, with 27 persons (37%) having a value of less than 25%. Seven persons had a WBC of less than 5,000 cells/cu mm, but it was 4,000 cells/cu mm or less in only two employees. None of the seven had an absolute granulocytopenia ($<$ 1,500 neutrophils/cu mm)²² and only one worker had a lymphopenia ($<$ 1,000 lymphocytes/cu mm).²² Since the normal hematologic values used here are the 95% confidence limits of a study of a normal population,²² single cases of granulocy-

Table 3.—Distribution of Certain Signs, Symptoms, and Test Scores Among Three Categories of Active Acne Severity

	Active Acne Score		
	0	1-8	\geq 9
No. of employees			
Hirsutism	3/25 (12%)	4/35 (11%)	9/13 (69%)
Hyperpigmentation	5/25 (20%)	15/34 (44%)	10/12 (83%)
Scarring	1/25 (4.0%)	22/35 (63%)	13/13 (100%)
Eye irritation (history of tearing, itching, sties, bloodshot)	1/25 (4.0%)	8/35 (23%)	6/13 (46%)
Mean score of Mania scale of MMPI	55.4 \pm 7.7	58.8 \pm 10.2	64.9 \pm 10.5*

* The persons with acne scores of $>$ 9 had significantly higher scores on the Mania scale on the MMPI ($P <$ 0.05).

Table 4.—Urinary Porphyrin Excretion

Test	Plant Values, µg/gm of Creatinine*	Normal Values**	Upper Limit of Normal, µg/gm of Creatinine
ALA	1,021 ± 406	1,900 ± 600 µg/gm creatinine	3,100
PBG	444 ± 237	700 ± 400 µg/gm creatinine	1,500
Coproporphyrin	33.3 ± 19.0	0-175 µg/liter	175‡
Uroporphyrin	Trace†	0-15 µg/liter	15‡

* Mean ± SD, N = 72.

† Measurable in only one person; value, 107 µg/gm of creatinine.

‡ Values derived from normal by assuming a 70-kg man excretes creatinine at ≥ 1.5 gm/day and 1,500 ml of urine.

topenia and lymphopenia would not be unexpected in a population of 73. The red cell morphology and platelet count, determined by scan of the peripheral blood smear, were normal in all subjects.

MMPI Results.—The MMPI scores of production workers (including on-line personnel, supervisors, and maintenance men [N = 52]) and the administrative staff (including laboratory technicians [N = 17]) were analyzed separately because of the difference between the two groups in environmental exposure and educational level. Four janitors, currently working in the administration building, were eliminated from the analysis of the administrative staff because of a different educational background and previous exposure as production workers.

MMPI results are based on an analysis of scores of all subjects on 13 separate scales. Ten of these scales are designated by common clinical terms and are thus somewhat self-explanatory (Table 6). Detailed descriptions of each scale are found in *An MMPI Handbook*.¹⁶ The remaining three scales, the L, F, and K scales, measure the validity of the test results as an accurate profile of the subject. A high L score indicates that the subject answered most questions according to socially desirable standards rather than according to individual preferences. More highly educated subjects tend to have lower L scores; this is consistent with our finding of significantly lower L scores in the administrative staff. A high F score may be obtained if a subject answers in a prankish way, if he has a poor ability to read or comprehend the items, or if he is severely mentally disturbed. Since only one subject out of 69 had a high F score (F > 76), the test seems to have been both understood and taken seriously by the workers. A high K score indicates a high degree of

defensiveness in a person (an unwillingness to admit that he differs in any respect from what he considers normal); this score increases with educational level. The mean K scores for both groups in this plant are normal for their educational levels and do not significantly differ from each other.

The only significant differences in means on all scales between administrative staff and production workers were on the L and Hypochondriasis scales, with the production workers presenting a more hypochondriacal picture than the administrative staff. When scores of both groups of employees were compared with the normal values given for the MMPI test scales (N, approximately 300; mean, 50; standard deviation, 10), administrative staff and production workers varied significantly from normal on a total of six and nine scales, respectively (Table 6). The normal values for the MMPI, however, were based on scores of a small population of Minnesota males who took the test just before World War II.¹⁶ Since many obvious demographic differences exist between the plant population and the "normal population," it was thought that a more meaningful definition of the plant population would be obtained by searching for personality patterns appearing in high frequencies within the plant. A high-point code system was used which grouped subjects according to the two scales in which they scored the highest. The following high-point codes had the greatest frequency (F): administrative staff, hypomanic-hysterical, f = 23%; production workers, hypomanic-psychopathic, f = 12%. It is apparent from these small frequencies that no one personality pattern tended to dominate either administrative or productive group.

Correlation coefficients were calculated

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for several MMPI scales with other parameters, such as porphyrin excretion, chloracne, job history, and several biochemical tests. A significant correlation was found between the score of severity of active acne and the hypomanic scale ($r = 0.33$, $P < 0.01$). Furthermore, the mean manic scale score for the group with the most severe chloracne was significantly higher than the means of the two groups with less severe acne ($P < 0.05$ [Table 3]).

Comment

Acne.—Forty-eight of 73 (66%) employees in our study had some degree of acne, but only 13 (18%) had moderate to severe lesions. Most previous investigations of acne occurring in workers in 2,4,5-T plants have selectively presented clinical and pathologic findings in those severely affected. In contrast, the present study surveyed the prevalence of acne in the entire employee population and found the acne absent or minimal in 82% of the workers.

The severity of active acne correlated with the presence of scarring, hyperpigmentation, hirsutism and complaints about eye irritation (Table 3). Dugois et al¹⁰ reported a 50% incidence of conjunctivitis in 2,4,5-T workers with acne. Although we had many complaints about eye irritation, only three workers were observed to have conjunctivitis. However, 23 (32%) of the employees had hyperemia of the nasal mucosa and eight (11%) had hyperemia of the buccal mucosa.

Our findings that the presence of hyperpigmentation and hirsutism correlate quite significantly with the severity of acne and not at all with coproporphyrin excretion suggests that these two signs, which are usually thought of as part of the PCT syndrome, may be more closely related to chloracne in 2,4,5-T plants. Other studies support this view, such as (1) the findings of Bleiberg et al¹² that the presence of hirsutism and hyperpigmentation correlated better with

Table 5.—Clinical Laboratory Data

Test	Mean	SD	N*
BUN (mg/100 ml)	14.5	3.9	72
Uric acid (mg/100 ml)	5.4	1.0	72
Cholesterol (mg/100 ml)	237	44	71
Two-hour serum glucose (mg/100 ml)	95	32	58†
Alkaline phosphatase (King-Armstrong units)	11.2	2.5	71
LDH (Wacker units)	146†	46	70
SGOT (Karmen units)	22	13	71
Bilirubin (mg/100 ml)	0.44	0.16	71
Albumin (gm/100 ml)	4.6	0.3	71
Hemoglobin (gm/100 ml)	14.9	1.1	72
Serum iron (µg/100 ml)	97	32	70
Total iron-binding capacity (µg/100 ml)	348	44	69
Saturation of iron-binding capacity (%)	27.4	9.0	69
WBC (cells/cu mm)	7,160	2,190	72

* Variation in N secondary to sampling difficulties; for N = 73, mean age \pm SD = 39.3 \pm 11.1; 25% of population are Negroes, 75% are white.

† For N = 58, mean age \pm SD = 39.3 \pm 10.9; 29% of population are Negroes, 71% are white.

‡ Elevated value is probably due to poor sample handling.

the presence of chloracne than with uroporphyrinuria, and (2) the findings of other studies of 2,4,5-T factories^{1,2,3} in which workers were noted to have chloracne and hyperpigmentation but no mention was made of skin fragility, vesicular eruptions, or red urine.

As stated in the introduction, Kimmig and Schulz¹⁻⁶ have demonstrated the potent acnegenic properties of TCDD, an unwanted side product in the synthesis of 2,4,5-T. There is a tendency in the plant we studied for the maintenance men, who have the most direct exposure to all products of synthesis, to have the most severe acne and for the administrative personnel, who have the least exposure, to have the least acne. However, an association of a higher prevalence of acne with any particular location in the plant could not be demonstrated, eg, in the TCP synthetic area where one would expect TCDD concentration in the environment to be the highest. The plant has taken steps to decrease the contamination of the TCP end product by dioxin, and the concentration of the contaminant in the TCP has dropped from 10 to 25 ppm to 1 ppm (see the following subsections on chemistry and the plant). At the time of the study the effect of the safety measure to decrease contamination on the severity or prevalence of chloracne in the factory could not be evaluated since (1) there were no previous prevalence

Table 6.—Scale Scores on the MMPI

Scale	52 Production Workers			17 Administration Workers		
	Mean	SD	P*	Mean	SD	P*
L	52.5	8.2	NS	46.1	5.8	NS
Ft	54.6	7.4	<0.0025	54.4	8.8	NS
K	53.2	8.9	<0.025	55.4	6.3	<0.025
Hypochondriasis†	55.5	9.3	<0.00025	48.8	8.5	NS
Depression	59.5	11.2	<0.0001	56.7	11.5	<0.01
Hysteria	59.0	8.8	<0.0001	58.9	6.7	<0.001
Psychodiviance	59.8	12.1	<0.0001	55.5	12.1	<0.025
Masculinity	57.4	7.6	<0.0001	60.7	6.1	<0.00025
Paranoia	52.9	8.3	<0.05	52.6	9.6	NS
Psychasthenia	52.1	10.4	NS	50.8	8.9	NS
Schizophrenia	51.2	9.8	NS	51.2	10.0	NS
Mania	60.0	9.0	<0.0001	56.8	12.4	<0.01
Social introversion	51.4	8.4	NS	50.1	9.8	NS
Years of schooling	10.9 ± 2.1			15.2 ± 1.5		P 0.0011
Coproporphyrin excretion, µg/gm of creatinine	38.8 ± 16.0			37.9 ± 24.7		NS‡
No. of persons with some degree of acne	36/52			10/17		NS‡
Active acne score	6.2 ± 9.6			2.5 ± 3.2		NS‡

* Significance values by Student's t-test, comparing the above populations to the normal population as defined in the text of the results.

† The two plant groups are significantly different ($P < 0.005$). This would be expected on an education basis.

‡ The two plant groups are significantly different ($P < 0.01$).

§ Significance by Student's t-test.

¶ Significance by χ^2 test.

figures on chloracne in the plant with which to compare and (2) the effect of such a measure on the severity or prevalence of a chronic disease such as chloracne may take longer than six months to become evident.

Individuals seemed to vary greatly in their susceptibility to acquire chloracne. This observation is consistent with (1) the lack of correlation between the duration of employment in the plant and the severity or presence of chloracne and (2) the tendency toward an increased susceptibility to chloracne in persons with history of teen-age acne.

Chemistry.—Although the structures of 2,4-D and 2,4,5-T (Figure) differ only by one chlorine, the commercial syntheses of the two compounds are dissimilar. The starting product for 2,4,5-T is 1,2,4,5-tetrachlorobenzene which reacts with methanol and aqueous sodium hydroxide to form 2,4,5-trichlorophenolate, 2,4,5-trichloroanisole, and small amounts of several unwanted side products, eg, TCDD. The reaction product is steam-stripped to remove the anisole. At this point, sampling of various batches shows

the TCDD to be present in 10 to 25 ppm. About six months before our survey, the company installed a device which removed most of the TCDD. The TCP thus produced contained less than 1 ppm TCDD.

The TCP reacts with monochloroacetic acid (MCA) to form 2,4,5-T. The latter is esterified with various alcohols or allowed to react with dimethylamine, and then formulated and packaged. Some 2,4,5-T and 2,4-D is sold as the unesterified acid in solid form.

The starting materials for 2,4-D are phenol and chlorine (gas) which react in an exothermic process to form DCP. Subsequent reactions with MCA to the phenoxyacetic acid are similar to 2,4,5-T. In 2,4-D production there is no formation of the TCDD.

The Plant.—The plant employs several measures in an attempt to improve industrial hygiene. Clean work clothes are issued daily, and separate lockers for street and work clothes are provided. All production workers said they showered daily before leaving the plant. The DCP and TCP are made in one building and the 2,4-D and 2,4,5-T (acids) and their esters in another. Attempts have been made to improve ventilation, and recently the company has been successful in removing most of the TCDD before the TCP leaves the area in which it is synthesized. A dermatologist employed by the company visits the plant at least weekly, largely to treat the chloracne.

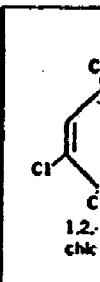
Almost all operations are carried out in closed processes (eg, tank car to pipeline to reaction vessel to next pipeline to next reaction vessel). There is of course some leakage, and frequently men working in maintenance must clean the inside of the reaction tanks or open pipelines.

Porphyria Cutanea Tarda.—A large outbreak of PCT in Turkey in 1956 due to the accidental ingestion of hexachlorobenzene²¹⁻²³

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to be present in ppm. About six years before our survey, a new plant was installed and removed most of the TCP thus retained less than 100 ppm.

P reacts with acetic acid to form 2,4,5-T. This is esterified with phenols or allowed to react with dimethylolurea then formulated as a dust. Some 2,4,5-T is sold as the acid in solid form. The reaction materials for the production of 2,4-D and 2,4,5-T which react in an exothermic process to form 2,4-D and 2,4,5-T are similar to those used in the production of 2,4-D. No formation of 2,4,5-T occurs.

The plant employs several measures to improve industrial hygiene. These are issued for street and residential areas. All production is carried out daily before 8 AM and TCP are not used. The 2,4-D and 2,4,5-T are stored in another plant. The company has been successful in improving ventilation. The company has been successful in improving ventilation. The company has been successful in improving ventilation.

The reaction is carried out in a closed system from one line to next reaction. Some leaking in maintenance of the reaction.

a.—A large outbreak in 1956 due to the chlorobenzene.

plus the high prevalence of PCT described by Bleiberg et al¹⁵ in this 2,4-D and 2,4,5-T plant in 1964 support a direct toxic etiology of many cases of PCT. The actual etiologic agent of PCT in this plant is unknown. We have administered reagent grade DCP to rats and observed an increase in the urinary excretion of coproporphyrin (unpublished data). A single oral dose of DCP caused a threefold increase in the activity of hepatic ALA synthetase, the rate-limiting enzyme in porphyrin biosynthesis. Rimington and Ziegler²⁹ reported a series of structurally similar chlorinated benzene compounds which caused experimental porphyria in rats. The TCDD, because it is a potent hepatotoxin and acrogen, was not examined for its ability to cause porphyria in experimental animals.

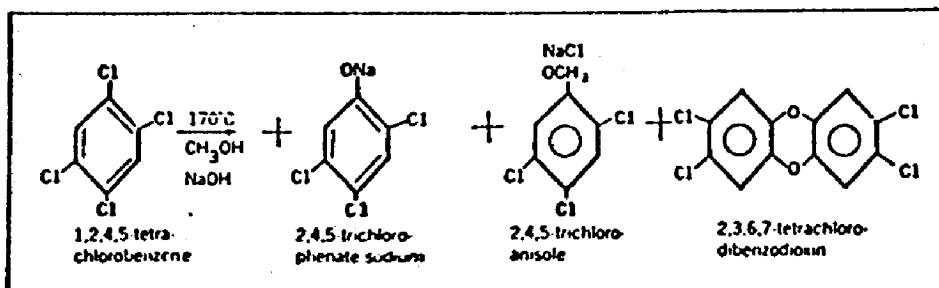
In the report of Bleiberg et al¹⁵ in 1964 of this same plant, 11 employees had uroporphyrinuria and several had hirsutism, hyperpigmentation, or skin fragility, or all three. In the three case histories presented, two patients had vesicular eruptions on exposed areas of the body, two had hepatic dysfunction, and the tissue obtained from the two reported liver biopsies fluoresced intensely with ultraviolet irradiation. These three case histories unquestionably fulfilled the criteria for the diagnosis of PCT.

Our reexamination of the same plant six years later revealed no clinical PCT: only one employee had mild persistent uroporphyrinuria. The reason for the decrease in severity and prevalence of PCT in this plant is unknown. Possible reasons include (1) increased encouragement of personal safety habits of workers, and (2) decrease in the contamination of PCT by the hepatotoxin, TCDD, and perhaps simultaneously by porphyrinogenic chemicals.

Porphyria cutanea tarda (ie, uroporphyrinuria, skin fragility, and vesicular eruptions on the skin) does appear to be a symptom-complex distinct from that of chloracne (ie, cysts, pustules, comedones, and scarring of the skin); both were found in workers in this plant in which 2,4-D and 2,4,5-T are manufactured. The independence of these syndromes is supported by (1) the lack of correlation between the severity or even presence of chloracne and uroporphyrinuria in the previous study,¹⁵ and (2) the persistence of chloracne in the factory six years later, despite the disappearance of the uroporphyrinuria and skin fragility. Even if the etiologic agent is the same, the syndromes apparently can occur independently and certainly have different clinical courses.

The statistically higher coproporphyrin excretion in the maintenance men suggests that they have a higher toxic exposure; they also have a tendency towards more severe acne. These men repair the inside of reaction vessels and leaking pipelines, and although their exposure is sporadic, it is apparently more intense.

Recently, much attention has been directed towards the finding of hemosiderosis and hyperferremia in patients with PCT, often in those with an alcoholic history.³⁰⁻³² Although studies of iron metabolism were not reported in the patients with hexachlorobenzene intoxication, chelating agents did appear to reverse the clinical symptoms and porphyrin excretion.³³ In our study, despite the absence of uroporphyrinuria in the workers at the present time, a tendency towards hyperferremia might be expected. On the contrary, we found an unexplainable trend towards hypoferremia and a lower iron-binding saturation, with little demonstrable anemia.



Hepatotoxicity.—TCDD, which has been incriminated as a potent acrogenic agent, is also very hepatotoxic. A single oral dose of 0.05 to 0.1 mg/kg to rabbits resulted in death in one to two weeks. Autopsy revealed extensive necrosis and enlargement of the livers.⁸ Similarly, dermal application of the tarry residues in 2,4,5-T synthesis caused gross hepatic lesions and rapid death in guinea pigs.¹⁰ Clinically, several investigators have looked for evidence of hepatotoxicity in 2,4,5-T-plant workers affected with chloracne. Bauer et al⁷ noted that two of nine cases had slightly delayed sulfobromophthalein excretion and three had abnormal liver biopsies. In the report of Bleiberg et al¹² of patients with chloracne and porphyria, two subjects had hepatic dysfunction and two had abnormal liver biopsies. Dugois and co-workers^{9,10} have noted hyperlipemic and hypercholesterolemic sera in their subjects. Hofmann and Meneghini¹³ found no hepatic damage in six patients with chloracne. Of the liver tests performed in this study (bilirubin, albumin, SGOT, and alkaline phosphatase), only four values were elevated. Three of these four elevations were extremely mild, and the fourth was accompanied by no other abnormal liver test values. Of the six patients with palpable livers, only one had a mildly elevated liver function test. Although TCDD and other chemicals produced in 2,4,5-T synthesis may be hepatotoxic in humans, the prevalence of demonstrable chemical liver dysfunction in this plant is minimal.

Systemic Toxicity.—As noted in the introduction, a variety of other signs, symptoms, and laboratory findings have been noted in various studies of 2,4,5-T workers with acne. We found no unexplainable significant increases in abnormal function of cardiovascular, pulmonary, intermediary metabolic, or hematologic systems in comparison with normal populations. Although the prevalence of gastrointestinal complaints seems high (30%) and although physical examination revealed occasional unexplainable neurologic deficits (decreased hearing, six of 73 subjects; diminished proprioception, one of 73; absent ankle jerks, two of 73), we could find no figures of comparable studies with which to compare; hence, a judgment on the normality or abnormality of the prevalence

of these findings in this population would only be conjectural.

MMPI.—The MMPI results are important in that they offer an objective profile of the workers in one herbicide synthesizing plant. Conclusions about personality changes secondary to chronic exposure in a plant in which 2,4-D and 2,4,5-T are manufactured can only be tenuous, however, because we have no suitable group with which to compare these results. The comparison of MMPI results of these factory workers with the normal population of pre-World War II, white subjects from Minnesota was inescapable since the scoring system for the test is based upon this "norm."¹⁴ Nonetheless, we consider these groups incomparable. The only evidence to suggest any environmental effect of this herbicide plant on personality is the significant correlation between severity of chloracne (a known toxic effect) and the score on the hypomanic scale. This is an interesting finding and somewhat contradictory to the apathy and psychomotor retardation reported by Bauer et al.⁷

Many previous investigations of both acute and chronic poisoning in 2,4,5-T plants have reported the symptoms of anorexia with weight loss, fatigue, debility, and asthenia.^{4,7} However, only one author has described in detail personality changes thought to be associated with chemical exposure. Bauer et al⁷ studied nine workers with severe chloracne which still persisted five years after termination of their exposure in a 2,4,5-T plant and described a syndrome of general weakness, fatigue, apathy, and decreased libido alternating with fits of anger and irritability. Rorschach tests showed a weakened emotional reaction, a lack of concentration, slowed thought processes, and perseveration. This whole syndrome was designated by the term "psychovegetative disorder."

The inconsistency of our finding of a significant correlation between hypomania and chloracne and the previous description of lethargy, dulled emotional response, and apathy⁷ remains to be adequately explained. Possible reasons include a basic difference in methodologies and a difference in testing period with relation to the time of exposure. Additionally, the severity and chronicity of the organic disease in subjects studied by

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Bauer et al⁷ may have induced personality changes which masked any manic effects found with less severe disease.

Thomas Ashby, MD, Augustin Gombart, MD, Jerome Schulz, MD, and Arthur DePalma, MD, provided clinical assistance. Patricia Hickman performed the ALA, PABG, and porphyrin determinations. Janet Daling, MS, Community Study on Pesticides, Washington State Department of Health, assisted in preparing a subset of our data for computer analysis. Frank Clark, PhD, Assistant Professor of Psychiatry (Psychology) at Emory University, assisted in interpretation of MMPI results.

Jacob Bleiberg, MD, gave permission for entry of the factory studied and provided written records of past medical histories for comparison on some workers.

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