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The Three Syndromes of Fat Embolism: Pulmonary Manifestations

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The clinical course and radiographs of 30 patients with fat embolism syndrome were reviewed. In all cases the classic triad of neurologic dysfunction, respiratory insufficiency, and petechiae were present. Three responses to embolized fat were noted. The hyperacute response was seen in two patients with paradoxical embolization of fat to the systemic circulation. A "classic response" was noted in 18 patients with transient respiratory compromise and variable radiographic findings. The two deaths in the group responding in the classical manner were attributed to massive pulmonary emboli. The third response, noted in ten patients, consisted of a chest radiograph compatible with pulmonary edema in the clinical setting of the adult respiratory distress syndrome. In this group the degree of respiratory dysfunction and pulmonary damage correlated with the development of disseminated intravascular coagulation. Pathologic correlations are presented and the mechanisms by which embolic fat produces tissue damage are discussed.

The fat embolism syndrome following major trauma consists of the triad of neurological dysfunction, respiratory insufficiency, and petechiae. While systemic fat embolization following major trauma is common, the full-blown clinical syndrome is a relatively rare event. Perhaps as a result of the rarity of the classical syndrome, early diagnosis, course, and treatment are poorly understood. This study was undertaken to examine the pulmonary manifestations of fat embolism when the pathognomonic signs of the full-blown syndrome were present. The data for this retrospective study were accumulated from the histories of 30 patients selected from a review of the medical records and autopsy reports of over 400 patients seen at the San Francisco General and Yale-New Haven Hospitals over the past ten years.

CLINICAL MATERIAL

As our primary interest was the effect of fat embolism on the lungs, we attempted to exclude patients with conditions themselves associated with pulmonary compro-

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mise. Thus, excluded were patients with prolonged shock from hypovolemia and/or hemorrhage, left ventricular failure or fluid overload, aspiration or bacterial pneumonia, and hypoxia requiring more than 50% O_2 during the first 12 hours of admission. Despite these precautions, certain pulmonary abnormalities may have been caused by factors other than those relating directly to embolic fat.

Of the 30 patients who met the criteria for the study (neurological dysfunction, respiratory insufficiency, and petechiae), 17 were men and 13 were women; ages ranged from 17 to 81 with a mean of 50 years. All patients had sustained skeletal trauma, particularly of the pelvis, hips, and/or long bones; half had multiple fractures involving at least two of the major long bones. All patients demonstrated pathognomonic signs of fat embolism syndrome: disturbances in respiratory function (hypoxemia, hyperventilation, and respiratory alkalosis were common); unexplained fever in the first four post-trauma days; inconstant neurological deficits not explained by head trauma, anemia, and/or unexplained hemorrhage; petechiae; thrombocytopenia; and abnormal blood gas values. The average onset of clinical symptoms was 40 hours post trauma. Two patients demonstrated symptoms 2–3 hours following orthopedic procedures. In one case, signs and symptoms related to fat embolism were noted as late as five days after initial insult. Twelve patients died from complication of their injuries.

Serial chest radiographs were available on all patients. The film quality varied both because of the frequent use of portable technique for the seriously injured patients and because of limitation in positioning imposed by orthopedic supports and restraints. Twenty-five of the patients had abnormal chest radiographs at some point during the first seven days of hospitalization. Four radiographic patterns were identified on review of these serial examinations: normal chest radiograph, bilateral infiltrates extending from the hila to the periphery, localized patchy infiltrates (most frequently in the lower lobes), and diffuse pulmonary edema. Both the central bilateral infiltrates and pulmonary edema patterns generally occurred at least three days after the skeletal injury.

RESULTS

Combining the radiographic findings with the morbidity and mortality data, it became apparent that these patients responded to embolized fat in one of three general ways. The first was sudden death within 48 hours; the second, the "classic response," was characterized by transient pulmonary dysfunction and a variable radiographic picture; the third was the development of the adult respiratory distress syndrome and a radiographic pattern consistent with pulmonary edema.

The following case reports illustrate these three general responses.

Hyperacute Syndrome

Two patients responded in this manner and died within 48 hours of admission.

Case Report 1. A 64-year-old black man sustained fractures to the pelvis and both femurs. A chest radiograph taken approximately one hour after injuries occurred demonstrated prominent hilar shadows but otherwise clear lungs (Fig. 1). Physical examination and laboratory study findings were within normal limits with the exception of a cardiac murmur consistent with an atrial septal defect. Twenty-four hours after admission, arterial blood gas analysis revealed a pO_2 of 48 mm Hg and a pCO_2 of 60 mm Hg. Increased oxygen concentration, as well as digitalization and diuresis, produced little improvement. The patient gradually became unresponsive

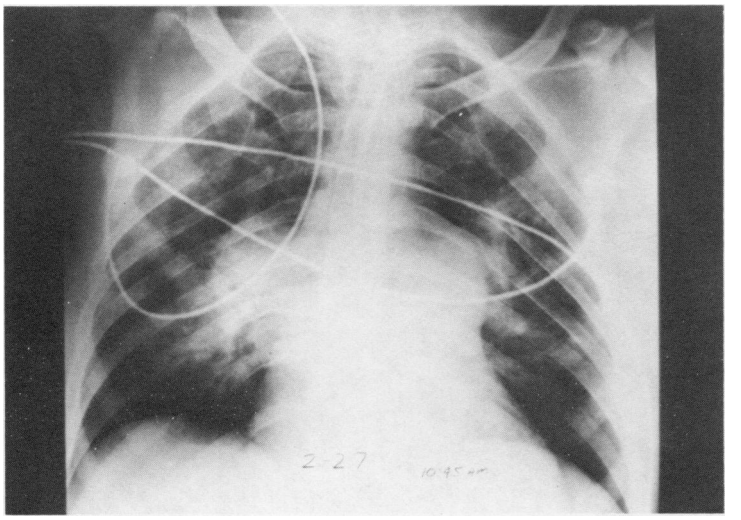

FIG. 1. Portable supine chest radiograph demonstrating large central pulmonary vessels, consistent with atrial septal defect. Parenchyma is clear. Patient was one of two hyperacute responders.

and died 40 hours after admission. At autopsy, the lungs were edematous and congested, weighing approximately 1,000 grams each. Multiple fat droplets were seen in the capillaries of the lungs, brain, and kidneys (Fig. 2). In this patient, a large ostium secundum defect allowed massive shunting of fat emboli to the arterial supply of numerous organ systems with subsequent infarction (Fig. 3).

In the other case, paradoxical embolism to the coronary artery was responsible for abrupt death. No anatomic intracardiac shunt was identified. This latter finding might be explained by Sevitt's hypothesis that arteriovenous shunts may develop in the lungs, thus allowing fat emboli to pass to the systemic arterial circulation [1,2].

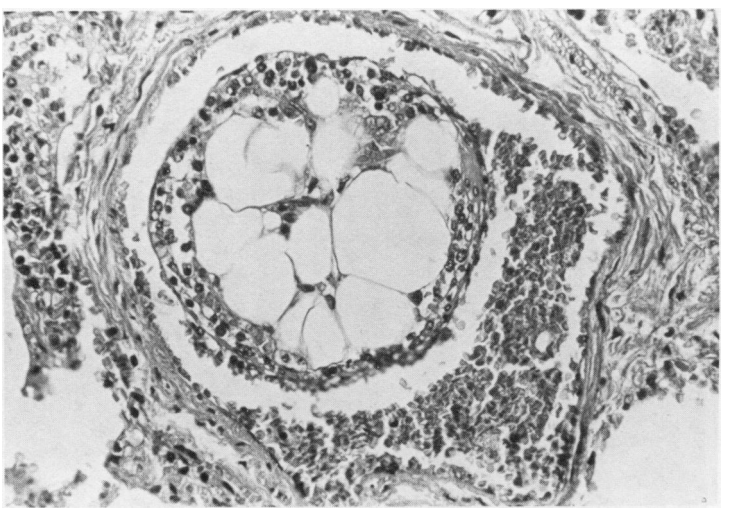

FIG. 2. Lung H & E × 250 A bone marrow embolus lies within a small pulmonary arteriole.

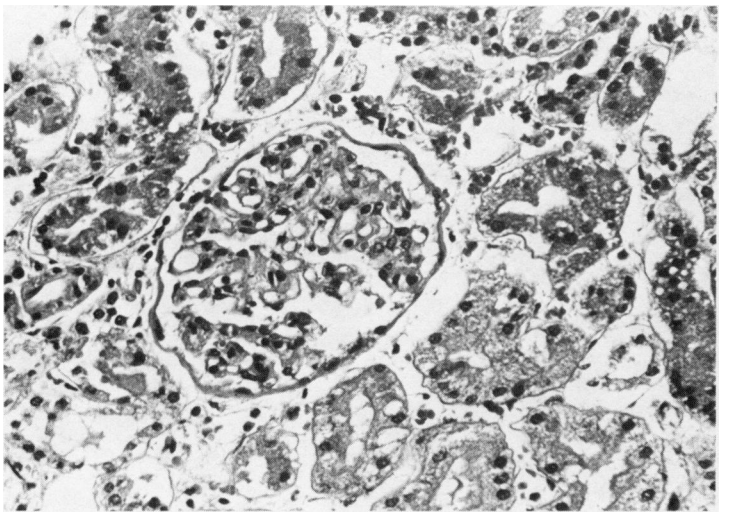

FIG. 3. Kidney glomerulus H & E × 250 Multiple capillary loops are distended with fat emboli.

Classic Response

Eighteen patients responded in the "classic" fashion. Three had normal chest radiographs throughout their hospital courses; three developed localized patchy densities; six progressed to bilateral linear densities extending from hila to periphery consistent with interstitial edema; and six developed a pattern consistent with frank pulmonary edema. Two of these 18 patients died and, at autopsy, multiple large pulmonary emboli were identified in both cases; these were the only two patients in the group who demonstrated pleural effusions on the chest radiographs. Hypoxia was noted in all with a pO_2 of less than 50 mm Hg during the first 72 hours. In all cases, it was correctable with an inspired oxygen concentration of between 20 and 40%. The calculated alveolar-arterial oxygen gradient was between 150 and 200 mm

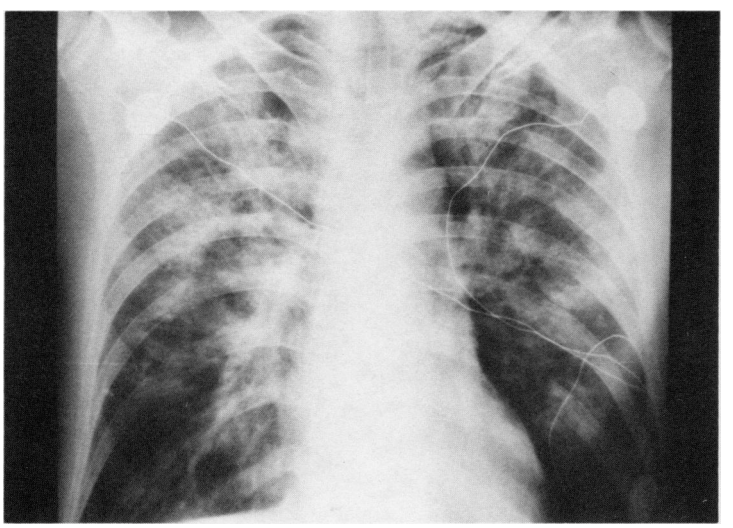

FIG. 4. Portable supine chest radiograph demonstrating patchy densities extending from hila to periphery.

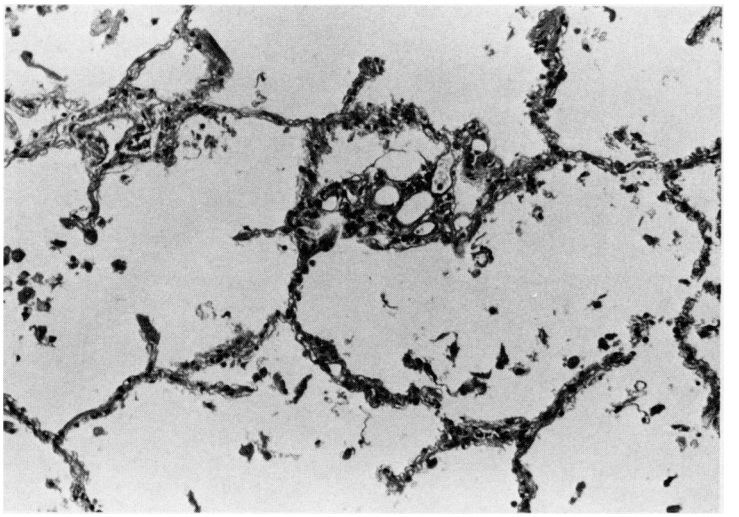

FIG. 5. Lung H & E × 100 Fat emboli are lodged within pulmonary small vessels.

Hg. Prothrombin time and partial thromboplastin time were generally approximately 75% of normal controls. The platelet count was slightly depressed between 75,000 and 100,000 per mm^3 (normal 250,000 to 300,000 per mm^3). Representative lung biopsies in this group demonstrated obstruction of scattered pulmonary capillaries and arterioles with fat droplets and thickening of the interstitium with edema fluid (Fig. 5). The results of biopsies taken later in relation to the initial symptoms demonstrated increased alveolar and interstitial edema without evidence of hemorrhage or necrosis. Also of note were scattered areas of perfectly normal alveoli and interstitium. At no point was extensive alveolar hemorrhage, hyaline membrane formation, or interstitial fibrosis noted. The following case represents an example of this response.

Case Report 2. A 48-year-old white male sustained fractures of the right femur and tibia and of the left shoulder. An admission chest radiograph was normal, although pO_2 was 66 mm Hg on 40% O_2. Within 24 hours, bilateral densities more pronounced in the upper lung fields were noted on the chest radiograph (Fig. 4). At the same time, the patient developed prolonged prothrombin time of 15.9 seconds compared with control of 12.5 seconds, partial thromboplastin time of 42.5 seconds compared with control of 33.9 seconds, and platelet count of 90,000 per mm^3. Fibrinogen fell from a normal of 300 mgm% to 195 mgm%. Steroids and positive pressure ventiliation were instituted on the fourth hospital day. On the fifth day the chest radiograph demonstrated some clearing with gradual resolution over the next five days. The patient finally recovered respiratory function and was discharged two months after the initial injury.

Adult Respiratory Distress Syndrome

Ten patients developed progressive pulmonary compromise consistent with adult respiratory distress syndrome. The pulmonary functional abnormalities in this group of patients were characterized by an alveolar-arteriolar gradient of more than 300 mg of Hg. An oxygen concentration of more than 60 to 80% was required to correct the hypoxemia. At some point, all ten developed evidence of disseminated intravascular coagulation, as characterized by a hematocrit of less than 30, platelet count of less

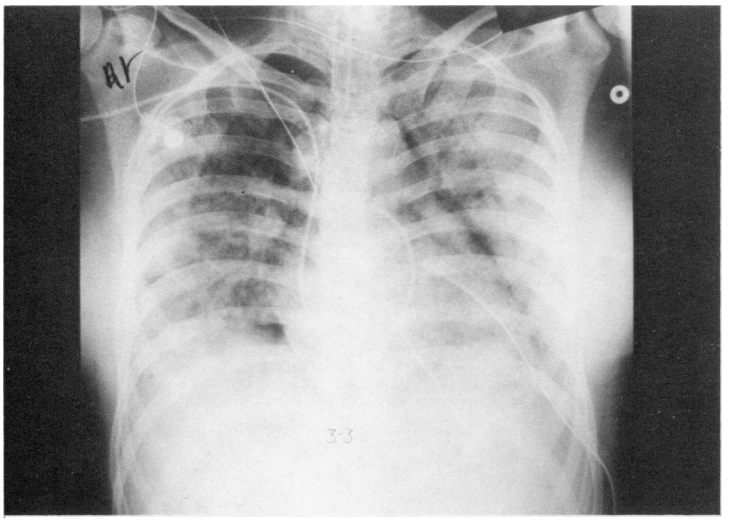

FIG. 6. Adult Respiratory Distress Syndrome: Diffuse parenchymal densities consistent with pulmonary edema. Chest tube also in left hemithorax for decompression of ventilator-induced pneumothorax.

than 100,000 per mm^3, prothrombin time of more than 6 seconds above control, partial thromboplastin time of more than 10 seconds above control, and fibrinogen of less than 100 mgm% with concomitant elevation of split fibrin products. Six died as a result of pulmonary hemorrhage or fibrosis. In this group, characteristic histologic findings on lung biopsy included occlusion of multiple pulmonary arterioles as seen in the classic response. Hemorrhage and necrosis were noted as well (Fig. 7). Electron microscopy demonstrated platelet and fibrin aggregation within multiple capillaries and arterioles. Hyaline membranes could be found four to five days following the onset of respiratory distress and, depending on the pulmonary reserve, a variable degree of fibrosis ensued.

Case Report 3. A 23-year-old white woman was admitted with multiple femoral

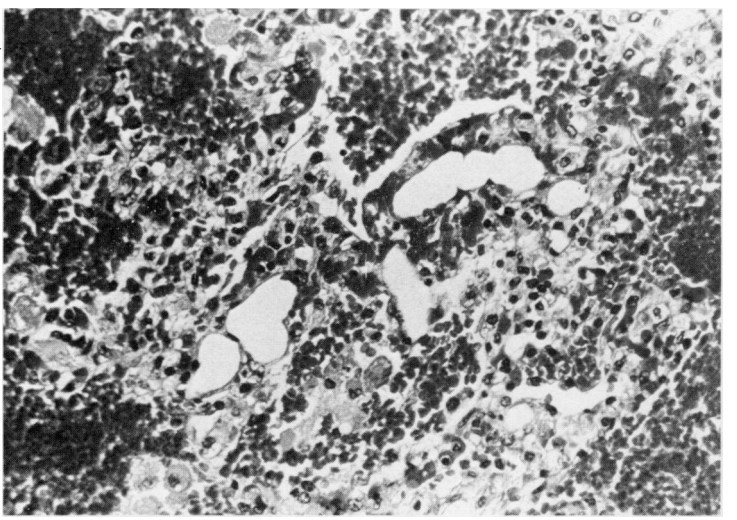

FIG. 7. Lung H & E × 250 Fat emboli in pulmonary capillaries are surrounded by atelectasis, hemorrhage, macrophages, and mononuclear cell inflammatory response.

fractures. There had been a history of transient loss of consciousness, but the patient was alert without neurological deficit shortly after admission. The admission hemogram was normal with the exception of the white count of 16,000 per mm^3. The admitting chest radiograph was normal. Thirty-two hours following open reduction and pinning of femoral fractures, she became disoriented, lethargic, and tachypneic. Arterial blood gases on room air showed a pO_2 of 38 mm Hg and a pCO_2 of 43 mm Hg. The hematocrit was 39 and the white count was 12,300 per mm^3 with a left shift. The urine demonstrated fat droplets. A chest radiograph 36 hours after admission was consistent with pulmonary edema, although a Swan-Ganz catheter demonstrated a normal wedge pressure (10cm H_2O) (Fig. 6). Oozing was noted from the debridement site and platelets had fallen to 40,000 per mm^3. Prothrombin and partial thromboplastin times were 50% of normal control. The oxygen requirement increased to the point of requiring a tracheostomy with constant positive pressure ventilation to maintain a pO_2 of 50 mm Hg. High dose steroid therapy was begun. By the third hospital day, the arterial pO_2 was 30 mm Hg despite a delivered oxygen concentration of 100%. The patient continued to develop a consumptive coagulopathy. She lapsed into coma and died ten days following the initial injury.

DISCUSSION

The mechanisms by which embolic fat produces tissue damage, particularly pulmonary damage, are not completely understood. Several theories postulate the direct toxic effect on pulmonary parenchyma of free fatty acids, which are metabolized either at the systemic or local level from circulating fat emboli [3–7]. Other investigators have demonstrated pulmonary capillary endothelial damage as a result of intravenous injection of free fatty acids [8–11]. However, this occurs only with a large bolus injection and only when protein binding is saturated. In addition. toxicity occurs only with the free fatty acid and not with neutral fat as presumably is extruded from the disrupted marrow cavities. In the laboratory, intravenous neutral fat and mineral oil have produced acutely fatal cor pulmonale, but not endothelial damage, once the lethal dose is exceeded [8,9,12]. Herndon and co-workers demonstrated release into the blood stream of substantial amounts of marrow fat during total hip replacement procedures. They did not observe, however, a single case of the fat embolism syndrome either intra-operatively or during the three-day follow-up period of observation [13].

Free fatty acid levels in serum were elevated in our patients; however, the degree of elevation did not correlate with the extent of pulmonary damage and presumably was largely secondary to the physiologic response to stress.

Several authors have proposed that pulmonary lipase converts the neutral triglyceride to more toxic free fatty acids [14–16]. Whether pulmonary lipase has a role in the pathophysiology of fat embolism in humans has not yet been demonstrated. Gossling has shown that triglyceride breakdown to free fatty acid is an intracellular event followed by further breakdown prior to release to the extracellular space [17]. This would appear to limit the effect of free fatty acid at the alveolar membrane. All of our patients had elevated lipase levels at some point during their hospitalization. Again, there was no correlation between the degree of elevation and the extent of pulmonary damage. To date, the greatest support for the theory of free fatty acid toxicity is the consistent latent period between the onset of injury and symptoms, as related to interstitial pneumonitis and toxic vasculitis. The delay is presumably related to the time required to metabolize the embolized fat to free fatty acids [3]. However, the lag may also be explained by loss of surfactant activity as a direct result

of shock, hypoxemia, or the accumulation of another byproduct of fat embolization damaging the surfactant-producing cells.

The only abnormality we were able to correlate with the degree of pulmonary damage in any consistent manner was the quantitative platelet count and the eventual development of a consumptive coagulopathy. The earliest laboratory indicators that separated patients with the classical response from those who would eventually develop the adult respiratory distress syndrome were the magnitude of thrombocytopenia and coagulation defects. Murray et al. [18] reviewed successful therapy of patients with fat embolism syndrome, stressing the importance of careful monitoring of blood gases and aggressive ventilatory support. Their group of patients with fat embolism syndrome, or ARDS, would appear to correspond to our sub-group of patients with ARDS. The authors made no mention of features other than hypoxia which might predict the manner in which a patient might respond to embolized fat.

Experiments have indicated that intravenous infusion of fat, high fat meals, or hyperlipemia may produce reticuloendothelial blockage, coagulation abnormalities, and the inhibition of fibrinolysis [19–29]. Skeletal trauma releases tissue thromboplastin as well as fat from the damaged tissues. Both of these may stimulate aggregates. The congestion and sludging within pulmonary arterioles may contribute further to hypoxia and acidosis which, in turn, can potentiate the consumptive coagulopathy. In addition, vasoactive and bronchoactive peptides may be released during the process of coagulation and fibrinolysis, which may produce further respiratory compromise.

The histologic changes seen in the lungs, with the development of the adult respiratory distress syndrome, are consistent with an increase in vascular permeability secondary to platelet aggregation. Nachman has isolated a cationic protein which is capable of producing permeability changes in the capillaries within three to four minutes following injection [30]. Periarterial and intra-alveolar hemorrhage may result either from a bleeding diathesis secondary to consumptive coagulopathy or from arterial wall damage produced by the fat emboli. In addition, massive fat emboli may occlude enough pulmonary arterioles to cause microinfarction with resulting interstitial edema and hemorrhage. The physiologic cause of hypoxemia can be explained on the basis of platelet aggregation, increased vascular permeability, disruption of terminal lung units, and, in some cases, the development of hyaline membranes and eventual pulmonary fibrosis. It is not clear what determines a particular patient's response to the phenomenon of embolized fat. The development of a pattern radiographically consistent with pulmonary edema in the presence of thrombocytopenia and coagulation abnormalities suggests the onset of the adult respiratory distress syndrome.

SUMMARY

We have reviewed 30 cases of fat embolism where the classic triad of neurologic dysfunction, respiratory insufficiency, and petechiae were present. Despite our attempt to exclude concomitant pulmonary complications, it is apparent that with fat embolism the degree of pulmonary compromise is variable. Our experience would suggest there are three general responses to the phenomenon of embolized fat. The hyperacute response is rarely recognized before death, is unpredictable, and depends on paradoxic embolization. The classic response, characterized by equivocal findings on chest radiographs with transient respiratory compromise, proceeds, with ventilatory support, to an uneventful recovery. The two deaths seen in this second group were associated with massive pulmonary emboli. The third form of response, the

most serious, is characterized by coagulation abnormalities and chest radiographs showing diffuse pulmonary edema.

Therapy initially must be directed toward good ventilatory support and the correction of the developing acidosis. The onset of disseminated intravascular coagulation warrants a therapeutic trial of heparin. Because of the obvious risks of heparinization in these patients, we do not advocate its use in all patients with fat embolism, but only in those who show alterations in the clotting and fibrinolytic systems as determined by careful sequential studies of their coagulation parameters.

REFERENCES

1. Sevitt S: The Significance and Classification of Fat Embolism. Lancet 2:285, 1960
2. Sevitt S: Fat Embolism. London, Butterworth and Co, Ltd, 1962
3. Baker PL, Pazell JA, Peltier LF: Free Fatty Acids, Catecholamines, and Arterial Hypoxia in Patients with Fat Embolism. Journal of Trauma 11:1026-1030, 1971
4. Ellis HA, Watson AJ: Studies on the Genesis of Traumatic Fat Embolism in Man. American Journal of Pathology 43:245, 1968
5. Derks CM, Peters RM: The Role of Shock and Fat Embolism in Leakage from Pulmonary Capillaries. Surgery, Gynecology & Obstetrics 137:954, 1973
6. Derks CM, Peters RM: The Effect of Shock and Fat Embolus on Pulmonary Mechanics and Gas Exchange. Surgery, Gynecology & Obstetrics 138:413, 1974
7. Hallgren B, Kerstell J, Rudenstam EE, et al: A Method for the Isolation and Chemical Analysis of Pulmonary Fat Emboli. Acta Chir Scand 132:613, 1966
8. Peltier LF: Fat Embolism I. The Amount of Fat in Human Long Bones. Surgery 40:657, 1956
9. Peltier LF: Review of Fat Embolism. Int Abstr Surg 104:313, 1957
10. Szabo G, Sereny P, Loesar L: Fat Embolism: Fat Absorption from the Site of Injury. Surgery 54:746, 1963
11. King EG, Wagner WW, Ashbaugh DG, et al: Embolism. Chest 59:524, 1971
12. Armin J, Grant RT: Observations on Gross Pulmonary Fat Embolism in Man and the Rabbit. Clin Sci 10:441-464, 1961
13. Herndon JH, Bechtol CO: Fat Embolism during Total Hip Replacement. J Bone Jt Surg 56-A:1350, 1974
14. Fonte DA, Hausberger FX: Pulmonary Free Fatty Acids in Experimental Fat Embolism. Journal of Trauma 11:668, 1971
15. Armstrong HJ, Huenzig MD, Peltier LF: Long Lipase Levels in Normal Rats and Rats with Experimentally Produced Fat Embolism. Proc Exp Biol Med 124:959-961, 1967
16. Peltier LF: Fat Embolism: A Current Concept. Clin Orthop Rel Res 66:241, 1969
17. Gossling HR, Ellison LH, Degraff AC: Fat Embolism. The Role of Respiratory Failure and its Treatment. J Bone Jt Surg 56-A:1327, 1974
18. Murray DG, Racz GB: Fat-Embolism Syndrome (Respiratory Insufficiency Syndrome). J Bone Jt Surg 56-A:1338, 1974
19. Bridges JM, Dalby AM, Hadden DR, et al: The Effect of *in vivo* Alterations of Free Fatty Acids on Platelet Stickiness. J Atherosclerosis Res 7:695-699, 1967
20. Brockner J, Amris CO, Larsen V: Fat Infusion and Blood Coagulation. Effect of Various Emulsions on Blood Coagulability. A Comparative Study. Acta Chir Scand Suppl 343:48, 1965
21. Allardyce DB, Groves AC: Intravascular Coagulation Hyperlipemia and Fat Embolism: Their Association During the Generalized Schwartzman Phenomenon in Rabbits. Surgery 66:71-79, 1969
22. Groves AC, Duff JH, McLean AP, et al: Hyperlipidemia and Pulmonary Fat Embolism in Dogs with E. coli Bacteremia. Surgery 68:656, 1970
23. Keith RG, Mahoney LJ, Garvey MB: DIC: An Important Feature of the Fat Embolism Syndrome. Canad Med Assoc J 105:74, 1974
24. Lasch HG, Heene DL, Huth K, et al: Pathophysiology, Clinical Manifestations and Therapy of Consumption Coagulation. Am J Cardiol 20:381, 1967
25. Saldeen T: Intravascular Coagulation in the Lungs in Experimental Fat Embolism. Acta Chir Scand 135:653, 1969
26. Lasch HG: Alimentare Fettzufuhr und Blutgerinnung. Med Welt 324-327, 1961
27. Lasch HG, Roka L, Heene D: The Defibrination Syndrome. Thromb Diath Haemorrh (Supplement) 20:97, 1966
28. McKay DG, Wong TC: Studies on Generalized Schwartzman Reaction Produced by Diet. I. Pathology. J Exp Med 115:111, 1967
29. Rodriguez-Erdmann R: Bleeding Due to Increased Intravascular Blood Coagulation. New Engl J Med 273:1370, 1965
30. Nachman RI, Weksler B: The Platelet as an Inflammatory Cell, Ann NY Acad Sci 201:131, 1972