Cancer Immunol Immunother (1986) 21: 6–11

Cancer Immunology Immunotherapy

Long-term follow-up of general immune competence in breast cancer

II. Sequential pre- and post-treatment levels: A 10 year study

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Summary. Pre-treatment and sequential post-treatment (at 3 months, 6 months, 1, 2, 3, 4 and 5 years) examination of general immune competence was performed in 185 consecutive breast cancer patients. The patients were followed for 5 to 11 years to monitor the dynamic relationship between host immunity and cancer and to examine the effect of the treatment method. The tests of immune competence used were immunoglobulins IgG, IgA, IgM, leucocyte counts, percentage and total lymphocyte counts and Mantoux and DNCB skin hypersensitivity tests.

Serum IgG and IgA showed no change relating to treatment method in recurrence-free patients; but IgG levels were higher when recurrent disease was imminent or established; IgM diminished ($P<0.001$) after treatment and this continued at 5 years in all patient groups. Simple lymphocyte counts showed the most interesting changes. They remained depressed for as long as 60 months following radiotherapy ($P<0.01$). After treatment by surgery, lymphocyte counts rose in patients without recurrence, but fell when systemic recurrence was imminent or established. This effect was not seen in patients with local recurrence only. There was no change in immune competence immediately before recurrence sufficient to be of clinical usefulness, but a low pre-treatment lymphocyte count with a steady rise after surgery carried a good prognosis. Similarly a high initial lymphocyte count with a fall after surgery was indicative of recurrence. Universal and prolonged depression of lymphocyte counts following radiotherapy was confirmed, and the effect was additive to that of tumour load in recurrent disease.

Because of the large number of statistical calculations carried out, some of the apparently significant findings may be due to chance. However, the general trends emerging suggest that similar long-term studies, using the more sophisticated measures of lymphocyte function now available, might be rewarding.

Introduction

It is recognised that the behaviour of breast cancer is unpredictable in individual patients. In the host the tumour and the general resistance are necessarily in a dynamic, changing equilibrium. The recognition of this relationship will be missed in studies that examine each patient just once, though such studies have nevertheless shown significant stage-related findings [19]. Limited follow-up studies would also, for the same reasons, not be representative of the changes taking place. In a long-term prospective sequential analysis, there are further important factors requiring consideration, such as treatment methods and changing tumour load. Radiotherapy for breast cancer produces depression of immune parameters independent of the tumour load which may last for up to 2 years [10, 15], and surgery also affects immune parameters [10]. However, the long-term effect of surgery or radiotherapy on the tumour-host inter-relationship is not known. There is, in general, no information on the quantitative relationship between immunological change and tumour load which continues when viewed longitudinally throughout the course of the disease. Long-term follow-up reported previously suggests a correlation between pre-treatment lymphocyte count and micrometastasis [11]. Although these findings cannot be regarded as reaching unequivocal statistical significance, they suggest that long-term sequential studies would be necessary if dynamic changes in host immunity and tumour are to be demonstrated. Since any sequential relationship between host resistance and a tumour is likely to occur in those patients where the relationship is evenly balanced, studies should concentrate on patients with late recurrence – e.g. after 5 years. This study was set up because it is likely that the failure of studies to date to produce a definite relationship between tumour load and immune status may be a consequence of inadequate duration of follow-up. This paper presents the results of 5 years of sequential tests and follow-up to a maximum of 11 years in a prospective study of general immune competence in 185 breast cancer patients.

Materials and methods

The details of patients and pre-treatment assessment have been given previously [3, 11]. In each patient between 3 and thirteen follow-up examinations for general immune competence have been carried out at intervals of 3 months to 12 months over a 1 to 5-year period.

The arrangement of data for statistical analysis was carried out as follows. For patients remaining free of recurrence pre-treatment, 3 and 6 months post-treatment and 1, 2, 3, 4 and 5 years sequential data were analysed. Two groups were considered: patients treated by surgery and those receiving surgery with postoperative radiotherapy or

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treated with radiotherapy alone. For patients developing local or systemic recurrence, three observations – pre-treatment, before recurrence and after recurrence – were analysed. Patients with both local and systemic recurrence were grouped as systemic recurrences. For patients in Stage IV disease sequential values over 12 months were analysed, dividing patients into two groups according to whether survival was less than or greater than 24 months. This selection of data was chosen to examine the host-tumour balance at critical times of tumour activity.

The mean and standard deviation for each quantitative variable and each patient group were calculated. Sequential comparisons within patient groups were performed using the paired t-test. In order to improve normality and homogeneity of variance, these tests were performed on log-transformed values for the immunoglobulins, white cell count and absolute lymphocyte count, and the Mantoux reading; the latter was increased by 5 prior to transformation.

The number of sequential dinitrochlorobenzene (DNCB) tests is less than for other tests. The severity of reaction on repeat challenge precluded serial testing in many patients.

Results

Table 1 shows the patient stage, method of treatment and type of recurrence over a minimum period of 5 years of follow-up examination. Tables 2 and 3 show the long-term sequential changes in patients without recurrence, separated into groups treated by surgery and surgery with post-operative radiotherapy (or primary radiotherapy) respectively. Tables 4 and 5 show pre-treatment, pre-recurrence and post-recurrence changes for patients developing systemic recurrence and Table 6 for local recurrence in patients treated by surgery and surgery with post-operative radiotherapy (or primary radiotherapy). Table 7 shows observations for patients with Stage IV disease surviving for more or less than 24 months.

With such a large number of statistical calculations the possibility that some significant correlations will arise by chance must be considerable. Equally, there is a possibility that some positive correlations might be missed, since the 95% confidence levels will be very wide, particularly in the smaller sub-groups. For these reasons we have given the individual significance figures but presented only trends, without claiming that any are of unequivocal statistical significance.

In no recurrence (NR) patients (Tables 2 and 3), irrespective of treatment, there was an initial rise in IgG followed by a long-term fall. With imminent or established disease, however, there was a rise in IgG level (Tables 4 and 6). There were no changes in IgA in the follow-up period, and the overall levels did not correlate with follow-up disease status and type of treatment (Tables 2–7). In the post-treatment period, IgM levels showed a general tendency to decrease. This showed no correlation with treatment method or disease recurrence.

WBC counts were depressed in patients treated by radiotherapy ($P<0.01$). Imminent recurrent disease or rapid death from cancer did not affect the levels significantly. Distinct trends in percentage lymphocyte counts were seen in different groups, when compared to pre-treatment levels. In NR patients after treatment with surgery, the lymphocyte levels improved over the 5-year period (Table 2), but in those receiving radiotherapy (Table 3) low levels persisted up to 5 years of follow-up. Lymphocyte counts fell as patients developed systemic recurrence, and this post-recurrence depression of percentage lymphocyte levels was greater in patients receiving radiotherapy as compared to patients treated by surgery alone (Table 4, 5, 6). The absolute lymphocyte levels approximately followed the pattern of percentage lymphocyte change, but the degree of change was more marked. (Tables 2–7).

There was marked variability in the Mantoux test but the response tended to become weaker with progressive disease ($P<0.05$). There was no obvious relationship to recurrence, and interestingly radiotherapy had no consistent effect. Random variations and inconsistencies were seen in sequential testing. There was no significant change in DNCB response in NR patients treated by surgery, but those receiving post-operative radiotherapy had continued low levels over 5 years (Tables 2 and 3). There was a tendency for the DNCB response to increase with the onset of recurrence after surgery – especially in the 50 µg group where numbers were larger (Table 4). There was severe depression in Stage IV patients dying within 24 months of presentation.

Table 1. Treatment methods and type of recurrence in patient groups

		S	POX	S	POX	S	POX			
Clinical Stage	I	36	0	7	2	15	2	0	1	
	II	5	6	0	2	6	13	0	0	
	III	5	11	3	6	7	25	1	1	
	IV	0	1	0	1	0	0	12	17	
		46	18	10	11	28	40	13	19	185
		NR		LR		SR (Micrometastasis)		Dying 24–60 months	Dying 24 months (of Breast Cancer)	

S – Surgery POX – Post-operative radiotherapy
NR = No recurrence LR = Local recurrence SR = Systemic recurrence (with or without local recurrence)

Table 2. Patients treated by surgery – sequential observations on general immune status in recurrence-free patients. Significance levels refer to comparison with pre-operative values in the same subjects

	Pre-operative	6 months	12 months	24 months	36 months	48 months	60 months
	1	2	3	4	5	6	7
IgG	1270 ±296	1334 ±338	1343 ±295 $0.05 < P < 0.1$	1450 ±350 $P < 0.01$	1302 ±256	1236 ±275	1162 ±218
	(46)	(38)	(43)	(40)	(38)	(29)	(25)
IgA	210 ±86	219 ±97 $P < 0.05$	218 ±94	227 ±91 $P < 0.05$	222 ±86	220 ±98	211 ±87
	(45)	(39)	(44)	(41)	(37)	(28)	(25)
IgM	170 ±86	177 ±79 $0.05 < P < 0.1$	157 ±76	141 ±68	132 ±84 $P < 0.018$	94 ±62 $P < 0.001$	103 ±56 $P < 0.010$
	(46)	(39)	(43)	(38)	(38)	(28)	(24)
WBC	6.75 ±12.06	6.14 ±1.49	6.23 ±1.63	6.24 ±1.51 $0.05 < P < 0.1$	6.58 ±1.71	6.33 ±1.54	6.91 ±2.02
	(46)	(35)	(44)	(39)	(40)	(28)	(25)
Percentage lymphocyte counts	27.3 ±10.6	31.8 ±7.3 $P < 0.01$	33.7 ±9.4 $P < 0.001$	33.7 ±12.9 $P < 0.05$	30.6 ±8.8	34.2 ±10.8 $P < 0.05$	32.4 ±8.6 $P < 0.05$
	(44)	(35)	(44)	(40)	(40)	(27)	(25)
Absolute lymphocyte counts	1.71 ±0.62	1.91 ±0.52 $P < 0.01$	2.04 ±0.61 $P < 0.01$	2.06 ±0.79 $0.05 < P < 0.1$	1.95 ±0.58	2.11 ±0.70	2.18 ±0.69 $P < 0.05$
	(45)	(36)	(44)	(39)	(39)	(27)	(25)
Mantoux	8.0 ±9.7	6.1 ±6.9	6.3 ±7.8	3.9 ±5.4	6.3 ±7.8	8.3 ±11.6	4.2 ±6.1
	(45)	(33)	(36)	(26)	(29)	(23)	(10)
DNCB 100 µg	2.15 ±1.08	1.67 ±1.12	1.40 ±1.34	1.50 ±0.84	2.00 ±1.00	1.00 ±1.00	1.20 ±0.84
	(26)	(9)	(5)	(6)	(7)	(5)	(5)
DNCB 50 µg	1.73 ±1.23	2.12 ±0.97 $P < 0.05$	2.00 ±1.19	1.65 ±0.89	1.75 ±0.75	2.05 ±0.90	1.50 ±0.71
	(30)	(25)	(28)	(23)	(28)	(22)	(10)

Table 3. Patients treated by surgery and post-operative radiotherapy – pre-treatment and sequential post-treatment observations in recurrence-free patients. Significance levels refer to comparison with pre-operative values in the same subjects

	Pre-operative	6 months	12 months	24 months	36 months	48 months	60 months
	1	2	3	4	5	6	7
IgG	1281 ±339	1305 ±312	1386 ±354	1386 ±382	1437 ±385	1284 ±497	1182 ±344
	(16)	(17)	(15)	(15)	(13)	(6)	(8)
IgA	239 ±85	238 ±87	236 ±88	299 ±99	271 ±85	238 ±88	229 ±81
	(16)	(17)	(15)	(15)	(12)	(7)	(8)
IgM	142 ±71	145 ±83	133 ±65	136 ±76	130 ±67	105 ±36 $0.05 < P < 0.1$	105 ±43 $0.05 < P < 0.1$
	(16)	(17)	(15)	(15)	(12)	(7)	(8)
WBC	6.44 ±1.40	5.77 ±2.74 $P < 0.05$	5.68 ±2.03 $P < 0.05$	5.24 ±1.74 $P < 0.01$	5.64 ±1.74	6.18 ±2.59	5.85 ±2.16
	(18)	(17)	(15)	(15)	(13)	(9)	(7)
Percentage lymphocyte counts	28.6 ±12.1	21.1 ±6.1 $P < 0.05$	20.1 ±6.2 $0.05 < P < 0.1$	23.3 ±9.7 $P < 0.05$	24.8 ±11.1	28.2 ±10.3	24.7 ±10.4 $P < 0.01$
	(17)	(16)	(11)	(16)	(14)	(8)	(7)
Absolute lymphocyte counts	1.81 ±0.82	1.15 ±0.40 $P < 0.05$	1.11 ±0.45 $0.05 < P < 0.1$	1.13 ±0.46 $P < 0.05$	1.58 ±0.79	1.49 ±0.59	1.10 ±0.38 $P < 0.01$
	(17)	(16)	(12)	(14)	(9)	(5)	(5)
Mantoux	5.7 ±8.2	5.0 ±7.2	5.6 ±8.2	2.5 ±6.0	4.2 ±7.8	7.1 ±9.2	10.0 ±10.0
	(19)	(16)	(15)	(11)	(7)	(7)	(3)
DNCB 100 µg	2.00 ±1.35	1.00 ±1.07	0.33 ±0.58	1.60 ±1.52	0.50 ±0.58	0.50 ±0.71	–
	(13)	(8)	(3)	(5)	(4)	(2)	–
DNCB 50 µg	1.77 ±1.23	1.54 ±1.27	1.33 ±1.21	1.33 ±1.22	1.62 ±1.68	2.00 ±1.63	2.33 ±0.58
	(13)	(13)	(6)	(9)	(8)	(7)	(3)

Table 4. Patients treated by surgery – pre-treatment, pre-recurrence and post-recurrence observations in patients developing systemic recurrence. Significance levels refer to comparison with pre-operative values in the same subjects

	Pre-treatment	Pre-recurrence	Post-recurrence
IgG	1254 ±333	1350 ±411	1424 ±452 $P<0.05$
	(26)	(27)	(24)
IgA	206 ±83	223 ±99	226 ±85
	(28)	(27)	(24)
IgM	140 ±53	117 ±50 $P<0.05$	109 ±35 $P<0.05$
	(28)	(27)	(24)
WBC	7.30 ±2.10	6.73 ±1.70	6.54 ±2.44
	(27)	(26)	(24)
Percentage lymphocyte counts	31.0 ±9.1 (26)	20.1 ±8.1 (26)	28.3 ±9.3 (23)
Absolute lymphocyte counts	2.15 ±0.68	2.02 ±0.80	1.87 ±1.13 $P<0.05$
	(26)	(26)	(22)
Mantoux	6.1 ±6.3	8.1 ±7.2	8.6 ±7.9
	(28)	(19)	(13)
DNCB 100 µg	1.92 ±1.12	2.67 ±1.03 $0.05<P<0.1$	2.50 ±1.29
	(13)	(6)	(4)
DNCB 50 µg	1.69 ±1.38 (13)	2.00 ±1.16 (13)	2.30 ±1.06 (10)

Table 5. Patients treated by surgery and post-operative radiotherapy – pre-treatment and sequentially pre-recurrence and post-recurrence observations in patients developing systemic recurrence. Significance levels refer to comparison with pre-operative values in the same subjects

	Pre-treatment	Pre-recurrence	Post-recurrence
IgG	1312 ±410	1316 ±394	1318 ±399
	(19)	(21)	(17)
IgA	262 ±138	252 ±159	215 ±139
	(20)	(21)	(17)
IgM	106 ±46	118 ±39	102 ±56
	(20)	(21)	(17)
WBC	7.06 ±1.71	5.90 ±1.66	5.78 ±2.26
	(21)	(21)	(17)
Percentage lymphocyte counts	29.6 ±8.3 (20)	21.0 ±7.8 (21)	19.8 ±8.6 (17)
Absolute lymphocyte counts	2.07 ±0.72 (20)	1.28 ±0.72 (21)	1.21 ±0.67 (17)
Mantoux	8.0 ±11.3	6.8 ±9.1	1.2 ±2.0 $0.05<P<0.1$
	(22)	(16)	(11)
DNCB 100 µg	2.07 ±1.21 (14)	1.50 ±1.75 (10)	2.0 ±1.16 (4)
DNCB 50 µg	1.94 ±1.25	1.00 ±1.21	1.88 ±0.84 $P<0.05$
	(17)	(12)	(8)

Table 6. Patients treated by surgery or surgery and post-operative radiotherapy developing local recurrence

		Pre-treatment	Pre-recurrence	Post-recurrence
IgG	S	1276 ±319 (10)	1397 ±287 (10)	1426 ±271 (6)
	S+X	1258 ±317 (11)	1422 ±420 (11) $0.05<P<0.1$	1407 ±309 (10)
IgA	S	276 ±90 (10)	251 ±89 (10)	241 ±99 (6) $0.05<P<0.1$
	S+X	259 ±86 (11)	235 ±90 (11)	214 ±92 (10)
IgM	S	194 ±92 (10)	146 ±75 (10) $0.05<P<0.1$	167 ±149 (6)
	S+X	126 ±37 (11)	121 ±53 (11)	104 ±46 (9) $0.05<P<0.1$
WBC	S	5.90 ±1.57 (10)	6.13 ±1.05 (10)	5.91 ±1.00 (5)
	S+X	8.08 ±2.24 (11)	6.49 ±1.39 (10) $P<0.01$	6.94 ±1.79 (10)
Percentage lymphocyte counts	S	30.6 ±10.7 (10)	29.4 ±9.6 (10)	23.2 ±12.1 (5)
	S+X	25.6 ±7.0 (10)	22.7 ±10.3 (10)	19.5 ±8.2 (10) $0.05<P<0.1$
Absolute lymphocyte counts	S	1.66 ±0.66 (9)	1.78 ±0.51 (10)	1.29 ±0.76 (5)
	S+X	2.12 ±0.89 (11)	1.48 ±0.99 (10) $P<0.05$	1.27 ±0.48 (10) $P<0.05$
Mantoux	S	5.2 ±6.6 (9)	0.3 ±0.88 (7)	3.6 ±4.0 (5)
	S+X	9.0 ±7.3 (11)	11.7 ±9.7 (7)	3.3 ±4.7 (9) $P<0.01$
DNCB 100 µg	S	1.50 ±1.00 (4)	0.50 ±1.00 (4)	0.00 ±0.00 (1)
	S+X	2.25 ±0.50 (4)	1.50 ±2.12 (2)	1.00 ±1.41 (2)
DNCB 50 µg	S	1.50 ±1.22 (6)	1.71 ±1.50 (7)	1.20 ±1.30 (5)
	S+X	1.33 ±1.16 (3)	2.00 ±1.16 (7)	2.00 ±1.29 (7)

Discussion

General host immune competence has been widely investigated in breast cancer over the last decade. It appears evident that host defence mechanisms can destroy small number of cancer cells (10^6–10^8, the number required to seed viable growth) beyond which it escapes control by a mechanism which is yet not fully understood, though a "serum factor" has been recognised [10]. After successful surgery it is again surmised that the immunological defences

Table 7. Pre-treatment and sequential observations in patients (Stage IV) dying within or after 2 years

		Pre-operative	6 months	12 months
		1	2	3
IgG	< 24 m	1510 ±880 (19)	1314 ±501 (15)	1322 ±530 (3)
	> 24 m	1404 ±373 (13)	1514 ±494 (12)	1436 ±425 (3)
IgA	< 24 m	231 ±162 (19)	220 ±103 (15) $0.05 < P < 0.1$	213 ±103 (3)
	> 24 m	214 ±54 (11)	215 ±49 (11)	177 ±169 (3)
IgM	< 24 m	153 ±64 (19)	136 ±69 (15) $P < 0.05$	99 ±78 (3)
	> 24 m	150 ±47 (13)	161 ±79 (12)	155 ±81 (3)
WBC	< 24 m	7.05 ±2.27 (18)	7.10 ±1.95 (15)	6.13 ±0.25 (3)
	> 24 m	6.40 ±1.63 (13)	6.95 ±2.13 (12)	6.86 ±2.54 (3)
Percentage lymphocyte counts	< 24 m	22.7 ±9.2 (18)	20.0 ±11.5 (15)	19.0 ±10.8 (3)
	> 24 m	28.2 ±7.2 (13)	29.2 ±13.3 (12)	23.0 ±17.3 (3)
Absolute lymphocyte counts	< 24 m	1.50 ±0.56 (18)	1.42 ±0.60 (15)	0.89 ±0.12 (4)
	> 24 m	1.65 ±0.30 (13)	1.93 ±0.87 (12)	1.58 ±0.78 (3)
Mantoux	< 24 m	5.6 ±9.2 (19)	3.2 ±5.0 (11)	0.00 (1)
	> 24 m	7.7 ±6.5 (12)	4.0 ±5.7 (9)	6.7 ±11.5 (3)
DNCB 100 μg	< 24 m	0.67 ±1.05 (15)	0.56 ±0.53 (9)	0.00 (1)
	> 24 m	1.17 ±0.98 (6)	1.00 ±1.00 (5)	1.50 ±0.71 (2)
DNCB 50 μg	< 24 m	0.47 ±0.83 (15)	0.55 ±0.69 (11)	0.00 (1)
	> 24 m	1.17 ±0.98 (6)	1.38 ±1.30 (8)	0.50 ±0.71 (2)

recover and destroy any remaining cells [4]. It is also thought that metastasis from breast cancer is determined by the balance of "immunological" control and the aggressiveness of the tumour. A less than radical surgical approach for treatment of breast cancer has been recommended by some authoritis [2, 5], based on the premise that if the regional lymph node is involved, the tumour has overcome the host defence and gone beyond, and if not involved, it is useful in maintaining host resistance. If immune competence is of central importance, it should be possible to demonstrate this, particularly in relation to tumour mass and the dynamic changes it undergoes due to surgical removal or radiotherapeutic destruction of the tumour. It would then be possible to derive a model of general immunological change seen over sequential testing to serve as an immunological prognostic index. The inter-relationship of general immune parameters with the end results of treatment, viz recurrence-free survival, local recurrence or systemic recurrence, would become a critical feature of tumour biology, but in interpreting it one would also have to take into consideration the method of treatment.

There are many pitfalls in studies based on this concept. It is now apparent that immune competence diminishes in patients with advanced disease [7, 12] and that in this situation the behaviour of malignant disease and immune competence correlate with each other [6, 8]. The importance of studying a homogenous tumour group [3] and the effects of age, ill helath [17] and primary treatment method [10] have been stressed if meaningful analysis is to be obtained. These factors have been taken into consideration in this study. Nevertheless, the first report on the 2-year follow-up results [16] showed no relationship between immune competence and prognosis over and above that which could be predicted from standard clinico-pathological staging. Other reports in the literature show findings very similar to 2-year follow-up results [1, 14, 18]. Now after 5 years of follow-up of the same patients, a certain pattern has emerged with three aspects.

Firstly, IgM diminishes after treatment and this continues at 5 years, even though the tumour may have recurred in the meantime. The cause of this consistent change is not immediately apparent, and it appears to be independent of recurrent tumour. The second finding is that lymphocyte counts in NR patients move in opposite directions when the patients are treated by surgery and radiotherapy or by surgery alone. The previously demonstrated depression of lymphocyte counts following radiotherapy has been shown to continue for as long as 60 months, but the prognostic effect of this change in relation to radiotherapy is not known. In patients treated by surgery the lymphocyte counts actually improve. The changes in lymphocyte counts in patients developing local recurrence tend to follow the pattern of NR cases.

This study has shown that the simple parameter of lymphocyte count shows a more distinctive correlation with long-term outcome than functional tests such as the Mantoux and DNCB reaction. It suggests that future studies should concentrate on analyses of individual aspects of lymphocyte function, rather than the use of complex tests reflecting a number of immunological mechanisms.

It is disappointing that this study provides little evidence that immune competence changes immediately before recurrence – although a low pre-treatment lymphocyte count with a steady rise after surgery carries a good prognosis, and a high initial lymphocyte count with a fall after surgery is indicative of recurrence. This is clearly of great interest from the point of view of general principles of tumour biology – but not of great help in an individual patient. Where radiotherapy had been used, the effects of therapy are so profound that any dynamic changes in lymphocyte counts are obscured. However, the dynamic changes demonstrated in the lymphocyte count in breast cancer patients treated by surgery give renewed hope that further investigation of host tumour interaction may be valuable. Understanding of immune competence has progressed a long way since we commenced this study in 1972, and immune competence can now be analysed with

much greater precision. Such studies must take cognizance of the factors discussed above – study of homogenous patient groups, before treatment and associated with long-term follow-up. Short-term studies are unlikely to prove fruitful.

The tumour side of the host-tumour equation cannot be ignored. Our study has defined the characteristics of the tumour only in terms of outcome, and this may indeed be the best method of assessment of the tumour. But the rate of cell division is a fundamental determinant of the time required for any cancer to reach a state of clinical presentation or recurrence [13]. Assessment of this function simultaneously with immune competence would provide a more definitive analysis of the overall host-tumour equation.

In view of the demonstration in this study that the well-recognised post-radiation depression of lymphocyte count continues unchaged for as long as 5 years, further consideration should be given to the findings of Meyer [9] that patients treated by radiotherapy show a high incidence of second tumours.

Acknowledgement. This project was carried out under a grant from The Cancer Research Campaign.

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Received August 20, 1984/Accepted July 3, 1985