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Untoward Effects of Exogenous Inhalants on the Lung[1]

This collection of cases is presented for a number of reasons. In several instances no difficult diagnostic pathological problem is posed, although the interrelationship between injury or disease and subsequent litigation is such that the discussion is worthwhile. In several other instances, somewhat perplexing differential diagnostic clinical pathologic problems are presented. In at least one of these cases, the ability to render a diagnosis may have substantially affected the course of the litigation. It is not possible, within the scope of such a presentation, to present all of the medicolegal ramifications which may arise in any given section of the country, but an attempt has been made to delineate, to the practicing pathologist not devoting all of his time to the forensic subspecialty, the nature of most of the common medicolegal ramifications that may arise.

"Diffuse alveolar damage," a series of pathologic alterations, including hyaline membrane formation, pulmonary edema, interstitial mononuclear cell infiltration, and the secondary changes resulting therefrom, is demonstrated to be a nonspecific reaction to injury resulting from a variety of noxious agents. In order to provide some documentation of the temporal sequence of injury and repair, several of these conditions are presented in multiple cases, with slight variation in duration of exposure and survival.

Chlorine Gas Poisoning

Clinical Summaries

Case 1A—A robust 29-year-old man was brought to the hospital within 15 minutes after he inhaled chlorine which had leaked into his home while he was sleeping. The source of the gas was a mechanical malfunction in a water filtration plant located across the street from his house.

On admission he was alert, dyspneic, coughing, deeply cyanotic, and his conjunctivae were hyperemic. His blood pressure was 108/50, pulse 80 and respirations 16. Admission arterial blood gas studies indicated mild metabolic acidosis and moderate hypoxemia with a pH of 7.34, pCO_2 34 mm, and a pO_2 45 mm with a hemoglobin saturation of 78 percent while he was breathing 100 percent oxygen.

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One hour after admission moist rales were audible at both lung bases, and a chest roentgenogram showed diffuse patchy bilateral densities associated with coarse perihilar nodulation.

Initial therapy consisted of 100 percent oxygen bubbled through ethanol and delivered by face mask under positive pressure for 10 min every half hour, intravenous hydrocortisone, prednisone, and aqueous penicillin.

He remained alert without severe respiratory distress until about 10 h after his exposure when he suddenly became acutely hypertensive (blood pressure 210/80), tachypneic with a respiratory rate of 50 and obtunded. Blood gas analyses revealed respiratory acidosis with a pH of 7.23, pCO_2 51 mm, and pO_2 37 mm. Lanatoside C was given in an attempt to bolster his heart action.

His clinical course was further complicated by filling of his airway with pink frothy fluid which prevented blood oxygenation despite the use of positive pressure. Insertion of an endotracheal tube and institution of controlled mechanical ventilation were fruitless. He lapsed into a coma and died 25 h after his exposure to chlorine.

Postmortem examination revealed an enlarged dilated heart (410 g), and edematous, rubbery, reddish-purple lungs which exuded voluminous quantities of frothy bloody fluid on section. The trachea and major bronchi contained bloody, frothy, watery fluid. The mucous membrane about the site of tracheostomy was inflamed. The liver and spleen were congested. Microscopic findings, in addition to those in the lung, included acute laryngotracheobronchitis and fatty vacuolization of the liver.

Case 1B—The 27-year-old wife of the preceding victim was admitted with him, coughing and vomiting. Although she supposedly had had somewhat less exposure to the chlorine than her husband, she promptly became extremely dyspneic and cyanotic. Moist rales, audible over both lung fields, were her sole other abnormality. Her blood pressure was 120/80, her pulse was 108 and regular, and her respirations were 24 and deep.

A chest roentgenogram showed diffuse patchy densities in both lung fields and initial blood gas studies revealed a pO_2 49 mm, pCO_2 27 mm, and a pH of 7.39 while she was receiving 100 percent oxygen with a face mask. Her white cell count was 17,450 (94 percent granulocytes) and her hemoglobin level was 16.1 g percent.

She was placed on the same therapeutic regimen as her husband, and over the next 24 h her respiratory distress and cyanosis improved and moist rales were heard only intermittently. However, shortly thereafter she became acutely and severely dyspneic and started to cough up frothy pink fluid. A tracheostomy was performed and mechanical ventilatory assistance was instituted. Her dyspnea, cyanosis, and hypoxemia persisted despite these measures and were now complicated by confusion.

Thirty-one hours after exposure she was placed on a cardiopulmonary bypass for a period of 6 h with resultant marked improvement in her physical and mental status. Blood gas analyses carried out during this interval revealed pO_2 108 mm, pCO_2 38 mm, and a pH of 7.41. She was kept off the bypass for the next 12 h and was given oxygen under positive pressure through her tracheostomy. She remained alert and eupneic and had only a few basilar rales on auscultation.

However, 57 h after exposure she suddenly became cyanotic, lethargic, and then deeply comatose. Blood taken for chemical studies did not clot on standing. A test for fibrinolysis was negative and no fibrinogen was demonstrable in her blood. A thrombin test failed to produce a clot. Despite the administration of intravenous fibrinogen and other heroic measures, she died 75 h after exposure.

Autopsy revealed slightly dilated heart chambers, and edematous rubbery lungs, which on section yielded copious amounts of frothy, watery, dark salmon colored fluid. Multiple hemorrhages were demonstrated in the epicardium, pleura, urethral mucosa, glottis, coronary arteries, mediastinum, pons, cerebellum, subarachnoid space, scalp, cerebral hemispheres, and ventricles.

Microscopic findings, in addition to those in the lungs, included acute tracheobronchitis, interstitial myocarditis, fatty metamorphosis of the liver, and multiple fibrin thrombi in the renal glomeruli.

Pathology Discussion

Case 1A—This patient, upon admission, was already in shock, overbreathing somewhat, although the respirations are stated to have been only 16. The pCO_2 was slightly decreased. There was already evidence of desaturation with arterial pO_2 of 45. The hemoglobin was diminished to 78 percent at the time when oxygen therapy was commenced, this initial therapy consisting of 100 percent oxygen bubbled through ethanol, probably for treatment of pulmonary edema which the patient might be presumed to have had. This therapy is somewhat outmoded, if this was the rationale. It has been shown by many investigators, including Pattle, that ethanol, effective for some purposes, is of no value in the control of pulmonary edema. The patient's pO_2 continued to decrease while he was presumably on oxygen therapy, indicating respiratory obstruction, since the pCO_2, which had been decreased, became elevated and the blood pH was 7.23. There is also indication that he was developing pulmonary edema before he lapsed into coma and died 25 h after his exposure to chlorine.

There is evidence of severe damage, first to the bronchioles, with necrosis and plugs of exudate in the lumina in as short a period of time as 24 h (Fig. 1). This combination of respiratory tract obstruction and necrosis is very likely to lead to interstitial emphysema, with these plugs functioning as valves. The entrapped air dissects into the interstitial tissue. Massive pulmonary edema is also present (Fig. 2), and some of the alveoli are filled with polymorphonuclear leucocytes. In some areas a sharply defined cell layer has been lifted from the residual wall of the alveoli. This probably represents a layer of flat membranous pneumocytes and the residua is probably the basement membrane, representing, even in a hematoxylin and eosin preparation, the condition termed "diffuse alveolar damage." In addition to this, in the periphery of the lungs, there is obstruction of small vessels, in many instances, approaching capillary size. In the proximal or more central lung, large vessels are also thrombosed. The damage resulting from inhalation of chlorine includes bronchioles and the more distal pulmonary parenchyma and blood vessels.

Case 1B—The first patient's wife, with a similar course, died somewhat later, at 75 h after exposure, thus affording a basis for comparison of a similar injury at two time intervals.

In the distal portion of the lung parenchyma, in a structure representing either a respiratory bronchiole or an alveolar duct, are precisely the same changes present in case 1A. Also present are rather massive hyaline membranes (Fig. 3), representing a later stage of diffuse alveolar damage, associated with more extensive exudate, arising from the capillaries. Thus, there is evidence, not only of damage to the lungs themselves, but also to the capillaries, revealed by the presence of fibrin (Fig. 4). This, too, is a component of the hyaline membranes as will be illustrated subsequently by the electron microscope.

These two patients illustrate the manifestations of war gas poisoning, as studied experimentally by Winternitz, founder of the Chemical Warfare Laboratory at Edgewood Arsenal in World War I. During the course of his studies, dogs were exposed to chlorine gas, producing necrotizing bronchitis similar to that produced in the human being. Hyaline membrane formation was present in alveolar ducts and within the walls of the alveoli associated with pulmonary edema. Many of the alveoli contained polymorphonuclear leucocytes and the alveolar epithelium had, in some areas, been sloughed or lifted by exudate from the damaged wall. Grossly, the lungs of the dogs were similar to those described in the first patient. They were boggy, with hemorrhage alternating with pallor, resulting from the diminution of blood flow associated with vascular obstruction. With longer exposure, particularly with higher concentrations, focal necrosis develops. These patients did not survive long enough for the development of massive necrosis. Ultimately, in the dogs exposed, as the necrotizing pneumonia organized, bronchiectasis developed. Similar bronchiectasis developed in many of the soldiers who were gassed by chlorine in the trenches of France during World War I.

Phosgene produces lesions similar to these. The gas is hydrolyzed to hydrochloric acid in the respiratory tract. With high doses, bronchiolar damage and pulmonary edema develop; with lower doses, the end result is similar to that of chlorine, namely, bronchiectasis. With even smaller doses, the end result is bronchiolitis obliterans. This was described by Winternitz [9] in his monograph on war gas poisoning.

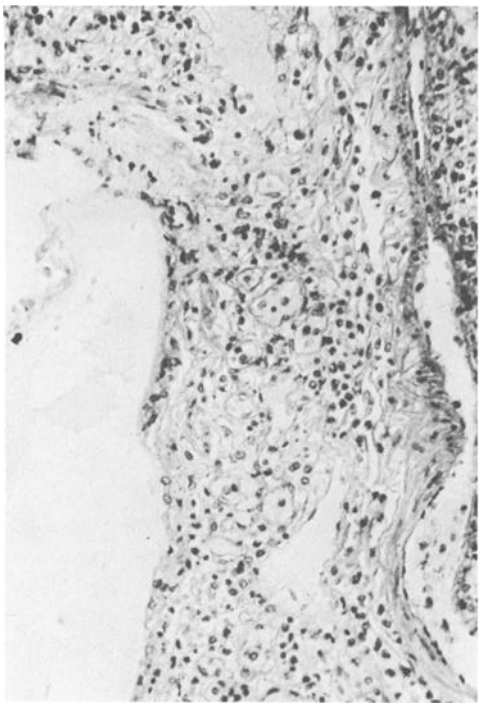

FIG. 1—*Chlorine poisoning. In the bronchiole, at right, the epithelium has sloughed, and there is a plug of exudate in the lumen. At left, the artery contains a thrombus which is adherent at one point.*

Many of the changes produced in these lungs are similar to those described in "shock lung," essentially diffuse alveolar damage with minute thrombi in blood vessels. The process is so complex that the changes in no two cases are exactly the same. Wilson, at Duke University, has treated "shock lung" with massive doses of methylprednisolone, 30 mg per kilogram of body weight every 12 h, with dramatic alteration in the clinical course, probably by reducing the amount of proliferation. The degree of resulting proliferation in a short time is astonishing. Hamman and Rich, in describing the lesion now referred to as the Hamman-Rich syndrome, expressed great surprise that, in as short a time as four months after injury, there was extensive proliferation. From studies of lungs such as these it has been shown that this may occur in as few as 6 to 10 days. The pulmonary changes described are not specific. As outlined in later discussion, there are hundreds of substances which may produce exactly the same effects. The changes are a type of tissue response designated "diffuse alveolar damage."

A large number of the deaths in the Coconut Grove fire may have resulted from inhalation of phosgene, chemically related materials, or nitric acid, produced by combustion of plastic material such as was used to cover benches and chairs. The resulting changes are similar with both gases. Similar deaths were encountered in the Crile Clinic disaster when nitrate X-ray film caught fire, emitting large quantities of nitric oxide. This was hydrolyzed to nitric acid in the respiratory tract. This is the same gas inhaled in some parts of Southern California and elsewhere in the country in smog. In somewhat lower concentrations, over a longer period of time, this, too, could produce adverse effects.

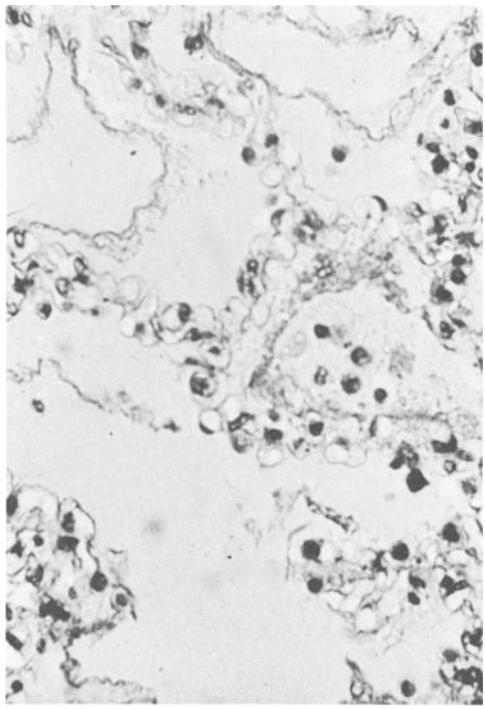

FIG. 2—*Chlorine poisoning. Massive pulmonary edema. Note sharply defined layer of acidophilic material that has been lifted from the remainder of the wall in some alveoli. This may represent a layer of necrotic membranous pneumocytes.*

Medicolegal Discussion

These two cases are of dramatic interest because of the magnitude of the jury verdict of $1,359,032 against the city of Cleveland, Ohio in favor of the three children left as orphans by this incident.

Three legal questions may arise in this case.

Accident Insurance—If either of the deceased persons carried a policy of life or accidental insurance which was contingent upon death, disability or the incurrence of medical bills because of an accident, the legal cause of death becomes of prime importance. This is a mixed medical and legal problem because it entails, not only a medical opinion concerning the cause of death, but also the legal finding concerning the circumstances and events leading to the incident. A full investigation with knowledge of all the facts and circumstances is necessary to arrive at a proper legal conclusion.

In the litigation that followed this incident, the city of Cleveland readily admitted storing 1100 lb. of liquid chlorine in an unsafe manner, knowing that the chlorine could be fatal if it entered the atmosphere in sufficient concentration. The filtration plant had a powerful exhaust system that spread the fumes rapidly throughout the neighborhood and there was no effective detection or warning system. The workers were unable to reach locked gas masks and consequently unable to readily stop the leak. In the absence of evidence of an intentional act to release the poisonous fumes, this would be classified as an accident for the purposes of any insurance policy.

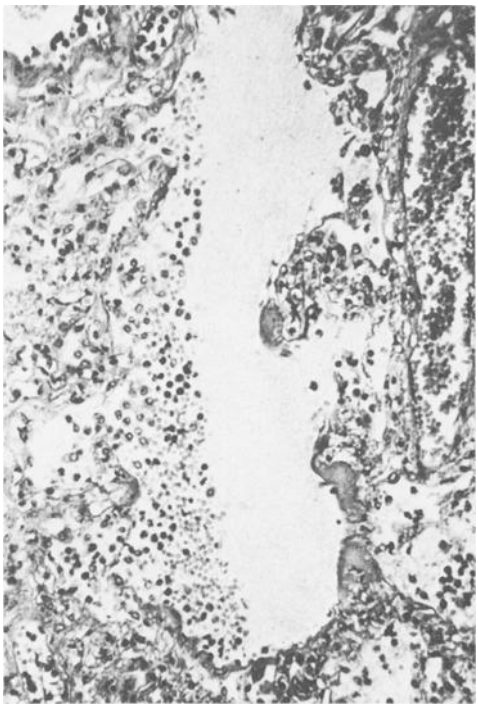

FIG. 3—*Chlorine poisoning. Necrosis involving respiratory bronchiole or alveolar duct. Hyaline membranes are prominent. Edema and polymorphonuclear exudate also within adjacent alveoli.*

Although of no particular significance in this case, the medical cause of death may have great legal importance if there was a significant preexisting disease which may have contributed to death under otherwise unnatural circumstances, since many insurance policies have provisions which exclude payment if preexisting disease or bodily condition indirectly contributed to death or disability.

Criminal Negligence—The second question that may arise concerns the possibility of criminal negligence or punishment, or both in an incident such as this. Storage and handling of dangerous and hazardous substances is usually controlled by voluminous laws at the federal, state, and local levels. If any of the safety practices required by these laws are violated, the offender could be subject to criminal punishment. Agencies and individuals that employ and transport dangerous chemicals are presumed to be familiar with these laws and ignorance of such is not a defense. A violator of the law can be subjected to jail sentences and required to pay fines. A court may further order an individual or agency to conform to proper practices in the future.

Civil Liability—The third consideration, of particular significance in this case, is that of civil liability. The city of Cleveland was the actual operator of the water filtration plant. Civil action was brought against the city by the survivors for monetary damages for the loss of their parents. There are several legal theories under which a person may be held civilly liable for damages. The most common basis is the theory of negligence. In this case, the city of Cleveland failed to take the appropriate precautions for an extremely hazardous substance and did admit its negligence. The court, in addition, found the city was guilty of

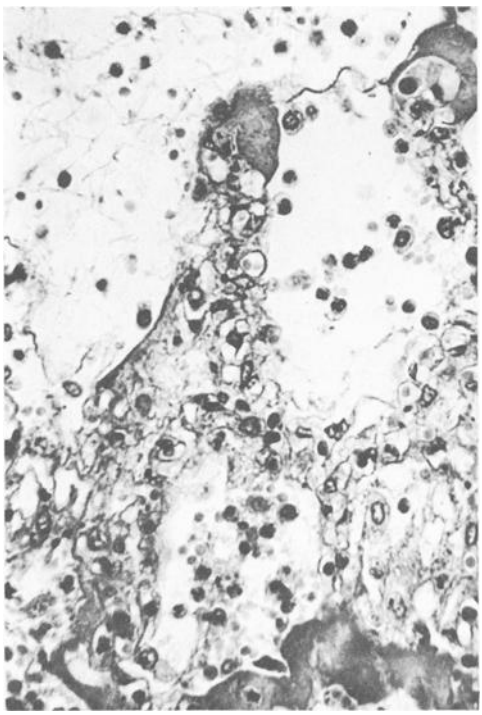

FIG. 4—*Chlorine poisoning. Hyaline membranes. The lumina of alveoli also contain fine strands of fibrin, polymorphonuclear leucocytes, and some large mononuclear cells.*

aggravated negligence or recklessness. The degree of culpability or guilt may have an effect on the type of damages that are awarded or upon the defenses available to the guilty.

Under the laws of many states, a person who engages in activities which are extremely hazardous to human life such as those involved in blasting activities, land occupiers who maintain dangerous watch dogs, and crop dusters using dangerous chemicals, is held strictly liable for any harm which may arise.

Furthermore, many American courts are now holding that the manufacturers and sellers of dangerous and defective equipment are to be held liable for any injury caused by defects in this equipment. Although there was no such litigation apparent in this incident, had one of the chlorine tanks been defectively manufactured or not properly designed to withstand the stresses or abuses to which it would probably be subjected, many states would permit a lawsuit against the manufacturer, the distributor, and the retailer of this article. With the increasing number of household accidents associated with defective appliances, inflammable clothing, and contaminated food, this type of recourse is becoming more popular. Similar actions have been brought against the automobile manufacturing industry for vehicle defects, such as steering and brakes.

With increasing awareness of the physician's liability, many practitioners have found themselves named as joint defendants with the person who was reportedly originally negligent and responsible for the injury. Although not relevant in this incident, many physicians have been fighting judgments awarded against them when they allegedly undertook to treat a clinical problem which was beyond their level of skill and competence. A timely consultation or referral is the obvious solution to such a claim.

In a civil lawsuit there are generally four types of relief available from the court:

Special Damages—In this case the surviving children were awarded $2600 for funeral expenses, $1055 for hospital and medical expenses for the care of their parents, and $2722 for direct physical damage to the home caused by the chlorine. Reimbursement for these direct out of pocket expenses is called special damages.

General Damages—Included in general damages are the intangible pain and suffering experienced by the parents prior to their demise. This amounted to $125,000 for the wife's conscious pain and suffering for a period of 30 h before she lapsed into a coma, and $50,000 for the husband's conscious pain and suffering for a period of approximately 12 h before he lapsed into a coma.

General damages also include reimbursement to the children for the loss of their parents. This includes a sum for the loss of intangible love and supervision of the parents and also a sum for the loss of financial support which the children would have received had the parents survived. In this case, this amounted to $235,000 for loss of the nonemployed mother, a housewife, and $185,000 for the loss of the employed father. The general damages were granted because the city admitted it was negligent in the operation of the plant.

Punitive Damages—Usually only compensatory damages, special and general, such as those listed above, can be awarded to an individual for loss incurred by the negligence of others. A criminal action with the imposition of fines or general sentences or both is the usual manner of punishing a person or corporation for a seriously wrong act. However, in those instances wherein a person has been guilty of gross, willful, or intentional misconduct, there may be an exception, and punitive damages may be awarded. An intentional assault or battery, an intoxicated driver involved in a traffic accident, or other instances wherein an individual recklessly performs activities offering a substantial risk to others, may justify civil award of punitive damages to the injured party. Punitive damages need not bear any relationship to the compensatory damages awarded. Their purpose is to act

as a major deterrent to the continuation of the hazardous activity in question. In this case, the jury awarded the sum of $375,000 in punitive damages, each, to the estates of the deceased persons as notice that such serious hazardous activities would not be tolerated. This case is particularly unique in that a municipal government, which usually cannot be punished in a criminal court, is here reprimanded by award of punitive damages.

When an activity is illegal or extremely hazardous and threatens to cause further harm to an aggrieved individual, a private party may obtain a court order or injunction preventing the continuance of such activity if adequate safeguards to protect the interest of others are not provided.

Paraquat Poisoning

Clinical Summaries

Case 2A—This patient "accidentally" swallowed some Paraquat solution while spraying her home on 27 Oct. 1968 with this herbicide. Some of the material spilled on her hands and forearms. She was seen shortly thereafter by her physician for burning of the mouth and a productive cough. A diagnosis of severe stomatitis and gingivitis was rendered.

One week later she was hospitalized. Her presenting complaints were severe anorexia, nausea, vomiting, weakness, and jaundice. She had symptoms of early renal and hepatic damage and pulmonary involvement. (On 5 Nov. 1968, multiple infiltrates were present radiographically.)

Laboratory examinations revealed: on urine—sp. gr. 1.010; pH 5.0; WBC 4-6/hpf; RBC 3/hpf; on blood—bilirubin 11.5 mg%; SGOT 114; hematocrit 35 percent; hemoglobin 11.8 mg%; WBC 8, 100.

She was transferred to a chronic care facility with a diagnosis of possible tuberculosis. Her condition continually worsened. The laboratory studies at this institution revealed: hematocrit 36.8 percent; hemoglobin 11.7 mg%; WBC 27,500; BUN 129 mg%; blood sugar 159 mg%; thymol turbidity 4.1; bilirubin and SGOT too high to read. Her physical condition continued to deteriorate with signs of hepatic and renal failure and she was transferred to Jackson Memorial Hospital (in a semi-comatose condition) on 14 Nov. 1968 with the admitting diagnosis of Paraquat poisoning. At that time her blood pressure was 90/50 and she was markedly jaundiced with small purpuric areas on her trunk and extremities. She was considered oliguric and was given IV fluids, and a blood transfusion for hemolytic anemia, but expiration occurred one month after exposure in acute respiratory insufficiency.

Thirty days after poisoning, the urine specimen contained 1.6 ppm of paraquat by gas chromatography. This was corrected for osmolality. This appears to refute the published reports of total excretion within the first 24 h.

Autopsy revealed diffuse consolidation of the lungs. The sectioned surfaces revealed discrete nodular and large confluent areas of hemorrhagic consolidation with exudation of blood tinged fluid from minimally aerated parenchyma. The liver and kidneys were bile stained. The pancreas was indurated with areas of adjacent fat necrosis. Mucosal erosions were found in the esophagus and larynx.

Case 2B—On 13 April a 6-year old, previously healthy boy became ill with abdominal pain and vomiting. On 16 April, his mother noticed that his skin was yellow and that he was passing little urine. Two days later he was admitted to the hospital.

On examination he was afebrile and very ill. He had dyspnea and jaundice. There was marked subcutaneous emphysema of his neck and of the entire chest wall anteriorly and

posteriorly. His lips were excoriated and his buccal mucosa ulcerated. His heart sounds were normal and his blood pressure was 105/70 mm Hg. Auscultation of his chest was difficult due to the subcutaneous emphysema but crepitations were definitely heard at his right base. His liver was enlarged 5 cm below the costal margin. He had no neurological signs.

Laboratory findings included: hemoglobin 12.8 g/100 ml, leucocytes 11, 600/mm^3, neutrophils 70 percent, lymphocytes 30 percent, E.S.R. 4 mm/1 h (Wintrobe), bilirubin 6 mg/100 ml (direct 4 mg/100 ml/, blood urea 240 mg/100 ml. Urine contained albumen +++. Leptospiral agglutination tests were negative. Chest radiograph revealed air in the subcutaneous tissues and anterior mediastinum with widespread bronchopneumonia.

It was difficult to explain the bizarre clinical picture of subcutaneous emphysema, bronchopneumonia, jaundice, and uremia. Poisoning was considered to be a definite possibility. Since the child was too ill to give a coherent history, the parents were repeatedly questioned about his activities on 13 April, the day on which he became ill. Eventually, a history was obtained that on the way home from school he had called at a neighbor's house where Gramoxone W was being sprayed on the garden. The undiluted Gramoxone W, obtained from a local farmer, was in the kitchen in a bottle which had contained a household disinfectant. Though it was known that the child had been in the kitchen, he had not been seen to touch the bottle.

Because of this history, urinalysis for Paraquat was carried out. This was present in a concentration of 0.36 mg/100 ml.

The child was treated with oxygen, intravenous fluids, ampicillin, and hydrocortisone. His condition rapidly deteriorated. His urine output remained low and his blood urea rose to 380 mg/100 ml. He died on 20 April, 2 days after admission to the hospital.

Subcutaneous emphysema of the neck and chest wall was present. There was also marked emphysema of the interstitial tissues in the chest, particularly involving the pericardium and mediastinum. In the lungs were subpleural hemorrhages. Many subpleural bullae were on the mediastinal aspect of the right upper lobe and in the interlobal fissure of the left lung. On section, bronchopneumonic changes were present in both lungs. No abnormality was seen in the esophagus. In the stomach were numerous, small, acute submucosal erosions. All other organs were normal.

Biochemical analysis of the liver revealed a concentration of Paraquat of 208 μg/100 g of tissue and in the kidneys a concentration of 180 μg/100 g of tissue.

Pathology Discussion

These two cases exemplify the effects of an interesting material, the herbicide called Paraquat. This material may produce damage, not only to the lungs, but also to the kidneys and liver. In both cases, the patients probably ingested the solution. The same has been true in some of the other cases described in the literature. There is, however, one patient who was injected with Paraquat, and the ultimate result was the same. This is of interest, since, although the effect of the material on the lungs is like that of an inhalant, it may reach the lungs after having been absorbed into the blood stream. A similar phenomenon occurs with some other substance. It is entirely possible, however, that Paraquat, under certain circumstances, could damage the respiratory tract as an inhalant.

The first of these patients died one month after exposure, with injury, not only to the lungs, but also to the liver and kidneys. There was elevation, both of the bilirubin, and of the blood urea nitrogen. It is of interest in that dyspnea, which is an important manifestation of diffuse alveolar damage, did not occur initially. This suggests that the damage may

have occurred quite late, although it has been stated that Paraquat is rapidly excreted. In the present case, 30 days after poisoning, 1.6 ppm of Paraquat was still recovered from the urine specimen.

The second patient was a 6-year-old boy who probably also swallowed the material, although this was not observed. He died 1 week after exposure. Urinalysis on this patient revealed 0.36 mg of Paraquat per 100 ml of urine, thus confirming the diagnosis. The combination of progressive pneumonia with the syndrome of alveolo-capillary block, in association with jaundice and renal failure, allowed the physician to render a diagnosis of Paraquat exposure. Paraquat is used rather widely in Great Britain and is available, and rather extensively employed, in this country.

Case 2A—One month after exposure, the lungs had a remarkably nodular hemorrhagic appearance (Fig. 5). There was residual evidence of bronchiolar damage. The possibility of infection should be considered upon finding such damage after such a long interval following exposure by inhalation or ingestion of suspicious material. Such infection was present in this case, making it difficult to determine exactly which changes represented the consequences of the infection and which were the direct result of the agent per se. Again there was bronchiolar obstruction with plugs of very deeply staining material, a combination of exudate and mucin (Fig. 6). In the remainder of the pulmonary tissue was some interstitial fibrosis associated with edema and moderate exudate of polymorphonuclear leukocytes, possibly the result of infection. One of the more interesting findings was the evidence of moderate revision of the architecture with "honeycombing." This is an end stage in the evolution of interstitial pneumonia, probably present earlier. This had become chronic and was resolving. Although this was not diffuse enough to produce severe respiratory depression initially, it progressed and, as it resolved, was associated with loss of alveolar substance. The interstitial tissue became fibrotic, leaving residual rarified parenchyma resembling a honeycomb. Some of these spaces were lined by hyaline membranes (Fig. 7). In addition, there were hemorrhages, possibly the result of late damage (Fig. 8). Again, there was focal thrombosis of small blood vessels (Fig. 9). Even 30 days after the initial injury, this may have represented a slowly progressive specific toxic effect on respiratory substance. Evidence for such a mechanism will be presented subsequently. Grossly in the lungs, hemorrhage was more extensive than suggested by the microscopic sections, the nodular structure resembling that of the cirrhotic liver, a common appearance of lungs in the chronic state of interstitial fibrosis. Some writers have termed this process "bronchiolar emphysema," a poor term, since it suggests a separate disease rather than one already recognized, healing interstitial pneumonia.

Case 2B—In this case, bronchiolitis is also present. The presence of this change in both cases suggests that it is the result of the toxic substance rather than of superimposed infection. Even in this relatively short interval there was diffuse alveolar damage characterized by hyaline membranes and even early interstitial fibrosis. Those portions of parenchyma which remained undamaged were overexpanded, probably as a consequence of atelectasis of the remainder of the tissue and not the honeycombing of more chronic disease. The interstitial infiltrate was predominantly mononuclear, as is characteristic of diffuse alveolar damage. Interstitial emphysema, a complication noted in the earlier cases of chlorine gas poisoning, was also present in this case. The septa of the lung were dissected by gas, extending into the pleura.

Many other substances introduced into the environment may produce diffuse alveolar damage, including perchlorethylene, a material used to preserve textiles such as sleeping

FIG. 5—*Paraquat poisoning. Gross appearance of lung approximately 1 month after its exposure to Paraquat, presumably by ingestion. The lung has a nodular hemorrhagic appearance. The nodulation results from honeycombing.*

bags. A young boy who slept in a new bag on a camping trip in the woods died approximately 8 days later after a period of severe and increasing respiratory insufficiency. In the lungs was diffuse alveolar damage, much as in oxygen poisoning, with thickening of the alveolar walls, proliferation of lining cells, and a predominantly mononuclear infiltrate.

Two men died approximately 25 years apart, following exposure to hot mercury vapor in two identical accidents that occurred in a plant in Hartford, Connecticut, where mercury was used as a coolant in a generator. In both instances, the pipe burst and the mercury seeped into the generator pit. Numbers of men were sent to reclaim this valuable material while it was still warm. Mercury, even at room temperature, has considerable vapor tension, increasing at higher temperatures. Most of the men who went down to recover the mercury complained of a metallic taste in the mouth, cough, and dyspnea. In each accident, one man died; the remainder recovered. Radiographically, the lungs of

several of the men presented the appearance of pulmonary edema. The changes within the lungs were similar to those described earlier, representing diffuse alveolar damage. Hyaline membranes were present. Even at three days, there is extensive mononuclear cell infiltrate and proliferation with microses in the lining cells. In the man who died three weeks after exposure in the second accident, 25 years later, there are not only residual hyaline membranes, but also early honeycombing with striking proliferation of the residual connective tissue and lining cells. This represents an excellent model for the development of chronic interstitial pneumonia.

A metallurgist, exposed to beryllium, expired 16 days later. The lungs presented the appearance of a viral pneumonia, with changes already in a chronic state.

Another industrial worker, engaged in welding of large vats lined by cadmium, developed interstitial pneumonia, proliferation of the lining cells of the alveoli, and striking interstitial thickening. The lungs of a dog, 16 days after unilateral exposure to cadmium spray, resembled those in the worker.

Certain agents, such as kerosene, may produce diffuse alveolar damage when ingested. Radiographically, an infiltrate is visible and histologically there is hyaline membrane disease with mononuclear cell infiltration exactly as in the Paraquat poisoning. Experiments have demonstrated that kerosene injected intravenously into dogs produces an identical lesion. A few patients who received Myleran, otherwise known as Busulphan, have developed an interstitial pneumonia with remarkable atypical epithelial proliferation,

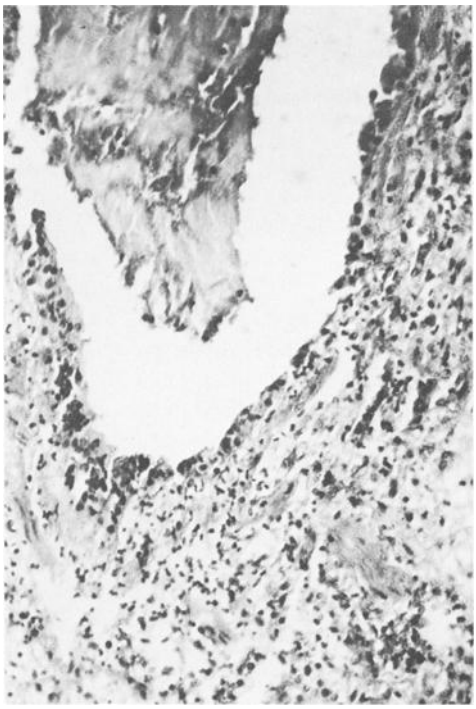

FIG. 6—*Paraquat poisoning. Bronchiole in which the epithelium has partly sloughed and there is a plug of mucinous material in the lumen. The wall is infiltrated with polymorphonuclear leucocytes and some small mononuclear cells.*

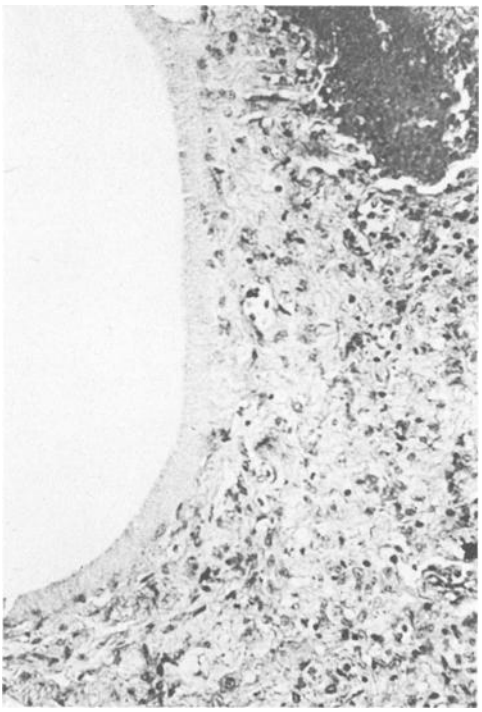

FIG. 7—*Paraquat poisoning. Hyaline membrane lines one of the dilated distal air spaces.*

another example of interstitial pneumonia which may develop after ingestion, possibly, in this instance, as a hypersensitivity reaction.

A great variety of agents, some as inhalants, and some after ingestion, as in the case of Myleran and kerosene, may produce diffuse alveolar damage. Attempts to measure the material producing the pneumonitis in the pulmonary parenchyma have not been very successful. This has been attempted with beryllium and it has not been possible to demonstrate the agent above background concentrations even though the exposure was quite obvious, suggesting that the usual lesion of beryllium exposure, a granulomatous one, is a hypersensitivity reaction. The nature of the lesion also suggests this.

Hair spray has been suspected of producing pulmonary lesions but no proven injury has been produced by such material in experimental animals or human beings. In the few instances which were allegedly caused by exposure to hair spray, the resulting condition was desquamative interstitial pneumonia. This condition occurs as frequently in adult males and sometimes also in children, presumably not exposed as frequently to the hair spray. The vehicles that are used for the spray vary. They are proprietary and the companies usually will not divulge their identity, although in some instances it has been shown to be polyvinylpyrrolidone, a material which, when inhaled or sprayed into guinea pigs' lungs, appears to be entirely innocuous. The same material, injected intravenously, as it was used as a plasma expander by the Germans in World War II, is stored in the reticuloendothelial system, but produces no change in the lungs.

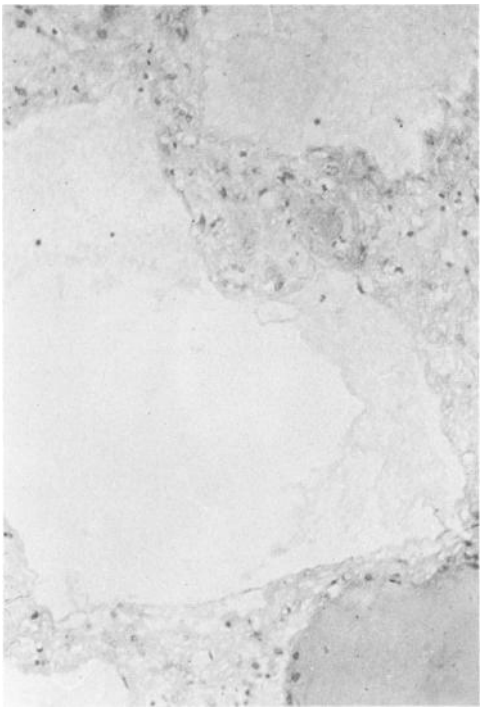

FIG. 8—*Paraquat poisoning. Honeycomb pattern of pulmonary parenchyma. Interstitial fibrosis involves residual walls of distal air spaces.*

Medicolegal Discussion

These Paraquat poisoning cases raise a number of questions in the public health community. The herbicide is very toxic. Over 60 deaths have been reported from its accidental ingestion. The chemical is a useful agricultural agent sold in a powerful concentrated form of which a small volume is sufficient for toxicity. Serious hazards are associated with its use. On the commercial container are a number of precautionary statements. However, the advertising, combined with the agent's effectiveness, have resulted in significant secondary distribution to associates of the commercial users. This and similar chemicals have been placed in improvised containers which do not bear the warning label calling attention to their hazards and often fall into the hands of individuals, inexperienced in their handling, who unwittingly expose themselves and others to danger and possible death.

Unfortunately, there are relatively few regulatory laws which protect the citizenry from these hazards. Only a small number of legal jurisdictions limit the sale of these hazardous substances to properly qualified and trained professional users, and there are few laws which prohibit the transfer of such chemicals to unlabeled or inadequately labeled containers. Although there are numerous regulations requiring the manufacturer and distributor to label the container with appropriate warnings and necessary precautions, many of these are inadequate to give the ultimate consumer the necessary information for the proper use of such a substance. Consequently, the regulatory and criminal laws do not offer the public a significant umbrella of protection from such harmful substances.

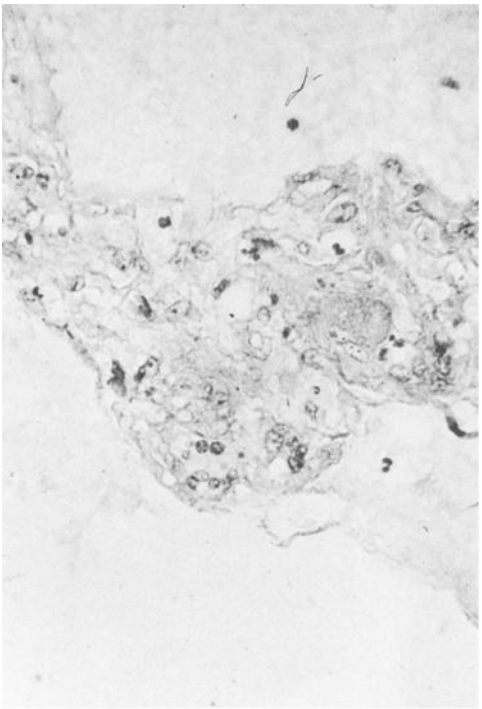

FIG. 9—*Paraquat poisoning. Close-up of septum between two air spaces showing proliferated spindle-shaped cells in wall. There is a thrombus in a small vessel.*

Accident Insurance—Consideration of the mode or manner of death in cases such as these may present a problem. In an instance such as the 6-year-old child in case 2B, who cannot possibly appreciate the hazard of this or similar substances, the determination of the manner of death poses no problem. Such cases are invariably unequivocally classified as accidental death.

When an adult ingests a lethal dose of such a substance, the problem is more complex. When death arises out of an overt suicidal act, benefits of accidental death and double indemnity payments are not derived. Of importance in arriving at the determination of the mode of death are the facts that the deceased in case 2A had a history of chronic alcoholism; with a previous propensity to taste various unknown liquids in order to ascertain whether they contained alcohol. She was apparently intoxicated at the time she consumed the herbicide. Also to be considered in evaluating this case is the unlabeled container and the information that the decedent, immediately upon developing gastrointestinal complaints, sought relief from her physician. It appears that this was in no way a conscious intentional act nor one performed with any actual knowledge that great harm or death would be the result. Thus there are no grounds for a ruling of suicide. The history of chronic alcoholism, considered to be a constitutional disease in one sense, or an addiction in another, might prove to be grounds for disallowing straight accidental death benefits. This is not invariably the case. In at least one state, accidental death benefits were awarded the estate of a known narcotic addict who died of a self-injected overdose, thus setting aside the consideration that drug addiction, for these purposes, was a predisposing constitutional condition. This was upheld at the state supreme court level.

Civil Liability—In each of these two instances, two major questions arise concerning potential civil liability for the death of the individuals. The first asks whether there is a legal theory under which a person or persons may be held responsible for the death and the second whether there is a possible defense to this liability based upon the considerations of contributory negligence or assumption of risk.

Upon initial inquiry one might ask whether the manufacturer might be liable for death caused by such a toxic agent. It is conceivable that he could be considered liable for such a death if an act of negligence is shown. It is quite unlikely that any court would hold the manufacturer liable under a theory of a breach of warranty or under strict liability. Although this chemical is admittedly very toxic, it would probably be shown that it has a redeeming social value, with numerous useful agricultural applications. The use of the product is virtually outside of the control of the manufacturer, without any practical opportunity for direct supervision. Consequently, it is likely that virtually all courts would hold the manufacturer would face liability only if it was demonstrated that he failed to take reasonable precautions in the distribution and use of the chemical. A court might impose a number of duties upon a manufacturer. If the company failed to label the agent, to include proper warning in accordance with appropriate regulations or laws of the hazardous substances acts, and, if this were a proximate cause of death, the manufacture might be considered liable. Of particular interest in consideration of the warnings is the necessity of the manufacturer to revise the warnings when more recent knowledge of the chemical and physiological effects of such a substance becomes available. A warning which is reasonable on a given date, based upon the knowledge available, might be considered inadequate at a later time, in view of experimental and practical knowledge derived since the earlier warning. In addition, the laws and regulations are constantly changing. The duties imposed by the laws and regulations do not end the implications involved in the duty to warn. In many instances the legal regulations are grossly inadequate when taking into consideration the practical use of the product. Thus, the manufacturer can meet the legal duty required by regulation but still give an inadequate warning to the consumer utilizing the product and thus be found liable under the latter theory. For example, the manufacturer may have two methods of distribution of the product. In the first avenue, it may be made available to professional spraying experts who are knowledgeable and well trained in the precautions necessary for the use of this and similar products. The warning on the side of the container may be quite adequate to appraise these professionals of the specific hazard involved with this chemical. Conversely, the manufacturer may also be distributing the product to retail sales stores, knowing that it is readily absorbed into the skin, and knowing that the atomized spray from the recommended garden type sprayer will certainly reach the lungs. The manufacturer should be apprised that the chemical would be used by persons who had not had any special training in the various precautions of handling such a product, and it should be common knowledge that the product may be spilled upon the hands, absorbed through the skin, or the aerosols inhaled. It is obvious that the risk to this consumer is far more substantial and the warnings should so state. There is a distinct possibility that the manufacturer could be considered liable for knowingly distributing a product to persons who obviously were not capable of taking the necessary precautions.

The manufacturer may attempt to limit his liability in such instances by printing on the sides of the container a notice that the product is to be used only by experienced or trained individuals. A recent court decision has invalidated such an attempt when it ruled that the fine print on the side of the package was too small to be considered reasonable notice of the hazards and, furthermore, the warning did not specify, in sufficient detail, the nature

of the risk. Also to be considered in such cases is the knowledge that the manufacturer was knowingly and intentionally distributing such an agent to retailers in locations where trained professionals were not available or the question of whether the manufacturer's advertising literature was of such a nature as to appeal to the general sale of the product rather than to the professionals in the field. The manufacturer's obligation to apprise the distributor of the risks should also be considered.

The manufacturer may, in addition, be liable for withholding dangerous knowledge about a product or for disseminating information found to be untrue. In case 2A, the patient lingered for over 30 days before expiration. Had a diagnosis of Paraquat poisoning been made immediately after ingestion, a significant question might be raised concerning the efficacy of renal dialysis, exchange transfusion, or other heroic measures. If the manufacturer's literature contained an incorrect statement that all of the agent is excreted within 24 h and this is subsequently brought to the manufacturer's notice by avenues such as medical literature, specifically in this instance, the previous case reports from Great Britain, the manufacturer may be legally responsible for disseminating false information which may have a significant effect upon the treatment which the patient would receive and the ultimate prognosis.

The distributors and retailers of a product such as this may also be held liable under rationales similar to those enumerated above for permitting unqualified persons to take possession and use these chemicals. In case 2B, however, the manufacturer and distributor are one step further removed from civil liability in that the poison was obtained by a farmer from an individual allegedly skilled in its use. This individual faces a serious risk of liability when he places such a dangerous substance in a nonlabeled bottle without clearly detailing, in writing, the necessary precautions for the drug, and permits it to be used by another individual not specifically trained in its use or precautions. He may be judged liable either for placing the toxic substance in a nonlabeled container, illegal by the hazardous substances act in the given jurisdiction, or for general negligence.

Finally, the householder who placed the open bottle in a position accessible to a 6-year-old may also be held responsible. If the householder was aware of the dangerous propensities of this poison, and placed this material in such a position, knowing that the child would not be similarly informed, this might constitute dangerous activity which might be legal basis for liability against the householder.

Pulmonary Carcinoma Following Uranium Exposure

Clinical Summaries

Case 3A—A 39-year-old uranium miner complained of pain in the left precordial area intermittently for 2 years. There was no history of cough, shortness of breath or weight loss. He had smoked ½ package of cigarettes per day since about age 14, but quit smoking at age 29, at about the time his brother died of carcinoma of the lung.

He had mined uranium for 15 years but quit mining 2 years ago. Because of his occupation, he had been repeatedly reviewed by sputum cytology on routine miners examinations and the uranium miners survey between 1960–1969. Repeated X-rays during this period were negative. Bronchial biopsies in October 1967, February 1968, and March 1969, were negative for malignancy.

The patient was hospitalized in August 1969, for evaluation of a left hilar mass reported by X-ray in July.

In August 1969, a left upper lobectomy was performed. This revealed a tumor 40 mm in diameter near the hilum, approximately 3 cm distal to the orifice of the upper lobe bronchus, with no evidence of metastasis.

Case 3B—A 55-year-old uranium miner, who was a heavy smoker, was hospitalized in June 1965, with complaints of intermittent febrile illness during the previous two months and a 20-lb. weight loss during this time. Chest roentgenogram was normal. Bronchoscopic examination was negative.

He was again hospitalized in October 1966, for treatment of urinary tract infection and diabetes mellitus. At this time chest roentgenogram revealed a linear infiltrate of left mid-lung field.

One month later, he was again admitted for bronchoscopy. Physical examination at this time revealed a Virchow's node on the left and a few palpable, firm, non-tender lymph nodes in the right supraclavicular area. The right supraclavicular lymph node biopsy revealed undifferentiated squamous cell carcinoma. The patient was considered inoperable and treated with nitrogen mustard. He expired 7 months later.

Postmortem examination revealed a small primary undifferentiated carcinoma of the main stem bronchus with extensive intrapulmonary, pleural, lymphatic, and hepatic metastases.

Pathology Discussion

The next two cases are of interest because they are representative of the culmination of studies over many years by Saccomanno of Grand Junction, Colorado, near uranium mining areas. Many of the patients that he has studied have also come from adjacent states. This work has been carried out very meticulously. It has now been proven that there is a very high incidence of cancer of the lung in uranium workers, exposed for a sufficient length of time. There are, of course, additional factors, among which is cigarette smoking. Most of the miners are cigarette smokers. The incidence of carcinoma is so high in this particular population that there is little doubt that the uranium is a major factor in the genesis of cancer. Similar problems arise with other occupational cancers; for example, asbestosis in its relationship to cancer of the lung, likewise appears to depend upon cigarette smoking as an additional factor in the vast majority of instances. Saccomanno, in following these miners, performed continuing cytological studies on sputum in the hope of finding early manifestations of pulmonary cancer. One of his most interesting findings is that most of these miners developed an undifferentiated type of pulmonary carcinoma, the so-called oat cell cancer, the same type of tumor which occurred in the miners in Central Europe in Joachimstal. These tumors were at first thought to be lymphosarcomas until Schmorl and others recognized that they were, in fact, undifferentiated carcinomas involving usually the major bronchi. Not all of the tumors in Saccomanno's series are of this small cell, undifferentiated or oat cell type. Some are squamous cell carcinomas, but it is the small celled tumors which have so high an incidence that it is highly probable that uranium and its daughter products are involved. There is not only epidemiological evidence but also biological evidence that these tumors are related to radon, which is a radioactive gas emitted from uranium as a decay product. This, in turn, has numerous daughter products, many of which are also radioactive and which continue to decay, with considerable radiation.

Case 3A—Early cytological preparations made in 1964 revealed cells which were atypical, but not diagnostic of carcinoma. In 1967 more atypical cells with rather bizarre nuclei were present with large squamous elements containing deeply staining nuclei. Such preparations may result in smokers from severe metaplasia or so-called carcinoma *in situ.* In 1967 examination of the sputum revealed quite bizarre cells (Fig. 10a) and most cytologists would certainly suggest that carcinoma was present.

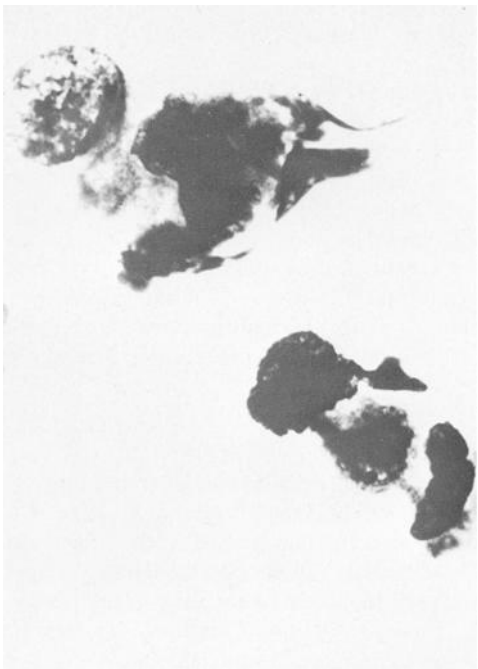

FIG. 10a—*Sputum cytology, uranium worker, 1967. Field with cells so highly atypical as to suggest epidermoid carcinoma.*

The patient's chest film in 1967 revealed a somewhat suspicious area in the left hilum (Fig. 11a). In 1968 there were bizarre multinucleated cells in a cytologic preparation. Most would accept these as tumor cells. In a bronchial preparation, prepared in 1969, was a clump clearly representative of squamous cell carcinoma (Fig. 10b). The chest film in 1969 clearly demonstrated a tumor in the left hilum (Fig. 11b). Biopsy revealed the lining epithelium to be atypical and invasion had occurred, representing an invasive squamous cell carcinoma (Fig. 12). Visualization of only the lining epithelium might pose difficulty in distinguishing carcinoma *in situ* from simple metaplasia. The disarray of the cells with atypical cells extending to the basement membrane, very much as in the cervix, suggests that this was, at least, carcinoma *in situ.*

The mechanism of the positive sputum is suggested by a plug of desquamated atypical cells in a fairly normal bronchiole.

Case 3B—The next case in this series is even more interesting because the cytological examination in 1965 revealed bizarre cells resembling squamous carcinoma (Fig. 13a). Some of these were highly suggestive although perhaps some would take exception to interpreting them as tumor. Examination two years later revealed cells which were diagnostic of anaplastic or oat cell carcinoma (Fig. 13b). This represents a rather remarkable finding of atypical squamous clls from surface epithelium in a man who ultimately developed an oat cell type of carcinoma, characteristic of that which develops following exposure to radioactive materials. In the sections is atypical hyperplasia of epithelium in some of the bronchi (Fig. 14), but the significant lesion is anaplastic carcinoma (Fig. 15).

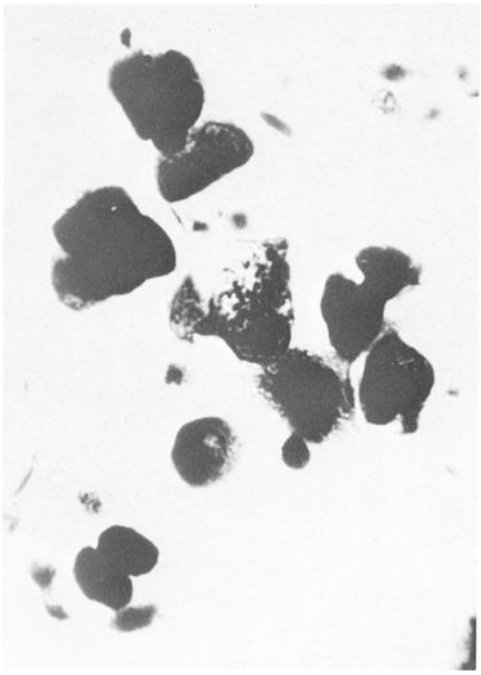

FIG. 10b—*Sputum cytology, 1969. Highly atypical squamous cells clearly indicative of squamous cell carcinoma.*

Saccomanno has intended to suggest the value of continuing cytological examination as a method of surveillance of such miners, yet in this instance, the cytologic findings were not representative of the actual cancer until its very end stages, when the oat cells were coughed up from the characteristic radiation associated tumor.

If a physician is maintaining surveillance of individuals working under these circumstances and atypical cells appear, there should be a vigorous quest to locate the tumor; however, if the man felt well and had no evident lesion radiographically, it would be difficult to deny him a living. Cigarette smoking in these individuals certainly increases the risk. Both of these miners stopped cigarette smoking, although they continued to work within the mine. (For the medicolegal discussion, see case 5.)

Analogue of Caplan's Syndrome in Sandblaster with Scleroderma

Clinical Summary

Case 4—A 44-year-old male worked for 17 years as a sandblaster cleaning out locomotive boilers. During the last 5 years of his life he had progressive respiratory insufficiency manifested by dyspnea, initially on exertion and finally at rest. Initial X-rays revealed bilateral small areas of infiltration scattered throughout both lung fields. These became progressively more confluent during the last year of his life, especially at the bases. His past medical history included scleroderma; however, this was not considered to have contributed to his ultimate demise. The terminal episode was one of progressive

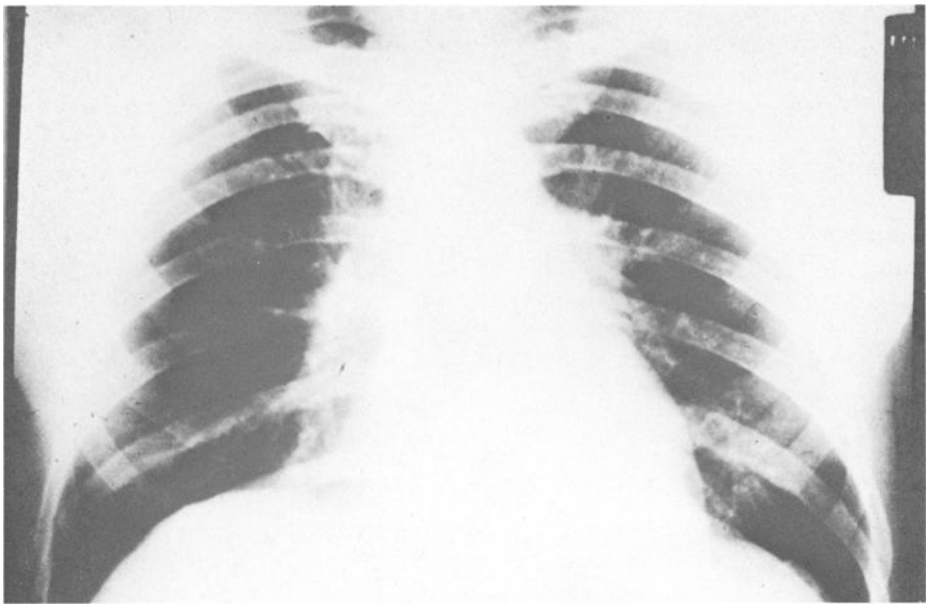

FIG. 11a—*Chest film, same patient; somewhat suspicious prominence in region of left hilum.*

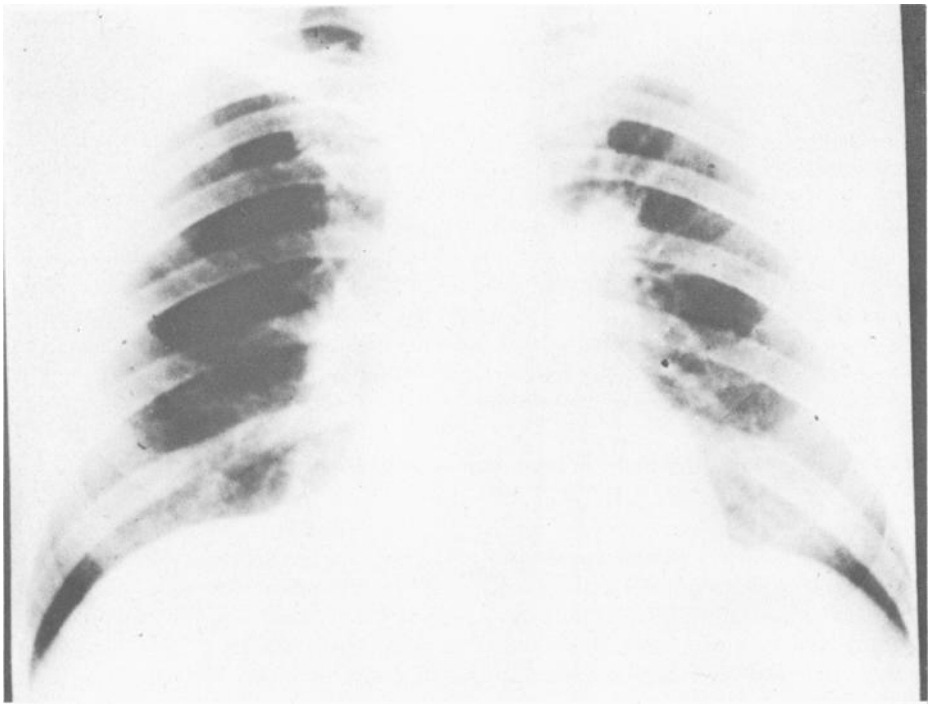

FIG. 11b—*Chest film, 1969. Prominence in left hilum has now increased. (Compare with Fig. 11a)*

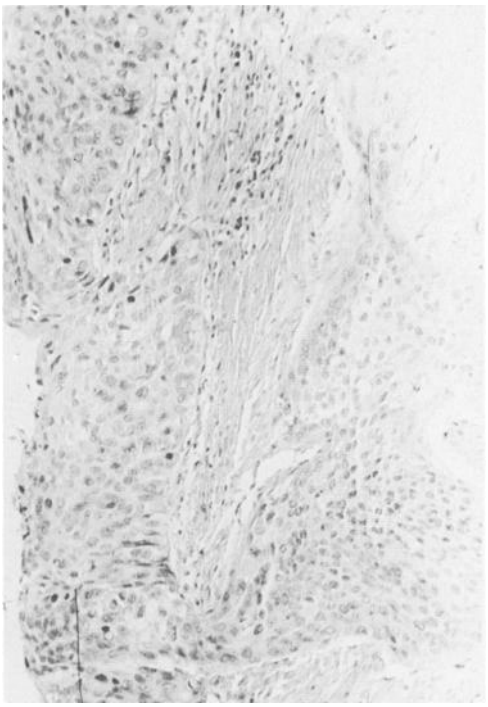

FIG. 12—*Histologic section, same patient, revealing invasive epidermoid carcinoma.*

pulmonary hypertension secondary to the changes within his lungs with progressive right-sided cardiac failure and death as a result of respiratory insufficiency.

At autopsy in the upper lobes of both lungs there were nondiscrete, firm, fibrous nodules which in some areas extended in finger-like projections into the adjacent parenchyma. In the lower lobes the lungs were uniformly, markedly increased in consistency, rubbery, alternately gray-tan and slightly red-orange. The fibrosis was confluent throughout both lower lobes. In association with these changes there was apical emphysema with pleural thickening overlying blebs measuring 2 to 3 cm in diameter. The heart was moderately enlarged with dilatation and hypertrophy of the right ventricle, moderate dilatation of the right atrium and minimal insufficiency of the tricuspid valve.

Microscopic examination, except for the changes within the lungs and the associated right-sided failure, was not unusual.

Pathology Discussion

This case presents the problem of a sandblaster who, for 17 years, was engaged in cleaning locomotive boilers, and who developed progressive respiratory insufficiency. There are some very interesting findings in this man who had scleroderma. The pulmonary lesions were becoming highly confluent, and were distributed predominantly in the bases of the lungs, suggesting that this perhaps represented an analogue of Caplan's syndrome. Originally this was described as a confluent nodular rheumatoid disease of the lung in coal workers. All of the features that have been mentioned were present; namely, massive confluence of lesions of pneumoconiosis, ordinarily scattered; second, predominance in

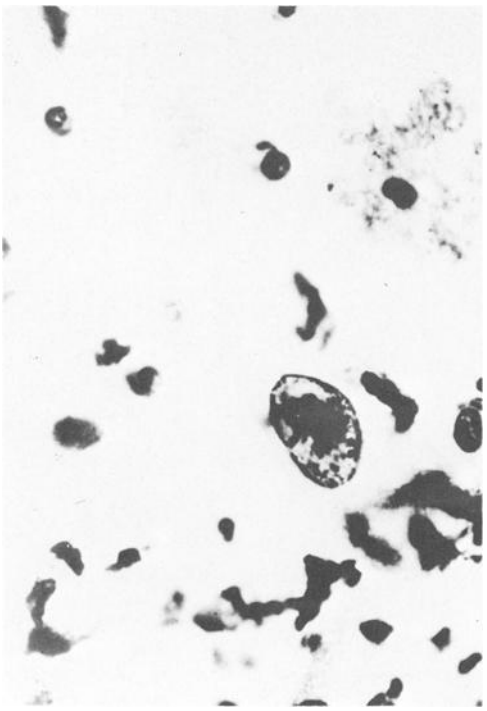

FIG. 13a—*Sputum cytology, uranium worker, 1965. Bizarre "tadpole" cells suggestive of epidermoid carcinoma.*

the lower lobes; and third, a relationship to blood vessels, which, unfortunately, cannot be demonstrated in this case. The question arises whether scleroderma, which might be related to rheumatoid disease, could produce, in a sandblaster, the same type of syndrome which occurs in patients with rheumatoid disease exposed to coal dust. Other diseases in which a similar kind of localization occurs include sarcoidosis, where inhaled dust may produce lesions resembling those of Caplan's syndrome.

One of the features of the present case which is deviant from that of silicosis, as ordinarily seen, is rather extensive calcification of hyaline material (Fig. 16a). This kind of calcification occurs rather commonly in rheumatoid disease.

At the margins of many lesions there is considerable pigment (Fig. 16b). When examined with polarized light, large quantities of crystalline doubly refractile material are not found. It should be stressed that such material may be absent in silicosis in sandblasters, and, while silicosis is not very common in sandblasters, it certainly may occur. However, in these lesions, rather than finding the doubly refractile crystalline material that is actually fibrous sericite, a complex silicate, there were partly refractile, minute granules (Fig. 16c). Firm evidence that this was silica can only be obtained by chemical analyses. Such findings have been observed in a number of instances of silicosis in sandblasters, by Groth of the Occupational Health Research Laboratory operated by the Public Health Service in Cincinnati, Ohio.

Another question that might arise in this individual, engaged for a long period in sandblasting locomotive boilers, is whether the lesion could, in part, be the result of inhalation of iron oxide. Might this be analogous to arc welders' disease? To some degree, this is probably true. A special preparation of the lung of this patient revealed considerable quantities of iron focally distributed. The iron oxide contributes very little, however, to the pathogenesis of the focal massive confluent hyalinized fibrosis present.

In another patient who had rheumatoid disease, not a coal miner, but a sandblaster with Caplan's syndrome, there is no fibrous sericite, but only doubly refractile material. There is a remarkable relationship of the lesions to blood vessels. Not only are the large mononuclear cells containing the deposited material concentrated about the vessels but

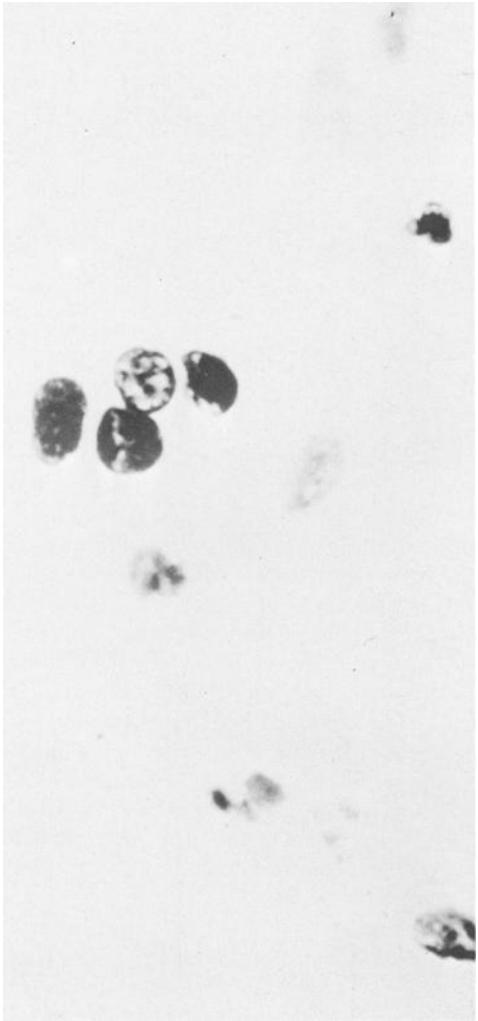

FIG. 13b—*Clump of small, extremely hyperchromatic, ovoid nuclei considered diagnostic of anaplastic carcinoma.*

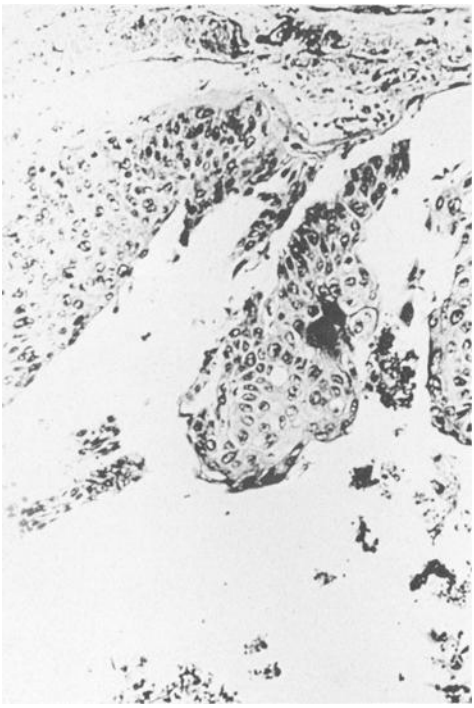

FIG. 14—*Biopsy, same patient, 1967. Atypical squamous hyperplasia of epithelium of bronchus.*

the vessels themselves reveal focal necrosis with palisading of cells similar to the lesions of rheumatoid arthritis, as described by Caplan and Leopold. Such a lesion could represent an infectious granuloma, but the tissue was cultured at lung biopsy, as should always be done, and the cultures were negative for acid fast bacilli, fungi, and other organisms. In patients with rheumatoid nodules in the lung, without pneumoconiosis, are characteristic foci of necrosis surrounded by cells in a palisaded arrangement.

The first paper on the peculiarities of pneumoconiosis in coal miners, associated with rheumatoid arthritis, was by Caplan from Gough's department in Wales. Subsequently, a more extensive review was written by Gough and his associates. Subsequent reports have demonstrated the existence of the same complex in boiler scalers and foundry workers with rheumatoid disease. The evidence in this case suggests that the syndrome with another "collagen disease" may not be different from that with rheumatoid disease.

In a patient with arc welder's disease, radiographically there is a stippled perihilar appearance. Histologically there is abundant black material mingled with some dark brown material. The latter is not hemosiderin but iron oxide, demonstrable by iron staining. A number of these patients have, in addition, infectious granulomas. Most of these are reported from Ohio and Wisconsin and have associated histoplasmosis. A number also have associated adenocarcinomas. It is not generally acknowledged that lung cancer is associated with arc welders' disease. These tumors have all been isolated lesions and have all been adenocarcinomas of the peripheral type. It should be pointed out that carcinoma of the lung is not rarely associated with interstitial fibrosis. (For the medicolegal discussion, see case 5.)

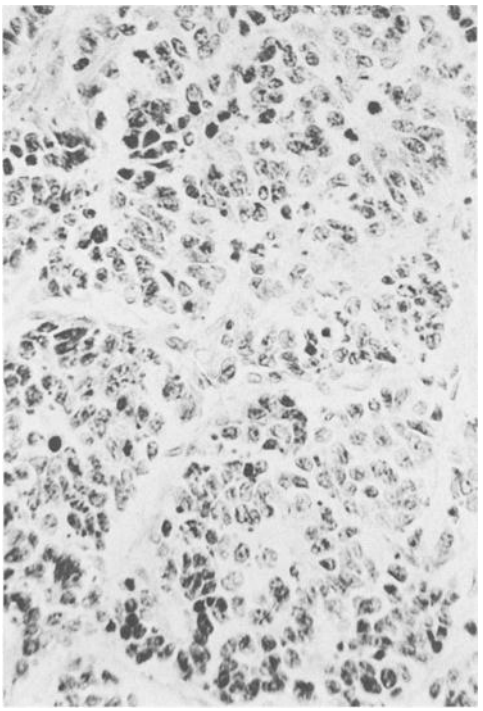

FIG. 15—*Histologic section demonstrating anaplastic carcinoma.*

Pleural Mesothelioma Developing in Association with Asbestosis

Clinical Summary

A 55-year-old Caucasian male had an occupational history of exposure to asbestos for 30 years as a naval shipyard pipe coverer both on board ships and ashore. His past medical history included progressive dyspnea, initially an intermittent dry hacking cough and, for the last 10 years of his life, productive constant cough associated with considerable expectoration. Serial respiratory function tests revealed a progressive decrease in vital capacity associated with a progressive decrease in efficiency of gas exchange. Roentgenographic examination initially revealed scattered small densities in the lower lung fields. These were associated with thickening of the pleura. A progressive confluence of these densities was associated with a marked progression in the thickening of the pleura which ultimately revealed the development of a neoplasm in the right lower lung field. The patient expired with progressive respiratory insufficiency, right-sided cardiac failure, and direct extension and indirect intrathoracic metastasis of the malignant neoplasm. Biopsy one month prior to his demise revealed the nature of the tumor which was considered to be inoperable.

Pathology Discussion

The tumor in this patient, extensively involving the pleura and adjacent lung (Figs. 17 and 18) is composed of proliferating cells that are quite bizarre and certainly represent a neoplasm. The subjacent tissue is densely fibrous with many highly atypical cells entrapped

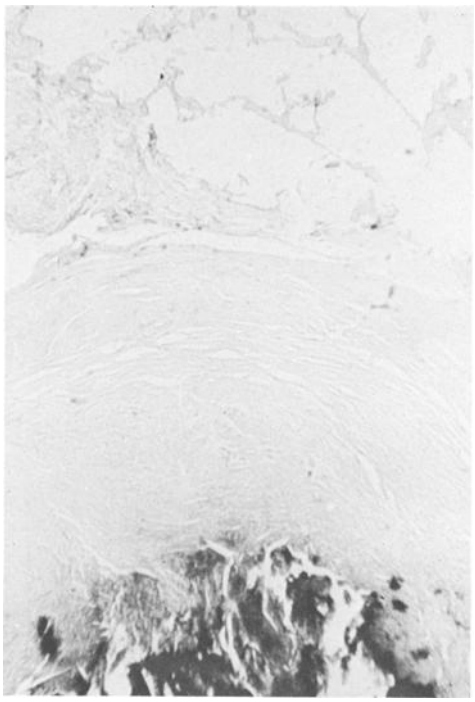

FIG. 16a—*Caplan's Syndrome. A rounded, hyalinized lesion with central calcification. In many foci such lesions form large confluent masses.*

within. With such atypical cells occurring en masse in the pleura, the first consideration should be of metastatic carcinoma, either from an extrathoracic source or, more likely, from an intrapulmonary origin. Willis, the Australian pathologist, has stressed this point, perhaps to an extreme, even holding himself forth as a nonbeliever in the existence of mesotheliomas. However, the very association which exists in this man, of a pleural tumor with asbestosis, suggests that Willis was probably incorrect and that there is an entity, mesothelioma, which may extend into the lung and insinuate itself into the vessels (Fig. 19). Mesotheliomas are unusual in that they may involve lymph nodes within the thorax, but do not often metastasize outside the thorax. The tumor may often begin on one side of the thorax, spread to the adjacent lymph nodes, the subcarinal tissue within the lung, and then extend to the opposite pleura without ever metastasizing outside of the thorax. These tumors tend to have very little alcian positive material, and very little, if any, PAS positive material.

In the lung in this case was moderate scattered fibrosis. Within the interstitial fibrous tissue was black pigment and interesting linear brown bodies with bulbous projections like a shishkebab stick (Fig. 20). In appropriate stains, these were found to contain iron. It has been pointed out by many that these should not be designated asbestos bodies, or even asbestosis bodies, since other conditions may produce intrapulmonary structures resembling these. Caution is necessary, before concluding, without further evidence, that the principal disease is asbestosis. The history confirms the fact in the present case.

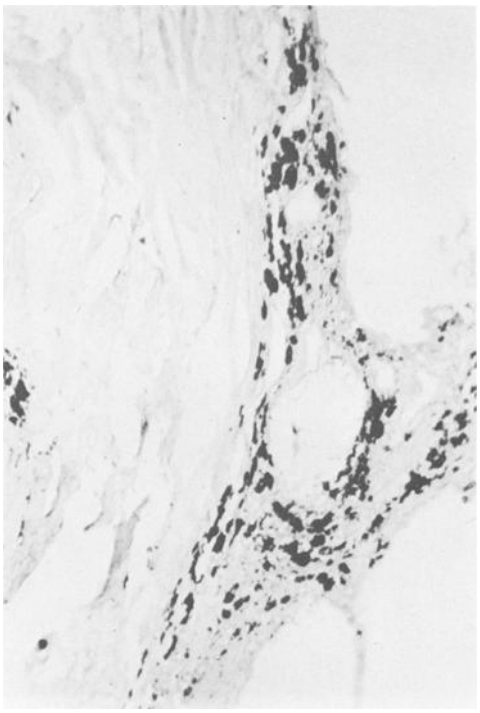

FIG. 16b—*Masses of dark pigment at margin of this lesion.*

A pleural mesothelioma which began on the right side, in a man 43 years of age, without known history of exposure to asbestos, revealed superficial invasion of the lung but the lesion was primarily pleural. Characteristically in diffuse pleural mesothelioma, there are residual areas of pleura free of tumor. Characteristically in the diffuse type of tumor there is also an admixture of epithelial and sarcoma-like components. Sometimes these have an almost cartilagenous appearance. A pleural biopsy obtained with a thoracoscope contained mostly epithelial tissue. Pleural sediment revealed a mixture of epithelial and spindle cell structures suggesting the diagnosis of mesothelioma, found later in autopsy tissue. In this patient, just as was described, the lymph nodes in the thorax were involved and there was extension to the opposite lung. Ultimately, there was involvement of the pleura with massive hemothorax on the opposite side.

Asbestosis bodies may be found within the tumor itself, but usually are found only in the lungs. These bodies may be demonstrated by iron staining. The material which encrusts fibrous minerals, including asbestos, is rich in iron. The same procedure may be employed on sputum for demonstrating asbestosis bodies.

Localized pleural mesotheliomas are composed essentially of spindle cells and the vast majority behave in a benign fashion. Some have called such tumors fibromas, but Murray has demonstrated that, when grown in tissue culture, the cells resemble mesothelioma, not fibrous tissue. Furthermore, inspection of the surface covered by mesothelium reveals actual transition to the spindle celled dominant component of the tumor.

FIG. 16c—*High magnification of same lesion under polarized light. Rounded, partly refractile, minute granules are seen, but there is no crystalline substance suggestive of fibrous sericite.*

A third type of mesothelioma behaves in an intermediate fashion. While still being localized, it nevertheless invades the lungs. These tumors are composed mostly of spindle cells with many mitoses. They do not tend to metastasize, but, when they are removed, they tend to recur, and the prognosis is not as good as with the localized spindle cell form. As soon as the cells invade, the prognosis becomes much more serious.

A question is often raised concerning the significance of asbestosis bodies at autopsy without a history of asbestos exposure. In examining the lungs of people who live in cities such as Miami or Cleveland, the pathologist finds such bodies usually in direct proportion to his diligence in the search. This is extremely interesting and, to some people, alarming, because this might constitute a basis for an epidemic of cancer. It has been found in animals that in order to produce mesotheliomas, it is necessary to introduce massive quantities of asbestos; probably the same phenomena is true in human beings. Before fibrosis appears, long occupational exposure usually is necessary. There are a few exceptions to this, among housewives who have insulated their own cellars or attics, but these are very uncommon. Only those having pulmonary fibrosis associated with asbestos develop carcinoma of the lung or mesothelioma, so, at present, there does not seem to be any great cause for alarm in finding asbestosis bodies in lungs carefully examined in thick sections using iron stains. Structures resembling asbestosis bodies may be produced in the lung in congestive heart failure. These are accumulations of hemosiderin related to protein particles very much resembling asbestosis bodies.

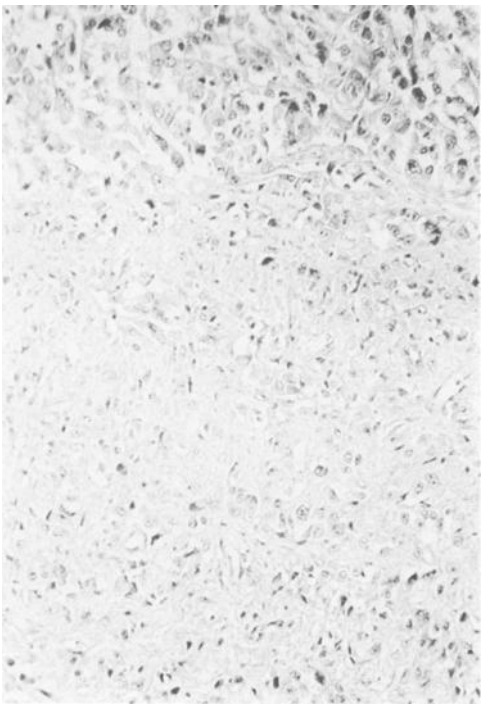

FIG. 17—*Mesothelioma involving pleura. Extending into the former pleural cavity at the right are masses of bizarre, polygonal, and spindle cells. At the top is the visceral pleura that is thickened by fibrosis and by invasion of cells of similar type.*

It is of great interest that Selikoff and Hammond, in their studies among asbestos workers, have found that all who developed pulmonary carcinoma have also been smokers. The relationship of smoking to the development of mesothelioma is not so well established.

Asbestosis is also associated with peritoneal mesothelioma. A patient, exposed to asbestos, developed abdominal pain, distention, and intestinal obstruction. The peritoneum was tremendously thickened, both on its visceral and parietal surfaces. Microscopically, the tumor had all of the characteristics of mesothelioma, with bizarre cells, some of which were in mitosis. This patient had no asbestosis bodies in the peritoneum but had focal pulmonary fibrosis. This patient, like so many others, also had evidence of talc crystals which, under polarized light, were doubly refractile.

People in dusty trades are apt to continue to work in dust. Thus, one often finds multiple mineral substances, either at lung biopsy or at necropsy, and one should explore the occupational history very carefully. This, of course, is of medicolegal significance, since it may be the less obvious material that is responsible for the greater pulmonary damage.

The term "asbestos" in chemical parlance is not very meaningful and refers to a number of fibrous minerals, of which at least five are of some industrial importance, one much more important than the remaining. In Africa, where the material is mined, a large number of natives have developed a rare tumor, mesothelioma, and Wagner and others who have studied this neoplasm have made a fascinating contribution in demonstrating this relationship.

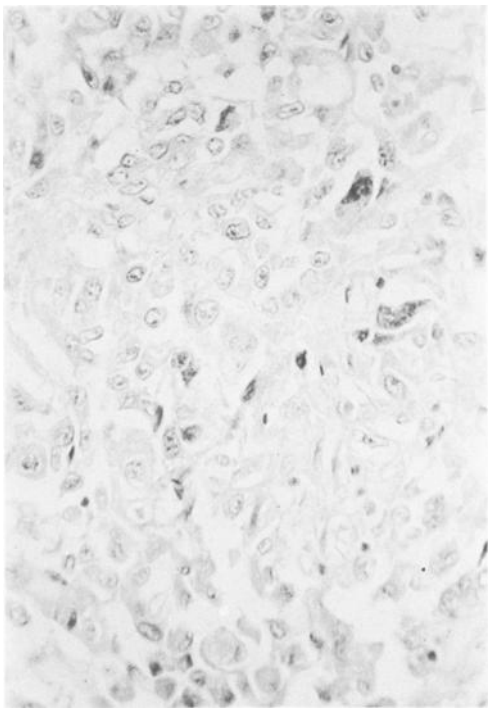

FIG. 18—*Bizarre, rounded polygonal, and spindle cells of the pleural mesothelioma.*

The cellulose fibers identified in the cases of bagassosis reported from New Orleans, resemble vegetable material and present no similarity to asbestosis bodies. The lesions are similar to those of farmers' lung with multiple tiny granulomata.

Medicolegal Discussion

Cases 3A, 3B, 4, and 5 are joined for discussion of medicolegal problems which they share, while the unique medicolegal questions of each case are discussed thereafter.

Causation—Each of these cases presents a medical problem which arises from exposure to hazardous substances in an industrial occupation. The resulting diseases are common and ultimately severely disabling. They exact an enormous toll of decreased productivity, premature retirement, loss of family respect, and early death. The economic loss to the family of a breadwinner stricken with one of these diseases may cause profound changes in social standing, standard of living, and educational opportunities to the children. Historically, society has never made available to these victims adequate compensation for their affliction. Dating from the earliest ages of formation of the roots of our legal system, an employer was not considered responsible for disability of his coworkers. Thus there was, and still is, no available system for distributing the economic costs of such activities amongst the consumers of the manufactured product associated with the disability or society in a more general sense. Hardships exacted by this injustice prompted the enactment of workmen compensation laws. The basic premise of such regulations was to compensate individuals for the losses caused by illness or disability resulting from their occupation.

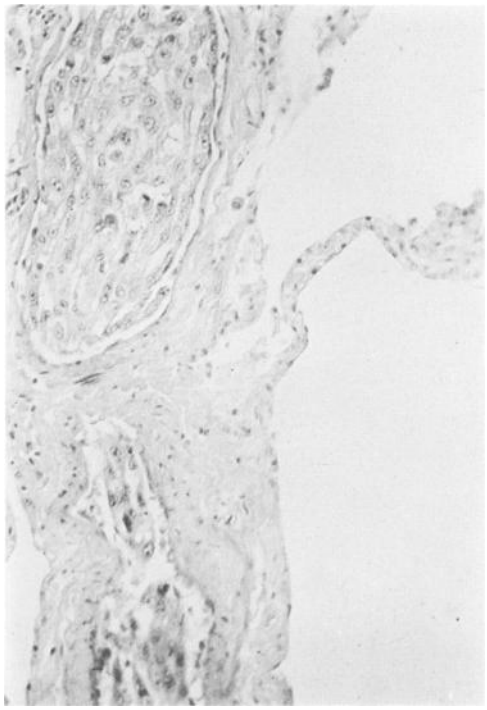

FIG. 19—*Masses of mesothelioma within intrapulmonary vessel.*

Even in their inception, however, these laws were a compromise. Employers recognized the great cost of fully repaying these industrially disabled individuals for such disability and no attempt was made to compensate a man for wages lost, but, rather he was awarded a fixed sum for a given disability. Thus, if a man lost a finger in the course of his employment, the extent to which he used that finger for his vocation was not considered in the settlement. A pianist, a hod carrier, or an individual who primarily used his intellect for a living would all be awarded a fixed dollar amount for loss of this portion of their body. The established awards are usually specifically written into the workmen compensation rules, which are generally state regulations. Often the amounts fixed many years ago remain on the books as inadequate compensation for present and future disease and disability. Under the laws of many states, a 20 to 25-year-old man with a 40 year work expectancy may be compensated only to the equivalent of one and a half to two years wages for an industrial accident that left him so paralyzed or crippled that he was unable to engage in any occupation to maintain his family.

Prior to workmen compensation laws, it was held that a worker could not make a claim against his employer for injuries or disability that resulted from the fault of a fellow worker nor could he make a claim for any injury or illness if he knew or should have known that his employment offered a risk of such injury or illness. Under such rules, virtually all industrial concerns were completely exempted from occupational disease claims, since most accidents were considered to be caused by fellow workers, and most employees had sufficiently long time in service to become exposed to industrial disease.

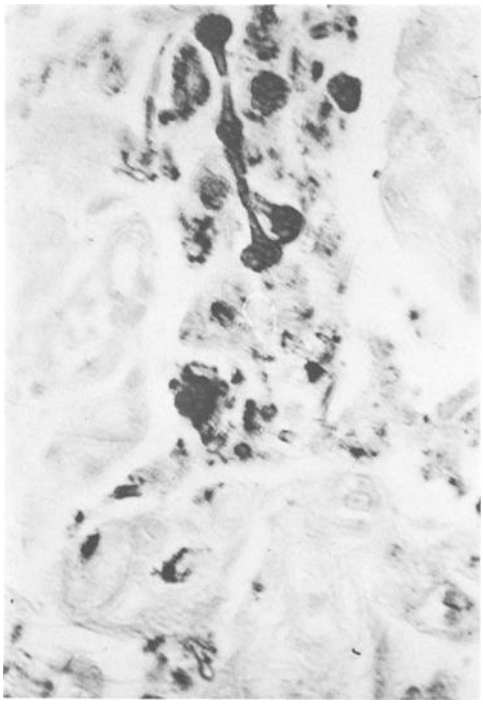

FIG. 20—*Typical "drumstick" or "shishkebab" asbestosis bodies within pulmonary tissue. The brown color results from impregnation of proteinaceous material with iron.*

The net result of these severe restrictions on the ability of an employee to otherwise make a claim has been a striking swing toward more liberal interpretation of the compensation laws, such that, in most courts in many states, employers are required to pay for virtually any disease or disability which has even a minor actual connection with the employee's occupation. Ultimately, this may be reduced to a legal proof of causal connections between the occupation and the resultant disease or disability before the worker can receive settlement. This proof of causation often requires the ultimate in sophisticated medical testimony. In its skepticism the law has historically regarded medicine as an art rather than a science. This position has been reinforced by innumerable examples wherein the medical opinions of competent physicians have clashed directly, one with another. It is very common to see physicians disagree in the courtroom on the clinical diagnosis of a patient; and, in the absence of confirmatory laboratory findings, it is often virtually impossible to objectively disprove the clinical conclusions of either. The etiology of some diseases may pose similar problems. In many medical conditions the etiology and often the pathogenesis is a matter of conjecture. Such a dilemma is illustrated in cases 3A and 3B wherein carcinomas of the lung have developed in individuals who had exposure to two agents known to be associated with the development of this neoplasm, an occupational exposure by uranium mining and a long history of cigarette smoking antedating the occupational exposure. Statistical studies reveal an increased incidence of pulmonary carcinoma upon exposure to either of these agents, yet no physician would deny that pulmonary carcinoma may occur without exposure to either. The legal question this

presents is: Did the pulmonary carcinoma arise due to (1) exposure to uranium during mining, (2) exposure to cigarette inhalation, or (3) exposure to an unknown agent which may be responsible for those neoplasms in the absence of either the first or second. It should be immediately apparent that multiple etiologic agents play a role in these cases, and it is impossible to ascertain quantitatively the role of one or the other to the exclusion of the remaining.

Often in civil litigation, the law makes impossible demands upon the physician by asking him to testify with reasonable medical certainty that a disease was "caused" by a given factor and was "not caused" by another. Obviously the well trained physician recognizes that there are rarely absolute answers to such questions, and the law thus places the premium upon the testimony of the physician willing to perjure himself by claiming such an absolute certainty while he might actually feel that there is a possibility of other considerations. Such a premium is also placed upon the testimony of the uninformed physician who may not be aware of a recognized correlation by etiologic agents other than that which he desires to attribute the disease to. This legal philosophy, therefore, places ethical burdens upon any physician, and often leads to a real art of gamesmanship in court. It is well known within many of the bar associations that there are certain physicians who will commit themselves repeatedly to absolute statements that are not scientifically justified, either because of ignorance of all the facts or their desire to assist in a favorable verdict, or, in some instances, because of the remuneration. Thus, a physician may "go to court" for a patient or his widow and commit himself to such an absolute stand in order to compensate for what he feels is an obviously unjust law which should be dealing in probabilities. In cases 3A and 3B, the physician might feel that the increased incidence of carcinoma of the lung among uranium workers would justify requiring the company to pay all such claims, irrespective of other known or unknown contributing factors which may play an etiologic role in the development of the neoplasm.

A philosophy of a particular physician may thus become implicitly known to the attorneys in a given locale and thus, in most sections of the country, an individual who can be relied upon to advocate a position based upon such conscious or subconscious philosophy can be recognized by both plaintiff and defense attorney groups. The obvious result of this is the semifarcical court room drama wherein apparently eminently qualified physicians sharply disagree with each other on the witness stand. As a result of this obvious exercise in ethical gymnastics, the law has changed slightly in workmen compensation. Whereas in civil and criminal litigation, the previously discussed rules apply, within the realm of workmen compensation, many states have adopted a far more liberal rule which does not require the physician to commit himself to such an absolute position. Under this legal theory, a number of courts have held that it matters not whether one can be absolutely certain that a given agent, such as exposure to silica dust, was the sole cause of the patient's problem, if it can be shown that the agent was a contributing cause of the disability or death. When such is determined, the employer is usually responsible under the workmen compensation acts for resulting disability. Obviously it becomes easier to take a more tenable position in court under this ruling than under the philosophy of reasonable medical certainty. The implications of this, however, have frequently extended beyond the understanding of many physicians, leading to rulings in many states which have required an employer to be financially responsible for myocardial infarctions where there is medical proof that during the worker's employment, additional exertion or stress made a significant contribution to the onset of the illness, disability, or death. Thus, it is readily apparent that in many areas a new level of medical inconsistency has been reached in an attempt to arrive at a level of legal consistency.

Another problem related to testimony concerning causation in workmen compensation litigation frequently arises when a person has been employed by more than one employer, each of whom has required exposure to an agent or agents leading to the same clinical condition. For example: an asbestos worker may work for five different companies over a period of 30 years, doing the same task with each company, before finally developing sufficient symptoms to be legally disabled for the purposes of compensation. This difficulty has arisen because the law does not provide for any compensation for a person who is made more prone to a disability by exposure to a toxic agent. Thus, such an individual may work for 26 years, developing increasingly significant X-ray findings and increasing dyspnea without the employer being responsible for disability under the workmen compensation laws. This company may then recognize its impending liability and terminate the worker, who then goes to work for another firm. The patient may then develop severe incapacitating respiratory symptoms over a short period measured in months to years. Although the first employers have been the substantial cause of the person's final disability, the exposure to work by the last employer may have been the ultimate cause of vocational disability. Legal difficulty may result in several alternative forms of injustice. The employer who added "the last straw" of pulmonary disability may be financially responsible under the workmen compensation laws for a total disability in the worker. In such a situation the worker may not be employable after being released from the first company because of this potential impending claim, and he may find himself physically capable of working in that particular trade as his pulmonary insufficiency is not incapacitating at that time, yet he may find that no firm desires to hire him, faced with such a potential claim. This dilemma often results in such an individual being unemployed at the only vocation for which he has suitable training or experience. Although this interaction of economics may prevent him from proceeding to a complete pulmonary disability, this may indeed be a mixed blessing.

Negligence Claim—As the inequities of the workmen compensation system have become more obvious, a number of detours on this road to economic justice have developed. Although no universal change has taken place, a few states and a few industrial situations may justify a negligence claim. Such a claim may be brought against an industrial employer for negligence or for violation of statutory or industrial codes providing for a safe or healthy working environment. Where such a claim is permitted, a multitude of problems discussed elsewhere may arise, including the proof of causation, with reasonable medical certainty, as discussed heretofore.

Cigarette Smoker's Dilemma—Since the Surgeon General's report associating cigarette smoking with carcinoma of the lung, a number of law suits have been brought against the cigarette manufacturers, under various theories, in an attempt to collect for the death or disability of a smoker who subsequently developed carcinoma of the lung. Most of the hypotheses upon which these cases have been based have been thrown out of the courts, leaving the claimant without recovery. In addition to the uncertainties that have been raised concerning the causation of carcinoma by cigarette smoking, the query of whether the manufacturer or the consumer or both knew about the dangerous propensities of the product has been raised, the supposition being that, if a manufacturer knew of its hazardous qualities, he should be responsible and alternately, if the consumer had reason to suspect the inherent dangers, then the consumer was assuming the risk and, therefore, could not recover. Most of these cases have ultimately been resolved in favor of the cigarette manufacturers. However, a very few courts have rules that, if it could be shown that cigarettes were not reasonably safe for use by the general public, the manufacturer had breached an implied warranty fitness for human consumption, and would be re-

sponsible for the resulting death or disability, even though the company did not know that the cigarettes were harmful. The effect of this ruling was to make the cigarette manufacturers responsible for the death or disease of a cigarette consumer if there is reasonable and acceptable medical proof that (1) the cigarettes actually caused the disease and (2) that the cigarettes were not safe or fit for human consumption. This may initially appear to be a relatively simple hypothesis to prove until consideration is given to all of the inhalants to which such an individual may be exposed within his lifetime, including, of course, those within his natural urban environment.

The most difficult problem to resolve to date, however, evolves from the fact that most people have changed cigarette brands a number of times during their smoking career, thus raising the issue of which brand was responsible for development of the pulmonary carcinoma. Intellectually, objective physicians may thus have a great difficulty in testifying in court, with reasonable medical certainty, that a certain brand of cigarettes was the cause of a person's pulmonary disease, to the exclusion of a second or third variety.

Diffuse Alveolar Damage (Oxygen Toxicity) and Possible Earlier Fat Embolism

Clinical Summary

Case 6—The patient was a 20-year-old Caucasian female involved in a vehicular accident. The motorcycle on which she was riding was struck from the side by an automobile. The patient arrived in the emergency room conscious with pulse 76, respiration 20, blood pressure 120/64. Physical examination revealed abrasions over the lower extremity and buttock and an external rotation of the left foot. Roentgenograms revealed a comminuted, displaced fracture of the midshaft of the left tibia and fibula. This was treated by reduction. The postoperative course was uneventful for 48 h. Chills and fever (temperature: 102 F) developed on the third postoperative day, followed by tachypnea, tachycardia, cyanosis, and confusion. Petechial hemorrhages were noted on the conjunctivae, chest, and axilla. Roentgenogram revealed bilateral pulmonary infiltrates. The patient was treated for fat embolism with 5 percent ethanol in 5 percent dextrose in water and heparin. However, her hematocrit dropped to 24 from 40 percent on admission on the fourth postoperative day.

On the fifth postoperative day the patient was placed on the respirator. Blood gases at that time were: pO_2, 84; pCO_2, 24; pH 7.46, at oxygen saturation of 98 percent. She remained on the respirator for the terminal 3 days with high O_2 concentrations. Blood gases deteriorated to: pO_2, 40; pCO_2, 23; pH, 7.47; with oxygen saturation of 85 percent. Hemoglobinuria developed and the heparin and dextrose were discontinued. Serum hemoglobin at that time was 440 mg% (45–100 mg% normal). Urine hemoglobin was 216 mg%. The blood administered two days earlier was recross-matched and found compatible. The laboratory elucidated no other cause for the hemoglobinemia. Terminally (postoperative day 8) an endotracheal tube was changed; the patient became apneic, and had a cardiac arrest from which she was unable to be resuscitated.

Postmortem examination revealed heavy, dark red-brown lungs which on section appeared mottled and exuded foamy pink fluid. Other organs, namely, kidneys, brain, and meninges, were unremarkable.

Pathology Discussion

The problem presented in this case is the determination of the nature of the initial respiratory insult, whether an episode of fat embolism, possibly culminating in respiratory damage or another example of "respirator lung," "oxygen toxicity lung," "respiratory distress syndrome," "shock lung" or some combination thereof.

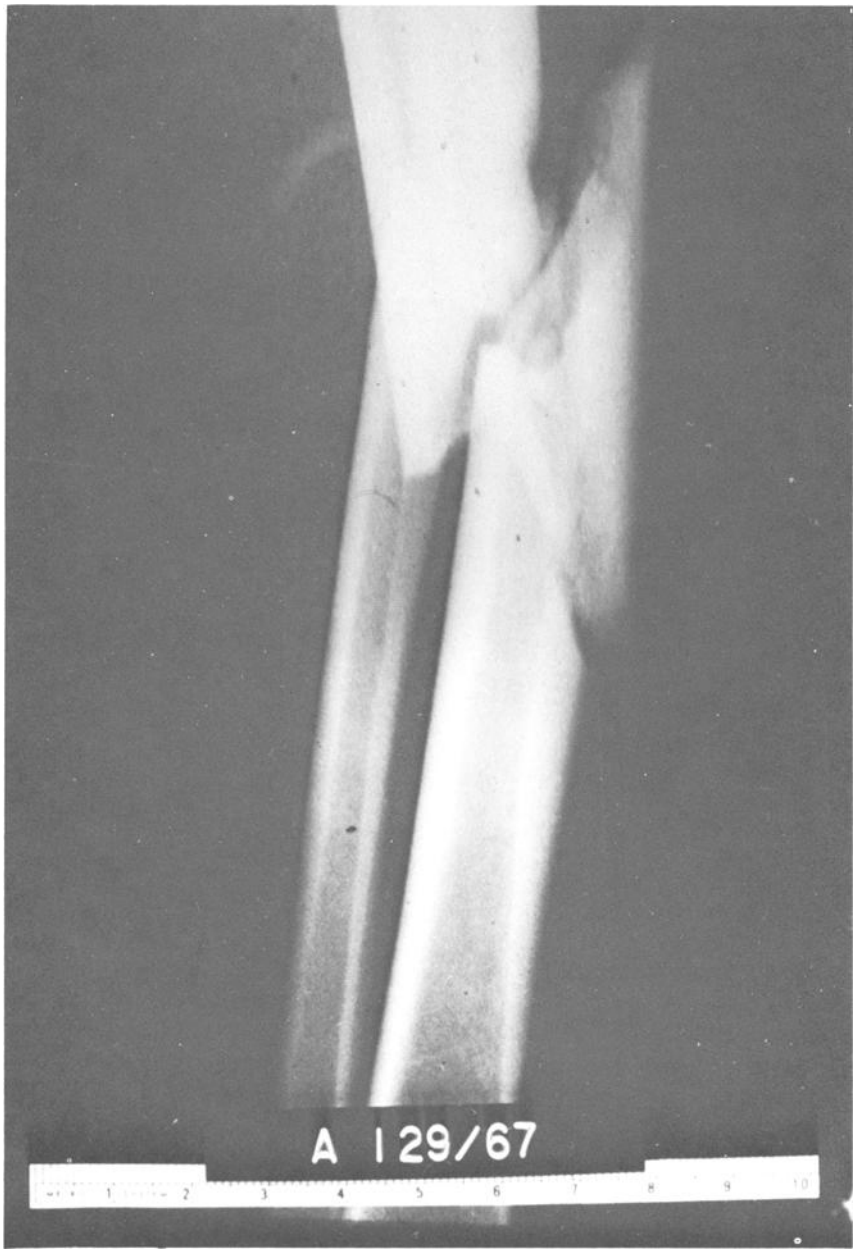

FIG. 21a—*Roentgenogram demonstrating fractures of tibia and fibula, occurring during motorcycle accident.*

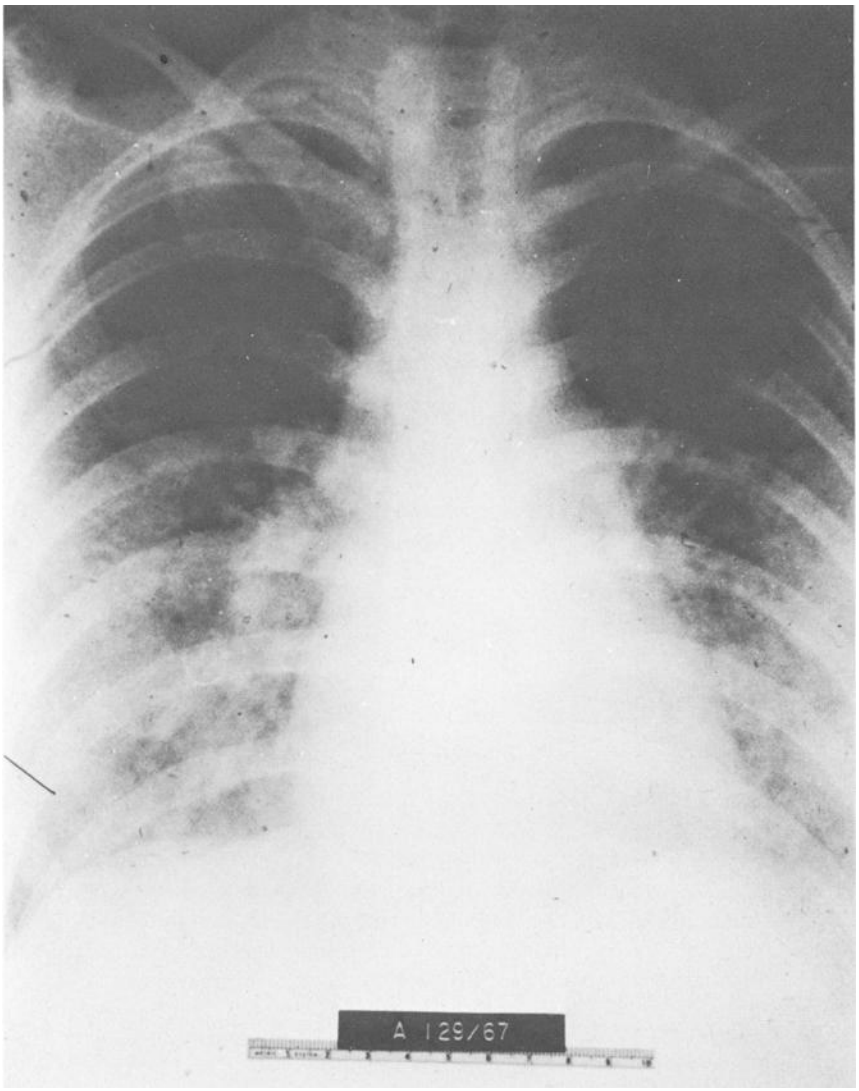

FIG. 21b—*Chest film, shortly before death, revealing somewhat irregular but diffusely hazy appearance.*

The extensive fractures are certainly sufficient to have resulted in fat embolism (Fig. 21a). In fact, shaking trauma may produce fat embolism. In a chest film before death, a diffuse haziness (Fig. 21b), corresponding to the lesion at autopsy on the eighth day after injury, was noted. Hyaline membranes in the process of organization are present (Fig. 21c). These membranes ultimately may become completely organized and thus seemingly part of the interstitial substance of the lung. This process is extensive in this patient, and is identical to others with so-called "oxygen toxicity." Many of the lining cells, in the regenerative process, are highly atypical; some are in mitosis (Fig. 21d). Thrombiotic lesions present in many patients who have acute respiratory distress syndrome or "shock

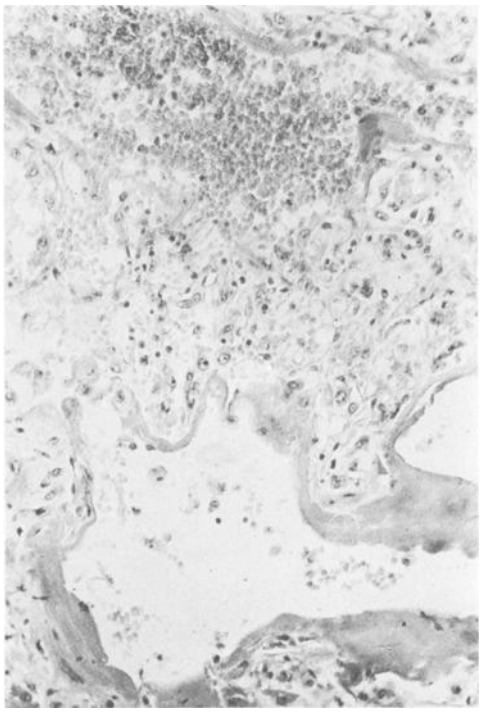

FIG. 21c—*Massive hyaline membranes, focal hemorrhage, extensive proliferation in walls of alveoli, and of alveolar lining cells.*

lung," are noted in vessels of various sizes. In this patient there is no evidence of any fat in the glomeruli or within the lungs. The hyaline membranes contain, as is always the case, a small quantity of material that stains with the Sudan dye, and the large mononuclear cells, as they become elderly, begin to contain lipid material. At the time of autopsy there was no evidence of fat embolism. In experiments carried out by Halasz andMarasco some years ago, homologous homogenized fat was injected into the right atrium of dogs and produced minute emboli, which may result in all of the manifestations of acute cor pulmonale. In those animals that survived, fat was absent when the lungs were examined a few weeks later. It is, therefore, impossible to say whether some of the early changes in this patient's lungs may have been caused by fat embolism although the major lesions are those of oxygen toxicity or shock lung, not from fat embolism as we have come to recognize it.

In view of its medicolegal significance, it may be well to discuss some aspects of fat embolism. Fat embolism may occur without trauma; for example, in sickle-cell disease, with multiple infarcts in the bone marrow. In the studies of Halasz and Marasco, it appeared that the first effect is the blocking of pulmonary capillaries, resulting in immediate pulmonary hypertension, followed by a reflex analogous to the Jarisch-Bezold reflex which was associated with slowing of the heart, apnea, or very rapid shallow breathing and systemic hypotension. Cardiac output was diminished because the pulmonary capillaries are blocked by emboli and also possibly by reflexly induced vasospasm.

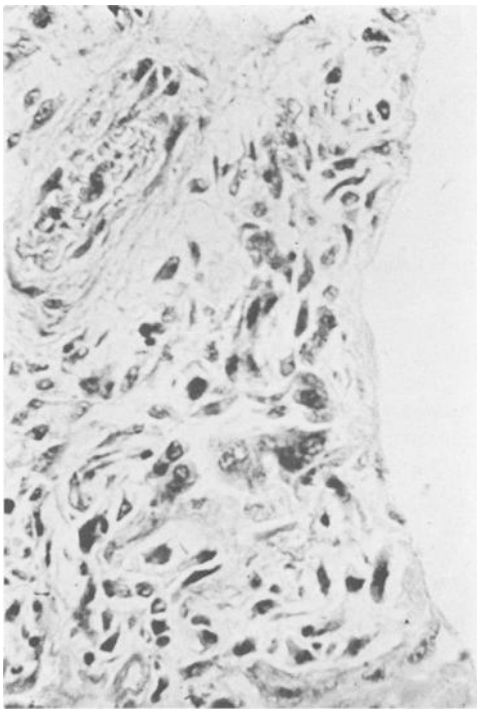

FIG. 21d—*Lining of distal air spaces revealing early organization of hyaline membranes and extensive atypical proliferation of alveolar lining cells. There is also proliferation of fibroblasts and of vessels.*

In the experimental animals, these effects, when not fatal, very quickly disappeared. The mechanisms are interrelated. The diminished cardiac output is not only the result of block of pulmonary capillaries but also is a consequence of inefficiency of the heart associated with bradycardia. This contributes to the systemic arterial hypotension which is also, in part, reflexly induced. With diminishing spasm, pulmonary hypertension decreases, fat traverses the lungs, and there may be peripheral embolization and death. In those animals that survive, however, the fat very quickly disappears, certainly in a matter of a couple of weeks.

A large collection of lungs from individuals expiring after exposure to oxygen at high tensions is now available. At only three days, remarkable hyaline membranes and mononuclear infiltrations are seen. At four days, there are similar phenomena with more severe interstitial infiltration, again largely composed of mononuclear cells. At eleven days, the process includes not only hyaline membranes but is associated with considerable interstitial fibrosis and atypical epithelial proliferation. All of these patients were subjected to oxygen at high tension, many following trauma, and in some instances following operations for nontraumatic indications. In another patient only 14 days after commencement of therapy with oxygen, advanced interstitial fibrosis was demonstrated. Rich would be astonished if he could visualize such a lesion at such a short interval after its onset. All of these patients presumably had normal lungs before they were exposed to the oxygen at high tension. This process might well be termed "diffuse alveolar damage," produced by

innumerable agents, some of which have already been cited, including Paraquat, hot mercury vapor, kerosene, beryllium under certain conditions, and many others.

Diffuse alveolar damage therefore, in substance, is necrosis of alveolar lining cells without damage to the basement membranes of alveoli, but with increase in permeability of blood vessels resulting in a proteinaceous exudate. This, together with fragmented lining cells, serves as the origin of the nonhomogeneous structures termed hyaline membranes. There are also mixed cellular exudates. It is probable that in most instances this process resolves without residua. Approximately 10 percent of the population have had either influenzal or mycoplasmal pneumonia which probably presented changes similar to those of oxygen at high tension, but resolved, leaving no residua. In a few instances organization of some of the alveolar exudate may occur by mural application. This process is similar to plastering of a wall, thereby thickening it. In addition to this, there is interstitial proliferation of fibrous connective tissue, even of muscle cells, and of lining epithelial cells which may be quite atypical. The end stage of this chronic interstitial pneumonia is honeycombing, the pathogenesis of which has already been described. This process of diffuse alveolar damage may be demonstrated by comparing electron micrographs of a normal lung of a guinea pig with those damaged by exposure to 15 percent CO_2. After several hours exposure the endothelial cells, while not necrotic, were highly vacuolated and probably sufficiently damaged to permit exudation to occur (Fig. 22). At approximately 24 h the lining cells were grotesquely swollen but the basement membrane was intact (Fig. 23). Within the endothelial cells were vacuoles suggesting the passage of fluid. There was a hyaline membrane, a material that contained still recognizable organelles of damaged lining cells and also granular proteinaceous material and some material with structure resembling fibrinogen (Fig. 24). Hyaline membrane, thus, is a complex material resulting from diffuse alveolar damage. The CO_2 experiment, considered with the other examples cited, is clear evidence that diffuse alveolar damage is a type of tissue response, rather than a reaction specific for any particular agent.

The question might arise, after study of individuals who had been on a respirator, if it is possible to distinguish those exposed to high pressures of oxygen from those with high volumes. Tension of the gas must be the important factor. In a series of experiments performed by Moore and his associates in Boston, a number of volunteers were exposed in chambers to oxygen at high tensions. Pulmonary function tests were performed before and after 12 h of such exposures. These individuals did not suffer any distress except for temporary abrogation of their liberties. Thus there must be some additional damage to the lung before oxygen produces the lesions we have been discussing.

It has been stated that pulmonary fat embolism played no role in the development of the pulmonary distress syndrome, its only significance being as a source of systemic embolism. This was borne out by the animal experiments referred to earlier. However, in humans, temporary distress from conditions such as a fat embolism may predispose to damage from high oxygen tensions. The process within this patient is probably multifactorial.

Medicolegal Discussion

The automobile-motorcycle collision is a variant of the most common destructive weapon of young adults, the motor vehicle. It is well known that these accidents frequently result in civil litigation among the participants, based on the assumption that the other party was negligent, and, therefore, should be required to pay for the consequent injuries. The negligence is usually based upon a violation of a local traffic ordinance with which most people are familiar or upon failure to use common sense on the road. As previously noted, when a negligence claim is brought against an individual, a recovery or

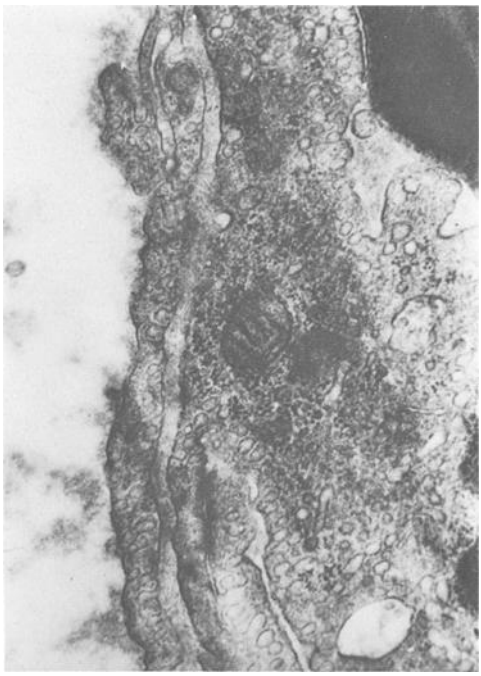

FIG. 22—*Effect of breathing 15% CO_2 in air on lung of guinea pig. At 4 h the structure is almost normal except for vacuolation of lining epithelium above the basement membrane, and of endothelium below the basement membrane (pinocytosis).*

award may be denied if the injured party was determined to be contributory. Thus, if the injured party also violated the traffic ordinance, or, in any other sense contributed to the accident which resulted in his injuries, it matters not whether one party was more negligent than the other, and neither party is entitled to recover. In motor vehicle accidents such ruling usually refers only to the driver so that the passengers in one vehicle may recover from the driver of another vehicle if that driver was negligent in spite of the fact that the claimant's own driver was also negligent. Under these circumstances, however, the passengers may not make a claim against their own driver. This ruling, a guest statute, in effect in most states, effectively bars the decision of financial responsibility by a driver who has been merely negligent to one of his passengers. If the driver has been exceedingly reckless or operating the vehicle under the influence of alcohol, this statute is usually set aside. Under these circumstances, the quality of the toxicologic examination and the expert interpreting these results may be of paramount importance. Such toxicologic evaluation is also important under another exception to the above stated rules, wherein, in a number of legal jurisdictions, if one driver is operating the vehicle recklessly under the influence of alcohol, he cannot assert the defense of contributory negligence against another driver who was involved. In such a case the laws weigh competitive fault of the two individuals and contributory negligence is not a bar to claim against the more serious reckless behavior. Punitive damages, designed to deter or punish an individual for serious misbehavior may also be awarded in favor of an injured claimant if it can be shown that the driver was seriously intoxicated.

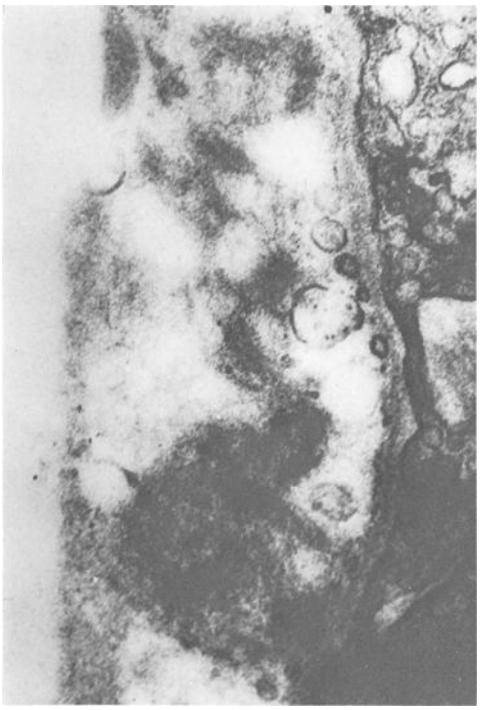

FIG. 23—*Lung of guinea pig after approximately 24 h of exposure to 15% CO_2. Epithelial cell is swollen with loss of architecture. Basement membrane, however, is intact. Extensive pinocytotic vesicles are present in the endothelial cells.*

Since it is quite obvious that the role of toxicology may be very important in the subsequent civil litigation, the physician's and toxicologist's role should be well understood. The laws of the states vary considerably with respect to the legal rights of a physician to draw a blood sample for such a determination. Under the terms of the old unwritten common law, a person may be guilty of a technical battery and possibly assault if he collects a blood specimen from an individual without their permission. When such permission has been obtained prior to collection of the sample there is usually no subsequent issue unless the fact of such consent cannot be proven subsequently in court. This results in many institutions requiring execution of a written consent form, not because this is a legal necessity, but rather that proof of the consent is a practical requirement and the written form is unequivocal. Obviously, a recorded, witnessed verbal consent would be satisfactory although this may lead to subsequent conflict of testimony wherein a defendant becomes aware of the seriousness of the evidence arising out of such examination and, being intoxicated at the time of such consent, is unable to recollect the incident. If the individual refused to give consent, the issue of the legality of forcibly extracting such a specimen becomes of concern. In this situation, the various state laws and interpretations are much more confusing and a local attorney in each state should be consulted for the precise legal alternatives. Generally, however, it has been held that it is constitutional to forcibly obtain such evidence, and since elimination and detoxication occur so rapidly after ingestion, one usually need not wait for a court order to proceed. Although it may

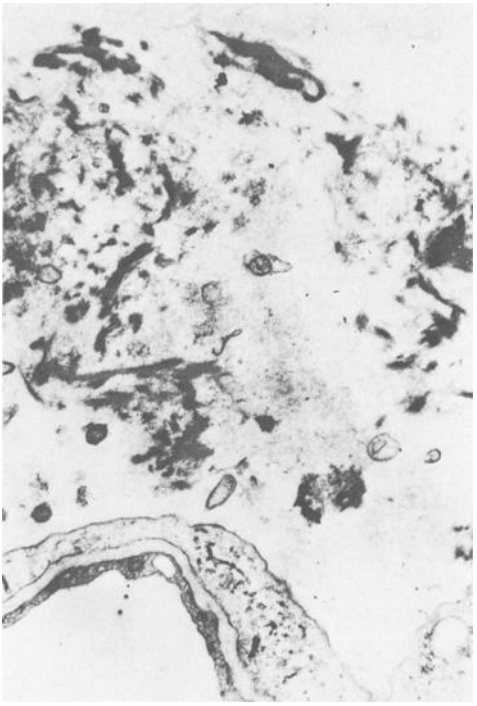

FIG. 24—*Hyaline membrane in lung of guinea pig after exposure to 15% CO_2. In the lumen of the alveolus at the top there are remnants of cell organelles and fibrillar structures with the periodicity of fibrin, as well as finely granular homogeneous proteinaceous material.*

not be unconstitutional to draw such blood, the wording of a number of states' laws may be such that the drawing of the blood specimen may be illegal in that it is either unauthorized or contrary to the specific applicable state statutes. Even in those states where legal authority is specifically given for recovery of such a specimen against the person's will, this often may be done only upon request of a law enforcement officer. A cooperative physician who obtains such a blood sample from an unwilling patient prior to the police officer's request may still find himself responsible for a legal battery. When the subject is unconscious and obviously cannot give consent to the drawing of blood for ethanol determination, again the various state laws may vary considerably. Some states specifically provide that a person driving on the road is presumed to give his consent unless his consent is withdrawn. Obviously, the physician may proceed in these cases without difficulty. In other states, where the law is less precise, this may be ruled a technical battery. There may, however, in some clinical situations, be a loop-hole which may alleviate the problem, so that a physician, involved in the care of an unconscious victim, can reasonably obtain blood for the necessary clinical determination that may assist him in the treatment of his patient. Obviously, this could include blood ethanol or other toxicologic studies. This information, received for medical purposes, cannot ethically be released without the patient's consent, although in some states it may be subpoenaed into court and the doctor required to produce this by specific court order, without fear of ethical interference with the patient under the given state law. Similarly, when such blood is

recovered from a patient, an extra sample may be properly collected and stored in such a manner that it cannot be contaminated or altered in accordance with the rules of evidence. At a later time, when the patient is capable of giving his consent, he may then consent to the release of this specimen or a court order might be obtained directing a physician to release such a sample. The evidentiary problems associated with this are discussed subsequently in more detail.

When the subject is deceased, the law again varies considerably from state to state; although, in this situation, one is dealing with a cadaver rather than a person and no battery action could be brought against the physician for the recovering of a blood sample for ethanol or other toxicologic determinations. A physician might be prosecuted for mutilating the body if he draws blood without the legal right to do so. This legal requirement may be met by a postmortem examination consented to by appropriate private party or authorized by statute. Under such circumstances, no further consent is needed for the collection of the blood specimen. In some states, as indicated above, when the unconscious subject is presumed to have given consent to the recovery of this specimen, such consent continues after death and the physician may thereby draw blood without fear of legal reprisal. In some states, specific medical examiner or safety regulations may authorize such examination. While a claim might be brought against a physician who mutilated the body upon recovering such a specimen without legal consent nor statutory privilege, we are unaware of any such claim. It should be readily apparent to most physicians that an intracardiac puncture through the chest would not cause serious injury to the body and be even less mutilating than the standard mortician's incisions necessary for embalming procedures and a court would obviously find very little basis for awarding any general damages for such an act. There may be a more real danger when a punitive damage claim is made, and the willful extraction of blood from the body may provide the legal basis for the awarding of punitive damages. This matter has not been resolved in the courts to date.

Rules of evidence are poorly understood and often pose a very real problem for the physician handling physical evidence. With property rights or even an individual's life possibly at stake, the laws of evidence are designed to insure that proper procedures were carried out to prevent a miscarriage of justice as the result of error. Such laws insure that a given sample of physical evidence, such as blood, came from the given identified individual; that this sample was not contaminated or otherwise altered in such a way as to invalidate the testing; that the physical evidence could not possibly be confused with samples from other individuals; and that all examinations conducted on such a sample were properly performed. The requirements for collection, handling, and testing of such specimens are usually a matter of general knowledge to the law enforcement officers responsible for these procedures. However, for those physicians who are only infrequently consulted, a review of the most satisfactory procedure may be in order. Commercially available or locally constructed kits containing all of the paraphernalia necessary for collecting a blood sample in a kit form which is sealed upon its preparation and can be guaranteed to be free of contamination may be provided to the police officer. When the specimen is collected, the label sealing this kit is broken and only the paraphernalia contained therein are utilized in recovery of the specimen. Such a kit should never contain ethanol nor any chemically related similar substance to be used as a disinfectant. Such a kit should be provided to the law enforcement officers by the laboratory conducting the examination and, if purchased commercially, this laboratory should conduct occasional examinations upon similar kits to verify the purity of the containers and the nature of the disinfectant.

With the law enforcement officer thereafter providing the kit to the technician or physician recovering the sample and, in addition, witnessing the collection of the sample from an individual he can later identify in court, it may be unnecessary for the physician or technician, serving only as an intermediary, to later appear in court. After the sample is collected, it should immediately be sealed and appropriately labeled to identify the subject from whom it was drawn, the precise date and time, and other relevant circumstances associated with its collection, including the identity of the individual who drew the blood specimen or otherwise handled it and the appropriate record for each transfer to the custody of another individual, including the method of storage of this specimen in the intervening time. Such a practice insures an accurate written record, an absolute necessity in the light of the fact that subsequent litigation may not occur until years thereafter. This further insures that the container will not be confused with samples from other individuals. When a blood sample must be stored thereafter, it should be stored in a locked container so that it may not be inadvertently or intentionally altered; and when such a specimen is released to the custody of another person, a written receipt, recording the name of the individual and the correct date and time, are necessary in order to assure a legal step-by-step record of custody. Obviously, the problem may be more complicated than discussed above, and those individuals concerned should always familiarize themselves with the peculiarities of local laws of evidence, remembering that each law enforcement jurisdiction may be faced with specific differences in its evidence rulings.

Motor vehicle accidents may also pose a number of other peculiar legal problems. For example, it is generally accepted that the use of seat belts and shoulder harnesses in automobiles and the use of crash helmets on motorcycles would reduce morbidity and mortality associated with these accidents. One might ask, therefore, whether a person might be negligent, in a contributory sense, thereby barring him from any recovery, if he failed to wear these protective devices. Although legal jurisdictions vary slightly on this matter, the majority of courts now hold that failure to use these devices in the anticipation of a crash is not contributory negligence. In a small number of states, the medical question of the degree to which the resulting injuries might have been altered by wearing the appropriate safety device may arise. Obviously, if it can be shown that the protective devices would not have altered the injury, the matter is irrelevant and such a claim is not barred. However, if the facts are not obvious, a thorough medical evaluation may be necessary in order to form an opinion concerning the association of the injury with the possible use of protective devices. A postmortem examination may also be necessary to prove that the lethal injury sustained by an individual resulted from unrestrained body motions which could have been prevented by the wearing of the seat belt, and it should be obvious that appropriate training and experience, including a thorough knowledge of the injuries associated with the wearing of seat belts and understanding of vehicular and occupant kinematics during and following an automobile accident are necessary prerequisites to rendering such an opinion.

Another consideration of interest in civil litigation involving automotive vehicle accidents is the possibility of legal responsibility of a third party in the event the operator of the vehicle is found liable for the injuries caused to another. This is known as the Law of Agency. Under the Laws of Agency, when a person is acting in behalf of another, the third party, known as the principal, may be responsible for the negligent acts of his agent. The most common examples of this agency's relationship occur in the employer-employee situation whereby the person going about the business of another, under that individual's guidance and direction, is considered his agent. Common examples of this include truck

drivers, delivery men for business firms, and, under some circumstances, office employees on the way to a business appointment. This may include an individual who has undertaken a task in behalf of another, even without remuneration.

Insurance Considerations—In addition to the civil court liability, most commonly involved in cases of this nature, a number of other legal considerations may be affected by similar facts. This accident victim was riding a motorcycle. A number of different types of insurance policies specifically restrict their responsibility in itemized, dangerous activities. Depending upon the policy, dangerous activities might include: flying a private airplane, riding a motorcycle, skydiving, dynamiting oil wells, racing automobiles, or a myriad of other specific high risk vocations or avocations. Under the terms of some of these policies, if one is engaged in such an activity, he is not covered by the double indemnity accidental death provisions and in some extreme cases, he is afforded no coverage whatsoever. In certain health and accident policies, the terms of these contracts may also limit the payments which would be made for medical bills due to such injury. Some insurance policies also may limit the period of time following injury within which an individual must expire, either directly or indirectly as the result of these injuries, in order for the benefits to accrue. These intervals may vary from less than a month up to one year from the date of the original accident.

Interstitial Pneumonia, Pulmonary Burn Injury

Clinical Summary

Case 7—A 2-year-old white male infant was involved in a house fire in which he suffered first and second degree thermal burns over 40 percent of his body including the thorax, legs, arms, neck, and face. Those burns over the face were considered to be primarily first degree burns although the hair of the head and nares was slightly singed. Within the nares there were deposits of brownish, black, sooty material indicative of smoke inhalation.

Physical examination revealed an irritable, young, white male with burns as described. The pharynx was congested and there was evidence of mild inflammatory distress. Physical examination was otherwise within normal limits.

Initial laboratory work revealed: hemoglobin 13.5 g with white blood cell count of 33,150; urinalysis was normal; electrolytes, initially, were normal.

Respiratory distress continued in association with persistent leucocytosis. The hemoglobin fell to 9 g. Tracheostomy was carried out. Additional therapy included antibiotics and steroids after X-rays revealed evidence of pneumonitis. Repeated blood gas studies within 10 days of his admission revealed a consistently elevated CO_2 combining power of 38 to 40 mEq./l. Blood gas studies on numerous occasions revealed pCO_2 values of 45 to 50 mm of mercury and pO_2 levels varying from 40 to 55 mm of mercury. Repeated pneumonic infiltrations occurred over the hospital course. Tracheal aspirations at various times grew out a chromobacter or coagulase negative staphylococcus. One month after admission, the patient had a cardiac arrest but was resuscitated. Immediately thereafter Amphoteracin B therapy was started for possible bronchopneumonia although this could not be identified within the laboratory. The patient became extremely lethargic and progressively comatose. Five weeks after admission he again developed cardiac arrest and attempts at resuscitation were unsuccessful. On the day prior to his death, his CO_2 combining power was greater than 40 mEq./l, pCO_2 was 100 mm Hg and pO_2 was 35 mm Hg.

Postmortem examination revealed healed second and third degree thermal burns involving the scalp, thorax, arms, legs, and face. The heart was enlarged (110 g) and dilated. The pulmonary surfaces had a cobble-stone appearance with areas of atelectasis alternat-

ing with slight emphysematous bleb formation. Multiple petechiae and ecchymoses were noted. The parenchymal surfaces of the lungs revealed nodular areas of hemorrhagic pneumonitis with foci of necrotic degeneration. Within the right lower lobe was an extensive hemorrhage. The tracheal mucosa was yellow and necrotic while the lumen of the major airways contained watery light-yellow fluid distal to the tracheostomy opening. Examination was otherwise not unusual except for enlarged kidneys with a prominent, bulging cortex which microscopically revealed tubular necrosis and nephrocalcemia.

Pathology Discussion

Autopsy revealed healed second and third degree thermal burns on the scalp, thorax, arms, legs, and face. The heart was enlarged (110 g) and was dilated. The pulmonary surfaces had a cobblestone appearance with atelectasis alternating with overexpanded foci. Examination was not otherwise unusual except for enlarged kidneys with a bulging cortex. Microscopically there was evidence of tubular necrosis and nephrocalcinosis.

This patient was on oxygen therapy during his hospital course. This, of course, is significant in interpreting the pathogenesis of the pulmonary lesion, wherein there is considerable hemorrhage and an interstitial pneumonia (Fig. 25a). Some of the large mononuclear cells were full of brown material, which might represent the residue of soot, although some of the cells contained material resembling hemosiderin as well (Fig. 25b). There was not only an interstitial pneumonia but considerable numbers of polymorphonuclear leukocytes, suggesting the possibility of superinfection (Fig. 25c).

The respiratory complications that occur in burns are very significant, with various manifestations. This was one of the major conclusions in a review of necropsies reported from the Beaumont Army Medical Center, conducted under the auspices of the Committee on Pathology of the National Research Council some years ago.

Injury involves not only the lungs, but also the upper respiratory tract. The effect of hot air, as such, on the lower respiratory tract is essentially nil, unless there is also moisture in the material that is inhaled. The specific heat of dry air is very low. If there is abundant moisture, however, large quantities of heat transfer can occur. This depends on the particular circumstances under which the burning occurred. It is impossible, under experimental conditions, to produce a burn more than just below the larynx in an experimental animal with hot, dry air, but deep damage of the respiratory tract occurs with steam. The lesions that occur very quickly are those of necrosis, exudation, and hemorrhage in the nose and larynx and adjacent tissues. If steam is inhaled, injury may extend into the very depths of the respiratory tree. Not only bronchi but bronchioles may be involved. There is some superficial sloughing of epithelium, smoke or sooty material in the lumen, some mucin, intense congestion and edema and, even soon after injury, some polymorphonuclear infiltration.

The interpretation of pulmonary edema and hemorrhage occurring soon after burning may be difficult indeed. It could be the result, not simply of heat, but of the inhalation of toxic gases, particularly acids. Phosgene has been mentioned, and oxides of nitrogen may produce a similar effect. Lesions resembling diffuse alveolar damage with hyaline membrane formation develop, followed by accumulation of polymorphonuclear leukocytes and their exudation into the lumina of alveoli. Not only can there be direct damage to the respiratory tract but indirect damage from shock and immediate failure of the heart. Damage from embolization also is important (Fig. 26). In the upper respiratory tract and, of course, in the skin, one of the effects of severe burning is thrombosis. These thrombi then become emboli which lodge in the pulmonary vessels. After the first week or ten days, infections, particularly with gram negative bacilli, become more important. The

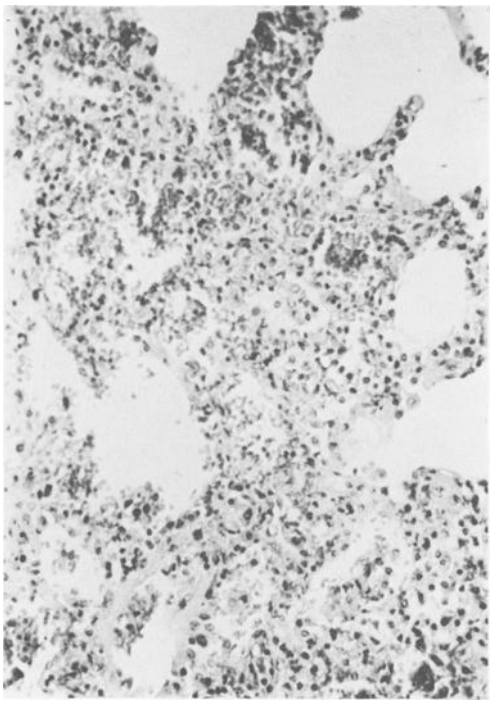

FIG. 25a—*Burn injury. Pulmonary hemorrhage and focal atelectasis. The walls of the alveoli are thickened also by a scattered infiltrate, predominantly of lymphocytes. The changes represent interstitial pneumonia.*

emboli may then contain masses of bacteria. Pseudomonas pyocyanea characteristically involves the walls of the vessels, sometimes with very little reaction, but sometimes with considerable polymorphonuclear infiltrate (Fig. 27).

From the National Research Council burn study, conducted on approximately 55 patients, the effects of burns may be summarized as follows: stimulus of injury which is both nervous and homogeneous; tissue damage with hemolysis, loss of fluid, and electrolyte imbalance; direct damage to the respiratory tract, not only thermal, due to steam primarily, but possibly also chemical; indirect damage to the respiratory tract, embolic, or the result of congestive failure; and infection, relatively late. The physician, in attempting to treat these patients, may also produce injury, particularly by overexpansion of fluid volume or by injudicious use of antibiotics.

The mechanism of death from burns in the National Research Council study was summarized according to a general grouping: the schema of the first two weeks reveals that most of the patients who died early had extensive burns. Many of these patients expired of respiratory tract damage, frequently with thromboembolic lesions. Renal tubular necrosis was present in more of the later fatalities, often associated with electrolyte imbalance. Ulcers of the gastrointestinal tract were present in some of these patients expiring after the second week and, after the eleventh week, necrosis of the liver, representing serum hepatitis, was a significant mechanism of death.

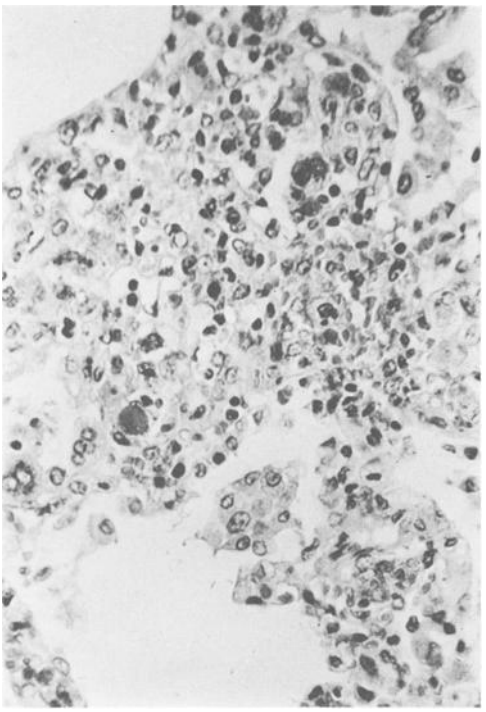

FIG. 25b—*Burn injury. Pigmented large mononuclear cells within lumina of alveoli. Many of these contain hemosiderin.*

Medicolegal Discussion

The case of death secondary to smoke inhalation raises a number of issues previously discussed in earlier cases and some additional problems.

The relationship of the care of the child to his death is of extreme importance. If the death of this child resulted from an intentional act on the part of one or both of the parents, these individuals could, in no way, accrue benefits from a policy of life insurance upon the child. If the death of this child resulted from the negligence of a parent or parents, then the question of whether or not the parents could collect such life insurance benefits following their negligent act often arises. Depending upon the terms of the life insurance policy and upon the state law where this occurred, the proceeds of the life insurance policy either may not be paid, or may be paid to a secondary beneficiary. Negligently caused death, in contrast to intentionally causing injury, is usually not a bar to payment to the guilty beneficiaries.

A similarly complex problem may arise in a wrongful death action. In case 1A of these discussions, the family breadwinner, an adult man, was killed and his surviving children were successful in bringing suit against the persons responsible for their loss. Likewise, under most state laws, a claim may be brought for the financial loss resulting from the death of a child. Depending upon the state, this may include the parents or the legal heirs or estate of the child. The estate is the legal entity created for group consideration of a deceased person's affairs and finances. Obviously, if the parents were the heirs of the

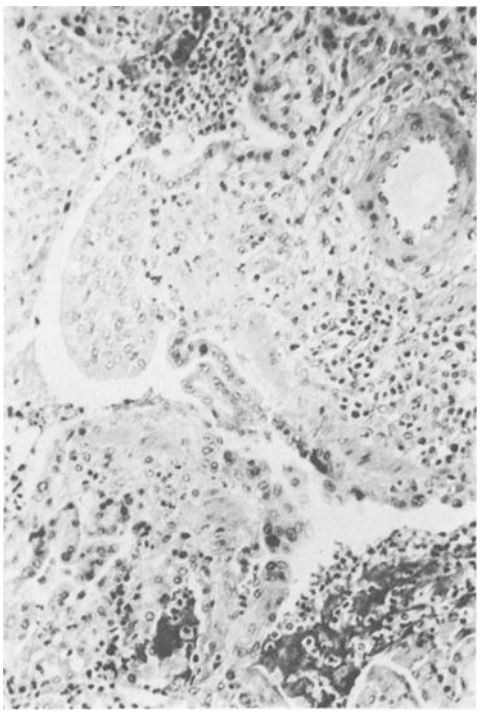

FIG. 25c—*Acute and chronic bronchiolitis following thermal burns.*

child, as well as the negligent parties responsible for the child's death, any resulting claim would constitute an instance of the beneficiaries suing themselves. This does not create practical problems unless a number of the beneficiaries were not the guilty parties, which would then result in one or several beneficiaries suing the remaining.

This matter may be further complicated by the fact that, under the laws of most states, a child cannot sue his parents for a civil negligent court claim, since it is generally felt that permitting such an action would create family disruption. This ruling usually extends after death such that if the deceased person could not institute a claim against an individual or individuals, in this instance his parents, during lifetime, for acts which resulted in his later demise, then the estate of that individual may not make a claim after death, although obviously no family disruption may ensue under these circumstances

In a situation such as illustrated in this case, investigation into the cause of the fire may result in other sources of legal responsibility for this child's death. This investigation should determine if there was compliance with the building code in that correct materials and installation were conducted and that subsequent maintenance was in accordance with prescribed procedures. Liability might ultimately rest upon one individual for improper installation, another individual or agency for improper maintenance, the individual who may have improperly inspected the device determined to have resulted in the fire, or even to the property owner who might have had reasonable cause to be aware of this dangerous defect, and took no action. If an item of equipment was determined to be responsible for the fire, the individual or agency which manufactured it and the vendor

might be held responsible under the theory that the device was improperly designed and manufactured with defects, making it inherently dangerous. Obviously a certifying laboratory such as Underwriters Laboratory, which certifies to safe design, may also be involved in such litigation. Occasionally a dangerous, volatile material may have been improperly stored or used or secondarily placed in an unsafe container. Cleaning solutions have been common offenders until recent legislation, requiring that some materials be appropriately labeled with warnings and others withdrawn from the market.

In investigating the circumstances of fires and death associated with fires, it should be kept in mind that this may be a method of attempting to disguise a homicide by destroying the body and the scene of the crime. It should be pointedly emphasized that an autopsy with detailed examination of the respiratory tree, chemical determination of carbon monoxide, and radiographic examination of the head and trunk, is sometimes a virtual necessity in avoiding a gross miscarriage of justice.

Diffuse Alveolar Damage and Chronic Interstitial Pneumonia in Respiratory Distress Syndrome

Clinical Summaries

Case 8A—The patient was a 2-day-old male infant spontaneously delivered at 28 weeks gestation at which time he weighed 1170 g (2 lb., 9 oz). Due to the infant's small size and episodes of apnea, he was transferred to the newborn intensive care unit and placed on a Bowns respirator.

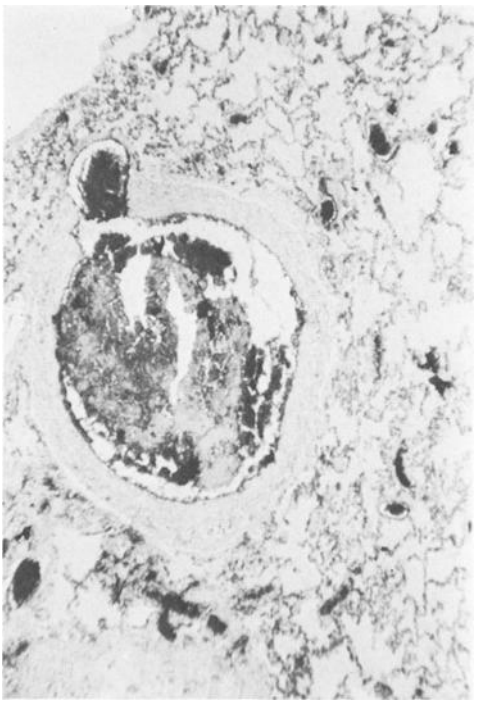

FIG. 26—*Congestion and edema of the lung. A pulmonary artery contains what is probably an embolus from thrombosed vessels in the burned skin. Death occurred 47 h after burn injury.*

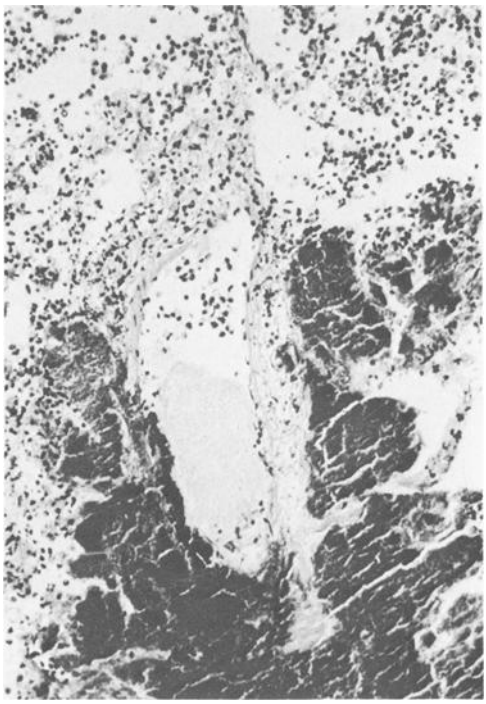

FIG. 27—*Thermal burns with sepsis. Masses of bacilli involving the wall of a pulmonary artery in the lung. Culture of lung revealed* Pseudomonas pyocyanea.

His pulse was 154 and respirations 60, with marked subcostal, intercostal, and sternal notch retraction. Chest roentgenogram revealed grade IV hyaline membrane disease with nearly complete opacification of lung fields and well visualized air bronchograms bilaterally. Initial arterial blood gases were: pO_2 78 mm; pCO_2 78 mm; and pH 7.17 while on 60 percent O_2.

The infant was maintained on the respirator for 48 h with O_2 concentrations in the 90 to 100 percent range. His course was complicated by the development of a pneumoperitoneum from a suspected ruptured viscus and terminally by bilateral pneumothoraces, seizure activity and a fall in hematocrit from 32 to 24 percent.

Postmortem examination revealed firm homogenous gray-tan lungs with the appearance of pancreatic parenchyma. The airway contained only a small amount of thin clear mucus. Also present was a perforation in the fundus of the stomach and massive germinal plate hemorrhage with rupture into the ventricles.

Case 8B—The patient was an 8-day-old, premature (33 weeks gestation) infant weighing 1590 g (3 lb., 6 oz) at birth. The infant, who was delivered by Cesarean section from a 24-year-old mother with severe toxemia, developed respiratory distress at the time of delivery and required endotracheal tube resuscitation. He had gasping respirations, bilateral rales, and was cyanotic when not on controlled respirations. His heart rate was 80. He had limp extremities. His chest roentgenogram revealed a reticulogranular pattern

consistent with severe hyaline membrane disease. Fourteen hours after delivery he was transferred to the newborn intensive care unit and placed on the Bowns respirator on 80 percent O_2. His arterial blood gases were: pO_2 30 mm; pCO_2 31; pH 7.50 with 79 percent O_2 saturation.

The patient remained on controlled respirations of 90 to 100 percent oxygen for 8 days. Even with this therapy he became progressively more hypoxic and hypercarbic. Terminally, his arterial blood gases were: pO_2 16; pCO_2 96; pH 7.17. He sustained a cardiac arrest and expired.

Post mortem examination revealed findings in the lungs only. These were firm, mottled, gray-tan, pink, and red-brown. The parenchyma resembled pancreatic tissue and the airways contained soupy yellow-gray liquid.

Case 8C—The patient was a 4-week-old, premature male infant (34 weeks gestation) weighing 2100 g at birth. He was born following a brief labor with possible early separation of the placenta. Following delivery, severe respiratory distress with episodes of apnea developed, requiring administration of 100 percent oxygen. The infant was transferred to the newborn intensive care unit where his initial findings were: grunting respirations, pulse 180, respiratory rate 40, severe subcostal and intercostal retractions. Arterial blood gases were: pO_2 97; pCO_2 63; and pH 7.17 on 75 percent O_2. Chest roentgenogram revealed a diffuse ground glass pattern in the peripheral lung fields with bilateral air bronchograms compatible with hyaline membrane disease.

The baby progressively deteriorated over a 4-week course, complicated by numerous episodes of tension pneumothorax. He was maintained on the Bowns respirator with O_2 concentrations varying from 75 to 100 percent. The chest roentgenographic picture progressed from opacified lung fields to a honeycombed cystic appearance to areas of consolidated focal atelectasis. Terminally the patient had arterial blood gases of: pO_2 46; pCO_2 115; and pH 7.19. He sustained a cardiac arrest and expired.

Postmortem examination revealed lungs in which subpleural and interstitial emphysema was prominent, accompanied by focal areas of atelectasis. The parenchyma was firm, noncrepitant, and gray-tan. Also present was a germinal plate hemorrhage of the brain with rupture into the ventricles.

Case 8D—The patient was a 4½-month-old, premature, male infant (about 26 weeks gestation) weighing 1 lb., 13 oz at birth. The delivery was uncomplicated. In the second day of life the patient began having apneic spells and was maintained in an isolette with 40 to 50 percent O_2. Chest roentgenogram demonstrated bilateral hazy parenchymal infiltrates, a picture consistent with hyaline membrane disease. He was transferred to the newborn intensive care unit and placed on a Bowns respirator at 60 percent O_2 concentration. Arterial blood gases were: pO_2 42 mm; pCO_2 60 mm; and pH 7.22.

The patient was maintained on the respirator with 50 to 60 percent O_2 concentration for the first 12 weeks of life. His chest roentgenographic picture progressed from opacified lung fields to a cystic honeycomb lung pattern similar to that observed following long term O_2 therapy. The infant's acidosis was treated with $NaHCO_3$, and the pulmonary infection with courses of penicillin, kanamycin, and gentamicin. At 12 weeks of age, he was weaned from the respirator and treated with O_2 concentration in the 40 to 50 percent range via a face mask or head box apparatus. The patient's hospital course was complicated by frequent seizure activity and upper airway obstruction relieved by tracheostomy on 20 Oct. 1970. Seizure activity increased terminally with prolonged apneic spells.

The post mortem findings were confined to the lungs. They were firm with areas of atelectasis alternating with emphysematous blebs. The parenchyma was homogenous, yellow-tan, and of pancreatic consistency.

Case 8E—A 32-year-old, white, female, secretary entered the hospital via the emergency room on the evening of 15 April 1970. She was comatose and was suspected to have ingested a large quantity of drugs.

She had been hospitalized for emotional problems on two occasions. As of her final hospital admission, she was presumed to be in good physical health but still under the care of a psychiatrist. There was no allergic history. Previously, she was thought to have had early diabetes and tolbutamide had been prescribed, but upon stopping oral contraceptives, the blood sugar level became quite normal and no further drug therapy for the supposed diabetes was required. Both parents died by suicide.

Upon admission, the woman was comatose with a body temperature of 98.8 F, a pulse rate of 104/min and the blood pressure was recorded at 110/64 mm Hg. The pupils were dilated, equal in size, and did respond to light. Numerous rales and rhonchi were present in the left chest area. The patient responded only to painful stimuli.

Drugs available to the woman included Diabinase, Mellaril, Elavil, and Triavil. Because of the tolbutamide, the blood sugar level was soon checked and found to be hovering at the 60 to 70 mg percent level. It dropped to 28 and was brought to more normal levels by the intravenous administration of glucose in a 50 percent solution. This pattern of low blood sugar level, corrected to a degree by intravenously administered glucose, continued for 3 days.

Respiration was assisted by a MA-1 respirator and an endotracheal tube. Approximately 52 h after admission, a tracheostomy was performed. At that time the patient was still comatose, the vital signs were stable, and the patient was ventilating well on her own. Blood gas determinations carried out up to the time of the tracheostomy with the supplemental oxygen delivered by the respirator were as follows:

Date	Time	Supp. O_2	Resp. Rate	pH	PCO_2	PO_2	O_2 Sat.
4/23	Adm.	...	10	7.35	41.4	89	95.8
4/23	9:50 PM	...	13	7.51	22.7	600	100.0
4/24	4:10 AM	...	20	7.46	25.5	90	96.8
4/24	11:05 AM	100%		7.48	25.2	250	100.0
4/24	2:00 PM	40%		7.45	28.0	89	96.8
4/25	9:35 PM	60%	23	7.43	26.9	102	97.6

From this point on, the patient remained comatose and was kept on the MA-1 respirator at oxygen percentages varying between 60 and 100. (Since the actual percentage of O_2 delivered cannot be determined by the dial setting between 60 and 100, in the following chart such settings are indicated as: 60–100.) Repeated blood gas determinations were carried out and as time passed, even the highest oxygen percentage was unable to prevent the gradual changes in the vital blood gas pattern. Ventilation was always assisted, not controlled. Representative figures are listed below:

Date	Time	Supp. O_2	Resp. Rate	pH	PCO_2	PO_2	O_2 Sat.
4/28	7:40 AM	60	28	7.42	28.3	87	96.3
4/29	7:15 AM	60–100	25	7.47	42.3	70	93.5
5/2	7:00 AM	60–100	13	7.50	35.8	156	100.0
5/6	7:10 AM	60–100	20	7.42	41.7	56	87.8
5/9	8:00 AM	60–100	28	7.43	48.3	42	75.0
5/12	10:05 AM	60–100	18	7.45	57.0	73	93.4

On 26 April, pulmonary congestion or infiltrate was noted by chest X-ray. Two days later there was obvious progression of this and Amphocillin obviously was not controlling it.

On 29 April, the patient was said to be desaturated when on 60 percent supplemental oxygen, and when taken off the respirator developed marked rigidity. The level of consciousness was said about this time to be improving, and on 30 April, the general clinical status was said to have deteriorated, and the pulmonary infiltrate by X-ray was increasing.

On 6 May, a partial occlusion of the expiratory tube of the respirator provided a degree of constant positive pressure.

The course was entirely downhill with death occurring on 15 May. There was no toxicologic identification of drug or drugs taken in addition to the tolbutamide which was identified but not quantitated.

Postmortem examination revealed firm, brownish-gray to whitish-gray lungs. The parenchymal surfaces were whitish-gray, with the alveolar spaces demarcated by interstitial fibrous tissue. No fluid was expressed from the lung parenchyma. In the brain were scattered microscopic areas of complete cortical necrosis. Examination was otherwise not significant.

Pathology Discussion

This next series of patients was selected to reveal the manner in which the respiratory distress syndrome in the premature infant may become chronic. Again the role of oxygen used at high tension may be considered.

Case 8A—The patient weighed only 1170 g at birth and died 4 days later. Chest film revealed a mottled hazy appearance with evidence of interstitial emphysema (Fig. 28a). Necropsy revealed bilateral pneumothorax and pneumoperitoneum, the latter associated with perforation of the stomach, although the mechanism of the pneumothorax was different. As in many patients who have the respiratory distress syndrome, there are minute foci of overexpansion involving alveolar ducts and sometimes more proximal structures. These foci alternate with depressed zones of atelectasis. There is also a suggestion of hemorrhage (Fig. 28b). Hyaline membranes are present, largely in structures proximal to alveoli (Figs. 28c and d). Interstitial emphysema is a common complication in these patients, particularly if put on respirators or if other attempts at resuscitation are made by vigorous oversized house officers. This may, however, occur spontaneously as the result of respiratory effort. In this patient, there is extensive interstitial emphysema (Fig. 28b).

Case 8B—The patient weighed only 1590 g at birth and died 16 days later. In this instance, the radiographic appearance was somewhat more homogeneous, but, on close inspection, characteristic of respiratory distress syndrome. As the lungs became consolidated, air bronchograms became evident. Focal atelectasis alternated with striking overexpansion (Fig. 29a). Respiration was very inefficient. Hyaline membranes, with early organization, were associated with the presence of masses of mucin and exudate within the bronchioles. an important mechanism in the trapping of air (Fig. 29b). Reticulum stains were useful in distinguishing immaturity of the lung from atelectasis. In the latter, solid lung was shown to be really unexpanded lung. In other instances, it is quite evident that the lung is immature with incomplete development of alveoli. In this case the reticulum stain demonstrated in part, unexpanded alveoli, and, in part, increase in interstitial tissue (Fig. 29c).

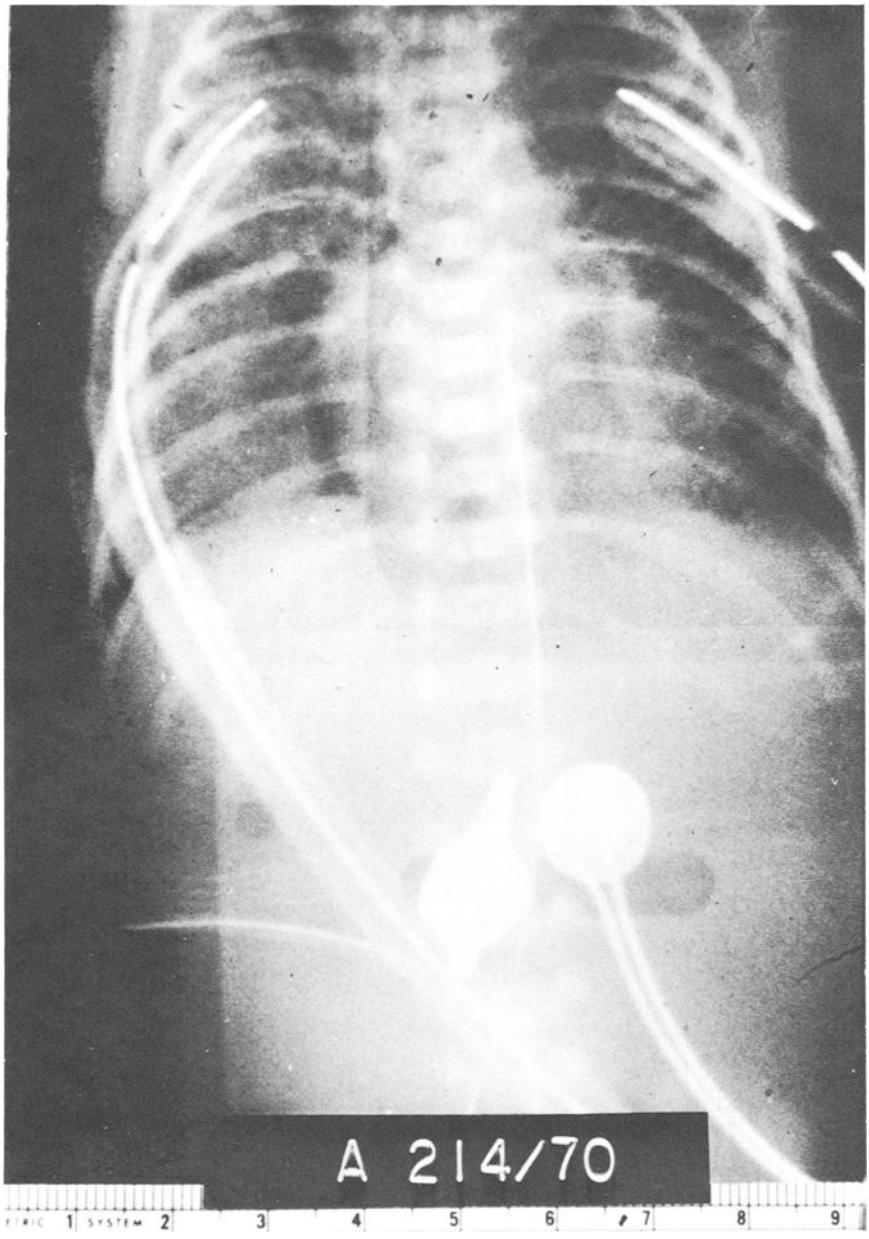

FIG. 28a—*Diffuse alveolar damage. Chest film, revealing multiple areas of hazy consolidation and evidence of interstitial emphysema indicated by paracardiac radiolucency on the right.*

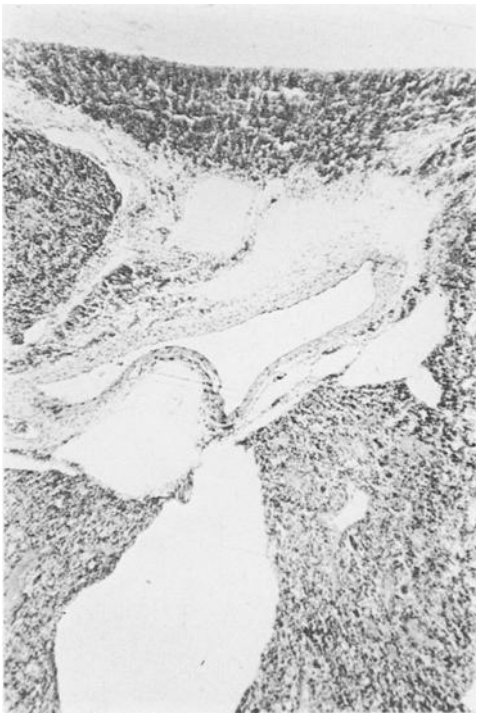

FIG. 28b—*Massive interstitial emphysema in this patient's lung. Hyaline membranes are visible in this low magnification as rings or masses of pink staining material.*

Case 8C—This baby had a birth weight of 2100 g and lived for 4 weeks after birth. Again, atelectasis is complicated by interstitial emphysema. These lungs appeared homogeneous in the roentgenograms but with very fine stippling. In a later film were seen structures resembling cysts, probably representing bullae or localized pneumothorax. This is a complication, and a serious one, of interstitial emphysema, sometimes resulting in tension pneumothorax with shift of the mediastinum. In this case this is minimal. The lungs, at necropsy, were quite solid, although there were some persistent bubbly lesions indicating interstitial emphysema (Fig. 30a). In this patient, there was much more extensive fibrosis, in part interstitial, and partly of a massive nature. Residua of some of the distal air spaces were visualized in the areas of interstitial fibrosis. The focal massive necrosis probably represented the consequence of infection (Fig. 30b). Again, there was interstitial emphysema corresponding with the gross appearance and still a few residua of hyaline membrane. In this patient, who was quite mature at birth, some of the alveoli appeared relatively well expanded. The interstitial fibrosis and massive fibrosis were also identified in the reticulum stains.

Case 8D—This patient, who lived for 4½ months, is of the greatest interest. This child was very small at birth, weighing only 725 g. This is a remarkable example of survival of a patient with respiratory distress syndrome, on oxygen therapy, revealing some of the late changes which may occur. The lungs at necropsy were quite solid and rather resistant,

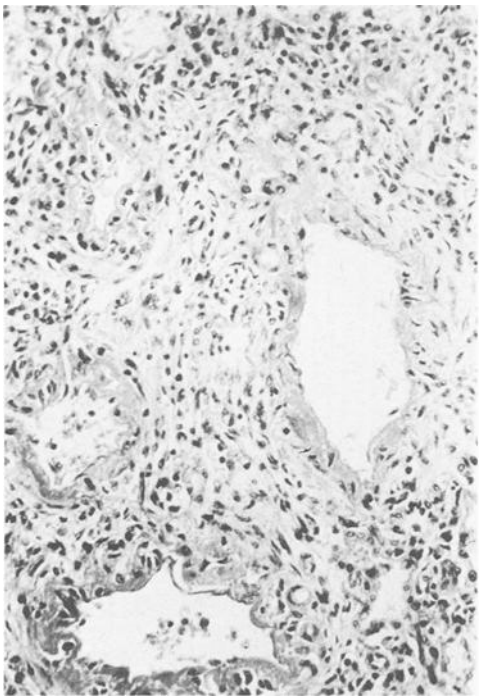

FIG. 28c—*Hyaline membranes at higher magnification in same patient. The air spaces that contain these are quite large, but most of the parenchyma appears to be atelectatic.*

indicating the presence of considerable fibrous tissue. At low magnification this presents the appearance of an immature lung, even at 4½ months of age. Also of interest are the dilated lymphatics. These probably represent simply an accommodation on the part of the lymphatic system to atelectasis and fibrosis in some portions of this lung. These are distinguished from congenital lymphangiectasis by their thin walls. There are also foci of rarefied or overexpanded lung, with very thick walled distal air spaces, representing, not merely emphysema, but rather honeycombing (Fig. 31a). Interstitial emphysema is also present. These revised air spaces are lined by proliferated epithelial cells. There is considerable interstitial fibrosis. In some locations there are masses of fibrin in process of organization, contributing to the induration of the lung (Fig. 31b).

As a consequence of interstitial emphysema, the air accumulates in the interstitial tissue with resulting collapse of vessels, particularly veins, and reduction in perfusion of the lung. The lung also is rendered mechanically stiff by the presence of air under tension in the interstitium; therefore, it becomes less useful in respiration.

In a family of four children, three, although of normal weight at birth, possessed underdeveloped lungs which resulted in respiratory distress syndrome. One of these survived for approximately 1 year in an oxygen tent; siblings 1 and 2 both died soon after birth. The lungs were underdeveloped with sparsity of alveoli. This may be considered familial alveolar dysplasia or hypoplasia in this sibship. In a third sibling, who had to be maintained in an oxygen tent continuously, the chest films at 5½ and 8 months of age revealed a

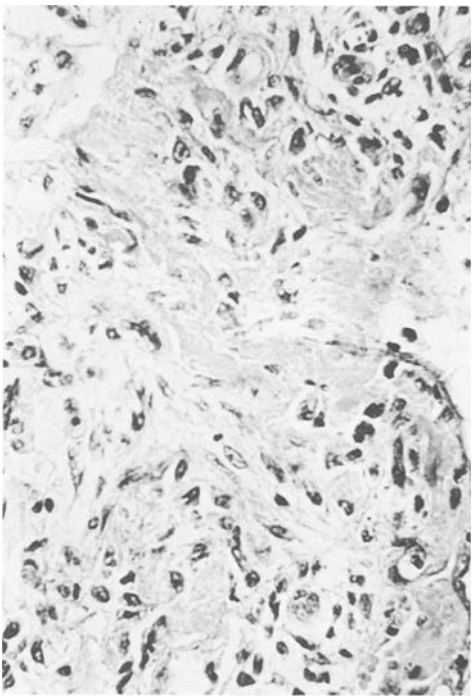

FIG. 28d—*Hyaline membrane at high magnification in same patient revealing intrusion of spindle-shaped cells interpreted as evidence of early organization.*

finely stippled or reticular appearance. The retraction of the tissue in the intercostal spaces was remarkable. After death at 1 year of age, the lungs were large and heavy but their structure was very simple, suggesting an underdeveloped lung. There was some increase in interstitial connective tissue, which may have represented interstitial fibrosis resulting from preexisting diffuse alveolar damage. However, since the condition was familial, and since the lungs in the siblings appeared underdeveloped at birth, this probably represented the same process in this patient. Consideration of a patient with the Wilson-Mikity syndrome reveals pathological findings which vary but which are also thought now to be underdeveloped lung within which are some zones of relatively solid tissue with some overexpansion and many normal alveoli. Such lungs apparently continue to develop and, if the patient can be kept alive, there is complete restitution to normal function and presumably to more normal structure. In the earlier stages the lungs radiographically resemble those of respiratory distress syndrome with a reticular or bubbly appearance. It is now well established that continuing development and expansion of alveoli may take place for at least the first 10 years of life. In some patients, although the remainder of the body is mature at birth, the lungs are much less mature.

Case 8E—This case is interesting because the patient, about 30 years of age, lived for approximately 3 weeks with respiratory distress syndrome. The lungs, grossly, were quite solid, with extensive organization of an interstitial process, some of which was intrabronchiolar with plugs of partly necrotic, predominantly mononuclear exudate which may

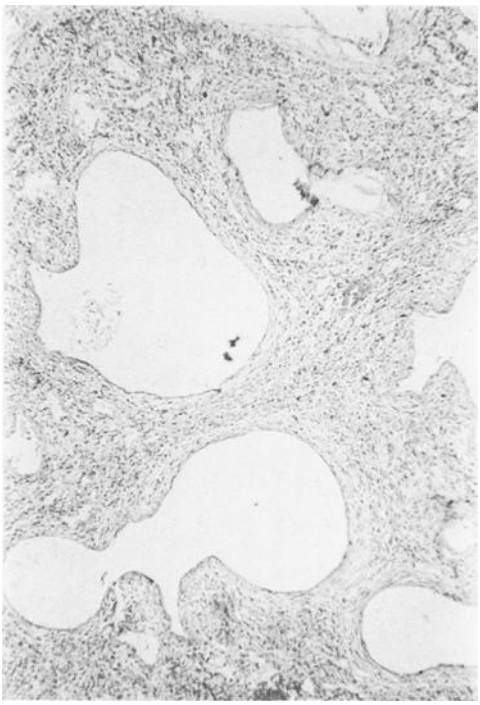

FIG. 29a—*Diffuse alveolar damage. "Swiss cheese" appearance of lung under low magnification. Some air spaces are grossly over-dilated, and contrast markedly with the remainder of the parenchyma which is atelectatic.*

have represented the result of an infection. Of particular interest was the organization of the hyaline membranes to the extent of producing large sheets of more or less hyalinized tissue (Fig. 32). Fibrosis involves the interstitial tissue among alveoli as well as the larger septa.

This series of cases demonstrates that some patients with acute respiratory distress syndrome may progress to a state similar to that of typical interstitial pneumonia.

Medicolegal Discussion

Cases 8A, B, C, and D—Cases similar to these have raised a hornet's nest in the medical malpractice literature recently. In such instances, involving physically immature children who often require extensive hospitalization with accompanying high medical bills and, occasionally, in spite of this, permanent disability in the surviving child, the parents may seek a deeper pocket to satisfy the financial dilemma.

As noted by the gestational age of the patients involved in this series, the vast majority are premature infants. The obstetrician should be very cautious to avoid making a contribution to this story of woe, and he should be very certain that each child who is taken by cesarean section has appropriate indications for the delivery. This usually insures, if the section is elective, that the child is of full gestational age. Radiographic bone maturation studies and surfactant levels in the amniotic fluid are reported to be important indicators of maturity. When it is determined that a child must be delivered prematurely, it is best to insure that the medical records document very clearly the necessity for the delivery of a

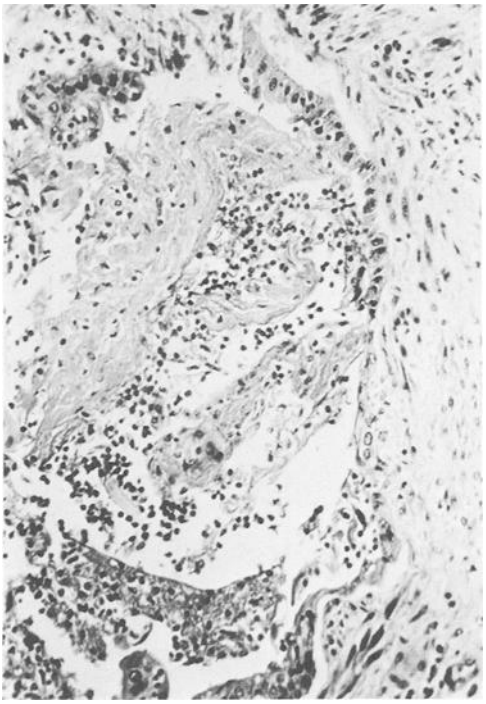

FIG. 29b—*Bronchioles showing lumen filled with masses of mucin and clumps of polymorphonuclear leucocytes. There is squamous metaplasia of the lining epithelium.*

possible high risk infant, and, where practical, the same indications should be clearly delineated to the parents to insure that an unequivocal informed consent to the procedure has been obtained. This will help in several ways by insuring no subsequent medical battery action and by psychologically assisting the parents to prepare for any potential complication. It also serves to make the parents feel that they have been partners in making the decision for the premature delivery. Such factors often preclude subsequent commencement of a law suit.

Following delivery of the infant, it becomes the responsibility of the pediatrician or neonatologist to insure that the child received appropriate care. The first consideration should be that the physician and institution are properly prepared to manage such care, and if not, referral, under prudent circumstances, to a properly equipped facility. If this is not accomplished, the traditional pediatrician may face legal consequences. However, even with proper skill and necessary equipment for caring for such a premature infant, there are associated legal hazards. This very serious potential for harm creates a clinical situation which is explosive since the child's status may literally change from minute to minute, requiring intensive monitoring and regular testing to avoid disaster. A number of recent law suits have been instituted against physicians for the resulting retrolental fibroplasia in children who had respiratory distress syndrome and survived therapy. The physician who undertakes this treatment should have ideal working conditions, facilities, and his staff must have the personality and perseverance to meet these difficult requirements for medical care.

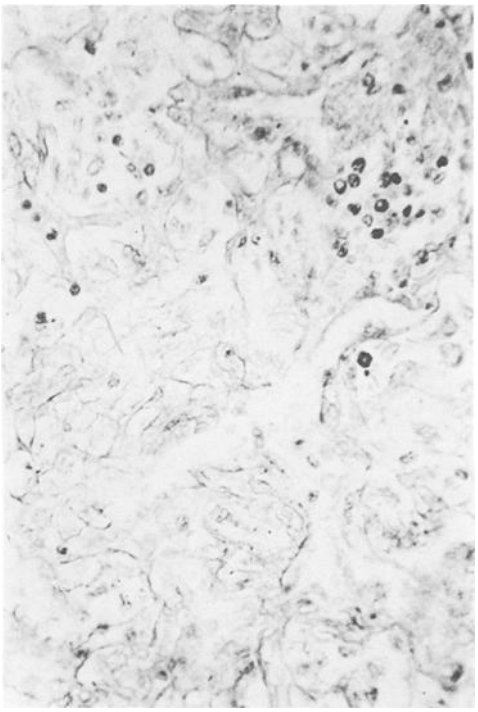

FIG. 29c—*Reticulum stain demonstrating that some air spaces are simply unexpanded. There is also an apparent increase of interstitial reticulum.*

This poses another very difficult legal problem. How long must the overworked physician remain in the care of such an acutely ill person, and under what circumstances may he withdraw? If a physician undertakes the care of a patient with reasonable knowledge that this will require a prolonged course of treatment with continuous and frequent monitoring, he is implicitly acknowledging that he recognizes that this patient has these foreseeable needs and he will undertake to meet these requirements. If he cannot do this, he should make proper arrangements, either by finding a substitute or by advising the patient or the patient's representative of this difficulty at the outset, in order that they may seek assistance elsewhere. Once a physician has undertaken the care of a patient, he may not abandon that care without warning. The law requires that sufficient notification be afforded to find a proper substitute, depending upon the nature of the disease. Such care may be readily available or quite difficult to procure. If the physician withdraws from the care of a patient without making these arrangements, he may be liable for all of the harmful consequences that might occur as the result of failure to provide medical treatment. Some physicians have even found punitive damages assessed against them for this willful withdrawal of services during a time of critical need for care.

With increasing reliance upon modern electrical equipment and other machinery within the operating room, the intensive care facility, and even upon the floors of the modern day hospital, a comment should be rendered concerning the legal aspects of use of this equipment. The hospital or the physician may be held financially liable for injuries which

result from the use of defective equipment, when either the physician or the hospital staff has reasonable cause to know that this equipment is defective or may fail. If the equipment is absolutely vital to the life processes of the patient, such as a bypass pump used in open heart surgery or a respirator, the absolute reliability of the equipment is a necessity. A single prior unexplained failure of the equipment would justify extensive overhaul and testing of this equipment to insure that it would not subsequently cost a patient's life. Conversely, if the equipment is not necessary for the maintenance of vital processes or for conducting vital determinations, the circumstances might justify some question of reliability without legal responsibility.

The manufacturer of medical equipment may find himself with an even greater burden, since he may be faced with the liability without prior notice that a machine of his manufacture was defective or becoming defective. A number of legal jurisdictions now hold that advertising of a given piece of equipment may be considered to the purchaser as a warranty and if the equipment has either defective parts or in other ways is functionally defective in normal use, the equipment manufacturer may face liability. Thus, a respirator, which becomes inoperative as a result of excessive respiratory secretions, may be ruled inherently inadequate for its advertised and intended use, and failure under such circumstances might lead to legal liability. If the machine has an inherently defective part, either because of faulty manufacturing or inadequate design, the manufacturer may also be liable for the damage resulting when the equipment fails while in the care of a patient.

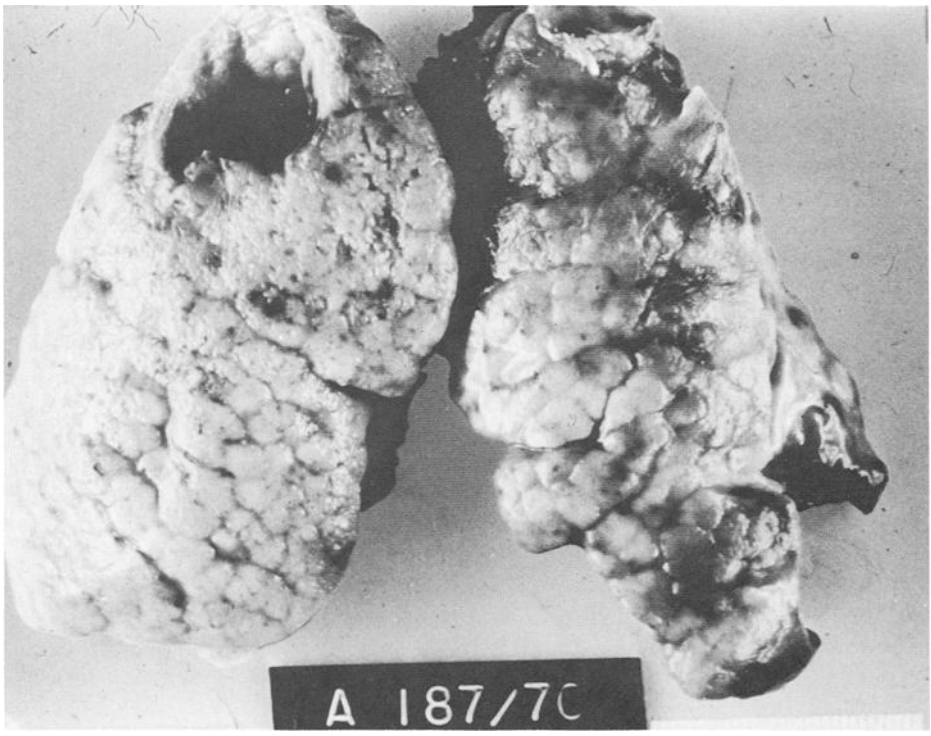

FIG. 30a—*Diffuse alveolar damage. Pale, solid lungs with blebs indicating interstitial emphysema.*

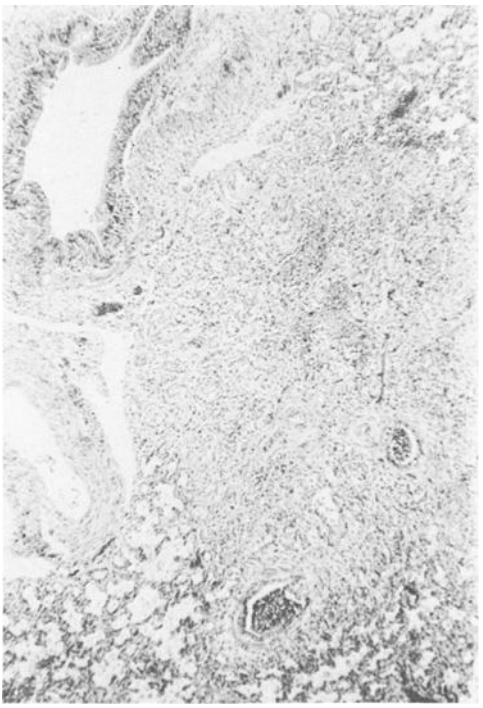

FIG. 30b—*A focus of acute bronchiolitis and pneumonia in this lung.*

Case 8E—In the case of the emotionally ill secretary who ingested a suicidal overdose of drugs, a number of additional significant legal questions are raised. Consideration of insurance benefits has been discussed earlier. Basic life insurance coverage is usually in effect for suicidal death occurring in excess of two years after initiation of the policy, whereas either double indemnity or accidental death benefits are never afforded when it can be shown that the death was an intentional self destruction. A more difficult problem is posed in the instances associated with suicidal gesture. It is well known that hysterical individuals have a propensity to use suicidal gestures to manipulate their environment. Unfortunately, a significant number of these people successfully take their own life, although this is not their actual intention. Such individuals may ingest a full bottle of barbiturates in the presence of a friend who will call for medical assistance or they may lock the door and similarly ingest medication before calling their husband to advise him what they have done in an attempt to coerce him to dramatically rush home, take down the door, and prove his concern by rescuing them. Unfortunately, some people are not at the telephone at the appropriate time and an episode which commenced as a manipulative act may result in the actual demise of a mentally ill person. The question of whether this should be considered accidental or suicidal may be posed. If accidental, the survivor's finances may be significantly affected; and if suicide, in addition to financial loss, a social stigma may be placed upon the surviving relatives. From a strictly medical viewpoint, these people are not usually considered true suicides, although an exhaustive investigation, utilizing the expertise of consultant psychiatrists may be necessary to reach this conclusion.

The courts have split on this decision. Some have been reluctant to term these accidental deaths for consideration of public policy and sound processes of reasoning. They have held that if a person undertakes to do an act which reasonably should offer a very serious risk or harm or death to that individual, this is tantamount to an intentional act. These instances may be clarified only by careful insistence upon a full and detailed investigation into the circumstances surrounding each death alleged to be suicidal. If the death is to be considered accidental, associated with the failure of a suicidal gesture, the physician should be prepared to marshal all of the medical evidence and present this to the court in such a manner that the court may have a completely reasoned legal basis for arriving at such a decision. The very act of signing the death certificate as either accidental or suicide often closes the question for practical purposes and the physician must be exceedingly careful in this process to insure that his initial conclusion is the most accurate under all circumstances.

Liability of Others for the Death of a Suicide—A number of legal claims have been instituted against physicians who allegedly were treating individuals known to be mentally ill and have prescribed therapeutic agents which ultimately became the cause of their death. A number of claims have been instituted against psychiatrists with the allegation that the patient was released from the hospital prematurely and was sufficiently psychotic and depressed that he took his own life. The bases for such action have been either misdiagnosis, in that the person was considered no longer dangerously mentally ill, or that the

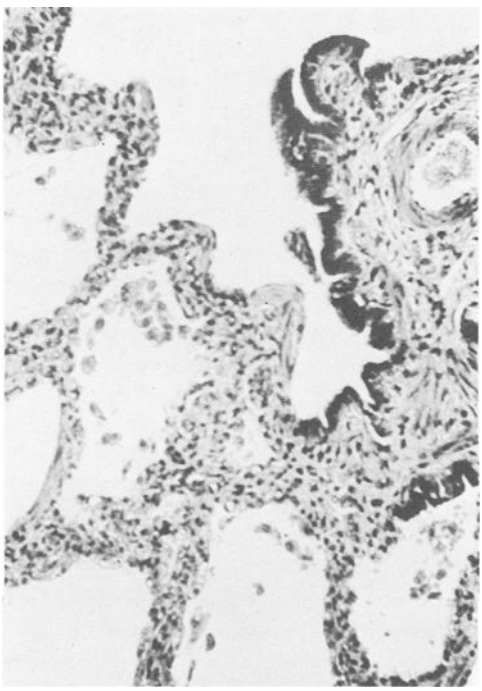

FIG. 31a—*Diffuse alveolar damage. Remarkably thick-walled distal air spaces are in direct connection with conducting airways. The septa among distal air spaces are infiltrated with lymphocytes. Such coarsening of architecture approaches honeycombing.*

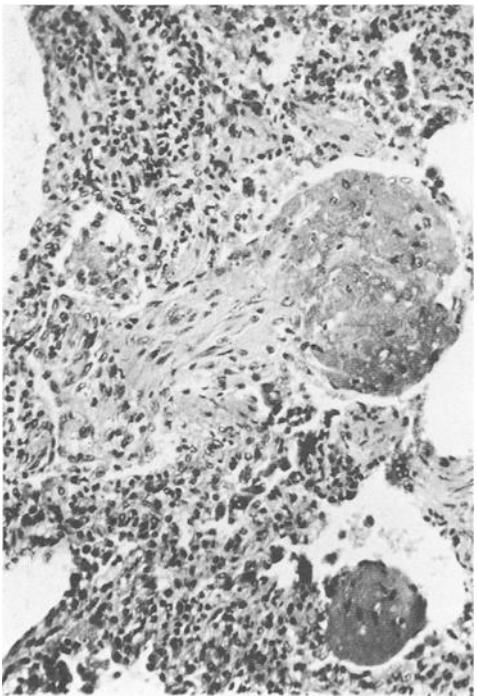

FIG. 31b—*Masses of fibrin in process of organization within distal air spaces of same patient. There are also numerous large mononuclear cells containing brown pigment, probably hemosiderin.*

premature release was an inappropriate form of treatment for a patient who had such dangerous propensities for himself. In several other instances, psychotic patients had been allegedly prematurely released, thereby causing harm to others who, in turn, had instituted action against the psychiatrist who afforded this release on similar ground.

Most physicians are well aware of the other possible malpractice implications of the care of the suicidal patient. These involve the classical legal problem of failure to make an adequate diagnosis as a result of inadequate diagnostic procedures or failure to render the intensive care required by these patients while the poisons are being metabolized by the body. One additional legal problem which has been infrequently litigated may ensue when the physician has successfully treated the physical injuries occurring during the suicide attempt such that the patient has been able to return to prior tasks and yet has ignored the psychiatric manifestations which precipitated the incident, discharging these patients to recycle through their stages of mental illness, frequently with even greater stress resulting from the stigma of an attempted suicide, and the financial stresses resulting from hospitalization and loss of work. Obviously, from a psychiatric viewpoint, many of these people require further treatment and it is probable that in the future the physician will be held to the obligation that such further psychiatric treatment be obtained. In those situations where the patient is incapable of coping with his environment, the physician who has once undertaken to treat this patient may have an obligation to recommend further custodial protective care, regardless of whether or not he, himself, is a psychiatrist.

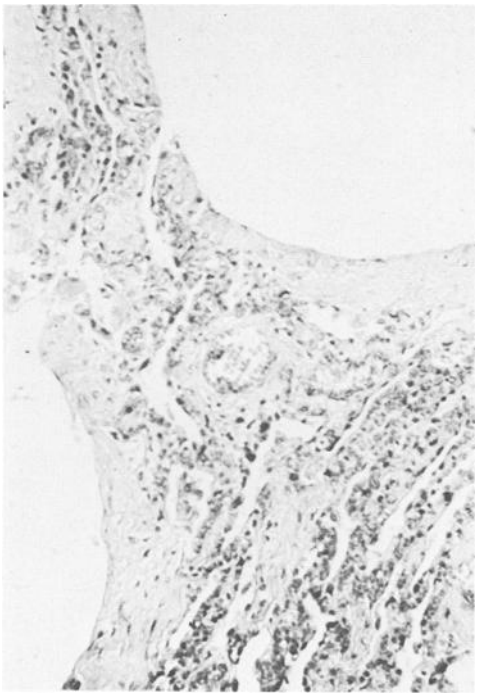

FIG. 32—*Diffuse alveolar damage. Organized hyaline membranes line large spaces interpreted as alveolar ducts. Surrounding alveoli are atelectatic.*

Every state has a legal procedure for the involuntary commitment of mentally ill patients who are a threat to themselves or to society. To this date, more claims have been instituted alleging that the physician incorrectly sought to hospitalize a patient than those claiming that this should have been done. In many of the former cases, the suits were instituted by the patients who remained emotionally ill at the time they asserted their legal claim. Obviously, the physician must have a reasonable basis for involuntary commitment before contacting the appropriate agencies, and yet must be prepared to do so if the patients constitute a threat to themselves.

There might be a question of the workmen compensation following death or disability from a suicidal attempt. Obviously, one can point to environmental stresses in work as a possible significant precipitating factor leading to an individual's desperate act of suicide or suicidal gesture. Although this reasoning may be as medically sound as the presumption that such stress aggravates the development of coronary atherosclerosis, most workmen compensation laws distinguish between mental disability and specifically exclude any payment for the precipitation or aggravation of mental disorders or their sequelae.

Diffuse Alveolar Damage and Other Complications Following Cardiac Arrest

Clinical Summary

Case 9—A 9-year-old Negro male entered the hospital for elective surgery. His chief complaint was "crossed eyes" since birth. The mother stated that she noted ocular devia-

tion since birth and also believed that the eyes "turned out." She indicated that occasionally the left eye "looks funny." The past history, family history, and systemic review were noncontributory. The physical examination revealed a well developed child in no distress with 20/20 vision in the left eye and 20/25 vision in the right eye. Epicanthosis was noted bilaterally with widening of the interpupillary distance. The external ocular muscles showed exotropia for 30 degrees. There was an over-reactivity of the left superior oblique muscle. The remainder of the physical examination was unremarkable. Laboratory work-up revealed a hematocrit of 40, adequate platelet numbers, and a white blood cell count of 6500 with 38 segs, 39 lymphs, 15 monos, 2 bands, 5 eosinophils, and 1 basophil. The urinalysis showed 0 to 1 white blood cell per high powered field, a specific gravity of 1.007 and a pH of 5.

Surgery was undertaken the following morning. No known drug allergies were noted by the anesthesiologist. Premedication included demerol 30 mg, phenergan 20 mg and atropine 0.3 mg given intramuscularly. The evening prior to the surgery and in the morning of surgery, 250 mg of ampicillin were given. The induction was listed as satisfactory and anesthesia was begun at 11:15 AM with intubation by a no. 22 Davol catheter at 11:20 AM. Nitrous oxide-fluothane-oxygen anesthesia was employed. At 12:15 PM a cardio-respiratory arrest occurred, the pupils appeared to be smaller than usual but responded to light and a hypothermic blanket was ordered. External cardiac massage and intubation with assisted ventrilation were immediately performed and intravenous levophed, sodium bicarbonate, and intracardiac epinephrine were given at once. Spontaneous respirations occurred but the patient developed pulmonary edema and showed no signs of pupillary reaction. He then received intravenous lactate and was put on a positive pressure breathing apparatus. His condition at this time was guarded. An X-ray taken at approximately 3:30 PM revealed pulmonary edema and a bilateral alveolar infiltrate which was suggestive of bronchopneumonia to the radiologist.

Throughout that evening the child showed only slight movement of the lower extremities and a minimal reaction to light of the right pupil only. Electrolytes performed on two occasions revealed CO_2 to be 24 and 21, chloride 52 and 76, sodium 128 and 134, and potassium 6.1 and 3.2. The former figures were noted immediately postoperatively and the latter figures were reported at 6:45 that evening.

Vigorous resuscitative measures including constant intubation continued throughout the evening. Continuous intravenous pressure determinations were performed with levels ranging as low as 3.8 and as high as 9.0 cm. Supportive measures continued through the evening but there was no obvious improvement. The child was pronounced dead at 10:20 AM the following morning, approximately 23 h following the induction with premedication and approximately 22 h following the cardiorespiratory arrest at surgery. No subsequent X-rays had been performed. The total fluid intake over this 24 h period was 700 cc, all parenteral in nature and total urine output was 450 cc. A final temperature of 104 F was reached several hours prior to death.

Postmortem examination revealed six acute gastric perforations. The largest (27 mm in diameter) was contiguous with a single perforation of the left hemidiaphragm. The left pleural space was filled with 300 ml of gray-brown serous fluid. Fibrinous adhesions bound the left lung to the diaphragm. The lungs were boggy, engorged, and gray-brown. The pulmonary parenchyma adjacent to the diaphragm was hemorrhagic. Moderate amounts of edema fluid oozed from the upper lobes of both lungs on section. The abdominal organs in the left upper quadrant were stained gray-brown. Microscopic examination of the sites of gastric perforation revealed coagulation necrosis without inflammatory reaction. Examination was otherwise not significant.

Pathology Discussion

The patient suffered a cardiac arrest following a minor operation and expired in approximately 23 h, presumably after oxygen therapy. Radiographically, the lungs initially appeared relatively normal but subsequently presented a mottled and stippled appearance (Fig. 33a), all within approximately 24 h. At necropsy, the lungs were intensely congested, partly hemorrhagic and quite stiff with exquisite hyaline membranes in a very acute stage (Fig. 33b). This case illustrates the most acute phase of hyaline membrane formation.

An additional complication in this patient was the presence of damage to the lower esophagus and gastric and diaphragmatic perforations with the production, even in this short interval of time, of a serositis of the spleen and other organs, indicating this was an antemortem lesion.

Medicolegal Discussion

This instance of a nine year old boy who entered the hospital for elective surgery, suffered a cardiopulmonary arrest on the operating table, and subsequently expired, is a dramatic illustration of many of the factors which may be involved in subsequent malpractice action.

This again dramatizes the dilemma of the physician faced with the legal necessity of obtaining an informed consent for proposed surgery or therapy, while attempting to avoid instilling fear and uncertainty in the mind of his patient or the parents. By hindsight, many persons may empathize with the parents of this child who went into the hospital for seemingly minor, nondangerous surgery and ultimately lost their son. Although physicians are customarily aware of the complications of these procedures and receive dramatic revivification of this periodically by medical tragedies within their community, the general public has only a vague notion of the dangers of surgery. This may be enhanced or suppressed by the physician's representation to his patient. Obviously, no physician wants to paint himself in an unsuccessful light, but, at the same time, the law requires that everyone who undergoes a surgical or therapeutic procedure give an informed consent prior to its commencement. The patient or his representative should have a reasonable knowledge of the consequences of the surgery in order that he may make the decision whether the possible advantages to be accrued outweigh the risks and dangers of the procedure. When the patient specifically notifies the physician that he does not desire to be advised of these risks, the physician obviously has no further obligation. When the patient is a child who cannot give consent for himself, the authorized consent must be by the parent or legal guardian unless an emergency situation arises which precludes the taking of time to obtain such consent. When the child is in the older age group but still legally a minor, the courts have generally held that in relatively minor nondangerous surgery, the child may give consent, particularly in an emergency situation. If the surgery is elective and major risks are contemplated, the uncertainties of the law require that legal guardians provide formal consent for the procedure.

The obtaining of informed consent must be emphasized. If a physician thrusts a hospital consent form in front of a patient and directs him to sign thereon with a statement that "everything will be all right," this is obviously not an informed consent. A small number of courts have protected the physician in this instance by holding that the patient, under these circumstances, had an obligation to inquire about the possible risk. The majority of the courts have ruled that this is not a legally acceptable form of consent and the physician would be liable for any untoward results on the grounds that this is a legal battery in that the physician committed an illegal physical act upon the body of the patient by performing the therapy or surgery.

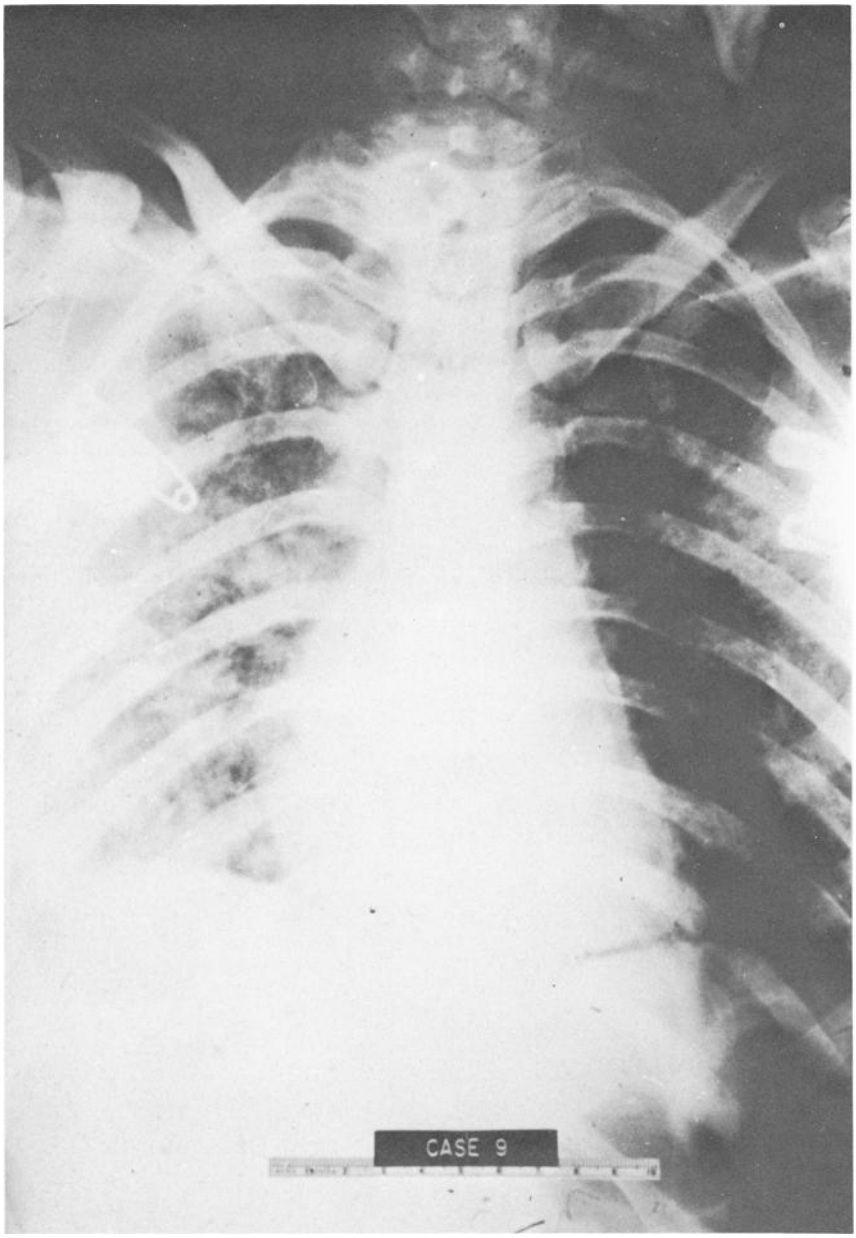

FIG. 33a—*Diffuse alveolar damage. Chest film several hours after cardiac arrest, revealing mottled and stippled appearance.*

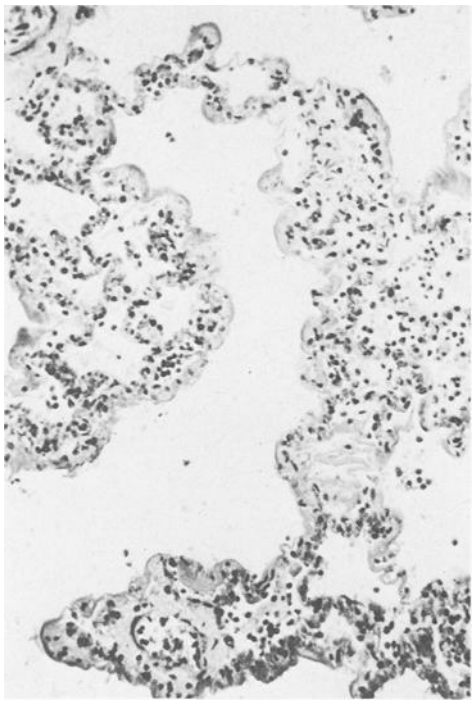

FIG. 33b—*Distal air spaces of patient's lungs lined by hyaline membranes.*

Under the circumstances, the physician has an obligation to advise the patient of the risks involved. This is an extremely difficult task in that it would probably be impossible to itemize all of the potential hazards of any given procedure, and it is doubtful that any one physician would even be aware of all of the rare problems that may have been encountered by such a procedure. If he were, the list would be too long to practically enumerate and explain fully to the patient and there may be strong sound medical reason for not fully explaining the risk to the patient. Many physicians feel certain that the complications are increased thereby and the healing processes are slowed as the result of induced anxiety. This is a function of the patient's own ability to cope with this distressing mental data and depends upon the age and judgment of the individual. In the pediatric patient this could not be considered, since the legal explanation must be provided to the parents of the child rather than the patient himself. In other situations involving senile, comatose, or mentally ill patients, a similar consent must be obtained from that individual's legal guardian unless an emergency situation justifies therapy without consent.

As a practical matter, the legal consent can probably be best dealt with by explaining to the patient that there are hazards involved in the surgery and explaining to the patient the likelihood of these hazards occurring. After this, the physician may offer to explain in complete detail any hazards about which a patient may request additional information, asking the patient to advise the physician of what hazards they wish to be better informed. Obviously, if a particular procedure has a high risk of complication or of failure, the patient should be forewarned of this. A number of suits have been recently instituted

against physicians who, for all practical purposes, guaranteed the result to the patient. This was regarded by the court as a legally binding contract and when the procedures failed, the patient was able to successfully make a claim against the physician. Again, to the physician it may be quite difficult to explain to the patient that you are capable of failing and still worthy of requesting the appropriate surgical fee. Many physicians have overcome these problems by presenting, in a historical context, an outline of the procedures of this nature which they have accomplished in the past without complication, although informing the patient that complications may occur since they have been observed in patients managed by other physicians. An accurate recital of this type in historical context, has been considered a fair and reasonable way of informing the patient.

In addition to the problem of consent for therapy, a multitude of surgical and anesthetic errors that might lead to a malpractice claim could not be enumerated in this discussion. As a practical matter, technical mistakes may be made in preoperative workup, to exclude pre-existing conditions which may cause complications, technical surgical errors, technical anesthesia errors, breakdowns or defects in vital equipment, and deficient postoperative care, in the recovery room, intensive care facility, and subsequently. A bad result is not necessarily a basis for a malpractice action. It is a common precipitating cause of a malpractice action when combined with a deficient doctor-patient relationship which possessed no sociological or psychological bonds to deter a malpractice action. It should be emphasized that patient satisfaction or antipathy are more important factors in determining if a malpractice action will be initiated than any technical errors or their results. A very high percentage of malpractice actions result from a combination of technical error and poor doctor rapport, precipitated finally by a bill for professional services forced upon the patient by a vigorous collection agency representing the physician.

A cardiopulmonary arrest during surgery such as occurred in this instance affords an important basis for consideration of the high jury awards that have been extensively publicized in the press of late. As previously discussed, the jury's award of damages is based upon the economic losses involved. During the course of a busy medical practice, physicians frequently fail to recognize that they are not only treating a disease in a patient but they are also repairing a very expensive economic machine. A business man who makes $50,000 to $100,000 a year suffers an extreme economic loss if he is unable to work as a result of a medical mishap. The economic earnings lost over a working lifetime by an individual in this income bracket can readily adapt to a large sum of money. In addition, small numbers of extreme cases have also involved high medical expenses over a prolonged period of time. For example, in several of the most highly publicized cases involving damage awards over $500,000, cardiopulmonary arrest during surgery left the patient alive, but with only the basic vital signs, unable to care for himself. Such an individual, with severe brain damage, may remain subconscious or unconscious for months or even years, requiring an intensive care facility, extensive special nursing, laboratory examinations, medication, and therapy at costs ranging up to several hundred dollars per day. Under such circumstances, astronomical special damages would have to be considered by a jury arriving at a final award.

Assuming an incident has occurred during the care of a patient, resulting in his death or disability, a question may arise concerning the physician's responsibility to reveal these facts to the patient or his representative. Two very important practical considerations are raised by this dilemma. First, under the laws of most states, if a physician "hides the facts" involved in a potential malpractice claim, the statute of limitations to commence subsequent legal action does not commence until the patient has due notice of what actually transpired. This has resulted in many claims brought against physicians after intervals of

up to 20 years or more after the alleged act of negligence. However, most malpractice or liability insurance policies provide protection only for a designated interval, regardless of the statute of limitations, thereby leaving the physician uninsured. Obviously a very important question ensues concerning the meaning of "hiding the facts." The physician who states that he "forgot" to tell the patient or his relative the circumstances, does not present a very good appearance in court when applying the hindsight test and the courts often feel very strongly that the physician had an obligation to completely explain all of the pertinent details. Failure to do this might well be construed as an intentional hiding of the facts because of guilt. This may occur even in cases associated with an honest error or bad result which ordinarily would not lead to liability.

The implications of the statute of limitations are extremely important to the physician involved in the care of pediatric patients. In most legal jurisdictions, a child is not qualified to bring a law suit in his own name. If he is injured in any way, he may not sue the person directly but must have the action instituted by a legal guardian appointed by the court. This may, therefore, delay such a negligence action until the child reaches the age of 18 or 21 and may institute it in his own name. A number of recent court decisions have held that the interval of the statute of limitations does not commence until after these children have reached legal age and, if the alleged malpractice occurred in a state with a 6-year statute of limitations, it is conceivable that an action could be brought against the physician or hospital for alleged misconduct 27 years later, representing an interval of 21 years until the child reaches adulthood and is legally capable of instituting a suit and six years of the statute of limitations thereafter. Obviously, this may result in a malpractice claim long after the memory of the event is gone, records are destroyed and witnesses who could make a significant contribution to the results of the case have expired. This may also be long after the malpractice insurance policy has lapsed.

Silo-Filler's Disease

Clinical Summary

Case 10—A 29-year-old, white male was admitted to the hospital, extremely ill, with complaints of dyspnea, cough, and wheezing of approximately 4 weeks duration. The onset of his present illness occurred when he and his brother were exposed to irritating fumes, or dust or both in a silo chute which was poorly ventilated. The patient had gradually become more dyspneic and cyanotic since the initial episode, at which time he had immediate severe choking and coughing. He first became acutely ill 5 days prior to admission with fever, cough, and severe dyspnea. These symptoms progressed in spite of antibiotic therapy as an outpatient.

At physical examination, he was noted to be cyanotic with extremely fast grunting respirations (60/min) and dry paroxysmal cough. Occasionally he coughed up mucopurulent sputum. There was no evidence of hemoptysis. Breath sounds were present although reduced at the apices. There were numerous fine medium moist rales with many wheezes of the asthmatic type, predominantly on expiration throughout both lung fields. Roentgenographic examination revealed miliary lesions in both lung fields with some confluence over the upper portion. Two days following admission, although the patient was still very restless and coughing a lot, he was considered to be slightly improved. The rales were about the same with the wheezes varying, although they persisted most of the time. The following day he was noted to be moderately pale, cyanotic, and unresponsive. Examination at that time revealed a temperature of 102 F, pulse of 140/min with a blood pressure of 180/80. Respirations were shallow and ineffective and the patient was unable

to cough. A diagnosis of pulmonary edema was established and he became progressively comatose. No medication, except small doses of chloral hydrate, was given. The pulse was rapid and thready, paradoxical in character, with occasional extra systoles. Examination of the lungs revealed them to be resonant. Breathing was still shallow but breath sounds were better than at any time, with no wheezing. Moist rales were heard at the bases and over the lower one-half of both lungs. The patient appeared to be going into progressive toxemia with early shock and respiratory insufficiency. Hydrocortisone was given in an attempt to reduce the progressive inflammatory response. The patient was placed on oxygen therapy with occasional doses of aminophyllin. Respiratory difficulty increased until his demise, 3 days after admission. Pertinent laboratory findings included CO_2 combining power, 35 mEq./l on admission progressing to 45 mEq./l: chlorides, 524 mg %, sodium 150 mEq./l and potassium 4.5 mEq./l. A sedimentation rate was 77 mm/h. Blood cultures on two occasions were negative.

At postmortem examination the lungs aggregately weighed 1500 g. In the parenchyma was a diffuse shotty nodulation with the nodules measuring up to 5 mm in diameter. Section revealed slight excess of blood and fluid. In the upper lobes bilaterally were areas of irregular consolidation measuring up to 4.0 by 3.0 by 3.0 cm. These were firm and gray-white.

Pathology Discussion

The patient was one of two brothers who entered a silo at approximately the same time, survived several weeks, and presented similar pathologic findings. The lesion, in contrast

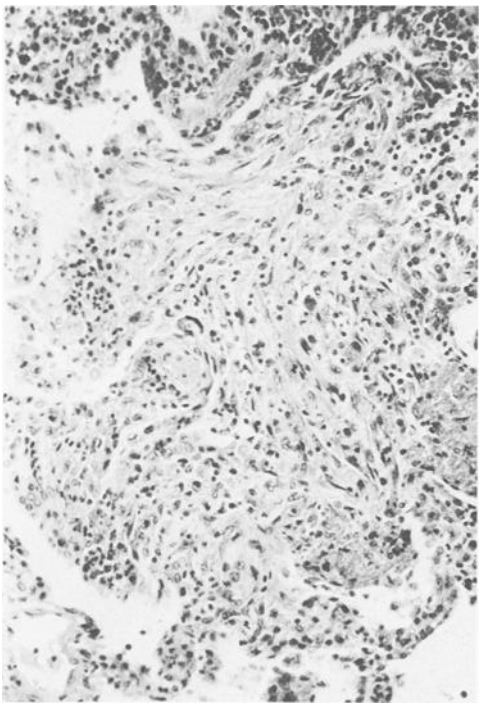

FIG. 34a—*Silo-Fillers' Disease. Granulation tissue within bronchiole forming a polypoid mass (bronchiolitis obliterans). At the margins are partly organized masses of fibrin and red blood cells. Some are within alveoli.*

to many of the others, was centered primarily within the bronchioles, which were partly or completely filled with polypoid masses of organization tissue (Fig. 34a). The walls of the bronchioles may be demonstrated by an elastic stain since the muscle fibers are embraced by elastic tissue, presenting a characteristic segmented appearance. The lesion, which on first inspection resembled a conventional scar, was shown to be an obliterated bronchiole. Initially, there was necrosis followed by regeneration, again with atypical proliferation. A massive organized exudate was converted into a polyp, with the end result, bronchiolitis obliterans.

The chest film revealed the typical nodular appearance, characteristic of patients with silo-fillers' disease. This is a historic case, one of the first two reported by Coe from Minnesota.

Comparison of a patient who was actually exposed to nitric acid as such, an electroplater in Massachusetts who developed respiratory difficulty, reveals, by an elastic tissue stain, the walls of obliterated bronchioles that would probably not have been recognized as such otherwise (Fig. 34b). Another clue is the presence of a muscular artery with no adjacent bronchiole.

Most cases of bronchiolitis obliterans are not the result of the action of acids but probably of bacterial superinfection of viral pneumonia.

Medicolegal Discussion

This case, involving the death of a 29-year-old man with a relatively long work life expectancy, could involve a judgment for a large sum in damages if the legally responsible

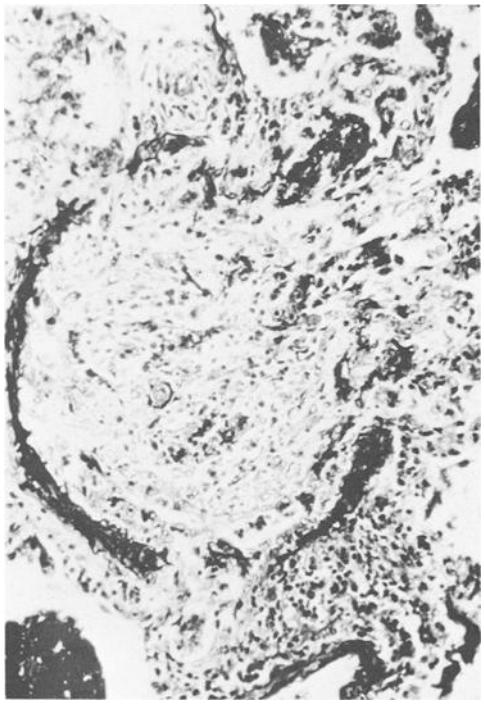

FIG. 34b—*Elastic stain of this lung demonstrating clearly the outlines of the bronchiole with typical relationship of the elastic tissue to the muscle. The lumen of the bronchiole contains granulation tissue some of which extends into adjacent alveoli.*

party could be identified. Claim for this responsibility would probably be made against a number of different parties, including the manufacturer of the silo on the premise that it was poorly designed for the intended purpose and offered hidden danger, or breaching a legal warranty of fitness for the intended use. As quoted in earlier discussions, the legal assertions against the manufacturer of a particular product have varied considerably, depending upon the circumstances of the given case or the legal jurisdiction where the action is brought. A claim may be instituted for breach of warranty if the device, in this case the chute, silo, or a pertinent portion thereof, was considered to be designed or manufactured negligently, or against the agency responsible for servicing the equipment, if this was considered defective.

Once a silo, with the hazardous propensities found herein, is placed upon a plot of ground, one might claim that this constituted a nuisance and a claim brought against the land owner for maintaining such a nuisance. In the alternative, the occupier of the land might also have a claim asserted against him on the basis of negligence because he or his employees failed to warn the deceased of the dangerous propensity of the silo or, as enumerated in earlier discussion, may be found liable under the statutes of some states which require that a safe working location be provided. Obviously, if the deceased was an employee of the owner of the silo, the workmen compensation problems previously discussed must be considered.

Under the circumstances of this case, the persons against whom claim was made would probably assert that the deceased was at fault himself in that he knew of the risk, assumed that risk in entering the silo, and was therefore contributorily negligent. Assumption of risk as a defense has been permitted in instances based upon negligence, but the law varies from state to state where a claim based on unsafe working conditions or breach of warranty is instituted. A vigorous legal dispute might ensue to determine if the deceased knew or should have known of the dangers involved in working in the chute. This might be of great importance in the outcome of a law suit. The physician might find himself in court in a battle ascertaining whether the noxious fumes produced by the fermenting silage should alert the worker of potential danger. Once again, the physician is forewarned that he should restrict his testimony to those areas of which he has knowledge and training and should not speculate upon other matters wherein he may find himself deeply embarrassed in the court room under cross examination.

This case also raises the possibility of a potential medical malpractice action against the treating physicians for failure to make an appropriate diagnosis and institute vigorous treatment immediately. The attending physician can unwittingly become a party if plaintiff's attorneys join as defense in the law suit all persons who had any contact with the injured or deceased patient. The question of malpractice will depend upon the specific facts upon which the physician based his diagnosis and upon the therapy he afforded the patient thereafter. These may involve serious technical problems such as receiving misleading history from the patient or alternatively in failing to take an adequate history. It may involve tortuous questions of degree involved associated with the necessary dosage of drugs used to treat the condition, or the efficacy of the vigorous treatment upon the end result. Obviously, if a proper diagnosis was made and treatment commenced immediately for a disease not amenable to the therapy, the physician should not be held responsible. Likewise, even if the physician were negligent in either diagnosis or treatment, neither of which would have had any significant effect upon the end result, again, technically the physician should not be responsible. Of course, such a legal theory may not have a technically satisfactory outcome under the jury system if a jury becomes so incensed at the physician's mismanagement of the case that they award a compromise verdict against him,

although they may have concluded that the therapy would not, nor could not, have altered the results. One suspects that in many court room situations this actually occurs and this problem may account for the tendency of many defense attorneys to recommend a substantial settlement rather than to risk the judgment of a jury's ire in a particular case.

The most difficult question often posed is whether appropriate early treatment would have altered the outcome in a very small percentage of similar cases or should the physician be held responsible for the death of the patient if 98 percent of all such persons adequately treated would have expired in spite of therapy. Should the jury award only a 2 percent verdict, that is, 2 percent of the value of this man's life? Many courts have been unclear in answering this question. Historically, the courts have insisted upon statements ignoring such statistical probability, insisting upon the statement that the patient either would live or die in similar circumstances, thus making an all or none basis for awards.

A small number of recent court decisions have completely evaded the question by leaving the decision solely to the jury, based upon facts which obviously are not present. The complexity of the problem has made it impossible for any legal scholar to step forth with an acceptable answer to this question.

Summary

A series of patients in whom there are gross morphologic alterations within the respiratory system, many representing variations of diffuse alveolar damage, resulting from extensive exposure to a variety of exogenous agents, has been presented. In the next several decades, the environmental pathologist may well find himself searching for subtle clues indicating the development of similar processes following minimal exposure to similar agents in our ambient environment over extended intervals.

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