THE NEW-CAR

By Kevin P. Shea

THE PLEASANT SMELL of the new car; the annoying oily film that appears on the inner surface of its windshield; the slightly slick texture the steering-wheel acquires when the car has been parked in the hot sun with windows closed; these are minor signs that a variety of chemicals are evaporating from the plastics with which the interiors of new cars are lined. Sitting in a new car on a hot day may provide the most intensive exposure to the vapors of plasticizers, stabilizers, and other components of plastics that the ordinary citizen is likely to encounter, but so nearly ubiquitous are these materials that their effects have begun to come under question in situations varying from battlefield blood-transfusions to outer-space probes.

The assumption that plastics, particularly polyvinyl chloride (PVC) plastics, are inert is so widespread that they are routinely used in the storage of blood, in various medical appliances, in scientific instruments, and, of course, in hundreds of thousands of consumer products.

Recent discoveries, however, have shown evidence that components of the plastics may be the cause of an increasingly common and sometimes fatal syndrome, called "shock lung," which follows massive blood-transfusions. Laboratory experiments have identified a number of other possible toxic effects of PVC plastic components, including effects on the nervous systems of laboratory animals and on developing chick and rat embryos. Most frequently implicated are compounds called phthalates, generically related to thalidomide, which are used as plasticizers.

The first widely publicized indication that polyvinyl chloride plastics were not completely inactive began with some unusual observations made by Dr. Rudolf J. Jaeger and Dr. Robert J. Rubin at Johns Hopkins School of Hygiene and Public Health.[1] The two scientists were studying isolated rat livers in an apparatus in which the blood being passed through the livers was delivered via polyvinyl plastic tubing. Dr. Jaeger and Dr. Rubin found three ultraviolet absorbing materials accumulating in the plasma of the blood. One of the materials was found in the plasma when the blood was circulated through the apparatus regardless of whether the liver was absent or present. This compound was soon identified as uric acid. The other two compounds were found only when the livers were present. Of the latter two, one is yet to be identified, but the other was quickly identified as glycolyl phthalate (GP). Further work showed that GP arose as a metabolite (a material formed by the chemical breakdown of another compound) of a phthalate plasticizer leached from the plastic tubing used to deliver the blood to the isolated rat livers. Further testing, in which Dr. Jaeger and Dr. Rubin deliberately introduced the plasticizer into the apparatus, confirmed the conversion of the plasticizer in the rat livers to its metabolite, GP.

Dr. Jaeger and Dr. Rubin then tested another formulation of polyvinyl tubing containing a different plasticizer. This one, di (2-ethylhexyl) phthalate (DEHP) was also found in the plasma after it had circulated through the tubing alone, but it was not found when circulated through the livers. Furthermore, no metabolite of DEHP could be detected. It was found that unlike the first plasticizer, DEHP was not metabolized, but rather it was accumulated entirely in the liver in an unmetabolized form.

This led the two scientists to further studies on the ability of various fluids to extract plasticizers from plastic materials. They found that simple salt solutions did extract plasticizers, while a 4 percent solution of bovine serum albumin was able to extract measurable amounts of DEHP.

Release Into Stored Blood

More significant, however, was the finding that whole human blood, stored in polyvinyl chloride blood bags, could also extract the plasticizer DEHP. It was found that at the end of the maximum storage period of 21 days, blood stored in polyvinyl chloride bags contained 5 to 7 milligrams of DEHP per 100 milliliters of blood (50 to 70 ppm). Dr. Rubin has calculated[2] that under these conditions

It is now known that certain plasticizers, once thought to be inert, can escape from numerous plastic products into fluids or into the air.

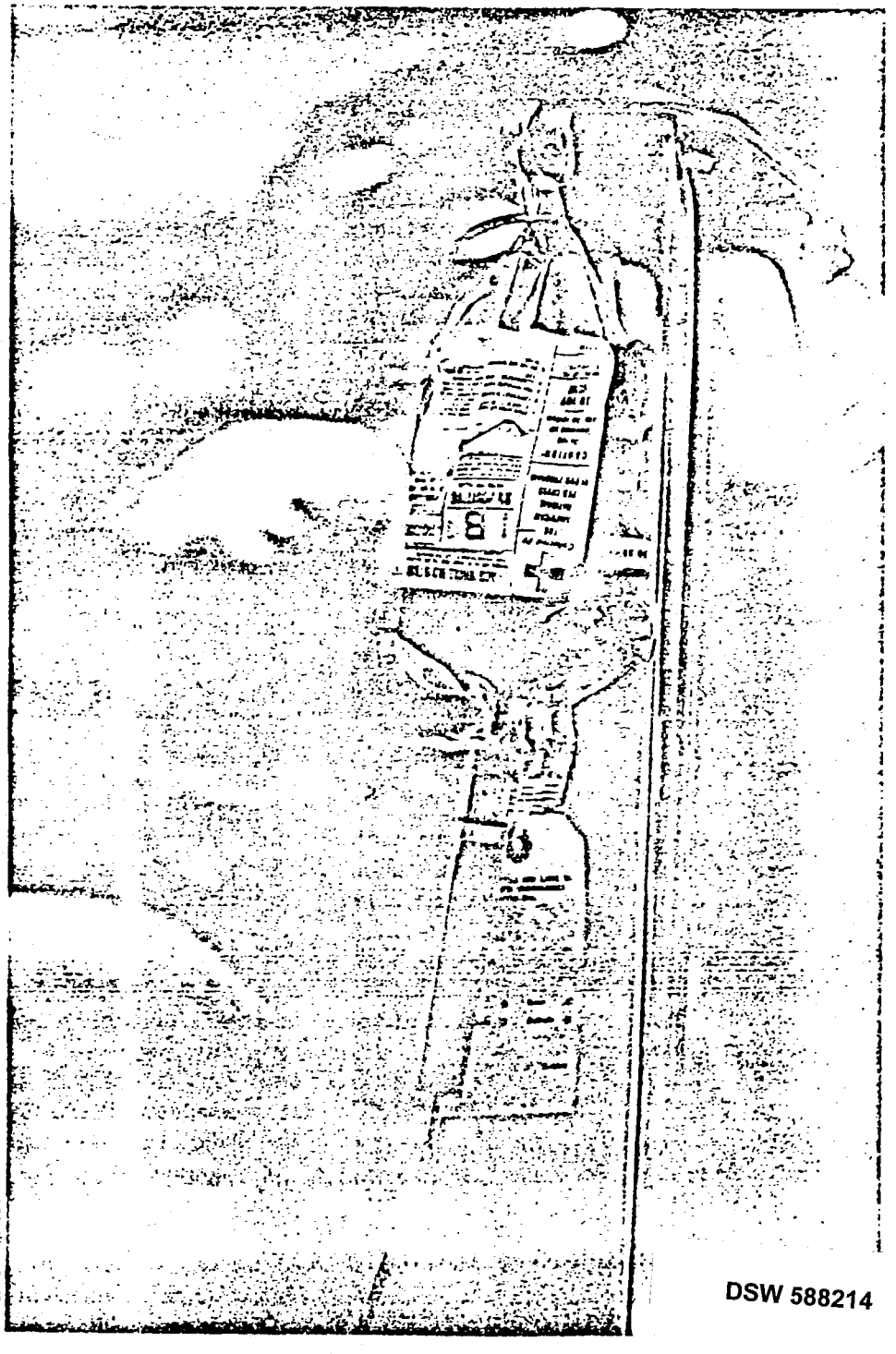
DSW 588213

STLCOPCB4093549

SMELL

an average-size man needing a total transfusion of 14 pints (not uncommon in the treatment of severe hemorrhage) could receive intravenously as much as 350 milligrams of a plasticizer at one time.

The significance of the appearance of plasticizers in materials used in medical practice is not clear, but Dr. Rubin has speculated that there may be an association between the contaminants and a sometimes fatal syndrome known as shock-lung, a congestive lung disease. This condition has been observed after patients have been transfused with large volumes of blood, and Dr. Rubin is concerned that the documented increase in the occurrence of shock-lung in the past few years[3] may in some way be related to the use of polyvinyl bags. Dr. Jaeger and Dr. Rubin

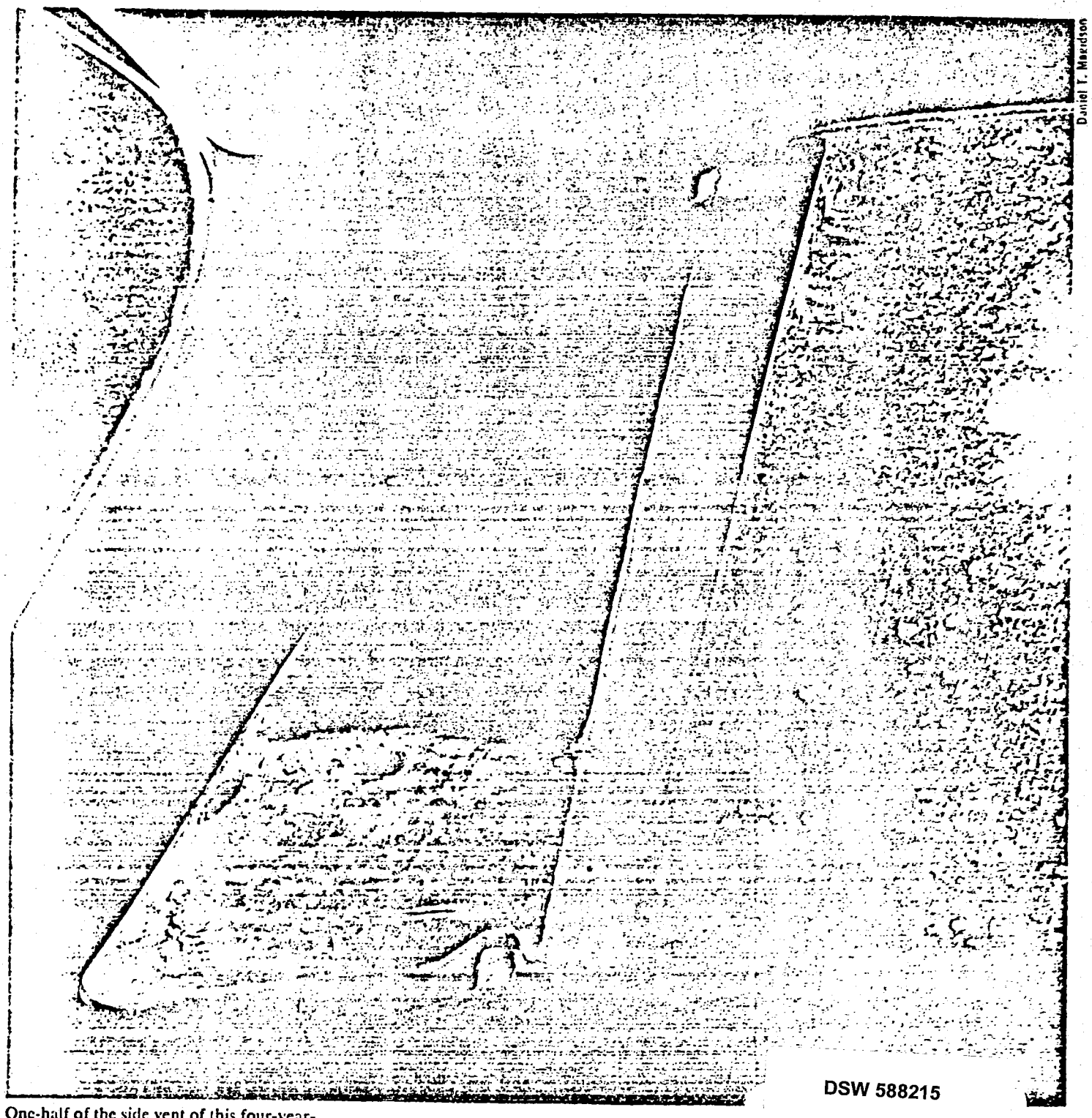


Daniel T. Manirison

DSW 588214

...vinyl chloride bags such as this one are now widely used to store whole human blood. It has been demonstrated that as much as one-quarter of a milligram of phthalate plasticizer can leach into the blood during each day of storage. Blood can be stored up to twenty-one days in such bags.

STLCOPCB4093550



One-half of the side vent of this four-year-old car has been cleaned to show the deposit of plasticizers on the inside.

have accumulated preliminary evidence that some migration of DEHP is correlated with the clumping of blood platelets into small clusters. This phenomenon may then contribute to the congestive condition which is characteristic of shock-lung. Further evidence suggesting this relationship is that tissue samples from patients that had received transfusions at Johns Hopkins Hospital showed residues of DEHP in spleen, liver, lung, and abdominal fat ranging from 0.025 milligram per gram (25 parts per million of dry weight) in the spleen to 0.270 milligram per gram (270 parts per million) in abdominal fat.[2] DEHP was found most frequently in lung tissue. The Johns Hopkins investigators considered

STLCOPCB4093551

this to be of special significance to their hypothesis concerning the role of plasticizers in shock-lung.

Experimental Effects

The fact that polyvinyl plastics can affect living tissue has been known for some time. In another group of experiments[4] conducted in 1964, 48 prepackaged medical administration units, mostly of the polyvinyl material type, were tested for toxicity by injecting tiny slivers of the plastic into the muscle tissue of rabbits, rats, and mice. A toxic reaction was indicated when a zone of white flesh formed around the slivers. The control (substance used for comparison) for these experiments was a vinyl material that had previously been studied and did not show the tissue reaction. Of the 48 devices tested (catheters and tubing of various kinds), 25 showed a definite toxic reaction. The researchers conducting this experiment were unable to obtain from the manufacturers of the devices the formulations used in their production, so they were not able to say precisely what the toxic agents were. However, they did state that they were probably something other than plasticizers.

In another incident,[5] a group of Danish physicians using kidney machines had been treating 27 patients for chronic kidney failure from 1966 to 1970. Because of a planned remodeling of the laboratory, the team of doctors began testing some new kidney machines. From late September 1969 to early February 1970 the new equipment was used for a total of 93 treatments; three patients received a total of 75 of the treatments. One patient was treated 33 times and the other two 24 and 18, respectively. After only a few treatments each of the three patients complained of nausea and abdominal pains, and showed an unusually high blood concentration of liver enzymes. Liver biopsy showed one patient to have liver changes similar to those which occur in viral hepatitis. As the treatments increased, so did the severity of the symptoms. However, in each case, when the patients were changed back to the normal equipment, all symptoms disappeared. The physicians then found that the polyvinyl chloride plastic tubing used in the new equipment was leaching 10 to 20 milligrams of the plasticizer diethyl phthalate into every liter of the dialysis fluid. The plasticizer was not found in the fluids when the old equipment was used. The authors state emphatically that despite this rather convincing clinical evidence, they have not shown a cause-and-effect relationship between the hepatitis symptoms and the plasticizer. They do, however, plan to continue both chemical and toxicological investigations in order to determine more precisely the nature of their clinical observations.

Polyvinyl chloride plastics, like many other plastics, are a mixture of a number of materials, each lending to the final product a specific quality. The basic material is the resin or monomer, a chemical compound of relatively simple structure. The monomers are joined together at their ends to form long chains, or polymers. A number of materials can then be added: plasticizers to give the material pliability, stabilizers to protect the polymers from the degrading effect of ultraviolet light, and dyes to give the material color.

Phthalate ester plasticizers have been found in aquatic ecosystems, and may be stored in fish tissues and concentrated in food chains.

Of the plasticizing compounds, phthalates are among the most widely used in the production of plastic materials. Figures for 1968[6] show the total production of at least 10 different phthalate compounds to be 714,728,000 pounds. This is not total production, however, as information about many phthalate compounds is classified as proprietary information by producers and therefore the substances are not identified. These account for another 125,400,000 pounds. As stated above, phthalates are incorporated into polyvinyl plastics to give the end product its desired pliability. Oddly, however, the plasticizer is not combined chemically with the polymer resin, but simply acts to "lubricate" the polymer molecules in such a way as to allow them to be flexible. The plasticizer materials can sometimes account for as much as 50 percent of the entire weight of a plastic product. Because they do not actually combine chemically with the resin, they are able to migrate out of the plastic, either into the atmosphere or into a liquid such as blood in blood bags.

Toxic Properties

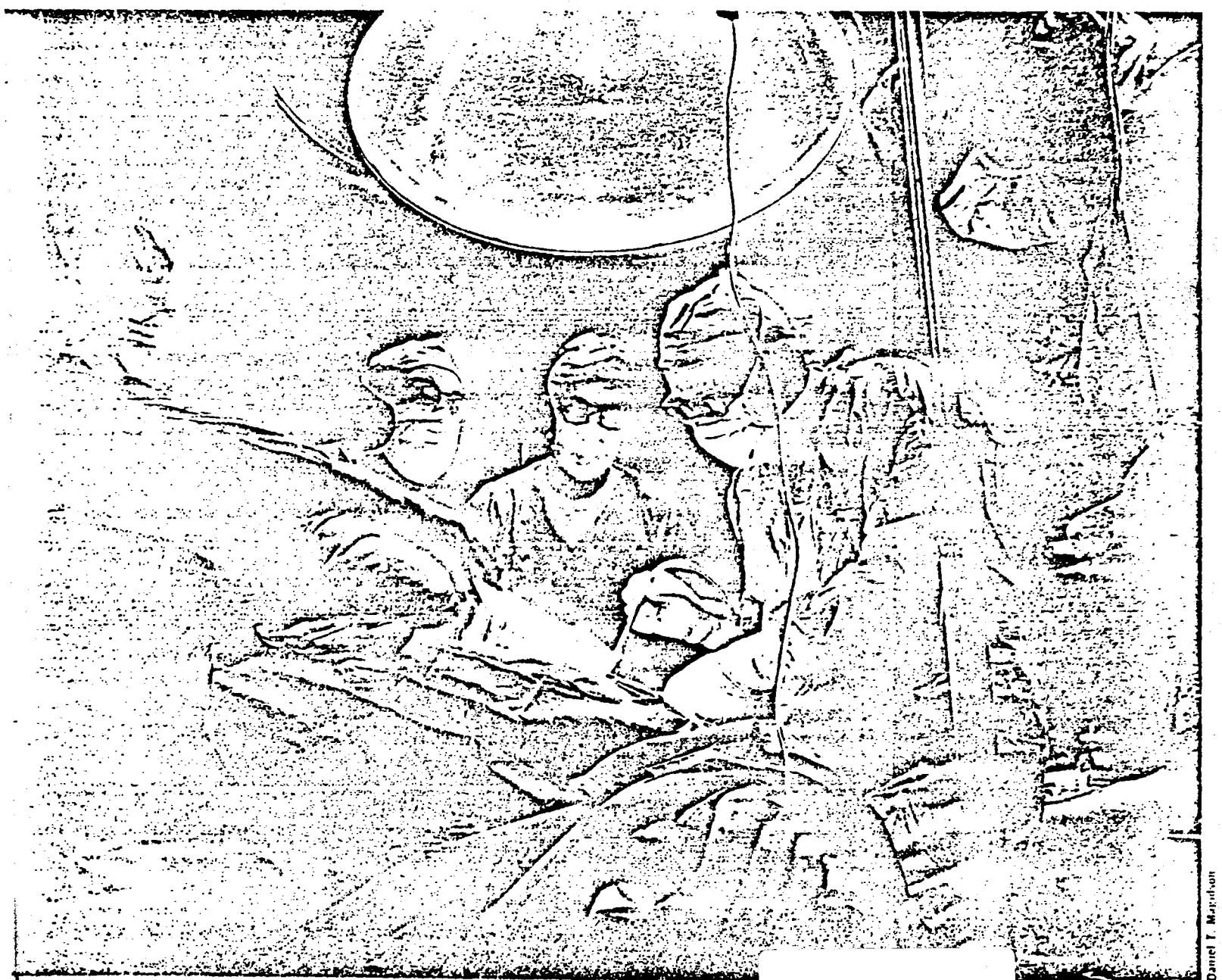
The phthalate plasticizers have generally been considered to be of very low toxicity, at least when administered orally or by injection and only when observations related to acute poisoning were investigated. Of eight phthalates examined in one study,[7] the LD_{50} (the lethal dose for 50 percent of an experimental population) when injected into the peritoneum (the membranous lining of the body cavity) ranged from 1.58 grams per kilogram of mouse body weight to 14.19 grams per kilogram (these are very low orders of toxicity). In the same study, however, some observations were made on more sensitive sub-acute symptoms of toxicity.

A test was conducted to determine whether or not phthalates had an effect on the central nervous system (CNS), either in depressing or stimulating activity. Mice were injected with 500 milligrams per kilogram of body weight of various phthalates and, after an interval of thirty minutes, were given an injection of 60 milligrams per kilogram of body weight of sodium hexobarbitol. After the injections, sleeping time for the treated animals was compared with that of a control group given only sodium hexobarbitol. From the results it appears that two of the phthalate compounds stimulated the central nervous system,

DSW 588216

STLCOPCB4093552

It is not unusual after a severe accident followed by major surgery for a patient to require as many as fourteen pints of blood. Under such conditions as much as 350 milligrams of plasticizer can be injected directly into the body as the result of storing whole blood in polyvinyl chloride blood bags.



Daniel F. Marshall

DSW 588217

STLCOPCB4093553

Phthalate plasticizers have the potential effect of causing deformities in developing chick embryos.

in that sleeping time was significantly shortened. The other six compounds depressed the CNS and lengthened sleeping time, one by as much as two times. The fact that the lengthening or shortening of sleeping time was due to an effect on the CNS was borne out by electroencephalographic tracings recorded after the administration of the drugs. When relatively high doses were used, other toxic effects noted in this study were lowered blood pressure and increased respiratory rate in rabbits, cell death on cultured mouse fibroblast cells when exposed to 0.05 milligram of a 50 milliliters emulsion, and a slight retardation of growth in mice.

A factor complicating the use of plasticizers in plastics used for medical purposes was discussed in another research paper published in 1967.[8] The authors found that upon careful analysis of a commercially prepared medical-grade plasticizer [di(2-ethylhexyl) phthalate], the material found in blood bags at Johns Hopkins, there were actually several related chemicals present. The contaminating chemicals were thought to be closely related compounds (homologues) of a chemical structure slightly different from the plasticizer that became incorporated into the product during the production process. Among other things, the authors synthesized the same homologues and tested them for toxicity. Most of the homologues were about as toxic as their plasticizing relatives. Special note was made of the fact that specially synthesized pure di-n-decyl phthalate was not toxic, while a commercial preparation was extremely toxic to mice. In conclusion, the authors stated that:

> A pure plasticizer may have no demonstrable toxic response, but the presence of related homologues and isomers could add toxic potential to the plasticizer. To this possibility one must also include potential toxic effects from degradation products present or forming in the plasticizer during manufacture of a plastic device, or occurring after the device had been stored under various conditions for undetermined amounts of time.

The most recently studied effect of phthalate plasticizers on biological systems was their potential for causing deformities in developing chick and rat embryos.[9] In an experiment done in 1970, eight different phthalate compounds were tested by innoculating developing chicken eggs with levels ranging from 0.025 milliliter to 0.1 milliliter of the various materials on the third day of incubation. All of the materials caused some mortality in the developing embryos, some as high as 92 percent, but only one of them (dibutoxyethyl phthalate) clearly caused abnormal embryos. At the 0.1 milliliter dose, only 43 of 118 innoculated embryos hatched, and of these 4 had clearly defined abnormalities. At half that dose (0.05 milliliter) 41 of 82 innoculated embryos hatched with two having the same deformities as occurred at the higher dose.

Neurological effects were also observed with the dibutoxyethyl phthalate-treated embyros. Ten of the 43 hatchlings given the higher dose (0.1 milliliter), although showing no signs of severe abnormality, were unable to stand and exhibited nonpurposeful and unpredictable body movement. At the lower dose four chicks were affected in this way. Four other phthalates produced this effect in surviving hatchlings without producing abnormal development.

The authors point out that in the chick embryo the nervous system undergoes rapid development between the sixtieth and seventy-second hours of growth, and that it is possible that some cells in the nervous system may be especially vulnerable to the toxic effects of phthalates during that period. None of the 185 birds that hatched in the three control groups showed either neurological symptoms or abnormal development.

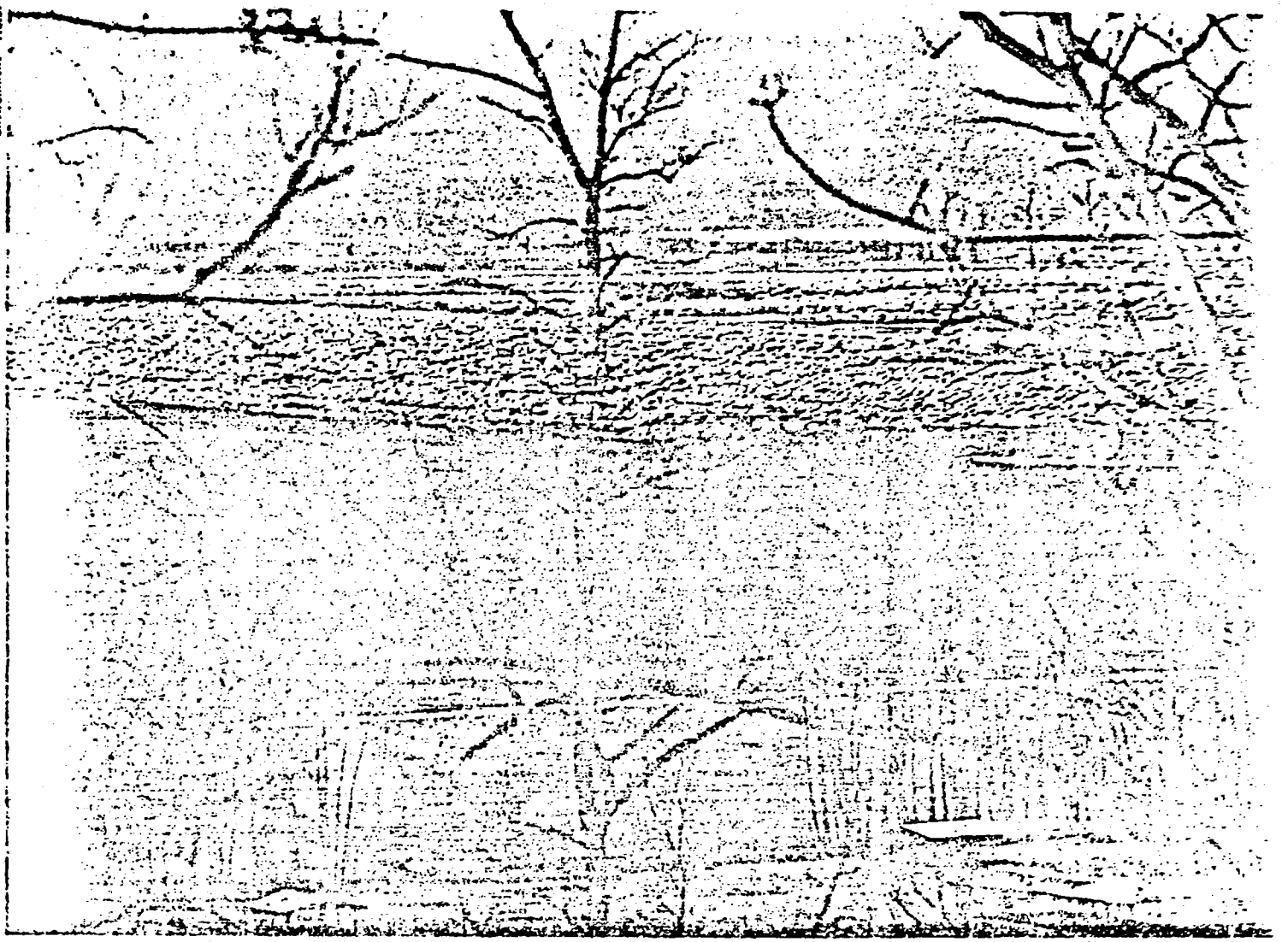
At the Tenth Annual Meeting of the Society of Toxicology held on March 7 to 11, 1971, in Washington, D.C., A. R. Singh and his colleagues described an experiment in which they found rat fetuses to be susceptible to the teratogenic (capable of causing deformities) effects of phthalates when their mothers were fed amounts ranging from one-tenth to one-third of the orally toxic dose. Commonly observed abnormalities were absence of tail, absence of eyes, and twisted hind legs. In some cases, the fetuses died and most of the phthalate-treated fetuses that survived were smaller than those born to mothers who had not been fed the chemical.

In both experiments the numbers of test animals was

There may be an association between plasticizers which have migrated from polyvinyl chloride blood bags into the human blood stored in them and a sometimes fatal syndrome known as shock-lung, a congestive lung disease.

DSW 588218

STLCOPCB4093554



Acres of new cars are parked outside an assembly plant before distribution.

admittedly small, but the apparent dose-response relationship and the specific nature of the abnormalities is ample reason for further investigation.

Stabilizer Problem

DSW 588219

While the phthalate plasticizers have been shown to possess toxic properties, other additives in PVC plastics may be more toxic but are present in less abundance. Stabilizers, the compounds which protect the plastic from the degrading effect of ultraviolet light, usually comprise about 1 to 3 percent of the plastic material by weight. When the plasticizers migrate from the plastic, they are likely to carry with them some of the stabilizing compounds. The most toxic of the stabilizers are organic compounds of tin, cadmium, zinc, and barium. The most widely used of these compounds are the organotins. Unfortunately, they are also among the most toxic. Of eleven organotin compounds evaluated for toxicity in one study,[10] all were highly toxic. Even though this toxicity is widely known, organotin stabilizers are still used in plastics for medical use such as catheters and tracheostomy tubes (tubes inserted into the trachea to aid breathing during blockage of the upper respiratory tract).[10]

Cadmium is another widely used stabilizer that is quite toxic (see "Building a Shorter Life," *Environment*, September 1971). It is also used as a pigment to color plastics. The total cadmium metal content used in the manufacture of plastics in 1968 amounted to 3.8 million pounds.[11] Figures for organotin compounds are not available, but the amounts used must be greater than that of cadmium compounds because of the wider use of organotin. Probably because the Food and Drug Administration does not allow cadmium and tin compounds to be used in food wrapping, neither of these stabilizer groups has undergone thorough toxicological evaluations. At this time the Food and Drug Administration has no regulatory authority over medical uses of plastics.

Although toxicological literature is surprisingly meager on the sublethal effects of both plasticizers and stabilizers, the sources leading to human exposure are many and increasing yearly. It is difficult to pass a single hour without coming into contact with objects from which both plasticizers and stabilizers might escape into the air. They are used in clear bottles, medical tubing, shoe soles, clear vinyl packaging films for foods, flexible tubing, garden

STLCOPCB4093555

hose, hi-fi and stereo records, house siding, pipe, wall covering, flooring, furniture, upholstery, and automobile interiors, to name just a few.

Auto interiors are of special interest as it is here that one is likely to encounter the highest atmospheric concentrations. Dashboard coverings, side-panels, interior roof lining, and seats are all sources of both stabilizing and plasticizing compounds. The new-car smell is largely the result of the release of plasticizers into the air in vapor form as is the thin film of sticky material deposited on the inside of auto windshields. *Environment* contacted the Ford Motor Company to determine if any measurements of atmospheric concentrations of plasticizers or stabilizers had been made in new cars. We were informed that no measurements had been made, but that the company was aware of windshield fogging and had made some adjustments in the formulation of their vinyls used for interiors in order to alleviate the fogging problem.

Clouding Space

The ability of plasticizers to migrate out of plastics and into the atmosphere has caused some exotic problems for scientists. The National Aeronautics and Space Administration has banned the use of PVCs in space capsules and space research because the plasticizers leave the plastic material and condense on extremely sensitive optical equipment. Because they absorb heavily in the ultraviolet light range, the plasticizers can distort sensitive optical measurements.[12] Another scientist found them contaminating very pure chemicals in a brand new laboratory[13] set up to study organic chemicals in sea water. After a great deal of detective work he found that they were used in a new air-filtering system designed to clean the air before it entered the laboratory. Such is the ubiquitous nature of materials emanating from "inert" PVC plastics.

Finally, a short announcement by the United States Bureau of Sport Fish and Wildlife in Columbia, Missouri, adds another dimension to the problem of wandering plasticizers.[14] On June 29 it was announced that the Fish-Pesticide Research Laboratory had confirmed the widespread occurrence of phthalate ester plasticizers in aquatic ecosystems. The compounds, identified in various species of fish, were di-n-buty and di-2-ethylhexyl phthalate. The concentrations ranged from 0.2 to 3.2 parts per million. The biological significance, according to the bureau, is unknown. What is clear is that at least two of the many plasticizers used in PVCs are apparently quite stable, are stored in fish tissue, and are probably concentrated in food chains. These facts may or may not be of ecological importance, but, again, they surely warrant further investigation.

Ecological systems, including man, are continually being bombarded with an enormous variety of synthetic chemicals. We now recognize that some have caused serious ecological damage and that some are of no consequence. An even larger group are those we cannot judge, simply because we know so little about them. The phthalate plasticizers probably fall into this group. To investigate them individually is a long and arduous job, and to investigate them in combination with the many other compounds in our synthetic chemical environment for synergistic or potentiation effects is seemingly impossible. However, given their ubiquitous distribution, the volumes in which they are used, their biological activity, and the apparent stability of at least two, the phthalate plasticizers demand serious study. □

The National Aeronautics and Space administration has banned the use of polyvinyl chloride plastics in space capsules and space research because the plasticizers leave the plastic material and condense on extremely sensitive optical equipment.

NOTES

1. Jaeger, R. J. and R. J. Rubin, "Plasticizers from Plastic Devices: Extraction, Metabolism and Accumulation by Biological Systems," *Science*, 170(3956):460-461, 1970.

2. Jaeger, R. J. and R. J. Rubin, *Lancet*, 2:151, 1970.

3. "Medical Staff Conference—Shock-Lung," *California Medicine*, 112(2):43-50, February 1970.

4. Lawrence, W. H. et al., "Toxicity of Plastics Used in Medical Practice," *Journal of Pharm. Science*, 52(10): 958-963, 1963.

5. Neerguard, J., et al., "Observations on Plasticizers in PVC and the Occurrence of Hepatitis in a Haemodialysis Unit," *Scandinavian Journal of Urology and Nephrology*, 5:141-145, 1971.

6. *Synthetic Organic Chemicals, U.S. Sales and Production*, U.S. Tariff Commission Publication No. 327, 1968, p. 166.

7. Calley, David, et al., "Toxicology of a Series of Phthalate Esters," *Journal of Pharm. Science*, 55:158-162, 1966.

8. Nematollchi, Jay, et al., "Plasticizers in Medical Application I. Analysis and Toxicity Evaluation of Dialkyl Benzene-dicarboxylates," *Journal of Pharm. Science*, 56(11):1446-1453, 1967.

9. Bower, R. K., et al., "Teratogenic Effects in the Chick Embryo Caused by Esters of Phthalic Acid," *Journal of Pharm. and Exp. Thera.*, 171(2):314-324, 1970.

10. Guess, W. L. and Sol Haberman, "Toxicity Profiles of Vinyl and Polyolefinic Plastics and Their Additives," *Journal Biomed. Materials Research*, 2:313-335, 1968.

11. *Report: National Inventory of Sources of Cadmium, Nickel, and Asbestos, 1968*, for National Air Pollution Control Administration, Department of HEW. Cadmium, Section 1. Contract No. CPA 22-69-131.

12. Personal communication, Mr. Fred Gross, NASA.

13. Blumer, Max, "A Contamination of a Laboratory Building by Air Filters," *Contamination Control*, 4:13, 1965.

14. Press release, U.S. Bureau of Sport Fisheries and Wildlife, Columbia, Mo., June 29, 1971.

DSW 588220

STLCOPCB4093556