

may act presynaptically¹¹ on dopamine-containing terminals to control dopamine release.¹²

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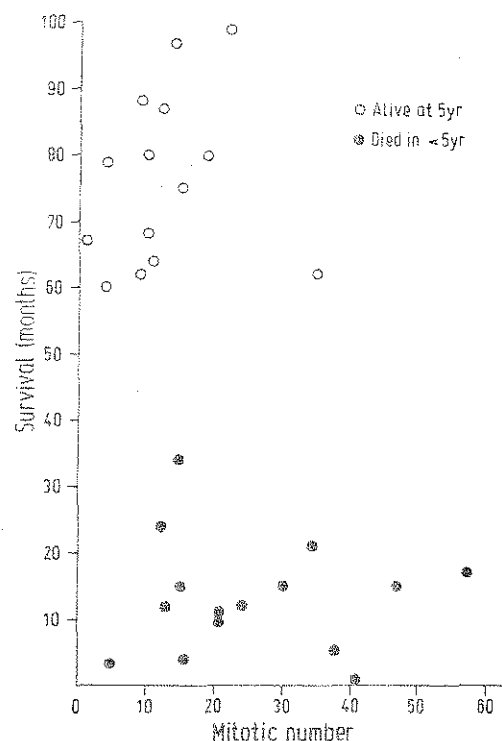
MITOTIC INDEX IN CARCINOMA OF THE LUNG

SIR,—In clinical trials aimed at improving survival-rates in carcinoma of the bronchus, the results are usually stratified according to stage and histological type and, as far as is possible, like is compared with like for both treatment arms. Unfortunately, we cannot stratify lung cancers according to the most important variable of all—namely, growth-rate. Geddes¹ and others have suggested that in this condition survival-times are still determined by the growth-rate of the tumour rather than by the treatment. There is considerable evidence to support this view. Doubling-times, measured from serial chest X-rays, vary by a factor of five. The presence of residual tumour after resection is compatible with five-year survival² and long-term survival has also been recorded after radiotherapy alone for lung cancer. However, it is unlikely that such patients are cured, for when tumours are resected after high doses of radiation, 60–70% are found to contain viable tumour,³ and patients do die of their tumours five years or more after radiotherapy.⁴

We have completed a study which may give more information on the growth rates of bronchogenic carcinomas. We counted the number of mitotic figures in immediately fixed, small biopsy specimens taken for diagnosis, on a series of high-power fields from two groups of patients treated by radiotherapy. 14 cases had survived over five years and 15 less than five years. The identity of these two groups was unknown to the pathologist doing the counts. There was no statistical difference in age, sex, histological type, or radiotherapy dose in the two groups. With respect to TNM stage, the long-term survivors were at a slight disadvantage.

Long-term survivors had statistically fewer mitoses than did short-term survivors ($p < 0.01$) (see figure). This suggests that survival after radiotherapy in the dosage given is determined primarily by growth-rate of the primary tumour.

We intend to repeat this work on surgically treated patients before reporting it fully. We recognise that mitotic figures may not be an accurate measure of growth-rates; they will depend on thickness of sections, site of biopsy, and time to fixation. Nevertheless, other studies have suggested that mitotic index gives at least some measure of growth-rate.^{5,6} More detailed



Mitotic numbers in 14 long-term survivors with bronchogenic cancers and in 15 who died in less than 5 years.

measurements are time-consuming, expensive, and often expose the patient to doses of radioactive tracers.

We suggest that some measurement of this type be included in the protocol of any clinical trial which aims to improve treatment of lung cancer. If not, the results will be subject to an uncertainty—namely, the extreme variability in natural progression of this disease.

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MAGNESIUM IN LUNG CANCERS OF OAT-CELL TYPE

SIR,—Parsons and his co-workers have reported the regression of lung-cancer tumour mass in patients on a magnesium and potassium depletion diet.^{1,2} We have found that tumour tissue from oat-cell type lung cancer contains more magnesium than does tissue from other types of cancer or normal soft tissue. This suggests defective magnesium metabolism in oat-cell cancer and could provide a rationale for the Parsons regimen.

All tissues were obtained at necropsy and the tumours were classified by standard histopathological techniques, in the laboratories that provided the specimens. 100–200 mg from each specimen was minced and put into individual Erlenmeyer flasks with 2.5 ml of a mixture of concentrated nitric acid and 60% perchloric acid (1:2). The flasks were then placed directly on a hot plate and the contents boiled until dry. Trichloroacetic acid (5 ml of 5%) was added to each flask, and this solution was assayed for magnesium using the titan-yellow method.³ These titan-yellow magnesium measurements have recently been confirmed by atomic-absorption spectroscopy on those materials still available.

Oat-cell type cancer tissue contained larger amounts of magnesium (range 7.9–15.6 mmol/kg wet tissue) than did any of

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TISSUE MAGNESIUM

Tissue	Mg ²⁺ (mmol/kg wet tissue)	Mean $\pm$ SD
Oat-cell tumours (n=6)	15.6, * 12.3, * 9.4* 10.5, 10.1, 7.9	11.0 $\pm$ 2.7
Other tumours (n=5)		
Glioma	3.7	3.5 $\pm$ 0.7
Fibroma	2.9, 2.9	
Meningioma	3.4, 4.5	

* Patients with myasthenic syndrome.

the other type of cancer tissue measured (2.9–4.5) (see table). The difference was significant (Student's *t* test; $p < 0.005$).

Skeletal muscle contains more magnesium than any other normal soft tissue,⁴ so the fact that the magnesium content of oat-cell type cancers was much larger than the content of normal human skeletal muscle (6.8 ± 0.4 mmol/kg, $n=10$)⁵ supports the hypothesis of abnormal magnesium metabolism associated with oat-cell carcinoma leading to magnesium accumulation in the tumour. Furthermore, this hypothesis provides a rational basis for magnesium and potassium depletion therapy for inoperable lung cancer.

Oat-cell cancer is occasionally associated with neuromuscular weakness, called the "myasthenic" syndrome.^{6,7} The pathophysiological mechanism of this syndrome is exactly the same as the defect in neuromuscular transmission caused by increased levels of magnesium (i.e., a reduction in the quantal content). The finding of an increased magnesium content in oat-cell type lung cancers may therefore have implications for our understanding of the "myasthenic" syndrome.

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LATENCY PERIOD FOR MESOTHELIOMA

SIR,—Some texts¹ and published papers² leave the impression that mesothelioma due to asbestos is a tumour that develops in old age, a very long time after exposure. In Ontario this is by no means always true. The Workmen's Compensation Board of Ontario has, since 1970, been compensating cases of mesothelioma attributable to occupational asbestos exposure. Claims have been accepted for 26 cases that had occurred between 1958 and 1978. Most have been workers in industries with high potential exposures, mainly to chrysotile fibres. The age at diagnosis (or death) has ranged from 37 to 78 years with a mean of 56.0. Latency, defined as the period from first known exposure to diagnosis, has ranged from 6 to 44 years with a mean of 26.9 (we cannot rule out additional earlier non-occupational exposure). 19 of the cases were

pleural in origin and 7 peritoneal. Our series is small, but certainly does not fit the textbook picture. Elmes and Simpson³ have suggested that latency for this tumour may be a function of dose. This may account for our observations.

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CHROMOSOMES, LEUKÆMIA, AND
OCCUPATIONAL EXPOSURE TO LEUKÆMOGENIC
AGENTS

SIR,—It has been suggested that patients presenting with de novo acute non-lymphocytic leukaemia (ANLL) who experienced occupational exposure to a possible carcinogenic agent, are more likely to show chromosome abnormalities in the bone-marrow at diagnosis than are patients with no history of such exposure.⁴ This information was obtained by a retrospective survey of hospital notes, although Mitelman et al.⁴ were fully aware of the shortcomings of this procedure. Using a similar approach and the same criteria for assessment of exposure, we have been unable to demonstrate a correlation with chromosomal findings in patients treated at the Royal Marsden Hospital (table 1). The cytogenetic findings on these patients have been correlated with survival and the results are to be published⁵ but the analysis of chromosomal status in relation to occupation reported here has not been made previously.

Unlike Mitelman et al. we did not find more non-random chromosomal abnormalities amongst the "exposed" than "non-exposed" patients. The series were comparable in that in both about 50% of the patients had chromosomal abnormalities in the bone-marrow at diagnosis and this frequency accords with the findings of the 1977 Helsinki workshop.⁶ However, the two series differed in that the chromosomal abnormalities in the cases reported by the Swedish group were all clonal, whereas our series includes patients with non-clonal changes.⁵

TABLE 1—ASSOCIATION BETWEEN CHROMOSOMAL ABNORMALITY IN ANLL AND HISTORY OF EXPOSURE AT WORK TO POTENTIALLY LEUKÆMOGENIC AGENTS

Chromosomes	Mitelman et al. ⁴		Royal Marsden		Total no. patients
	Exposure	No exposure	Exposure	No exposure	
Abnormal	19	8	12	22	61
Normal	4	25	10	23	62
Total	23	33	22	45	123
Association	Positive ($p < 0.001$)		None ($p = 0.70$)		..

An excess of males in the exposed category is found in both the Swedish and British series ($p=0.015$), the exposed:non-exposed ratios being 15:12 for males and 8:21 for females in the Swedish series and 19:17 and 3:28, respectively, in our series. This is a reflection of the method used to assess exposure, most of the females being recorded as housewives and therefore in a non-exposed occupation.

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