

of the decreased absorption of aspirin which has been shown during the migraine attack. It is hoped to provide further evidence for this mechanism by absorption studies which are in progress to determine whether metoclopramide can overcome the decreased aspirin absorption during migraine attacks.

The finding of impaired gastrointestinal absorption of drugs during migraine attacks has a definite clinical significance. Most of the drugs used in acute migraine are less readily absorbed in normal individuals than effervescent aspirin and absorption of such drugs may be reduced to an even greater degree. Many migraine patients report that aspirin and paracetamol do not relieve their headaches. Since different formulations of aspirin (Martin, 1971) and paracetamol (Hedges and Kaye, 1973; Hedges *et al.*, 1974) have very different rates of absorption the failure of response in migraine may often be related to the use of formulations which are slowly absorbed even in normal circumstances. To take account of impairment of drug absorption it is recommended that in the treatment of migraine preparations should be used which are rapidly absorbed or which bypass the gastrointestinal tract. In addition, the gastrointestinal symptoms should be noted and, if necessary, treated with antiemetics.

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Host Resistance in Relation to Survival in Breast Cancer

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Summary

The degree of lymphocytic infiltration in and around breast tumours together with sinus histiocytosis and follicular hyperplasia in regional lymph nodes has been studied in 310 cases of breast cancer treated with standard radical mastectomy. The presence of these features was regarded as evidence of host resistance against the tumour and made possible the division of patients into three classes—no or poor reaction, good reaction, and strong reaction. The grading was shown to have a close correlation with prognosis. The relationship between host defensive factor grading and malignancy, nodal metastases, and survival was also examined. The results support the hypothesis that prognosis in breast cancer is closely related to a histological picture of cell-mediated immunity against the tumour.

Introduction

Among the factors thought to influence survival in cases of breast cancer treated surgically lymphocytic infiltration in and around the tumour and follicular hyperplasia and sinus histiocytosis in regional lymph nodes have received particular attention. These features have been regarded as evidence of an immunological response to the tumour but whether they correlate with a good prognosis is still open to controversy.

After the report of Foote and Stewart (1946) on lymphocytic infiltration of the stroma of medullary carcinoma the study was extended to regional lymph nodes (Black *et al.*, 1953; Anastasiades and Pryce, 1966; Cutler *et al.*, 1969; Wernicke, 1972), and a lymphocytic infiltration was found in all histological types of breast cancer (Hamlin, 1968), particularly medullary carcinoma (Bloom *et al.*, 1970).

Hamlin (1968) reviewed 272 cases of breast cancer and found a close correlation between prognosis and the intensity of lymphocytic infiltration around the tumour. In a study of 1,411 cases of breast cancer followed for 20 years Bloom *et al.* (1970) showed that the highly malignant medullary carcinoma carries a remarkably good prognosis when there is increased lymphocytic infiltration around the tumour. Recently increased benign lymphoid tissue in the lymph nodes of the apex of the axilla has been described as a favourable prognostic sign (Berg *et al.*, 1973). Other workers, however, have found that sinus histiocytosis (Kister *et al.*, 1969), follicular hyperplasia (Moore *et al.*, 1960), and lymphocytic infiltration (Morrison *et al.*, 1973) do not correlate with prognosis in breast cancer.

We have already made a preliminary report (Di Paola *et al.*, 1973) of our findings in a limited number of cases of a relation-

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ship between host immunological response and prognosis in breast cancer. This paper reports on studies in greater detail and evaluates the data.

Subjects and Methods

We reviewed 507 patients with breast cancer who had undergone radical mastectomy in our department from 1946 to 1966. The fate of 466 (91.9%) of the patients was known. From this group 156 were excluded for want of enough histological evidence (116 cases) or because the cause of death was uncertain or other than breast cancer (36 cases) or because they had received radiotherapy (4 cases), which is known to deplete lymphocytic deposits (Meyer, 1970). Thus 310 cases were finally studied, 135 stage 1, 150 stage 2, and 25 stage 3 (TNM clinical staging).

As an index of host resistance to the tumour we used a modified version of Hamlin's (1968) method (Di Paola *et al.*, 1973). We graded the lymphocytic infiltration around and in the centre of the tumour at scores of 0 to 3. The mean of these scores was taken to represent the degree of host resistance at the tumour level and was used as the first partial score. Follicular hyperplasia and sinus histiocytosis in regional lymph nodes were also scored from 0 to 3. The mean of these scores was taken to represent the degree of host resistance at the lymph node level and was used as the second partial score. The sum of these two partial scores was taken to represent the host defensive factor (H.D.F.). This was divided into three grades: D- (H.D.F. scores 0-2), reaction absent or poor; D+ (H.D.F. scores > 2-4), reaction present; and D++ (H.D.F. scores > 4-6), strong reaction present.

The grade of malignancy of the tumour was assessed on histological criteria M+ and M++ being used. Thus M+ included all well-differentiated tumours and M++ moderately differentiated and undifferentiated tumours.

The D score was compared in each case with survival, the M grading, and the presence of nodal metastases. Histological assessment of the tumour and lymph nodes was made by one of us (A.B.) without knowing the fate of the patient. This was disclosed only after the H.D.F. had been calculated.

Results

The overall survival at five years for all 507 cases was 56.0%. The five-year survival for the 310 cases studied for H.D.F. was 59.3%.

Analysis of the 310 cases by H.D.F. (table I) showed that the five-year survival rate of the D- patients was much lower than that of the D+ and D++ patients and lower than that of all 507 patients operated on.

In table II the five-year survival rates are correlated with the M and D gradings combined. Altogether 253 cases were graded M+ and 57 M++. The grading seemed to affect survival in all three groups of patients. For D+ and D++ the decrease of five-year survival from M+ to M++ appeared to be higher than for the D- patients. Survival plotted against D grading and the presence or absence of nodal metastases as assessed histologically is shown in table III. Survival appeared to be related to the state of the regional lymph nodes in all groups of patients but D+ and D++ patients with nodal metastases had a better prognosis than did D- patients without nodal metastases.

The incidence of metastases in regional lymph nodes was significantly higher in the D- patients (133/182; 73%) than in the D+ (62/114; 54.4%) or D++ (7/14; 50%) patients.

Discussion

Our overall five-year survival rate of 56% for all 507 patients after standard radical mastectomy is consistent with the find-

ings of others (Cáceres, 1967; Butcher, 1969; Haagensen and Cooley, 1970).

In the 310 patients studied for an immunological response to the tumour we found a good correlation between putative host resistance and long-term survival. Analysis of the cases by H.D.F. showed a striking difference in five-year survival between the D- and the D+ and D++ patients, ranging from 40.8% (D-) to 85.8% (D++) (table I). The patients with a strong defence (D++), however, accounted for only 4.5% of the total — too small a sample on which to base a meaningful conclusion.

TABLE I—Five-year Survival among 310 Patients According to D Score (See Text)

Score:	D-	D+	D++
No. of cases	182	114	14
Five-year survival	40.8%	68.4%	85.8%

We further divided the D- patients into those without a defence (score 0 to < 1) and those with a poor defence (score 1 to 2). The difference in five-year survival between these two groups, however, was not statistically significant. This shows that the H.D.F. score has a positive influence on survival only if a D+ or D++ reaction is recorded. Considering both the H.D.F. and the malignancy (M) grading of the tumour (table II) we found that the M grading of the tumour was related to survival in all three groups; the M++D+ and M++D++ patients (the worst combinations for patients with a defence) had an overall mortality significantly lower than that of the M+D- patients (the most favourable combination for patients with a poor defence). When survival of the D+ and D++ patients was related to the degree of malignancy of the tumour the results were as expected; the prognosis was significantly better for those patients who had a strong response even when the tumour scored M++.

TABLE II—Five-year Survival among 310 Patients with M and D Scores Combined (See Text)

Score:	M+D-	M+D+	M+D+	M++D+	M++D+	M++D++
No. of cases	150	33	97	16	6	8
Five-year survival	52.0%	36.4%	74.3%	56.9%	100.0%	75.0%

When we analysed the influence of metastases in regional lymph nodes on survival (table III) we found that all three groups had a worse prognosis when metastases were present. D+ and D++ patients with nodal metastases, however, had a significantly better survival than did the D- patients without metastases. Thus host resistance plays a part even when metastases are present. But, more interestingly, the incidence of metastases in regional lymph nodes was significantly higher in the D- patients (73%) than in the D+ (54.4%) or D++ (50%) patients. Thus it seems that metastases are less frequent when the host resistance is good. So one of the main ways in which host resistance prolongs survival may be by acting as a

TABLE III—Five-year Survival Plotted against D Grading and Presence or Absence of Nodal Metastases. Overall Survival at Five Years for H.D.F. Scores is Also Shown

Score:	D- (n=182)	D+ (n=114)	D++ (n=14)
No. (%) with metastases who survived	42/133 (31.6)	35/62 (56.5)	5/7 (71.4)
No. (%) without metastases who survived	26/49 (53.1)	44/52 (84.6)	7/7 (100.0)
Overall survival	40.8%	68.4%	85.8%

local barrier to the diffusion of the tumour. As we have shown, however, the presence of metastases in regional nodes is not incompatible with a D+ or D++ score and long-term survival. Our results confirm those of other series on all histological types of breast cancer, particularly medullary carcinoma (Hamlin, 1968; Bloom *et al.*, 1970; Wernicke, 1972). Other workers have found no correlation between survival and sinus histiocytosis (Berg, 1956; Moore *et al.*, 1960; Kister *et al.*, 1969), follicular hyperplasia (Moore *et al.*, 1960), and lymphocytic infiltration (Morrison *et al.*, 1973) but we believe that the histology of both tumour and lymph nodes must be studied to obtain an accurate picture of host resistance. There is undoubtedly a close relationship between host immunological response and prognosis in the breast cancer. That this response is cell mediated was confirmed by Fisher *et al.* (1973), who showed that lymphocytes from lymph nodes draining a breast cancer were stimulated *in vitro* by phytohaemagglutinin. This transformation was associated with follicular hyperplasia and lymphocytic infiltration, whereas no clear-cut correlation could be shown with the presence or absence of sinus histiocytosis.

We believe that further studies of the immunological response of lymph nodes draining a tumour removed at operation would provide more information about prognosis (*Lancet*, 1973). At present we are correlating tumour lymphocytic infiltration and follicular hyperplasia and sinus histiocytosis in

regional lymph nodes with preoperative and postoperative lymphocytic responses to phytohaemagglutinin, aspecific and specific delayed cutaneous hypersensitivity reactions, and distribution patterns of T and B cells at tumour and lymph node levels.

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MEDICAL MEMORANDA

Malignant Hyperpyrexia Induced by Nitrous Oxide and Treated with Dexamethasone

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Though fever has been recognized as a complication of anaesthesia for over 80 years the specific condition of malignant hyperpyrexia has only comparatively recently been described. It is known that susceptible patients, who have been found to have a subclinical myopathy (Harriman *et al.*, 1973), develop a fulminating and often fatal hyperpyrexia when given certain anaesthetic drugs or depolarizing muscle relaxants (Britt and Kalow, 1970). A working definition of malignant hyperpyrexia is an unexplained fever during anaesthesia in which the body temperature rises at a rate of at least 2°C an hour (Keaney and Ellis, 1971). Most patients develop muscle contracture, acidosis, and hyperkalaemia. The condition is inherited as a Mendelian autosomal dominant.

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The screening test for susceptibility to malignant hyperpyrexia (Ellis *et al.*, 1972) requires muscle tissue obtained by motor point muscle biopsy. The biopsy is performed under general anaesthesia for three reasons. Firstly, the procedure takes about 90 minutes, which is too long for conscious patients, especially children, to lie quietly. Secondly, if the local anaesthetic reaches the muscle tissue the identification of the motor point is impossible owing to the blockade of the motor nerve terminal, and, thirdly, the muscle test on living muscle *in vitro* is much less sensitive.

The general anaesthetic technique used involves intermittent thiopentone and nitrous oxide via a mask after diazepam premedication; recently fentanyl has been included. This regimen, which has proved satisfactory and uneventful in over 50 such patients, was felt to be safe because none of the drugs have ever been implicated in the induction of malignant hyperpyrexia. Intensive body temperature monitoring is mandatory.

We report here, however, a patient in whom nitrous oxide was shown conclusively to be responsible for the malignant hyperpyrexia episode under anaesthesia. The malignant hyperpyrexia was dramatically and successfully treated with dexamethasone.

Case Report

An 11-year-old apparently healthy girl required dental extractions. As her father had died of hyperpyrexia under anaesthesia for tendon suture during which he received thiopentone, suxamethonium, nitrous oxide, and halothane it was decided to investigate the patient for malignant hyperpyrexia susceptibility by muscle biopsy at the same time as the dental treatment. The patient was premedicated with diazepam, and anaesthesia was induced with thiopentone and maintained with 70% nitrous oxide and 30% oxygen via a mask. Body core temperature, measured with a rectal thermocouple probe, began to rise and after 12 minutes anaesthesia was abandoned as the rectal temperature had risen 1.2°C—that is, at a rate of 6°C per hour. An attempt to cool the patient with ice in the axillae, groins, and over the precordium and with cold water blankets failed. She was given