An investigation of the chest radiographs in a controlled trial of busulphan, cyclophosphamide, and a placebo after resection for carcinoma of the lung

H. STOTT[1], R. STEPHENS[1], WALLACE FOX[1],
G. SIMON[2], and D. C. ROY[3]

*MRC Tuberculosis and Chest Diseases Unit[1], Brompton Hospital[2], Fulham Road, London
SW3 6HP, and Department of Medicine, Banaras Hindu Hospital, Varanasi-221005, India[3]*

Stott, H., Stephens, R., Fox, W., Simon, G., and Roy, D. C. (1976). *Thorax*, **31**, 265–270.
An investigation of the chest radiographs in a controlled trial of busulphan, cyclophosphamide, and a placebo after resection for carcinoma of the lung. A standard series of radiographs of 588 patients allocated at random to treatment with busulphan (B patients), cyclophosphamide (C patients), or a placebo (P patients) for two years after surgery for bronchial carcinoma were viewed in three stages (following procedures which avoided bias) by an independent assessor, unaware of the allocated treatment of any patient, with a view to identifying pulmonary changes due to busulphan.

Radiographic appearances consistent with busulphan lung were not reported in any of the 195 B patients (receiving a mean dosage of 464 mg of busulphan over 301 days) or of the 192 C patients but were present in one of the 201 patients receiving placebo.

In 1964 a Medical Research Council Working Party undertook a double-blind cooperative study of long-term cytotoxic chemotherapy after surgery for carcinoma of the bronchus. The results of treatment at random with busulphan, cyclophosphamide, or placebo in over 700 patients have been reported for the first two years after operation (Medical Research Council Working Party, 1971) and a report at five years is in preparation. There have been reports of the occurrence of what is now commonly termed 'busulphan lung', characterized by cough, dyspnoea, fever, and usually bilateral diffuse infiltrations in patients under treatment with busulphan (Oliner *et al.*, 1961; Leake *et al.*, 1963; Heard and Cooke, 1968). The opportunity was therefore taken to investigate radiographic abnormalities occurring in the five-year period in the lungs of patients receiving busulphan in comparison with those receiving cyclophosphamide or placebo.

PLAN AND CONDUCT

PATIENTS In all, 726 patients with carcinoma of the bronchus drawn from 23 chest centres throughout Britain between January 1965 and January 1968 were admitted to the main study of cytotoxic chemotherapy (Medical Research Council Working Party, 1971). They had had the diagnosis confirmed histologically and had no detectable extrathoracic metastases, and at operation all visible intrathoracic growth had been resected.

CHEMOTHERAPY The procedure for random allocation to a drug regimen and the dosages have already been reported in detail (Medical Research Council Working Party, 1971). In brief, immediately after the successful removal of all visible growth a patient was randomly allocated to receive tablets of busulphan (B series), cyclophosphamide (C series), or an indistinguishable placebo (P series) by mouth for two years.

For the first 10 days of therapy every patient received eight tablets in a single dose daily, the dosage of active agent in the B series being 4 mg busulphan daily and in the C series 200 mg cyclophosphamide daily.

Maintenance therapy began on the 11th day, and during the first phase of the intake all patients

C

were prescribed six tablets in one dose daily, equivalent to 3 mg of busulphan in the B series or 150 mg of cyclophosphamide in the C series (early intake). However, because of an unexpectedly high incidence of clinical and haematological toxicity the maintenance dosages were reduced, nearly one year after the intake had begun, to busulphan, 1·5 mg daily, and cyclophosphamide, 75 mg daily, all patients (including those receiving placebo) being prescribed three tablets in one dose daily (late intake).

The maintenance dosage was controlled by the physician at monthly intervals on the basis of symptoms and the blood picture, including platelet count. The study was conducted 'double-blind' throughout the two-year period of medication and the subsequent three-year follow-up, neither the patient nor the physician knowing the allocated therapy.

MANAGEMENT OF THE PATIENT   Follow-up reports were obtained monthly for the first three years and three-monthly thereafter. A chest radiograph was taken monthly for the first six months and three-monthly thereafter.

Clinical side effects, which were mainly gastric upsets, were managed by giving the medicament in divided doses and, if this was ineffective, by reducing or temporarily interrupting the drug. Only if this failed was the treatment stopped. For haematological abnormalities the medicament was normally interrupted if the platelet count fell below $100 \times 10^9/l$ (100 000/mm^3) or if the total white count fell below $2 \times 10^9/l$ (2000/mm^3) or slowly below $1 \times 10^9/l$ (1000/mm^3). If a patient died a necropsy was done when possible.

REGULARITY OF DRUG TAKING   Wherever possible a home visit was made without warning during each month in the first two years by a health visitor in order to assess the regularity of self-administration of the patient's medication by a count of the stock of tablets.

RESULTS

Of 726 (243 B, 234 C, 249 P) patients admitted to the study, 137 (47 B, 42 C, 48 P) have been excluded from the radiographic assessments, 136 because their radiographs had been lost or destroyed because the patient had died, and one (B) patient because her medication had been stopped after one week due to a psychiatric condition. After these exclusions there remained 588 patients (195 B, 192 C, 201 P) with a series of radiographs available for assessment.

DURATION OF TREATMENT WITH THE ALLOCATED REGIMEN   Although the tablets were prescribed for two years, in the event the mean period for which the 588 patients actually received them was considerably less, being 301 days for the busulphan, 445 days for the cyclophosphamide, and 527 for the placebo series. Thus, many patients received less than their full course. This was due principally to the substantial number of deaths which occurred in the first two years in all three series and to interruptions and/or the premature termination of treatment for side effects, which was especially common in the busulphan series.

RADIOGRAPHIC ASSESSMENTS   A standard series of radiographs for each patient was shown to an independent assessor (GS). For patients who were alive at five years he viewed the pretreatment radiograph together with those at 3, 6, 12, 18, 24, 36, 48, and 60 months, and for patients who had died he viewed the standard series up to the time of death and the two most recent radiographs before death. In addition, for any patient whose medication had been interrupted or stopped on account of toxicity he viewed the radiograph nearest to the date of each interruption or termination.

The series of radiographs were viewed by the assessor in three stages (Table). In the first stage he viewed the full series for the 588 patients twice, being unaware of any clinical details of the treatment of any patient or even the dates on which the radiographs were taken. He considered that there were radiographic abnormalities (other than those normally associated with resection) in 151 patients (61 B, 45 C, 45 P). Reviewing these 151 patients, the cause was clearly evident in 95, 84 being extension of growth and/or lung metastases, nine pleural effusions, one pneumothorax, and one abnormally large heart shadow.

In the second stage, he reviewed the radiographic series of the remaining 56 patients, being provided with the dates of the radiographs and the dates during which a medicament was being prescribed (but not which medicament). From this information he was able to relate the date of the first appearance of the shadows and their progress to actual periods when the patients were receiving their allocated medicament. In 22 (14 B, 5 C, 3 P) the radiographic shadowing had first appeared after the medicament had been stopped (Table), in all at least one month after and in 13 more than two years after. Of these 22, there were four patients (all B) who developed the shadowing within three months of stopping medication; the

TABLE
RESULTS OF THE THREE STAGES OF RADIOGRAPHIC VIEWING

Stage of Viewing		Assessment	Series			
			All	Busulphan (B)	Cyclophosphamide (C)	Placebo (P)
First	I	Patients with radiographs available	588	195	192	201
		Patients with abnormal shadowing	151	61	45	45
	II	Definite diagnoses of growth, pleural effusion, etc.	95	34	28	33
Second		Remaining patients with radiographic abnormalities	56	27	17	12
		Abnormality not attributable to medicament:				
		(a) first appeared after medicament stopped	22	14	5	3
		(b) disappeared or regressed on medicament	15	7	6	2
Third		Remaining patients with radiographic abnormalities	19	6	6	7
		Abnormality diagnosed as:				
		(a) terminal event	10	6	3	1
		(b) infection, metastases, etc.	8	0	3	5
		(c) consistent with 'busulphan lung'	1	0	0	1

abnormality first appeared in three within six weeks of death. In the fourth, who developed myelomonocytic leukaemia, it first appeared one month after busulphan had been stopped, subsequently occurring sporadically for up to five years. In 15 other patients (7 B, 6 C, 2 P) the shadowing either disappeared or regressed while the patient was still receiving the medicament.

There remained 19 (6 B, 6 C, 7 P) patients in whom the shadowing persisted unchanged or increased in size while the medication was still being given (Table). The assessor reviewed these in the third stage, being provided with the full clinical details, including dates of intercurrent illnesses, of respiratory infections, of the appearance of clinical metastases, and of death but still not the treatment regimen. In 10 (6 B, 3 C, 1 P), the shadowing was first observed within 21 days of death and was ascribed to terminal respiratory infections, pulmonary oedema and/or metastases. In eight (3 C, 5 P) more, the shadowing was ascribed to intercurrent respiratory infections (4 patients), to infection from a bronchopleural fistula (2 patients), and to metastases (2 patients). In the remaining patient he considered that the shadowing was consistent with busulphan lung. This patient, a man aged 54 on admission, was in fact receiving placebo. It was stopped at eight months because the platelet count dropped to $83 \times 10^9/l$ (83 000/mm³). However, as the count was normal the following month the tablets were restarted. Although the counts were normal for the next two months the medicament was stopped because of the appearance of mottled shadowing in both lung fields. A lung biopsy was reported (Dr. K. F. W. Hinson) to contain small granulomatous lesions with histological appearances not typical of those described for busulphan lung. Treatment with corticosteroids was started at the time of the appearance of the radiographic shadowing. Six months later the radiograph was normal and remained so subsequently. Corticosteroids were continued for up to five years, at which time the patient was at work and able to walk more than 91 m (100 yards) on the flat without dyspnoea.

DURATION AND DOSAGE OF BUSULPHAN Busulphan was prescribed for a two-year period but, mainly on account of haematological toxicity, 33% of the 195 patients in the present analysis actually received it for a total of less than 200 days, 39% for 200 to 399 days, 21% for 400 to 599 days, and only 7% for 600 days or more, the mean number of days on which it was received being 301.

If the duration of treatment is measured from the day on which busulphan was started to the last day it was received (that is, including periods of interruption) 27% of patients received it over a period of less than 200 days, 35% over a period of 200 to 399 days, 15% over a period of 400 to 599 days, and 23% over a period of 600 days or more, the mean being 375 days.

Fifty-eight per cent of the patients on busulphan received a total dosage of less than 500 mg, 33% from 500 to 749 mg, and 8% 750 mg or more, the mean total dosage being 464 mg.

DISCUSSION

Since the first report on busulphan by Galton (1953) the drug has been widely used in the treatment of chronic myelogenous leukaemia. Among the side effects attributed to it is a condition, first described by Oliner *et al.* (1961) in two patients,

characterized by cough, dyspnoea, fever, and abnormal radiographic findings. The radiographic abnormalities, which may not always be present, are diffuse, bilateral, lace-like, mottled or nodular opacities. Heard and Cooke (1968), who first termed the condition busulphan lung, have described the histological appearances as those of a fibrinous intra-alveolar oedema associated with large prominent atypical alveolar epithelial cells.

In the present investigation an assessor interpreted the radiographic series in three stages, the possibility of bias being avoided by the procedures followed for viewing the radiographs. In only a single patient was the radiographic abnormality considered to be consistent with busulphan lung, and that patient was one of the 201 who received the placebo tablets; in none of the 195 patients receiving busulphan were any of the radiographic changes ascribed to the drug, nor in any of the 192 who received cyclophosphamide.

It is difficult to assess the frequency of busulphan lung. The relatively few cases reported in the literature suggest that it is uncommon, but the number of patients at risk among whom the reported cases have arisen is usually not given. Considering studies reporting post-mortem findings, Heard and Cooke (1968) found fibrinous intra-alveolar oedema of the lungs at necropsy in six of 14 patients with chronic myelogenous leukaemia treated with busulphan and in one of seven not treated with the drug. Kirschner and Esterly (1971) reported histological changes at necropsy regarded as typical of busulphan lung in one (3%) of 40 patients with chronic myelogenous leukaemia treated with busulphan and in none (0%) of 41 not treated with the drug, and Woodliff and Finlay-Jones (1972) in three (8%) of 39 patients receiving busulphan for chronic myelogenous leukaemia. Koss, Melamed, and Mayer (1965) reported changes in one (2%) of 44 patients receiving busulphan, 25 of whom had chronic myelogenous leukaemia. Thus, in a total of 137 necropsies of patients treated with busulphan, mostly for chronic myelogenous leukaemia, histological appearances attributed to busulphan lung were found in 11 (8%), and in four (3%) of these radiographic abnormalities had been reported.

The absence of radiographic abnormalities in the present series might be a consequence of the relatively low total dosage of busulphan. The patients were due to receive busulphan daily for two years but because of a high mortality from carcinoma of the lung during the period and the need to lower the maintenance dose and sometimes interrupt or terminate chemotherapy on account of toxicity, the mean total dosage received was 464 mg over a mean period of just over one year. This is considerably less than the mean total dosage of 3000 to 4000 mg received over a period of approximately four years by 25 patients reviewed in the literature with 'typical' radiographic and histological appearances of busulphan lung (Oliner et al., 1961; Leake et al., 1963; Koss et al., 1965; Harrold, 1966; Smalley and Wall, 1966; Min and Györkey, 1968; Heard and Cooke, 1968; Feingold and Koss, 1969; Korbitz and Reiquam, 1969; Littler et al., 1969; Burns, McFarland, and Matthews, 1970; Comhaire et al., 1970; Kolarz, Pietschmann, and Regele, 1970; Pintos Fuentes and Reissenweber, 1970; Massachusetts General Hospital Case Records, 1971; Batzenschlager et al., 1972; Jeanmart et al., 1972; Brynes et al., 1973; Etcheberry et al., 1973; Podoll and Winkler, 1974). Moreover, none of these 25 patients received less than 600 mg of busulphan, whereas only 13 (7%) of the patients in the present series received more than this. However, in a Medical Research Council (1968) study of chronic granulocytic leukaemia, there was no evidence of pulmonary fibrosis in 48 adult patients who received a mean dose of 1641 mg of busulphan over a period of two years, 42 of whom had received more than 600 mg and five more than 3000 mg (Galton, personal communication). Comhaire et al. (1972) found no correlations between the total dosage of busulphan (ranging from 212 to 1400 mg) and the vital capacity in 23 patients.

Littler and Ogilvie (1970) found no association between dosage (ranging from 93 to more than 6000 mg) and transfer factor in 23 patients suffering from myeloproliferative disease. On the other hand, Woodliff and Finlay-Jones (1972) reported that three (12%) patients, including two with radiographic abnormalities, of 26 receiving 'long-term' busulphan showed histological features of busulphan lung in specimens obtained at necropsy or lung biopsy compared with none of 13 who had received 'short-term' busulphan.

Of the 25 patients with radiographic abnormalities reviewed in the literature and referred to above, 24 were being treated for chronic myelogenous leukaemia. Further, it may be relevant that lung abnormalities also occur in patients with leukaemia who have not had busulphan. Thus Nathan and Sanders (1955) have reported pulmonary infiltrations in myelogenous leukaemia, although less frequently than in lymphatic leukaemia, and Vieta and Craver (1941) have described peripheral infiltration of the lungs in the radiographs of 8% of 52 patients with myelo-

genous leukaemia. There is also necropsy evidence of pulmonary changes similar to those described as busulphan lung. Kirschner and Esterly (1971) found that, in patients with chronic myelogenous leukaemia, fibrinous oedema and fibrosis of the lungs were as common in those who had not received busulphan as in those who had. Heard and Cooke (1968) described intra-alveolar oedema of the lungs in one of seven patients who had not received busulphan and suggested that leukaemia may have a contributory effect in producing the lung damage. There is, therefore, the possibility that the changes in the lung can be the result of the leukaemic process or the leukaemic process modified by busulphan rather than due to busulphan itself.

In conclusion, this report has produced no evidence that busulphan or cyclophosphamide, in the dosages received by the patients, resulted in radiographic abnormalities of the lung. Further, the published series give no reliable evidence on the incidence of lung changes attributed to busulphan or the influence of dosage or duration of busulphan therapy. The position would be clarified if, when reporting individual cases, authors would also report the total number of patients treated with busulphan and full details of the dosage given.

REFERENCES

Batzenschlager, A., Oberling, F., Guerbaoui, M., and Vetter, J. M. (1972). Fibrose pulmonaire mortelle avec lésions cellulaires du poumon et du pancréas, attribuées au busulfan. *Archives d'Anatomie Pathologique*, **20**, 291.

Brynes, R. K., Mostafavipour, S. H., Fennessy, J. J., and Variakojis, D. (1973). Diagnosis of busulphan lung by transcatheter biopsy. *Chest*, **64**, 771.

Burns, W. A., McFarland, W., and Matthews, M. J. (1970). Busulfan-induced pulmonary disease: report of a case and review of the literature. *American Review of Respiratory Disease*, **101**, 408.

Comhaire, F., van Hove, W., van Ganse, W., and van der Straeten, M. (1972). Busulphan and the lungs—Absence of lung function disturbance in patients treated with busulphan. *Scandinavian Journal of Respiratory Diseases*, **53**, 265.

——, van der Straeten, M., van Hove, W., van Ganse, W., and Roels, H. (1970). Longafwijkingen tijdens Busulfan behandeling. *Acta Tuberculosa et Pneumologica Belgica*, **61**, 471.

Etcheberry, R., Becker, P., Delmastro, J., and Donoso, H. (1973). Fibrosis alveolar pulmonar por Myleran (Busulfán). *Revista Medica de Chile*, **101**, 42.

Feingold, M. L. and Koss, L. G. (1969). Effects of long-term administration of Busulfan—report of a patient with generalized nuclear abnormalities, carcinoma of vulva and pulmonary fibrosis. *Archives of Internal Medicine*, **124**, 66.

Galton, D. A. G. (1953). Myleran in chronic myeloid leukaemia—results of treatment. *Lancet*, **1**, 208.

Harrold, B. P. (1966). Syndrome resembling Addison's disease following prolonged treatment with busulphan. *British Medical Journal*, **1**, 463.

Heard, B. E. and Cooke, R. A. (1968). Busulphan lung. *Thorax*, **23**, 187.

Jeanmart, L., Klastersky, J., Verhest, A., Debusscher, L., Potvliege, P., Tagnon, H., and Tombroff, M. (1972). Les pneumopathies diffuses au cours de la chimiothérapie par le busulfan et la bleomycine. *Journal Belge de Radiologie*, **55**, 425.

Kirschner, R. H. and Esterly, J. R. (1971). Pulmonary lesions associated with busulfan therapy of chronic myelogenous leukaemia. *Cancer*, **27**, 1074.

Kolarz, G., Pietschmann, H., and Regele, H. (1970). Lungenveränderungen unter Busulphantherapie bei einem Fall von chronischer Myelose. *Zentralblatt für allgemeine Pathologie*, **113**, 539.

Korbitz, B. C. and Reiquam, C. W. (1969). Busulfan in chronic granulocytic leukemia: a spectrum of clinical considerations. *Clinical Medicine*, **76**, 16.

Koss, L. G., Melamed, M. R., and Mayer, K. (1965). The effect of busulfan on human epithelia. *The American Journal of Clinical Pathology*, **44**, 385.

Leake, E., Smith, W. G., and Woodliff, H. J. (1963). Diffuse interstitial pulmonary fibrosis after busulphan therapy. *Lancet*, **2**, 432.

Littler, W. A., Kay, J. M., Hasleton, P. S., and Heath, D. (1969). Busulphan lung. *Thorax*, **24**, 639.

—— and Ogilvie, C. (1970). Lung function in patients receiving busulphan. *British Medical Journal*, **4**, 530.

Massachusetts General Hospital Case Records (1971). Case 40–1971. *New England Journal of Medicine*, **285**, 847.

Medical Research Council Working Party (1971). Study of cytotoxic chemotherapy as an adjuvant to surgery in carcinoma of the bronchus: report. *British Medical Journal*, **2**, 421.

Medical Research Council Working Party for Therapeutic Trials in Leukaemia (1968). Chronic granulocytic leukaemia: comparison of radiotherapy and busulphan therapy: report. *British Medical Journal*, **1**, 201.

Min, K. W. and Györkey, F. (1968). Interstitial pulmonary fibrosis, atypical epithelial changes and bronchiolar cell carcinoma following busulfan therapy. *Cancer*, **22,** 1027.

Nathan, D. J. and Sanders, M. (1955). Manifestations of acute leukemia in the parenchyma of the lung. *New England Journal of Medicine*, **252,** 797.

Oliner, H., Schwartz, R., Rubio, F., Jr., and Dameshek, W. (1961). Interstitial pulmonary fibrosis following busulfan therapy. *American Journal of Medicine*, **31,** 134.

Pintos Fuentes, R. J. and Reissenweber, N. (1970). El pulmon de busulfan. *Hoja Tisiológica*, **27,** 84.

Podoll, L. N. and Winkler, S. S. (1974). Busulfan lung: report of two cases and review of the literature. *American Journal of Roentgenology, Radium Therapy and Nuclear Medicine*, **120,** 151.

Smalley, R. V. and Wall, R. L. (1966). Two cases of busulfan toxicity. *Annals of Internal Medicine*, **64,** 154.

Vieta, J. O. and Craver, L. F. (1941). Intrathoracic manifestations of the lymphomatoid diseases. *Radiology*, **37,** 138.

Woodliff, H. J. and Finlay-Jones, L. R. (1972). Busulphan lung. *Medical Journal of Australia*, **2,** 719.

Requests for reprints to: Dr. H. Stott, MRC Tuberculosis and Chest Diseases Unit, Brompton Hospital, Fulham Road, London SW3 6HP.