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FROM: A. S. Cummin

DIV. / DEPT. Technical Division

ADDRESS: New York, New York

TO: James T. McCrory H. A. Peed
Paul Josenhans David Weinstein
Henry Schmidt
SUBJECT: American Medical Association Journal - VCM

TELEPHONE: 4158

Attached for your information is a copy of an article which appeared in the June 10th issue of the AMAJ.

The article summarizes many of the papers delivered at the recent N. Y. Academy of Science meeting on Vinyl Chloride as well as giving some insight into the on-going studies of NIOSH/Sellikoff and Creech.

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How hazardous to health is vinyl chloride?

In the months since John L. Creech, MD, associated four deaths from the rare angiosarcoma of the liver with exposure to vinyl chloride in the Kentucky polymerization plant of B.F. Goodrich Co., both the Food & Drug Administration and the Environmental Protection Agency have urged makers of aerosols propelled by vinyl chloride to withdraw them from the market as potentially hazardous.

Just how dangerous the ubiquitous plastic ingredient is became clear last month at a conference held by the New York Academy of Sciences with American Cancer Society support. During the sessions in New York City, epidemiologists, pathologists, and oncologists from the United States, West Germany, Italy, Romania, and Japan reported on studies that showed:

- Those at risk of liver damage are not just the estimated 6,500 workers (in the United States alone) who produce the polyvinyl chloride polymer from the vinyl chloride monomer. Thousands of other workers are also at risk—those who work in warehouses where the resin is stored, and those who work in plants where the polymer is heated before being used to make tiles, containers, and other products.

- Vinyl chloride disease, as it is now fast becoming known, is not limited to the liver. Inhaling the fumes can damage pulmonary function, produce thrombocytopenia, enlarge the spleen and lead to excessive production of immature erythrocytes.

- Handling vinyl chloride can produce acroosteolysis in the fingers and Reynaud phenomenon in the hands.

- Exposure to aerosols containing 50 to 10,000 ppm of vinyl chloride can regularly induce tumors in rats, mice, and hamsters—not only in the liver but in other tissues as well.

- The usual battery of liver function tests cannot be relied upon to detect the periportal fibrosis that precedes sarcoma growth.

- The liver does not return to normal for up to 2½ years after a polyvinyl chloride worker changes jobs and is removed from exposure.

Hans Popper, MD, the Mt. Sinai Hospital pathologist who is now a visiting fellow at the National Institutes of Health, told the New York meeting that the fibrosis and tumors induced in the polyvinyl chloride workers is virtually identical to the disease suffered by German vineyard laborers as a result of exposure to inorganic arsenic sprays. His studies of liver biopsies from two patients currently under treatment for hepatic angiosarcoma show "widespread activation of

hepatocytes and de-differentiation of fibroblasts consistent with pre-malignant changes in liver tissue far removed from the primary tumor." (Dr. Creech said in an interview that both patients undergoing chemotherapy for their angiosarcoma have shown improvement.) Dr. Popper said he has no doubt that one or more of the compounds involved in the production of vinyl chloride and its resin polymer are specific carcinogens.

On the epidemiologic front, Clark W. Heath, Jr., MD, of the Center for Disease Control in Atlanta told a press conference that 13 cases of hepatic angiosarcoma have now been traced to 4 American polyvinyl chloride plants. One British case and two German cases have also been documented.

These cases, except for the two now under treatment, were found through retrospective investigations, and after an average exposure of 12 years, Dr. Heath said. Furthermore, one child of an angiosarcoma patient has developed a primary hepatoma.

Concerned Manufacturers

Chemical industry representatives at the conference made it clear that they were taking the matter very seriously. The companies have instituted, in some cases, detection warning systems to alert workers to don respirators in case of dangerous concentrations of vinyl chloride. (That is, concentrations of more than 50 ppm.) Maurice N. Johnson, MD, head physician at Goodrich, said his company has now reduced general levels of the chemical in the air of the plants to about 15 ppm.

The National Institute of Occupational Safety and Health (NIOSH) has called for levels of less than 1 ppm of vinyl chloride. The levels in the Goodrich plants fall short of this, but the reduction could still reduce the danger, according to Cesare Maltoni, MD, of the University of Bologna, Italy. Dr. Maltoni first called attention to tumor induction by the chemical in the fall of 1972 in reports presented to the Italian government and industry, and to representatives of the Manufacturing Chemists Association of the United States.

Dr. Maltoni's first reports were based on the studies where rats were administered aerosolized vinyl chloride. The Italian oncologist is presently conducting year-long rat exposure tests at 10 and 25 ppm in an attempt to determine the limits of dose-related carcinogenesis. He said that in one trial, animals that were exposed to 50 ppm

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Irradiation patients get thyroid cancer check

An extensive campaign is underway to find the 5,000 patients given radiation therapy for tonsillitis between 1938 and 1955 at the Michael Reese Hospital and Medical Center, in Chicago.

The recall was prompted by increasing reports of radiation-associated thyroid carcinomas in patients who had been irradiated during childhood for thymic enlargement, recurrent tonsillitis, acne, and impetigo (*JAMA* 225:487 [July 30] 1973).

Radiation therapy for these conditions is no longer in vogue. However, from the 1930s to 1950s the delayed effects of radiation were not apparent, and hundreds of thousands of patients around the world probably received the treatment, Louis M. Sherwood, MD, chairman of the Department of Medicine, told *MEDICAL NEWS*.

With the problem now in focus, "it was deemed essential to reach these people and not ignore the possible risk. We made a commitment to find and evaluate former Michael Reese patients free of charge," Dr. Sherwood said.

A staff of secretaries under Margaret Arnold, RN, examined the radiation therapy files and sent letters to all patients at risk. When announcements of the search appeared in Chicago newspapers in March, the hospital switchboard was jammed. In one week nearly 6,000 calls were taken from patients treated at Michael Reese and other facilities.

Since the program began in January "we have seen about 700 patients, and many more are scheduled," Dr. Sherwood said. The patients are seen by an endocrinologist who discusses the problem and explains the laboratory procedures. Thyroid function tests and a rapid, small-dose scan are done.

Two endocrinologists perform the examinations independently to avoid bias, Dr. Sherwood explained. The physicians confer and compare their results to the scan. If there is any disagreement, the patient is reexamined by both physicians.

The same day, the results are discussed with the patient, and in his presence a phone call is made to his private physician. A follow-up letter includes test results and recommendations for treatment.

If all tests are normal, the patient will be seen annually for an indeterminate number of years, Dr. Sherwood said.

So far, the incidence of abnormalities in thyroid scans or physical examinations is 15% to 20%, but the number of tumors is unknown. It is too early to make a definitive statement, he stressed.

In addition to the benefits to the individual,

the program will yield important scientific information about the relationship of irradiation to thyroid disease. Hopefully, the results will lead to methods of preventing thyroid tumors, a better understanding of irradiation risks, and biochemical differentiation between patients at risk and normals.

At present, one group of normal-scan patients are taking thyroid hormone to see whether this will have any effect on subsequent development of nodules. The results will be compared to a group of matched controls. A good follow-up is essential, with cooperation between hospitals and physicians throughout the country, Dr. Sherwood said.

The program is expensive, costing the hospital \$5,000 to \$6,000 a week (\$60 per patient) for laboratory tests alone. The yearly cost is estimated at several hundred thousand dollars, he said.

The program is being conducted by Lawrence Frohman, MD, head of the divisions of endocrinology and metabolism; Martin Colman, MD, associate director of radiation therapy, and Steven Pinsky, MD, head of the Division of Nuclear Medicine.

Vinyl chloride symposium

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for four months and then observed for eight more months developed 75% fewer tumors in comparison to animals exposed for an entire year. This would at least offer some hope that vinyl chloride and polyvinyl chloride workers whose exposure is now minimized may not develop the liver cancer.

Descriptions of vinyl chloride disease came from researchers at the University of Bonn, West Germany, and were, except for the thrombocytopenia, in a very recent survey of 354 workers (including death certificates of 24) at the Goodyear Tire & Rubber Co. plant in Niagara Falls. Irving J. Selikoff, MD, of the Mt. Sinai School of Medicine, who led the investigation of asbestos fiber pathology a few years ago, headed the Mt. Sinai team that made the Niagara Falls check. Dr. Selikoff, conference co-chairman with E. Cuyler Hammond, ScD, vice president of the American Cancer Society, said the platelet loss might also have been confirmed with better equipment.

Albert Miller, MD, of the Mt. Sinai team reported that 80% of the Goodyear workers showed some evidence of pulmonary obstructive disease after 20 years of exposure to vinyl chloride fumes regardless of cigarette smoking history.

At Louisville, Dr. Creech has attempted a controlled study. He included all Goodrich workers

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adiology, professor told the press and uterine disorders numerous Today's onal and ing both s." artment Texas, nstitute, mes and d tract n civiline indi-point of ion dur-

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in an SMA-12 biochemical survey, screening both office workers and butadiene rubber workers along with those exposed to vinyl chloride. Dr. Creech, who first noticed acro-osteolysis in polyvinyl chloride workers in 1964, found no significant changes in the serum levels of lactic dehydrogenase, alkaline phosphatase, bilirubin, or SGOT—even in workers who had been heavily exposed over some time. There were some changes, though: 66% of the workers, compared with 0.02% of a general hospital population sample, had elevated levels of factor IV of lactic dehydrogenase. Those workers who twice showed any abnormality on the SMA 12 screening were subjected to technetium liver scans and angiography, followed by transjugular vein biopsy when a tumor was indicated.

This was done in 16 cases—and 2 of the workers had angiosarcomas. Dr. Creech said that angiography showed a 20-second "blush" around the tumor in the sarcomas. In his previous experience with hepatic metastases from extrahepatic primary cancers, he added, angiographic blushes persisted only about five seconds.

Persistent Liver Damage

Paul D. Berk, MD, of the National Institute of Arthritis, Metabolic and Digestive Diseases presented the bad tidings of the persistence of liver damage. He described the case of a 27-year-old man who worked 5½ years as a reactor cleaner in Goodrich's vinyl chloride polymerization unit in Louisville. When he complained of fever and weight loss, he was found to have an enlarged spleen and liver and slight elevations in SGOT and serum bilirubin. Three months later he was hospitalized for what appeared to be acute hepatitis. During those three months he had been on sick leave and had not been exposed to vinyl chloride. A laparotomy was performed during convalescence, his spleen was removed and a biopsy showed surface fine nodularity and fibrosis in the portal region of his liver. He also had proliferation of bile duct cells and activation of sinus lining cells.

He went back to work, but since environmental toxicity was suspected, the new job was far from the vinyl chloride polymerization area. This was long before the reports linking cancer and vinyl chloride; but after these reports, Dr. Creech referred the patient to NIH. By then 2½ years had passed since the hepatitis-like episode.

The man's liver function tests and liver scan were normal. But, according to Dr. Berk, a biopsy showed the liver was still covered with rice-

grain-sized nodules and the portal fibrosis was still strongly in evidence. In addition, the NIH pathologists saw some bridging between portal areas and hepatic veins, and hepatic vein catheterization revealed a 12 mm Hg wedge pressure.

In an effort to find a diagnostic test, NIH researchers tried radioactively labeled bilirubin elimination, BSP and indocyanine green clearance. All appeared normal. Only an experimental bile acid clearance test proved abnormal, at least raising some hope of a screening test for vinyl chloride hepatic fibrosis.

Meanwhile, Dr. Joseph K. Wagoner, SD Hyg NIOSH, told reporters of the start of a major prospective-retrospective study of polyvinyl chloride workers in six major US chemical plants.

This study should eventually include 3,000 persons exposed in the manufacture of vinyl chloride, in the polymerization process and during storage of the resin. Hopefully, it may clarify both the length of exposure required to produce disease. The occurrence of seemingly excess deaths from lymphomas and certain other cancers among the 24 Niagara Falls workers whose death certificates were examined by the Mt. Sinai group.

The Germans provided some ominous data on the length of exposure required to produce disease. H.J. Marsteller, MD, and colleagues at the University of Bonn have performed extensive peritoneoscopy on exposed polyvinyl chloride workers. They found one patient with a marked lesion on the surface of the liver after only 2½ years work in a polyvinyl chloride plant. This patient was awaiting biopsy, but in Dr. Marsteller's words "The lesion looks very much like an angiosarcoma." Spokesmen for the Rubber, Cork, Linoleum & Plastic Workers, AFL-CIO, thus may have reason to complain over delays in government regulation of polyvinyl chloride exposure.

Public awareness of Pap test

A small piece of good news for a change: more women than ever are aware of the Pap smear test and more are having it performed.

The American Cancer Society recently reported the results of a Gallup poll, which showed that 87% of women surveyed are aware the test exists, up from 78% in 1963. Better still, 78% of the respondents in the current survey have had the test, up from 48%; and best of all, 52% said they have had a Pap smear within the past 12 months. In 1963, the figure was only 23%.

Justin J. Stein, MD, president of the ACS, said these increases indicate that the society's goal of a Pap smear for all women at risk by 1976 "is more realistic than many of us dared hope."