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ON THE HORNS OF THE VINYL CHLORIDE DILEMMA

by Paul H. Weaver

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If government allows workers to be exposed to the gas, some of them may die. If it eliminates all exposure, a valuable industry may disappear.

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Not long ago, cancer and plastic were associated with each other only in the writings of Norman Mailer, where they serve as symbols of decadence and self-destructiveness in the high-technology society. Since January of this year a series of medical reports has shown this association to be a real scientific fact as well. It is now clear that vinyl chloride, a gas from which the second most widely used U.S. plastic is made, causes a fatal cancer of blood-vessel cells in the liver; the gas is also implicated in a host of additional diseases, ranging from gastrointestinal bleeding to chromosome damage.

These discoveries have touched off a flurry of regulatory activity. The Food and Drug Administration, the Environmental Protection Agency, and the Consumer Product Safety Commission have all banned aerosol sprays using vinyl chloride as a propellant. But the measure that cuts deepest was taken by the Occupational Safety and Health Administration. OSHA has moved to reduce the permissible level of worker exposure to vinyl chloride in the plants where it is made or converted into plastic.

Preparing for the iceberg

In the course of these developments, it has become clear that our regulators have a hard time thinking sensibly about problems like vinyl chloride. The businessmen being regulated and the workers affected seem to find it no easier. The fact is that our society seems to have no agreed-upon standards for dealing with situations in which medical and economic considerations collide head-on. Since collisions of this sort will plainly be numerous in the years ahead—the vinyl chloride case is widely identified as the tip of an enormous regulatory iceberg—it seems useful to get clear on the issues involved.

If vinyl chloride were an unimportant substance, or if it were known to be dangerous only in very high concen-

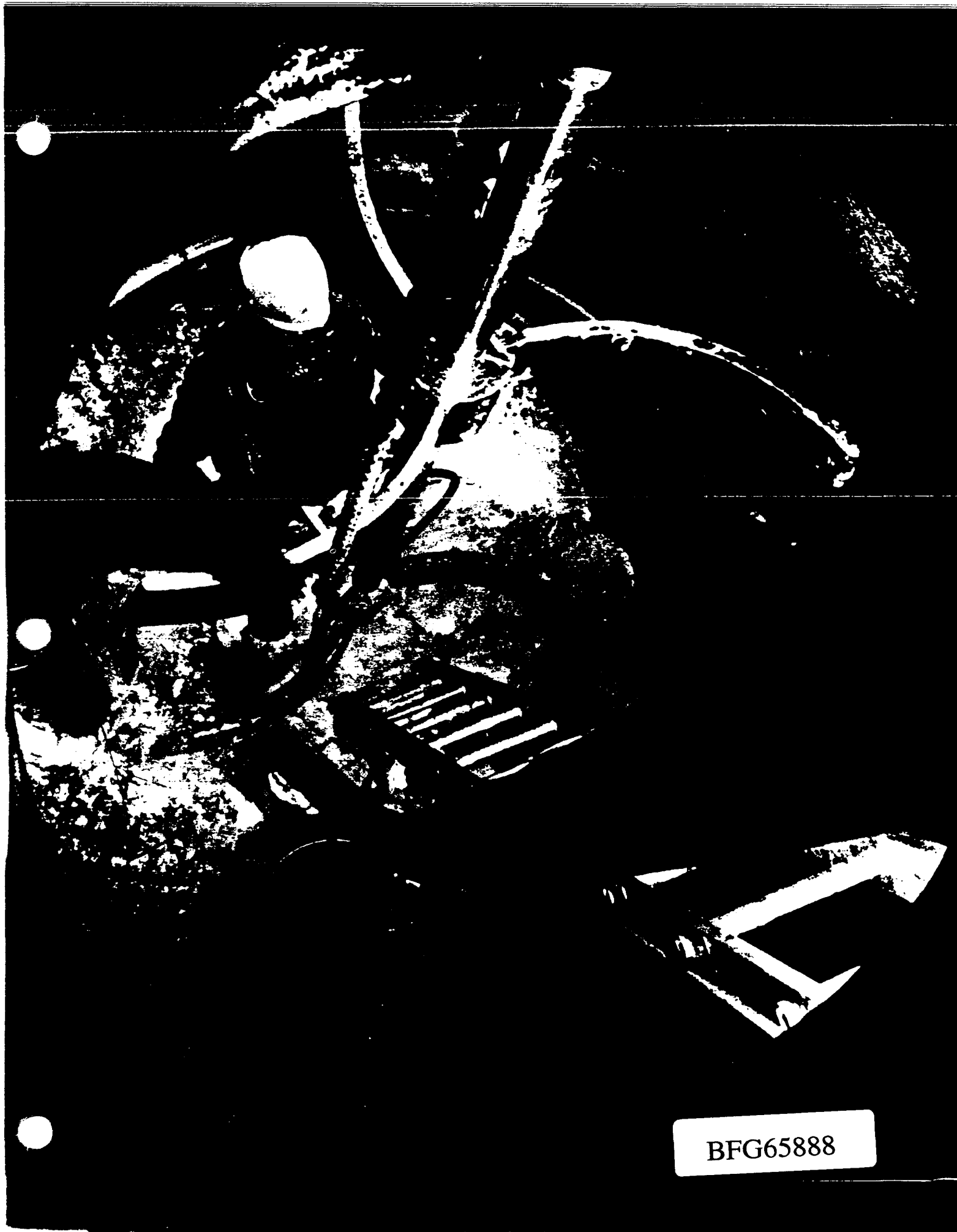
trations, or if it were easy to keep human beings out of contact with it, there would be no particular problem. In that case the health danger could be completely eliminated at little or no cost, and the question of what to do would answer itself.

Unfortunately, the vinyl chloride issue isn't so simple. It seems to be very difficult and costly—and it may be impossible—to guarantee that no vinyl chloride worker will be exposed to the gas. Though no one knows for sure, it is possible that even very small exposures may cause sickness or death. Yet it is also true that the plastics made from vinyl chloride are extremely important to the American economy. The market value of the gas being produced this year, and of the resin made from it, is perhaps \$1.5 billion; the gas and resin industries together employ about 6,000 workers. But what most people think of as the "plastics industry"—the transformation of resins into products—is a far larger operation. The total number of jobs involved in polyvinyl chloride (PVC) alone is about 320,000; the sales volume runs to many billions. And there are no entirely satisfactory substitutes for PVC at hand. Banning it would be certain to cause grave economic dislocations.

Thus the regulators at OSHA are caught between the proverbial rock and a hard place. It is clear that their task should be to find the right "trade-offs"—to devise regulations in which the benefit of increased health for

The most hazardous job in polyvinyl chloride plants used to be the cleaning of the vats in which vinyl chloride polymerized into PVC—that whitish resin at the worker's feet. Of the sixteen known cases of vinyl-chloride-related liver cancer, fourteen occurred in cleaners. The job is presumably a lot less hazardous since the introduction of the respirators, protective clothing, and air evacuation (conducted by the dangling hose) that are shown here. The stainless-steel vat shown is in B.F. Goodrich's Pedricktown, New Jersey, plant, perhaps the most modern in the U.S. The vat is entered and cleaned manually only once a month. Until recently vats in most older plants were cleaned once or twice a day.

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The View from NIOSH: Make It Safe

On January 22, 1974, Dr. Maurice Johnson, environmental health director for B. F. Goodrich, called on Marcus Key, director of the National Institute of Occupational Safety and Health. Johnson had a discovery to report. Three workers in Goodrich's Louisville polyvinyl chloride plant had died from angiosarcoma of the liver since 1971. Key summoned his top aides, who agreed that they had an emergency on their hands. Two days later a small army led by NIOSH Standards Development chief Vernon Rose, invaded the Louisville plant to conduct the first of many "walk-through" inspections.

Within a week, Rose's task force had a list of recommendations for reducing worker exposure to vinyl chloride:

- protective coveralls, shoes, and gloves for workers exposed to PVC.
- airtight suits and respirators for reactor cleaners.
- daily showers for exposed workers.
- a 50 parts per million suggested ceiling on vinyl chloride monomer exposure.

Normally, writing a criteria document—NIOSHese for a recommended standard—is an eighteen-month process involving exhaustive study. In this instance, however, Rose relied on guesswork and precedent. Assuming that vinyl chloride causes cancer through inhalation and skin contact, he modeled his standards on those used earlier by NIOSH for industrial carcinogens.

Aiming for a mid-March deadline, NIOSH organized a hectic series of meetings and studies. By the end of February, its toxicology group had been unable to determine the carcinogenicity of VCM below 50 ppm. The medical group had suggested a battery of liver tests for PVC workers,

but industry and labor had split over the exposure ceiling. Industry urged 50 ppm, which it knew it could achieve; labor advocated "no detectable level," refusing to treat workers as guinea pigs.

In this situation, Rose simply toughened and expanded on his earlier recommendations. Most important, he decided that the ceiling for vinyl chloride be set at "no detectable level"—the only exposure he knew to be safe. "It is doubtful," he conceded in a memo to Key, "that *any* plant can show workroom levels of non-detected." To meet it, respirators would have to be worn at all times. He wasn't sure this was practical, but he was certain it was safe.

On March 11, Dr. Key submitted NIOSH's recommendation to Assistant Labor Secretary John Stender. When OSHA proposed its permanent standard two months later, it incorporated most of the NIOSH text verbatim, including the "no detectable level" provision.

The View from Firestone: Make It Practical

To Todd C. Walker, the towering, outspoken president of Firestone Plastics, OSHA's proposed standard was as much a crisis as the Goodrich bombshell had been to NIOSH. He was determined to resist the standard with "the maximum information" at the OSHA hearings in Washington, D.C., this summer.

Walker assembled four task forces—legal, engineering, financial, and medical—to develop a Firestone-recommended standard on a crash basis. Four alternatives were to be studied: the interim 50-ppm standard, "non-detectable," and two intermediate levels chosen arbitrarily—40 ppm maximum with a time-weighted average (TWA) of 25 ppm, and a 15-ppm ceiling with a TWA of 10 ppm. For each level the questions were: is it safe and is it feasible?

Weeks later, the medical group was unable to say positively that any of the levels was unsafe. An epidemiological study of Firestone's rubber and PVC workers showed no significant differences, suggesting that 50 ppm was not relatively unsafe.

The engineering group reported that the nondetectable level was unattainable. It also forwarded a critique of OSHA's proposed work practices. Protective clothing for all workers was unnecessary, it said, because PVC dust is not a carcinogen. VCM gas, which is, could be kept away from the skin only by air-tight suits, which would be "hot, cumbersome, expensive, and dangerous." OSHA's provision for air-supplied respirators for all exposed workers was also ill advised. These would be uncomfortable ("an instrument of torture"), fatiguing, probably hazardous, and would interfere with work. One portable type weighs twenty-eight pounds and would have to be changed three times an hour. Nonportable respirators could be

used, but workers would be attached to air hoses (themselves a workplace hazard) and confined to a radius of less than fifty feet.

The financial group reported that capital investment would have to double to attempt reaching a nondetectable level. The legal staff concluded that OSHA's proposed standard was unfeasible and therefore illegal.

When it came to deciding what level he *would* recommend, Walker had a problem. His medical evidence showed the three levels above nondetectable to be equally safe. His engineers said that the feasibility of the lowest of these (15-ppm ceiling with a 10-ppm TWA) was uncertain, and Walker ruled it out. Left with a choice between the two higher levels, he opted for the 40-ppm ceiling with a 25-ppm TWA to show that Firestone was willing to do more than the minimum. Thus, with a practicality reminiscent of NIOSH's decision to recommend a level it *knew* was safe, Firestone ended up recommending a level it *knew* it could achieve.

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workers is balanced against the increased cost to the plastics industry and society as a whole. Unfortunately, this task has remained largely unacknowledged.

OSHA probably will end up compromising on the degree of exposure to the gas it will allow; its decision is apt to be announced this month. But the agency has been under terrific pressure to view the issue before it in absolutist terms, as if its only legitimate concern were the preservation of absolute security for the vinyl plastics industry, or the achievement of perfect safety for vinyl chloride workers.

For a while, it seemed a foregone conclusion that OSHA itself would opt for perfect safety. On May 10, it formally proposed that the new standard for vinyl chloride be set at "no detectable level," i.e., that no plant would be allowed to operate so long as any of the gas could be found in the air or in contact with workers. The industry replied, in effect, that any such standard would be technically impossible and economically disastrous, and that if OSHA went through with it, the polyvinyl chloride industry would be put out of business.

OSHA's final decision will affect more than this single industry and its customers. The vinyl chloride issue may be viewed as the first major test case for a new movement in government regulation. The leaders of the movement are three of the newest federal regulatory agencies, all created since 1970: EPA, CPSC, and OSHA. One general idea behind all of these agencies is that business can no longer promiscuously pass on to society all the indirect costs of running a modern economy. As Sheldon W. Samuels, health director of the Industrial Union Department of the A.F.L.-C.I.O., put it, "The free ride on social costs is at an end. In the plastics industry you're seeing a manifestation of social costs."

With jurisdiction over virtually every product and substance, these agencies, together with the FDA, are beginning to use their sweeping powers to reduce the public's risk of chronic disease, especially from industrial products. Some of the agencies are subjecting new substances to rigorous pretesting before they are allowed onto the market. And with the vinyl chloride case, they have tackled the first of a long list of basic substances on which our industrial economy is already built.

It could put you to sleep

During the first decades of its commercial existence, vinyl chloride seemed a most unlikely candidate for the role of heavy in a historic regulatory drama. Put into full-scale U.S. production in 1939, polyvinyl chloride was hailed as a "miracle" material: cheap, stable, fire-resistant, and able to assume an extraordinary range of soft and hard forms. Its major applications now include coated fabrics (like those used in automobile seat covers), wire insulation, floor tiling, pipe and conduit, phonograph records, and medical supplies, e.g., blood-storage bags.

In the beginning the vinyl chloride gas seemed to be

virtually harmless. The only apparent dangers were of explosion (at concentrations beginning around 36,000 parts per million) and narcosis. In fact, during the 1940's the gas was tried out as a medical anesthetic, but doctors abandoned it when it was found to cause heart arrhythmia. With low prices providing little incentive for conservation, producers paid no particular attention to workplace exposure levels so long as they were safely below the point of fire and explosion.

And yet exposure levels in plants producing the gas itself were probably not very high even in the early years. Vinyl chloride is synthesized from chlorine and petrochemical feedstocks (usually ethylene) in a continuous closed process. The plants, which resemble oil refineries (and in some cases are attached to them), are open to the air. Historically, the heavy exposures have occurred in the plants where vinyl chloride is polymerized into PVC, the whitish powdery resin from which actual plastics are made.

It could make you "high"

Polymerization is a batch process: vinyl chloride monomer (VCM) and other substances are put into a pressurized vat, heat is applied, and hours later, when polymerization is completed, the vat is emptied, opened, and cleaned for the next batch. The process is full of leaks. In most of the early plants the gas could be smelled almost constantly (VCM has a faintly sweet odor that seems to be detectable at concentrations above 2,000 parts per million), and workers occasionally got "high" from the fumes. It is widely agreed that in this early period, lasting into the 1950's, exposures of several thousand ppm were common.

During the 1950's, as the vinyl industry grew, a trickle of little-noted and often inconclusive medical reports began to raise doubts about the monomer's presumed harmlessness. In 1949 a Russian group found a hepatitis-like condition in more than one-fourth of seventy-three PVC workers examined, and over the next ten years European researchers encountered other symptoms: skin lesions, a circulatory disorder, gastritis, and dermatitis, to name a few. By the mid-1960's these had been confirmed and were described collectively as "vinyl chloride disease." Later in the 1960's, acroosteolysis, a disease involving a degeneration of the finger bones, was identified among workers who clean polymerization vats.

As these findings accumulated, producers began to reduce exposure levels. In 1961 the American Conference of Governmental Industrial Hygienists, a voluntary standards-setting organization, had put the maximum safe exposure at 500 ppm. During the 1960's industry began working to get much lower than that, and by the early 1970's exposure levels were generally in the 100-to-200-ppm range, with short-term "excursions" to levels many times higher.

In this general downward movement, Dow Chemical

was far and away the leader. In 1961 it had conducted an animal experiment showing liver effects at levels as low as 100 ppm and had decided to get its own plants below 50 ppm. By the early 1970's, Dow had achieved average exposures in the neighborhood of 25 ppm in its copolymer plants (one of which produces resins for Saran Wrap).

In 1970, Dr. Pierluigi Viola, an Italian physician studying acroosteolysis for Solvay, a major European PVC producer, reported an unexpected discovery. After twelve months' exposure at 30,000 ppm, many of his experimental rats had developed cancers. Doubts about Viola's procedures led Montedison and other European producers to commission Dr. Cesare Maltoni to undertake a large-scale animal experiment to see if this carcinogenic effect could be replicated at lower exposure levels. By the end of 1973 Maltoni's well-executed study had shown that levels of VCM as low as 250 ppm induced a variety of cancers in rats, including angiosarcomas of the liver. In June, 1974, he reported angiosarcomas at 50 ppm.

American producers began to join the inquiry into vinyl chloride and cancer in 1973. Early that year the Manufacturing Chemists Association decided to commission two massive studies. One was an animal study somewhat like Maltoni's (it has since confirmed his findings). The other was an epidemiological analysis of the morbidity and mortality history of American vinyl workers.

In December, Dr. John L. Creech, a Louisville, Kentucky, surgeon who is plant physician for B.F. Goodrich's massive PVC installation there, received a report that one of the workers had died of angiosarcoma of the liver. Remembering that another worker had died of the same disease two years earlier, he notified a superior. In mid-January, 1974, while a systematic mortality study of Goodrich workers was being organized, Creech received a report of a third angiosarcoma death. On January 22, B.F. Goodrich announced the three deaths and their cause. To date, a total of eight persons employed at the Louisville plant have been found to have contracted this disease.

They blew the whistle themselves

As of January, 1974, literally all the information linking vinyl chloride to cancer had been developed by the industry on its own initiative. As Ralph L. Harding Jr., president of the Society of the Plastics Industry, observed, "This is a unique situation. Industry financed the studies, and industry blew the whistle on itself."

But this was quickly forgotten in the furor that arose during the weeks following B.F. Goodrich's announcement. Within days, regulators, public-health doctors, and union officials had begun to dominate public discussion of the vinyl problem. Within weeks, the Louisville *Times* initiated a series of stories alleging that industry had engineered a Watergate-style cover-up of the angiosarcoma discovery, which it abandoned only when it saw that the information was about to leak anyway. This

charge was symbolic of the manner in which the initiative passed out of the hands of industry.

It was seized, rapidly, by a loose but not uncoordinated network of regulatory agencies, government research institutes, academic medical teams, labor unions, and other groups united by a common commitment to eradicate environmental causes of disease. This "regulatory-medical complex" is largely the creation of a decade's federal legislation in the medical and environmental fields. Its unofficial leader is Dr. Irving J. Selikoff, professor of community medicine at the Mount Sinai School of Medicine in New York City.

The one-man power elite

White haired, gracious, and preternaturally energetic, Selikoff is best known as the man who explored the hazards of asbestos and who fought for many years to get them reduced. But a glance at his credentials shows him to hold so many other distinctions and positions that he constitutes a virtual power elite all by himself: a recipient of the Albert Lasker Award of the American Public Health Association, he is also director of Mount Sinai's Environmental Sciences Laboratory, governor and past president of the New York Academy of Sciences, editor in chief of *Environmental Research*, president of the Society for Occupational and Environmental Health, and consultant to the A.F.L.-C.I.O. as well as to an almost endless list of medical organizations and government institutes. He seems personally as well as professionally close to nearly everyone who matters in government occupational medicine, and has excellent contacts in the press, which he uses skillfully. Though he insists that he is only a scientist, Selikoff is also a crusader and reformer, and the weapons he takes into battle, aside from his many personal talents, are research and publicity.

Within a month of B.F. Goodrich's announcement, half of Selikoff's staff was working on a series of medical and epidemiological studies of workers at three older PVC plants. Researchers from the Harvard School of Public Health began an analysis of morbidity and mortality in Goodrich's Louisville plant. The National Institute of Occupational Safety and Health, which does research and standards development for OSHA, began a major epidemiological study of workers at four older plants, and together with OSHA sent out numerous teams to conduct "walk-through" inspections of PVC production facilities across the nation. In May, Selikoff convened in New York City a large international working group on vinyl chloride, held under the auspices of the New York Academy of Sciences. As Dr. Joseph K. Wagoner of NIOSH described the position of the many researchers who entered the field, "'Seek and ye shall find' is where we're sitting right now."

What they found was a great deal of information that linked vinyl chloride ever more closely to a variety of

diseases, and this information in turn generated newspaper copy. To an attentive reader, the cumulative impression conveyed was of a hidden crisis slowly uncovered. With each passing week, the discovery of yet another angiosarcoma case or the release of a new report seemed to show the crisis to be graver and more widespread than it had been the week before. The tacit message was that industry had failed, and that government would have to step in and do something fast.

Federal regulators were quick to respond. By early February NIOSH and OSHA were actively at work on the problem of workplace exposure. (See the report on page 4.) By the beginning of April OSHA had issued an emergency temporary standard of 50 ppm and in May it proposed "no detectable level" as a permanent standard.

But during the summer, the plastics industry, which had maintained a low profile during the preceding months, reassumed the initiative under the leadership of S.P.I.'s Ralph Harding and Jerome H. Heckman. The burden of the industry position was that OSHA's proposal was not required on medical grounds and was technically and economically unfeasible. In its place S.P.I. advocated a phased reduction to 10 ppm as an average and 25 ppm as a ceiling by 1976. The industry case was set forth in considerable detail and with much documentation during the OSHA hearings that began on June 25.

Making policy in a desert

It was clear at the hearings that, in the end, the vinyl chloride decision was going to be made in an informational desert relieved by only the most occasional oasis of knowledge. It was established that vinyl chloride causes cancer and other diseases. It was also established that, over the course of two decades, industry had reduced exposure levels in its plants by a factor of something like 50 without experiencing notable hardship or burdensome expense. But beyond that almost everything was uncertain.

One large area of uncertainty concerns the shape of the so-called "dose response" curve for vinyl chloride between 0 and 50 ppm—the range within which, presumably, OSHA will set the permanent standard. To date, no animal experiments have been completed at exposure levels below 50 ppm, and since historic exposure levels in most existing plants have been above that level, it is extremely unlikely that epidemiological studies can reveal anything about human response below the level. The data for Dow Chemical's Midland, Michigan, copolymer plant, where exposures have been monitored for upwards of a decade, are difficult to interpret. Dow's own studies suggest no adverse health or mortality effects for workers at exposures below 200 ppm; however, Dr. Selikoff's group reports a significant incidence of abnormal symptoms even among Dow workers.

Where data are unsatisfactory, one must fall back on

inference and theory—but these have proved even less satisfactory, and much more subject to dispute. At the theoretical level, there is disagreement over how cancer is caused. Advocates of the "no detectable level" argued for the so-called "one-hit" theory of cancer causation, which holds that there can be no such thing as a risk-free exposure to a carcinogen. The theory implies that *any* identifiable exposure to vinyl chloride is certain to cause angiosarcoma, at however low a rate.

But there is another theory of cancer causation, which emphasizes the role of the body's immune system in combating cancer. According to this theory, cancers appear when the immune system breaks down. If what a carcinogen does is to weaken the immune system, and if the weakening process requires a certain level of dose, then it is possible that there is a risk-free level of exposure.

At the present time, there is no definitive way to evaluate the truth of these competing models. Thus when OSHA chooses a standard, it will do so in almost total ignorance of the different rates of cancer and other diseases to be expected at different exposure levels.

The cost of approaching zero

The agency will be just as uncertain about the other major point in dispute—the level below which it is not economically feasible for industry to reduce exposure. "No detectable level" advocates point to the huge exposure decreases that industry has already achieved, to the fact that many producers got below 50 ppm soon enough after the emergency standards were issued on April 5, and that not a few were far below that. To many regulators, it seemed obvious that industry could get to a near-zero level if it really wanted to.

Industry representatives argued vehemently that a nondetectable level simply could not be attained. "Even a system that doesn't leak, leaks," thundered Todd C. Walker, president of Firestone Plastics, at the OSHA hearings. The companies also argued that efforts to approach zero would be extremely expensive. Firestone, for instance, detailed every capital expenditure that would be necessary if it tried to reach "nondetectable" exposure levels and concluded that the total cost would equal the entire value of its existing plant. Even then, Firestone insisted, it would not ultimately achieve a "nondetectable" exposure and would be forced to go out of the plastics business.

By the end of the summer, it appeared that even the OSHA staff felt the standard might be unjustified. An August, 1974, report by the agency's Division of Program Evaluation and Research observed: "First, it is not clear that it is technically feasible to comply with the proposed standard without a shutdown of the entire vinyl chloride industry. Second, it is not clear from existing experimental and other historical data that a 'no detectable level' standard is justified. And third, it is quite clear that compliance

with the proposed standard will require substantial capital investments and lead times."

They'd call it a sellout

If these findings should lead OSHA to compromise—to set an exposure standard of, say, 25 ppm—the agency should not expect to be praised for its moderation. It may even be assailed for violating its charter. The Occupational Safety and Health Act of 1970 states that OSHA, in regulating toxic materials, "shall set the standard which most adequately assures, to the extent feasible, on the basis of the best available evidence, that no employee will suffer material impairment of health or functional capacity even if such employee has regular exposure . . . for the period of his working life."

Members of the regulatory-medical complex would surely insist that a compromise was incompatible with these words—and would see it as an unprincipled sellout, sacrificing lives for dollars. Industry, meanwhile, is apt to view whatever level is allowed as an arbitrary intervention, reflecting political emotionalism rather than reason. And whatever the level, it is hard to believe that the new vinyl chloride standard will do much to end the confusion and uncertainty that currently prevail in many different industries subject to regulatory power.

The vinyl chloride hearings have made it clear that practically nobody in government, industry, or labor is willing to discuss these regulatory issues in trade-off terms. "We don't equate lives with dollars and cents—not at the Department of Labor," John Stender, Assistant Secretary of Labor in charge of OSHA, declares.

Even spokesmen for industry seem unwilling to challenge Stender's formulation head-on. "If we know we're exposing our workers to a known health hazard, we get out of the business," says Dr. Ben Holder of Dow. In the course of the long argument about vinyl chloride standards, businessmen have shied away from asserting that some level of mortality might actually be "worth it." Instead, they have tried to smuggle some practical considerations into the discussion by pointing to problems of "engineering and economic feasibility"—as if feasibility were an absolute.

One reason for the general reluctance to think in cost-benefit terms is to be found in the language of the Occupational Safety and Health Act itself. But another reason lies in the ethos of the regulatory-medical complex, which has something more on its mind than the rate at which people get sick or die. It is committed as well to a larger conception of the good society.

In this society the idea of health is central. Ever more remote causes of disease would be eliminated. The role

of medicine in this society would be different; it would no longer merely cure, but would actively redesign the environment and ways of living to prevent disease. Inevitably, it would be a society in which doctors, by virtue of their expertise, possessed considerable power. The role of markets would be sharply curtailed, inasmuch as they often lead people to make decisions contrary to their best medical interests. In this sense the regulatory-medical complex is a political movement. As such it perceives in issues such as the vinyl chloride standard a symbolic importance that transcends the particular merits involved.

They don't like business

And, of course, it is an antibusiness movement in its underlying commitment. American regulatory agencies seem to reflect the times in which they were founded; the new regulation was established in an era of intense conflict and hostility to business, and there is little prospect of the movement's suddenly acquiring another personality. For all its unattractive implications for regulatory equity and consistency, this fact is not entirely without its redeeming aspects. By pressing industry hard, these agencies will hasten economic modernization. It is clear that they have long since achieved immense success in raising health consciousness in industry and labor alike. As Dr. Ralph Langner, an industrial hygienist at Dow Chemical, says, "Vinyl chloride is to industrial hygiene what Rachel Carson was to the environmentalists."

In any case, if Americans are now going to assume the responsibility of deciding what is a "socially acceptable risk," and thus of implicitly putting a price on human life, surely it is desirable that the critical decisions not be left entirely to business—or to any one group or center of authority. A process of indeterminate struggle between business and antibusiness forces, yielding decisions more political than rational, seems preferable to a system in which a single cooperative establishment coolly announces the exact going rate at the close of every business day.

Even so, it seems clear that the process of consciousness-raising could usefully flow in the other direction as well. The regulatory-medical complex would not be any the worse if it had a clearer sense of the novelty of the concept of health it is promulgating and of the uneasiness of its relationship to the existing economic system. And it could take more fully to heart the potential consequences of its regulatory interventions for ordinary living standards. As G.J. Williams, vice president of Dow Chemical, remarked recently, "You could probably not find a single thing in the world that's essential, but they all go towards making life pleasurable. You can do without almost anything, but not without everything." END

Hemangioendothelial Sarcoma of the Liver and Hemochromatosis

Edward B. Sussman, MD; Irwin Nydick, MD; George F. Gray, MD, New York

A patient who had idiopathic hemochromatosis with cirrhosis, that was treated by multiple phlebotomies, developed hemangioendothelial sarcoma (Kupffer cell sarcoma) of the liver with widespread bony metastases. The possible relationship between hemochromatosis, cirrhosis and this rare tumor is discussed.

An exceptional instance of hemangioendothelial sarcoma occurred in a patient with long-standing idiopathic hemochromatosis. Less than 100 cases of this rare tumor have been reported in adults.¹⁻⁴ While the cause of this tumor is unknown, many cases have been associated with cirrhosis or the administration of thorium dioxide suspension (Thorotrast).

Report of a Case

A 46-year-old white man (NYH 77-40-15) was admitted to the New York Hospital-Cornell Medical Center in July 1968 because of diabetes, weakness, impotence, pancytopenia, edema, and hepatosplenomegaly. Past medical history included severe "typhoidal" infectious mononucleosis in 1957, adult onset diabetes mellitus that was diagnosed in 1964, treated initially with oral hypoglycemics and then insulin, and onset of pancytopenia in 1966. Family

history included a 37-year-old brother with adult onset diabetes mellitus and obesity who was said to have hemochromatosis, diagnosed after this was established in our patient.

A physical examination showed blood pressure, 110/60 mm Hg; fair complexion without pigmentation; pretibial edema; splenomegaly; and testicular atrophy. Pertinent laboratory studies disclosed the following values: hemoglobin, 13.6 gm/100 ml; hematocrit reading, 42.5%; white blood cell count, averaging 3,400 cu mm; platelet count, 40,000 cu mm; serum iron, 228 µg/100 ml; total iron-binding capacity, 228 µg/100 ml; total serum bilirubin, 1.8 mg/100 ml; serum glutamic oxaloacetic transaminase (SGOT), 52 milli-international units/ml (normal, 10 to 50 m-IU/ml); serum glutamic pyruvic transaminase (SGPT), 40 units (normal, 5 to 40 units); serum alkaline phosphatase, 5.3 Bodansky units (normal, 1.5 to 5.0); fasting blood glucose, 276 mg/100 ml; and +4 glycosuria. There was no evidence of hemolysis. Electrocardiograms showed nonspecific S-T segment and T wave abnormalities. The red blood cell (RBC) agglutination test for anti-thyroid bodies was positive 1:2,500. Radioactive iodine uptake in 24 hours was 23%.

Percutaneous liver biopsy specimen showed a marked increase in iron deposition, especially in periportal hepatocytes (Fig 1), periportal fibrosis, and glycogen vacuolization of hepatocyte nuclei. The diagnosis of idiopathic hemochromatosis complicated by diabetes mellitus and a diagnosis of hypothyroidism were made. Biweekly phlebotomies were begun.

Two years later, in June 1970, after 63 units of blood (31,500 ml) had been removed by phlebotomy, a liver biopsy specimen showed that iron stores were still

present but greatly decreased in comparison to the original specimen. The amount of iron removed by phlebotomy was estimated to be 16 mg; however, serum iron was 200 µg/100 ml and total iron-binding capacity was 200 µg/100 ml.

Over the next three months the patient lost 5 kg, had a low grade fever, and pain in the left upper quadrant, back, and left shoulder. In September 1970, he was readmitted because of multiple pathologic rib fractures. He had developed scleral icterus, lymphadenopathy, and hyperpigmentation of pretibial skin. The serum iron was now 174 µg/100 ml and total iron-binding capacity, 164 µg/100 ml. Abnormal liver function was now indicated by the following values: SGOT, 103 m-IU/ml; SGPT, 25 units; alkaline phosphatase, 164 m-IU/ml (normal, 30 to 85); and total bilirubin 2.7 mg/100 ml. A biopsy specimen of a soft tissue mass surrounding a pathologic fracture of the sixth rib on the left side of the chest showed metastatic anaplastic malignant tumor. The only clinical evidence of a primary site was a large defect in the right lobe of the liver demonstrated by a liver scan, but a definite diagnosis was not established. The patient was treated with medroxyprogesterone acetate (Depo-provera), cyclophosphamide (Cytoxan), prednisone, and radiation therapy to the fracture site.

Three months later the patient was admitted because of severe generalized bone pain. He had tenderness over multiple ribs, neck vein distention and decreased higher integrative functions. Laboratory data included: serum iron, 122 µg/100 ml; total iron-binding capacity, 130 µg/100 ml; total bilirubin, 2.1 mg/100 ml; direct bilirubin, 0.6 mg/100 ml; alkaline phosphatase, 269 m-IU/ml; and negative α-feto globulin. Multiple osteolytic metastases were seen

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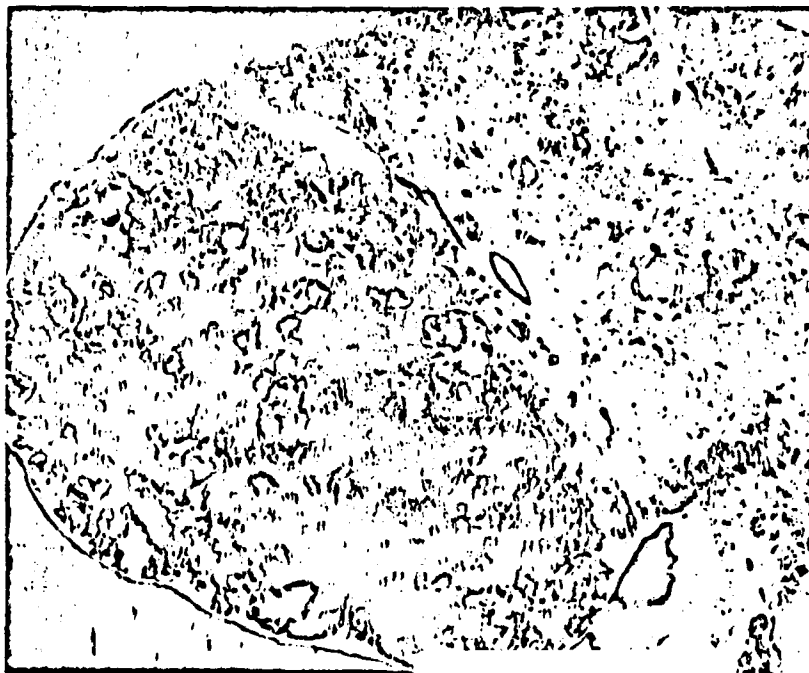
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Fig 1.—Pretreatment percutaneous liver biopsy showing marked increase in iron deposition in hepatocytes and Kupfer cells (hematoxylin-eosin, original magnification $\times 400$).

Fig 2.—Hemangioendothelial sarcoma in liver. Hemorrhagic and necrotic mass replacing a large portion of right lobe of liver. Multiple smaller tumor nodules are scattered throughout remainder of the cirrhotic liver.



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in roentgenograms of ribs, cranial vault, long bones, clavicles, scapula, and pelvis. Liver scan showed hepatosplenomegaly with a grossly irregular distribution of radioactivity in the liver. A regimen of fluorouracil was added to his therapeutic program but he developed hepatic failure and hypotension and died.

The final clinical diagnoses were metastatic malignant tumor of unknown primary site and hemochromatosis with diabetes mellitus and mild hypothyroidism.

Autopsy Findings

The liver weighed 1,600 gm and was chocolate-brown with diffuse, firm, 0.3- to 1.0-cm nodules separated by thin bands of connective tissue. Microscopically, there was a pigmentary cirrhosis with hemosiderin deposits at approximately the same level as seen on the last antemortem liver biopsy specimen. Glycogen vacuolization of hepatocyte nuclei, bile stasis, and scattered foci of necrosis in regenerating nodules were seen. The pancreas, submandibular glands, and lymph nodes were also dark brown and the testes and thyroid were atrophic. Iron deposits were most marked in the pancreas, submandibular salivary glands, lymph nodes, zona glomerulosa of the adrenals, choroid plexus of the brain, testes, thyroid, and the kidneys.

A largely necrotic and hemorrhagic $11 \times 10 \times 8$ -cm tumor was found in the posterior portion of the right lobe of the liver (Fig 2). Multiple 0.5- to 2.0-cm hemorrhagic nodules were scattered throughout the remainder of the right and left lobes of the liver, primarily in and around portal veins. Microscopically, the tumor consisted of large, plump, spindle-shaped cells with large, vesicular nuclei with coarse, clumped chromatin (Fig 3). Mitoses and tumor giant cells were numerous. Reticulin stains showed that the tumor cells lined anastomosing vascular channels containing RBC. The tumor diffusely infiltrated between hepatocytes and, in some areas, bore a striking resemblance to hyperplastic Kupfer cells. A few tumor cells contained hemosiderin granules and some also showed erythrophagocytosis. Extramedullary hematopoiesis within the tumor or remaining liver was not seen. Identical

tumor tissue was found in many ribs and adjacent soft tissue, vertebra, and the cranial vault. This lesion was interpreted as being hemangioendothelial sarcoma.

There was also cytomegalic inclusion virus pneumonia of the middle and lower lobes of the right lung.

Comment

Hemangioendothelial sarcoma of the liver is a rare tumor. Only one instance was found in 52,000 autopsies at the Los Angeles County Hospital¹ and this lesion constituted only 3% of primary malignant tumors of the liver at Memorial Hospital for Cancer and Allied Diseases in New York during a 25-year period.² Less than 100 cases of hemangioendothelial sarcoma of the liver have been reported in adults,¹⁻¹⁴ but the exact number of cases is uncertain because of the proliferation of names resulting from uncertainty of the cell of origin. Designations have included hemangioendothelial sarcoma of the liver, malignant vascular tumor of the liver, Kupffer cell sarcoma, hemangioendothelioma, hemangioblastoma, angiosarcoma, endothelioblastoma, reticuloendothelioma, angioplastic sarcoma, primary hepatic sarcoma, angioblastic sarcoma, endothelioma, hemangiosarcoma, and malignant hemangioma.

Hemangioendothelial sarcomas may arise in a variety of sites including liver, bone, spleen, breast, and subcutaneous tissue. The exact primary site is sometimes difficult to determine because of rapid spread and possible multicentric origin. Hemangioendothelial sarcomas are occasionally difficult to distinguish from extremely vascular spindly hepatocellular carcinomas or vascular metastases, particularly of adenocarcinoma of the kidney and leiomyosarcoma. The differential diagnosis also includes Kaposi sarcoma and choriocarcinoma.

Two distinct age peaks in the distribution of the reported cases of hemangioendothelial sarcoma of the liver have been noted by Videbeck,² one at 8 months and the other at 49 years. The tumor in infants is different from that seen in adults in clinical and morphologic presentation,

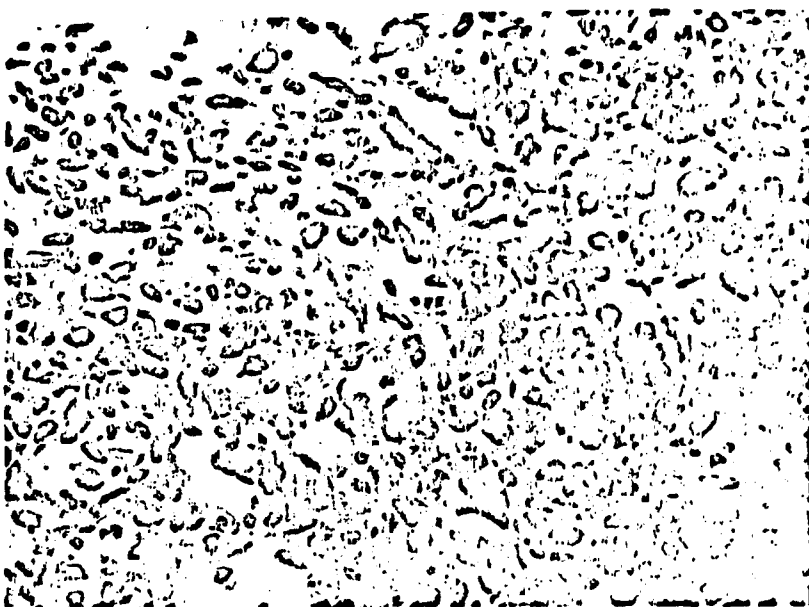


Fig 3.—Hemangioendothelial sarcoma consists of multiple anastomosing vascular channels lined by plump endothelial-like cells with pleomorphic nuclei and bizarre mitotic figures (hematoxylin-eosin, original magnification $\times 250$).

and prognosis.¹⁵⁻¹⁷ In adults, males are affected approximately three times as frequently as females.

Hemangioendothelial sarcoma of the liver is a rapidly progressive fatal disease in adults. Clinical findings frequently include rapid hepatic enlargement, hemorrhagic ascites and jaundice. Occasionally, a vascular bruit is heard over the hepatic region.³ Microangiopathic hemolytic anemia⁴ and hypercalcemia⁵ have also been reported in association with this tumor. Distant metastases are present in approximately 50% of cases at autopsy, most commonly in portal lymph nodes, lungs, bones, and spleen. Death may follow intraperitoneal hemorrhage secondary to rupture of the tumor or from hepatic coma.

Several associations of possible etiologic importance have been noted with these tumors. MacMahon et al¹⁶ reported the development of this tumor after the administration of a thorium dioxide suspension, and Da Silva Horta et al¹⁷ found 22 cases of hemangioendothelioma in 1,107 patients exposed to a thorium dioxide suspension. This suspension is also associated with other malignant tumors in-

cluding hepatocellular carcinoma and cholangiocarcinoma.¹⁸ The latent period between the administration of the thorium dioxide suspension and the clinical onset of hemangioendothelial sarcoma was often as much as 20 years. Further support for the role of thorium dioxide suspensions came with the experimental induction of this tumor in animals injected with colloidal solutions of thorium dioxide.¹⁹ Another implicated iatrogenic agent is arsenic, according to a report by Regelson et al²¹ concerning hemangioendothelial sarcoma of the liver in a patient who had received Fowler solution. There was no history of or morphologic evidence of exposure to either thorium dioxide suspension or arsenic in our patient.

Cirrhosis was present in approximately one third of the reported adult cases of hemangioendothelial sarcoma of the liver.² The types of cirrhosis included alcoholic, postnecrotic, and pigmentary. Ansari and Weigent⁴ have explained the association of cirrhosis and hemangioendothelial sarcoma of the liver in two ways: one, that cirrhosis plays a role in the genesis of this tumor as it does in hepatocellular carcinoma; two, that the tu-

mor itself may initiate fibrosis and nodular regeneration. The latter explanation seems less likely, since in cases like the one reported here, diffuse cirrhosis was demonstrated prior to any evidence of existence of the tumor.

Only two cases of hemangioendothelial sarcoma in hemochromatosis have been previously reported.^{1,2} In one instance,² hemochromatosis was suspected only at autopsy because of pigmentary cirrhosis and iron deposition in pancreatic acini; however, other causes of hemosiderosis were not ruled out clinically and iron was not identified within tumor cells. In the second instance,¹ the antemortem diagnosis of pigmentary cirrhosis was made only a few weeks before death and was not treated. Iron was found in many of the tumor cells. In three of the four cases of hemangioendothelioma of the liver reported by Alpert and Benisch,³ hepatic siderosis was noted and the authors suspected that this was a consequence of microangiopathic hemolytic anemia due to the tumor.

In the case reported here, the presence of diabetes 1½ years before hemochromatosis was diagnosed, suggests that the latter condition may have been present at least four years antemortem. The patient was treated with multiple phlebotomies that resulted in decreasing serum iron levels and diminution of liver iron load as seen on the biopsy specimen. Nevertheless, he went on to develop a hemangioendothelial sarcoma of the liver, a situation analogous to an instance of hepatoma arising in treated hemochromatosis as reported by Hines et al.²² It would, therefore, appear that the removal of iron does not prevent the development of either hepatoma or hemangioendothelial sarcoma once cirrhosis has developed.

Kupffer cell origin of these tumors is suggested by the tendency to form anastomosing vascular elements lined by prominent endothelial-like cells. The presence of hyperplastic Kupffer cells in areas of the liver remote from frank tumor as described by Baker et al.⁸ also supports a Kupffer cell origin of this tumor. Phagocy-

tosis of a thorium dioxide suspension and hemosiderin by tumor cells mimics the activity of Kupffer cells, but does not prove Kupffer cell origin, since other tumors may demonstrate phagocytic activity including erythrophagocytosis. The significance of extramedullary hematopoiesis within the tumor is unknown.

Many of the clinical features seen in patients with hemangioendothelial sarcoma of the liver are shared with patients having hepatocellular carcinoma. Because of the extremely vascular nature of this tumor, aspiration or needle biopsy is contraindicated and may result in fatal hemorrhage. Early diagnosis and partial hepatectomy might offer some hope of increased survival but unfortunately nearly all lesions in adults are diagnosed at an advanced stage and characterized by a rapidly progressive course leading to death within six months.

Nonproprietary Name and Trademark of Drug

Fluorouacil-Esfudex, Fluoroplex.

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