

# Fat Embolism

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## ABSTRACT

**Objective:** To review the pathophysiology and management of patients with clinical manifestations of fat embolism.

**Data sources:** A review of studies reported from 1976 to 1998 and identified through a MEDLINE search of the literature on fat embolism and fat embolism syndrome.

**Summary of review:** Fat embolism occurs when bony or soft tissue trauma has caused fat to enter the circulation, or in atraumatic disorders where circulating fat particles have coalesced abnormally within the circulation. The fat particles deposit in the pulmonary and systemic circulations, although only 1 - 2% develop a clinical disorder with respiratory, cerebral and dermal manifestations known as the fat embolism syndrome. Rarely, fat embolism produces a fulminant fat embolism syndrome due to mechanical obstruction within the pulmonary circulation causing a severe right heart failure.

The fat embolism syndrome is believed to be caused by the toxic effects of free fatty acids liberated at the endothelial layer which cause capillary disruption, perivascular haemorrhage and oedema. The clinical manifestations of respiratory failure, petechiae and a diffuse or focal cerebral disturbance, are characteristic but not pathognomonic of the syndrome. The syndrome is largely self limiting with treatment being symptomatic. Therapy is directed at maintaining respiratory function and largely follows the same principles of management used in patients who have the acute respiratory distress syndrome. Early immobilization of fractures and methods to reduce the intramedullary pressure during total hip arthroplasty have reduced the incidence of operative fat embolisation. Corticosteroids either before or after the development of respiratory or cerebral symptoms have not been shown to be of any benefit.

**Conclusions:** Fat embolism occurs in many traumatic and atraumatic conditions and is largely asymptomatic. Preventative measures include early immobilization of fractures and methods to reduce intramedullary pressure during surgical manoeuvres. Treatment is largely symptomatic with therapy for respiratory failure similar to that used in management of acute respiratory distress syndrome. Corticosteroids have not been found to be of significant benefit. (**Critical Care and Resuscitation 1999; 1: 276-284**)

**Key Words:** Fat embolism, fat embolism syndrome, fulminant fat embolism syndrome, nitric oxide, corticosteroids

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Fat embolism may be defined as a blockage of blood vessels by intravascular fat globules ranging from 10-40  $\mu\text{m}$  in diameter.<sup>1</sup> In more than 90% of cases it is associated with accidental trauma to long bones or pelvis, or during surgical trauma (e.g. joint reconstruction), and in up to 5% of cases it has an atraumatic cause (e.g. bone marrow transplantation, pancreatitis, sickle cell disease, burns, prolonged high-dose corticosteroid therapy, diabetes mellitus.) Other

rare causes include hepatic trauma, liposuction, lipectomy, external cardiac compression, gas gangrene, decompression sickness and lipid infusions.<sup>2,3</sup>

### *Traumatic fat embolism*

Histological fat deposition in the pulmonary capillaries occurs in all patients who have long bone and pelvic fractures, although only 1-2% of these patients develop a respiratory and/or neurological syndrome

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known as the fat embolism syndrome.<sup>4</sup> Rarely, fat embolism will cause a cardiovascular syndrome known as the fulminant fat embolism syndrome.

Intramedullary fat is the source of the fat embolism in patients who have fractures or during intramedullary surgical fixation (during the latter procedure echocardiography has confirmed the embolic phenomenon<sup>5</sup>). The fat enters torn venules which are kept patent in the Haversian canals and enter the circulation at the site of injury.<sup>6</sup>

While fat globules ranging from 7-10  $\mu\text{m}$  in diameter may traverse the pulmonary vasculature, with 25% of individuals having probe patency of the foramen ovale,<sup>7</sup> if severe pulmonary hypertension occurs during fat embolism, then the pressure differential between the right and left atria will allow fat globules ranging from 20-40  $\mu\text{m}$  in diameter to traverse the atrial septum and embolise into the systemic circulation.<sup>6</sup>

#### *Atraumatic fat embolism*

The origin of the fat in conditions not associated with adipose tissue disruption (e.g. pancreatitis, prolonged high-dose corticosteroid therapy, diabetes mellitus, lipid infusions, etc) is unclear, although, it is thought that intravascular agglutination of chylomicrons, Intralipid liposomes or fat macroglobules (induced by stress induced elevated free fatty acid levels and hypoalbuminaemia<sup>8</sup>) by elevated levels of C-reactive protein during acute illness, may play a role in this variety of fat embolism.<sup>9</sup>

#### CLINICAL SYNDROMES<sup>1,10</sup>

The clinical syndromes of the fulminant fat embolism syndrome and the fat embolism syndrome are caused by different pathophysiological effects associated with the systemic liberation of fat. For example, the fulminant fat embolism syndrome is caused by an acute cardiovascular pulmonary obstruction by fat, whereas the fat embolism syndrome is caused by perivascular haemorrhage and oedema following the accumulation of fat in the pulmonary, cerebral or dermal microvasculature and local liberation of free fatty acids (FFAs).

#### *Fulminant fat embolism syndrome*

This is caused by a sudden intravascular liberation of a large amount of fat causing pulmonary vascular obstruction, severe right heart failure, shock and often death within the first 1-12 h of injury.<sup>11,12</sup> The acute pulmonary vascular obstruction by fat is also exacerbated by platelet aggregation and release of vasoactive and thrombogenic substances which contribute to the pulmonary hypertension and oedema. In an adult, the acute lethal intravenous dose of fat

ranges from 20-50 ml. The volume of marrow fat from a femur is approximately 70-100 ml.

Echocardiography is the investigation of choice as it will detect the presence of pulmonary obstruction with right heart dilation and pulmonary hypertension. While the treatment is largely supportive, percutaneous pulmonary artery aspiration or cardiopulmonary bypass and surgical removal of the fat, would seem to offer a solution if readily available.

#### *Fat embolism syndrome*

Fat collects in the pulmonary or systemic capillary network and is acted upon by lipoprotein lipases (activated by catecholamine release) liberating high concentrations of toxic FFAs locally, causing platelet aggregation, a mild disseminated intravascular coagulation and disruption of the pulmonary and cerebral capillary walls.

Pulmonary histology reveals intra-alveolar haemorrhage, fat within pulmonary capillaries and oedema. Cerebral histology reveals diffuse cerebral oedema with multiple haemorrhagic petechiae.<sup>1,13</sup> Histology of the dermal petechiae reveals perivascular haemorrhages. The capillary disruption of lung, cerebral and cutaneous vessels causes a subacute syndrome known as the fat embolism syndrome. While fat deposits have been identified in other organs (e.g. liver, kidney, heart, skeletal muscle) disordered function in these organs is rarely, if ever, seen. For example, while lipuria, proteinuria and oliguria may occur, acute renal failure has never been reported as a consequence of renal fat embolism.<sup>14</sup>

#### **Clinical features**

The fat embolism syndrome is characterised by an asymptomatic period of 12-72 h (commonly 36 h, although up to 6 days has been described) following bony injury or manipulation of the fracture site, and a symptomatic period which includes respiratory effects (95%), cerebral effects (60%) and petechiae (33%).<sup>15</sup> Tachycardia (> 120 per minute in up to 93% of cases), pyrexia (> 39 °C in up to 70% of cases), and pallor are also characteristic of the disorder. However, in trauma patients there are many causes of respiratory and neurological disturbances with petechiae, pyrexia and tachycardia and while specific criteria have been proposed,<sup>16-19</sup> the diagnosis is usually one of exclusion.<sup>15</sup>

*Respiratory effects.* The clinical features include dyspnoea, chest discomfort, wheeze, haemoptysis, tachypnoea, crepitations, and rhonchi.

*Cerebral effects.* These usually precede the development of respiratory symptoms by 6-12 hours<sup>20</sup> and may occur in the absence of respiratory dysfunction.<sup>21</sup> They include features of a diffuse cerebral abnormality,

although approximately one-third of patients with cerebral fat embolism may also have focal neurological manifestations.<sup>22,23</sup> The clinical features include somnolence, restlessness, agitation, disorientation, expressive dysphasia, choreoathetoid movements, hemiparesis, hemiplegia, tetraplegia, aphasia, scotomas, rigidity, hyper-reflexia, decerebration, coma, seizures, unilateral or bilateral extensor plantar responses or failure to regain consciousness following a general anaesthetic.<sup>15</sup>

Funduscopy may reveal fat in the retinal vessels, fluffy exudates, haemorrhage and macular oedema. A severe form of retinal oedema known as Purtscher's retinopathy has also been described.<sup>24</sup>

*Petechial rash.* This is believed to be the only pathognomonic feature of the fat embolism syndrome (although in trauma patients petechiae can be induced by nonspecific dermal injury) and usually appears on the second or third day after injury (i.e. 24 hours after the respiratory or cerebral effects<sup>6</sup>), with crops of petechiae being visible for 1-2 days before they fade.<sup>25</sup>

They appear bilaterally in the axillae, neck, front of the chest, mouth, palate and conjunctiva. Petechiae only rarely appear on the legs and they are never seen on the face or the posterior aspect of the body. The latter may be due to the fact that fat globules float and therefore distribute to branches of the aorta that arise from the top of the arch, and to the side of the body that is uppermost.<sup>26</sup> While fat globules may be found in sputum, urine or blood, they are nonspecific findings that may be observed in conditions unrelated to fat embolism.<sup>25</sup>

### Investigations

There is no pathognomonic test which will confirm the diagnosis of the fat embolism syndrome.<sup>2</sup> Investigations are usually performed to confirm the diagnosis or to monitor therapy and include:

*Detection of fat droplets.* Detection of fat droplets in urine, sputum and blood is not particularly helpful in patients with long bone fractures, as it is known that all patients who have fractures have fat embolism, yet only few develop the fat embolism syndrome.

One study found that bronchoalveolar lavage (BAL) macrophages containing fat droplets were frequently observed in trauma patients irrespective of the presence of fat embolism syndrome.<sup>27</sup> Nevertheless, quantification of macrophages containing fat droplets in BAL material<sup>28</sup> has been used to diagnose fat embolism in non trauma patients (e.g. the 'acute chest syndrome' of sickle cell disease<sup>29</sup>) and even in patients in whom the aetiology of respiratory failure in trauma patients is obscure, with one study suggesting that a quantitative count of lavage cells containing fat of greater than 30% being significant of fat embolism contributing to the

respiratory failure.<sup>30</sup> Similarly, using a right heart catheter with the catheter in the wedge position, pulmonary venous blood has been aspirated and examined for fat embolism particles in patients with the fat embolism syndrome.<sup>31,32</sup>

*Plasma biochemistry and haematology.* An unexplained anaemia (in 70% of patients) and thrombocytopenia (the platelet count is  $< 150,000/\text{mm}^3$  in up to 50% of patients) are often found.<sup>15</sup> Hypocalcaemia (due to binding of the FFAs to calcium<sup>33</sup>) and an elevated serum lipase have also been reported.

*Chest X-ray.* This is usually normal on admission but develops signs of generalized pulmonary interstitial and alveolar opacification over 1-3 days and no pleural effusions. The radiological signs may remain for up to three weeks.<sup>34</sup>

*Arterial gas analysis.* The blood gas analysis often reveals hypoxia and hypocapnia which usually precede the clinical features of respiratory distress. If an arterial gas analysis is performed regularly in patients with long bone fractures, hypoxia is often the first sign of the development of the fat embolism syndrome (cyanosis is usually not associated with hypoxia as the patient is often anaemic).

*ECG.* Apart from sinus tachycardia, the ECG is usually normal, although in the fulminant pulmonary embolism syndrome it may reveal nonspecific T wave inversion (particularly in early precordial leads, indicating right ventricular strain) or RBBB.

*Cerebral CT scan.* This may show generalized cerebral oedema in patients with severe cerebral fat embolism.<sup>35</sup>

*Cerebral magnetic resonance imaging.* This may be useful in detecting cerebral lesions in patients with neurological features of fat embolism and a normal CT scan<sup>36</sup> (or clinical features of neurological fat embolism only<sup>37</sup>), as the T2-weighted imaging correlates well with the clinical severity of brain injury.<sup>38</sup>

### Treatment

There is no specific therapy for the fat embolism syndrome,<sup>1</sup> so prevention, early diagnosis, and adequate symptomatic treatment are of paramount importance. Heparin, aspirin, alcohol, hypertonic glucose with insulin, surfactant, clofibrate, alpha-blockers, corticosteroids, albumin, dextran and aprotinin have not been shown to reduce its morbidity or mortality when given either to reduce the incidence (i.e. as prophylaxis) or as treatment for fat embolism syndrome.<sup>2,39</sup>

Corticosteroids have been extensively studied and recommended by some in the management of the fat embolism syndrome. Their proposed mechanism of action is largely as an anti-inflammatory agent, reducing

the perivascular haemorrhage and oedema. However their use is controversial. While numerous prospective, randomised and controlled trials have concluded that large doses of methylprednisolone when given prophylactically, have beneficial effects,<sup>17,18,40-42</sup> the confidence intervals in these studies were wide and there was no significant change in mortality. Concerning the use of corticosteroids to treat the fat embolism syndrome; an experimental study showed no beneficial effect,<sup>43</sup> and there have been no prospective, randomised and controlled clinical studies that have demonstrated a significant benefit with their use. Currently, corticosteroids (either high or low dose) are not recommended for prophylaxis or treatment of fat embolism syndrome.<sup>2</sup>

### **Prophylactic treatment**

*Early immobilization of fractures.* While internal fixation may cause fat embolism, fracture mobility also exacerbates the liberation of fat into medullary venous sinusoids and promotes continued fat embolization.<sup>44</sup> The prompt immobilisation of fractures (e.g. intramedullary fixation of long-bone fractures within 24 hours) has been found to reduce the incidence of fat embolism syndrome.<sup>45</sup>

*Reducing intraosseous pressure during total hip arthroplasty.* Experimental studies have shown that during nailing procedures after femoral osteotomy, fat embolisation increases with increasing intramedullary pressure.<sup>46</sup> Thus, there have been numerous attempts to reduce the intraosseous pressure rise to reduce the incidence of fat embolism.<sup>47</sup> In one prospective randomised study of patients undergoing total hip replacement, the insertion of a venting hole posteriorly between the greater and lesser trochanters (in the prolongation of the linea aspera), to drain the medullary cavity during the insertion of the femoral component, prevented the rise of intraosseous pressure and reduced the incidence of fat embolisation from 85% to 20%.<sup>48</sup> In another study, fat embolism was reduced from 85% to 5% using a bone-vacuum cementing technique to prevent the rise in intraosseous pressure.<sup>49</sup>

The monitoring techniques of pulse, blood pressure, pulse oximetry and end expired CO<sub>2</sub> are often used to detect the occurrence of intraoperative fat emboli. Transoesophageal echocardiography has recently been used to monitor the effects of intraosseous manipulation and detect even minor embolic episodes.<sup>5</sup>

### **Symptomatic treatment**

The fat embolism syndrome is a self-limiting condition, with a mortality of 10% - 20%<sup>7</sup> relating to the degree of respiratory failure.<sup>50</sup> Therefore, treatment is aimed at maintaining satisfactory pulmonary gas

exchange throughout the course of the disease, and follows the same principles of management used in patients who have the acute respiratory distress syndrome (ARDS), which include;<sup>39</sup>

*Spontaneous ventilation and increased inspired oxygen.* The initial management of hypoxia associated with pulmonary fat embolism should be with spontaneous ventilation.<sup>51</sup> A face mask with a high-flow gas delivery system can be used to deliver an the inspired oxygen concentration (F<sub>I</sub>O<sub>2</sub>) of up to 50-80%.

*CPAP and noninvasive ventilation.* Using a high-flow gas delivery system to deliver oxygenated gas under a constant pressure with an inflatable soft-cushion seal face mask and secured to the face with head straps (i.e. continuous positive airway pressure or CPAP) may be added to improve PaO<sub>2</sub> without increasing the F<sub>I</sub>O<sub>2</sub>. Mechanical ventilation may also be applied via the CPAP mask (i.e. non invasive ventilation) and has been used successfully in patients with acute respiratory failure.<sup>52</sup> If an F<sub>I</sub>O<sub>2</sub> of > 60% and CPAP > 10 cm H<sub>2</sub>O are required to achieve a PaO<sub>2</sub> > 60 mmHg, then endotracheal intubation, mechanical ventilation and positive end expiratory pressure (PEEP) should be considered.<sup>53</sup>

*Mechanical ventilation and PEEP.* Sedation and muscle relaxation are often required to allow the patient to tolerate mechanical ventilation. The respiratory modes of intermittent mandatory ventilation (IMV) and pressure support ventilation are often used to reduce the adverse cardiovascular effects of mechanical ventilation as well as to reduce the patient's sedation requirements. Neither mechanical ventilation nor PEEP have intrinsic beneficial value on the process of pulmonary fat embolism, and they may even promote acute lung injury (in this regard excessive tidal volumes appear to be more injurious than excessive pressures<sup>54</sup>) causing hyaline formation, granulocyte infiltration<sup>55</sup> and elevation of inflammatory mediators.<sup>56</sup> Therefore, the principle objective of mechanical ventilation and PEEP is to accomplish adequate gas exchange without inflicting further pulmonary damage or retard healing (by ventilating between upper and lower inflection points which may require ventilation with tidal volumes of 6 ml/kg<sup>57</sup>).

While PEEP may be associated with an increase in PaO<sub>2</sub>, occasionally it will decrease the PaO<sub>2</sub> by, 1) further increasing the right atrial pressure causing a right-to-left inter-atrial cardiac shunt through a patent foramen ovale,<sup>58,59</sup> 2) redistributing pulmonary blood flow from normal lung through the diseased lung region in asymmetric lung disease,<sup>58,60,61</sup> and 3) decreasing cardiac output and the mixed venous oxygen content (i.e. increasing the effect of a right-to-left shunt) as well as a reduction in pulmonary perfusion (i.e. increasing

West zone I and increasing dead-space ventilation). Therefore, close monitoring of the arterial blood gas and haemodynamic status is required when mechanical ventilation and PEEP are used.

Other forms of respiratory support (e.g. ECMO, partial liquid ventilation, prone ventilation) have been used in patients with severe ARDS, and may be considered in patients with the fat embolism syndrome with severe respiratory failure, although in adult patients with ARDS they have not yet been shown to significantly reduce mortality.

*Reduction in transmural pulmonary capillary pressure.* In theory there are many ways to reduce the accumulation of fluid in the lung by manipulating the pulmonary 'Starling forces'. However, in practice, the only effective way of treating pulmonary oedema is by reducing the pulmonary vascular hydrostatic pressure, and diuretics and fluid restriction may be used to achieve this.<sup>39,62</sup> The reduction in left atrial pressure produced, should not be to the detriment of cardiac output, as this can reduce the PaO<sub>2</sub> (see previously) and oxygen delivery.<sup>2</sup> While therapy with diuretics and/or fluid restriction has not been shown to reduce mortality, it has been shown to reduce ventilation time and time in the intensive care unit,<sup>63</sup> although close haemodynamic monitoring with right heart and arterial catheterisation will be required, which may be associated with added risks.<sup>64,65</sup>

There is no evidence to suggest that infusing albumin to reduce the effects of FFAs, or hyperoncotic albumin to increase plasma oncotic pressure,<sup>2</sup> benefits patients with respiratory failure due to fat embolism.<sup>66-68</sup> On the contrary, the infused albumin may accumulate in the pulmonary interstitial compartment and worsen the respiratory failure.<sup>69</sup>

#### *Other supportive therapy*

*Nitric oxide.* Inhaled nitric oxide produces a maximum effect on arterial oxygenation up to 10 - 20 ppm,<sup>70</sup> whereas pulmonary vasodilation continues up to levels of 80 ppm<sup>71</sup> and has been used in patients with ARDS. In seven patients with ARDS, inhaled nitric oxide (5 to 20 parts per million) for 3 - 53 days, improved the ventilation-perfusion match (increasing the PaO<sub>2</sub> by increasing blood flow through well ventilated lung units) and reduced the mean pulmonary artery pressure, without evidence of tachyphylaxis.<sup>70</sup> In one prospective study of patients with ARDS, while there was a temporary benefit, after 72 hours there was no difference between the inhaled nitric oxide group compared with the conventionally treated group in terms of reduction of F<sub>I</sub>O<sub>2</sub> or reduction in PaO<sub>2</sub>/F<sub>I</sub>O<sub>2</sub> ratio.<sup>72</sup>

In two randomised controlled trials<sup>73,74</sup> and one retrospective analysis,<sup>75</sup> nitric oxide had no influence on

the survival rate in patients with severe ARDS, although (at 5 ppm), it may have decreased the duration of mechanical ventilation.<sup>76</sup> In the experimental animal, inhalation of NO either just before a fat embolism insult or two to three minutes after the onset of pulmonary hypertension, did not attenuate the acute pulmonary hypertension or RV dilation after cemented arthroplasty.<sup>77</sup>

With these data in mind, it has been recommended that nitric oxide be used only,<sup>78</sup>

- in patients with ARDS when optimal mechanical ventilation and PEEP have been used and the PaO<sub>2</sub> is < 100 mmHg with an F<sub>I</sub>O<sub>2</sub> of 100%
- in patients with right ventricular dysfunction (i.e. CI < 2.5 L.min<sup>-1</sup>.m<sup>-2</sup>) when it is associated with pulmonary hypertension (i.e. mean pulmonary artery pressure of > 24 mmHg and pulmonary vascular resistance index > 250 dyne.sec.cm<sup>-5</sup>.m<sup>-2</sup>), and
- at doses ranging from 20-40 ppm.

The dose used is determined by a response test, beginning with 20 ppm for 30 minutes, reducing to 10 ppm then 5 ppm for a further 30 minutes at each dose, then decreasing to 0 ppm followed by continual delivery of the lowest effective dose. A 20% rise in PaO<sub>2</sub> during the test dose being the minimum required to continue use of nitric oxide. If this is not achieved, a 30 minute trial of 40 ppm is then tried. The above titration should be performed on a daily basis.

The side effects include prolongation of bleeding time and rebound hypoxia and pulmonary hypertension on withdrawal. While at low doses (i.e. at normal clinical doses of glyceryl trinitrate or sodium nitroprusside) nitric oxide has a positive inotropic effect,<sup>79</sup> at higher doses attenuation of inotropic effects of catecholamines<sup>80</sup> and a direct negative inotropic effect<sup>81</sup> have been found. Also at higher doses (e.g. > 100 ppm), higher oxides of nitrogen (nitrogen dioxide with worsening of ARDS), and methaemoglobinaemia may be found.

*Prostacyclin.* In three patients with ARDS, nebulised prostacyclin (PGI<sub>2</sub>), using a nebuliser which delivered aerosol particles with a mass median diameter of 2.7 μm and PGI<sub>2</sub> at 17 - 50 ηg.kg<sup>-1</sup>.min<sup>-1</sup>, decreased the mean pulmonary artery pressure, and increased the PaO<sub>2</sub>/F<sub>I</sub>O<sub>2</sub> ratio, with minimal effect on the systemic blood pressure.<sup>82</sup> In another report of two patients with ARDS, nebulised prostacyclin, using a nebuliser which delivered aerosol particles with a mass median diameter of 2.1 μm at 30 - 40 ηg.kg<sup>-1</sup>.min<sup>-1</sup> (but not at levels below 30 ηg.kg<sup>-1</sup>.min<sup>-1</sup>), decreased the mean pulmonary artery pressure and reduced the P(A-a)O<sub>2</sub>.<sup>83</sup> However,

lower doses (e.g. 2 - 10  $\mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ ) may be just as effective, and in one study demonstrated an efficacy profile similar to nitric oxide.<sup>84</sup> There have been no reports of inhaled prostacyclin use in experimental or clinical studies of the fat embolism syndrome.

### Outcome

The mortality rate attributable to fat embolism ranges from 5-10%,<sup>85</sup> with higher mortalities associated with fulminant fat embolism syndrome due to severe right heart failure, compared with the fat embolism syndrome in which the mortality relates largely to the mortality of the underlying respiratory failure (or rarely cerebral oedema causing brain death<sup>86</sup>).

The prognosis for patients who survive fat embolism is good, with recovery from the fat embolism syndrome usually being complete within 2-4 weeks, although some neurological signs may remain for up to 3 months.<sup>87</sup> While complete neurological recovery from cerebral fat embolism often occurs (e.g. full recovery from decerebrate posturing<sup>88,89</sup>), in some cases permanent neurological disorders may persist.<sup>22</sup> The visual changes are commonly reversible, although permanent changes in the retina and optic atrophy can occur.<sup>90</sup>

Received: 20 July 1999

Accepted: 18 August 1999

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