

# Busulphan lung in childhood

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**SUMMARY** A child receiving busulphan treatment for adult-type chronic myeloid leukaemia responded well for four years before the onset of complications leading to "busulphan lung". Pulmonary function tests (PFT) were useful in monitoring the development of this condition and we recommend regular PFT for patients receiving busulphan treatment.

Since busulphan-induced pulmonary fibrosis was first described in 1961,<sup>1</sup> further reports have been published,<sup>2-15</sup> and there is evidence that other chemotherapeutic agents cause similar lesions.<sup>16-20</sup> Only two children have been reported with pulmonary fibrosis that developed after treatment with the cytotoxic drugs busulphan<sup>14</sup> and BCNU (1,3-Bis(2-chlorethyl)-1-nitrosourea).<sup>16</sup>

We report on a child with adult-type chronic myeloid leukaemia (CML) who developed busulphan lung. A second child who may have had busulphan lung recovered when busulphan treatment was withdrawn.

## Case report

In June 1973, a 3-year-old boy, one of monozygotic twins, presented with a month's history of diarrhoea and vomiting. He had widespread lymphadenopathy; his liver was palpable 3 cm and his spleen 2 cm below the costal margins. The results of laboratory investigations were Hb 11.4 g/dl, platelet count  $307 \times 10^9/l$  ( $307\ 000/mm^3$ ), white cell count  $41.6 \times 10^9/l$  ( $41\ 600/mm^3$ ) (neutrophils  $32 \times 10^9/l$  ( $32\ 000/mm^3$ ), lymphocytes  $7.1 \times 10^9/l$  ( $7100/mm^3$ ), myelocytes  $0.8 \times 10^9/l$  ( $800/mm^3$ ), eosinophils  $0.4 \times 10^9/l$  ( $400/mm^3$ ), basophils  $0.4 \times 10^9/l$  ( $400/mm^3$ ), fetal Hb 4.5%, leucocyte alkaline phosphatase score 5 (control 136). A chest x-ray film taken at this time was normal. A diagnosis of adult-type CML was made, as a marrow aspirate showed a marked increase in myeloid precursors and the Philadelphia chromosome. Haematological and chromosome analyses of blood and marrow in his twin have been normal.

Treatment with busulphan was started 1 mg/day

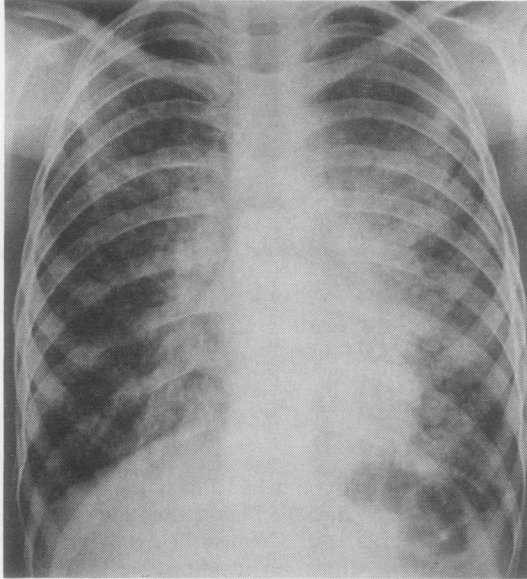
until the white cell count had fallen to  $15 \times 10^9/l$  ( $15\ 000/mm^3$ ), and then 0.5 mg on alternate days. He received a total dose of 355 mg ( $421\ mg/m^2$ ) over 47 months, during which he remained well. In July 1977, the patient developed a fever and an unproductive cough. A chest x-ray examination showed widespread opacities, consistent with an infection and therefore busulphan treatment was stopped. Sputum and viral studies failed to show any pathogenic organisms and a tuberculin test 1/1000 was negative. After treatment with cotrimoxazole 80 mg twice a day there was clinical improvement and the opacities seen on the x-ray film had resolved.

Pulmonary function tests were performed two weeks after the infection was treated and again in January and April 1978. On the first occasion the twin was used as a control (Table). These tests

## Pulmonary function tests in the patient

	August 1977		January 1978	April 1978
	Patient	Twin		
Forced expiratory volume in 1 second (FEV <sub>1</sub> )	0.74 l	1.37 l	0.71 l (-4.39)*	
Forced vital capacity (FVC)	0.88 l	1.45 l	0.82 l (-3.37)	
FEV <sub>1</sub> /FVC	84	94	86 (-0.39)	
Peak flow rate			3.52 l/s (-4.58)	
Expiratory reserve volume			0.24 l	
Inspiratory capacity			0.52 l	
Vital capacity			0.70 l (-3.58)	0.44 l
Functional residual capacity			1.85 l (-0.95)	
Residual volume (RV)			1.61 l (+3.91)	
Total lung capacity (TLC)			2.37 l (-0.18)	
RV/TLC			68 (+7.77)	

\*Figures in parentheses are the number of standard deviations by which the reported value differs from predicted value.

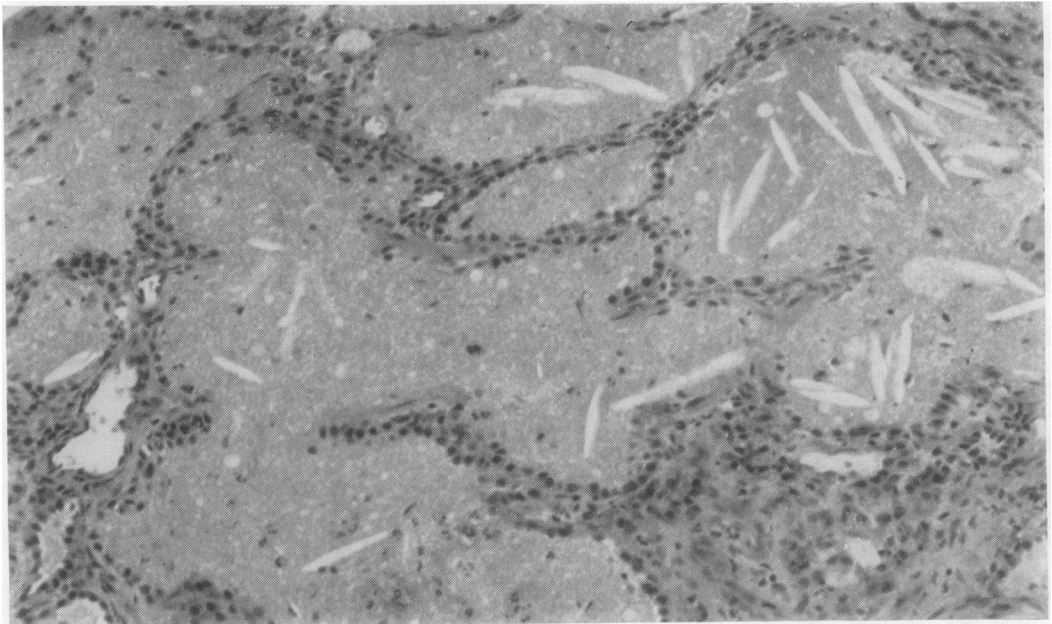


**Fig. 1** *Chest x-ray nine months after stopping busulphan treatment, showing a widespread infiltrative pulmonary lesion with extensive coarse nodular opacity, confluent blotchy opacity in the left lung, especially the lower lobe, and widespread tiny translucencies in both lungs.*

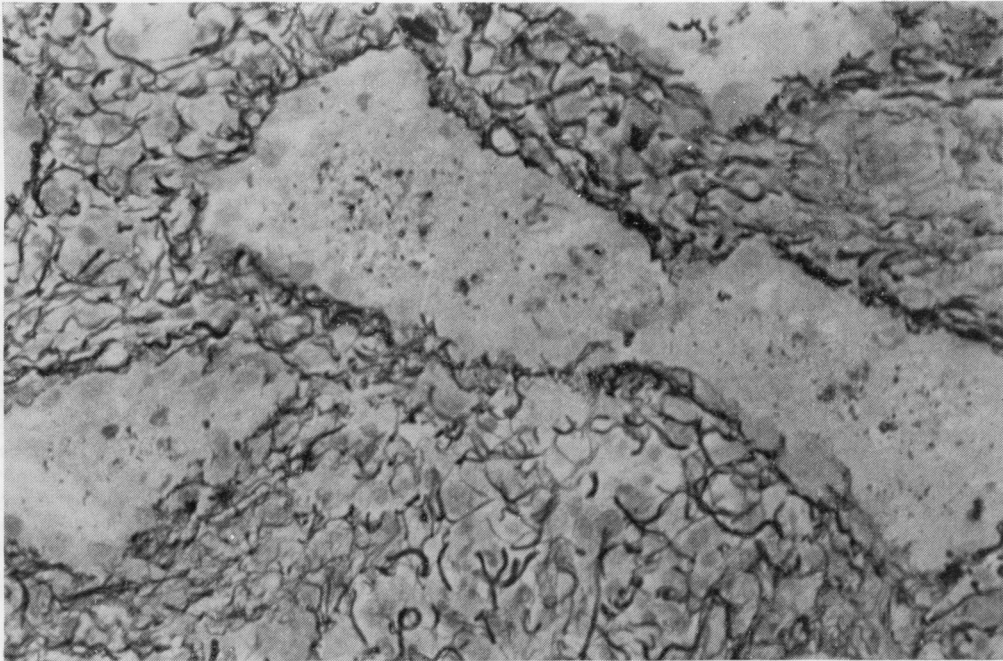
showed that the patient had a severe mixed ventilatory defect, so no more cytotoxic treatment was given.

The child remained well, apart from poor weight gain, for four months but then was found to have finger clubbing and reduced chest expansion, although there was no abnormality on auscultation. Although his pulmonary function worsened he was asymptomatic until April 1978 when he had diarrhoea and lost weight. A chest x-ray examination then showed widespread infiltration with extensive coarse nodular opacities (Fig. 1) that were confluent in places. His vital capacity was greatly reduced (Table). The results of the following investigations were all normal: blood count, liver function tests, 1-hour blood xylose test, urea and electrolyte concentrations. Sputum culture, gastric washings, swabs of the oropharynx, and viral and fungal studies failed to show any evidence of infection.

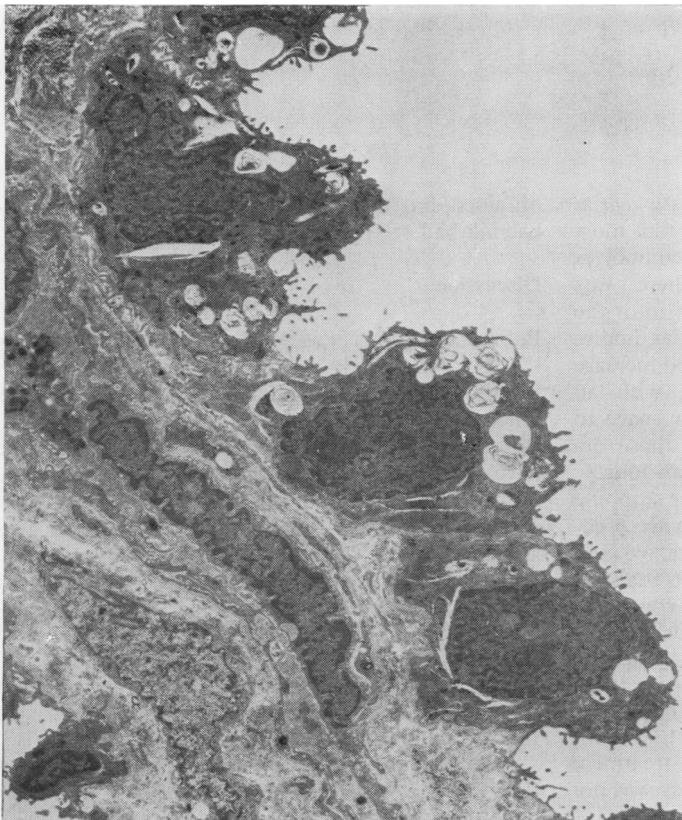
A lung biopsy was performed. Light microscopy showed distinct distortion of normal lung architecture, and regular cuboidal cells resembling type II pneumocytes (Fig. 2) lined the alveoli. Granular polymorphs and cholesterol clefts filled the alveolar spaces (Fig. 3). The intra-alveolar material stained strongly with periodic acid Schiff and there was reticular fibrosis of the interstitium (Fig. 4). There



**Fig. 2** *Lung biopsy specimen. The air sacs are filled with granular material containing many cholesterol clefts and a little nuclear debris. Many of the lining cells are cuboidal. Haematoxylin and eosin  $\times 192$ .*



**Fig. 3** Lung biopsy specimen, showing fibrosis of alveolar walls. Reticulin  $\times 480$ .



**Fig. 4** Electron micrograph of a lung biopsy specimen, showing part of the alveolar sacs. They are lined by type II pneumocytes with microvilli and secretory vacuoles containing myelin bodies. An intervening capillary is cut lengthwise and there are bundles of collagen at either end.  $\times 4200$ .

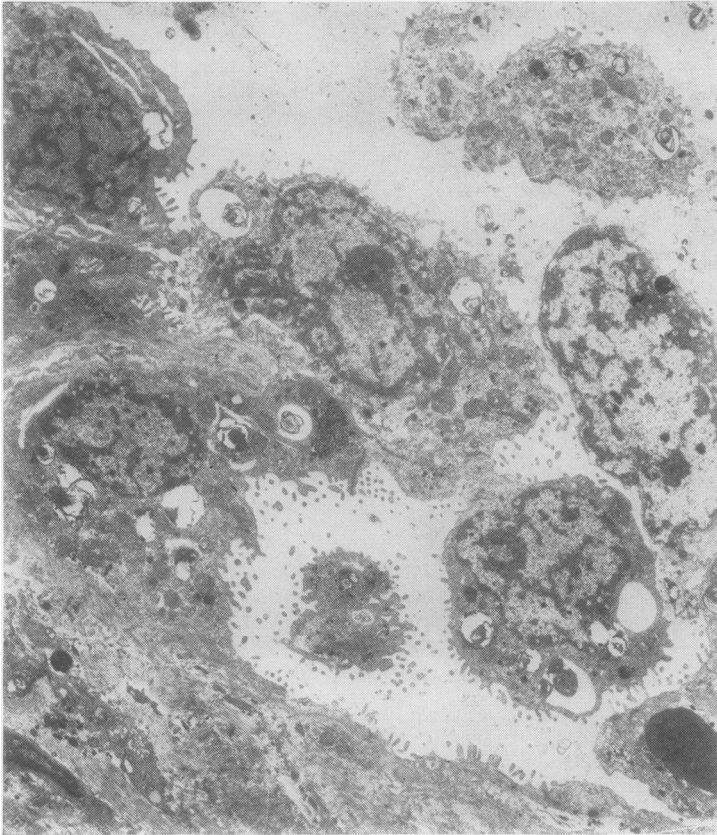


Fig. 5 *Electron micrograph of a lung biopsy specimen, showing part of an alveolus. Some of the type II pneumocytes appear to be becoming detached and fragmented. Some of the lining cells are flat like type I cells but have prominent microvilli and are probably regenerating type II cells. There is a lot of collagen in the alveolar wall. × 4200.*

was no evidence of viral or *Pneumocystis carini* infection. Electron microscopy confirmed that most of the aveoli were lined by type II pneumocytes containing many lamellar bodies. There was desquamation of type II pneumocytes into the alveolar spaces and release of free lamellar bodies into the spaces (Fig. 5). There was a marked increase in the amount of interstitial collagen, with an increased diffusion distance from alveolar space to capillary. These findings are similar to those described in an adult patient with busulphan lung.<sup>7</sup>

After the lung biopsy (nine months after stopping busulphan treatment) he was treated with prednisolone 30 mg/day, and with cotrimoxazole and 5-flucytosine for any pneumocystis, bacterial, or fungal infection. His condition, however, continued to deteriorate and he developed severe breathlessness at rest, cyanosis, and widespread bronchial breathing. Chest x-ray examination showed gross deterioration. He died in September 1978 of respiratory failure, 63 months after the diagnosis of CML and 13 months after pulmonary toxicity from busulphan treatment was first suspected. Permission for necropsy was not

obtained, but there was no evidence that the leukaemia had relapsed at the time of death.

### Discussion

Pulmonary fibrosis has been reported in 20 patients<sup>1-15</sup> as a complication of the treatment of CML with busulphan. The true incidence of busulphan lung is unknown. Of 48 patients treated in the Medical Research Council's first CML trial, only one developed progressive pulmonary disease while the symptoms in a second, in whom the condition was suspected clinically, abated after busulphan was stopped (DAG Galton, personal communication, 1979). Several other cytotoxic drugs have now been implicated in causing pulmonary fibrosis. Methotrexate, bleomycin, and busulphan are the most commonly reported, but cyclophosphamide, melphalan, and azathioprine<sup>22</sup> may also cause a similar process. Recently a child receiving BCNU treatment for medulloblastoma developed pulmonary fibrosis.<sup>16</sup>

The clinical features of busulphan lung have been described in 12 adults aged from 24 to 72 years

<sup>1-5 7 13 15</sup> and also in the only child, a 16-month-old boy with juvenile-type CML.<sup>14</sup> The total dose of busulphan was recorded in only two of the 12 adults; one received 1 g<sup>7</sup> and the other 1.6 g<sup>2</sup>—approximately 550-950 mg/m<sup>2</sup>. The onset of the complication varied from 10 months to as long as 10 years after starting busulphan (mean 50 months). The 13 patients presented with the following complications: dyspnoea 7; weakness or malaise 7; cough 4; weight loss 3; fever 3, and hyperpigmentation 1. Only two were cyanosed. When busulphan lung was first suspected the chest x-ray film was abnormal in eight patients; equivocal in one; and normal in three, becoming abnormal after six months in two and after three months in the third. The diagnosis was confirmed by lung biopsy in five patients, at necropsy in four, and on clinical and radiological criteria in four. Pulmonary function tests were done in four patients<sup>1 2 3 7</sup> but recorded in detail in only one who had restrictive lung disease with severe reduction in transfer factor.<sup>7</sup>

Our patient is the first child with adult-type CML reported to have developed progressive pulmonary fibrosis after busulphan treatment. He was given 355 mg (421 mg/m<sup>2</sup>), a smaller total dose relative to body area than prescribed to the adults.<sup>2 7</sup> Despite an initial improvement in the appearance of his lungs on chest x-ray examination after antibiotic treatment, serial PFTs showed progressive restrictive abnormality. As PFTs are a more sensitive index of pulmonary disease than x-ray examinations and are simple to perform in children over the age of six years,<sup>23</sup> we now do regular PFTs on all patients receiving busulphan. As a result of this policy a restrictive abnormality has been detected in another patient, an asymptomatic girl aged 15 years, with a normal chest x-ray film. She had received only 312.5 mg (223 mg/m<sup>2</sup>) of busulphan over 30 months for adult-type CML. Although her pulmonary function has not deteriorated during the nine months since busulphan was withdrawn, she recently developed acute lymphoblastic leukaemia.

Stopping busulphan treatment may allow the pulmonary disease to resolve.<sup>7</sup> It is important therefore to recognise this complication early and to stop treatment before irreversible lung damage has occurred. Regular PFTs are therefore recommended for patients who have received more than 200 mg/m<sup>2</sup> of busulphan, and these should include gas transfer measurements if possible as they are the most sensitive indicators of disease.<sup>7</sup>

The role of corticosteroids in the treatment of busulphan lung is controversial. In the original report by Oliner *et al.*,<sup>1</sup> pulmonary function improved in two patients after high doses of steroids. As the pathogenesis seems to be a chemically-

induced alveolitis with proliferation of type II pneumocytes it has been suggested that steroid treatment would be effective only if used in the early cellular phase of the disease, as it is unlikely to have any effect once pulmonary fibrosis is established. The change from busulphan treatment to steroid treatment was probably too late to halt progress of the disease in our patient.

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