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Clinical Manifestations of 2,4,5-T Exposures

Raymond R. Suskind, M.D.*

I shall attempt in this discussion to present what is known about the clinical and laboratory findings in humans who have been exposed to 2,4,5-T, the chemical agents used or produced in its manufacture and the incidental contaminants. The two most commonly employed processes start with 1,2,4,5 tetrachlorobenzene which is reacted with either methanol or ethylene glycol in the presence of sodium hydroxide to produce sodium trichlorophenate (Fig. 1). Trichlorophenol (TCP), in an alkaline medium, will condense, especially if the temperature exceeds 230°c to form 2,3,7,8 TCDD. Hence, in runaway reactions, such as occurred in Nitro, West Virginia in 1949 and in Seveso, Italy in 1976, the contents of the kettle when expelled contained large amounts of sodium trichlorophenate, perhaps some unreacted tetrachlorobenzene and caustic soda as well as the alcohol and the toxic contaminant TCDD. In the regular process of manufacture of 2,4,5-T, the sodium trichlorphenate is transformed into 2,4,5-T, but may carry over with it significant amounts of TCDD. Hence, the populations exposed heavily to 2,4,5-T may also be exposed to TCDD. In the production of the trichlorophenol, chlorinated anisoles are also formed. Populations exposed to the trichlorophenate runaway reaction would be exposed to sodium trichlorphenate as well as TCDD, chlorinated anisoles and even unreacted alkali. The acute symptoms and findings, post accident, are chemical burns of the skin and eyes and irritation of both areas, respiratory irritation, nausea, vomiting and headache.[1] It is uncertain as to whether the TCDD causes any of the acute manifestations. The acute symptoms, if the exposure is either controlled or eliminated, subside in several days. Within about 10 days to two weeks the acneform reactions of the skin become manifest. The characteristic lesions

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include comedones, keratin cysts and after several weeks, hyperpigmentation and hypertrichosis.[1] It has been our experience that the hyperpigmentation is the result of ultraviolet exposure from solar radiation, from UVL treatment for the acne, or x-ray treatment for the skin problems.[1,2] In the Nitro, West Virginia incident, a number of workers who were exposed to the runaway reaction material and who developed chloracne also developed hepatomegaly and peripheral neuritis. The latter was characterized by severe aches and pains in the skeletal and intercostal muscles. These manifestations were described in my previous presentation and is summarized in Table I. The laboratory findings in the most severely affected persons included a marked decrease in prothrombin concentration, an increase intotal lipids and myelin degeneration of peripheral nerve observed in biopsy. The significant findings are listed in Table II. Typical severe cases are seen in Figure II. One of these employees, a chemical operator, had an extensive acneform eruption of the scalp which is infrequently observed in chlorinated hydrocarbon acne.

In the population of workers at the Diamond Alkali Co. plant in New Jersey, who were exposed to 2,4 dichlorophenoxy acetic acid (2,4-D) and trichlorophenoxy acetic acid (2,4,5-T) 29 persons with chloracne were studied.[3] Eleven had elevated urinary uroporphyrins and 11 of the 29 workers investigated had porphyria cutanea tarda (PCT) of varying degrees of severity.[3] Two patients who were hospitalized for study demonstrated increased levels of urinary uroporphyrins, coproporphyrins and urobilinogen. Other significant findings included elevated SGOT. Liver biopsies showed evidence of parenchymal cell regeneration and hemofuscin deposition. The skin manifestations of PCT such as epidermal fragility and a vesiculobullous eruption were noted on face, ears, hands and those areas exposed to sun or pressure. Hyperpigmentation and hirsutism were also noted in this group. Poland et al[4] in 1969 restudied the Diamond Alkali group and found that 13 of 78 exposed still had moderate to severe acne. One had a mild persistent

uroporphyrinuria but no clinical PCT. Forty eight of this group still had some acne.

In 1975, Oliver[5] described the toxic effects of 2,3,7,8 TCDD in three laboratory workers who were apparently exposed to pure material. Two of the three had typical chloracne. The other symptoms which appeared to occur two years after the initial exposure in two of the three scientists included personality changes, neurological disturbances and hirsutism. All three were found to have abnormal serum cholesterol levels. No porphyria was observed. Two of the three had gastrointestinal symptoms, one complained of blurring of vision and difficulty in muscular coordination. Another complained of "neuralgia of the left thigh."

Probably one of the most heavily exposed populations is those reported by Jirasek.[6,7] This population was exposed to sodium 2,4,5-T acetate, the butyl ester of 2,4,5-T and pentachlorophenate. The exposure occurred from 1965 to 1969. The number of persons affected was 78; 76 of these had acne, hypertrichosis and hyperpigmentation. The complaints included: fatigue, weakness and pain in the extremities, sweating and headache. The clinical findings included hepatomegaly, porphyria cutanea tarda, and increases in urinary ALA and alkaline phosphatase. Many of the affected group had polyneuropathy. The authors describe the two fatalities as a result of the intoxication--one of severe atherosclerosis with porphyria and another from acute pentachlorophenol intoxication.

Table III lists the constant, inconstant and occasional clinical features and laboratory findings of the populations exposed to trichlorophenol runaway reactions, 2,4,5-T, PCB's and 2,4-D.

Earlier this morning we heard about some of the dermatological manifestations of TCDD exposure. In the 1950's, not long after the runaway reaction occurred at Nitro, West Virginia, experiments were carried out at the Kettering Laboratory to determine the biologic events involved in chloracnegenesis.

The first series of experiments attempted to determine the cutaneous effects of four materials found in 2,4,5-T synthesis. The materials used were trichloroanisol, pentachloroanisole, 2,4,5-trichlorophenoxy acid, and the sodium salt of 2,4,5-T. In all instances, Halowax 1014^{R} was used as the positive control substance. Halowax 1014^{R} was a product containing hexa and penta chloronaphthalene and known to be acnegenic to humans.

Initially weanling rats and rabbits were used. A 5% acetone solution of each of the 5 materials was applied daily for 60 applications. We were unable to produce pilosebaceous changes. Human volunteers were exposed to the same materials by daily skin applications for 96 days and produced neither clinical nor histological changes. In the next study a group of human volunteers were exposed to three different samples of sodium 2,4,5-trichlorophenate. One sample was from the Monsanto plant process-which was involved in the runaway reaction, another by distilling trichlorophenol and taking it up in caustic soda to form the phenate, a third was prepared by the process of another manufacturer. The plant material contained 22.4% trichlorophenol and its pH was 10.0.

Three groups of three (3) persons were exposed to each sample in 5% concentrations of each of the trichlorophenate, and three (3) to 20% Halowax 1014^{R}. There were 12 persons in the test. Applications were made 5 days per week for 6 weeks to the flexural surface of the forearm, over a skin area measuring approximately 70 cm^{2}. The area of the application was wrapped in gauze bandage and retained for 24 hours until the next application.

The vehicle used to dilute each material was Plastibase^{R} an oleaginous, non-water absorbing base containing 95% liquid petrolatum and 5% polyethylene. Physical examinations, CBC, and liver function tests were performed prior to the start of this test, at the end of the 2nd, 4th, 6th week of the test, and at intervals up to 12 weeks after the end of this test. All of the materials

induced very mild irritant reactions and itching which persisted in some instances throughout the exposure. Skin biopsies were taken prior to and at intervals during the study (10 days, 3 weeks, 4 weeks, 6 weeks and 12 weeks post exposure).

Within 5-14 days the follicles became somewhat prominent, some developing changes earlier than others. At this time no gross plugging was noted in most lesions. In 3 to 5 weeks frank widening of the follicular openings, as well as gross plugging, were observed. This was indistinguishable from the clinical comedo. After 6 weeks of exposure to the acnegen, almost every follicle orifice was affected and yellowish milia-like lesions, as well as comedones were noted. Following discontinuation of the exposure, the comedones and small cystlike lesions persisted for 3-4 months. The most acnegenic of the three trichlorophenates was that which came from the involved plant.

The sequence of histological events or cellular kinetics was as follows:

The first event observed is an increase in keratin production at the level of the sebaceous gland duct within the first 10 days. This is then followed by keratinization of the infundibulum and pore, as well as hyperplasia of the follicular epidermis.

In 14-18 days keratinization of the follicular opening and hyperplasia of the outer root sheath cells occurs. Progressive decrease of lipid bearing cells is observed. In most instances, a perifollicular inflammatory infiltrate is seen and in two instances eosinophilic infiltrate. Occasionally small pustules are seen. Not infrequently microscopic pustules were noted. Here is an instance following 21 days of exposure in which the collection of leukocytes and debris occurred below the keratin plug. Some pustules appear to be deeper than others. The pustule is most often continuous with the keratin plug and separated from it by a narrow opening. The total effect is an inverted keyhole type of structure with the keratin plug above and the pustule below.

In the 3rd to 6th week there is further dilatation of the follicular pore with keratin. The keratin mass is lamellated and contains fat globules when stained with Sudan 4 or Sudan black. A true comedo has formed but the follicular cells, especially in the inferior portion of the structure, may become markedly hyperplastic. In the distal portion of the structure--that nearest the surface of the skin--the epidermis of the outer root sheath becomes flattened to one or two cell layers in thickness. Subsequently even the thickened epithelium of the proximal part of this structure thins out and the onion-like mass of keratin lamellae with interspersed extracellular lipid is surrounded by a thin single cell layered wall. By the time 6 weeks have elapsed almost every follicle has been altered in this manner.

In summary, the cellular kinetics of chloracne is characterized by the modulation of sebaceous cells to keratinocytes. The process appears to start at the level of the sebaceous gland duct which empties into the follicle lumen. These keratinizing cells replace the sebum forming cells and after a period of time, in this experiment, 6-12 weeks, produce open and closed comedones.

Occupational acne or chemically induced acne can result from exposure to crude petroleum, cutting oils, coal tar and pitch as well as chlorinated aromatic compounds. Of the chlorinated hydrocarbon acnegens those which have been described previously are chlorinated naphthalenes, chlorinated biphenyls, chlorinated phenyloxides and the dioxins. The structure of these compounds is seen in Figure III.

The numerous experiences with populations which have been exposed to 2,4,5-T and its contaminants such as the dioxins indicate that there are numerous knowledge gaps about the biologic activity of 2,4,5-T itself, its contaminants and the metabolic products of such materials. These deserve high priority in any research program.

It is well to consider the similar pattern of pilosebaceous response which occurs with exposure to TCDD, contaminants of pentachlorophenol and PCB exposure (Yusho) as expressions of a common metabolic product(s) or common aromatic configuration. This is still to be ascertained by appropriate experiments.

In summary the clinical and laboratory assessment characteristics of persons affected by exposure to 2,4,5-T and its contaminants have been presented. All have acne as a common and contant finding. The presence of other adverse reactions vary with the type of incident and/or process. Pertinent factors are degree or extent of exposure to the toxic agent or combination of agents. The pathogensis and cell kinetics of acneform lesions induced by contaminated trichlorophenate is described. The essential feature is the modulation of sebaceous cells to keratinocytes and formation of keratin filled comedones.

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FIGURE 1

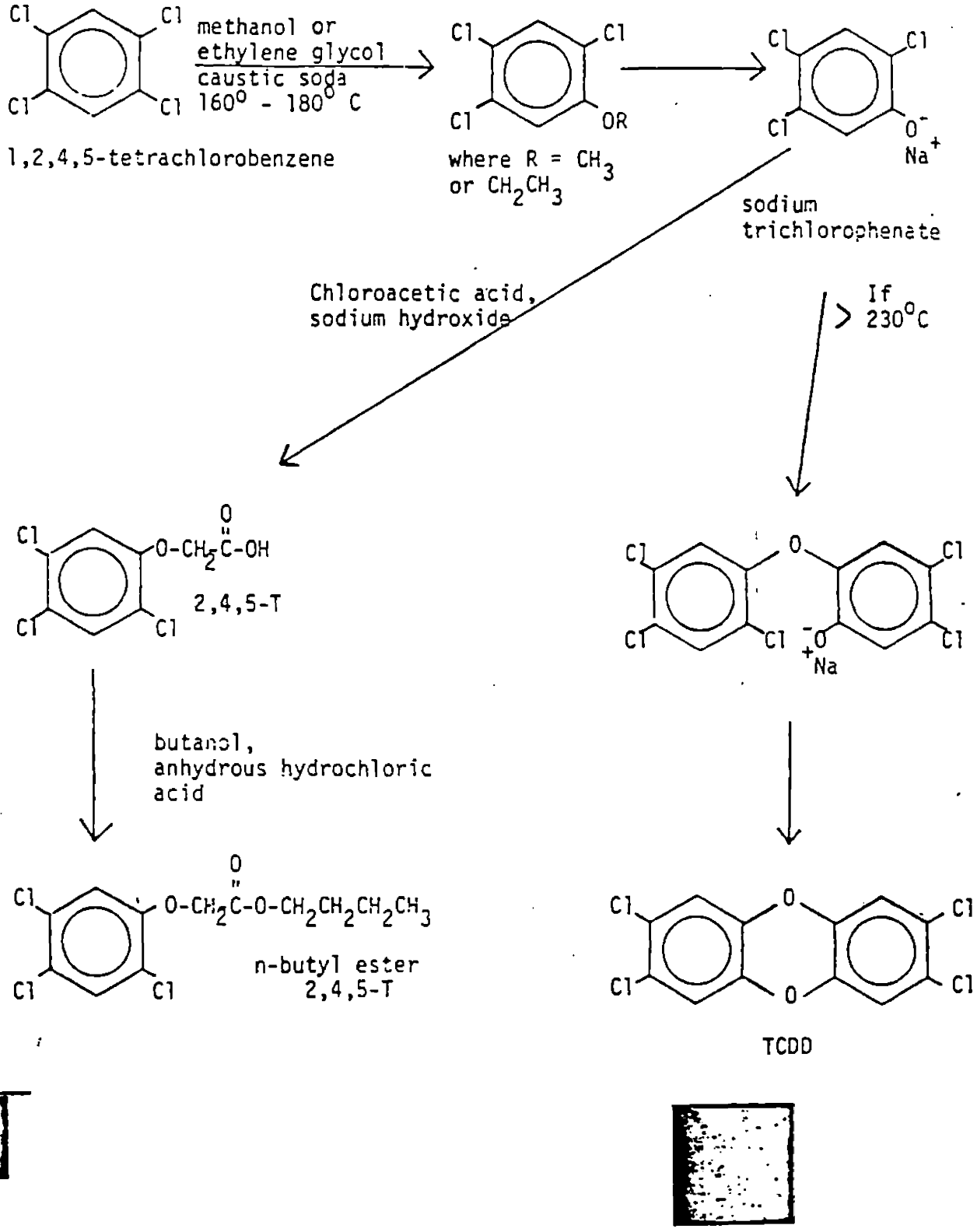

methanol or
ethylene glycol
caustic soda
160° - 180° C
1,2,4,5-tetrachlorobenzene
where R = CH3
or CH2CH3
sodium
trichlorophenate
Chloroacetic acid,
sodium hydroxide
If
> 230°C
2,4,5-T
butanol,
anhydrous hydrochloric
acid
n-butyl ester
2,4,5-T
TCDD

FIGURE II

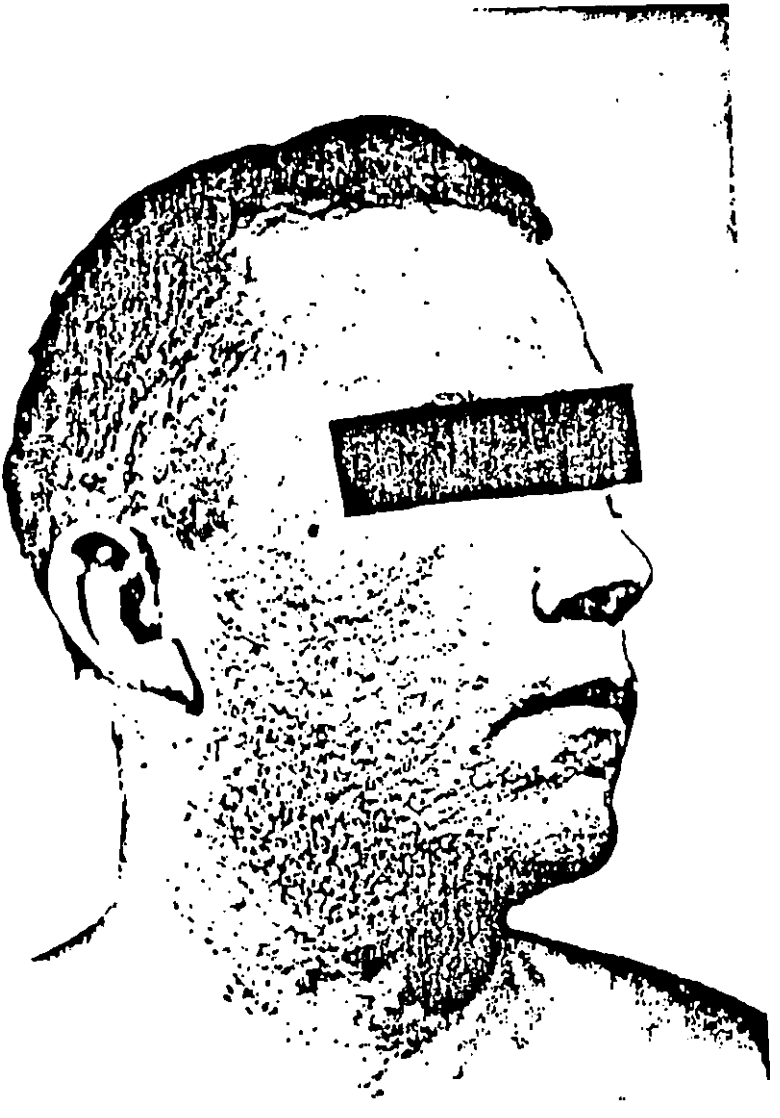


FIGURE II

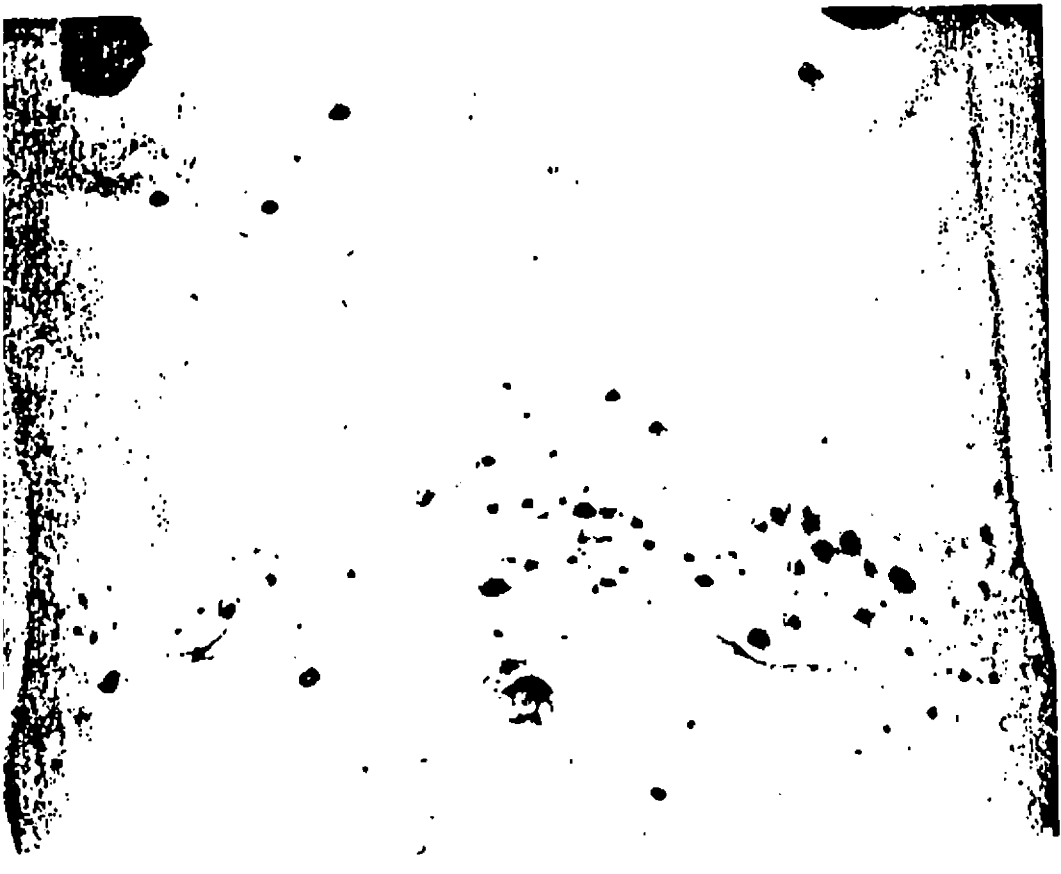
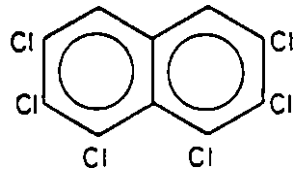
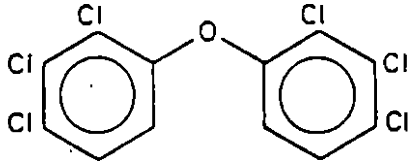


FIGURE III

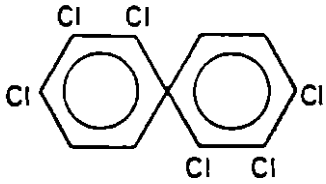
CHLORINATED HYDROCARBON ACNEGENS



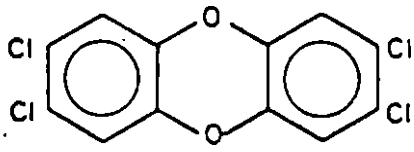
CHLORONAPHTHALENE



CHLORODIPHENYLOXIDE



CHLORODIPHENYL



TCDD
2,3,7,8 TETRACHLORODIBENZO-P-DIOXIN

Table I

WORKERS AFFECTED BY RUNAWAY REACTION

Nitro, West Virginia

1949

Clinical Symptoms

In Order of Relative Incidence

1. Pilosebaceous lesions
2. Aches and pains in muscles
3. Fatigue
4. Nervousness, irritability and insomnia
5. Decrease in libido
6. Dyspnea
7. Melanosis
8. Vertigo
9. Intolerance to cold

Table II

CLINICAL AND LABORATORY FINDINGS

Clinical:	Acne
	Liver enlarged and tender
	Sensory loss - feet
Laboratory:	Total serum lipids ↑
	Prothrombin time ↑
	Glucuronates ↑
	Muscle biopsy - normal
	Peripheral nerve biopsy
	Destruction of myelin sheaths and nerve fiber

TABLE III

CLINICAL AND LABORATORY FINDINGS

HUMAN EXPOSURE TO

TCDD in 2,4,5-T and or TCP, PCB's

	Clinical Features	Laboratory Findings
CONSTANT	Acne	
INCONSTANT	Neuromuscular Symptoms Severe Pain in Chest and muscles extremities Weakness - Extremities	Peripheral Neuritis
INCONSTANT	Enlarged, Tender Liver	Decrease Prothrombin Concentration Increase SGOT
OCCASIONAL	Porphyria Cutanea Tarda	Uroporphyrinuria
INCONSTANT	Hyperpigmentation Skin	Increase in Triglycerides
INCONSTANT	Hirsutism of Face - Malar	
INCONSTANT	Irritability	