STATE OF CALIFORNIA
GEORGE DEUKMEJIAN, Governor

AIR RESOURCES BOARD
1102 Q STREET
P.O. BOX 2815
SACRAMENTO, CA 95812

May 31, 1984

Dear Sir or Madam:

Subject: Request for Information Regarding Ethylene Dichloride

I am writing to request information on the health effects of ethylene dichloride as part of our toxic air contaminant program. This program is based on legislation enacted in September 1983, Assembly Bill 1807 (Tanner). AB 1807 (Health and Safety Code Sections 39650, et seq.) requires the ARB to identify compounds as toxic air contaminants and once identified to develop and adopt control measures for such compounds. After consultation with the staff of the Department of Health Services (DHS), we have selected ethylene dichloride as a candidate toxic air contaminant to be evaluated in accordance with the provisions of AB 1807.

Before the ARB can formally identify a compound as a toxic air contaminant, several steps must be taken. First, the ARB must request the Department of Health Services to evaluate the health effects of candidate compounds. Second, the ARB staff must prepare a report which includes the health effects evaluation and then submit the report to a Scientific Review Panel for its review. The report submitted to the Panel will be made available to the public. Information submitted in response to this request will be considered in the ARB report to the Panel. Although, any person may also submit information directly to the Panel for its consideration, I urge you to submit all information at this time for our consideration in the development of the report for the Panel. The Panel reviews the sufficiency of the information, methods, and data used by the DHS in its evaluation. Lastly, after review by the Scientific Review Panel, the report with the written findings of the Panel will be considered by the Air Resources Board and will be the basis for any regulatory action by the Board to officially identify a compound as a toxic air contaminant.

Prior to formally requesting the DHS to prepare a health effects evaluation of ethylene dichloride, we are providing, pursuant to the provisions of Section 39660(e) of the Health and Safety Code, an opportunity to interested parties to submit information on the health effects of ethylene dichloride

which he or she believes would be important in DHS's evaluation of ethylene dichloride as a candidate toxic air contaminant.

In May 1984, ARB staff received a reference search on ethylene dichloride health effects using the MEDLARs II and DIALOG Information Services. These information services include material available to the public on or before November 1983. The attached bibliography lists the references from this information search. We are requesting pertinent information on ethylene dichloride health effects, including any material that may not be available to the public, that is not included in the attached bibliography.

I would appreciate receiving any relevant information you wish to submit by June 30, 1984. To expedite the review process, we ask that any information which you believe should be regarded as "trade secret" be clearly marked and separated from other information. Your help in expediting our review will be greatly appreciated.

You may identify portions of the information you submit as "trade secret" in accordance with Health and Safety Code Section 39660(e). The claim of trade secrecy must be supported upon the request of the Air Resources Board. Other information claimed to be trade secret and information otherwise claimed to be exempt from disclosure may be identified as confidential in accordance with Section 91011, Title 17, California Administrative Code. Section 91011 requires that the claim of confidentiality be accompanied by specified supporting information.

Pursuant to the provisions of the Public Records Act (Government Code Sections 6280 et seq.), the information you provide will be a public record and subject to public disclosure, except for trade secrets which are not emission data or other information which is exempt from disclosure or the disclosure of which is prohibited by law. The information may also be released to the Environmental Protection Agency, which protects trade secrets and confidential information in accordance with federal law, and to other public agencies, which are also required to protect such information.

Please send the information to the attention of:

William V. Loscutoff, Chief
Toxic Pollutants Branch
Re: Ethylene Dichloride
California Air Resources Board
P. O. Box 2815
Sacramento, CA 95812

If you have any further questions regarding health effects information, please contact Mr. John Batchelder at (916) 323-1505. For any other questions, please contact Mr. Don Ames at (916) 322-8285.

If you are not the person to whom this request should be addressed, please forward it to the appropriate person in your organization. Also, please let us know whether you would like to continue to receive information inquiries for other candidate compounds, and if not, if there is anyone in your organization to whom such requests should be sent.

Sincerely,

Peter D. Venturini, Chief
Stationary Source Division

cc: Alex Kelter, DHS
Lori Johnston, DFA
Wayne Morgan, President CAPCOA
Jan Bush, Executive Secretary CAPCOA
David Howekamp, EPA Region IX
Assemblywoman Tanner
APCO's

Attachment

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PPG Industries, Inc. One PPG Place Pittsburgh, Pennsylvania 15272 (412) 434-2801

A. Philip Leber, Ph.D.
Manager of Industrial Toxicology
Environmental Affairs
Industrial Chemical Division

July 3, 1984

William V. Loscutoff, Chief
Toxic Pollutants Branch
California Air Resources Board
P.O. Box 2815
Sacramento, CA 95812

Dear Dr. Loscutoff:

Re: Ethylene Dichloride

This is in response to your request for information on the chemical ethylene dichloride (EDC). In reviewing our toxicology files for this material, only one relevant reference was found that was not included in your reference list. A copy of this article is attached to this letter.

PPG appreciates the opportunity to contribute to California's efforts in developing rational assessments of hazards from airborne chemicals.

Sincerely,

A. Philip Leber

mec

Attachment

cc: S. Angrist
R. Davis

SL 039089

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(Requests for reprints should be addressed to:-
Universitäts-Frauenklinik
78 Freiburg, Germany)

Ethylene Dichloride EDC Toxicity FIE

Clinical Features, Pathogenesis and Management of Dichloroethane Poisoning[1]

G. Martin, K. Knorpp, K. Huth, F. Heinrich and C. Mittermayer

Department of Medicine
(Joint Directors: Prof. H. J. Dengler, Prof. H. A. Kühn and Prof. H. G. Lasch) and the Department of Pathology
(Director: Prof. W. Sandritter), University of Giessen

Summary:- A 57-year-old man died of therapy-resistant cardiovascular failure 24 hours after ingestion of an dichloroethane-containing embrocation. Apart from gastro-enterocolitis and hepatic necrosis he developed a severe haemorrhagic diathesis. The complex disturbance of the haemostatic mechanism, which included thrombocytopenia and reduced activity of all clotting factors examined (Factor I, II, V, VII and XIII), was ascribed to consumption ("using up") of these substances by disseminated intravascular coagulation ("Verbrauchskoagulopathie") and secondary hyperfibrinolysis. Therapeutic principles for the management of oral dichloroethane poisoning are suggested taking into account the likely pathogenesis. They include prompt gastric lavage with addition of paraffin (in which dichloroethane dissolves), measures to protect the liver, continuous supervision and adjustment of blood gases. Incipient consumption of the clotting factors is counteracted by heparin infusions. Cardiovascular function is supervised by continuous registration of the electrocardiogram, even after apparent improvement in the patient's condition or subsidence of the initial stupor. Should renal failure occur, treatment is the same as for other types of acute renal failure.

Some analgesic and anti-inflammatory embrocations include dichloroethane (CH_2-Cl-CH_2-Cl) as their main hyperaemia-inducing constituent. Accidental or deliberate ingestion of such embrocations which are meant solely for external use, may result in severe and sometimes fatal dichloroethane poisoning (2, 3, 13).

To the few reports of poisoning by swallowing dichloroethane a further case is added here. It was characterized by very severe cardiac arrhythmias and disturbances of the clotting mechanism causing a haemorrhagic diathesis due to intravascular consumption of clotting factors.

Case Report

At about 18.30 on November 4, 1966, patient R., a 57-year-old man, swallowed, presumably with suicidal intent, about 40 ml of an initially unidentified embrocation used by him for the relief of rheumatic complaints. He was admitted to hospital at 20.00 on the same day in a somnolent condition. As the patient could not be roused, information about the poison swallowed was unobtainable. Relatives could not be contacted. The expired air smelled strongly of camphor. A few minutes after admission to hospital the patient vomited about 300 ml of a bilious liquid smelling of camphor and about 30 minutes later voided copious, apparently normal, faeces on three occasions. Otherwise there were no alarming signs of severe poisoning.

Clinical Features and Course

Apart from a postgastrectomy scar external appearance was normal. There were no demonstrable neurological defects, cyanosis, dyspnoea, oedema, jaundice, skin rash or haemorrhagic diathesis. Blood pressure was constant at 140/80 mm Hg. The electrocardiogram (ECG) showed sinus tachycardia of about 100/minute and ventricular extrasystoles but normal A-V conduction.

Serum glutamic-oxaloacetic transaminase (SGOT) and serum glutamic-pyruvic transaminase (SGPT) activities were normal (4.5 I and 6.7 IU, respectively). After gastric lavage, which produced only small quantities of food residue, infusion of a 5% Ringer-laevulose solution combined with strophanthin and antibiotics was instituted. Oral paraffin, which binds ethane dichloride and in this way prevents or delays its absorption, was not given as there was no information on the type of poison (9). A gas analyser which would have immediately detected the presence of halogenated hydrocarbon

[1] Translated from Drsch. med. Wschr. 93 (1968), 2002.

in the expired air was not available at that time. In view of the continued improvement in the patient's condition no further therapeutic measures were adopted.

In the morning of November 5th, twelve hours after admission to hospital, the patient responded to stimuli. It was only then, 14 hours after the accident, that the patient and relatives who had since been summoned by telephone provided the information that he had swallowed Marament®. This embrocation is made up of: 100 g dichloroethane, 2.0 g oil of pine-needles, 0.2 g methyl salicylate, 0.05 mg cobra (Naja tripudians) toxins and an unspecified emulsifier in 100 ml of the liquid.

At about 8.30, almost immediately after the toxic nature of the remedy had become known, the patient's condition suddenly deteriorated with dyspnoea, orthopnoea and progressive clouding of consciousness. Blood pressure could no longer be recorded. At 8.40, during attempts at improving the circulation, cardiac arrest suddenly supervened.

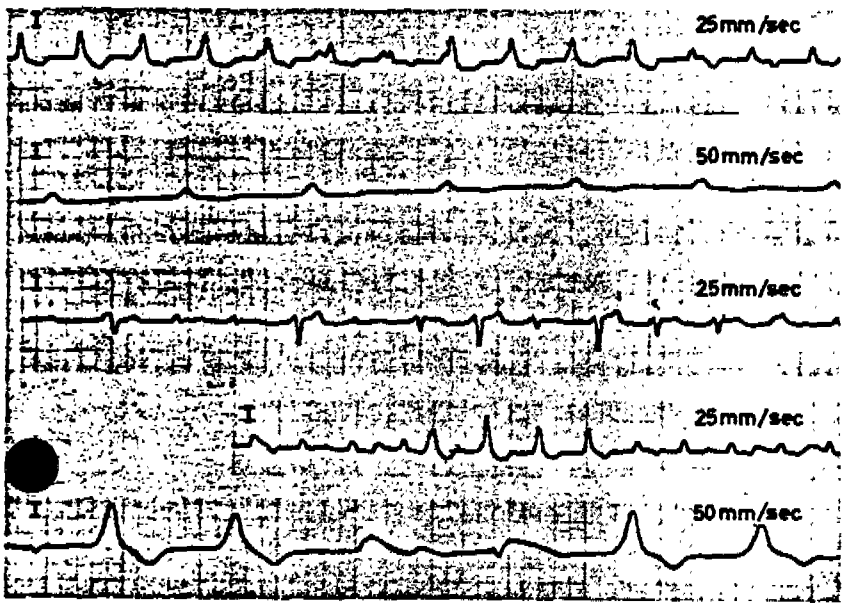

Fig. 1. Electrocardiogram recorded on 5 November 1966, after successful resuscitation: probably complete atrio-ventricular dissociation with changing site of pacemaker.

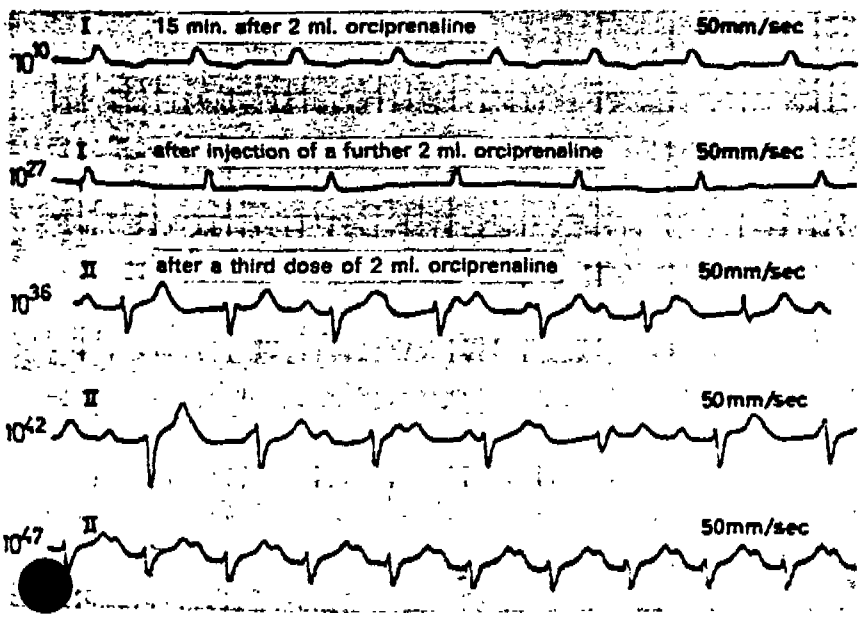

Fig. 2. Electrocardiogram recorded at 10.10–10.47 a. m. on 5 November 1966: sinus tachycardia after injection of a total of 6.0 ml of orciprenaline (Alupent®).

After successful resuscitation by external cardiac massage for 25 minutes and artificial respiration with oxygen (by intubation) the ECG showed complete atrio-ventricular block with a regular idioventricular rate of 70/minute. The P-waves, so far as they were discernible, indicated an atrial rate of 75/minute (Fig. 1).

The ventricular and atrial rates responded to the intravenous injection of 1.0 mg orciprenaline with a rise to 85/minute and 120/minute respectively. Finally, complete A-V block subsided and a regular rhythm of 110/minute returned (Fig. 2).

Rapid infusion of Haemaccel®, sodium bicarbonate, 5% Ringer-laevulose solution and noradrenaline succeeded at about 10.40 (two hours after cardiac arrest) in restoring the circulatory state to normal. Unaided by adrenergic agents the blood pressure rose to 105/85 mm Hg and the patient responded to stimuli.

ECG recordings (precordial leads) showed episodes of right bundle branch block. 17 hours after the accident the sinus rhythm was again disturbed by occasional ventricular extrasystoles which became more frequent in the course of the next half hour (Fig. 3). After a further two hours, P-waves were no longer discernible; but the possibility that they were fused with the preceding T-waves could not be excluded.

During the day the ventricular extrasystoles became more frequent and changes in the site of impulse origin resulted in episodes of parasystole. 24 hours after ingestion of the poison the blood pressure fell rapidly within 30 minutes and cardiac arrest occurred.

During resuscitation attempts prolonged bleeding from venipunctures drew attention to an increased bleeding tendency.

At 10.40, after nodal rhythm and stable circulatory conditions had become re-established and consciousness was gradually returning, massive haematemesis occurred, presumably due to profuse bleeding from the gastro-intestinal mucosa. It effectively precluded oral administration of paraffin which even then might still have proved beneficial. Up to 14.00 a total of 1,500 ml of blood-containing gastric contents had been evacuated, partly by vomiting and partly by suction catheter. An analysis of the clotting factors (at 15.00) showed maximal reduction of Factors II, V, VII and XIII and complete defibrination, fibrinogen being no longer demonstrable in the tyrosine-tryptophan test (12). The platelet count had dropped to 14,300/mm³, fibrinolysis (Piper's method [10]) was increased to four times its normal value and pro-activator levels were below 10%. The thrombelastogram showed the blood to be incoagulable. Thrombin time after fibrinogen substitution was 59 seconds instead of the normal 12 seconds.

The complex coagulation disorder with thrombocytopenia and reduced activity of all coagulation factors was attributed to the consumption of these substances in a process of disseminated intravascular coagulation ("Verbrauchskoagulopathie") and to secondary hyperfibrinolysis (5, 7). The patient was given 5,000 U heparin by intravenous drip over a period of two hours and he was also given intravenously Cohn's fraction as a fibrinogen substitute, 4.0 g of ε-amino-caproic acid as an antifibrinolytic agent and 2.0 ml Vitamin K_1 (phytomenadione).

A further estimation of clotting factors at 18.00 showed a rise in fibrinogen level to 16 mg/100 ml and in the platelet count to 20,000/mm³. Factors II, V and VII remained low. As was subsequently confirmed at necropsy, the liver at that time was already irretrievably damaged. The steep rise of SGOT to 1,860 IU, of SGPT to 450 IU and of

lactate dehydrogenase to 4,555 IU and the reduction of serum-albumin concentration to 1.59 g/100 ml and of plasma-cholesterol to 76 mg/100 ml were presumably attributable to fulminating yellow atrophy of the liver. The abnormally high lactate-dehydrogenase activity may have possibly been due to haemolysis.

Blood-gas analysis (Astrup's method) after massive infusion of a total of 920 mEq. of sodium bicarbonate revealed extreme acidaemia (pH 6.8) which was partly of metabolic (reduced base excess and standard bicarbonate) and partly of respiratory origin (marked increase in CO_2 tension). At the time the blood samples were taken the patient was already moribund. He died at approximately 20.00, about 24 hours after ingestion of the poison, of irreversible cardiac and circulatory failure.

Necropsy Findings

The most striking feature was acute yellow atrophy of the enlarged (1,800 g) and flabby liver. The cut surface showed irregular yellowish-brown mottling. Through the microscope the lobular structure was discernible only as a shadow outline.

The portal canals were crowded closely together. Goldner's stain revealed very dark, homogeneous and lumpy hepatic cells with only a few nuclei. Distended cells, hyaline bodies and large intracellular fat droplets were also seen. Only a few hepatic cells were of normal appearance.

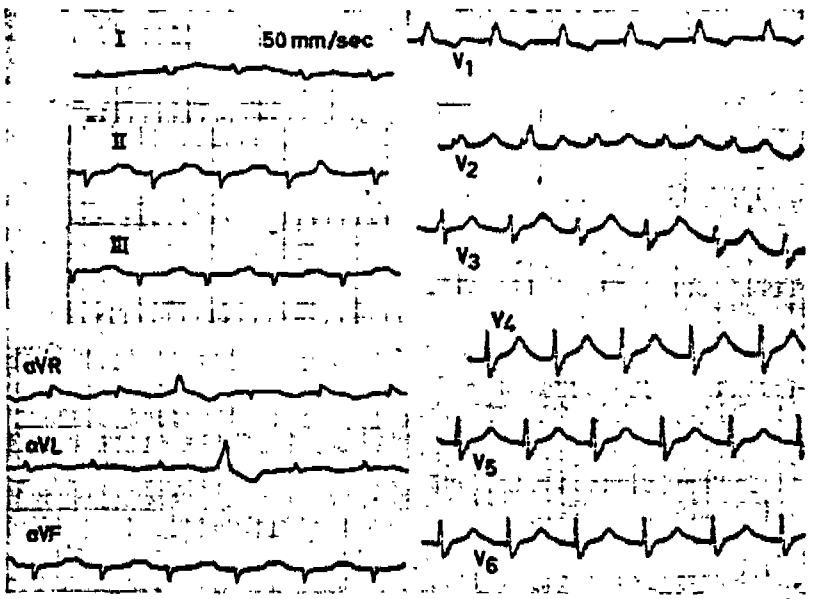

Fig. 3. Electrocardiogram taken at 10.53—10.58 a.m. on 5 November 1966. The tracings (the leads were not recorded simultaneously) show, first, sinus tachycardia with some extrasystoles; on the reight: complete right bundle branch block has developed which may indicate acute cor pulmonale.

Both ventricles were hypertrophied and the right one was also dilated. On microscopic examination the myocardial fibres were thickened and the cell nuclei enlarged and irregular. There were also recent, predominantly perivascular, focal necroses of the myocardial fibres (Fig. 4*). The coronary arteries were slightly arteriosclerotic but not narrowed.

The lungs showed bilateral chronic emphysema, membranous pleural adhesions, considerable congestion and oedema. Microscopic examination revealed both occluding and non-occluding thrombi in the small lung arteries and capillaries, of not quite recent origin (Figs. 5 and 6).

The haemorrhagic diathesis manifested itself in haemorrhages into the mucosae of oesophagus, stump of the stomach (after a Billroth II gastrectomy) and rectum, and into the subepicardial, subendocardial and myocardial tissues. Bleeding into the intestinal wall was noticeable in some jejunal loops. The attempts at resuscitation had resulted in fracture of several ribs, subpleural haematoma and haemothorax of minor degree on the left side.

Discussion

The signs and symptoms presented by this case of dichloroethane poisoning corresponded closely to the clinical picture described by others. Characteristic features were an initial stage of stupor followed by the development of gastro-enterocolitis, hepatic necrosis, haemorrhagic diathesis and cardiogenic shock within 48 hours. The frequently observed involvement of the kidneys was absent in our case. Toxic effects of dichloroethane resemble those produced by other halogenated hydrocarbons, especially carbon tetrachloride, chloroform and ethane tetrachloride. All these agents have in common that, being fat-soluble, they have narcotic effects and taken orally they cause gastrointestinal damage and necrosis of the liver and kidneys. The renal lesions generally do not develop until after a latent period of 24–48 hours (9). Cardiac arrhythmias and particularly ventricular fibrillations have been observed after poisoning with chloroform and carbon tetrachloride (4) and Friese (3) also noticed in a case of ethane dichloride poisoning a transient inversion of the T-wave in leads V_3–V_5 such as occurs in rudimentary infarction of the anterior wall. The haemorrhagic tendency that accompanies carbon tetrachloride and dichloroethane poisoning has been ascribed to a massive reduction in prothrombin concentration.

The post-mortem examination in our case revealed not only the signs of haemorrhagic diathesis but also thrombi in the pulmonary arterioles and capillaries. Taking into account the complex changes in the haemostatic mechanism and the not unfavourable effects of heparin administration, the assumption appears justified that the dramatic reduction in the platelet count and clotting factors was a sign of their marked depletion, the substrates having been consumed in the process of coagulation (8). This interpretation receives support from the fact that fibrinogen has a half-life of 3–4 days (1): the drop in the platelet count and plasma Factor I could not, therefore, be accounted for by the onset of hepatic necrosis and the resulting interference with the formation and synthesis of plasma clotting factors. As to the accompanying hyperfibrinolysis, this was presumably a reactive process to dissolve the fibrin thrombi as is frequently observed in generalized intravascular clotting (7).

Whether dichloroethane can trigger intravascular clotting is so far unknown. Being a fat solvent it might damage the platelet membrane and thereby release platelet Factor III; or it might activate the clotting process by inducing haemolysis and thereby releasing pro-coagulant erythrocytic lipoproteins (erythrocytin [11]). The snake venom in the embrocation (snake bites may cause intra

* Figs. 4–6 are on p. 66.

For the article by Turina et al. (pp. 49–50)

Crohn's Disease of the Oesophagus

Fig. 1. Crohn's disease of the oesophagus. Oesophagram: severe degree of stenosis with thread-like irregular lumen immediately above the diaphragm. Conical narrowing of the oesophagus above the stenosis.

Fig. 2. Same case as Fig. 1. Resected specimen of the distal oesophagus and proximal part of the stomach showing a 2 cm long granulomatous stenosis (S) below the upper margin of the resection.

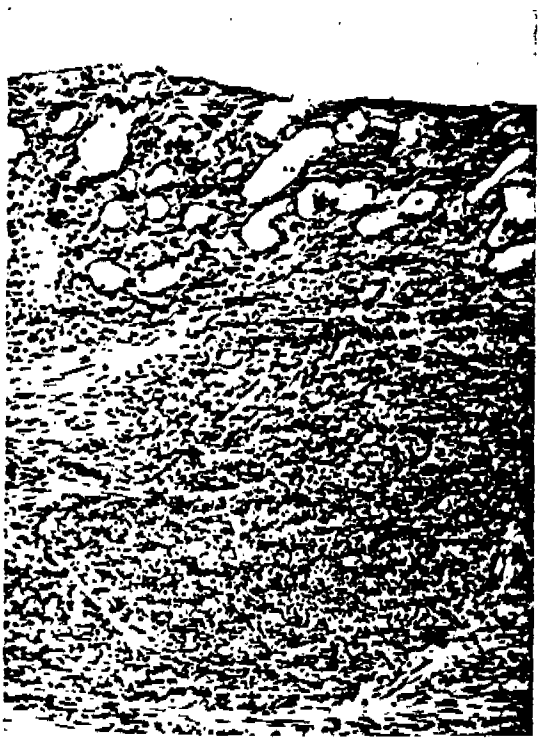

Fig. 3. Same case. Ulcer floor with non-specific granulation tissue and compact lymph follicles in the residual parts of the tunica propria, also in the submucosa which is fibrotic and hyperaemic. Magnification × 35.

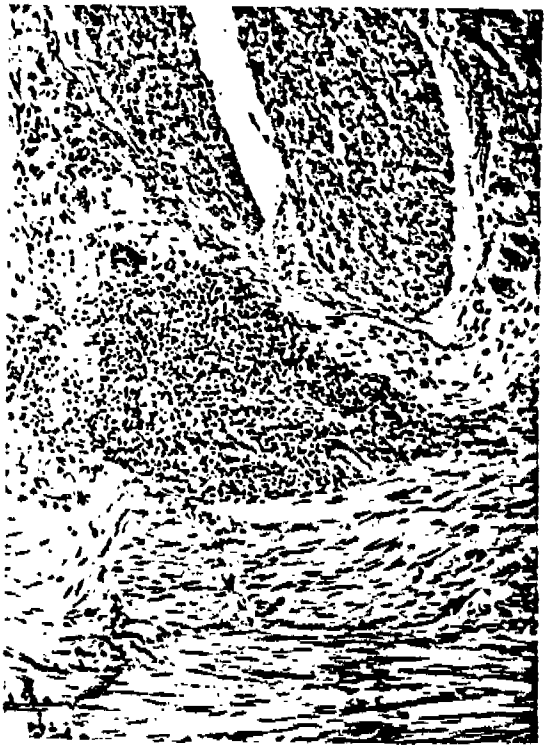

Fig. 4. Same case. Muscularis propria with compact lymph follicles. Magnification × 88.

For the article by Martin et al. (pp. 62–67)

Clinical Features, Pathogenesis and Management of Dichloroethane Poisoning

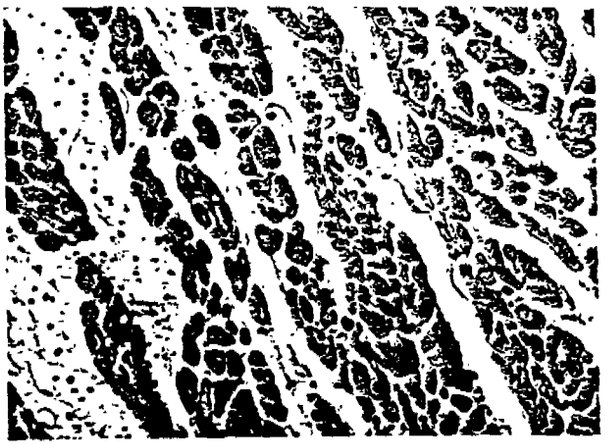

Fig. 4. Heart-muscle necrosis. Goldner's trichome stain. Magnification × 140.

Fig. 5. Hyaline thrombi in lung vessels. Goldner's trichome stain. Magnification × 140.

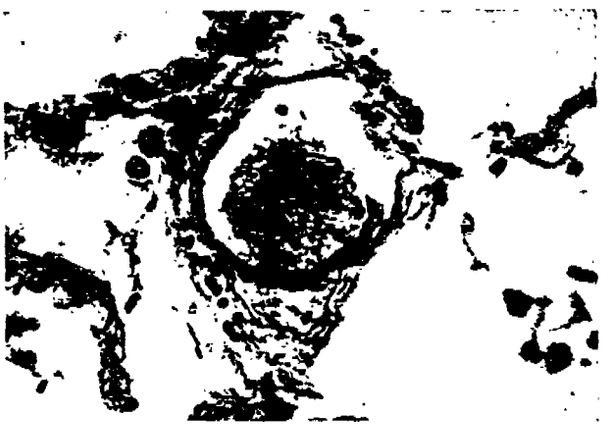

Fig. 6. Hyaline thrombus in lung vessels. Goldner's trichome stain. Magnification × 240.

For the article by Gedigk et al. (pp. 68–77)

The Morbid Anatomy of Marburg Virus Disease

Fig. 1. Irregularly arranged areas of necrosis (dark) affecting single cells and cell groups in the liver. Case 1 (PM No. 378/67). Formalin, Goldner, × 100.

vascular clotting) can be excluded as a causal factor as the poison was taken by mouth. The severe damage to the organs induced by dichloroethane could possibly bring about the release of tissue thromboplastins which, in conjunction with the excessive acidaemia and circulatory failure, could cause a shift in the physiological balance between fibrinolysis and clotting towards the latter.

There is also the possibility that the cardiac arrhythmia and the consequent reduction in cardiac output (cardiogenic shock) played a causal role in the pathogenesis of intravascular clotting. On the other hand, the dilatation of the right ventricle and development of acute cor pulmonale with cardiac arrhythmia, cardiogenic shock and myocardial necroses could equally well originate from intravascular coagulation and the resulting, histologically proven, blocking of the pulmonary circulation by thrombi. If this latter hypothesis is accepted the haemorrhagic diathesis, the cardiac arrhythmia and the disseminated necroses in the intestine and kidneys could be attributed to the action of a single mechanism since the fully developed syndrome of intravascular coagulation is characterized by infarction of, and haemorrhages into, various organs.

Conclusions

The clinical picture presented by dichloroethane poisoning is determined by the quantity of poison ingested. In man the tolerated single dose is not more than 1.0 ml, with a maximal daily dose of 3.0 ml (9). As there is no known specific antidote, measures to counteract the effects of orally taken dichloroethane are primarily confined to attempts at reducing or slowing down absorption of the poison from the gastro-intestinal tract. Further therapeutic measures aim at preventing acute hepatic failure and at restoring the disordered haemostatic mechanism, acid-base balance and cardiovascular function. Selective therapy directed to the restoration of a particular functional system is impossible. From considerations of the pathogenetic mechanism, published reports and our own observations some general principles for dealing with oral dichloroethane poisoning emerge:

1) Alertness to the possibility of dichloroethane poisoning is important. Inadequate specification of some dichloroethane-containing preparations as potentially dangerous is liable to mislead patients, relatives and the attending physician.

2) Analysis of the expired air by a gas analyser for the presence of chlorinated hydrocarbons, unless this type of poison can be absolutely ruled out.

3) Prompt gastric lavage, provided there is no contra-indication, with addition of paraffin; then administration of 100–150 ml of paraffin and saline purges, either by mouth or indwelling stomach tube. Paraffin administration is repeated every 6–8 hours for the first 24–48 hours.

4) Prompt measures to protect the liver similar to those employed in acute yellow atrophy (6). Repeated laboratory tests.

5) Supervision and constant adjustment of blood gases and steps to ensure excretion of an alkaline urine. Sodium bicarbonate administration should be supplemented by THAM, because the latter is more effective in counteracting intracellular acidosis.

6) Prompt and continuous analysis of the clotting factors to ensure that an incipient consumption of platelets and fibrinogen is immediately checked by an infusion of heparin (20,000 U in 24 hours). This therapy is applicable even in the presence of gastro-intestinal haemorrhage. If defibrination has already occurred, heparin combined with Cohn's fraction I as a fibrinogen substitute is given by infusion.

7) Continuous supervision of cardiovascular function with continuous recording of the ECG.

8) Administration of water and electrolytes as required and symptomatic treatment of the gastro-enterocolitis which is an almost invariable complication. Intestinal haemorrhages resulting in a critical reduction in haemoglobin concentration may require blood transfusion.

9) Renal failure setting in 24–48 hours after ingestion of the poison is a potential complication of the third stage of dichloroethane poisoning. Its occurrence depends on the quantity swallowed, the interval between ingestion and beginning of treatment and the success of the antecedent therapeutic measures. Treatment is the same as for acute failure from other causes.

10) An apparent improvement in the patient's condition after the initial stuporous stage has subsided must not lead to premature slackening of the therapeutic efforts.

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CHEMICAL MANUFACTURERS ASSOCIATION

July 2, 1984

Mr. William V. Loscutoff
Chief, Toxic Pollutants Branch
California Air Resources Board
P.O. Box 2815
Sacramento, CA 95812

Re: Ethylene Dichloride

Dear Mr. Loscutoff:

By notice dated May 31, 1984, you requested information as to the health effects of ethylene dichloride. The bibliography attached to your notice lists the draft health assessment document on ethylene dichloride prepared by the U.S. Environmental Protection Agency. CMA's Ethylene Dichloride Panel recently submitted comments on this document to EPA, along with a suggested revision. These materials are enclosed for your review.

Please let me know if we can be of further assistance to you in evaluating the health effects of this important industrial chemical.

Sincerely,

Hasmukh C. Shah, Ph.D.
Manager
EDC Program Panel

Enclosure

c.c. EDC Panel