THE FAT EMBOLISM SYNDROME

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The fat embolism syndrome, often a complication of major trauma, frequently passes undiagnosed. The classical picture of cerebral confusion, respiratory distress and petechiae of skin and mucosa is not always seen.

A distinction must be made between the clinical entity and fat embolism demonstrated pathologically. Post-mortem, fat embolism is often found after deaths from causes other than trauma (Sevitt 1957, 1962, Bergentz 1968). It is also found in deaths following fracture without clinical evidence of the syndrome (Warren 1946, Scully 1956). The finding of pulmonary fat emboli is of doubtful significance in cases where the clinical features of the syndrome are absent.

TABLE 1

DIAGNOSIS OF THE FAT EMBOLISM SYNDROME

<table>
<thead>
<tr>
<th>Injury</th>
<th>Latent period</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major features</td>
<td>1) Respiratory insufficiency; 2) Cerebral involvement; 3) Petechial rash</td>
</tr>
<tr>
<td>Minor features</td>
<td>1) Pyrexia; 2) Tachycardia; 3) Retinal changes; 4) Jaundice; 5) Renal changes</td>
</tr>
<tr>
<td>Laboratory features</td>
<td>1) Anaemia; 2) Thrombocytopenia; 3) High erythrocyte sedimentation rate; 4) Fat macroglobulaemia</td>
</tr>
</tbody>
</table>

In this series 100 cases of the syndrome seen over a period of four years are analysed. Certain clinical features were looked for in suspected cases (Table 1) and in addition blood samples were checked for pathological fat globules. A positive diagnosis was made on finding at least one major feature, four minor features, and fat macroglobulaemia (Gurd 1970). The assessment of pathological fat globulaemia has been criticised by Nolte, Olofsson, Schersten and Lewis (1974), who report finding large fat globules as often in normal patients and in patients with fractures as in proven cases of fat embolism syndrome. In the original description of the test it was pointed out that pathological fat was seen, often in considerable quantities, after fractures. It was found necessary to assess blood values daily because the important feature was not merely the demonstration of fat globules but the finding of either a recent onset of fat macroglobulaemia, or an increase in the number of globules, or a change in their appearance associated with the onset of the clinical condition.

As with the post-mortem finding of pulmonary fat emboli, so, too, fat macroglobulaemia in the asymptomatic patient is probably irrelevant. Bergentz (1968) asserts that the only finding which is specific in fat embolism is one of intravascular fat droplets. The diagnosis of the condition under discussion here is made when fat macroglobulaemia is found in association with accepted clinical features. The condition is then referred to as "the fat embolism syndrome" rather than the misleading term "fat embolism", which denotes the embolism of fat droplets with or without clinical evidence of their presence.
THE FAT EMBOLISM SYNDROME

PRESENT STUDY

Of the 100 patients seventy-seven were male and twenty-three female. The ages of the males ranged from fourteen to ninety-one years (average thirty-three) and of the females from sixteen to sixty-six years (average thirty-nine). The mean average age was thirty-four and a half years.

Forty-nine cases followed multiple fracture with two or more long bones involved (Table II). Thirty followed femoral shaft fracture, ten tibial fracture and four pelvic fractures. In seven cases the syndrome followed injury with either minor bone injury or no demonstrable fracture. Thus two patients fell from step ladders, both sustaining soft-tissue injury and a fractured calcaneus. A girl was involved in a car accident and lay unattended for six hours; she developed a severe fat embolism syndrome six hours after being admitted with hypothermia, bruising and a fractured mandible. A youth was severely assaulted and had bilateral fractured patellae. An elderly man fell down stairs and was badly bruised: two days after injury he developed a classical syndrome and died thirty-six hours later: no fracture had been found clinically or radiologically and none was found at necropsy. Two patients sustained severe crush injuries of the upper abdomen, chest and arms without evident fracture.

TABLE II

NATURE OF THE INJURY IN 100 CASES OF
FAT EMBOLISM SYNDROME

<table>
<thead>
<tr>
<th>Injury</th>
<th>Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Multiple fractures</td>
<td>49</td>
</tr>
<tr>
<td>Femoral shaft fracture</td>
<td>30</td>
</tr>
<tr>
<td>Tibial fracture</td>
<td>10</td>
</tr>
<tr>
<td>Pelvic fracture</td>
<td>4</td>
</tr>
<tr>
<td>Trauma: minor fracture</td>
<td>4</td>
</tr>
<tr>
<td>Trauma: no fracture</td>
<td>3</td>
</tr>
</tbody>
</table>

PRESENTATION

In all cases there was a latent period between injury and the onset of symptoms. This varied from four hours to fifteen days, with an average time of forty-six hours. The recorded latent period of fifteen days in one case may be misleading: the patient developed symptoms of embolism two days after remanipulation of a femoral fracture, fifteen days after the original injury. No significant correlation was found between the time of onset and the severity of the subsequent course.

There was marked variation in the clinical presentation. In thirty-four cases the earliest recorded symptoms were cerebral, usually drowsiness or confusion. In twenty-nine, otherwise unexplained tachycardia and pyrexia heralded more specific signs. Respiratory dysfunction was observed first in twenty patients with dyspnoea, tachypnoea or haemoptysis. A petechial rash was the presenting sign in only seventeen cases.

CLINICAL FEATURES

Respiratory involvement was predominant in seventy-five patients, most of whom had dyspnoea and tachypnoea with moist rales over the whole of the lung fields. Cyanosis was uncommon even when arterial hypoxia was marked, presumably because of concomitant anaemia. The arterial oxygen tension was monitored in only fifty cases. In twenty-four

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cases the minimum pO$_2$ level was less than 50 millimetres of mercury; in seventeen cases it ranged from 51 to 80, and in nine patients it was greater than 81.

Fifty-two patients had radiographic examination of the chest. In forty-three the films showed typical bilateral diffuse patchy areas of consolidation (Fig. 1). Of seven patients with normal radiographs, two had a pO$_2$ level of under 80 millimetres of mercury. Two patients with clinically normal lungs had moderate radiological changes. Haemoptysis occurred in twenty-two patients.

There was some cerebral involvement in eighty patients, of whom eleven had associated head injuries. Sixty-nine were awake and fully orientated on admission, and of these nine became confused, thirty-five drowsy, and twenty-five deeply comatose during the peak of their symptoms.

![Fig. 1](image)

*An antero-posterior radiograph of the lung fields showing typical appearances.*

A petechial rash was observed in fifty-seven patients; typically it was first seen over the anterior axillary fold and the root of the neck (Fig. 2). It was also found in the buccal mucosa and the conjunctiva. The distribution and intensity of the rash varied: at times it could be detected only with the aid of a magnifying glass.

Pyrexia of 39.4 degrees Celsius or above and tachycardia of 120 per minute or more were noted in eighty-three cases. Ophthalmoscopy was recorded in sixty-three patients and was normal in fifty-four. Retinal exudates and haemorrhages were noted in seven, and fat droplets in the retinal vessels in two. Five patients became jaundiced but the pigmentation always subsided within ten days. Some renal involvement was manifest in twenty-two patients; seventeen became oliguric, three were anuric and required dialysis, one had haematuria and one became incontinent.

**LABORATORY INVESTIGATIONS**

Daily haemoglobin estimations were recorded in sixty-eight patients. A drop of more than 20 per cent was found in forty patients, the maximum fall being from 16.3 to 8.1 grams in sixteen hours. Daily platelet counts were monitored in only thirty-eight cases: a drop of
50 per cent or more was found in twenty-three, with minimum values of under 90,000 cubic millimetre in twelve patients. In eighty-seven cases the erythrocyte sedimentation rate was raised, with values of 30 to 50 millimetres in sixteen cases, 51 to 70 millimetres in seventeen cases, and over 71 millimetres in fifty-four cases. Fat globules larger than 8 microns were found circulating in all cases. The amount of circulating fat did not appear to correlate with the clinical severity of the condition.

![Figure 2](image)

**Fig. 2**
A photograph showing the distribution of petechiae.

**COURSE AND TREATMENT**

Thirty-six patients recovered without any treatment. In the remaining cases treatment was directed towards: 1) the restoration of circulating volume with fresh blood or a physiological substitute; 2) the correction of acidosis; and 3) immobilisation of the affected part. Additional treatment was primarily concerned with respiratory support. In twenty cases routine ward care with chest physiotherapy and oxygen by mask was sufficient. Thirty-four required full respiratory care with assisted ventilation and 40 per cent oxygen, eight with endotracheal intubation; twenty-six had tracheostomies. Ten comatose patients who did not require ventilation received all the routine care of the unconscious patient.

Antibiotics were given to the fifty-four patients with moderate or severe lung involvement. Digoxin was required in twelve cases, six with uncontrollable tachycardia, four with atrial fibrillation and two with right heart failure. Eight patients were given intravenous calcium for hypocalcaemia. A protease inhibitor (Trasylol) was given to thirty patients in a dose of 500,000 units intravenously followed by a further 200,000 units six hourly by continuous infusion for three to six days.
Seventy-seven patients recovered fully, seven recovered with some residual deficit (one with epilepsy, one with scotomata and five with personality changes) and sixteen died. Eight of the deaths were from severe pulmonary insufficiency of the fat embolism syndrome and eight from other traumatic causes.

**DISCUSSION**

In this series of 100 cases of the fat embolism syndrome, the diagnosis was made from a combination of well known but variable clinical findings plus the demonstration of circulating globules of pathological fat. Fat macroglobulaemia has been shown to occur after minor operations, minor trauma and in a variety of medical illnesses (Bryans and Eiseman 1955; Tedeschi, Castelli, Kropp and Tedeschi 1968). Although the relationship of these large fat globules to the pathogenesis of the clinical picture remains obscure, we have found the demonstration of their presence helpful in diagnosis.

The origin of the pathological fat has remained controversial for more than a century. Basically two concepts have evolved: the mechanical and the metabolic. In the “mechanical” theory it is alleged that fat is liberated from the marrow of injured bones, driven out by an increase of intramedullary pressure and transmitted via the draining veins to the pulmonary capillaries, where it lodges. The “metabolic” theory suggests that emboli arise in the plasma from conglomeration and fusion of a pre-existing physiological suspension of tiny chylomicrons (usually less than one micron), possibly due to some biochemical change initiated by injury.

Other changes occur which augment the embolic effect of the large fat globules, such as agglutination of the formed elements of blood—particularly platelets and red cells—and an increase in the viscosity of plasma and whole blood (Bergentz, Gelin, Rudenstam and Zederfeldt 1961). Aggregation of platelets, chylomicrons and red cells can be produced by injection of thromboplastic substances, which also cause the formation of fat droplets (Bergentz 1961, Adkins, Foster and O'Saile 1962). The pathological sequence of events is not yet proven, but the triggering mechanism appears to be an over-compensation in response to injury, haemorrhage, decreased venous return and increased cardiac output (Fig. 3). Reactive vasoconstriction follows, causing local tissue hypoxia; carbohydrate metabolism is altered and there is an increased lactic acid production. In addition, post-traumatic activation of the coagulation factors results in the formation of microthrombi (disseminated intravascular coagulation) which further increases the local oxygen deficiency and the metabolic acidosis. A lowered pH activates tissue proteases which in turn liberate vasoactive polypeptides, among them the kinins, which are very potent in the production of post-traumatic shock. Indeed the fat embolism syndrome is probably only one particular facet of the post-traumatic shock syndrome. An association between pulmonary fat embolism and intravascular coagulation has frequently been reported (Bradford, Foster and Nossel 1970; Saldeen 1970; Soloway and Robinson 1972). It has been said that fat embolism potentiates shock (Porter 1917), but in reality the reverse applies (Peltier 1965, Volz 1966).

It is our impression that the clinical syndrome is not uncommon; it occurred in 19 per cent of the patients admitted to the Royal Victoria Hospital, Belfast, with major trauma. Over a third of the cases were so mild that no treatment was required, and these might have remained undiagnosed had they not been screened both clinically and for fat macroglobules. Pulmonary involvement was the most common feature, usually with tachypnoea, dyspnœa and evidence of bilateral diffuse pulmonary oedema. Arterial oxygen tension estimation proved valuable both in diagnosis and for monitoring treatment. Almost half of those investigated had minimum values of under 50 millimetres of mercury. Ross (1970) believes a lowered arterial pO₂ in injured patients is diagnostic when found in conjunction with a normal or reduced pCO₂.

Defective gas transfer across the alveolar/arteriolar membrane is caused by the severe degree of alveolar oedema that develops in this syndrome. Carbon dioxide is not retained
because it diffuses across the membrane at a much faster rate than does oxygen. Later in the course of the disorder veno-arterial shunting plays an important role (Sproule, Brady and Gilbert 1964). Chest radiography is also helpful, the significant positive features being evenly distributed, small fleck-like areas of consolidation, congested hilar shadows and at times dilatation of the right heart. Radiographs also help to exclude other pulmonary pathology, such as pneumothorax (Fig. 4).

The importance of arterial hypoxia in producing the cerebral features of the fat embolism syndrome has been stressed by Wertzberger and Peltier (1968) and by Ross (1970). In most cases reported here confusion, drowsiness and coma appeared to follow the onset of hypoxia. There were ten patients, alert and orientated on admission, who became deeply comatose and in whom respiratory involvement was minimal or absent. "Systemic fat embolism" where cerebral features predominate is less common than "pulmonary fat embolism", but does appear to occur occasionally.

A suggested scheme of the rationale of the fat embolism syndrome.

Petechial haemorrhages, first noted by Benestad in 1911, are a classical finding, usually on the second to fourth days after injury. Initially they occur across the front of the chest, particularly the anterior axillary fold, the root of the neck, the mucosa of the mouth and the conjunctiva. On occasions petechiae can be found all over and they were even noted on the hands and feet of one patient in this series. The rash may last only a few days and is very easily overlooked unless the patient is studied carefully every day. Both Peltier (1965) and Bergentz (1968) quote 20 per cent for the incidence of petechiae in diagnosed cases of fat embolism.

Pathological changes may be found on retinoscopy. Classically, multiple white fluffy exudates, fine streaks of haemorrhage and macular oedema are found (Newman 1948, Kearns 1956, Adams 1971). Scotomata may occur and usually resolve completely (Duke-Elder 1954). Oliguria is not uncommon and complete anuria does occur. Renal involvement is so frequent in fat embolism that Sevitt (1960) has suggested needle biopsy of the kidney as an aid to the diagnosis of obscure cases. Adebahr (1957) believes the sudden drop in the haemoglobin value, occurring even after adequate blood replacement at the time of injury, is due to pulmonary haemorrhage. It is much more likely that this anaemia follows an increased
tendency of red cells to aggregate, followed by trapping and haemolysis of the aggregated cells (Gelin 1956).

Prevention of the fat embolism syndrome in fact means the prevention of shock. In many hospitals it has not been a routine to give fracture patients prophylactic treatment of shock in the form of transfusions, sedatives, analgesics or general anaesthesia (Bergentz 1968). This may explain why fracture patients subjected to immediate internal fixation appear to develop the clinical syndrome less often than patients treated conservatively (Saikku 1954, Liljedahl and Westermark 1967). Adequate volume substitution is essential, using cell-free colloidal solutions or fresh blood. Miller, Fonkalsrud, Latta and Maloney (1962) showed that transfusion of stored blood can result in fat embolism. Bergentz (1968) attempts to keep the post-traumatic haematocrit around 30 to 35, which gives satisfactory oxygen-carrying capacity of the blood without interfering too much with flow. Correction of metabolic acidosis is also necessary, as is adequate early immobilisation of the fracture.

The role of proteases in the production of shock—This is currently under study. Protease inhibition by the naturally occurring enzyme Trasylol has been used in thirty patients. Unfortunately it was not given as part of a controlled trial and statistical conclusions cannot yet be drawn. It is difficult to evaluate specific treatment amongst the routine measures given to each patient because spontaneous recovery occurs and is unpredictable. The only attempt at analysis that can be made is to compare the first thirty-three patients, for whom only routine treatment was available, and a second group of sixty-seven cases where protease inhibition therapy was available but only given to thirty when routine measures appeared to be failing. In the first group 60 per cent recovered fully and 15 per cent died from the fat embolism syndrome, while in the second group recovery was full in 85 per cent and the mortality only 5 per cent (Table III). Zimmerman (1972), in controlled trials with protease inhibition in patients with the shock lung syndrome and the fat embolism syndrome, has reduced the mortality from almost 70 per cent with routine therapy alone to 39 per cent when using Trasylol in addition.

Three cases in this present study died of massive pulmonary embolism whilst on protease inhibition treatment. In retrospect we noted that Trasylol was not commenced until the pCO₂ had begun to rise, which is a bad prognostic sign. Protease inhibition ought to be used prophylactically and therefore given as early as possible. This, of course, makes evaluation even more difficult as so many cases recover spontaneously. It is our clinical impression that protease inhibition with Trasylol has a place in the treatment of this syndrome. No side-effects were observed in the thirty cases treated.
The established case—Here the aim of treatment is to ensure an adequate arterial pO\textsubscript{2}. Besides the correction of anaemia and the lowering of blood viscosity, respiratory care may include tracheostomy and mechanical ventilation, and such patients ought to be in an intensive care unit. Antibiotics are indicated for all patients with moderate or severe respiratory involvement. Digoxin may be required for tachycardia, arrhythmias or right heart failure, and calcium intravenously for hypocalcaemia. Volz (1966) suggested that hypocalcaemia can be severe enough to result in tetany, but this was not observed in any of these cases. A summary of treatment is given in Table IV.

### TABLE III
Comparative Results before and after the Advent of Trasylol

<table>
<thead>
<tr>
<th>Group</th>
<th>Number of cases</th>
<th>Trasylol</th>
<th>Partial recovery</th>
<th>Full recovery</th>
<th>Mortality Overall</th>
<th>Fat embolism syndrome</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>33</td>
<td>0</td>
<td>4</td>
<td>20 (60%\textsubscript{a})</td>
<td>9</td>
<td>5 (15%\textsubscript{a})</td>
</tr>
<tr>
<td>B</td>
<td>67</td>
<td>30</td>
<td>3</td>
<td>57 (83.5%\textsubscript{a})</td>
<td>7</td>
<td>3 (4.5%\textsubscript{a})</td>
</tr>
</tbody>
</table>

### TABLE IV
Scheme of Treatment

**Shock prevention**
1) Restoration of circulating volume
   - *a* fresh blood
   - *b* physiological substitute
2) Maintenance of normal pH
3) Protease inhibition
4) Early and adequate immobilisation of the injured part

**Established syndrome**
1) Maintenance of normal arterial pO\textsubscript{2}
2) Care of the unconscious patient
3) Non-specific drugs
   - *a* antibiotics
   - *b* Digoxin
   - *c* calcium

### SUMMARY
1. A distinction must be made between the fat embolism syndrome, a clinical entity, and fat embolism demonstrated pathologically, which may be found after death following fracture with no prior evidence of the syndrome.
2. One hundred cases of the syndrome encountered over a period of four years have been studied in detail and the diagnostic criteria have been defined. These include one major feature, four minor features and fat macroglobulaemia.
3. Sixteen of the patients died—eight from severe pulmonary insufficiency of the syndrome, eight from other traumatic causes.
4. The prevention of shock is the best measure for prevention of the syndrome. The role of proteases in the production of shock and the place of protease inhibition in treatment of the syndrome are briefly discussed.
5. For the established case the aim of treatment is to ensure an adequate pressure of arterial oxygen.
We wish to thank our orthopaedic colleagues for permission to study patients under their care, and Dr R.C. Gray, Dr D.L. Coppell and Dr W.F. K. Morrow of the Respiratory Intensive Care Unit, Royal Victoria Hospital, Belfast, for their invaluable help.

REFERENCES


