Title: Occupational Intoxication from the Processing of Chlorophenol Compounds

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General Introduction

In the last few years in at least three West German operations concerned with the industrial processing of chloronated phenols there have been epidemics characterized by acne with a prolonged course and other disturbances of health.

Badden and Bauer as well as Brinkman reported in 1950 and 1951 the illnesses of a group 17 workers in a shop in Nordrhein-Westfalen. The workers of this shop were engaged in the processing of pentachlorophenol. Besides an acne with comedones and various degrees of secondary pustular infection and furuncles, most of the workers during the first stage of the dermatitis also had pain and weakness of the lower limbs, mild paresthesias, complaints related to the heart and vague psycho-vegetative disturbances. An examination of the records of 17 cases gave the following findings:

All 17 had acne, four very severe, eight rather severe and five moderately severe to mild. Almost all demonstrated a pustular infection and folliculitis and four had bursitis of the elbow.

Additional disturbance were found. There were 11 workers with bronchitis, five had myocardial injury, and two cirrhosis, of which one had a fatal outcome. In nine cases symptoms of neuritis (in seven, strong pain of lower extremities in four, disturbances of sensation in two, mild paresis without atrophy and in two, absence or weakness of the achilles reflex). Seven workers complained of psychological problems such as prolonged weakness and a depressed mood, loss of appetite, nervousness, mild headaches, disturbances of sleep, diminution of libido and potency.

A larger number (some 60 cases, Professor Hergt) of similar illnesses developed in two Middle Rhine shops among workers who for a longer time, most several years, worked in the manufacture of trichlorophenol (the processing from 1, 2, 4, 5-tetrachlorobenzol to 2, 4, 5-trichlorophenol through treatment with sodium hydroxide and methanol). To describe more thoroughly the illness of a third group from the Hamburg region, further disturbances of health were seen in these trichlorophenol workers often for the first time a longer time after cessation of the industrial exposure. The first discussion of these findings in our Hamburg cases was briefly presented by Spiegelberg at the Northwest German Neurologic Psychiatric Congress in 1960 in Luneburg in the scope of a lecture on late and long lasting

psychopathologic injuries after occupational intoxication. In addition Janzarik described cases of similar complaints in workers from the Middle Rhine operations.

The third group comprised 31 workers from the Hamburg operation. This group of patients were employed in trichlorophenol production in a factory in which the herbicide 2, 4, 5-trichlorophenoxyacetate was processed from 2, 4, 5-trichlorophenol. This involved heating trichlorophenol with sodium hydroxide and monochloroacetic acid in an autoclave. After the course of this process, the end product was purified through a double crystallization. The job of the worker first in this process was to attend the autoclave. For this purpose he had to take the flake-form trichlorophenol from open vats with a shovel. In this procedure there developed a fine dust which dispersed throughout the room.

Further tasks were devoted to loading and attending centrifuges during inflow and discharge. The workers with the most severe skin findings were especially intensively in contact with the trichlorophenol. From this it was naturally assumed that the harmful agent was in the technical tetrachlorophenol. Insofar as this assumption proved to be correct, we will discuss under etiology in the summary.

Our Own Clinical Observations

Of the 31 workers of this Hamburg operation, we find five years after removal from the industrial exposure still nine under medical treatment for residuals of their acne, an unremitting neuro muscular weakness of the legs, vasovegetative (autonomic), lability and especially marked psychopathologic disturbances. The established complaints and injuries to health are reported in the table. The appearance of the skin findings, by and large, in these patients took a similar course. It appeared first in the face and here especially on the cheeks over the bony prominences, the forehead, the temples, the chin and ears. There were numerous comedones and later followed a secondary infectious folliculitis with pustules and follicles and retention cysts. Further in the course most patients developed a spreading of this skin appearance especially on the sides of the neck, and the nape of the neck, and the upper back, the chest, under the arms the genitals and the thighs. Numerous follicles were found, especially on the neck and the back. The pattern of the rash was in general so unusually dense that hardly a follicle was unaffected.

In the case of some obviously heavily exposed workers the development of this acne showed first erythema, and edema with a spreading dermatitis around the ears, cheeks and forehead. At the same time several of the patients had blepharo-conjunctivitis, which like the skin findings in part took a chronic course. As the tabulated summary of the findings shows in some of the patients some had a patchy and some a more superficial pigmentation on the face which gave the skin a dirty or grimy gray brown appearance.

In all this presents a picture of illness which for the first time was presented by Herxheimer in 1899 and later by several other authors (Bettmann, Holtzmann, Teleky, Herzberg, Braun, Grimmer and others.

These findings were after contact with chlorinated naphtalene, diphenyls and other aromatic compounds. More recently we see these reported by Braun as well as A. Riss-Sundermann in 1959. Although not entirely correct, for these reasons this type of industrial intoxication has been designated chloracne or "Pernakrankheit" in most reports.

The course of the dermatological findings in our cases was unusually severe. The various therapeutic procedures, emptying of the comedones, various keratolytic and anti-bacterial measures, and even in the more severe cases internal doses of antibiotic, did not in the first years, up to two, arrest the development of new comedones, retention cysts and follicles, although there was no further contact with the harmful agents. Only after a long time did the down-hill course come to a halt. We still find residuals today in all of the severely ill. Many have depressed scars which are especially located on the face, "Pseudo-Atrophodermia Vermiculata".

Uniformally reported by all of the workers was a pronounced lassitude and weakness of the legs often with pain especially in the area of the proximal leg musculature. These complaints were almost always pronounced in the early stages of the illness and some before the appearance of the severe skin changes. Paresthesias were found in two of the cases either from the records or in the spontaneous history. Localized weakness or atrophy, reduced reflexes or lack of muscle reflexes as would point to a toxic polyneuropathy were not found in any of these cases. Two of the investigated cases gave a lessening of a sensation with scattered disturbances of discrimination on the lower limbs. Electromyography gave no definite signs of neurologic injury as one would expect in peripheral nerve lesions.

In review, the establishment of progressive weakness in a series of [EMG] tests requires further validation of the method of eliciting the findings as they do not give the pattern of a typical neuromuscular disturbance of a toxic polyneuritis or polyneuropathy.

The electroencephalographic investigation showed in six cases abnormal EEG's with changes of frequency and dysrhythmias of asymmetrical character. One of the subjects showed accentuated dysrhythmia and cerebral activity after photo stimulation. The noted electroencephalographic changes were uncharacteristic and gave no diagnostic points of essential significance.

Some of the investigated workers complained of a headache, giddiness and orthostatic fainting. Five of the subjects had distinct signs of autonomic hyperactivity with a fine tremor of the hands, increased sweating in the hands, legs and the axillae, increased dermatographism and suspicion of a Chvostek sign. In the ambulatory controls the measured blood pressure was in the normal range and in five of the subjects at the lower limit of normal. Orthostatic fainting was not noted in either the out-patient or in-patient observations. In two cases there was suspicion of myocardial injury.

Abdominal complaints from distention, pressure on the stomach and surrounding area to mild pain were found in five of the nine subjects.

In four cases there were disturbances of stomach secretion. Three with reduced acidity and one with hyperacidity, and in one case the roentgenological signs of gastritis were found.

A very thorough investigation in the scope of repeated ambulatory tests and in-patient observations for liver injury was undertaken. While the variation in reaction in all cases was uncharacteristic, the BSP test in two cases showed a mild retention of the dye and in three cases liver biospy gave a pathologic finding. In two instances there were perihepatic changes of a mild grade and in one case a fatty liver with a spreading inflammation and mild liver fibrosis. On the basis of clinical and histologic findings we have here a suspicion of a condition like a viral hepatitis. In this case findings of iron containing and iron free yellow-brown pigments were demonstrated which, however, are not in accord with Kalk and Wildhirt who found in chlorophenol intoxication gray iron-free pigment. The red cells in urine of one of the worker with otherwise normal kidney findings remain unexplained.

Especially noteworthy were the psychopathologic changes in the chlorophenol workers who were all very thoroughly investigated for psychiatric and psychopathologic findings. In six of the cases the course could be observed for some two years. We have the capability for objective tests, questionnaires or history taking in experimental psychologic investigation.

With a very remarkable uniformity there was delineated by the tests a subjective syndrome of complaints which pointed to strange polyneuropathic symptoms in the region of the extremities, the cardiovascular system, and also abdominal symptoms, in the psychic sphere in particular the "vital motivation control" centers (Burger-Prinz). In nearly every case they would complain of disturbances of vitality with general weakness, lassitude, poor feeling, indisposition, indecisiveness, inner unrest and feelings of sickness. The basic psychic mood worsened being depressed in the direction of an agitated-unsatisfied or sullen - irritable behavior.

Often there was presented a anxious-restless component of the mood. Changes of emotional affect, in the narrow sense were in the form of increased irregularities of disposition, irritability and a inclination to angry outbreaks or else a certain lack of mood, an exaggerated calmness. A general fatigue or exhaustion, a decreased inner vitality and drive was elicited in everyone of the observed cases. The tested individuals portrayed poverty of initative and interest, a weakness of self determination or will, reduced efficiency, increased depletion of both the physical and psychic areas.

The subjective and objectively recorded psychocological picture is further completed by an enumeration of more or less ordinary symptoms. Disturbances of the motivational sphere were obtained in practically the entire group. All those tested described gross reduction in potency with most also having reduced libdo. The appetite was worse and occassionally there was a significant loss of weight. Sleep and the need for sleep were in most of those tested disturbed in the sense

of an increase in both the duration of sleep and in disturbance of the length of sleep and less often the inability to get to sleep.

In a few cases the mental performance was reduced particularly with disturbances of memory and ability to observe. In the majority of cases there was also intolerance of alcohol. Finally, there were signs of hyperesthesia with over-sensitivity to noise and light. Pronounced variation in the described psycholpathological symptoms were present in almost all cases.

Variations or alterations the intensity of the symptoms in the sense of diurnal changes either in the morning, before noon or even in the evening were described and in most of those examined there was a practically complaint free interval of a few days or weeks. Half of the whole group also portrayed two less common phenomena. Two of those tested found that cold applications, cold showers or baths sometimes more or less gave a day long alleviation of the general complaints of polyneuropathic symptoms. In one of the examined there was a perculiar abberation, sometimes varying diet namely the exclusive use of bread, meals of milk-soup, or drinking 3 liters of milk a day for a formerly inappropriate food intake.

In comparison with the polymorphic polysymptomatic subjective picture the objective psychopathologic signs are quick to recall. In exploratory discussions the majority of those examined had displayed a mild depressed-subdued basic mood which could be elevated only slightly or not at all. The tests portrayed a weak impoverished drive and the psychomotor status was weak and tired. One gets the impression of a mild cerebral organic-reduction in motivation rather than a dragging or hesitation. The emotional findings are occassionally of a lessened approachability, inadaptability also a pronounced lability, and decompensation. In two cases there was a pronounced hypochondriasis and in one a mild but definite fractionation of the integration of the personality. The psychologic tests showed finer or more subtle deficiencies in intellectual performance and disturbances of psycho-organic affect of significance. In the majority of those tested with the Hamburg-Weschler intelligence test for adults (HAWIE) there was a significant increase in withdrawal (Abbau) score (Wechsler) from which at least a certain indication of weakness of mental capability is present.

The Rorschach Psychogram was interpreted as showing a narrowing of personal experience, signs of weakened emotional reactivity, weak concentration, lessened pace, sluggishness of thought processes, and an inclination to perseveration in the direction of cerebral-organic rooted changes.

DISCUSSION

On the basis of the findings of three independent groups of chlorophenol workers, who in the total consist of over 100 patients, we have a characteristic pattern of illness in which certain essential features present the following disturbances:

1. After an initial dermatitis of the face and inflammatory appearance in the area of the skin about the eyes, there developes the gradual appearance of a spreading acne in the area of the face, then the neck, shoulders and upper trunk, in severe cases on the whole body with comedomes, retention cysts, nodules, pustules, furuncles, and patchy pigmentation. In several cases, there was a strong inflammation of the mucosa of the facial region and the upper respiratory tract and at times, a delayed blepharo-conjunctivitis.

2. In many cases, disturbances on the part of the inner organs, especially liver injury with a deposition of iron-free gray pigment was the characteristic biopsy finding. In some cases, a chronic bronchitis and also occasionally myocardial injury.

3. In all cases, a general fatigue and mainly a weakness of the proximal muscles of the lower limbs was encountered often with aches in the muscles and, in a few cases, parasthesias and slight hypesthesia. Only in isolated cases was there definite disturbance of sensation and insignificant paresis of a vague sort and weak or reduced reflexes.

4. A psychovegetative syndrome with the following symptoms:

   Subjective: Disturbances of vitality, disturbances of the basic psychic mood and affect, disturbances of drive, weakness of memory and concentration, a hyperesthetic tendency, vegetative hyperexcitability, inclination to orthostatic hypotention, disturbances of sleep, particularly an increased need for sleep, disturbances of the motivational sphere, reduction of libido and potency, and intolerance to alcohol.

   Objective psychopathology: A lessening of incentive, subdepressive tendency of the type of purely, vital impulses, of ill humor, disturbances of affect in the sense of a certain flatness, increased irritability, at times bluntness, hypochondrosis and dedifferentiation of the personality.

   Experimental psychology: HAWIE: Increased withdrawal percentage (ABBAU-this is some sort of score in one of the elements of the Wechsler test) and Rorschach psychogram: narrowing of personal interactions, signs of weakened emotional reactivity, weakness of concentration, reduced pace, sluggishness of thought processes, and inclination to perseveration.

The dermatologic pattern of the described chlorophenol intoxication, showed extensive similarity to that first described by Herxheimer and later several authors (Braun, Risse-Sundermann) described illnesses produced by chlorinated, aromatic coal-tars. On the basis of the observations that the preponderant cause was chlorinated naphthalene, Wauer and later Teleky, applied the name "Perna" illness from Per chlorinated naphthalene. Teleky deduced from the Herxheimer report in 1899, the described chloracne was not caused by pure chlorine, but from chlorinated coal-tars or the simultaneous processing of chlorine and tar. Further observations on the Perna illness by Mittelstadt,

Flynn and Jarwik, Drinker and co-workers and also Greenburg and co-workers show that besides the appearance of the skin, fatigue, loss of appetite, dizziness, severe liver injury with acute yellow atrophy and a fatal outcome could result from working with chlorinated naphthalenes. Baader mentions a group of illnesses in American shipyards during the World War II. From the accounts that appeared in American and England, in part fatal cases, Teleky infered from the report by Brown, President of the Hallowax Co. in New York (1937) that first the processing of a higher percentage of chlorination and the combination with chlorinated diphenyls and other materials led to severe injury to health and at times, fatal liver atrophy. Teleky pointed also to the animal experiments of C.K. Drinker and co-workers to support the assumption that the more highly chlorinated diphenyl amines evoked serious injury.

Often pronounced at the start with the use of the lower chlorinated naphthalenes were the general appearances of a industrial chlorophenol intoxication. These experiences were had by Truhaut and co-workers with workers using chlorophenol for the preservation of wood, by Kubota in Japan who mentioned multiple disturbances of the autonomic nervous system and also saw several fatal cases. In all three German groups of chlorophenol intoxication, liver injury was established. This was most pronounced and with regard to the liver findings was most intensively compiled from the patients of the Middle Rhine factories (Hergt, Kalk and Wildhirt). In all groups, there were several cases of chronic emphysema and bronchitis and myocardial injury, but these symptoms were not readily encountered as usually as the pronounced fatigue, and neuromuscular weakness which we saw in all of our patients. Just as common, was the described psychological syndrome, which in addition to us, also was found by Janzarik and Richert, in a completely similar pattern in the Middle Rhine workers.

The psychopathologic syndrome could be differentiated diagnostically with sufficient certainty from endogenous psychosis especially mild psychothymic illnesses, neurotic personality changes, and organic psychosyndromes of other etiologies, such as pre-senile or arteriosclerotic cerebral degeneration processes. The phenomena are related to the pseudo-neuraesthenic syndrome that has been described in a number of industrial intoxications (lead, carbon monoxide, manganese, arsenic, thallium, carbon disulfide, trichloroethylene and others: literature references by Borbely, Von Hattinberg, Meggendorfer, Moeschlin, Pentschew, Teleky). And above all, it unmistakably shows a relationship to certain endogenous irritable conditions. Flattening of vitality, depressive impulsive irritability, vegetative signs and not at the least, the fluctuation and the intensity are widely to be observed in the area of endogenous depressive conditions. On the other hand, alcohol intolerance, hyperesthetic irritability and polyneuropathic tendencies steer the differential diagnostic aspect more in the direction of an exogenous condition. It is to be recalled that the somewhat older psychiatric literature (Meggendorfer, Stertz) classifed the neuroesthenic syndrome quite unmistakably in the area of exogenous symptom complexes. Also, last but not least, the relationship of the phenomena in our observations is to be directed towards the exogenous, hyperesthetic, emotional instability of Bonhosser, which Ewal indicated should be

classifed no longer as far as the pathological picture goes as a "heteronom", but as a "homonom", in the sense of Kleist.

In spite of the discussed phenomenologic relationship, the psychopathologic sequelae of the chlorophenol workers is hardly completely compatible with any of the known clinical patterns. There arises the question that a special psychovegetative intoxication late syndrome such as that discussed by Spiegelberg in connection with his observations on chronic industrial injury from military materials may in some way be present in the case of the observations reported here.

Psychoneurotic motives could in our observations, in general be excluded as far as individual - neurotic, that is, character-disorder or personal-experience factors were concerned. Two of the nine which were examined exhibited essentially psychopathic or neurotic elements. These same two, however, in comparison with the other non-neurotic examinees, could be easily distinguished. Certainly, collective - neurotic factors, in our opinion, in all group tests, especially diagnostic tests, must be taken into account as difficult but unavoidable facts (Spiegelberg).

Such reactions were also seen in our cases, in the sense of an overlay of psychogenic exaggeration with so-to-speak, in some cases, individual neurotic complaints not adequately physiologically explained and related to a desire for compensation. The psychopathologic analysis of each individual case and comparison of the respective findings with such independent groups of the same etiology gives adequate safeguards against expert or scientific misjudgement. In spite of the long course, the prognosis for the psychopathologic sequelae to poisoning appears favorable, although the technicalities of the income situation have not ultimately been clarified, there have been predominantly a subjective, definite improvement or arrest of the described symptoms. Objective worsening has not been seen with the exception of the just noted fluctuations in intensity. Also the experiences of the Mainz Nerve Clinic (Richer) and impressions of industrial physicians, (Knecht) speak for a benign course in both the acute and chronic poisoning. As far as the toxic parenchymal damage, as such, the prognosis has not been determined to be unfavorable.

It would appear inescapable to ascribe the toxic factor to the highly chlorinated chlorophenols a conception which through the animal experiments of Machie and Thomas, H. Kitzmiller, in a series of further investigations (Keho, Deichmann, Grubler, Boyd, McGavack, Terranova, Piccione, to Oettingen) - that several animal experiments would support this assumption. Kimmig and Schulz were able, however to show that the changes were not produced by industrial, analytically pure, polychlorinated phenols, such as trichlorophenol, pentachlorophenol, that these did not show the characteristic appearance of the chlorophenol poisoning.

With the object of demonstrating the toxic agent responsible for these phenomena further animal experiments were undertaken. For a suitable test object it had already been demonstrated that chloraone stimulating substances would engender changes on the rabbit ear which

extensively corresponded to human chloracne (Hoffman and Neumann, Braun and Landes and others). The coating of the ear with one of these substances was effective in this regard leading first through a superficial spreading dermatitis with redness, swelling, and desquamation and a few days later appeared the follicles blocked with hyperkeratotic material and small cyst formations which could be well demonstrated histologically. Besides the experiments with the painting of the chemicals, tests for all sorts of toxicity were done on the rabbits and with a few agents also on cats. And by these was demonstrated conformity with the findings of Oettel as well as Hofmann with similar cases of intoxication in the large chemical works in South Germany that the chloracne-inducing substance also in the rabbits possessed a pronounced liver toxicity. The liver parenchymal injuries could be well demonstrated in vivo with the micro-modification of the BSP test of Hofmann and Oettel. Autopsy findings were of diffuse fatty infiltration and wide spread necrosis of liver cells. The investigation results were earlier reported by Schulz in 1956 and Kimmig and Schulz in 1957. They lead to the following conclusions: The effective substance had to be developed in the alkaline hydrolysis of 1, 2, 4, 5-tetrachlorbenzol to 2, 4, 5-trichlorophenol. In this technique under pressure and with a temperature of about 180 degrees centigrade in the presence of methanol and sodium hydroxide not the trichlorophenol itself but an incidental side-product encountered in the course of the pressure phenol process occuring in tiny amounts was the cause or noxious agent. For in the case of the rabbit ears, with pure many-times distilled 2, 4, 5-trichlorophenol and even just with 1, 2, 4, 5-tetrachlorobenzol none of the above noted changes could be evoked. However it could be done with technically produced trichlorophenol. (There are a number of illustrations of the histologic changes in the rabbit ears.)

The isolation of a definite compound from the residue of the distillate of technical trichlorophenol at first was not possible. From the chemical approach, compounds were synthesized and tested by us through animal demonstrations. It was established for a certain probability that these could also be produced as the side products of the process of tetrachlorobenzol to trichlorophenol. We had at our disposal at first various chlorinated products of the diphenyl ethers and dibenzofurans. While diphenyl ether and its 1, 2, tetrachlorinated derivatives as well as dibenzofuran and monochloro dibenzofuran were ineffective in animal experiments the tri and tetrachlorinated dibenzofurans even in concentration of .05 per cent lead to the known findings in the rabbit ear. Single orally administrated doses of .5 to 1 milligram per kilogram caused in the rabbits severe liver injury which in most cases led to the death of the animal.

The clinical observations that in another working laboratory in another location the exposure to tetrachlorbenzodioxin led to the illness of severe chloracne concerned us with the chloro-derivatives of dibenzodioxins. Tetrachlorinated dibenzodioxins especially 2, 3, 6, 7-tetrachlor dibenzodioxin were strongly effective on the rabbit ear even in small concentrations. Painting three times with a .01 to superficial inflamation proceding as well to a folicular pattern of

hyperkeratosis. All administrations of single doses of .05 to .1 milligrams per kilogram caused severe liver necrosis and in most cases death of the animal.

For the hypothesis that 2, 3, 6, 7 tetrachlorbenzodioxin was the agent of significance in the formation of the chloracne illnesses which appeared in the factory, we also found further essential support from the chemical aspect. It could be proven that this compound formed from two molecules of sodium trichlorphenolate under the influence of sodium chloride and in a autoclave with the prescribed pressures and temperature.

Furthermore, we did succeed in isolating the specified tetrachlorbenzodioxin from the technical phenol process under pressure (the alkaline conversion from tetrachlorobenzol to trichlorophenol). In order to be certain that the 2, 3, 6, 7-tetrachlorbenzodioxin was able to stimulate the chloracne not only in the rabbit ear but also in the human skin one of us conducted a self-experiment (Schulz). Two doses of a coat of a .01 per cent solution in a circumscribed area of the underarm lead in two days to a mild dermatitis and a few days later hyperkeratotic follicules and comedones developed which were also well demonstrated histologically. The certainty that this agent is of etiologic significance for the described illness in this article appears surely and thoroughly supported. You cannot exclude however that in the industrial process also other chlorinated aromatic compounds with highly toxic properties can be developed which have not been identified up to now and so could not be investigated in the animal experiments.

The experimental and clinical findings are an impressive example that there can be agents of occupational diseases of significance which in the mass chemical processes exist as a side products only in tiny amounts. In experiments to clarify the cause of repeatedly appearing industrial intoxications this point should not be disregarded. It is successfully demonstrated that impurities in the residue of the main products were the causal agents in a industrial illness and it is therefore an essential prerequesite for successful accomplishment of prophylaxis.

In our special case, it was succeeded though a chemical engineering approach to develop a modification of the process to avoid the formation of polychlorinated dibenzodioxins and dibenzofurans. Since then 2, 4, 5-trichlorophenol has been processed in this factory and continuously used to produce the herbicide 2, 4, 5-trichlorphenylacetate without there appearing any symptoms of intoxication of any sort in the workers.

Table

Skin & Mucous Membrane:									
Facial dermatitis at onset	+	+	(+)		(+)	(+)	(+)		
Comedones, Retentionoysts, nodules									
Pustules, furuncles	++	++	+	(+)	+	++	++	+	
Patchy pigmentation	+	+	++	+				+	
Blephoroconjunctivitis	+		++		(+)		+	++	
Internal Organs:									
Loss of appetite	+		+	+	+	+		+	+
Abdominal complaints	+	+			+			+	+
Weight Loss	+			+	+				
Reduction in general condition									
Changes in stomach acidity									
Gastritis								+	
Liver injury	+			Susp.				Susp.	+
Emphysema, dyspnea		+			+				+
Heart injury		Susp.						Susp.	
Blood pressure	120/80	125/80	120/80	120/75	150/90	120/75	135/85	160/80	150/100
Edema		+							
Pathologic renal findings							+		
Nervous System - Neurological:									
Muscle aches	+			+	(+)	+	+		+
Weakness of legs	+	+	+	+	+	+	+	+	+
General fatigue	+	+	+	+	+	+	+	+	+
Incresed need for sleep	+			+	+	+	+	+	
Parasthesias	+			+					
Headache	+		+	+				+	
Dizzy spells								+	
Orthostatic synoope	+				+	+	+	+	++
Paresis (vague)									
Disturbances of ooordination									
Hypesthesia				(+)		(+)			
Reduced reflexes									
Vegetative Hyperexoitability			+	+	+		++	+	
EEG findings	abn.	abn.	abn.	abn. p., n.	abn. n.	n.	p., abn.	abn. abn.	abn.
EMG findings	no findings		n.s.p. v.mu.		no findings		n.s.p. v.mu.	n.s.p. v.mu.	

Nervous System - Psychopathology:	
Reduced initiative & interest	++
Hyperesthetic - emotional tendencies	++
Marked fluctuations in intensity	++
Disturbances of memory & concentration	
Disturbances of Libido & Potency	++
Alcohol Intolerance	+
Depressive surges of bad temper	+
Lessening of drive	+
Disturbances of affect in narrow meaning	+
Experimental reduction in mental performance	
Organic Rohrschach test	+
Individual neuritic tendencies	

n. = normal, abn. = abnormal, p = pathological, n.s.p.
v. mu. = early fatigue in the EMG series.

+	+	++	++	+	+	+	+
+	+		+	+	+		++
+			+		+	++	
		+			+		
+	+	+	+	+	+	+	+
	+	+	+	+			
		++	+		+	++	+
	+	++	+		+	+	+
	+	+			+		
	+	++	++		+	+	
		++	+		+	+	
						+	++

no definite pathology