PAPERS AND ORIGINALS

Treatment of Early Breast Cancer: A Report after Ten Years of a Clinical Trial

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Summary

A controlled clinical trial has been carried out to compare radical mastectomy with wide excision (extended tylectomy) in the treatment of early breast cancer. Only patients aged 50 and over were included and 370 entered the trial during a period of 10 years. Postoperative radiotherapy was given in each case. In patients with clinically involved axillary nodes there was a significantly higher incidence of local and distant recurrence in those having a wide excision, and the survival of these patients was significantly less than those who had a radical mastectomy. In patients with clinically uninvolved nodes, although there was a significantly higher incidence of local recurrence in those having a wide excision, there was no increased incidence of distant recurrence and the survival rate was similar to those having a radical mastectomy.

Introduction

In treating cancer of any organ the removal of that organ and the lymphatic nodes most commonly affected, together with the intervening lymphatics, is seemingly a most reasonable method of procedure. This hypothesis was responsible for the development of the classical operation of radical mastectomy, which during the first half of the twentieth century came to be regarded as the routine treatment in most cases of cancer of the breast confined, so far as could be judged, to the breast and the axillary lymph nodes of the same side. Since that time, however, certain theoretical aspects of the pathology of cancer in general have stimulated inquiry into whether this original concept always applies and whether, in removing the involved organ and the field of immediate lymphatic drainage, there may not be a debit as well as a credit side to the balance sheet. More and more evidence has accumulated to the effect that, quite early in the history of many cancers, malignant cells are liberated into the blood stream. It is likely that single malignant cells, or clumps of a few cells, are not generally capable of surviving. If they do often survive then, in those cases where they are found to be circulating, the wisdom of performing a formidable operation on the local condition must be questioned. If, on the other hand, they are destroyed, as we believe, then either they die a natural death or their survival is determined by an immune mechanism. This in itself prompts the consideration of whether more is gained by removing the cancer tissue than is lost by a major operation which might disturb both the humoral and the cellular immune processes designed to suppress them.

The work of Wallace Park and Lees (1951), McKinnon (1954), and Hardin Jones (1956) suggested that the results of treatment of localized cancer of the breast, as measured by survival rates, would be equally good with minimal surgical interference as with radical mastectomy. Mustakallio (1954) reported an 84% five-year survival rate in 127 patients with clinical stage 1 cancers who had been treated only by local excision and radiotherapy. Furthermore, the experience of surgeons such as Sir Arthur Porritt at St. Mary's Hospital, London, who practised a restricted form of surgery in selected cases, and of one of us (A.B.W.), to whom was sent, for radiotherapy only, cases where the local practitioner had removed a lump which had turned out to be a cancer, encouraged the belief that the outcome in these cases might compare not unfavourably with that of patients treated by orthodox radical mastectomy with or without radiotherapy. The report of Justin Fleming and Atkinson (1961), analysing the results of 300 cases of carcinoma of the breast treated at St. Vincent's Hospital, Sydney, supported this view. At the Oncological Institute in Moscow restricted surgery with hormone therapy was freely practised in 1961.

In 1955 we considered the idea of testing the hypothesis that radical mastectomy was no more effective in preserving life in cases of early cancer of the breast than such restricted surgery as simple removal of the lump. We are indebted to Dr. W. J. Mann, who has proposed the term "tylectomy" from the Greek words "tyle" (Τύλη) or "tylos" (Τύλος) a "lump" for excision of a lump and we use the term "extended tylectomy" instead of "wide excision" throughout the paper.

Before embarking on such a trial the evidence in favour of the

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unorthodox method had to be so strong that all those engaged in the trial would be willing to allow their own relatives to enter it. As a result of the accumulation of the evidence quoted above, it seemed by 1961 not only ethical to conduct such a trial but imperative that this should be done in view of the mutilating character of one of the alternatives.

Present Trial

The trial as eventually designed was conducted as follows: the propositi were patients with carcinoma of the breast aged 50 or over who were judged suitable for radical mastectomy or extended tylectomy—namely, Manchester stages 1 or 2 (T_1 or $_2$, N_0 or $_1$). The two treatment programmes chosen by randomization were: (*a*) radical mastectomy and synoperative thiotepa in doses of 2 mg per stone (6·4 kg) body weight with premedication, 1·5 mg per stone on the second postoperative day, and 1 mg per stone on the fourth postoperative day, followed by radiotherapy; and (*b*) extended tylectomy, or wide excision, of the lump together with the surrounding breast tissue within 3 cm of palpable or visible growth and thiotepa administered as above, plus radiotherapy.

In 1961, when this investigation started, there were encouraging reports in the literature on the value of thiotepa as an adjuvant to mastectomy (Moore and Watne, 1961; Surgical Adjuvant Chemotherapy Breast Group, 1961). The drug was therefore prescribed in small doses detailed above to all patients in the series. Subsequently the improvement in survival and recurrence following the use of thiotepa was reported to be minimal and to be confined to premenopausal patients with more than three lymph nodes involved (Noer, 1963; Cole *et al.*, 1965). As all the patients in this series were aged 50 or over, and hence mostly postmenopausal, it was decided not to persevere with this therapy, and no patient entering the trial after 1968 was given adjunctive chemotherapy.

When a patient regarded as suitable for radical mastectomy was first seen randomization was carried out by drawing a ticket from a box. Before the elective treatment was carried out radiographs were taken of the chest, spine, and pelvis to exclude the presence of overt intrathoracic or skeletal metastases. More sensitive methods of detecting bony metastases were not then available. Biopsy evidence of malignancy was obtained before either operation, and the operations were carried out by a variety of trained surgeons. Because the axillary nodes were not removed pathological staging was not possible after extended tylectomy but care was taken to section all nodes included in the specimens removed at radical mastectomy.

Radiotherapy

Both groups of patients had radiotherapy but because of the different operative procedures the method of delivery had to be slightly different. Those who had radical mastectomies were given radiotherapy to the axilla, supraclavicular triangle, and internal mammary chain. Treatment was given on a 300 kV machine H.V.L. 3 mm of Cu. Field sizes were 10 by 8 cm for the axilla and supraclavicular triangle and 15 by 7·5 cm for the internal mammary chain. The supraclavicular and axillary fields were directed to cross at the apex of the axilla, giving a tumour dose at this point of between 2,500 and 2,700 rads, depending on the size of the patient. Patients were treated five days a week for 18 days. This produced a reaction of full moist desquamation in the axilla.

Those patients having an extended tylectomy were given the same course as the radical mastectomy patients except that the overall treatment time to the supraclavicular triangle and axilla was 12 days. In addition, the breast, including the internal mammary chain, was treated with parallel opposing fields on a 6 MeV linear accelerator using "Lincolnshire bolus" to bring the peak dose to the surface. A tumour dose of 3,500-3,800 rads in three weeks was given. This produced a reaction just bordering on moist desquamation.

Recurrence

In the event of recurrence each case was considered individually and the patient might receive further surgery, radiotherapy, hormone therapy, or endocrine ablation.

Cases were rejected if: (1) the lump was placed over the medial end of an intercostal space or rib (it was our practice to treat these patients, if clinically stage 1, by simple mastectomy and, if clinically stage 2, by radical mastectomy only if a biopsy of glands along the internal mammary artery showed that these were free from growth); (2) the referring doctor or the patient herself indicated that radical mastectomy was expected; (3) the patient presented with an involved gland in the axilla and no breast lump was palpable; (4) there was Paget's disease of the nipple; (5) the patient had received previous treatment for her breast cancer; or (6) there was a history of previous malignancy at another site.

The problem of informing the patient or her doctor that she was participating in a trial received careful consideration. One of us (H.J.B.A.), who was a member of the Medical Research Council's committee on the ethics of clinical trials, was able to establish to the satisfaction of that committee that, while in general terms it was preferable to inform a patient that he or she was included in a trial, when dealing with a potentially lethal condition for which the best treatment was not known, it would be improper to inform the patient that the choice of treatment was made randomly.

Follow-up

Both groups were followed up at the breast clinic and were examined clinically at three-monthly intervals for the first three years, then at six-monthly intervals for the next two years, then yearly. At these follow-up examinations routine skeletal surveys were not carried out and radiographs were taken only when the patient complained of symptoms referable to a specific bone. The two groups were assessed at frequent intervals to determine whether any difference had emerged.

In an attempt to assess morbidity and quality of life after the two procedures each patient had to answer a questionnaire during the third and fifteenth months after operation. These questionnaires tested the patients' ability to cope with their normal duties and investigated their mental attitude to what had been done. The questionnaire had been designed by the late Dr. Henry Eisenberg, of the Connecticut Tumour Registry, and has been detailed elsewhere (Eisenberg and Goldenberg, 1968). Also at these times the circumference of both arms was measured, 3 in (7·5 cm) below the acromion, 7 in (18 cm) above and 4 in (10 cm) below the olecranon, and at the wrist, to detect any postoperative lymphoedema.

When the radiotherapy reaction had settled the size and shape of the original lump were drawn with a felt marker on the skin of the opposite breast of those patients who had had extended tylectomy. A colour photograph (distance 3 ft (90 cm)) was then taken of the patient with her arms behind her head to illustrate the size of her breasts relative to the lump and the deformity to the breast resulting from the operation.

Criteria of Assessment

It was decided that three criteria were to be used in the assessment of the results: the survival rate, the incidence and site of recurrence, and disability.

At first these three criteria were measured on the two populations, considering together those patients who were judged clinically to be free from deposits in the axillary lymph nodes

and those who were judged to have deposits in the axillary lymph nodes. As more material accumulated it was possible to consider these classes separately in the two populations.

We had a great deal of difficulty in deciding how to designate these two classes. The facts were that after analysing our findings in regard to the three criteria described above, we found that if the populations were divided into one group where the notes had indicated that in the opinion of the clinician the homolateral axillary nodes were free from invasion, and into another group where these nodes were considered to have been invaded, significantly different findings emerged in the two groups so distinguished.

Such a differentiation being a clinical one we are only too aware that it is in a scientific sense imprecise and depends on care, judgement, and experience. Nevertheless, that it has significance will appear when we describe our findings. After discussion within the unit and with outside experts, we decided to call the first group by the old-fashioned term "clinical stage 1" and the other "clinical stage 2" or, for brevity, "stage 1" and "stage 2." In the TNM system stage 1 is equivalent to N_0 and N_1a and stage 2 to N_1b.

It may well be that whether or not the lymph nodes harbour a few cancer cells is unimportant and that it is the size of the population of these cells within such nodes which is crucial and which, of course, is the most important factor in determining the clinical staging. The level of correspondence between clinical and pathological staging is shown in Table I.

TABLE I—*Correspondence of Clinical and Pathological Staging in Patients having Radical Mastectomy*

	Pathological Stage 1	Pathological Stage 2	Error in Clinical Staging
Clinical stage 1 (107 cases) ..	81	26	24%
Clinical stage 2 (81 cases) ..	20	61	25%

This division into stages is the only stratification of our material which we have attempted. In a proportion of the patients the tumours have also been graded but an insufficient number has been investigated at present to warrant classification.

Criteria for Conclusion of the Trial

This investigation was unlike most of such investigations since, in addition to a significant difference between the two treatments, a determinant result could be achieved—that is, the preferred method of treatment could be determined—if, after "adequate trial," there was no difference in survival rate, in which case the less formidable procedure would then be preferred.

When the trial was designed ten years ago we did not know what method of analysis of our results would prove to be the most sensitive and we set out as our criterion of determinance that either the survival rates or the distant recurrence rates (two of the three criteria of assessment described above) should be better by 10% after one method of treatment than after the other; this 10% betterment being demonstrable at an acceptable level of statistical probability. In the event, and by the methods of analysis which were applied, this somewhat rigid definition of determinance had to be modified, but the underlying principle was retained.

We decided that the investigation would be concluded (1) when the 10% level in favour of one or other treatment had been achieved, or (2) when it could be shown that, at an acceptable probability level, a 10% betterment of one method of treatment over the other would never be achieved.

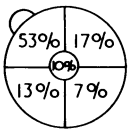
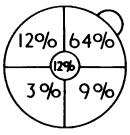
If a restricted operation were to challenge the efficacy of a more radical one, as in this investigation, the success of the former might well depend on an immune reaction to take care of the small number of cancer cells, perhaps inevitably, left behind. We might be criticized therefore in that it was illogical to add cytotoxic drugs and radiotherapy (both of which agents might be supposed to damage the immune response) to the programmes of treatment in the two contrasted populations. We have no reply to this charge except to say that in 1961 when the trial began the evidence that cytotoxins and radiotherapy were damaging to the immune response was not sufficiently persuasive and we have so far modified our protocol only in respect of cytotoxins which are now no longer prescribed in either population.

Results

Throughout the ten years of the trial the death and recurrence rates of the two populations, taking stage 1 and stage 2 cases together, were monitored continuously by means of pegs on extensible threads, so that on any day it was possible to see at a glance the number of deaths and recurrences recorded in the two populations and any difference was readily appreciated. During all these years the pegs representing the survival of the two populations moved on almost in step so that at no time were we fearful that one method of treatment was curtailing the survival period of one population in respect of the other.

So far 370 patients have entered the trial. Of these, 188 have had a radical mastectomy and 182 an extended tylectomy. The average age of patients subjected to extended tylectomy was 61·0 years and to radical mastectomy 60·9 years. Other factors, such as average length of history and siting of the lumps within the breast, were sufficiently equally distributed between the two populations as to make them scientifically comparable (Table II).

TABLE II—*Comparison of Related Factors in the Two Populations*

		Radical	Excision
Tumour size	<1 in (<2·5 cm)	53 (28%)	54 (30%)
	1-2 in (2·5-5·0 cm)	89 (47%)	96 (53%)
	>2 in (>5·0 cm)	46 (25%)	32 (17%)
Length of history	< 4 weeks	76 (40%)	71 (39%)
	4-12 weeks	54 (29%)	58 (32%)
	>12 weeks	58 (31%)	53 (29%)
Family history: total		36	34
Site: % incidence			
Premenopausal		14	21
Postmenopausal		174	161
Mean age in years		60·9	61
Clinical stage 1		108	112
Clinical stage 2		80	70

SURVIVAL

A life table was calculated to compare the survival experience of the two populations (Fig. 1). In studying the graph of this life table it must be appreciated that significance can be attached only to the early stages (towards the left end of the abscissa) because here large numbers are involved. Each year the number of cases under study becomes progressively fewer and at 10 years the numbers are so few that conclusions can be drawn only with the greatest caution. No significant difference between the results of the two operations can be detected at any time up to 10 years after treatment.

After the series had continued for 10 years a sufficient number of patients had been treated, so that it was possible to separate

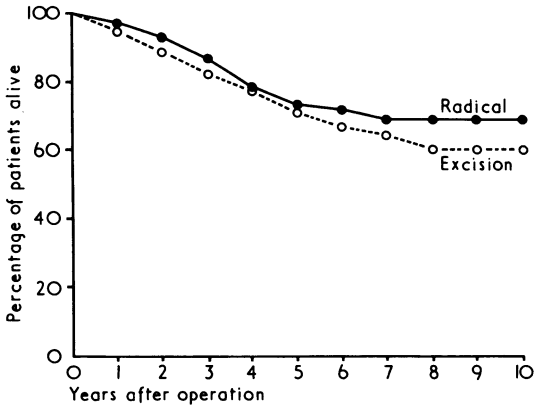


FIG. 1—Survival proportions—all cases.

the stage 1 cases from the stage 2 cases. A second life table was constructed to compare the survival after each operation of patients with clinically stage 1 or stage 2 tumours (Fig. 2).

A statistical analysis of these results shows that in stage 2 cases radical mastectomy gives significantly better survival than that given by extended tylectomy at 10 years ($0{\cdot}025 < P < 0{\cdot}05$) but not at five years ($0{\cdot}3 < P < 0{\cdot}4$). However, the difference between radical mastectomy and extended tylectomy for the two groups of patients with stage 1 tumours in favour of extended tylectomy is not significant.

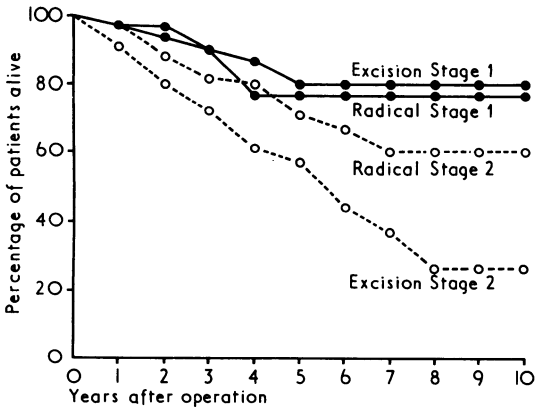


FIG. 2—Survival proportions according to stage.

LOCAL RECURRENCE

For the purpose of this study local recurrence has been defined as recurrent growth in the lymph nodes in the homolateral axilla, supraclavicular fossa, or internal mammary chain, or cutaneous deposits occurring in an area bounded superiorly by the clavicle, inferiorly by the costal margin, medially by the midline, and laterally by the posterior axillary line. In patients treated by extended tylectomy, recurrent tumour in the homolateral breast has also been considered as a local recurrence. Recurrence has been confirmed histologically except when there has been associated widespread distant disease.

The local recurrence rate in the two populations can be estimated by a life table and this is illustrated for stage 1 cases in Fig. 3 and for stage 2 cases in Fig. 4. For both groups of patients there is a significantly greater recurrence rate in those that had an extended tylectomy. The distribution of local recurrence is given in Tables III and IV. In nearly 50% of the patients with stage 2 tumours the local recurrence presented as part of widespread disease. When not accompanied by development of distant metastases, local deposits could usually be successfully treated by further local surgery. The treatment given to these patients is detailed in Tables V and VI. Five patients originally treated by extended tylectomy subsequently

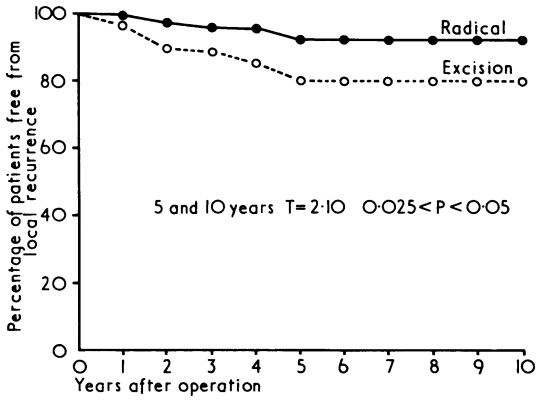


FIG. 3—Proportions free from local recurrence—stage 1 cases.

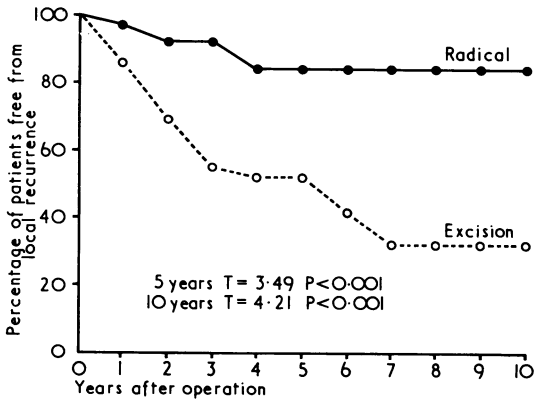


FIG. 4—Proportions free from local recurrence—stage 2 cases.

TABLE III—*Distribution of Local Recurrence in Patients having an Extended Tylectomy*

Site	Clinical Stage 1	Clinical Stage 2	Total
Axilla	7	13	20
Cutaneous	2	8	10
Breast	0	3	3
Supraclavicular fossa	1	1	2
Multiple (axilla 8, cutaneous 6, breast 3, supraclavicular fossa 3, internal mammary chain 1)	5	5	10
	15	30	45

TABLE IV—*Distribution of Local Recurrence in Patients having a Radical Mastectomy*

Site	Clinical Stage 1	Clinical Stage 2	Total
Cutaneous	4	8	12
Supraclavicular fossa	0	1	1
	4	9	13

TABLE V—*Surgical Treatment of Local Recurrence in Patients having an Extended Tylectomy*

Treatment	Clinical Stage 1	Clinical Stage 2	Total
Excision supraclavicular fossa node	1	0	1
Radical mastectomy	2	1	3
Simple mastectomy	0	2	2
Excision axillary nodes	7	8	15
Excision skin nodules	2	2	4
Excision further breast lump	0	1	1
Total	12	14	26
Subsequent distant recurrence	6	7	13
Currently free from disease	6	7	13

TABLE VI—*Surgical Treatment of Local Recurrence in Patients having a Radical Mastectomy*

Treatment	Clinical Stage 1	Clinical Stage 2	Total
Excision skin nodules	1	1	2
Subsequent distant recurrence	0	1	1
Currently free from disease	1	0	1

had a mastectomy. Thirteen (42%) of the 31 extended tylectomy patients who developed a local recurrence without simultaneous widespread dissemination are currently free from disease.

DISTANT RECURRENCE

Distant recurrence has been regarded as spread of the disease beyond the limits defined in the section on local recurrence. In this study a carcinoma developing in the opposite breast has been regarded as a distant recurrence although it has been treated in the same way as the carcinoma in the first breast if there were no other evidence of spread.

In patients with stage 2 tumours the incidence of distant recurrence is significantly greater in those having an extended tylectomy than in those having a radical mastectomy (Fig. 5). There is no significant difference in the distant recurrence rate in patients with stage 1 tumours treated by either surgical procedure (Fig. 6).

If we consider the survival rates and recurrence rates together, the following considerations emerge with a greater or lesser degree of conviction. The higher rate of distant recurrence in stage 2 patients treated by extended tylectomy as compared with those treated by radical mastectomy mirrors the diminished survival rate in these patients. The higher rate of local recurrence in stage 1 patients treated by extended tylectomy seems to have little or no effect on the survival rate in this group.

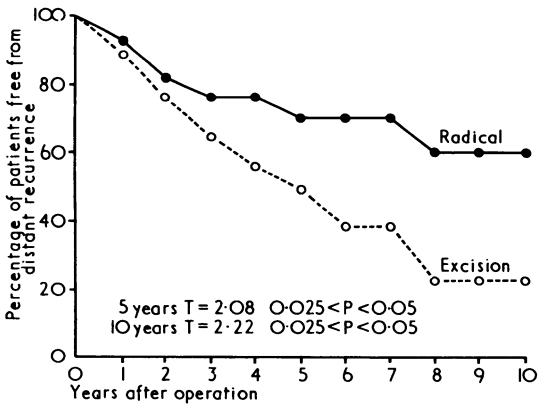


FIG. 5—Proportions free from distant recurrence—stage 2 cases.

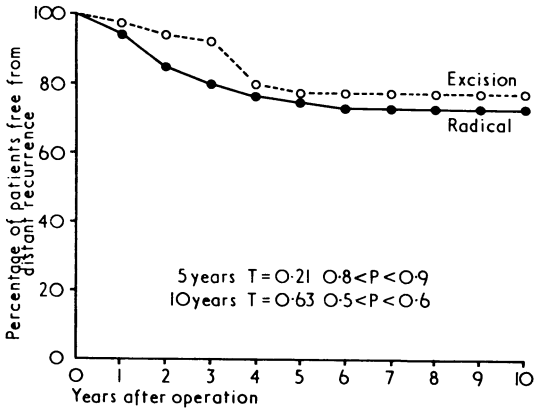


FIG. 6—Proportions free from distant recurrence—stage 1 cases

DISABILITY

In the treatment of early breast cancer the principal reason for advocating an extended tylectomy rather than a mastectomy is that the local deformity and morbidity should be less. Nevertheless, in this series an extended tylectomy did not leave a good cosmetic result in all circumstances. If the lump was big and the breast small an extended tylectomy (defined above as removing 3 cm of normal breast tissue round the tumour) resulted in considerable deformity. Not only was the cosmetic result bad but also it was difficult to fit a prosthesis. On the other hand, when a small tumour was removed from a big breast there was minimal alteration in the size and shape of the breast, and a good cosmetic result was obtained in a patient in whom a mastectomy would have resulted in considerable mutilation.

Table VII summarizes the main findings of an analysis carried out on the answers to the questionnaires set at 3 and 15 months after operation. It can be seen that three months after operation arm movements are more restricted in radical mastectomy patients than in those who had an extended tylectomy, but the difference disappears after 15 months. Also the patients' activity status and their attitude to what has been done are similar by 15 months after either operation. Only in the case of lymphoedema is there persistent higher incidence in radical mastectomy patients.

The only complication experienced by patients receiving extended tylectomy, but not those having a radical mastectomy, resulted from the course of irradiation to the breast. In a number of cases considerable fibrosis of the breast and sometimes "marbling" of the overlying skin resulted. Occasionally it was extremely difficult to distinguish between this fibrosis and

TABLE VII—*Evaluation of Quality of Survival at 3 and 15 Months after Operation (N.B. Only a Proportion of Patients have been Assessed. The Patients Interviewed at 15 Months are not necessarily the same as Those Interviewed at 3 Months)*

Type of Surgery	No. of Cases	Months	Arm Function		
			Good	Fair	Poor
Radical mastectomy	90	3	44 (49%)	41 (46%)	5 (5%)
Extended tylectomy	77	3	59 (77%)	18 (23%)	—
Radical mastectomy	100	15	83 (83%)	14 (14%)	3 (3%)
Extended tylectomy	88	15	70 (80%)	17 (19%)	1 (1%)

Good = Uses arm freely. Fair = Cannot do usual tasks. Poor = Very unsatisfactory use of arm.

Type of Surgery	No. of Cases	Months	Lymphoedema			
			None	Slight	Moderate	Severe
Radical mastectomy	93	3	18 (19%)	66 (71%)	6 (6%)	3 (4%)
Extended tylectomy	81	3	36 (44%)	43 (53%)	—	2 (3%)
Radical mastectomy	104	15	27 (26%)	71 (68%)	6 (6%)	—
Extended tylectomy	91	15	39 (43%)	52 (57%)	—	—

Slight = 0-2·5 cm. Moderate = 2·5-4·5 cm. Severe = > 4·5 cm.

Type of Surgery	No. of Cases	Months	Activity		
			Good	Fair	Poor
Radical mastectomy	92	3	45 (49%)	46 (50%)	1 (1%)
Extended tylectomy	80	3	62 (77%)	16 (20%)	2 (3%)
Radical mastectomy	101	15	85 (84%)	14 (14%)	2 (2%)
Extended tylectomy	92	15	78 (85%)	13 (14%)	1 (1%)

Good = Normal activity, back at work, or resumed usual activities involving self and family. Fair = Light work only because of operation; has not resumed usual social and recreational activities. Poor = Inactive.

Type of Surgery	No. of Cases	Months	Attitude		
			Good	Fair	Poor
Radical mastectomy	92	3	81 (88%)	9 (10%)	2 (2%)
Extended tylectomy	80	3	71 (89%)	7 (9%)	2 (2%)
Radical mastectomy	101	15	91 (90%)	8 (8%)	2 (2%)
Extended tylectomy	92	15	87 (94%)	5 (6%)	—

Good = No complaints. Fair = Complaint about some aspects of experience. Poor = Very unhappy about experience.

induration due to recurrence of the carcinoma. Indeed, on one occasion a mastectomy was subsequently carried out in the mistaken belief that the tumour had recurred. The "marbling" also could be very unsightly but was experienced only rarely and neither complication presented in more than 5% of cases.

Discussion

The analysis of the life tables referring to survival indicates the superiority of radical mastectomy in stage 2 patients. This finding was sufficiently determinant to persuade us that in regard to these patients the trial should be stopped, and stage 2 patients are now treated by radical mastectomy.

However, if we recall that the survival of stage 1 and stage 2 patients taken together is, in regard to the significant parts of Fig. 1, the same for both populations a superiority for extended tylectomy in stage 1 patients might be postulated if this redress is to be achieved. At present there is no convincing evidence that this is so, and therefore, acting on the dictum of Bradford Hill (Atkins, 1968), that if a trial was ethical to start with it is unethical to conclude it until an acceptable result has been achieved, the trial on stage 1 patients will continue.

It is of interest to observe that of the 15 stage 1 patients treated by extended tylectomy who developed local recurrence, the recurrence in 13 was in lymph nodes. It is questionable therefore whether simple mastectomy would have prevented the local recurrence in these 13 patients. It was more likely to have resulted from gross discrepancies between clinical and pathological staging. We are less interested at this stage in the equally significant increase in local recurrences in stage 2 cases after extended tylectomy as these patients are now submitted to radical mastectomy.

The analysis of quality of survival shows a surprisingly high incidence of lymphoedema and limitation of arm function in patients having an extended tylectomy. This probably results from the radiotherapy treatment to the axilla. Also, within the compass of our analysis, removal of the breast was tolerated almost equally as well as wide excision of the lump. After either procedure only about 10% of the patients had other than a reasonable acceptance of what had been done.

COMPARISON WITH OTHER TRIALS

This report is essentially factual and the reader is invited to draw his own conclusions. No comment is made on the relative value of simple mastectomy versus removal of the lump, nor of simple mastectomy versus radical mastectomy. Nevertheless, two other trials have been reported in which a radical operation has been compared with a lesser procedure. In one trial Kaae and Johansen (1968, 1969) compared on a random basis simple mastectomy plus radiotherapy with extended radical mastectomy without radiotherapy. They were unable to show any appreciable difference in survival or in local or distant recurrence up to 10 years after either operation. Comparisons between series are dangerous because many unknown factors may be affecting the results. Nevertheless, there are certain features of Kaae and Johansen's trial and of the current investigation on which comment can be made. Their patients having a simple mastectomy received a slightly higher dose of radiotherapy to the axilla than our patients having an extended tylectomy. Calculated as a tumour dose, using Ellis's formula (Winston *et al.*, 1969) for correction of dosage to time and fractionation, the axilla of the patients having extended tylectomy in the present series received 2,700 rads whereas the patients having simple mastectomy in Kaae and Johansen's trial received 3,286 rads, or nearly 18% more.

In stage 1 cases the fate of the patients in the two trials is almost identical and it is only in stage 2 patients that a difference between the treatments is noted in the current series which is not present in Kaae and Johansen's patients. The five-year figures for stage 2 patients in the two trials (Table VIII) show that whereas the incidence of local recurrence is higher in the present series (precise comparison here is difficult because the definitions of local recurrence differ), survival and the incidence of distant recurrence in Kaae and Johansen's simple mastectomy patients is almost identical with our extended tylectomy patients. On the other hand, survival or local and distant recurrence is much better in our patients having radical mastectomies than in Kaae and Johansen's patients having extended radicals. It seems possible that the reason why they were unable to show a difference between simple mastectomy and extended radical mastectomy in their stage 2 patients was not that their simple mastectomy patients did well but that their extended radical patients did badly. The reason for this is not clear.

TABLE VIII—*Survival and Recurrence Incidence of Stage 2 Patients in Kaae and Johansen's Trial and the Present Series*

	No. of Cases	5-year Survival (%)	Local Recurrence (%)	Distant Recurrence (%)
Kaae and Johansen:				
Simple mastectomy ..	70	46	26	59
Extended radical mastectomy	65	48	37	58
Guy's Hospital:				
Extended tylectomy ..	70	56	48	52
Radical mastectomy ..	80	72	16	30

In another trial, Brinkley and Haybittle (1966, 1971) compared radical mastectomy with simple mastectomy in patients with clinically stage 2 breast cancer. Both groups of patients received postoperative radiotherapy. They were unable to show any appreciable difference in survival or recurrence up to ten years after operation. The difference between their results and ours is unlikely to be explained by the retention of the breast in the extended tylectomy patients. In our trial, if as primary treatment a simple mastectomy rather than an extended tylectomy had been carried out, there would probably have been little difference in the local recurrence rate. Recurrence in the breast was a rare development. Also the radiotherapy regimen in their trial was almost identical with ours. Calculated as a tumour dose the simple mastectomy patients in Brinkley and Haybittle's trial were given 2,760 rads to the axilla compared with the 2,700 rads received by our patients. However, a large number of Brinkley and Haybittle's patients having simple mastectomy also had some dissection of the axilla, sufficient at least in 79% of the patients to comment on the histology of the nodes. Our current results suggest that if an excessive incidence of local recurrence and probably distant recurrence is to be avoided, clinically involved axillary nodes must be removed at the primary operation.

Our results suggest that there is no one treatment that should be applied exclusively to all cases of cancer of the breast at the stage of the disease when radical mastectomy is a practicable proposition. The importance of clinical staging would seem to be decisive and this would imply the exercise of clinical judgement and the value of experience. To what extent such judgement could be refined by the preliminary biopsy of a palpable axillary node remains to be determined (Lalanne, 1968; Forrest *et al.*, 1970); but it has been shown that the presence of very small deposits in the lower axillary nodes, which is all that could be detected by such a biopsy, probably has little influence on the prognosis of the disease (Huvos *et al.*, 1971).

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Effect of a Hot Milk Drink on Movements During Sleep

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Summary

The effects on sleep of a hot drink of milk and Horlicks were compared with those of hot water taken before retiring by medical student volunteers. Horlicks reduced the number of small movements made during sleep.

Introduction

Many people are dissatisfied with the way they sleep. In 1970 there were 20 million (8% of the total) National Health Service prescriptions for hypnotics (Parish, 1971), presumably mainly used to make patients more satisfied with their sleep. Some take hot drinks at bedtime under the impression that it helps them to go to sleep or to sleep better. The present work is concerned with testing one aspect of this impression by studying movements during sleep. It was found that a hot milk drink, Horlicks, did reduce the number of small movements made by a sleeper in the period from 4 to 7 a.m.

Methods

Records of movements during sleep were made by time lapse cinematography with a 16-mm camera silenced with a hood. A frame was taken every 15 seconds of the subject in dark pyjamas sleeping without bed covers on a white sheet in front of a white screen. On the screen was a clock and a calendar. The sleep room was moderately warm, 20° to 23°C, and there was a radiant electric fire which the subjects adjusted so that they were comfortable *without bed covers*. The room was lit by two tungsten bulbs, 100 and 150 watts, about 15 feet (4·6 m) from the bed.

Procedure.—The subjects, four male medical students without disorders of sleep, came to the sleep room between 11 and 11.30 p.m. They had agreed to take no coffee, alcohol, or strenuous exercise for that evening. On arrival at the sleep room the subjects took either no drink (control), or 350 ml of warm water, or 350 ml of warm milk plus five large heaped teaspoons of Horlicks powder. They then lay down and fell asleep. Each subject slept at least three and up to twelve times under the experimental conditions to accustom himself to them before the results were recorded. For the experiment each subject slept twice under each of the three conditions arranged in a block to take out any effect of order of experimental condition.

Analysis.—The film was projected slowly until a change in position was detected. After running back it was projected frame by frame, counting the recorded changes of position. These were divided into two categories: (1) big changes in which the trunk was turned or translocated without turning, and (2) small changes involving hand, foot, or head, or more than one of these. Small changes of position during large changes were ignored. The basic unit was a frame of movement. If there were movements in successive frames, and provided that no more than two frames without change of position were interposed between frames of movement, the several frames were classified as a "sequence." Because on some occasions the subjects were still awake at midnight only the records from 1 to 7 a.m. were analysed.

Statistical Methods.—The lines of the Chart were fitted by the method of least squares. To assess the differences between frequencies of movements under the three conditions the number of small movements during the first hour on the first occasion with Horlicks was subtracted from the number of small movements during the first hour on the first occasion with water. These differences tended to increase as the night passed. The differences were plotted against time, and a rectilinear regression was fitted by the method of least squares. The difference from zero of the slope of this line divided by the standard error of the slope was used to assess the statistical significance of the difference between the effects of water and Horlicks. To assess the differences in the variability of the movements the ratios of movements/hour, after taking out the variance due to regression, were used. All values of probability (P) were arrived at without preconception—that is, two-tailed.

Results

The four subjects were studied for six hours each with two replications under three conditions, no drink (control), water, or Horlicks, a total of 144 hours between 1 and 7 a.m. There were 500 frames of movements after no drink (control), 418 after water, and 412 after Horlicks.

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