CLINICAL RESEARCH

Low dose β blockade in acute stroke ("BEST" trial): an evaluation

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Abstract

The β blocker stroke ("BEST") trial was designed to see if the apparent protective effect of propranolol on cerebral function in patients with subarachnoid haemorrhage applied also to patients suffering from acute stroke. Three hundred and two conscious patients with clinically diagnosed hemispheric strokes sustained within the past 48 hours were randomly assigned to receive atenolol, propranolol, or matching placebo capsules for three weeks. More early deaths occurred among the patients allocated to receive β blockers, but this was largely explained by differences in the initial characteristics of the patients among the different treatment groups. By contrast, the outcome in a further 60 patients, who had been taking β blockers at the time of their stroke but were otherwise similar to the patients in the trial, was considerably better, suggesting that prior treatment with β blockers might be protective.

The search for an effective medical treatment for acute stroke must continue. The approach used here, in which neurological outcome was assessed in a modest number of patients with a view to proceeding subsequently to a full scale trial of functional outcome, allows practical benefits of a treatment to be evaluated under realistic conditions and an ineffective treatment to be eliminated without undue cost.

Introduction

Successful medical intervention to limit the extent of brain damage in patients with acute stroke could potentially reduce a great burden of disability in the community. Nevertheless, despite many different approaches to treatment none has achieved universal recognition.[1] Until recently most trials suffered from serious methodological flaws, in particular uncertainties over selection of patients, insufficient numbers of patients to detect a clinically useful effect, and use of unsuitable measures to assess outcome.[2-4]

Steiner and Clifford-Rose tried to deal with the clinical and pathological diversity of stroke by restricting their studies to patients with lesions of one particular type.[5] Such a process of selection may exclude many patients who might benefit from treatment, and the need to categorise the type of stroke by early computed tomography not only delays treatment but puts it beyond the reach of most patients with stroke in the United Kingdom, who are unlikely to have such an examination. Another approach, of widening the selection criteria and recruiting more patients[6] carries the danger that too many high risk patients will be included, resulting in high mortality and raising an ethical dilemma: death may be postponed in some patients, but only at the expense of an increased incidence of severe disability.

In this study we used the second, pragmatic approach but included only patients who were conscious and able to swallow drugs on admission, thereby excluding those at highest risk. We tried to use simple valid measures of functional outcome, concentrating on the number of patients who achieved a good result rather than trying to differentiate between the two undesirable outcomes of death and severe disability.

Animal experiments[7] and studies on people with stroke[8] showed that propranolol may reduce metabolic demand in ischaemic brain tissue and may therefore have a protective effect on cerebral function. β Blockade limits the cardiac[9] and neurological[10] damage mediated by catecholamines that occurs in patients with subarachnoid haemorrhage. Our aim was to investigate whether these benefits might be extended to patients with stroke and to distinguish cardiovascular effects from possible effects on cerebral metabolism. To this end we compared the effect of a lipophilic drug, propranolol, which penetrates brain tissue, with that of a hydrophilic drug, atenolol, which does not.[11]

Patients and methods

From 1983 to 1985 a register was kept of all patients admitted with acute stroke to the medical wards of this hospital and Nottingham City Hospital. The wards were visited each day by one of two clinical investigators, who assessed all patients with transient or persistent neurological deficits. Strokes were diagnosed clinically by exclusion of other possible causes.[12] Computed tomography was not routinely available at this time, so that most

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patients were characterised on clinical grounds. The results of this survey on the natural course of stroke were then used to determine the criteria for entry to the trial. These were that the patients should (*a*) have been seen within 48 hours after the onset of a hemispheric stroke; (*b*) be conscious and able to swallow tablets; (*c*) not have pre-existing major physical or mental disability; (*d*) not have been taking a β blocker; (*e*) not have contraindications to treatment with β blockers (for example, a heart rate of ≤56 beats/min; a systolic blood pressure of <100 mm Hg; second or third degree heart block; heart failure or bronchospasm causing dyspnoea at rest; a history of asthma or insulin-dependent diabetes; and (*f*) not have evidence of acute myocardial infarction or other cause of seriously reduced cerebral perfusion.

ENTRY PROCEDURE

Patients who satisfied these criteria were randomly allocated to one of three treatment groups: one group was given a placebo, one atenolol 50 mg daily, and one slow release propranolol 80 mg daily. Randomisation was done in blocks of three with separate schemes for each hospital. The container with the next serial number was selected and the first capsule given by the investigator to make sure that it was taken properly, the exact time being noted. Treatment was continued for three weeks or until discharge, whichever was sooner. The investigators remained blind to the treatment until the end of follow up except in one case, in which the treatment code was broken after the trial drug had been withdrawn. All other aspects of management were left to the medical team who admitted the patients; drugs, apart from other β blockers, were not restricted.

All patients, or the closest relatives of those who could not communicate adequately, were asked for their informed consent; relatives were also fully informed about the trial. The protocol was approved by the ethical committees of both hospitals.

Sixty patients were excluded from the trial because they were already taking β blockers, but they were followed up in the same way as the patients in the trial; 24 had their β blockers stopped on admission to hospital and 36 resumed their treatment within 72 hours after their stroke.

ASSESSMENT OF OUTCOME

Patients were examined neurologically on the day of entry to the trial (day 1), on day 8, and at one and six months; full functional assessments were made from day 8 onwards. Details of the neurological and functional assessment scales have been reported elsewhere.[13] In virtually all cases individual patients were followed up by one investigator.

To assess the effect of treatment on neurological recovery we compared the number of individual neurological signs showing improvement between examinations in the three groups. A pilot trial had shown that about 100 patients per group would be sufficient for this[13] (see below), but that many more would be needed for a comparison of functional outcome, so a second stage of the trial was planned for this comparison. To measure functional outcome we (*a*) assessed activities of daily living on an ordinal scale designed for patients with stroke[14] and (*b*) compared the number of days spent in hospital, or under nursing care, within the six months of follow up. As all randomised patients were assessed death had to be included on the scale of outcomes and was therefore regarded as equal to the worst neurological and functional outcome; for length of stay in hospital patients who died were regarded as if they had stayed in hospital for the duration of the trial. A form of survival analysis could then be performed, with discharge from hospital rather than death as the terminating event.

STATISTICAL ANALYSIS

Data were analysed by computer at the University of Nottingham with the SPSSX package. Treatment codes were entered at the end of the study after all other data had been checked.

Categorical outcomes (for example, deaths and discharges) were compared using χ^2 tests and confidence intervals for proportions calculated using the binomial approximation to the normal distribution. Logistic regression models were used to adjust for important confounding factors, and the log rank test and the Lee-Desu statistic were used to test for significant differences between patient groups in the survival analysis for the length of stay in hospital.

The distribution of neurological changes was negatively skewed, and a square transformation ($y=(x+10)^2$) was applied to stabilise variance[13]; the groups of patients were then compared by Student's *t* test or one way analysis of variance. The distribution of scores in the assessment of activities of daily living could not be normalised, so non-parametric tests (the Mann-Whitney or Kruskal-Wallis tests) were used for comparisons between groups.

SIZE OF TRIAL: POWER CALCULATIONS

From the variance in the transformed neurological scores obtained in our pilot trial[13] we estimated that a trial with 100 patients per group would have an 80% chance of detecting a significant difference ($p<0·05$) if patients in one group showed greater improvement than patients in the other by an average of one neurological item during the first week. Conversely, the second phase of the trial would require 250 patients in each group to have an 80% chance of detecting a 20% change in the proportion of patients discharged home within six months.

Results

BASELINE CHARACTERISTICS OF TREATMENT GROUPS

In all, 302 patients were recruited to the trial; table I compares the three treatment groups in terms of important prognostic factors. The random allocation resulted in groups that were well matched except for a preponderance of drowsy patients in both groups receiving β blockers and of patients with other adverse features in the group receiving propranolol.

TABLE I—*BEST trial: comparability of patients in three treatment groups at entry to trial. Figures are numbers of patients except where otherwise stated*

	Treatment		
	Placebo (n=100)	Atenolol (n=101)	Propranolol (n=101)
Male	49	53	57
Mean age (years)	68·9	70·4	68·7
Aged ≥70	51	64	54
Living alone	37	36	40
Previous stroke or transient ischaemic attack	24	27	22
With impaired mobility before stroke	10	13	13
With urinary incontinence before stroke	4	4	2
With mental impairment before stroke	3	4	3
Drowsy at entry	24	32	39
Incontinent at entry	51	57	59
With high severity score*	20	18	26
With low severity score†	50	46	34
Mean time from onset of stroke to entry (hours)	25·3	22·0	24·8

Severity score is *high if patients show four or five, and †low if they show none or one, of the following: drowsiness on admission; disorientation in time or place (or not assessable owing to severe dysphasia); complete hemiplegia; failure of conjugate gaze towards weak side; perceptual deficit (sensory inattention or visual field defect).

CARDIOVASCULAR EFFECTS OF TREATMENT

The haemodynamic effects and side effects of the drugs used had been established in the open pilot trial, and a pharmacokinetic study confirmed that adequate blood concentrations of atenolol and propranolol were being achieved. Changes in heart rate and blood pressure associated with treatment were similar in the pilot study and this trial; heart rate was reduced by 10-15% in patients receiving either β blocker, compared with those taking placebo, and mean blood pressure during the first 24 hours of treatment fell by 9% in the patients taking atenolol and by 6% in those taking propranolol, significantly more than the 2% fall in those taking the placebo.

OVERALL OUTCOME

Table II shows the state of patients in the three treatment groups at one week, one month, and six months. Deaths were more common among the patients taking β blockers compared with those taking the placebo even when the results were stratified by the initial level of consciousness, though the difference was not significant. The proportion of patients achieving a good outcome—that is, living at home—at six months showed smaller differences between the groups.

Differences in the number of deaths at one week between patients given placebo and those given propranolol were greater among patients aged 70 or over, regardless of their level of consciousness. When all ages were combined eight more deaths occurred in the first week in patients given atenolol and 12 more in patients given propranolol than in patients given placebo. Eight of these "excess" early deaths were ascribed to primary brain damage, six to bronchopneumonia, five to pulmonary embolism, and one to myocardial infarction.

Severity of hemiparesis may be another confounding factor in comparisons of treatments and was not included in table I. More patients treated

with propranolol were severely affected, and the small differences in outcome between treatment groups were virtually confined to the 55% of patients who initially had some movement on the affected side.

Table III shows differences in baseline characteristics and in outcome between patients in the trial and patients who were excluded because they were already taking β blockers. Patients who were already taking β blockers, particularly those whose treatment was resumed after admission, had a more favourable outcome in terms of death and discharge from hospital, but they tended to be younger and to have a lower prevalence of urinary incontinence initially.

TABLE II—*State of patients in three treatment groups during trial. Figures in parentheses are percentages*

	Time during trial								
	1 Week			1 Month			6 Months		
	At home	In hospital	Dead	At home	In hospital	Dead	At home	In hospital	Dead
Placebo (n=100)	9	88	3	33	53	14	64	13	23
Atenolol (n=101)	11	79	11	32	44	25	56	11	34
Propranolol (n=101)	8	78	15	22	52	27	58	10	33
95% Confidence interval*				(−5 to +17)		(−22 to −2)	(−4 to +20)		(−21 to +1)
Outcome by conscious level									
Alert (n=207)	27 (13)		9 (4)	86 (42)		23 (11)	144 (70)		40 (19)
Placebo (n=76)	9 (12)			33 (43)		6 (8)	54 (71)		13 (17)
Atenolol (n=69)	11 (16)		4 (6)	32 (46)		6 (9)	48 (70)		12 (17)
Propranolol (n=62)	7 (11)		5 (8)	21 (34)		11 (18)	42 (68)		15 (24)
Drowsy (n=95)	1 (1)		20 (21)	1 (1)		43 (45)	34 (35)		50 (53)
Placebo (n=24)			3 (13)			8 (33)	10 (42)		10 (42)
Atenolol (n=32)			7 (22)			19 (59)	8 (25)		22 (69)
Propranolol (n=39)	1 (3)		10 (26)	1 (3)		16 (41)	16 (40)		18 (47)

*Placebo *v* combined β blockers.

TABLE III—*Characteristics and outcome in patients in the BEST trial compared with patients taking β blockers at onset of stroke. Figures are numbers (percentages) of patients unless otherwise stated*

		Patients already taking β blockers		
	Patients in BEST trial (n=302)	All (n=60)	β Blockers stopped at admission (n=24)	β Blockers resumed within 72 hours (n=36)
Age (years):				
<60	54 (18)	16 (27)	6 (25)	10 (28)
60-69	79 (26)	21 (35)	6 (25)	15 (42)
70-79	112 (37)	19 (32)	9 (38)	10 (28)
≥80	57 (19)	4 (7)	3 (13)	1 (3)
Mean age (years)	69·5	66·2	69·0	64·3
Drowsy on day 1	95 (31)	19 (32)	10 (42)	9 (25)
Incontinent on day 1	167 (55)	29 (48)	13 (54)	16 (44)
With high severity score*	64 (21)	13 (22)	6 (25)	7 (19)
With low severity score*	130 (43)	24 (40)	7 (29)	17 (47)
Outcome at 6 months:				
At home	178 (59)	45 (75)	16 (67)	29 (81)
In hospital	34 (11)	5 (8)	2 (8)	3 (8)
Dead	90 (30)	10 (17)	6 (25)	4 (11)

*See footnote to table I.

TABLE IV—*Number (percentage) of discharges and deaths in each treatment group after adjustment for confounding factors by logistic regression*

	Patients home at 1 month		Patients dead at 1 month	
	Observed	Expected	Observed	Expected
Placebo (n=100)	33	32	14	20
Atenolol (n=100)	32	30	25	23
Propranolol (n=100)	22	28	27	25
Patients in BEST trial and patients taking β blockers after allowing for conscious level, continence, severity of hemiparesis, and age				
Patients in BEST trial (n=300)	87 (29)	93 (31)	66 (22)	66 (22)
Patients taking β blockers (n=60)	25 (42)	21 (35)	7 (12)	12 (20)

Table IV shows the effect of treatment on outcome after adjusting for the effects of conscious level, bladder control, and age by logistic regression. Although these adjustments did not entirely eliminate the apparent adverse influence of β blockers in patients in the BEST trial, the residual effect was small. Comparison of the observed and expected outcomes in patients in the trial with those in the patients taking β blockers at the time of their stroke suggested that much of the apparent difference in the rate of discharge was accounted for by confounding variables but that the difference in mortality was due to other factors. Logistic regression formulas for some of these models are given in the appendix.

NEUROLOGICAL CHANGES

Table V shows the mean neurological changes in the various treatment groups after a square transformation. On average, during the first week or month, neurological improvement was greatest in the patients treated with placebo. Patients given propranolol seemed to show greater improvement than those given atenolol, and when the two β blocker groups were combined the comparison with placebo was significantly different at the 2% level. The time course of neurological recovery seemed to be similar in the patients in the trial and those already taking β blockers.

FUNCTIONAL OUTCOME

Table VI records the scores for activities of daily living in the three treatment groups. At one month, differences between groups (in favour of placebo) were significant at the 5% level, but by six months the differences had decreased and were no longer significant.

LENGTH OF STAY IN HOSPITAL

The figure shows the results of the modified survival analysis as described above. The rate of discharge in the patients receiving β blockers was not significantly different from that in the patients receiving placebo.

TABLE V—*Mean numbers of neurological changes* (and 95% confidence intervals) according to treatment*

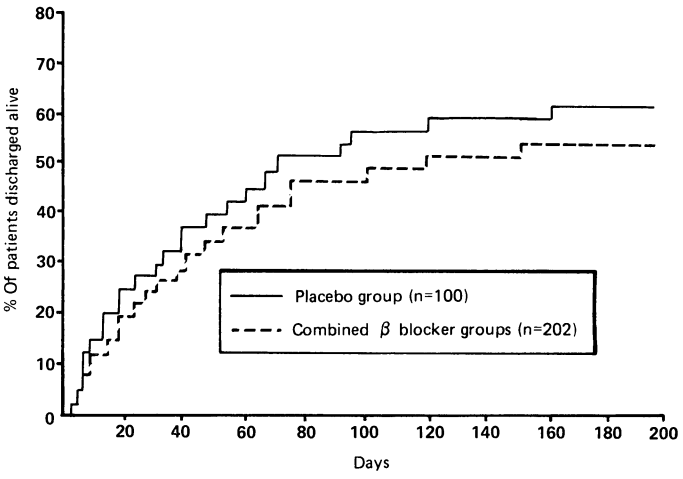
						β Blockers taken at onset of stroke	
	Placebo (n=100)	Atenolol + propranolol (n=201)	Placebo *v* atenolol and propranolol combined	Atenolol (n=101)	Propranolol (n=100)	Stopped on admission (n=24)	Resumed after admission (n=36)
1 Day to 1 week	1·9 (1·3 to 2·4)	0·8 (0·4 to 1·3)	p=0·006	0·3 (−0·3 to 0·9)	1·3 (0·6 to 2·0)	1·4 (0·0 to 2·6)	1·7 (0·9 to 2·5)
1 week to 1 month	1·3 (0·8 to 1·8)	1·1 (0·7 to 1·5)	p>0·1	1·1 (0·5 to 1·7)	1·1 (0·6 to 1·7)	1·4 (0·6 to 2·0)	1·3 (0·7 to 1·9)
1 day to 1 month	2·6 (2·0 to 3·2)	1·6 (1·0 to 2·1)	p=0·018	1·3 (0·6 to 2·0)	1·9 (1·0 to 2·6)	2·3 (0·8 to 3·7)	2·8 (1·9 to 3·6)

*Score x (=number of items showing improvement minus number showing deterioration) for each patient was transformed according to the formula $y=(x+10)^2$. Sample statistics were then computed and transformed back into the original units.

TABLE VI—*Mean score for activities of daily living according to treatment**

	All groups (median)	Placebo	Atenolol	Propranolol	Significance†
At 1 week	3·4 (3)	3·8	3·2	3·1	p=0·1
At 1 month	4·5 (3)	5·1	4·5	3·9	p=0·05
At 6 months	5·3 (6)	5·6	5·2	5·1	p>0·1

*Patients who died were given a score of zero.
†Between three treatment groups by Kruskal-Wallis test.



Survival analysis showing discharges of patients randomly assigned to receive placebo or β blocker.

WITHDRAWAL OF TREATMENT

Treatment was stopped prematurely in 95 patients; table VII shows that this generally happened because the patient had become moribund and all drugs had to be stopped. Only eight patients experienced definite side effects from β blockers, which improved after treatment was stopped. In 19 more patients treatment was withdrawn because of suspected adverse effects, but no appreciable improvement was seen afterwards, and the incidence of such supposed side effects was as high among patients taking the placebo as among those taking β blockers. One elderly woman taking propranolol developed severe bronchospasm six hours after the first dose and required assisted ventilation and bronchodilators. She eventually made a good recovery.

TABLE VII—*Reasons for withdrawal from treatment according to treatment group, age, and level of consciousness*

	Treatment group			Age (years)		Level of consciousness on day 1	
	Placebo	Atenolol	Propranolol	<70	≥70	Alert	Drowsy
Definite side effects		5	3	3	5	6	2
Possible side effects	5	9	5	8	11	8	11
Need for β blockade	4		3	7		3	4
Moribund or unable to swallow	14	20	23	15	42	17	40
Administrative error	1	1	2	3	1	1	3
Total	24	35	36	36	59	35	60

Discussion

IMPLICATIONS OF THE TRIAL

We had originally intended to assess the outcome in this trial in two stages. If the treatment significantly affected the neurological scores in the first 300 patients we had intended to continue recruiting patients until we had enough to detect an important difference in functional outcome or length of hospital stay. In the event we stopped the trial after the first stage because the neurological indices and the early mortality indicated that β blockers were not beneficial or were possibly harmful.

Treatment seemed to increase early mortality, particularly in very elderly patients, but this effect was small and further diminished after adjustment for differences in risk between the randomised groups. None of the deaths was attributed to established adverse effects of β blockers such as heart failure or bronchospasm, but, of course, the precise cause of death, even at necropsy, is difficult to determine in such patients. The proportion of patients discharged home by six months, which was the main end point of the trial, was negligibly different between the treatment groups.

The system of neurological assessment that we used was sufficiently sensitive to detect a significant adverse effect of treatment at a stage when the difference in overall outcome was small, thus preventing the trial being extended unnecessarily and possibly harmfully.

This study shows that the apparent cerebral protective effect of β blockade in patients with subarachnoid haemorrhage is not seen in patients with undifferentiated acute stroke. On the other hand, the difference in mortality between patients in the trial and those already taking β blockers at the time of their stroke could not be explained by differences in major risk factors, raising the possibility that prior treatment with β blockers might be protective. The better outcome in patients who continued to take β blockers compared with those who did not was, however, almost certainly due to differences in the severity of stroke between the groups. The decision to continue regular treatment often depends on the admitting doctor's assessment of the likelihood of recovery, and table III shows that there is some bias towards continuing treatment in younger patients and patients who are less severely affected.

DESIGN OF FUTURE TRIALS

This trial was based on a pragmatic approach and was concerned with the overall effects of treatment on a representative group of patients with a clinical diagnosis of acute stroke. Nevertheless, our two stage design allowed a definite negative conclusion to be reached with little, if any, real harm occurring to the patients. Could the same have been achieved with fewer patients who were selected more rigorously and investigated more intensively?

Firstly, even with 302 patients, random allocation of treatment resulted in an appreciable excess of elderly patients with severe strokes in the propranolol group and a relative deficit in the placebo group, an imbalance that could have been worse with fewer patients. Adjusting the results for imbalance post hoc is never satisfactory, and the log linear models that we used have a limited capacity to account for possible interactions between the various risk factors. Steiner and Clifford-Rose used a complex system of "paired stratification" to minimise differences between groups in terms of some of the main prognostic indicators,[5] but this could still have left important differences in factors that were not measured. Thus however careful the selection and allocation procedure the comparison of overall outcome in small groups will be unreliable. On the other hand, comparison of neurological changes as described above requires only a modest number of patients, as the treatment groups do not have to be matched so precisely. Large numbers are

needed to estimate the functional consequences of treatment with confidence, and better matching would thereby be ensured.

Thus a two stage pragmatic trial in patients with stroke such as ours can provide useful information about the success of treatment. Unsatisfactory treatments may be discontinued without exposing large numbers of patients to unnecessary risk, whereas those that give significant functional benefit may be recommended with confidence for conscious patients with stroke admitted to general hospitals with limited facilities for investigation.

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Appendix

The formulas for logistic regression models show how the predicted odds of surviving or going home may be calculated from the model parameters given the age of the patient, the initial conscious level, and so on, individual coefficients (odds ratios) being estimates of the relative risk associated with each factor.

Coefficients excluding treatment are:

$$\frac{P_H}{1-P_H}=5{\cdot}8^{C}\times 2{\cdot}0^{B}\times 0{\cdot}968^{Age}$$

$$\frac{P_s}{1-P_s}=1{\cdot}9^{C}\times 2{\cdot}9^{B}\times 1{\cdot}012^{Age}$$

Coefficients including treatment effect are:

$$\frac{P_H}{1-P_H}=5{\cdot}9^{C}\times 2{\cdot}0^{B}\times 0{\cdot}968^{Age}\times 1{\cdot}1^{T}$$

$$\frac{P_s}{1-P_s}=1{\cdot}9^{C}\times 3{\cdot}0^{B}\times 1{\cdot}013^{Age}\times 1{\cdot}4^{T}$$

where P_H=probability of returning home in first month; P_s=probability of surviving the first month; C=+1 if patient alert on day 1, −1 if patient drowsy on day 1; B=+1 if patient continent on day 1, −1 if patient incontinent on day 1; and T=+1 if patient taking placebo, −1 if patient taking a β blocker.

Thus, for instance, the odds of returning home within the first month for a 60 year old who is alert and continent initially are $5{\cdot}8\times 2{\cdot}0\times 0{\cdot}986^{60}=1{\cdot}6:1$ and for an 80 year old 0·9:1 (1·0:1 if taking placebo, 0·8:1 if taking a β blocker). Note that the model predicts a slight improvement in survival with age provided that the degree of consciousness and continence remain unchanged.

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Aromatase activity in adipose tissue from breast quadrants: a link with tumour site

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Abstract

To determine the importance of local oestrogen biosynthesis within the breast, aromatase activity was measured in adipose tissue from the breast quadrants of 12 consecutive mastectomies from patients with breast cancer. Activity was detected in all samples (range 3·6-35·0 fmol oestrogen/mg protein/h) but varied considerably not only among different patients but also among the quadrants of individual breasts. The highest activity in a breast was always found in a quadrant that contained tumour, whereas quadrants with the lowest activity were never associated with the presence of tumour.

These results provide evidence of a significant relation between breast adipose tissue and breast cancer. Whether such an association occurs because breast tumours are more likely to develop in areas with enhanced oestrogen biosynthesis or because they secrete into their local environment factors capable of stimulating oestrogen biosynthesis remains to be determined.

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Introduction

Unlike other glands in the body the human adult breast is invested with an abundance of adipose tissue.[1] Although the precise role of this adipose tissue remains to be elucidated, there is evidence of an association between mammary fat and the development of breast cancer.[2,3] Breast adipose tissue is not metabolically inert, being able, for example, to synthesise oestrogens by aromatising androgen precursors.[4-7] Although aromatase activity in adipose tissue varies among subjects and different sites in the body,[6-9] little is known about its activity within the breast. Our aims were to investigate the