PULMONARY INSUFFICIENCY AFTER LONG BONE FRACTURES

ABSENCE OF CIRCULATING FAT OR SIGNIFICANT IMMUNODEPRESSION

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Twenty young men with displaced fractures of one or more long bones in the lower limb, but with no evidence of cranial, thoracic or abdominal injury, were studied prospectively. Although all the patients became hypoxaemic, the six who developed signs of respiratory distress (Group 1) were found to have a significantly lower arterial oxygen tension and a significantly higher rate of urinary urea excretion than the remaining 14 patients whose pulmonary function appeared to be clinically normal (Group 2). Circulating fat macroglobules were identified in three cases, only one of whom was in Group 1, and hence the tests for fat embolism were not of prognostic value.

Although an immunodeficient state is considered to contribute to the pulmonary insufficiency which occurs after major trauma, convincing evidence of a lymphocyte-suppressive agent was found in only one patient.

The fall in arterial oxygen tension which accompanies fractures of the limbs is difficult to explain by any single mechanism. In most cases the disturbance of pulmonary function is mild and self-limiting, oxygen delivery by face mask being sufficient to ensure adequate arterial oxygenation. In a relatively small proportion of cases clinically obvious respiratory distress develops during the first three days after trauma, and in this group of patients there is still an appreciable mortality (Wildsmith and Masson 1978).

Although the embolisation of fat has been thought to promote this respiratory distress syndrome (Gurd 1970), the correlation between measurable fat in blood or urine and the pulmonary abnormality is poor (McCarthy et al. 1973; Nolte et al. 1974; McMiehan, Rosengarten and McNeur 1975); hence, tests based on the filtration of plasma or serum do not predict clearly which patients are at greatest risk. However, a new technique for identifying circulating fat has been described, based upon examination of frozen sections of blood clot rather than upon filtration of plasma or serum (Huaman 1974; Lahiri and ZuWallack 1977). We decided to undertake a prospective study with the object of assessing the value of both types of test for circulating fat in a group of young men suffering from clearly defined pulmonary and metabolic changes after long bone fractures.

A second investigation was incorporated in the study since interest has recently centred upon the immune status of patients after significant trauma (Constantian et al. 1977; McLoughlin et al. 1979). A lymphocyte-suppressive agent with a molecular weight of under 10000 has been identified and may prevent the recovery of patients who are critically ill after injury. Depression of the reticuloendothelial system also may predispose the patient to pulmonary insufficiency (Pardy and Dudley 1977) since the products of inflammation (Macnicol 1981) and of coagulation (Luterman, Manwaring and Curreri 1977) cease to be effectively inactivated by the liver.

We therefore assessed one aspect of immune function in a group of our patients by examining the effects of their sera on the lymphocyte proliferative response to the mitogen Concanavalin A. By this means the presence of a circulating inhibitor could be measured and related to the clinical and laboratory data from each patient.

MATERIAL AND METHODS

Patients. We classified the fractures into minor, moderate and severe, after Ellis (1958); these were labelled Grades 1, 2 and 3, and trauma scores for each patient were calculated by adding together the numerical grade of each fracture he had sustained. Young men with at least one significant fracture (Grade 2 or 3) of the femur or tibia were investigated during the first five days following injury. Patients were excluded if they had sustained cranial, thoracic or abdominal trauma. On admission to the Royal Infirmary, Edinburgh, each patient was monitored by one surgeon for a minimum of five days. Any clinical features of "fat embolism syn-
drome" were recorded, including the accepted signs of tachypnoea, mental confusion, pyrexia, tachycardia, petechiae, anaemia and jaundice.

A general anaesthetic (thiopentone sodium induction, followed by halothane and nitrous oxide) was used to permit reduction of the fractures during the first 12 hours after admission, but thereafter treatment was kept to a minimum unless respiratory distress developed. Fluid balance was ensured initially with infusions of electrolyte solutions, and blood transfusions were given when necessary. The patients ate a normal ward diet and no attempt was made to calculate the calorie or protein intake.

A total of 20 men aged between 17 and 37 years were studied prospectively. Clinical and pulmonary monitoring were undertaken in all cases and additional laboratory data obtained in the majority.

**Investigations. Pulmonary function.** Arterial blood gases were measured on admission to hospital and during the following five days. An equilibrium period of 10 minutes was allowed, during which the patient breathed room air before a sample of blood was taken from the femoral artery. In this way, the extent of pulmonary insufficiency was determined without interfering with the use of oxygen, if it was felt that oxygen was required during the remainder of the 24-hour period. A postero-anterior radiograph of the chest was taken routinely on admission; if a pulmonary distress syndrome developed a second radiograph was taken.

**Excretion of urinary urea.** Urine was collected daily in Winchester flasks and the successive 24-hour specimens analysed for their urea content. The peak urea excretion of one of these five consecutive assessments was used as an indicator of the maximum catabolic state of each patient, and expressed in millimoles per kilogram of body weight.

**Circulating fat.** Shortly after admission 10 ml of venous blood was collected by venepuncture from the femoral vein of the injured limb. On subsequent days the venous blood was taken from an antecubital vein.

The presence of fat globules was assayed in two ways.

1. After allowing the blood to clot, the specimen was centrifuged and the serum separated from the clot; the serum was then filtered through a millipore filter (pore size 0.45 μm); the residue was stained for fat using Oil red O and examined microscopically.

2. The separated and retracted blood clot was frozen in liquid nitrogen and cut with a cryostat into sections 10 μm thick; initially, sections were cut transversely at three different levels in the clot (Huaman 1974) but later, multiple longitudinal sections were preferred. Oil red O was applied to the section and the presence of fat globules sought microscopically. Both the micropore filter and cryostat tests were standardised using fresh control blood containing added marrow fat which provided a baseline for comparison with the clinical specimens.

**Immunosuppression.** The presence of an immunosuppressive agent is assessed by the effect of test serum upon lymphocyte transformation (Urbaniaq et al. 1978). A modification of this test was employed (Barclay, Greiss and Urbaniaq 1980) in which a concentration of 0.2 × 10^6/1 of lymphocytes in tissue culture medium was supplemented with 20% decomplemented human serum, to a volume of 150 μl on round-bottom microculture plates. Control cultures were established with pooled normal human serum only, whereas test cultures contained: (1) pooled normal and test sera in equal ratios (10% of each); and (2) test serum only (20%). The 10% concentration of test serum was preferred, as the added control serum reduces variability in the results by overcoming other test serum deficiencies. Thus, the 10% test shows significant inhibition of lymphocyte transformation whereas the 20% concentration may introduce other errors.

The response to stimulation of the cell cultures, using Concanavalin A, was measured by the incorporation of tritiated thymidine into the lymphocytes, and the results expressed as a percentage of the lymphocytic response in control culture. Significant inhibition of lymphocyte transformation was considered to occur when the test response was less than 20% of the control value.

**RESULTS**

Table I details the severity of the 29 femoral and tibial fractures sustained by the 20 male patients (mean age 24 years; range 17 to 37 years). Six patients (Group 1) developed clinically obvious respiratory distress with tachypnoea, confusion and petechiae. In the remaining 14 patients (Group 2) these features were absent, although in every case blood gas analysis revealed lowering of the oxygen tension (P_{02}) when breathing room air (Fig. 1).

Pulmonary function returned to normal over the

<table>
<thead>
<tr>
<th>Site of fracture* and grade</th>
<th>Trauma score</th>
<th>Number of patients</th>
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<tbody>
<tr>
<td>F2</td>
<td>2</td>
<td>7</td>
</tr>
<tr>
<td>T2</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>T3</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>F2+ (bilateral)</td>
<td>4+</td>
<td>1</td>
</tr>
<tr>
<td>T3 (bilateral)</td>
<td>6</td>
<td>1</td>
</tr>
<tr>
<td>F2+ + T1</td>
<td>3+</td>
<td>1</td>
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<td>F2 + T2</td>
<td>4</td>
<td>1</td>
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<tr>
<td>F2 + T2</td>
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<td>F2 + T3</td>
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<tr>
<td>F3 + T2</td>
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* F, femur; T, tibia
† Additional compound patellar fracture
‡ Additional scapular fracture
§ Additional acetabular fracture
subsequent five days of study, though there was still a mild degree of hypoxaemia even on the fifth day. Oxygen was given by face mask to 10 patients in order to maintain a normal oxygen tension, and one patient from Group 1 was ventilated with a positive end-expiratory pressure of 10 cm of water before making a satisfactory recovery.

A proportional relationship between the degree of pulmonary insufficiency and the catabolic response was confirmed: significant differences existed between Groups 1 and 2. In the group with pulmonary distress (Group 1) the mean lowest $P_{O_2}$ was 4.6 ± 1.2 kPa compared to a value of 8.9 ± 1.6 kPa in the asymptomatic patients ($P < 0.001$). Urea excretion was significantly higher ($P < 0.05$) in Group 1 where the mean maximal level was $9.9 ± 2.9$ mmol/kg/24 h compared to the Group 2 mean of $7.9 ± 2.1$ mmol/kg/24 h. There was no correlation, however, between the trauma score shown in Table I and either the pulmonary or metabolic changes.

Circulating fat (Fig. 2) was detected in only three patients; their details are shown in Table II. Only one of these three patients developed a respiratory distress syndrome, and the trauma sustained by these three was less than the average clinical injury for the whole group.

Owing to technical difficulties five consecutive tests of lymphocyte transformation were available in only 15 patients. Using a 10% test serum concentration a significant inhibition of lymphocyte transformation to 8% of the normal was found in one patient (Fig. 3) who sustained ipsilateral fractures of the femur (Grade 2) and tibia (Grade 1). Pulmonary insufficiency did not occur to a clinically obvious degree; the lowest arterial $P_{O_2}$ value was 8.8 kPa when breathing room air, but the catabolic index was high (peak urinary urea excretion of 1000 mmol/24 h).

In a further three patients there was a moderate reduction in lymphocyte transformation when measured with 10% serum concentration, but this did not approach an inhibition of 20% of the normal activity.
These patients did, however, become hypoxaemic, with arterial oxygen tensions of 5.6, 7.2 and 8.0 kPa. When 20% concentrations of test serum were used, four more cases of mild inhibition were encountered, but the interpretation of these results is difficult (Barclay et al. 1980) and immunosuppression was probably not significant.

DISCUSSION
The pulmonary insufficiency which accompanies fractures and their associated soft-tissue injuries has been fully described (Sevitt 1962) and only rarely endangers the life of the patient. Although the detection of pathological levels of circulating fat is not difficult technically, the interpretation of these tests and their relationship to overt respiratory distress remain controversial.

Measurement of the serum lipase is of no clinical value in this context as the test is non-specific (Peltier 1971), but the screening for larger fat globules in the blood was promoted as a valid test by Gurd (1970). Using a millipore filter he recorded an incidence of fat macroglobulinaemia of approximately 70% in 100 consecutive patients with "major injury". Not only was this a very high detection rate but his data showed that the incidence of circulating fat was the same in both those patients who did and those who did not develop frank respiratory distress. Blood gas analysis was not carried out in Gurd's study and hence the incidence of subclinical pulmonary dysfunction in the asymptomatic group was not known.

In order to ensure greater precision with Gurd's test Allardyce et al. (1974) recommended that the sample obtained from the injured patient should be taken either from the vein draining blood from the fractured limb or from an artery. It has also been stressed that tests should be conducted as soon after admission to hospital as possible, since the peak of circulating fat globules may be missed. Despite following these logical guidelines Chow et al. (1980) were unable to detect fat macroglobulinaemia in more than 18.5% of arterial samples from a series of patients with femoral fractures. Criticism of these filtration tests for measuring the levels of circulating fat have come from Nolte et al. (1974) who found that it was impossible to predict which patients would develop respiratory distress, and from McMichan et al. (1975) who could not establish a correlation between fat macroglobulinaemia and the levels of hypotension and hypoxaemia in patients after trauma.

New methods of detecting pathological levels of circulating fat have been proposed (Huaman 1974; Lahiri and ZuWallack 1977). Both the cryostat and filtration methods were tested in our study. However, the yield of positive results was very low: only three of the 80 tests (3.8%) identified fat globules. As the tests were positive in only one of the six patients who suffered from a respiratory distress syndrome, this method is clearly of little predictive value to the clinician. It is even less likely that the assessment of fat levels in the urine (McCarthy et al. 1973) and sputum (Viste et al. 1982) will prove of general use, as these tests are more indirect and regular samples are difficult to obtain. It appears unlikely that measurable levels of fat globules cause pulmonary dysfunction in patients who have sustained fractures, although the toxic effects of fat may be partly responsible for the progression of events leading to obvious respiratory distress.

There is increasing evidence that host resistance may be impaired after major operative and accidental trauma (McLoughlin et al. 1979) and that this may result partly from the circulation of an identifiable factor (Constantian et al. 1977). This agent might originate from the inflammatory focus produced in the body by the soft-tissue injury associated with fractures, as well as by burns, sepsis and pancreatitis. In all these examples of non-thoracic inflammation the lungs may be secondarily affected, with the subsequent development of a respiratory distress syndrome. Superimposed upon the effects of this immunosuppressive factor is the eventual failure of the reticuloendothelial system to clear bacterial and other particulate matter from the circulation in the critically ill patient (Niehaus, Schumacker and Saba 1980).

Pardy and Dudley (1977) have discussed the importance of the hepatic reticuloendothelial system as a "pre-pulmonary filter" in this context, and it may be that loss of normal hepatic function not only permits the circulation of toxic factors for longer periods than normal, with the production of post-traumatic pulmonary insufficiency, but also results in the characteristic alterations in protein metabolism which follow fractures of the long bones (Macnicol 1981).

In our study only one of the 15 patients investigated for the presence of an immunosuppressive factor showed a significant alteration in the test system used to measure lymphocyte transformation. Therefore, an inhibitory substance in the serum of this group of injured young men could not be convincingly demonstrated, despite the fact that six of the patients developed respiratory distress and the majority showed measurable alterations in pulmonary and metabolic function. It seems likely therefore that the hypoxaemia which develops after long bone fracture is part of a generalised physiological change of considerable hormonal and haematological complexity.

In conclusion, although pathological levels of circulating fat globules and other toxic agents may affect pulmonary and hepatic function in their own right, neither fat nor an immunosuppressive factor in the serum has been shown to be primarily responsible for the apparently linked abnormalities of pulmonary and hepatic function which result from fractures in the lower limb.

We wish to thank the consultants of the Orthopaedic Department at the Royal Infirmary of Edinburgh for permitting this study of the patients under their care, and to thank Sister Bryson and the nursing staff of Ward 5 for their willing assistance. Dr R. Barclay of the South of Scotland Regional Blood Transfusion Service and Mr S. Robertson of the Clinical Research Laboratory, Princess Margaret Rose Orthopaedic Hospital, gave invaluable technical help. The investigation received financial support from the Lothian Health Board.
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REFERENCES


