lymphedema.[4] In the case of an abnormal lymphoscintigram, we then recommend a roentgenographic lymphangiogram, as it still is a more definitive test.

Because of its safety, simplicity, and rewarding yield of diagnostic information, we strongly advocate the use of radionuclide lymphangiography as the diagnostic imaging procedure of choice in the initial evaluation of patients with unexplained lower-extremity edema.

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Blood Donors—Paid or Volunteer?

To the Editor.—Dr Allen, with characteristic zeal in the crusade for voluntary blood donation, has missed the point of our article (234:1051, 1975) in his letter (235:1327, 1976). The objective of our article was to report our experience in changing from a paid to a volunteer blood donor program in compliance with the American Association of Blood Banks definition of a volunteer donor. Our results emphasize the problem with the definition of volunteer vs paid blood donor. Dr Allen apparently believes he can intuitively define paid and volunteer donor. If the definition were as clear as he implies, there would not have been such a variety of opinion on this subject expressed at the March 18, 1976, Food and Drug Administration public meeting on blood labeling.

We have received inquiries concerning the actual number of cases of posttransfusion hepatitis identified as a result of blood transfusion from our volunteer and paid groups. From two weeks after the beginning to six months after the end of each study period, six cases of clinically overt posttransfusion hepatitis were identified from the volunteers, while no cases were identified from the paid group.

We have continued to follow up the donor population receiving three-day passes and have observed a decrease from the hepatitis B surface antigen (HB_sAg) positivity of 0.9% previously reported. From May 1975 through April 1976, five of 2,632 donors (0.2%) were HB_sAg-positive by radioimmunoassay. Since the donors still receive three-day passes, this decrease in HB_sAg positivity is unrelated to the three-day pass. Other factors, such as repeat donations with the elimination of HB_sAg-positive donors and possibly fewer drug abusers, must account for this change.

Dr Allen's comments do not contribute significantly, for it appears not to matter whether you call our donors receiving three-day passes paid or volunteer. Currently, they are a satisfactory donor population.

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Rocky Mountain Spotted Fever: Diagnosis

To the Editor.—DeShazo et al (235:1353, 1976) have shown that *Rickettsia rickettsii* infection in monkeys can be confirmed as early as four days after onset of fever. We agree that their data warrant investigation of the monocyte culture technique as a diagnostic tool in human rickettsial disease.

If the monocyte culture technique is to be successfully adapted as a useful diagnostic tool for humans with Rocky Mountain spotted fever (RMSF), a major obstacle will have to be overcome. Patients with RMSF often do not seek medical care promptly, and there are sometimes delays in the initiation of appropriate antimicrobial therapy by physicians. In a study of RMSF in the southeastern part of the United States, the mean duration of time from onset of symptoms (defined as the appearance of any one of the following: headache, fever, or skin rash) to the initiation of effective treatment (tetracycline or chloramphenicol) was 8.3 days for eight fatal cases and 5.4 days for 96 nonfatal cases of RMSF ($P < 0.05$) (J. N. MacCormack, D. J. Sexton, R. N. Philip, unpublished data). There was no significant difference between the mean intervals from onset of symptoms to consultation of a physician for fatal and nonfatal groups: 3.5 days for fatal cases and 2.7 days for nonfatal cases ($P < .25$). However, the mean interval between consultation of a physician and the initiation of specific antibiotic therapy was 4.8 days for the fatal group and 2.5 days for the nonfatal cases ($P < .05$).

Even a delay of four to six days from onset of symptoms to the initiation of antimicrobial therapy could be potentially fatal. Indeed, monkey No. 3 died five days after onset of fever—only one day after the appearance of a rash, and only one day after the monocyte culture was first noted to be positive. Similar rapid deaths have occurred in humans with RMSF.[1,2]

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1. Sexton DJ, Banks PM, Weig S, et al: Late appearance of skin rash and abnormal serum enzymes in Rocky Mountain spotted fever. *J Pediatr* 87:580-582, 1975.
2. Parker RR: Symptomatology and certain other aspects of Rocky Mountain spotted fever, in Moulton FR (ed): *The Rickettsial Diseases of Man*. Washington DC, American Association for the Advancement of Science, 1948, pp 139-146.

"Meat-wrappers' Asthma"

To the Editor.—The renewed interest in meat-wrappers' respiratory problems (235:915; 937; 943, 1976) is pleasing, particularly in the light of three unexpected disappointments in the three years since we wrote our original report on meat-wrappers' asthma[1]: (1) the hot-wire technique for cutting polyvinyl chloride (PVC) has not been eliminated; (2) the existence of any association between reversible bronchospastic disease and meat wrapping is still questioned[2]; (3) a prospective study designed to define the incidence, prevalence, and long-term morbidity, if any, of this condition remains to be done.

Although we have been unable to get the support necessary to do a randomized longitudinal study of pulmonary function in meat wrappers, I understand that such a large-scale study will be undertaken elsewhere. Until this is done, further anecdotes may be helpful to the practicing physician. I know of at least two "disabled" meat wrappers who remain free of symptoms after returning to work using mechanical cutters in lieu of the hot-wire. Several other patients who were receiving disability benefits elsewhere for "meat-wrappers' asthma" were found to have normal pulmonary function at the time of referral to me, suggesting reversibility of the disease process after cessation of exposure to PVC pyrolysis products.

I agree with Falk and Portnoy that respiratory illness other than asthma should be looked for. Some nonsmoking, healthy meat wrappers noted an association of smoking meat wrappers with frequent absenteeism because of pneumonia and bronchitis prior to our publication (from personal interviews). However, all of *our*

patients with objective illness had a reversible bronchospastic pattern of disease, ie, asthma. Asthma in meat-wrappers does appear to be a problem. This should be distinguished from other conditions occurring in meat wrappers, such as lacrimation and rhinorrhea (which tend to be universal with close contact to fumes) and bacterial respiratory infections.

Before accepting the conclusion of Andrasch and Bordana that the price-label fumes caused their patient's symptoms, I would like some assurance that their provocation actually simulated real working conditions; if not, did they test those who were not meat wrappers with asthma to rule out the possibility that perhaps any asthmatic would react dramatically to their challenge technique? Lastly, the term "restrictive disease" applied to their patients should be decried. Although the forced vital capacity was mildly depressed at 72% of predicted value (normal, ≥ 80%), the degree of obstruction suggests that the decrease was due to air trapping and that total lung capacity would be normal or "super normal." The term "restrictive" requires that total lung capacity be less than 80% of a predicted value, which would be unlikely, to say the least, considering the data presented.

While awaiting more definitive studies, physicians have an important responsibility to counsel meat wrappers not to smoke and, whenever possible, to support patients' efforts to minimize exposure to pyrolytic products of PVC.

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1. Sokol WN, Aelony Y, Beall GN: Meat-wrapper's asthma: A new syndrome? *JAMA* 226:639-641, 1973.
2. Finley T: Meatwrappers' asthma: What is it, if it is? Read before the California Thoracic Society Meeting, San Diego, Calif, April 1975.

In Reply.—We share Dr Aelony's pleasure with respect to the continuing interest in the respiratory problems of individuals exposed to components of PVC. We wish to emphasize that the term "meat-wrappers' asthma" is somewhat of a misnomer in that the spectrum of exposed individuals extends beyond the meat-wrapper, and the pulmonary involvement may occur as acute reactive airway disease or a chronic disorder with both obstructive and restrictive patterns. Wegman[1] has reported fine nodular changes on the chest x-ray films of three workers of 37 exposed to PVC only. Significant restrictive disease was noted in a larger study of vital capacity and PVC workers by Lilis and his associates.[2]

Recently, Maccia and his colleagues[3] have provided substantial evidence that phthalic anhydride (a component of some PVC soft wraps, and thermally activated labels) can induce clinical sensitization with high titers of specific IgE. Oddly enough, Kern[4] made the truly original observation of this phenomenon on clinical grounds in 1939. Phthalic anhydride also has a known irritative effect on the bronchi, and may aggravate existing chronic obstructive pulmonary disease in exposed workers.[5]

As a result of these and many other investigations,[6] the government has taken steps to protect the exposed worker (29 code of federal regulations: 1910.1017). In 1975, the Joint Labor Management Committee of the Retail Food Industry awarded a substantial grant to Dr Wegman and his associates at the Harvard School of Public Health to conduct a prospective five-year study of acute and chronic respiratory disease of workers in meat departments. Newly designed automatic wrapping and labeling units with efficient ventilation systems are replacing hot-wire cutting machines.

The work-simulated-inhalation provocation studies in our case report[7] simulated with as much accuracy as possible the actual work conditions. The results of a larger series with more specific details of the methodology used will appear in the *Journal of Allergy and Clinical Immunology* and was recently summarized with pictorial descriptions of procedures.[8] Similar provocation studies of those who are not meat wrappers with asthma may pose a potential hazard for sensitization of an uninvolved subject. With regard to the term "restrictive disease" in our patient, we agree that the measurement of total lung capacity is useful to indicate the presence of restrictive impairment in the setting of airway obstruction, but this was not performed. However, slow vital capacity was performed on numerous occasions and ranged from 37% to 74% of the predicted value and was similar to the fast vital capacity, suggesting true restrictive rather than the restrictive effect of air trapping.

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1. Wegman D: Further results in polyvinyl chloride production workers. *Ann NY Acad Sci* 246:18-21, 1975.
2. Lilis R, Anderson H, Miller A, et al: Pulmonary changes among vinyl-chloride polymerization workers. *Chest* 69 (suppl):299-303, 1976.
3. Maccia CA, Bernstein IL, Emmett EA, et al: In vitro demonstration of specific IgE in phthalic anhydride hypersensitivity. *Am Rev Resp Dis* 113:701-704, 1976.
4. Kern RA: Asthma and allergic rhinitis due to sensitization to phthalic anhydride: Report of a case. *J Allergy* 10:164-166, 1939.
5. Popa V, Teculescu D, Stanescu D, et al: Bronchial asthma and asthmatic bronchitis determined by simple chemicals. *Dis Chest* 56:396-401, 1969.
6. Selikoff IJ, Hammand EC (eds): Toxicity of vinyl chloride-polyvinyl chloride. *Ann NY Acad Sci* 246:1-322, 1975.
7. Andrasch RH, Bardana EJ: Thermoactivated price-label fume intolerance: A cause of meat-wrappers' asthma. *JAMA* 235:937, 1976.
8. *The NIH Record.* National Institutes of Health publication No. 11, US Dept of Health, Education, and Welfare, 1976, vol 28, p 7.

Mannitol and Amphotericin B

To the Editor.—We wish to comment on the recent report by Rosch et al (235:1995, 1976) that suggests a protective effect of mannitol when used in conjunction with the nephrotoxic antifungal agent amphotericin B. Although the single case report suggests a role for mannitol, it nevertheless remains anecdotal. The hazard of extending this type of information to clinical practice must be emphasized.

Although a report[1] from this institution likewise suggested a beneficial effect of mannitol in recipients of amphotericin B, a controlled study that we are currently concluding indicates no protective role. An identical conclusion was reached by Bullock et al.[2] These investigators found no differences in the degree of renal impairment between groups of patients receiving amphotericin alone, and amphotericin plus mannitol.

We therefore urge that purported beneficial results of therapy be subjected to controlled trial before acceptance by the medical community.

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1. Olivero JJ, Lozano-Mendez J, Ghafary EM, et al: Mitigation of amphotericin B nephrotoxicity by mannitol. *Br Med J* 1:550-551, 1975.
2. Bullock WE, Nuttall CE, Luke RG, et al: The efficacy of mannitol in reducing amphotericin B nephrotoxicity: A double-blind study, abstract No. 18, in *Abstracts of the 15th Interscience Conference on Antimicrobial Agents and Chemotherapy.* Washington, DC, American Society for Microbiology, 1975.

CORRECTION

Misspelled Name.—In the ORIGINAL CONTRIBUTION, "Chemoprophylaxis for Patients With Colorectal Cancer," published in the June 28 issue (235:2825-2828, 1976), an error was made in reference 15 (p 2828). The first author of that reference is Roswit B, not Rosvit, as published.

Letters

Letters, if clearly marked "For Publication," will be published as space permits and at the discretion of the editor. They should be typewritten double-spaced, with five or fewer references, should not exceed 500 words in length, and will be subject to editing. Letters are not acknowledged.

Polyvinyl Chloride in Fires

To the Editor.—The article "Polyvinyl Chloride Toxicity in Fires" by Dyer and Esch (235:393-397, 1976) contains a number of factual errors and certain misleading inferences.

In three places, the combustion of polyvinyl chloride (PVC) is said to produce chlorine and phosgene. In fact, these two materials have never been demonstrated to occur in the pyrolysis or combustion of PVC (*Journal of Polymer Science* 8:1887-1890, 1970; *Journal of Applied Polymer Science* 13:377-391, 1969; *British Polymer Journal* 3:186-193, 1971; *Journal of Applied Chemistry* 17:366, 1967). The authors point out, correctly, that hydrochloric acid and carbon monoxide are the main toxic combustion products of PVC but tie these to possible toxic synergy with chlorine or phosgene. It is wrong to raise the specter of toxicants which are not really there. In another instance, vinyl chloride is said to be produced. In work by Boettner et al (*Journal of Applied Polymer Science* 13:377-391, 1969), vinyl chloride was found in the combustion products of PVC corresponding to about 0.02% to 0.06% by weight of the original polymer. Carbon monoxide and HCl were formed at about 45% and 58%, respectively. The vinyl chloride was thus present at a tiny fraction of the primary toxicants and may indeed represent residual vinyl chloride from the original polymerization. The present-day levels of residual vinyl chloride in PVC are .01 or less the levels typical in 1969, when Boettner's work was done. Thus, whether vinyl chloride is a combustion product needs confirmation.

A discussion of the fuel loading in fire situations owing to the presence of plastics carries the statement that "... plastics posses a heat of combustion 2½ times that of other combustibles." The matter is not so simple. According to the National Bureau of Standards (*Modern Plastics* 52:81-82, 1975), the heats of combustion of PVC and some common materials, including other plastics, are

Cotton	7,122 BTU/lb
PVC	7,720 BTU/lb
Wood	8,825 BTU/lb
Wool	8,972 BTU/lb
Polyester fiber	9,300 BTU/lb
Polyurethane.	16,000 BTU/lb
Polyethylene	20,050 BTU/lb

One can conclude from this that, on a pound-for-pound basis, PVC contributes less to fuel loading than many other materials in common use. The assignment of a flat 2½-fold factor for plastics over other materials in heat of combustion is, to say the least, misleading.

The authors cite work by Cornish and Abar[1] on exposure of rats to CO and HCl from pyrolysis in air or oxygen of pure and formulated PVC. This work pointed out that death from pure PVC pyrolysis was due to CO inhalation unless oxygen was added to the gas stream to keep carboxyhemoglobin blood levels low. It should be noted that when PVC formulated for wire insulation or floor tile was pyrolyzed, higher exposure levels were tolerated before death occurred. Thus, formulated PVC is apparently less toxic in fires than pure PVC and the former should be the subject of research rather than the latter, which is never used commercially.

The commercial impact of PVC is exaggerated. The 8.3 billion kg/yr stated as the annual production in the United States translates to 17.6 billion kg/yr in contrast to the 3.7 billion kg/yr actually estimated for 1975 for all uses. Roughly 123 billion lb/yr of lumber and plywood were used for construction alone. Upholstered chairs are not stuffed with PVC, as claimed in the article. Chair covering is often PVC-based; the stuffing is usually rubber, urethane, or a nonsynthetic.

We want to make it clear that we do not take lightly the potential problem that may occur from the combustion of articles made from PVC. We stress, however, the need for dissemination of accurate information. It's reasonable to think that society can cope with the true problem, accurately understood, as well as it has with the toxicity problems from conventional materials. That means a lot of work remains to be done to make both natural and synthetic materials safer to use.

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1. Cornish HH, Abar EL: Toxicity of pyrolysis products at vinyl plastics. *Arch Environ Health* 19:15-21, 1969.

Cardiac Care Units

To the Editor.—Frieden and Cooper (235:816, 1976) stated that "recent experiences with monitored cardiac care units have demonstrated that mortality can be reduced in the first few days after an acute myocardial infarction." However, critical review of articles on coronary care units fails to confirm a properly designed trial that supports that statement. Adler et al (*Br Med Bull* 30:242, 1974), in a review dealing with research on medical care, point out:

> Mortality within most coronary care units has declined over the years, but there has also been a parallel reduction in mortality in patients suffering from myocardial infarction, who are nursed in conventional wards (MacMillan & Brown, 1971). There is no evidence that hospitals play any part in altering the total picture of the disease.

In fact, the first randomized controlled trial comparing home care vs that in cardiac care units (Mather et al cited by Adler et al *Br Med J* 3:334, 1971) showed no striking difference in case fatality ratios between groups treated in the two settings.

There may be other impressive advantages to grouping patients, equipment, and trained personnel in one location within the hospital setting. Grouping makes sense. However, reduced case fatality ratios have not been demonstrated.

The conviction that cardiac care units are effective has been associated with the view that trials are not only unnecessary but unethical. It is unfortunate that rigorous evaluation was not carried out when units were first introduced, but British experience suggests that it is not too late to start.

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In Reply.—It is important to delineate the perspective in which a situation is viewed. It is generally agreed that the majority of cardiac deaths occur early and outside of hospitals. Our report and the reports of the cited authors deal with the subgroup of treated patients. I believe that one should first determin whether or not we are helping these patients. If we

Edited by John D. Archer, MD, Senior Editor.

are having a positive effect, then we should try to expand the subgroup instead of trying to see if treating those within it has a significant effect on the larger group of patients.

The statement that "recent experiences with monitored cardiac care units have demonstrated that mortality can be reduced in the first few days after an acute myocardial infarction" was supported by references to Lown et al, Killip and Kimbal, and Day. Their very impressive results would make it difficult to set up a prospective study of the usefulness of cardiac care units unless a subgroup at low risk was identified. After reviewing the article comparing home vs hospital care by Mather et al, it is difficult to draw any conclusions except that healthier patients fared better than the sick patients.

I believe that the weight of evidence indicates that careful, vigorous therapy of arrhythmias in specialized, monitored units is lifesaving. As patients and physicians are educated to understand that myocardial infarction is best treated early after onset, the patient will appear in hospitals sooner, and perhaps the incidence of arrhythmic deaths will be further decreased.

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Sp ntaneous Rupture of the Esophagus

To the Editor.—Campbell and associates, in their article "Spontaneous Rupture of the Esophagus (Boerhaave Syndrome)" (235:526-528, 1976), have clearly indicated the necessity of early diagnosis and treatment of this condition. Because of the sporadic occurrence of this syndrome, it is not unusual to see a patient who has been treated for a number of days with a presumptive diagnosis of other intraabdominal or intrathoracic inflammatory processes. While misdiagnosis is seen at times, mistreatment (in spite of a correct diagnosis) rarely occurs. Correct diagnosis, therefore, should be followed by correct operative technical management of these patients.

The technique employed by Campbell and associates in the operative treatment of their patient (utilizing catgut to close the perforation) is inadequate and may lead to complications. Their patient developed an esophageal fistula and eventually required additional operations. This type complication occurs infrequently[1] but usually is preventable if the technique of closure is meticulous. In a previous publication from this institution[2] we indicated a new technique for management of these cases.

Our technique is based on the finding that the esophageal mucosal tear is always larger than the small opening seen in the muscular layer. Most surgeons close the rent seen on the muscular layer of the esophagus, ignoring the extent of mucosal layer tear. This, we believe, is the usual reason for fistula formation and postoperative leakage. In brief, the technique utilizes enlargement of the rupture in the esophageal muscular layer which is seen at the time of surgery. The opening is enlarged longitudinally above and below along its long axis. By this maneuver it is possible to see the ends of the esophageal mucosal tear—especially the lower end, which at times extends into esophagogastric junction. Two layers of closure are then accomplished, using 0000 silk cardiovascular sutures. Sutures are taken approximately 3 mm apart and are tied snugly. The muscular layer is closed in the same fashion by interrupted sutures. By this method, we believe the entire rupture is repaired in layers. The mediastinum is then washed thoroughly, as indicated by Campbell and associates.

With meticulous postoperative care for management of fluid and electrolytes, all our patients have survived. In our report, this technique was then used in six consecutive cases, and to date we have used it in ten cases. There have been no postoperative esophageal leaks, and no additional surgery was required in any case. We agree that a postoperative esophagogram should be done on the fourth or fifth day in all cases prior to initiation of oral feeding. In those patients in whom esophageal perforation has been present for longer than 48 hours and in whom there is extensive loss of esophageal wall, we suggest the operation advocated by Grillo and Wilkins.[3]

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1. Berne CJ, Shader AE, Doty DB: Treatment of effort rupture of the esaphogus by epigastric celiotomy. *Surg Gynecol Obstet* 129:277, 1969.
2. Bolooki H: Spontaneous rupture of the esophagus: Boerhaave's syndrome. *Ann Surg* 174:319-324, 1971.
3. Grillo HC, Wilkins EW Jr: Esophageal repair following late diagnosis of intra-thoracic perforation. *Ann Thorac Surg* 20:387-399, 1975.

To the Editor.—We refer to the publication of Campbell and his colleagues on spontaneous rupture of the esophagus (Boerhaave syndrome). The authors intended to emphasize the diagnostic approach to this entity. However, we feel that a simple but important diagnostic procedure was omitted: the determination of the pleural fluid pH. The ruptured esophagus and the repeated vomiting cause the gastric contents to invade the pleural cavity, and a pleural fluid pH of less than 6 is highly suggestive of esophogeal rupture.[1] Such a procedure resulted in a prompt diagnosis in one of our patients.

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1. Dye RA, Laforet EG: Esophageal rupture: Diagnosis by pleural fluid pH. *Chest* 66:454-456, 1974.

Propranolol Blockade of Stress Reaction

To the Editor.—Propranolol hydrochloride (Inderal) has the property of blocking catecholamine-induced increases in heart rate and blood pressure. As a result of this blockade, the stress response was altered in a patient with a duodenal perforation, resulting in delay in diagnosis and treatment.

Report of a Case.—A 51-year-old man with chronic glomerulonephritis and hypertension who received intermittent hemodialysis therapy underwent renal transplantation on Feb 15, 1975. He received prednisone and azathioprine in standard doses for immunosuppression. Propranolol hydrochloride, 10 mg four times per day, was administered for hypertension from the eighth postoperative day. Other medications included methyldopa, 500 mg four times per day; diazepam, 5 mg three times per day; and diphenylhydramine hydrochloride, 50 mg/day. On the 15th postoperative day, there was a decline in renal function, and the patient was treated for a rejection episode with daily injections of methylprednisolone intravenously: he received 1.75 gm during the next two days. The prednisone dosage was elevated to 100 mg/day. The patient complained daily of "gas pains," which he attributed to his antacid medications of magaldrate and aluminum hydroxide, both of which he often refused to take. The serum creatinine level was 3.1 mg/100 ml on the 16th postoperative day.

On the morning of the 17th postoperative day, the patient complained more bitterly of abdominal pain. On examination, he had a pulse of 60 beats per minute and blood pressure of 218/95 mm Hg. Bowel sounds were present, and the abdominal examination showed no abnormality. Six hours later the patient's blood pressure was 90 mm Hg systolic, but his pulse remained slow at 60 beats per minute. Examination of the abdomen at this time revealed muscle spasm and absent bowel sounds. Free intraperitoneal air was seen on a roentgenogram of the abdomen. At exploratory laparotomy, a superoposterior

Angiosarcoma of the Liver in a Rural Population

Four Cases Diagnosed in a 29-Month Period

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• **Angiosarcoma of the liver has recently been publicized because of its association with polyvinyl chloride (PVC) polymerization workers. Four cases of this rare tumor have been observed at the Marshfield Clinic within a 29-month period.**

There are no factories that manufacture PVC products in the immediate area, nor were any of the victims ever involved in such manufacturing work. Thus, it is possible that other factors may be related to this cluster of the disease.

(*JAMA* 236:1704-1706, 1976)

ANGIOSARCOMA of the liver (ASL), also known as primary hepatic hemangiosarcoma, Kuppfer cell sarcoma, malignant hemangioendothelioma, angioblastic sarcoma, and malignant or metastasizing hemangioma, is a rare disease. Alrenga[1] estimates that the literature until 1975 contains 165 case reports of the disease, with an autopsy frequency of 6 in 100,000. Heath et al[2] state that the expected annual incidence of the tumor is 0.014 in 100,000, or 25 to 30 cases a year, in the entire United States. There were only 8 cases in 40,000 autopsies reported over a 25-year period from Holland (population of 10 to 14 million).[3] However, 14 cases were noted in a population of 5,000 workers in the US PVC polymerization plants in a 15-year period.[4]

The purpose of this communication is to present observations on four cases of ASL evaluated during the 29 months from June 1973 to November 1975 at the Marshfield Clinic-St Joseph's Hospital in rural central Wisconsin (Table). Three of the cases came from within a population base of 130,000 and an 80-km radius. The fourth case came from a community 224 km from this center. The total number of autopsies performed in this time period at the hospital was 391.

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Reprint requests to Marshfield Clinic, 1000 N Oak Ave, Marshfield, WI 54449 (Dr Fiechtner).

REPORT OF CASES

CASE 1.—A 65-year-old man (lumber plant worker, retired) was admitted on Nov 12, 1975, with a three-week history of nausea, weakness, anorexia, and slight abdominal pain. A hemogram prior to admission indicated a Coombs-negative hemolytic anemia. Physical examination disclosed severe diaphoresis, restlessness, and tachycardia. His left hemithorax had many moist rales, the abdomen was tender in the right upper quadrant, and the liver was palpated 10 cm below the right costal margin. His skin contained ecchymoses, and a bleeding time taken at the bedside was 11 minutes. Soon after the patient was admitted his blood pressure decreased precipitously, and he had a cardiopulmonary arrest. Resuscitation was successful, but it was soon apparent that renal failure had occurred. Laboratory studies were consistent with a diagnosis of disseminated intravascular coagulopathy and profound hemolytic anemia. A gingival biopsy specimen taken to test for thrombotic thrombocytopenia purpura was unrevealing. The patient was treated with heparin sodium, blood replacement, and large doses of methylprednisolone sodium succinate. A liver scan showed a large lesion in the right lobe.

On Nov 19, 1975, an open liver biopsy was performed. Findings included massive hemoperitoneum and spongy consistency of the liver, which bled profusely when the biopsy specimen was taken. A hepatic angiogram taken the same day suggested tumor with hematomas, especially in the right lobe of the liver. The biopsy specimen was interpreted as showing angiosarcoma. The patient's condition deteriorated, and he died Nov 24. At autopsy, there was a large angiosarcoma of the right lobe of the liver with metastatic implants in the parietal and visceral peritoneum, the lungs, and the left lobe of the liver. There was also evidence of pulmonary edema and acute bronchopneumonia.

CASE 2.—A 45-year-old male postal employee was referred to the Marshfield Clinic in October 1973 for evaluation of jaundice following urological surgery. The history included ankle edema for two years and a mild, nonproductive cough. On examination at that time, findings included dermal and scleral icterus and a barely palpable liver. The prothrombin time was 15 seconds (control, 11.5 seconds); total bilirubin level, 7.6 mg/100 ml; indirect bilirubin level, 4.7 mg/100 ml; and there was no evidence of hepatitis-associated antigen (HB$_s$Ag). An intravenous pyelogram showed chronic atrophic pyelonephritis of the right kidney and a large left kidney. Radioisotope liver-spleen scan showed a small, poorly functioning liver with splenomegaly. An open liver biopsy provided a pathological diagnosis of peliosis hepatis.

The patient's jaundice cleared and he did well until August 1974, when he was again admitted to St Joseph's Hospital. At that time he had jaundice, fetor hepaticus, a harsh grade 4/6 systolic murmur at the cardiac apex, a protuberant abdomen with obvious ascites, and peripheral edema (3+). Results of laboratory studies suggested hemolytic anemia with hypoplastic marrow. The chest roentgenogram showed bilateral pleural effusions. The patient lapsed into hepatic coma and died Sept 3. Autopsy findings were diffuse angiosarcoma of the liver with bone marrow metastasis, fibrinous pericarditis, and a hypo-

Cases of Angiosarcoma of the Liver*				
Case/Age at Death, yr/Sex	Length of Illness,† mos	Symptoms, Length and Type	Diagnosis Method	Occupation
1/65/M	11/75-11/75	3 weeks; abdominal pain, weakness, nausea	Open liver biopsy	Press operator for paper company
2/46/M	8/74-9/74	3 years, jaundice, abdominal discomfort	Autopsy	Postal carrier, bleacher company worker
3/57/M	7/74-7/74	2 months; peripheral edema, jaundice	Open liver biopsy	Rock crusher at roofing paper plant
4/35/M	6/73-6/73	1 month, shoulder pain and fatigue	Autopsy	Postal clerk

*Seen at the Marshfield Clinic between June 1973 to November 1975.
†From diagnosis.

plastic right kidney caused by severe atherosclerosis of the renal artery.

CASE 3.—A 57-year-old man (rock crusher in a roofing paper plant) was referred to the Marshfield Clinic on July 11, 1974, for evaluation of jaundice. He had peripheral edema for two months, increasing abdominal girth, choluria, and acholia for one month. A liver biopsy at another hospital had been interpreted as showing chronic aggressive hepatitis. Findings at physical examination were icteric sclerae and skin, globose abdomen with a grossly enlarged liver, obvious ascites, a palpable spleen, and peripheral edema. Laboratory data included evidence of mild anemia, an alkaline phosphatase value of 218 IU (normal, 19 to 91 IU), and absence of HB_sAg. A radioisotope liver scan showed evidence of diminished hepatic function and a focal lesion in the right lobe. An open liver biopsy on July 24 was interpreted as showing angiosarcoma. The patient died the following day. Postmortem examination showed a large angiosarcoma disrupting most of the liver, with metastasis to one vertebral body.

CASE 4.—A 35-year-old male postal clerk was initially seen at the emergency room at St Joseph's Hospital on June 12, 1973, complaining of shoulder pain and fatigue for one month and dark urine and pale stools for ten days. Physical examination showed obvious jaundice, bilateral palmar erythema, distended abdomen with ascites, and a liver palpable 4 cm below the right costal margin and xiphoid process. Laboratory studies showed an elevated white blood cell count of 31,600/cu mm, bilirubin level of 25.5 mg/100 ml, an alkaline phosphatase value of 985 IU, and absence of HB_sAg. An open liver biopsy showed acute hepatic necrosis. The patient deteriorated rapidly. Exchange transfusions were of no avail, and the patient died on June 15. The autopsy showed widely disseminated liver angiosarcoma with metastases to the mediastinal lymph nodes and lung.

COMMENT

Etiology

There are several known agents that cause angiosarcoma of the liver.

Fig 1.—Cut surface of tumor shows blood-filled, cavernous spaces and satellite nodules. Solitary nodule (arrow) in left lobe.

These include thorium dioxide, a radioactive substance used for angiography in many medical centers as recently as ten years ago. MacMahon et al[3] reported the first such case in 1947. Since that time, approximately 50 additional cases due to ThO_2 exposure have been reported in the literature. Reviews[4,7] indicate that a latency period of 22 years exists between injection of the material and appearance of clinical manifestations. In addition, the biological half-life of ThO_2 is estimated at 400 years.[4]

Arsenic has also been implicated in the disease. Roth,[9] between 1956 and 1959, discovered eight cases of hepatic angiosarcoma among vineyard workers in the Moselle district of Germany. He estimated an average intake of 53.7 gm of arsenic over a 12-year period in the form of arsenic trioxide insecticide. Two cases of ASL have also been reported after ingestion of potassium arsenite (Fowler solution) used to treat psoriasis.[10,11] One patient took the substance for 17 years (estimated 50 gm) and the other for 15 years (approximately 15 gm). The latency periods in all these cases ranged from 13 to 22 years.

Most recently, ASL has been associated with PVC polymerization workers. Block[12] and Creech and Johnson[1] initially called attention to the relationship following the discovery of several cases of the disease in a small population at a manufacturing plant. Since that time, much has been written to substantiate the toxicity of vinyl chloride gas and imply that the danger may involve large segments of the population with only low-level exposure.[14,15] Most authorities, however, believe that there is no measurable risk to the general public.[16] As with ThO_2 and arsenic-induced ASL, the latency period is about 20 years from first exposure to diagnosis.[7]

None of our patients underwent ThO_2 arteriography, and only one of the four had any known occupational exposure to a polyvinyl derivative (polyvinyl acetate, not previously implicated in this disease). Arsenic exposure has not been documented in any of the cases, but the common thread among them is a past history of farming or farm labor. Arsenical pesticides have been used for many years, but it remains to be seen whether exposure was sufficient to cause disease. It must also be emphasized that a very large proportion of central Wisconsin residents have lived or worked on farms at some point in their lives. Thus, speculation on cause must certainly await further investigation.

Clinical Aspects

Our patients had symptoms of advanced liver disease, abdominal pain and distension, ankle edema, weakness, anorexia, and weight loss. The duration of symptoms was usually brief, except for one patient in whom three years elapsed from onset of

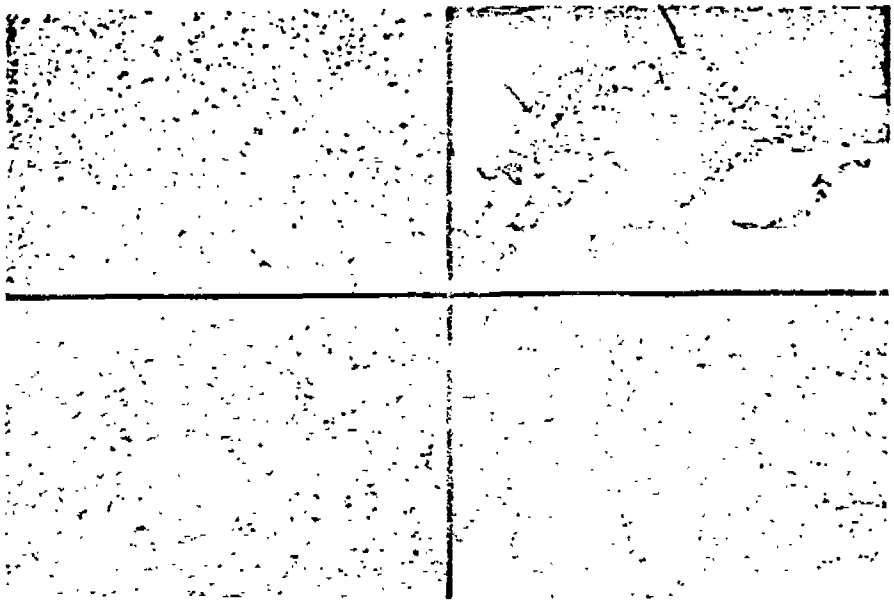

Fig 2.—Varying histological patterns of angiosarcoma of liver (case 1). Upper left, Sinusoidal pattern. Malignant endothelial cells line dilated sinusoids that separate cords of hepatocytes (hematoxylin-eosin, ×125). Upper right, Papillary pattern. Apparently shattered hepatic cords surrounded by malignant endothelial cells (hematoxylin-eosin, ×31.25). Lower left, Cavernous pattern. Blood-filled spaces lined by malignant cells (hematoxylin-eosin, ×125). Lower right, Solid pattern. Sheets of malignant cells, no intervening hepatocytes (hematoxylin-eosin, ×125).

jaundice to death. Physical findings included hepatomegaly, splenomegaly, dependent edema, and cirrhotic stigmata. Laboratory studies confirmed jaundice and liver disease, often with associated anemia and abnormal bleeding tendencies. The association of hemolytic anemia with the disease seen in two of our cases has been noted before,[17] and a single report of concomitant disseminated intravascular coagulopathy exists in the literature.[18] Diagnosis was established most efficiently by open liver biopsy. This technique is preferred because of (1) the high risk of bleeding in these patients and (2) the chance for gross inspection of the abdomen for hemorrhagic ascitic fluid and for characteristic tumor appearance. The diagnosis should be suspected before biopsy, however, since two of our patients had initial diagnoses of simple peliosis hepatis and acute hepatic necrosis.

Pathology

The livers were enlarged, with weights ranging from 1,825 gm to 4,500 gm (average, 3,114 gm). Three of the four cases had a dominant mass with numerous smaller, satellite nodules (Fig 1). The fourth case had multiple varying-sized nodules with no single dominant mass. These masses and nodules were characteristically described as trabeculated, loculated, or spongy, with varying-sized cystic spaces that were filled with blood. Scattered, small areas appeared solid. In one of the cases (case 4) there was extensive necrosis.

The histological features were almost monotonously similar in all cases. The predominant picture was one of varying-sized, blood-containing spaces lined by single or multiple layers of neoplastic endothelial cells. Several histologic patterns were observed. These patterns, in addition to the cavernous pattern, are sinusoidal, papillary, and solid.[19] In case 1, all four patterns were observed (Fig 2). Thomas et al[19] described a peculiar intralobular and capsular fibrosis in tumor-free portions of livers with angiosarcomas as well as in livers of workers without angiosarcoma that had vinyl chloride polymerization exposure. This was not observed in any of our cases. Unfortunately, none of the autopsy tissues were analyzed for the presence of arsenic.

Conclusion

We have observed four cases of angiosarcoma of the liver within a 29-month period in a rural population, with no documented risk-factor exposure. The role of an etiological agent in this group of patients must await further investigation. Because of the long latency period of this tumor, we may have observed only the beginning of a series of such cases. It therefore behooves all clinicians to consider this diagnosis at the earliest possible time.

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