Chemoimmunotherapy of advanced breast cancer: prolongation of remission and survival with BCG

JORDAN U GUTTERMAN, JUAN O CARDENAS, GEORGE R BLUMENSCHEIN, GABRIEL HORTOBAGYI, MICHAEL A BURGESS, ROBERT B LIVINGSTON, GIORA M MAVLIGIT, EMIL J FREIREICH, JEFFREY A GOTTLIEB, EVAN M HERSH

British Medical Journal, 1976, **2**, 1222-1225

Summary

Forty-five patients with disseminated breast cancer were given a trial of combination chemotherapy consisting of fluorouracil, adriamycin, and cyclophosphamide (FAC) and immunotherapy with BCG given by scarification. The results were compared with those in a comparable group of 44 patients treated with FAC alone immediately before the chemoimmunotherapy study. The remission rates (73% and 76% for FAC and FAC-BCG respectively) were similar in both studies. The durations of remission for patients on FAC-BCG (median 12 months) were longer than remissions achieved for patients given FAC alone (median 8 months) ($P=0.068$). The most notable effect of BCG was on survival. Thus 21 out of 34 patients achieving remission on FAC-BCG were alive at the time of the last follow-up examination (median over 22 months) compared with 11 out of 32 patients achieving remission on FAC (median 15 months) ($P=0.01$). Twenty-six of the 45 patients given FAC-BCG were alive at the time of the last follow-up examination (median over 22 months) compared with 12 of the 44 patients given FAC (median 15 months) ($P=0.005$).

Although the apparent benefit of BCG could be explained by a maldistribution of some prognostic factors, the data suggest that further trials of chemoimmunotherapy of breast cancer should be carried out.

Introduction

Breast cancer remains the most common malignant disease causing death among women.[1,2] With the development of combination chemotherapy programmes, in which various active drugs with different modalities of action and toxicity are utilised, an encouraging increase in remission rates among patients with advanced disease has been achieved.[3,4] The introduction of adriamycin in various combination programmes has produced remission rates of 50-70%.[5,6] We recently reported a 79% overall remission rate with a combination of fluorouracil, adriamycin, and cyclophosphamide (FAC).[7]

Despite this encouraging trend in remission rates the duration of these responses has been short, with a median of 5-10 months. The overall median survival with most of these combination chemotherapy programmes has improved to about 10-15 months.

The importance of host defence mechanisms in the control of breast cancer and other tumours has become increasingly evident.[8,9] As a result, immunotherapy is becoming increasingly important in the treatment of cancer.[10] We recently showed that immunotherapy with BCG-prolonged chemotherapy-induced remissions and survival of patients with disseminated melanoma[11] and acute myelogenous leukaemia.[12] After successfully working out the use of intermittent chemotherapy with immunotherapy we explored the questions whether BCG immunotherapy could (*a*) increase remission rates, (*b*) prolong the duration of remission, and (*c*) prolong the overall survival of patients with metastatic breast cancer who were receiving combination chemotherapy. Thus a programme of chemoimmunotherapy for disseminated breast cancer was initiated, combining BCG with our previous best combination chemotherapy regimen of fluorouracil, adriamycin, and cyclophosphamide. We report here our preliminary results.

Methods

Forty-five women with disseminated breast carcinoma were treated with one or more complete courses of chemoimmunotherapy from 1 March to 15 August 1974. Baseline and follow-up studies included physical examination, complete blood counts, urine analysis, tests of liver and renal function, chest *x*-ray examination, liver and bone scanning, electroencephalography, metastatic bone survey, and bone marrow biopsy.

The design of the chemoimmunotherapy was as follows: fluorouracil 500 mg/m^2 intravenously on days 1 and 8 of each course, adriamycin 50 mg/m^2 intravenously on day 1, and cyclophosphamide 500 mg/m^2 intravenously on day 1. Lyophilised Tice strain BCG in a dose of 6×10^8 viable units was given by scarification in a rotating fashion on the upper arms and thighs[11] on days 9, 13, and 17 of each course. Courses were repeated every 21 days if blood counts permitted.

If during the previous course the absolute granulocyte count never fell below 2×10^9/l (2000/mm^3) and the platelet count never below 100×10^9/l (100 000/mm^3) all three chemotherapeutic agents were increased by 20%. If the granulocyte count fell below 1×10^9/l (1000/mm^3) or the platelet count below 50×10^9/l (50 000/mm^3), however, all agents were decreased by 20%. No change in dosage was made when falls were between these levels. If the patient had a documented infection or haemorrhage or both all agents were decreased by 25-40% regardless of blood counts.

The total dose of adriamycin was limited to 500 mg/m^2 because of the known increase in cardiotoxicity above this level.[13] At that point maintenance treatment was started with cyclophosphamide 500 mg/m^2 by mouth on day 1, methotrexate 30 mg/m^2 intramuscularly on days 1 and 8, and fluorouracil 500 mg/m^2 by mouth on days 1 and 8 (CMF regimen). BCG was given on days 9, 13, and 17 of each 21-day maintenance course. Adriamycin was discontinued if any evidence of

University of Texas System Cancer Centre, M D Anderson Hospital and Tumour Institute, Houston, Texas 77030

JORDAN U GUTTERMAN, MD, associate professor of medicine, department of developmental therapeutics
JUAN O CARDENAS, MD, fellow, department of developmental therapeutics
GEORGE R BLUMENSCHEIN, MD, associate professor of medicine, department of medicine
GABRIEL HORTOBAGYI, MD, fellow, department of developmental therapeutics
MICHAEL A BURGESS, MD, assistant professor of medicine, department of developmental therapeutics
ROBERT B LIVINGSTON, MD, assistant professor of medicine, department of developmental therapeutics
GIORA M MAVLIGIT, MD, associate professor of medicine, department of developmental therapeutics
EMIL J FREIREICH, MD, professor of medicine, department of developmental therapeutics
JEFFREY A GOTTLIEB, MD, associate professor of medicine, department of developmental therapeutics (Professor Gottlieb died on 1 July 1975)
EVAN M HERSH, MD, professor of medicine, department of developmental therapeutics

cardiac toxicity developed. If severe diarrhoea or cerebellar ataxia attributable to fluorouracil occurred this agent was withheld until these symptoms resolved. Fluorouracil was then reintroduced at a 20% reduced level.

Complete remission was defined when all objective and subjective manifestations of the disease had disappeared, with recalcification of all osteolytic lesions; partial remission when there was a 50% or greater reduction in the areas of all measurable tumour and partial recalcification of osteolytic lesions; stabilisation when there was less than a 50% reduction or less than a 25% increase in tumour masses; progression when there was a 25% or greater increase in tumour masses or any new masses had appeared; and relapse when a tumour mass reappeared.

The response to FAC-BCG was compared with the response of 44 patients treated in an identical fashion with FAC alone from 15 August 1973 to 1 March 1974.[5 7] The criteria for admission to the studies were identical. Although 60 patients were eligible for the FAC-BCG study and 50 for the FAC study, some were not treated according to the protocol and so could not be evaluated. These patients were treated either without BCG in the FAC-BCG study (7 patients) or with 25-50% lower doses of FAC in either study (FAC-BCG, 6 patients; FAC, 4 patients). Two patients in each study died before completing the first cycle of treatment (early death).

Table I shows that the FAC and FAC-BCG groups were comparable in the major features known to affect prognosis in breast cancer.[14 15] Although the distribution of visceral and non-visceral metastases was generally similar in the two groups, there was a higher proportion of bone metastases in the FAC group. The proportions of premenopausal and postmenopausal patients and the median times to dissemination were nearly identical (table I), but there was an 11% higher hormonal exposure in the FAC group, and the median age of the FAC group was five years less than that of the FAC-BCG group.

TABLE I—*Clinical features of 45 patients treated with FAC-BCG and 44 treated with FAC, and sites of metastases*

	Treatment group	
	FAC-BCG	FAC
Clinical features		
Median age in years (range)	56 (29-72)	51 (29-67)
Median disease-free interval in months (range)	16 (0-140)	15 (0-104)
No premenopausal at diagnosis	18 (40%)	19 (43%)
No with prior hormone treatment	31 (69%)	35 (80%)
No with prior chemotherapy	3 (7%)	3 (7%)
No with metastases in:		
Lymph nodes	20 (44%)	23 (52%)
Soft tissue	22 (49%)	19 (43%)
Lung	20 (44%)	24 (55%)
Pleura	5 (11%)	7 (16%)
Liver	12 (27%)	9 (20%)
Bone	22 (49%)	29 (66%)

Duration of remission was determined from the date of achieving a partial or complete remission. Survival was measured from start of treatment to date of death or date of last follow-up examination. Statistical methods used included a generalised Wilcoxon test with a one-tailed analysis[16] for testing differences between remission and survival curves, and the method of Kaplan and Meier[17] for calculating and plotting remission and survival curves.

Results

Forty-five patients received an adequate trial of one or more courses of FAC-BCG. Responses are shown in table II and are compared with those of the 44 patients who received FAC alone. Of the patients in the FAC-BCG group, 34 (76%) achieved a remission; in 14 (31%) it was complete and in 20 (44%) partial. In a further nine patients (20%) the disease was stable for two months or more, and in only two (4%) was there progression of the disease. The response in non-visceral areas—that is, lymph nodes and soft tissue—was 83%; response in lung and pleura was 76%, and in the liver 42%. These results are essentially the same as reported previously for the FAC regimen used alone[5] (table II).

Of the 32 patients (73%) who achieved complete or partial remission on FAC alone, 26 later relapsed (fig 1). The 0·75 percentile was five months and the median duration of remission only eight

TABLE II—*Overall response according to site of metastases*

	FAC-BCG group		FAC group	
	No	%	No	%
Response to treatment				
Remission	34/45	76	32/44	73
Complete	14/45	31	6/44	14
Partial	20/45	45	26/44	59
Stabilisation	9/45	20	12/44	27
Progression	2/45	4	0/44	0
Response by site of metastases				
Lymph nodes	17/20	85	23/23	100
Soft tissue	18/22	82	16/19	84
Lung	15/20	75	16/24	67
Pleura	4/5	80	6/7	86
Liver	5/12	42	4/9	44
Bone	7/22	32	6/29	21

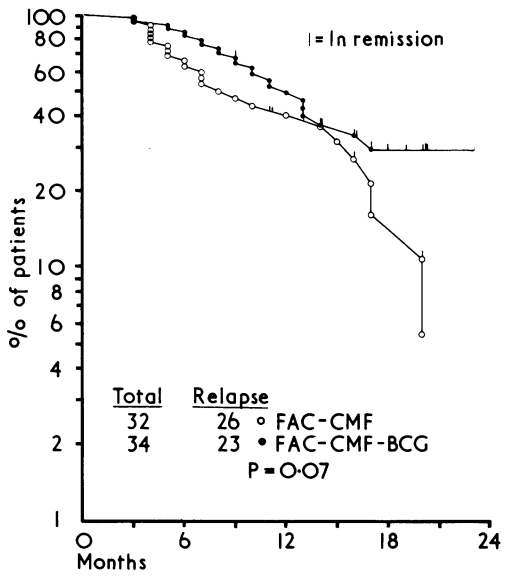

FIG 1—Durations of remission (complete and partial) in the FAC and FAC-BCG groups. CMF = Cyclophosphamide, methotrexate, and fluorouracil; see text.

months. Only 11 patients (34%) remained in remission beyond a year. Of the 34 patients achieving remission with FAC-BCG, 23 later relapsed (fig 1), with a 0·75 percentile of 7·5 months and a median duration of remission of 12 months. Altogether 17 of the 34 patients had a remission lasting more than one year. The difference in durations of remission between the two groups was only suggestive ($P = 0·068$).

So far there is no difference between the two groups in the durations of complete remission. Thus three out of six patients on FAC alone were in remission (0·75 percentile 5 months; median over 12 months), and five out of 14 on FAC-BCG were in remission when last seen (0·75 percentile 7·5 months; median 12·4 months) ($P = 0·4$). In contrast, the durations of partial remission were longer in the FAC-BCG group than in the FAC group. Thus only three out of 26 patients on FAC alone were still in remission when last seen (0·75 percentile 4 months; median 7 months) compared with six out of 20 on FAC-BCG (0·75 percentile 6 months; median 10 months) ($P = 0·09$).

The major therapeutic advantage of chemoimmunotherapy occurred in survival. The survival of patients in the FAC and FAC-BCG groups who achieved remission is shown in fig 2. Twenty-one of the 32 patients who achieved remission on FAC alone later died. The 0·75 percentile was 11 months and the median survival 15 months. In contrast, only 13 of the 34 patients who achieved remission on FAC-BCG later died. The 0·75 percentile was 17·3 months and the median survival over 22 months. The difference in survival between the two groups is significant ($P = 0·01$).

Figure 2 also shows the survival of stabilised patients. Only one out of 12 patients in this category on FAC alone was alive at the time of last follow-up. The 0·75 percentile survival was seven months and the median survival 10 months. In contrast, five of the nine patients on FAC-BCG were still alive, with a 0·75 percentile survival of 13 months and a median survival of over 19 months.

Characteristic of previous chemotherapy studies, the survival of responding patients on FAC alone was significantly longer than the survival of stabilised patients on FAC alone (P=0·04; fig 2). In contrast, the survival of stabilised patients on FAC-BCG was nearly

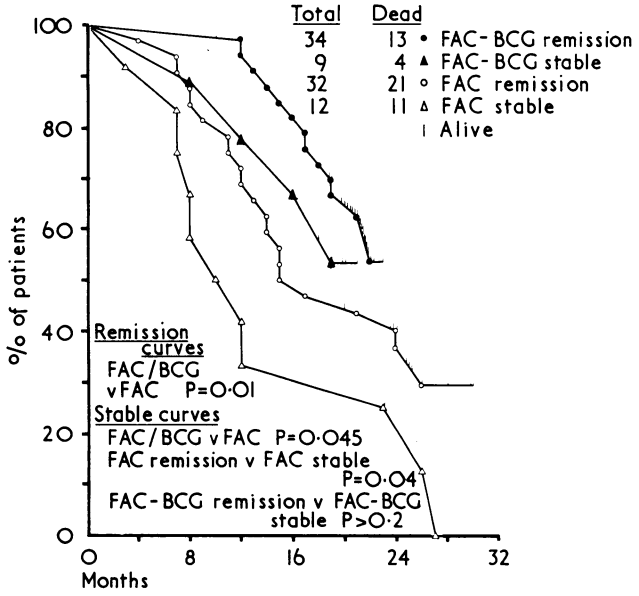

FIG 2—Survival of patients in FAC-BCG and FAC groups who achieved remission and of those who did not (stable group).

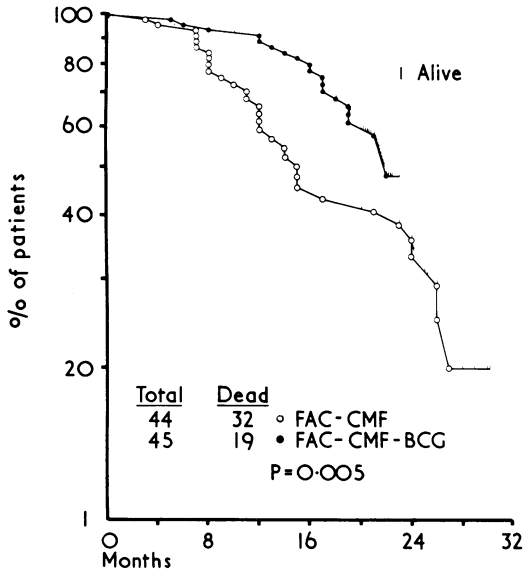

FIG 3—Survival of all treated patients.

identical with the survival of responding patients on FAC-BCG (P>0·2; fig 2).

The survival of all treated patients is shown in fig 3. Of the 44 patients treated with FAC alone, 32 died. The 0·75 percentile was nine months and the median survival 15 months. Of the 45 patients on FAC-BCG, 19 died. The 0·75 percentile was 17 months, which is longer than the median survival of the FAC group. Median survival was over 22 months. The FAC-BCG group survived significantly longer than the FAC group (P=0·005).

Chemoimmunotherapy was well tolerated. Although the type of care needed was similar for both groups, thrombocytopenia occurred less among patients on FAC-BCG than among those on FAC alone. Transient low-grade fever and a flu-like syndrome developed in most patients after BCG vaccination. BCG disease did not occur and isoniazid or other antituberculosis treatment was not required.

Discussion

These findings suggest that the prognosis of patients with advanced breast cancer treated with cyclic combination chemotherapy may be improved by adding immunotherapy. The data only suggest that BCG may have prolonged durations of chemotherapy-induced remissions.

The most important therapeutic effect of BCG immunotherapy in this study was the increase in survival among the responders and stabilised patients. Thus fewer than half of the patients who achieved remission on FAC alone survived 18 months (median 15 months). In contrast, 74% of the patients achieving remission on FAC-BCG survived for over 18 months. Thus the 0·75 percentile is already 17·3 months. Interestingly, the data on our FAC control group were identical with those reported by Jones *et al* with a similar chemotherapy combination (adriamycin plus cyclophosphamide; AC)[6] and similar to those in other chemotherapy studies.[18] The survival of patients with partial remission (FAC 15 months, AC 17 months) and overall survival (median 14-15 months in both studies) were nearly identical.[6]

The data also indicated a unique contribution of BCG immunotherapy—namely, prolongation of survival of patients not achieving remission (stabilised patients). The increased survival of patients achieving remission compared with those achieving stability on FAC alone was a function of time spent in remission, which is characteristic of most chemotherapy studies. A novel observation, however, was that the survival of patients achieving stability on FAC-BCG was nearly identical with the survival of patients achieving remission on FAC-BCG. If confirmed, this suggests an additional therapeutic effect of immunotherapy in prolonging survival of non-responding patients.

In a disease such as breast cancer it is critically important to be certain that the comparative treatment groups are matched carefully with regard to prognostic factors. Inevitable deficiencies may arise whether the study is randomised or carried out in a sequential fashion, as ours was. Thus the maldistribution of some prognostic factors, especially the 11% difference in prior hormone treatment and the difference in distribution of bone metastases between the two groups, and the five-year difference in median age could account for the benefits of BCG. Although this is unlikely, since the response rates were almost identical, these factors must be considered when interpreting the results.

If confirmed, these preliminary findings extend the principles established in other chemoimmunotherapy trials, in which remission rates were not significantly increased (except for tumour size regional to BCG scarification) but remission durations and particularly survival were significantly increased compared with chemotherapy alone.[11 12] Similar results have been reported when *Corynebacterium parvum* was added to chemotherapy in breast cancer.[19] We hope that this preliminary report will stimulate further trials of chemoimmunotherapy in advanced breast cancer.

Despite the encouraging results with FAC-BCG, improved modalities of immunotherapy[10] and combination chemotherapy are needed to increase the remission rates in visceral regions, to increase complete remissions, and to further prolong remissions and survival. Other immunological approaches appear to be beneficial in breast cancer.[20 21] Finally, since adjuvant chemotherapy prolongs the disease-free interval and survival in patients with histological evidence of spread to regional lymph nodes,[22 23] and adjuvant immunotherapy is beneficial in colorectal cancer[24] and malignant melanoma,[25 26] programmes of combination chemotherapy and immunotherapy should be designed for patients with residual microscopic disease after surgery.

This work was supported by contract N01-CB-33888 and grants 05831 and 11520 from the National Cancer Institute, Bethesda, Maryland 20014. Drs Gutterman and Mavligit are in receipt of career development awards (CA 71007-02 and CA 00130-01 respectively) from the National Cancer Institute, Bethesda, Maryland

20014. We gratefully acknowledge the technical help of Ms Karen Terry, Ms Kathy Dandridge, Mrs Shirley Livingston, Mrs Annette Matthews, and Mrs Terry Smith.

Requests for reprints should be addressed to: Professor Jordan U Gutterman, Department of Developmental Therapeutics, M D Anderson Hospital and Tumour Institute, 6723 Bertner Avenue, Houston, Texas 77030.

References

1 American Cancer Society, *Cancer Facts and Figures*. New York, American Cancer Society, 1975.
2 Cutler, S J, *Seminars in Oncology*, 1974, **1**, 91.
3 Greenspan, E M, *Journal of the Mount Sinai Hospital*, 1966, **33**, 435.
4 Canellos, G P, *et al*, *British Medical Journal*, 1974, **1**, 218.
5 Gottlieb, J A, *et al*, *Adriamycin Reviews*. Ghent, European Press Medikon, 1975.
6 Jones, S E, Durie, B G, and Salmon, S E, *Cancer (Philadelphia)*, 1975, **36**, 90.
7 Blumenschein, G R, Cardenas, J O, and Freireich, E J, *Proceedings of the American Society of Clinical Oncology*, 1974, **15**, 193.
8 Black, M M, Kerpe, S, and Speer, F D, *American Journal of Pathology*, 1953, **29**, 505.
9 Bloom, H J, Richardson, W W, and Field, J R, *British Medical Journal*, 1970, **3**, 181.
10 Gutterman, J U, Mavligit, G M, and Hersh, E M, *Medical Clinics of North America*, 1976, **60**, 441.
11 Gutterman, J U, *et al*, *New England Journal of Medicine*, 1974, **291**, 592.
12 Gutterman, J U, *et al*, *Lancet*, 1974, **2**, 1405.
13 Minow, R A, Benjamin, R S, and Gottlieb, J A, *Cancer Chemotherapy Reports*, 1975, **6**, 195.
14 Cutler, S J, in *Prognostic Factors in Breast Cancer*, ed A P Forrest and P B Kunkler, p 20. Edinburgh and London, Livingston, 1968.
15 Friedell, H, *Journal of the National Cancer Institute*, 1974, **53**, 603.
16 Gehan, E A, *Biometrika*, 1965, **52**, 203
17 Kaplan, E L, and Meier, P, *Journal of the American Statistical Association*, 1958, **53**, 457.
18 Brambilla, C, *et al*, *British Medical Journal*, 1976, **1**, 801.
19 Israel, L, and Edelstein, R, *Immunological Aspects of Neoplasia*, 26th symposium. Baltimore, Williams and Wilkins, 1975.
20 Rojas, A F, *et al*, *Lancet*, 1976, **1**, 211.
21 Oettgen, H F, *et al*, *Proceedings of the National Academy of Sciences*, 1974, **71**, 2319.
22 Fisher, B, Carbone, P, and Economou, S G, *New England Journal of Medicine*, 1975, **292**, 117.
23 Bonadonna, G, *et al*, *New England Journal of Medicine*, 1976, **294**, 405.
24 Mavligit, G M, *et al*, *Lancet*, 1976, **1**, 871.
25 Gutterman, J U, *et al*, *Lancet*, 1973, **1**, 1208.
26 Eilber, F R, *et al*, *New England Journal of Medicine*, 1976, **294**, 237.

Small intestinal transit in diabetics

J H B SCARPELLO, M GREAVES, G E SLADEN

British Medical Journal, 1976, **2**, 1225-1226

Summary

Small intestinal transit was assessed in diabetic patients and healthy controls by measuring the breath hydrogen appearance time after the ingestion of lactulose. Transit in diabetics with autonomic neuropathy was significantly slower than in diabetics without neuropathy and controls. Delayed transit is probably due to vagal denervation. These slower transit times would allow bacteria to proliferate, which might explain why some diabetics have diarrhoea. The test cannot be used in patients with bacteria in the small bowel because these may metabolise lactulose and release hydrogen prematurely.

Introduction

Gut symptoms in diabetics are usually associated with autonomic neuropathy.[1] Diabetic diarrhoea may sometimes be associated with small intestinal bacterial overgrowth, and symptoms can be relieved by antibiotics.[2 3] Bacterial colonisation of the small bowel may result from changed intestinal motility.

Transit through the small intestine is difficult to study, although various methods have been described.[4] Recently Bond and Levitt have advocated measuring the breath hydrogen appearance time after the ingestion of a non-absorbable carbohydrate.[5] This simple non-invasive technique measures the time taken for a bolus of the carbohydrate to reach bacteria in the ileocaecal region.

We have used this technique to compare small intestinal transit times in normal people and diabetics with and without autonomic neuropathy.

Patients and methods

Twelve well-controlled, insulin-dependent diabetics (mean age 45 years) were studied together with eight healthy controls matched for age and sex. None were receiving any drugs apart from insulin. The diabetics were assessed for evidence of autonomic neuropathy.[6] None of the diabetics had diarrhoea, and all had had normal results in the ^{14}C-glycocholic acid test, a sensitive test of bacterial deconjugation of bile acids in the small bowel.[3] This was considered important because small-bowel bacteria can metabolise lactulose[7] and would release hydrogen prematurely, invalidating the hydrogen test as a measure of small-bowel transit. To assess the validity of the hydrogen test two additional patients were studied: one had multiple jejunal diverticula before and after a course of tetracycline; the other was a diabetic with diarrhoea, a positive ^{14}C-glycocholic acid test result, and a previous symptomatic response to antibiotics (metronidazole).[3]

After an overnight fast all subjects were given a solution of lactulose to drink (13 g lactulose as Duphalac syrup (20 ml) diluted with water to 130 ml). Breath samples were obtained every 10 minutes by end-expiratory sampling[7] and analysed for hydrogen content using the apparatus described by Bergman *et al.*[8] Sampling was continued with the subject inactive until a definite and sustained rise in breath hydrogen concentration was observed. This point was defined as the hydrogen appearance time.

Results

Six of the diabetics had good evidence of changed autonomic function in addition to a clinical history suggestive of autonomic

University Department of Medicine, Royal Hospital, Sheffield S1 3SR
J H B SCARPELLO, MB, MRCP, research assistant
M GREAVES, MB, MRCP, registrar
G E SLADEN, DM, FRCP, senior lecturer (now consultant physician, Guy's Hospital, London)