

OCCURRENCE OF ACNE CHLORINA AND PORPHYRIA CUTANEA TARD A DURING THE PRODUCTION OF HERBICIDES

The authors submit after an evaluation of data reported in the literature results of the long-term follow-up of 78 patients with an occupational disease caused by manufacture of herbicides -- parathion, malathion and derivatives of 2,4,5 trichlorophenoxyacetic acid. Of this number 73 subjects suffered from acute chloracne manifested in mild cases only by comedones and in severe cases by large cysts, abscesses and nodules, scars on the whole body. The varied clinical picture is demonstrated on photographs. Twelve of the patients had a hepatic lesion with symptoms of porphyria cutanea tarda and 14 other patients had nervous and mental disorders.

It was revealed that the skin and general effects were caused by 2,4,5-trichlorophenoxyacetic acid which is formed during alkaline hydrolysis of isochlorobenzene with sodium hydroxide. The reaction was performed by an excellent procedure at a temperature of 130°C and pressure of 45 atm. From the work of Schult and Klemm it is known that this highly toxic substance is not formed when the above reaction is carried out at a lower temperature of 110°C. Not only workers engaged in production of herbicides were affected but also maintenance workers, research workers and workers digging the sewage channel.

In all the cases began as acute solar dermatitis. In all the remainder it started by a slow eruption of comedones and their development into cysts, inflammations and pustules were found only in the most severe and extensive affections. The skin and clinical manifestations corresponded to data reported in the literature. In 17 patients, however, some changes started in a unusual way by papulopustular eruptions on the extremities. In 20 patients the authors observed localization in the axilla which was not reported previously. The disease does not affect the hairy part of the head and in one patient it disappeared even from these sites in the face and on the neck where he grew a beard, while the condition persisted at other sites. Patients with an impaired porphyria metabolism suffered from typical hyperpigmentation and hypertrichosis and only one of them from bilateral actinic keratosis. Hypertrichosis and hyperpigmentation was observed also in 13 subjects with acne without laboratory signs of porphyria.

In the period prior to the disease no significant predisposing factors were noted. The latency differed in some instances severe dermatological and internal damage developed after short exposure. In other instances especially long and multiple exposures caused only mild symptoms. Despite this the authors are convinced that the latency of the disease depends more on exposure than predisposition. The patients had various complaints: itching, numbness and numbness and some of them had considerable weight loss. Two died from general intoxication, two from lung cancer but so far it is not possible to state reliably whether it was related to the occupational exposure. The carcinogenic effect of chlorinated hydrocarbons produced in the particular plant was not proved so far. The medical and neurological symptoms will be discussed by the authors in subsequent work.

All patients are being followed up in collaboration with specialists in internal medicine and a dermatologist. After the peak has been reached -- usually after 1-2 years duration -- the disease subsides very slowly. In some patients, however, the manifestations and symptoms of general intoxication persist already for 8 years. All therapeutic methods proved little effective. A certain improvement was obtained by regular exposure of comedones and scars. In all patients secondary prevention was caused, treatment and changes in accordance to legal provisions.

Part I

During the years from 1965 through 1969, a chemical plant producing herbicides - pentachlorophenol and 2,4,5-trichlorophenoxyacetic acid derivatives - reported a mass outbreak of acne chlorina. The number of persons stricken, 78, is one of the largest ever recorded. Furthermore, some of our patients were also stricken by a complete intoxication manifested by liver lesions, by a deficiency in porphyrin, fat and protein metabolism and by nervous and physical changes. In two cases, the intoxication was fatal. This part of the research will deal primarily with skin symptoms and the internal and neurological changes will be discussed in a subsequent work [23] and in more detail in another work [32].

The acne forming dermatoses are caused in most cases by crude oil derivatives - known as acne oleosa - and less often by tar and its derivatives - in these cases it is acne picea. In contrast to those acnes, acne chlorina is relatively very rare because it is only caused by a small number of certain chlorinated hydrocarbons which are produced and used only on a limited scale. Acne chlorina also differs from other acne forming dermatoses by its localization, clinical picture and course.

Mass occurrences of acne chlorina have been recorded during several time periods which are separated by decades, in accord with industrial and chemical development and with the gradual introduction into production of new chlorinated hydrocarbons.

The first cases were described by Herxheimer [18] in 1899 in the electrolytic production of sodium chloride and sodium hydroxide from brine. Herxheimer assumed that the illness was caused by the inhalation of chlorine and by its excretion through membranes and he therefore named the disease acne chlorina, i.e., chloracne. The French authors Thibierge [43,44] and Hallopeau [16] were of the same opinion as to the incidence of this disease. Furthermore, Hallopeau thought that the black coloration of the comedones

was caused by some lead compound that formed on the chamber's lead walls as a result of a reaction with chlorine. Renon [35] also connected chloracne with lung tuberculosis in one of his patients and ascribed both diseases to gaseous chlorine.

However, Hirsch [20] concluded in that same year that the cause must be a solid substance which formed on the anodes during electrolysis because exposure to chlorine gas alone did not cause the disease. This finding was supported by Bettmann [2] who observed 21 patients who were engaged in the production of hydrochloric acid and who were in contact with chlorinated tar compounds but not with chlorine gas.

Lehmann [26], in 1903, concluded that the actual causes of the disease were chlorinated products such as hexachlorobenzene, pentachlorobenzoic acid and hexachloroethane which formed on the carbon anode during electrolysis. Because similar cases of acne chlorina were also observed in the production and processing of p-nitrochlorobenzene, W. Lehmann [27] concluded that acne chlorina was caused primarily by chlorobenzenes. As soon as carbon anodes were replaced by magnetite anodes, the incidence of acne during electrolysis ceased.

Before World War I, Wahle [46] observed acne chlorina in two chemists which was probably caused by a chlorine compound - phenylene dioxide - not identified or known in more detail at that time.

The next wave of the disease's incidence occurred at the end of World War I during the production of chlorinated naphthalenes or perchloronaphthalenes. In this period the disease was given an additional new name - Pernakrankheit (Wauer [42]). Chlorinated naphthalenes and diphenyls with a waxy consistency, also known as halowaxes, have some very valuable properties such as waterproofness, flame resistance and acid resistance. These properties earmarked these materials for the production of protective gas masks and other military equipment.

A new increase in the incidence of the disease occurred in the nineteen-twenties during the use of chlorinated naphthalenes

as an insulating material in the mining industry (Telcky [42]). Acne chlorina also appeared in the electrolytic production of chlorine when insulating coatings of tar were used. This fact brought about numerous disagreements and questions as to whether the disease in those production processes was not actually acne picca. On the other hand, Telcky supported the contention that the tar acne could be caused by chlorinated hydrocarbons contaminating the tar.

The excellent dielectric properties of the chlorinated naphthalenes ("haftax", "halowax", "nibrene") led to their wide utilization in the production of cables and condensers and another mass occurrence of the disease was produced in the nineteen-thirties when the U.S.A. and other countries recorded hundreds of stricken individuals. Holtzmann [22] also noted the occurrence of acne among the family members of workers employed in the production of condensers. These family members handled and washed work clothes contaminated with the chlorinated naphthalenes. Based on these observations, Holtzmann corrected his previous original conclusions and stated that the chloracne was actually tar acne and judged the effect of halowaxes to be that of an external acnegenic cause.

Ormsby [31] observed acne chlorina with the use of a fungicide used in the impregnation of lumber (sodium tetrachloro-*o*-phenylphenolate). Jones and Alden [24], Schwartz [39] and later many others also observed total disorders in their patients and Flinn and Jarvik [8] noted a death due to yellow liver atrophy. In 1938, Mayers and his coworkers [28] were unsuccessful in clarifying the mechanism of occurrence of dermatitides and acne chlorina in their patients with the aid of epicutaneous tests - the tests were negative.

During World War II, chlorinated naphthalenes were used for the impregnation of ships' hulls when it was discovered that these substances could protect ships from damage of magnetic mines. The use of halowaxes increased significantly, especially in the electrical industry. American authors gave acne chlorina another name,

because of the occupation (cable production) of the
and coworkers [14], Schwartz [40], Morris [29]).

massive outbreaks of acne and several deaths were
er World War II, the incidence of acne did not sub-
the undesirable experiences with the chlorinated
did not prevent their use in the electrical industry

An interesting observation was recorded by Herzberg

He observed seven cases of acne chlorina in patients
ed chlorinated paraffins in the form of a food

This prompted Herzberg to conclude that acne chlorina
er the internal ingestion of chlorinated hydro-
larly, Fuchs [9] also noted the affliction of three

their mothers after they had eaten potatoes fried in

. Winkler [48] recorded 10 cases of dermatitis and

one chlorina among 23 workers in a condenser factory

were in the production sequence. From these cases

ded that "chlorinated hydrocarbons cause the forma-

ts that in turn cause an increased secretion from

lands". In 1949 Gavrilova [10] warned of the photo-

effect of polychloronaphthalenes. In recent years,

replaced chlorinated naphthalenes in industrial use.

y the production of sodium hydroxide may be a source

na. We have observed more cases between 1950 and

in causes of acne chlorina in these cases have been

on of chlorine gas with the hydrocarbons in the tar

ettings on the electrolytic containers and tubs and

tal oils which were used to protect the electrode

authors noted several cases of acne chlorina among

ckers after the use of nibrene in the electrical

ne 1950's.

ore, the acnegenic effects of the mineral oil based

res used in metal working increase when chlorinated

are added. Therefore, some cases of acne oleosa were

exhibited a partial acne chlorina character (more

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★ disorders of the liver, kidney, myocardium and nervous system. The author described the death of a patient from necrosis of the pancreas as a special case. Furthermore, he also observed dermatitis in a nurse who had had contact only with experimental animals. Finally, he diagnosed acne chlorina in the fourteen year old son of an employee whose disease was contracted only from the household environment - by wearing his father's contaminated scarf and by using his father's towel.

Actual observations

The process called PCP (pentachlorophenol) which caused mass damage in Czechoslovakia was, as far as production is concerned, identical to the process from which Kimmig and Schulz drew their patients for observation. The final products of this process were sodium pentachlorophenolate, 2,4,5-trichlorophenoxyacetic acid and the latter's sodium salt and butyl ester. The primary raw material was technical grade trichlorobenzene which was produced in a neighboring building for the production of hexachlorocyclohexane (HCH) and lindane. The table shows the entire production scheme (Table I). The chlorination of trichlorobenzene produced tetrachlorobenzene and hexachlorobenzene. Sodium pentachlorophenolate was formed by the alkaline hydrolysis of hexachlorobenzene. Sodium trichlorophenolate was produced by the alkaline hydrolysis of tetrachlorobenzene. The hydrolysis of tetrachlorobenzene with sodium hydroxide in the presence of methanol took place in an autoclave at 190°C and at 45 atm of pressure for one hour. After cooling, the methanol was distilled from the hydrolysate, the hydrolysate was diluted with water to a 25% concentration and it was then syphoned into a storage tank. The condensation of sodium trichlorophenolate with monochloroacetic acid produced sodium trichlorophenoxyacetate. Following cooling, centrifugation and flushing with water, the dried sodium trichlorophenoxyacetate was picked out by hand and placed in small barrels. Some of this product was used to produce the butyl ester of

trichlorophenoxyacetic acid. This production took place in another building.

The production of both the primary products took place in a four story building with grated floors (WEMA grates) which was one reason why the entire building was contaminated with the high risk substances. The building was not sufficiently airtight, the local exhausts were in most cases improperly installed and hermetization and mechanization were insufficient. Initially, the sodium tetrachlorophenolate [sic] was escaping from the centrifuge into the work space in the form of a mist. A series of tasks such as the removal of solid substances and the pumping of liquids were performed by hand. The workers were dressed in linen work clothes. The thorough cleaning and frequent changing of the work clothing was impossible to guarantee over the entire interval of production. Rubber gloves and respirators were used at some work sites. The conditions surrounding the production of the butyl ester of trichlorophenoxyacetic acid were the same as those described above.

Kimmig and Schulz [25] found that the main source of acne-genic hydrocarbons was that segment of the production process in which sodium trichlorophenolate is formed by the alkaline hydrolysis of tetrachlorobenzene in the presence of methanol. A co-worker of these authors, Doctor (of Chemistry) Sorge, had deduced on theoretical grounds that if this reaction were conducted at 190°C and 45 atm of pressure, chlorinated hydrocarbon by-products such as polychlorodibenzo-p-dioxines, polychlorodibenzofurans, polychlorodiphenyl ethers and polychlorodiphenyl oxides may be formed in small amounts (Schulz [36]). Sorge also prepared some of these substances by his synthetic process.

Animal tests carried out by the authors (Schulz and Kimmig) with tetrachlorodibenzofuran and 2,3,6,7-tetrachlorodibenzodioxine have proved an extraordinarily high toxicity for these substances. A simple smear of a 0.1% solution of tri- and tetrachlorodibenzofuran on a small area of a rabbit's auricle caused heavy liver

damage and death of the test animal within 2 to 3 weeks (Schulz [36]). 2,3,6,7-Tetrachlorodibenzodioxine, which also has very strong acnegenic effects, was proved to be far more toxic. Only then was Dr. Sorge successful in the identification of this enormously toxic substance in the production process and in the final product. He proved that this toxic substance is formed only at certain temperatures and pressures. If during the alkaline hydrolysis of tetrachlorobenzene to sodium trichlorophenolate the temperature is reduced below 153°C, the toxic substances do not form. However, at this low temperature, the reaction time is extended from one to five hours and the productivity is obviously lower. Furthermore, it was proved that the condensation of two molecules of trichlorophenolate to give tetrachlorodibenzodioxine is an exothermic reaction. Several explosions of autoclaves with injuries and the lethal intoxication of workers were reported to be the result of this reaction in the German Democratic Republic (East Germany) (Schulz [38], Goldmann [11,12]). Tetrachlorodibenzodioxine was also identified in the Czechoslovakian production process and in the products as well.

The first two cases of acne chlorina were noted in 1965 in two technicians who operated the production machinery. It was assumed at that time that these two cases were caused by careless work and an undeveloped production technology under semiproduction conditions. After one year without a reported case and during which production was temporarily halted, a mass outbreak of 78 cases was recorded within the following three years. Finally, after a detailed investigation and study of the entire problem, the process was terminated and production ceased in 1968. Workers from all stages of production were stricken. At that time, it was impossible to determine which production stage was the most risky because most of the workers were involved in several stages at various locations in the plant within a relatively short time. Workers directly involved in production as well as maintenance personnel and workers digging sewage ditches were stricken. Later, a research scientist working to isolate the acnegenic ballast

substances from the products of the individual production phases was even stricken. His research work was carried out outside the production plant in a research institute's laboratory. In addition to the 78 patients with dangerous symptoms of acne chlorina or porphyria, other workers in this plant had symptoms of acne which were, however, symptoms of juvenile acne or of a similar character and could not therefore be counted as an occupational disease.

With the exception of two female laboratory technicians, the patients consisted of males from 18 to 57 years of age (4 persons below 20, 46 persons from 21 to 30, 11 persons from 31 to 40, 10 persons from 41-50 and 7 persons from 51 to 57). Therefore, the acne chlorina patients were mostly young people. On the other hand, more than half the patients with porphyria cutanea tarda were older than 40 years.

Generally, the disease followed a normal course as described by other authors. In only six patients did the disease begin suddenly as acute solar dermatitis, i.e., by erythema and edema in regions exposed to solar radiation and continued by acne symptoms (Photographs 1 and 2), as observed by Goldmann [12], Grimmer [15], Braun [6] and before these authors, also by Touraine and co-workers [45]. Therefore, chlorinated phenols in some cases have similar photodynamic effects as the chloronaphthalenes described by Gavrilova [10]. Erythema and edema in these patients were obvious mainly on their auricles. Sometimes, small blisters in thick groupings were observed there.

In all the other patients the acne developed slowly. Among the less severe cases the disease was limited to single or densely grouped comedones, conditioned by follicular hyperkeratosis, which were so small and sometimes so numerous that they appeared to be a slate grayish-brown color, like dirty spots on the skin. These symptoms were noted mainly on the face, with maximum occurrence above the cheek bones (Photograph 3). In the more severe cases, the comedones gradually developed into small white cysts similar

to milia, although with black centers, and into large cysts ranging from the size of a pea to that of a nut (Photographs 4, 5 and 6). As opposed to other acne forming dermatoses, the described symptoms and manifestations mainly lacked signs of an infection. Only in the more severe cases and rather in the vicinity of large cysts were some reactive inflammations, infections and abscesses noted. The emptied cysts and abscesses left behind large atrophied scars with raised edges and with bridges of intact skin under which a probe could be inserted (Photograph 7). This basic clinical picture was supplemented by diffused hyperpigmentation in the face and by papulopustules on the torso and extremities. Patients who were found to suffer from a disorder in porphyrin metabolism had symptoms of porphyria cutanea tarda in regions exposed to the sun (hyperpigmentation and hypertrichosis, blisters, excoriation and small scars). However, in this group there were two patients with porphyria but almost without any acne at all.

Histological investigation is not much help in diagnosis. The symptoms begin with hyperkeratosis at the mouth of the follicles. After one to three weeks, the follicle changes into a cystic formation filled with a horny substance [keratin?] (Photograph 11) and to a small extent with sebum. However, the epidermal changes are small. After the rupture of the full follicle, the contents of the cyst penetrate into the surrounding tissue and a granuloma of foreign bodies forms around the area (Photograph 12).

The disease normally starts on the face above the cheek bones. However, in 17 patients the disease started in an unconventional manner by papulopustular eruptions on the extremities, primarily on the lower extremities. This characteristic, resembling more acne oleosa, remained in some of the patients for the entire duration of their illness.

The most common localizations of acne chlorina were the cheeks, temples and to a lesser extent, the entire face. Eyebrows, eyelids, the perioral region and the scalp and hair area remained free.

Other predilected areas were the auricles, the back of the neck, the back and the chest in a seborrheic localization and the genitals. The auricles and genitals and especially the scrotum were stricken by the formation of large cysts (Photographs 8 and 9). Among the five most seriously ill patients, the disease spread all over the body and had a discouraging effect that was heightened by the disease's usual persistence, the long term healing and by medical helplessness (Photographs 10 and 7). The contents of the cysts produced a repulsive and rancid odor. For some of the patients the disease disrupted their social and family relations and caused severe depressions.

Some authors, such as Braun [6], emphasize itching as the initial symptom, but we noted this symptom in only three cases.

In 20 patients with extensive symptoms, the occurrence of pustules, cysts and abscesses was also noted in axillae although this location was not mentioned by other authors. Because of the great number of follicles in the axillae and the similarity of the axillary skin to that of the genitals and for several other reasons, this finding appears to be just as valid as localization on the genitals and the genital area. On the other hand, it is surprising that acne chlorina does not strike at the hairline or scalp. In the case of one patient, the acne symptoms disappeared in the facial areas when he grew a full beard while in other areas, the symptoms continued without a reduction in intensity. So far there is no explanation for this phenomenon.

Hypertrichosis or hyperpigmentation or both were determined in the faces of 19 patients without a laboratory diagnosis of a deficiency in porphyrin metabolism. Bleiberg [3] made similar observations. These symptoms receded simultaneously with the healing of acne chlorina.

More younger persons suffered from acne chlorina than older persons.* This study group contained 50 persons (85%) below 30

*Translator's note: Beginning of this sentence illegible.

years of age. However, this fact cannot be used as a hard and fast rule or to support the findings because the production plant under study employed mostly young workers. The preillness medical history among the patients did not indicate any significant predisposing factors and no incidence of serious illnesses, intoxication or etiolation*. Furthermore, no relation to hair color, eye or complexion color, to the degree of body hair, to the perspiration of skin oils or to hereditary follicular hyperkeratosis and other skin diseases was noted. Only one patient reported a more severe prior case of acne juvenilis, 12 patients reported mild cases during puberty and 14 patients reported only insignificant acne juvenilis symptoms. 18 patients also had some infrequent contact with mineral oils either during the appearance of the symptoms or at some time in the past. These patients were mostly involved in maintenance work as mechanics. However none of them had ever had an oil acne in the past. Their illnesses following contact with tetrachlorodibenzodioxine were of the same character as the illnesses of the other patients. Their diseases were not similar to acne oleosa either in appearance or in localization.

The latent period from the initial contact with the risk substance to the appearance of symptoms was quite varied. Some workers became ill after exposure of from several months to several years and the disease in their cases was rather mild although the indications pointed to a massive exposure. In other cases, severe damage occurred after a very short time of several weeks and after an apparently small exposure. For example, one of the most seriously ill patients worked under the semiproduction conditions for only two and a half weeks before the outbreak of the disease (acne and porphyria cutanea tarda). After that he had no contact with the risk materials.

It is not clear whether individual predisposition or the level of personal and work hygiene is more responsible for the intensity

*Editor's note: This may be a dubious choice. The Czech "etylism" transliterates to "etilism".

of damage or latency of the disease. Most authors discount individual predisposition. However it is believed that the deciding factor must be the degree of actual exposure which is undoubtedly dependent on a series of other factors such as work discipline, personal discipline, adherence to preventive measures, frequency of changing work clothes and undergarments, the degree and regularity of hygienic decontamination, work site order and cleanliness, dust in the environment, etc. .

These patients also had a series of subjective difficulties: tiredness, weakness in the lower extremities, muscle pains, sleepiness and insomnia, increased perspiration, lack of appetite, headaches and other disorders in the mental and sexual spheres. These complaints were more recurrent and more intense in patients with the more extensive skin symptoms. In more serious acne cases, a significant weight loss was also noted. It is our opinion that all these difficulties and symptoms are manifestations of a rather overall intoxication than of only the acne chlorina.

All the patients were admitted to a dispensary. Regular examinations of their dermatological, internal and neurological conditions were arranged. The patients who were still working were transferred to prevent further contact with any acnegenic factor. All contact with chlorinated hydrocarbons of any type was prevented - even with those substances whose acnegenic effects have not been thoroughly proved. Furthermore, all contact with mineral oils and tar and its products were prevented. The application of mineral based ointments was discounted for external therapy. The plant's medical doctors were cautioned against prescription of any internal medication with an acnegenic effect (iodine and bromium preparations, corticoids and others). The patients were given detailed medical directions concerning their daily regimen, personal and work hygiene and secondary disease prevention and treatment.

All available medications for acne were utilized in the treatment. The expressions of comedones and the pressure relief of the contents of cysts and abscesses necessitated many periods of

hospitalization and special ambulatory treatment hours attended by a specially trained nurse. No special results were observed as a result of repeated hospitalization. The best results were noted after the expression of comedones by the use of a sauna constructed for the patients by the factory on the author's recommendations. It was not possible to test the effects of vitamin A acid (retinoic acid) which has been praised by some authors in the medical literature. However, in agreement with the findings of other authors, it was determined that no local or internal medication exists which has an effective and permanent healing effect on acne chlorina. Some of the patients have been under observation for eight years and their disease still persists. Dr. Schulz's [39] patients have manifested continuous symptoms for more than ten years. Goldmann [11] has now been treating one patient with comedones and cysts on his penis and scrotum for 18 years! In most of the patients discussed by these authors, the symptoms and manifestations of the disease progressed and reached a maximum after about one year, even after transfer of the patient from the high risk work area. A regression takes place after two or three years at the earliest. In some isolated cases, the progress of a mild course of the disease was observed even after five years. However, the regression of the disease in all the patients was very slow and, it may be said, even lasts a number of years.

Of the 78 patients treated by the authors, 76 suffered from acne chlorina. Of these, 11 simultaneously had hepatic lesions with a deficiency in porphyrin metabolism. Two patients did not have acne chlorina. One of these two had porphyria and the second one died in 1966 from acute intoxication. Pentachlorophenol was considered to be the cause of death in that instance. When the toxicological analysis was carried out at that time, the investigators were unaware of tetrachlorodibenzodioxine and, therefore, it is our contention now that in that case, this highly toxic substance was primarily responsible for the acute intoxication.

Gombos [13] mentioned one patient with acne chlorina and porphyria in connection with this production process.

The authors analyzed 55 patients internally and neurologically in detail. About half of these patients had a deficiency in lipid metabolism and in more than one-third, some minor biochemical deviations and mild hepatic lesions were noted in the first stages of the disease. In 17 patients, the authors found symptoms of central nervous system disorder, the majority with lesions of the peripheral neurons of the lower extremities (verified by EMG examination). In most of the patients, physical disorders, primarily an acute neurasthenic syndrome, were diagnosed. In addition to the death due to acute intoxication (pentachlorophenol? tetrachlorodibenzodioxine?), three more patients died. In one patient, the porphyria developed unusually rapidly into an arteriosclerosis of the brain with an atypical morphological diagnosis and dementia. Two patients died from bronchogenic carcinoma. All these patients with their complete symptoms are discussed in other papers [32,23].

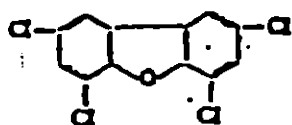
Discussion

In agreement with Kimmig and Schulz, we cite the tetrachlorodibenzodioxine which is formed during the production process as the main reason for the skin symptoms as well as for all the other deficiencies mentioned and diagnosed in the authors' patients. This toxic compound was confirmed in considerable quantities in the final product (Arboricide E50), in the butyl trichlorophenoxyacetate and also in the mortar and wall paint of the factory building. Even adjacent rooms such as worker dressing and locker rooms were contaminated with this compound. Test rabbits placed into these rooms soon died.

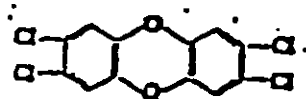
In his monograph, Braun [5] cited the following chlorinated hydrocarbons as the then known causes of acne chlorina: chlorobenzenes with various degrees of chlorination, chlorinated phenols (sodium tetrachlorophenolate, pentachlorophenol), para-nitrochlorobenzene, sodium tetrachloro-o-phenylphenolate, chlorinated

naphthalenes, various chlorinated diphenyls, trichloroxydiphenyl, chlorinated diphenyl oxides, sodium *o*-(2-chlorophenyl)phenolate and others. However, Kimmig and Schulz [25] ascertained that pure pentachlorophenol and pure 2,4,5-trichlorophenoxyacetic acid do not have any acneogenic effects. Therefore, they checked the presumed effects of the other substances that were blamed for causing acne and found that neither pure nor chlorinated benzenes (from 1 to 8 chlorinated positions) nor chlorinated diphenyl-ethers have any acneogenic effects. A definite acneogenic effect was proved only for the following substances: chlorinated naphthalenes (5 and 6 chlorinated positions) in agreement with Shelley and Klingman [41], higher chlorinated dibenzofurans (diphenyl oxides) and 2,3,6,7-tetrachlorodibenzodioxine.

Therefore, it is possible and even probable that some chlorinated hydrocarbons that have been previously considered to have an acneogenic effect do not have this effect and the actual causes were other ballast chlorinated hydrocarbons contained in those hydrocarbons.



Tetrachlorodiphenylene oxide
(tetrachlorodibenzofuran)



2,3,6,7-tetrachlorodibenzo-
dioxine (tetrachlorodiphenylene
dioxide)

In an animal experiment, Kimmig and Schulz found an exceptionally high toxicity for tetrachlorodibenzodioxine. In a local application on rabbits' auricles (keratosis test), this compound produced a strong reaction even at a concentration of 0.001%. Also, a skin application of this substance at the same concentration produced acne chlorina (Schulz [38]). Tetrachlorodibenzofuran was proved to be 10 to 20 times weaker. Chlorinated naphthalenes had a thousand times weaker effect. Generally, acne chlorina is caused by the direct contact of tetrachlorobenzodioxine with the skin. Absorption through the skin is not ruled out and an effect

through the ingestive or respiration tracts is also conceded. However, in a pure ingestive experiment with a test animal, acne chlorina did not occur. However, the cases of acne chlorina contracted after the ingestion of chlorinated naphthalenes as food fat substitutes should not be forgotten [19,9].

Tetrachlorodibenzodioxine used internally has a strong hepatotoxic effect. A dose of 20 to 50 mg per kg of rabbit's body weight causes death in all the test animals by yellow liver atrophy.

Because of this enormous toxicity, all the preventive measures taken at the high risk processes in East Germany and Czechoslovakia were proved to be completely ineffective. The only dependable solution to that problem was the reduction of the reaction temperature and pressure during the alkaline hydrolysis of tetrachlorophenolate to sodium trichlorophenolate. In East Germany, the decontamination cost of the high risk areas and buildings was extremely high. One chemical plant attempted to use for other purposes a contaminated building which had not been decontaminated after the building had remained unused for two years, but new cases of acne chlorina were shortly reported. With normal decontamination procedures new outbreaks of the disease occurred and therefore, decontamination had to be carried out using special pressurized chemical protective suits with pressurized breathing apparatus because gas masks were not sufficient. Doors, windows, the wooden trim and other wooden building components had to be burned; the steel construction materials in the building had to be sandblasted; the plaster, facade and floors had to be torn out and cast into cement blocks together with the tubing, plumbing and other equipment. These blocks were then transported to the Atlantic Ocean and sunk. The disposition of those non-flammable materials by burying would have run the danger of contaminating the subterranean water supply. Only the most expensive components, autoclaves and some valves, were successfully decontaminated by repeated washing with special detergents.

The Czechoslovakian plants are still closed and their fate is still undecided. The patients are still under a continuous observation.

41. Thulliez, G., *Page*
Ann. Derm. Syph. (Paris), 1931, 1, 415-422. — 42.
 Kraus, G. — 43. Tardieu, A., Solente, B.,
 Huetzel, B., Aubert: 31 cas de dermatites
 par trichloronaphtalène. *Bull. Soc. Derm.*
Syph., 11, 1931, 1, 245-252. — 44. Wabbe,
 F.: Über 2 Fälle von „Chloracne“. *Monatsschr.*
Derm. Syph., 1931, 1, 114-115. — 45. Kraus, G. —
 46. Wabbe: Gewebliche Erkrankung durch
 chlorierte Kohlenwasserstoffe (Perchloracne-
 leiti). *Zbl. Gewerb. Hyg.*, 9, 1931, 1, 100-
 101. — 47. Wabbe, K.: Zur Chloracne (Per-
 chloracneleiti). *Z. Haut. Geschl. Abh.*, 11,
 1931, 1, 433-434. — 48. Jäger, H., Schütz,
 F. H., Spiegelberg, H.: Berufliche Vergiftun-
 gen bei der Herstellung von Chlorophenoxy-
 Verbindungen. *Arch. Gewerb. Pathol. Ge-
 web. Hyg.*, 14, 1931, 1, 322-344.

- [10] Pathogenesis of photodermatides from chlorinated naphthalenes.
- [13] Gombos, et al., Porphyria cutanea tarda and acne chlorina occurring during the production of cyclic chlorinated hydrocarbons.
- [23] Symptoms of total intoxication in acne chlorina during the production of herbicides - in final preparation for printing.
- [31] Discussion on paper by Jones [24]
- [32] Health hazards to workers in production of sodium 2,4,5-trichlorophenoxyacetate.

TABLE I. Production Scheme

