Levamisole and surgery in bronchial carcinoma patients: increase in deaths from cardiorespiratory failure

H M ANTHONY, A J MEARNs, M K MASON, D G SCOTT, K MOGHISsI, P B DEVERALL,¹ Z J ROZYCKI,² AND D A WATSON

From the Department of Immunology, University of Leeds; Department of Pathology, Leeds (St James's) University Hospital; Departments of Cardiothoracic Surgery, Killingbeck Hospital, General Infirmary, Leeds, and Castle Hill Hospital, Hull, UK

ABSTRACT Life table analysis of early entry to this randomised blind trial of 318 patients has shown a significantly *poorer* survival for resected lung cancer patients treated with levamisole for three days before operation and three days a fortnight thereafter than for placebo-treated controls. This excess was largely due to deaths that had been attributed to operation or other causes (non-cancer deaths), most occurring in the six weeks after operation. In the 99 resected patients treated with levamisole there was a 15% excess of deaths in this category, compared with the placebo-treated controls. Extensive analysis excluded maldistribution of patients between the groups as a cause of this difference.

Many more died in respiratory distress, mostly without clear cause, in the levamisole group. Antibody (IgG) reacting with myocardial sarcolemma or sarcoplasm was found in the only serum samples available for testing which were drawn from patients during the syndrome. The findings are in keeping with a primary effect on the heart, possibly involving an autoimmune mechanism. The effect has not been noted in other trials.

The drug levamisole has been reported to restore certain aspects of weak cellular immune competence (Symoens and Rosenthal, 1977) of relevance to survival in lung cancer (Israel, 1973; Anthony *et al*, 1974) as in other malignancies (Eilber and Morton, 1970). Amery (1975, 1976) reported fewer cancer deaths among resected lung cancer patients treated with levamisole before operation and fortnightly during follow-up than in controls receiving a placebo.

Few important side effects have been reported among cases treated on an intermittent schedule (three days a fortnight or two days a week); these have been mainly minor gastric intolerance and rashes. Continuous dosage has been associated with a few cases of severe neutropenia, usually reversible but causing the death of two young patients (Amery *et al*, 1977).

This report is concerned with early deaths in a randomised trial of levamisole against placebo in 318 patients with lung cancer using a similar regimen to that of Amery (1975, 1976) and starting treatment three days before operation. Of the 135 patients resected before the end of 1976, there were significantly more deaths among those treated with levamisole than placebo because of an excess of cardiorespiratory deaths in the four to six weeks after operation.

Trial plan

Between August 1975 and November 1977 patients at three collaborating centres were randomly allocated to "X" or "Y" levamisole (one being the placebo) before operation for primary carcinoma of the bronchus, with separate randomisations for men and women patients of each surgeon. The dosage schedule was three days of treatment before operation and three days a fortnight thereafter,

¹Present address: Department of Cardiothoracic Surgery, Guy's Hospital, London.

²Recently deceased.

Levamisole and surgery in bronchial carcinoma patients

according to body weight, with one (50 mg) tablet given twice (<50 kg), three times ($50 < 75$ kg), or four times (≥ 75 kg) a day. All patients identified in time for preoperative dosage were included unless they had active tuberculosis, severe auto-immune or allergic conditions, or were unwilling to participate.

All data believed to be relevant to survival with lung cancer were recorded at the time of diagnosis (see table 2). At follow-up (usually at six weeks, three months, and six months after operation and three- or six-monthly thereafter) changes in symptoms and clinical findings were noted (including the presence or absence of oedema), and each patient was weighed and had a full blood count and a chest radiograph taken. Additional data, where available, were collected retrospectively from the notes of resected patients in centres A and B only, to determine the contribution of previous heart and lung disease, incision of the pericardium, digoxin treatment, and haemoglobin values to the unexpected deaths.

PATIENTS

Altogether 328 patients were admitted to the trial, had levamisole before operation, and had a histologically confirmed diagnosis of primary carcinoma of the lung. Ten patients had had fewer than three courses of treatment at the time the discrepancy in deaths from other causes was discovered: as most of the deaths had occurred in the six weeks after operation, these ten patients were removed from the trial but their progress will be followed. Of the remaining 318 patients, resection was considered complete at operation in 217 (182 men and 35 women). Despite balancing the randomisation after every four cases the numbers of resected cases allocated to levamisole and placebo were uneven

because some patients were not resectable and others were withdrawn with a final diagnosis other than primary lung cancer. All withdrawals were scrutinised carefully to ensure that no early deaths in primary lung cancer cases were overlooked.

ANALYSIS

Analysis of survival was performed using the life table analysis computer program recently described by Peto *et al* (1976, 1977). At each week after operation the number of deaths in each treatment group was compared with the "expected" number based on the experience of the patients as a whole and the numbers who were alive and followed to that time. This method of analysis gives a prediction of survival experience before the full follow-up period is complete for all the patients and makes it possible to compare treatment groups making allowance for other prognostic factors individually and in combination. Data were in all cases complete to the last follow-up appointment. The end-point used in the analysis was death irrespective of cause, but each death recorded was attributed to (a) operation, (b) other causes, or (c) cancer on the best evidence available. All deaths in patients with progressing tumour were attributed to cancer in the absence of clear contrary evidence.

The comparability of groups randomly allocated to levamisole and placebo was investigated using the non-parametric cross-tabulation facility in the SPSS package of computer programs (Nie *et al*, 1975).

Results

The numbers of patients in the trial, distribution between levamisole and placebo, the completeness

Table 1 *Levamisole and placebo treatment; side effects and non-cancer deaths in the 1975-6 trial entry (1977 entry in parenthesis)*

	Total no of patients	No of patients with incomplete tablet treatment < 3 days before operation		No of deaths attributed to operation or other causes	No of patients reporting side effects†			Gross total no of courses (to October 1977) (approximate)
		Missed or stopped in first 6 weeks in error			Severe (tablets stopped)	Moderate	Trivial	
<i>All patients</i>								
Levamisole	93 (61)	5	4	18 (7)	7* (5)†	7	19	1730
Placebo	98 (66)	3	8	5 (6)	0 (2)	3	19	1888
<i>Resected patients</i>								
Levamisole	62 (37)	4	2	16 (7)	7 (5)			
Placebo	73 (45)	3	3	5 (5)	0 (2)			

*Gastrointestinal (4), neurological (4), and Skin (1) > one (2).

†Gastrointestinal (3), neurological (1), and intermittent dyspnoea (1).

‡Reported after the second to fourth course of levamisole in 9/12 cases with severe and 6/7 with moderate side effects.

of tablet treatment, and reports of side effects are shown in table 1. Levamisole treatment was stopped in 12% of the resected patients because of side effects, but in two of these the clinical deterioration of the patient may have influenced the decision. Most side effects were reported after the second to fourth course of the drug. No cases of neutropenia were detected, and there was no suggestion of neutropenia in any patient who died while taking the drug. On the reported side effects alone we would have concluded that levamisole was relatively free of unwanted activity.

Among the 1975-6 trial entry the groups of patients randomly assigned to levamisole or placebo treatment were very similar in all the factors related to cancer and operative mortality (tables 2 and 3). Life table analysis, however, showed a significant difference in survival between the two treatment groups: when the levamisole code was broken this was found to lie in the poorer survival of levamisole-treated patients (figure 1 and table 4). The difference was largely due to deaths that had been attributed to operation or other causes (non-cancer deaths) since most of the difference was lost if all such patients were omitted (figure 2 and table 4). Most of these

deaths occurred during the first four to six weeks after operation (table 4); they were present in both the centres contributing substantial numbers of cases to the trial (centres A and B) and in these centres affected patients of all surgeons, irrespective of status. The difference was not due to any of the minor differences between the patient groups (tables 1 and 3) since the poorer survival of levamisole-treated patients on the life table analysis was unaffected by allowing for each of the factors separately or the major factors in combination.

The deaths affected men more than women, patients of blood group O more than other patients, and patients without coronary artery disease, hypertension, or previous lung disease more than those in whom these diseases had been recorded. On this evidence the difference in overall survival between the two groups could not be explained by differences in the health of patients before the operation, nor were deaths limited to patients with extensive operations, implying that levamisole must in some way have contributed to the deaths.

Analysis of the characteristics of the patients entering the trial in 1975-6 whose deaths had been

Table 2 Comparability of patients allocated to levamisole or placebo treatment

		No of patients				No of patients	
		Levamisole	Placebo			Levamisole	Placebo
Total		62	73	General condition	Very good	5	8
Surgical centre	A	26	28		Good	37	35
	B	31	36		Fair	18	29
	C	5	9		Poor	1	1
Sex	M	54	56	Symptom pattern	Long primary or none	15	15
	F	8	17	(Feinstein, 1968)	Short primary and/or systemic	46	57
Age	< 60 years	25	17	Weight loss	None	35	43
	60-69	26	30		< 3 kg	7	6
	≥ 70 years	11	11		3 < 6 kg	7	12
Operation	Lobectomy	32	36		≥ 6 kg	10	9
	Pneumonectomy	30	37	Parental age	Both over 80 years	3	7
Stage	Node - ve	31	31	(Abbey Smith	One over 80 years	15	17
	Node + ve	31	42	<i>et al</i> , 1973)	None over 80 years	25	35
Tumour size* (greatest diameter)	< 3 cm	28	24		(Not done)	(19)	(14)
	3 < 7 cm	24	42	Immunocompe-	Good	19	27
	≥ 7 cm	9	4	tence (by skin	Poor	14	16
Histology	Squamous	46	58	tests see Anthony		(29)	(30)
	Undifferentiated	11	11	<i>et al</i> , 1974)	(not done)		
	Adenocarcinoma	5	4	Preop lymphocyte	≥ 3.0/mL × 10 ⁹	2	3
Differentiation (squamous only)	Well-differentiated	13	17	count	1.5 < 3.0	31	33
	Moderately differentiated	22	30		< 1.5	7	13
	Poorly differentiated	11	11		(Not done)	(22)	(24)
				Preop blood	Normal	46	51
				urea	Raised (6 mmol/l)†	13	21

NB Distribution of following were also examined; inclusion of radiotherapy in the initial treatment schedule (two patients only), finger clubbing, smoking habits, preoperative white cell count*, and ESR.

Where data were missing for more than three cases in a group this is indicated; in other cases it can be deduced by comparing totals.

* $P < 0.05$ by χ^2 for differences between proportions, but no trend. No correction for multiple comparisons.

†Conversion factor for mg%, × 6.

Table 3 Comparability of patients allocated to levamisole or placebo treatment. Additional data retrieved retrospectively for patients at Centres A and B

	No of patients			No of patients	
	Levamisole	Placebo		Levamisole	Placebo
Total*	56	64	cont.		
History of previous chest disease	16	19	Blood group A	21	27
Hypertension (treated)	3	0	B	4	3
Hypertension or coronary artery disease	17	16	O	28	25
Chest, cardiac disease, and/or raised blood urea concentration	30	38	AB	1	2
Pericardium incised	31	38	Rh +ve	48	48
Intrapericardial pneumonectomy	16	16	Rh -ve	6	9
Preop blood pressure†			Digoxin treatment	24	26
High (or treated)	9	1	Preop FVC‡N	34	36
Moderate	4	11	Fair	15	13
Normal	39	48	Poor	0	2
Allergy (recorded)	4	7	(not done)	(7)	(13)

NB Following factors were also examined separately: coronary artery disease, chronic bronchitis, asthma, bronchiectasis, pneumoconiosis, and tuberculosis.

*Case notes were not found for one levamisole and three placebo patients.

† $p < 0.01$ by χ^2 for differences between proportions, no correction for multiple comparisons.

‡Based on patients' weight—height not available.

attributed to operation or other causes confirmed these findings by showing that the groups of patients over-represented were those in which operative mortality would be expected to be low

Fig 1 Life table for 135 patients (levamisole 62, placebo 73) resected 1975–6. Ratio of observed to expected deaths for levamisole 1.45, $p < 0.008$ (see table 4).

(ie those in good general condition, without previous chest diseases etc) (table 5). It appeared that patients with a history of coronary artery disease, digoxin treatment at or before operation, or a moderately raised blood urea concentration before operation might be more at risk on levamisole treatment.

No patients were admitted to the trial after the excess deaths on levamisole had been detected, and patients who had received less than three courses of the drug were withdrawn. Three months later all deaths in patients admitted during 1977 were attributed to cancer or other causes as before. Of the additional 82 resected cases, seven of 37 on levamisole and five of 45 on placebo were considered to have died from non-cancer causes. None of the earlier deaths had been suspect on clinical grounds but two of these later levamisole deaths were.

Of the resected patients on the trial 8% of those on placebo (10/118) and 23% of those on levamisole (23/99) had died as a consequence of operation or from other causes, including longstanding disease, during the follow-up periods examined. The difference, 15%, gives an estimate of levamisole mortality. The case notes of all the patients entering the trial whose deaths had been attributed to the "non-cancer" category were submitted to an independent observer (AJM) who was unaware of the levamisole status of the patients. Deaths of seven patients on levamisole and seven on placebo were explained by recorded complications of oper-

Table 4 *Effect of levamisole on survival in 135 patients with resected lung cancer entering the trial 1975-6 by life table analysis*

Patients	Analysis		No	Groups	No	Deaths		O/E†	χ^2	DF	P
	From	To				Observed	Expected*				
All	Operation	Oct 77	135	Levamisole	62	31	21.5	1.45†	7.2	1	<0.008
				Placebo	73	23	32.6	0.71			
All	Operation	4 weeks after operation	135	Levamisole	62	11	6.7	1.64	5.1	1	<0.05
				Placebo	73	4	8.3	0.48			
Omitting patients recorded as non-cancer deaths	Operation	Oct 77	114	Levamisole	46	15	12.2	1.23	1.0	1	NS
				Placebo	68	18	20.8	0.86			
Men (Centres A and B)	Operation	Oct 77	99	Levamisole	51	27	18.2	1.49	7.9	1	<0.005
				Placebo	48	14	22.9	0.61			

*Calculated from rate experienced by levamisole and placebo groups together.

†Observed/expected deaths.

‡Similar values obtained after allowing for each of the variables in tables 1 and 3 and for the more important in combination.

Fig 2 *Life table for 114 patients (levamisole 46, placebo 68) resected 1975-6 omitting 21 patients whose deaths were attributed to operation or other causes (non-cancer deaths). Ratio of observed to expected deaths for levamisole 1.23, not significant (see table 4).*

ations, concurrent disease, or necropsy findings; in four other patients there was insufficient evidence on which to judge. More of the levamisole-treated patients (16 compared with two) had died of cardio-respiratory failure, and for 10 of these the cause was not apparent from the case notes (table 6). In those that were adequately documented the similarity of the clinical picture was striking. Respiratory distress was often of fairly sudden onset but arrhythmias were not recorded in most cases: in

some, myocardial infarction was suspected on clinical grounds but not found at necropsy. The dates of deterioration and death showed no clear relation to the days of levamisole treatment, and the non-cancer deaths on levamisole and placebo were randomly distributed throughout the trial period. Among the non-cancer deaths on levamisole there was no excess of patients receiving transfusions of blood drawn from the donor less than three days before. Review of the small number of histological specimens retained from necropsies gave no further information.

Among the serum samples in store from patients on the trial there were samples taken from two of the levamisole-treated patients during the respiratory-distress syndrome. Using the fluorescent antibody technique, IgG antibody reacting with myocardial sarcolemma or sarcoplasm was detected in each of these sera but not in a sample from one of the patients taken before operation or in the first sample after operation from 25 levamisole- and 25 placebo-treated trial patients without the syndrome. Serum from another patient who reported attacks of dyspnoea worse on levamisole-treated days also showed antiheart antibody (IgG sarcolemmal pattern).

Discussion

In this randomised trial patients treated with levamisole before resection for lung cancer showed significantly poorer survival than placebo-treated controls. Each of the factors that affect survival in lung cancer patients or influence operative mortality have been examined and ruled out as a cause of this mortality either singly or in combination. The excess deaths were mainly in the first four to six weeks after operation and affected 15% of levamisole-treated patients. This estimate was based on a comparison of the numbers of

Table 5 Characteristics of the groups of patients whose deaths were attributed to operation and other causes (non-cancer deaths). Comparison of levamisole and placebo groups (1975-6 entry, Centres A and B only)

Categories of patients over-represented in the non-cancer deaths	No of non-cancer deaths over No of cases on				P†	Comments
	Levamisole		Placebo			
All patients	16/56	0.29	5/64	0.08	< 0.02	
Over 70 years of age	5/11	0.46	0/8	0	< 0.04	Digoxin used routinely in this age group by some participating surgeons
Good or very good general condition	12/42	0.29	2/43	0.05	< 0.005	Not the group in which non-cancer deaths would be expected
Weight over 75 kg	4/12	0.33	0/17	0	< 0.03	Received levamisole four times a day
No weight loss	10/42	0.24	2/49	0.04	< 0.01	
No previous chest disease	10/39	0.26	2/42	0.05	< 0.01	} Indicates that <i>poor</i> lung function before operation was <i>not</i> responsible for the excess deaths
Normal FVC	12/34	0.35	1/36	0.03	< 0.001	
History of coronary artery disease	4/6	0.67	1/4	0.25	NS	This may have contributed as lack of significance may result from small numbers concerned
No such history	12/49	0.25	4/58	0.07	< 0.02	Coronary artery disease does not <i>explain</i> excess deaths
Digoxin treatment at or before operation	9/24	0.38	2/26	0.08	< 0.02	May have contributed, but not used in seven patients
Intrapericardial pneumonectomy	7/16	0.44	2/16	0.13	< 0.02	May have contributed but not a major factor; digoxin given in most of these patients
Raised blood urea concentration (≥ 6 mmol/l)* (before operation)	6/13	0.46	1/21	0.05	< 0.01	Moderately increased blood urea only (median value for six levamisole patients 7.0 mmol/l highest 9.1)
Blood group O	10/28	0.36	1/26	0.04	< 0.005	} Few deaths of any kind in these groups on placebo. Group O patients stronger antibody producers (Ichikawa, 1959) more prone to most autoimmune diseases (Mourant <i>et al</i> , 1978), more at risk from haemorrhage (Mourant <i>et al</i> , 1971), and perhaps more cancer resistant (Mourant, 1976)
Rh -ve	4/6	0.67	0/9	0	< 0.02	

*Conversion factor for mg%, $\times 6$.

†By χ^2 for difference between proportions of non-cancer deaths in levamisole and placebo groups without correction for multiple comparisons. (This is a summary table—a full table will be sent with all requests for reprints.)

deaths attributed to operation and other causes in the two groups during assessment and it may be an underestimate, since these deaths did not account for the whole difference in survival experience among the 1975-6 trial entry.

Levamisole has been used in a similar manner in two other trials. Amery has reported significantly fewer "cancer deaths" in levamisole-treated patients (Amery, 1975, 1976) and has informed us that there has been no significant excess of non-cancer deaths in levamisole-treated patients in either trial. We have not been able to pinpoint any difference in management that might account for the difference.

The analysis suggests that digoxin treatment, a moderately raised blood urea concentration before operation, previous coronary artery disease, and levamisole treatment in four divided daily doses may have contributed to the excess deaths on levamisole and that men, older patients, and those who were blood group O or Rh negative were more at risk. These factors overlap and some of them are likely to be chance associations. A drug interaction between digoxin and levamisole may have contributed but is unlikely to have been responsible for the effect because digoxin had not been used in

several patients who died from unexplained respiratory distress, and the drug was used equally in other trials.

The only direct piece of evidence was the finding of antiheart antibody in serum samples from patients with the respiratory distress syndrome and not from other patients in the trial. It is a pity that so few samples from patients with the syndrome could be tested, but the positive results from all three suggest that the finding may have wider significance. If this were so the danger of cardiac deaths with levamisole treatment might occur only when the heart and great veins were handled (or perhaps affected by radiotherapy (Westerhof and van der Putte, 1976)) after the start of levamisole treatment. The slight excess of intrapericardial operations is in keeping with this possibility, but since all resections will have entailed this handling, our data cannot elucidate this point. The conditions in which antimyocardial antibodies have been suspect of pathogenicity have not normally been fatal (Bernstein, 1977), and the significance of antiheart antibody remains unclear (Talano, 1977). Any effect of antiheart antibody, however, might well be exaggerated in patients who have just had a lung resection, particularly in

Table 6 *Result of the retrospective assessment of the cause of death (made without knowledge of levamisole status) for all non-cancer deaths, 1975-7 inclusive*

	Levamisole group		Placebo group	
	No	Days after operation	No	Days after operation
Total	25		11	
I Deaths explained	7		7	
Pulmonary embolism	1	22	2	1, 11
Bronchopleural fistula	2	27, 63	0	
Haemorrhage	1	20	2	1, 1
Cerebral thrombosis	1	5	0	
Myocardial infarction	1	49	0	
Disseminated arterial disease	0		1	87
Other poor risk patients	1	9	2	5, 11
II Deaths possibly explained	6		1	
"Bronchopneumonia"	0		1	312
Respiratory failure	6	3, 3, 4, 10, 15, 4 (3rd op)	0	
III Deaths not explained				
A Not enough evidence	2		2	
Soon after discharge	1	41	1	17
Sudden death	1	158	1	14
B Other	10		1	
Sudden postoperative respiratory distress, no necropsy	5	3, 6, 6, 8, 14	1	15
Sudden post operative respiratory distress, necropsy—no cause	2	6, 10	0	
Respiratory distress, necropsy—no cause	1	10	0	
Sudden respiratory distress, no necropsy	1	190	0	
Sudden respiratory distress, necropsy—no cause	1	33	0	
Total with respiratory distress	16		2	
Of these, no cause found at necropsy	4		0	

view of the evidence that ventricular imbalance is an important factor in cardiac failure (Burch, 1977).

The syndrome might be more likely to occur in the presence of infective agents since myocarditis may result from infections such as *Mycoplasma pneumoniae*, coxsackie virus, or cytomegalovirus or after immunisation (Sands *et al.*, 1977; Levi *et al.*, 1977; Lamb, 1971; Bloth and Lundman, 1977). The distribution of deaths throughout the period of the trial was not in keeping with the contribution of an infective factor, but we have not been able to exclude the possibility there was one.

Recently, the neutropenia complicating levamisole treatment has been attributed to leucocytotoxic agglutinating antibodies (Rosenthal *et al.*, 1976) and a rash to immune complex deposition (MacFarlane and Bacon, 1978). If our levamisole deaths were due to an autoantibody mechanism this might account for the increased risk in patients with a raised blood urea concentration, through a tendency to immune complex nephritis.

It might also explain the blood group data since group O individuals have been reported to be better antibody producers (Ichikawa, 1959) and more prone to most autoimmune diseases (Mourant *et al.*, 1978) than group A individuals, and Mourant (1976) has postulated greater resistance to cancer in non-A individuals to account for excess cancer incidence in those of group A.

If our trial protocol had omitted from analysis all patients dying in the month after operation this effect of levamisole might have escaped detection. If levamisole is to be used in future it is essential that trials guard against the loss of any such patients from the analysis, and it would be wise to store frozen samples of serum taken before operation and in the postoperative period to allow comparison of antibody and autoantibody titres should morbidity or mortality of this kind occur again.

It may be that the use of any immunoadjuvant is necessarily associated with the possibility of autoimmune side effects in susceptible individuals. If this were so the high rate of side effects from

levamisole reported by Parkinson *et al* (1977) in a trial in which BCG was *also* given might be explained. Careful documentation may show which dosage regimens are least likely to result in unwanted autoimmune side effects and which groups of patients are most susceptible.

Conclusions

From this study we conclude that there is a substantially increased risk of death from cardio-respiratory failure in patients treated with levamisole before resection for lung cancer, and that the findings are in keeping with an autoimmune mechanism with exaggerated effects because of recent lung resection. The risk appeared greater in men, in those of blood group O, and in those with a moderately raised blood urea concentration before operation. Treatment with digoxin before or at the time of operation may have contributed but interaction of the two drugs did not explain the phenomenon.

The use of any immunoadjuvant may necessarily include some risk of autoimmune side effects in susceptible individuals. Careful documentation, full analysis of all trial deaths, and the routine storage of serial serum samples in such trials is essential to establish the groups of patients at risk and the safest dose regimens.

The study was approved by the ethical committees for all the areas of Yorkshire taking part in the trial and the Yorkshire Regional Cancer Organisation. All patients were informed about the study as intelligently as possible within the limits of their understanding of their clinical condition, which was in keeping with that imparted to them by their consultants. All patients consented willingly and understood that the drug was being given experimentally.

We thank Mr J S Davidson, Dr W H Helm, Dr S J Cameron, and Mr J W Haddon for active collaboration; many other clinical colleagues for their help; Mrs D J Grainger, Mrs C Lutley, Mrs J M Smith, Miss L Jones, Mr A D Geekie, and the YRCO Secretariat for devoted and efficient practical support, and the Yorkshire Cancer Research Campaign, Janssen Pharmaceuticals Ltd, and the Yorkshire Regional Cancer Organisation for financial support.

References

- Abbey Smith, R, Nigam, B K, and Thompson, J M (1973). Influence of parental age on survival after resection for lung cancer. *Lancet*, 1, 843-845.
- Amery, W K (1975). Immunopotential with levamisole in resectable bronchogenic carcinoma: double-blind controlled trial. *British Medical Journal*, 3, 461-463.
- Amery, W K (1976). Double-blind levamisole trial in resectable lung cancer. *Annals of the New York Academy of Sciences*, 277, 260-268.
- Amery, W K, Spreafico, F, Rojas, A F, Denissen, E, and Chirigos, M (1977). Adjuvant treatment with levamisole in cancer. A review of experimental and clinical data. *Cancer Treatment Reviews*, 4 (3), 167-194.
- Anthony, H M, Templeman, G H, Madsen, K E, and Mason, M K (1974). The prognostic significance of DHS skin tests in patients with carcinoma of bronchus. *Cancer*, 34, 1901-1906.
- Bernstein, A (1977). The postmyocardial infarction syndrome of Dressler. *British Journal of Hospital Medicine*, 17, 560-571.
- Bloth, B, and Lundman, T (1977). Pleuroperimyocarditis caused by immunisation with anticatarrhal vaccine—a case report. *Acta Medica Scandinavica*, 201, 137-140.
- Burch, G E (1977). Congestive heart failure is not due to low cardiac output per se. *American Heart Journal*, 94 (3), 269-273.
- Eilber, F R, and Morton, D L (1970). Impaired immunologic reactivity and recurrence following cancer surgery. *Cancer*, 25, 362-367.
- Feinstein, A R (1968). A new staging system for cancer and reappraisal of "early" treatment and "cure" by radical surgery. *New England Journal of Medicine*, 279, 747-753.
- Ichikawa, Y (1959). A study of the iso-agglutinin titres in the sera of Australian subjects (white). *Japanese Journal of Medical Sciences and Biology*, 12, 1-7.
- Israel, L (1973). Cell-mediated immunity in lung cancer patients: data, problems and propositions. *Cancer Chemotherapy Reports Part 3*, 4, suppl 4, 279-281.
- Lamb, S G (1971). Cytomegalovirus infections. *British Journal of Hospital Medicine*, 5, 347-354.
- Levi, G F, Proto, C, Quadri, A, and Ratti, S (1977). Coxsackie virus heart disease and cardiomyopathy. *American Heart Journal*, 93, 419-421.
- MacFarlane, D G, and Bacon, P A (1978). Levamisole-induced vasculitis due to circulating immune complexes. *British Medical Journal*, 1, 407-408.
- Mourant, A E (1976). Blood groups and diseases. *Biostat Bulletin* (Birmingham, UK), 1, 1-14.
- Mourant, A E, Kopec, A C, and Domaniewska-Sobczak, K (1971). Blood groups and blood clotting. *Lancet*, 1, 223-227.
- Mourant, A E, Kopec, A C, and Domaniewska-Sobczak, K (1978). *Blood Groups and Diseases*, p 49. Oxford University Press, London.
- Nie, N H, Hull, C H, Jenkins, J G, Steinbrunner, K, and Bent, D H (1975). *Statistical Package for the Social Sciences*, 2nd edn, p 230. McGraw Hill, New York.

- Parkinson, D R, Cano, P O, Jerry, L M, Capek, A, Shibata, H R, Mansell, P W, Lewis, M G, and Marquis, G (1977). Complications of cancer immunotherapy with levamisole. *Lancet*, **1**, 1129–1132.
- Peto, R, Pike, M C, Armitage, P, Breslow, N E, Cox, D R, Howard, S V, Mantel, N, McPherson, K, Peto, J, and Smith, P G (1976). Design and analysis of randomized clinical trials requiring prolonged observations of each patient. Introduction and design. *British Journal of Cancer*, **34**, 585–612.
- Peto, R, Pike, M C, Armitage, P, Breslow, N E, Cox, D R, Howard, S V, Mantel, N, McPherson, K, Peto, J, and Smith, P G (1977). Design and analysis of randomized clinical trials requiring prolonged observation of each patient. Analysis and examples. *British Journal of Cancer*, **35**, 1–39.
- Rosenthal, M, Trabert, U, and Müller, W (1976). Lencocytotoxic effect of levamisole. *Lancet*, **1**, 369.
- Sands, M J, Jay, E S, Turner, W E, and Soloff, L A (1977). Pericarditis and perimyocarditis associated with active *Mycoplasma pneumoniae* infection. *Annals of Internal Medicine*, **86**, 544–548.
- Symoens, J, and Rosenthal, M (1977). Levamisole in the modulation of the immune response; the current experimental and clinical state. *Journal of the Reticuloendothelial Society*, **21**, 175–221.
- Talano, J V (1977). Importance of myocardial antibodies in heart disease. *Archives of Internal Medicine*, **137**, 570–572.
- Westerhof, P W, and van der Putte, S C J (1976). Radiation pericarditis and myocardial fibrosis. *European Journal of Cardiology*, **4**, 213–218.
- Requests for reprints to: Dr H M Anthony, University Department of Immunology, General Infirmary, Leeds LS1 3EX.
- Correspondence: see page 141.