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The effect of *Corynebacterium parvum* on the humoral and cellular immune systems in patients with breast cancer

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SUMMARY

Corynebacterium parvum, a Gram-positive anaerobic bacillus thought to be a strong immunological stimulant, has been shown to decrease tumour growth and prolong survival in patients with metastatic disease. Study of the effect of a single injection of a strain of *C. parvum* (CN. 6134) in six patients with stage IV metastatic breast cancer is reported. Results of laboratory tests to judge the physical and immunological effects of the drug infusion 24 hr post-treatment and weekly thereafter for 3 weeks are evaluated.

Within 24 hr after *C. parvum* administration, most patients experienced fever and nausea. Blood counts and differential counts exhibited increased values 24 hr after treatment with a strong shift to the left. Lymphocyte and monocyte counts were greatly depressed at 24 hr. T-cell numbers in peripheral blood did not appear to be altered, but the picture with regard to B cells was less clear. Normal count was recovered by day 8.

It appears that intravenous administration of *C. parvum* produces a temporary marked immunological depression which returns to essentially normal values in 8 days. The return to normal may be accompanied by resolution of the endotoxin-like syndrome of side-effects. Further study of patients receiving this therapeutic agent is important to detect enhancement of the anti-tumour immunological response precipitated.

INTRODUCTION

Corynebacterium parvum, a Gram-positive anaerobic bacillus, has been shown to be a strong immunological stimulant, comparable in some respects to *M. bovis* (BCG) (Stiffel *et al.*, 1970). It has been noted that the degree of the immunological stimulation varies markedly with the strain of *C. parvum* used and the test animal employed. The Burroughs-Wellcome Company has developed a strain of *C. parvum*, CN. 6134, which is a very potent reticuloendothelial system stimulator (Adlan, Broughton & Scott, 1972).

The action of *C. parvum* on immunological systems is apparently multifaceted and includes: (1) reticuloendothelial stimulation via macrophage activation, (2) T-cell depression also evidenced by GVH suppression (graft versus host, a thymic lymphocyte-dependent function (Scott, 1972), and (3) change in the quantity and class of antibody which is produced. The studies carried out to date have been in animal models.

The use of C. parvum in animal anticancer models

C. parvum (strain 936B) was first shown to decrease tumour growth and enhance survival in mice by Woodruff & Boak (1966) and by Halpern *et al.* (1966). Since that time the Wellcome *C. parvum* has been shown to inhibit growth of mammary carcinoma, MCA-induced sarcoma, hepatomas and PC1 tumours

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in animal models (Lamensans *et al.*, 1968; Smith & Scott, 1972; Woodruff & Inchley, 1971; Woodruff, Inchley & Dunbar, 1972).

Human studies

Israel & Edelstein (1975) treated over 400 patients with *C. parvum* and noted that *C. parvum* significantly prolongs survival in metastatic disease. Mean survival in disseminated bronchogenic carcinoma increased from 5·6 months to 9·8 months. In advanced breast carcinoma, survival in *C. parvum*-treated patients was 85% at 1 year and 41% at 2 years compared with 41% and 16% in patients treated with the same chemotherapy without *C. parvum*.

Purpose of study

This study is designed to determine the effect of a single intravenous injection of *C. parvum* on the immune system in breast cancer patients.

PATIENTS AND METHODS

Six women with stage IV metastatic breast cancer involving the subcutaneous tissues, liver, lung, and/or bone were studied. All the patients were in good physical condition at the onset of the study. Patient 5 did have extensive bony metastases and was unable to walk because of pain when *C. parvum* was initially given. Each patient will be discussed later.

Following explanation of the protocol, informed consent was obtained and each patient's condition evaluated prior to initiation of the drug. The pre-infusion evaluations consisted of a bone scan, liver scan, brain scan, chest X-ray, serum electrophoresis, alkaline phosphatase, LDH, SGOT, SGPT, CBC, serum protein electrophoresis, serum immunoglobulin levels (IgG, IgA, IdD, IgE and IgM), and T and B lymphocyte counts in peripheral blood by rosette formation and antiglobulin membrane immunofluorescence. Intradermal skin testing was performed using histoplasmin, mumps skin test antigen, and purified protein derivative (second test strength). Antibody titres using *C. parvum* were measured by complement fixation, using 50% endpoint spectrophotometric measurement of haemolysis. Response of peripheral blood lymphocytes to the mitogen phytohaemagglutinin (PHA) was measured by incubating lymphoid cells with the agent for 72 hr and measuring the rate of proliferation by the incorporation of tritium-labelled thymidine into cellular DNA.

C. parvum (Burroughs-Wellcome CN. 6134) was supplied as a formalin-fixed, washed suspension preserved in 0·01% thiomersalate at 7 mg/ml. The drug was administered in 250 ml saline by intravenous infusion over a period of 2–4 hr at a body surface area adjusted dose of 5 mg per square metre. The intravenous route was chosen because it may be more effective immunotherapeutically, even though side-effects similar to endotoxaemia do occur (Woodruff & Inchley, 1971). (memo to investigators, Burroughs-Wellcome Company.)

Laboratory tests were obtained to judge the physical and immunological effects of the drug infusion 24 hr post-treatment and weekly thereafter for 3 weeks. This publication will discuss only those changes associated with the immunological status of the patients after drug administration.

Patient 1. This 60-year-old white woman originally presented in August 1968 with a mass in her left breast. A left radical mastectomy was performed for adenocarcinoma of the scirrhous type, with many cystic ducts and a few intraductal papillomas. Four of sixteen axillary lymph nodes were involved with metastatic disease, but the level of these nodes was not indicated in the pathologist's report.

In October 1968 the patient was given Cobalt teletherapy to the internal mammary and supraclavicular nodes. Therapy was terminated at a tissue dose of 3500 rads because of nausea and vomiting.

She remained asymptomatic until March 1974 when she developed left shoulder pain. Radiographs showed an osteolytic lesion in the proximal humerus. In addition, L2 and L3 had increased activity on bone scan. She was given 3000 rad of radiation to the left shoulder in May 1974 and radiation to the lumbar spine in July 1974. The radiation reduced her pain until September 1974 when an additional 2500 rad were given to the thoracic and lumbar vertebrae, sacrum and sacroiliac joints for pain.

In August 1974 she was also given Butazolidin Alka, Tylenol, and Halotestin 5 mg t.i.d. and in September 1974 a trial with L-dopa, which temporarily alleviated her pain.

On 2 October 1974 the patient was admitted to this hospital for evaluation. *C. parvum* was administered on 8 October. Within hours after administration of *C. parvum* the patient experienced chills, a fever of 104°F, nausea, vomiting, and general weakness. She was better in 24 hr and her myalgia subsided in a week. During this period she lost 6 lb.

Though her appetite remained suppressed she was asymptomatic until the 4th week after infusion when she again developed left shoulder pain. A week later she experienced abdominal pain with mucous diarrhoea, presumably a recurrence of old diverticulitis. Throughout the study the patient complained of a 'coldlike' symptom and frequent morning headaches.

Patient 2. A 49-year-old white woman presented originally in February 1974. Biopsy showed adenocarcinoma. A right radical mastectomy was performed and chest wall and pectoralis major invasion noted. The lower axillary nodes were

enlarged, but no tumour was noted in any nodes. Her X-rays and scans were all negative for tumour. Her serum chemistries including liver enzymes were normal.

As an outpatient she received six 1-ml injections of GCG (Glaxo) given at multiple intradermal sites at intervals of 4–6 weeks depending on her degree of reaction.

In October 1974 a 2×2 cm suture line metastasis was removed. Her bone scan was normal, the liver scan showed diffuse hepatomegaly without focal defects. Her LDH was slightly elevated, and all her other laboratory values were within limits.

A few hours after the administration of *C. parvum* on 7 October 1974 the patient noted extreme chilling, a fever of 102·4°F, nausea, vomiting, and malaise which lasted for 1 day. She complained of shortness of breath lasting 1 week. For the remainder of the study period the patient was asymptomatic.

Patient 3. A 68-year-old white woman with recurrent breast carcinoma had a history of breast cancer to 1961 when she had a simple mastectomy without radiation for adenocarcinoma in her scar. She was treated intermittently with Halotestin and did well until 1972 when nodules reappeared in the left pectoral area. At that time she was treated with radiation which produced regression. In March 1973 the left pectoral mass returned and in June 1973 a right axillary node was palpable. She had no additional treatment until November 1974 when her skin and pectoral metastases were bothersome. Physical examination on admission showed a 6×6 cm mass in the right breast and several masses at the incision site (mass 1: 2×3 cm; mass 2: 6 mm; mass 3: 2·7×1·6 cm). She was treated with *C. parvum* on 26 November 1974 and apart from a few hours of nausea and a temperature of 100°F, she experienced no side-effects.

Patient 4. A 67-year-old white woman had a right radical mastectomy in 1966 for cancer of the breast. In 1968 she developed recurrence in the area of previous excision and received radiation therapy at the site. Owing to degeneration and breakdown of the skin and failure of a split-thickness skin graft, an abdominal flap was placed to cover her chest wall. She did well until 1972 when a 4 inch ulcerated area developed in the graft site. Liver showed multiple focal defects compatible with metastasis. The patient was started on L-dopa suppression and Halotestin with a good clinical response. In November 1973, 5 Fu at 500 mg was started weekly because the disease showed progression. All drugs were discontinued in March 1974 because of a severe, unrelenting skin rash. At this time BCG was given weekly. Later, Cytoxan 100 mg was given each day when her white count was greater than 3900. Because of progression of the chest wall lesions while on this regime, *C. parvum* was administered to the patient. Transient nausea, vomiting, and hypotension were associated with drug administration.

Patient 5. A 60-year-old white woman was 2 years post-right radical mastectomy for adenocarcinoma. Twelve months prior to receiving *C. parvum* she developed right hip pain and suffered a 30 lb weight loss. Eight months before *C. parvum* therapy, her second lumbar vertebra collapsed due to bony metastasis and she was given fifteen cobalt treatments. Five months prior to initiation of *C. parvum* therapy the patient received some cytoxan, which was stopped in October 1974. During her hospitalization in December 1974 she was found to have extensive bony metastases but no demonstrable liver metastases. On 19 December 1974 she received *C. parvum*. She developed severe nausea, vomiting, tachycardia (176) and hypertension (170/100) for 12 hr and was ill with myalgia and weakness for 10 days.

Patient 6. A 58-year-old white woman had a left radical mastectomy 10 years ago and a right simple mastectomy 4 years ago for carcinoma of the breast. She had documented axillary metastasis and was treated with 500 mg of 5 Fu, 1 mg vincristine, 25 mg methotrexate, and 100 mg cytoxan daily by mouth. Treatments were stopped because the patient experienced severe drug toxicity. Intermittent BCG therapy was started in October 1972 and given at monthly intervals until April 1974 when the patient elected to stop the BCG treatments. On admission to the hospital in December 1974 she had a small nodule in the area of her right breast amputation scar. This was biopsied and shown to be a recurrence. *C. parvum* was given on 19 December 1974. She had an extremely benign post-*C. parvum* course.

RESULTS

Immune function

Table 1 indicates the blood counts and differential counts for each patient taken before *C. parvum* administration and at intervals following drug infusion. The only remarkable changes noted are increased values 24 hr after treatment with a strong shift to the left. Lymphocyte counts are greatly depressed at 24 hr. Normal count is recovered by day 8.

Table 2 shows the results of T- and B-lymphocyte enumerations on each patient. *C. parvum* does not appear to alter the T-cell numbers in peripheral blood. The picture is less clear with regard to B cells. Enumeration by membrane immunoglobulin (Fluor Ig) receptors is regarded the most reliable B-cell quantification method by the World Health Organization. The B cells by this criterion appear depressed in patients 1 and 2, about normal in patients 3 and 6, very high in patient 5, and changeable in patient 4. The EAC-rosette method, which depends upon the presence of receptors for the third component of complement on the B-cell surface, shows subnormal B-cell numbers in all patients compared to typical normal control values reported in the same laboratory.

Table 3 reports the results of two of the assay protocols. The centre column indicates stimulation of T-

TABLE 1. Peripheral blood counts and differential counts on cancer patients treated with *C. parvum* (figures are expressed as cells/mm^3)

	Day	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6
Total	Pre	7500	6500	5500	4400	5000	7400
WBC	1	14,000	13,500	13,500	13,500	7500	9500
	8	7000	n.d.	6500	5000	6500	5750
	15	n.d.	4500	4500	3500	6000	5100
	22	4300	3500	6900	3500	4250	4250
PMN	Pre	6375 (85)	3770 (58)	3685 (67)	2862 (65)	4100 (82)	3404 (46)
	1	13,300 (95)	11,465 (85)	12,285 (91)	12,555 (93)	6075 (81)	9310 (98)
	8	5180 (74)	n.d.	5720 (88)	3250 (65)	5200 (80)	3623 (63)
	15	n.d.	2790 (62)	2700 (60)	2170 (62)	4800 (80)	3009 (59)
	22	2310 (55)	1960 (56)	5382 (78)	2800 (80)	3060 (72)	2168 (51)
Monos	Pre	320 (8)	455 (7)	55 (1)	352 (8)	300 (6)	518 (7)
	1	140 (1)	0 (0)	270 (2)	405 (3)	825 (11)	95 (1)
	8	0 (0)	n.d.	260 (4)	500 (10)	195 (3)	188 (5)
	15	n.d.	270 (6)	405 (9)	245 (7)	60 (1)	153 (3)
	22	336 (8)	35 (1)	138 (2)	105 (3)	468 (11)	340 (8)
Lymphs	Pre	375 (5)	2275 (35)	1595 (29)	1144 (26)	800 (16)	3108 (42)
	1	700 (5)	540 (4)	1080 (8)	405 (3)	450 (3)	475 (5)
	8	1750 (25)	n.d.	455 (7)	900 (18)	1105 (17)	1725 (30)
	15	n.d.	1215 (27)	1170 (26)	1015 (29)	1200 (20)	1683 (33)
	22	1428 (34)	1330 (38)	1587 (23)	595 (17)	765 (18)	1573 (37)

n.d. = Not determined.
The figures in parentheses are the percentage of total WBC.

lymphocyte populations following exposure to PHA. The stimulation index is computed as the ratio of counts per minute titriated thymidine incorporated in the presence of PHA to counts incorporated in unstimulated matched controls. In general, there is a tendency towards low stimulation indices 24 hr following *C. parvum* administration. This may be due to the difficulty in isolating sufficient leucocytes to carry out an adequate assay. Counts are back to normal or increased by 8 days following *C. parvum* infusion. The increases in patients 1, 2 and 4 are not remarkable; they fall near the high normal range. Patient 3 shows exceptionally high stimulation 15 days following *C. parvum* treatment. Patient 6 is a highly exceptional PHA response, ranking among the highest responses yet seen in our laboratory. This is due to two factors; not only are the lymphocytes highly stimulated by PHA, but the control values are greatly depressed, increasing the ratio considerably. Patient 5 shows the typical pattern of reduced response on day 1 followed by an increase by day 8. Day 22, however, shows great depression, probably indicating a failing immune response secondary to malignant disease.

The other assay recorded in Table 3, the complement-fixation assay, indicates the serological response to *C. parvum* administration. No data has been found in the literature which indicates expected values for this parameter. It can be seen that two patients (2 and 4) form no complement-fixing antibody against the organism while the remaining four patients (1, 3, 5 and 6) show good titres. There does not seem to be any correlation between serological response of the IgM type, measured by this assay, and the course of disease.

Post-therapy clinical course

Patient 1. After a stormy month of intermittent chills, fever, myalgia, weakness and the sensation that 'the top of her head was going to come off', the patient became asymptomatic. She has remained well with only mild aches which were relieved with non-narcotic analgesic. At this time she has no major symptoms and is free of all the abnormal clinical findings she had prior to her *C. parvum* infusion. We consider her to demonstrate a very good clinical response.

TABLE 2. T- and B-lymphocyte numbers in peripheral blood of cancer patients treated with *C. parvum* (EAC = complement-receptor lymphocytes; Fluor-Ig = membrane immunoglobulin present by fluorescence; T cells by E-rosette assay)

Patient	Day	Percentage T cells	Percentage B cells	
			EAC	Fluor-Ig
1	Pre	83·7	1·0	3·8
	1	69·0	6·0	—
	8	80·3	2·3	1·0
	15	78·0	3·0	2·1
	22	78·0	4·5	15·8
2	Pre	87·2	3·8	3·9
	1	75·0	—	8·6
	8	81·7	6·8	5·8
	15	75·7	5·1	3·7
	22	77·0	5·3	6·2
3	Pre	77·0	6·5	4·8
	1	70·5	3·5	12·3
	8	72·0	10·0	7·4
	15	76·0	5·5	7·3
	22	86·7	7·0	8·2
4	Pre	78·5	8·0	5·9
	1	73·0	5·0	12·1
	8	77·3	6·0	5·5
	15	82·7	5·3	10·4
	22	87·0	3·0	3·0
5	Pre	84·3	4·5	4·0
	1	93·0	5·5	18·0
	8	76·3	4·8	12·9
	15	78·3	7·8	15·9
	22	74·7	3·8	20·1
6	Pre	83·7	4·8	7·8
	1	87·5	9·3	6·9
	8	79·3	6·3	5·3
	15	79·0	9·8	7·3
	22	79·0	2·3	6·1

TABLE 3. PHA stimulation indices of peripheral blood lymphocytes and units of complement fixed in presence of *C. parvum* by patient serum before and during *C. parvum* immunotherapy

Patient	Day serum drawn	Stimulation index	C′ 50 units fixed (ml)
1	0	7·1	0
	1	1·88	0
	8	12·74	0
	15	10·64	0
	22	12·40	0 (trace)
2	0	8·72	0
	1	2·32	0
	8	7·89	12
	15	13·92	24
	22	12·97	0
3	0	6·84	0
	1	2·54	n.d.
	8	37·62	0
	15	91·27	6
	22	47·24	12
4	0	6·56	0
	1	1·42	n.d.
	8	30·01	0
	15	24·64	0
	22	46·51	0
5	0	42·32	0
	1	2·86	0
	8	82·48	12
	15	43·37	12
	22	2·08 (?)	12
6	0	36·11	0
	1	2·23	0
	8	540·22	8
	15	105·01	8
	22	411·72	8

n.d. = Not determined.

Patient 2. Clinically, this patient had very few side-effects after the first week of the *C. parvum* infusion (October 1974). She has been active, up and about, with absolutely no complaints, and had no problems until examined the 1st week in February 1975, at which time she noted a 1 × 1 cm palpable nodule in the scar of her right breast amputation. She is essentially asymptomatic but will require additional evaluation.

Patient 3. This patient had very few side-effects and clinically did very well after her *C. parvum* infusion. However, during the infusion, the patient's systolic blood pressure dropped from its normal of 170 to 100 and she felt nauseated and weak but did not vomit. She developed chills and fever 4 hr after the infusion. The fever resolved rapidly and was never above 100°F. At the 2-week follow-up we noted white infiltrate in the centre of each chest wall metastasis. This appeared to be an attempt at rejection as the surface of each nodule began weeping by the next week. Her tumour has remained stable in size 2

months after her initial infusion with *C. parvum*. She is asymptomatic except for the recurrent chest wall tumour.

Patient 4. This patient had no post-infusion problems. She was asymptomatic and was up going about her normal activities immediately. She did not complain of myalgia or flu-like symptoms. She is clinically stable as far as the progression of her disease is concerned. We have seen essentially no progression since the *C. parvum* infusion on 26 November 1974.

Patient 5. This patient had an extremely stormy post-infusion course and was quite ill for 2 weeks. She had always come to the clinic in a wheelchair or on a cart, but walked into the clinic for the first time during the 3rd and 4th weeks after her *C. parvum* infusion because she had 'much less pain'. Her clinical improvement was transient, however, and she has just undergone a hypophysectomy in an attempt to relieve her intractable severe pain. Clinically, her bony metastases are at a critical point with regard to weight-bearing.

Patient 6. This patient had a benign post-*C. parvum* infusion course and has done well ever since. She has had no complaints except that 6 weeks after her infusion of *C. parvum* she had a mild flu-like syndrome that came and left in a period of 48 hr. Clinically she has not demonstrated adverse side effects and is doing well without evidence of recurrent or activated tumour at this time.

DISCUSSION

This report describes the immunological sequelae of the intravenous injection of *Corynebacterium parvum* and is part of a Phase I clinical trial of this biological in breast cancer patients. *C. parvum* has traditionally been thought to be a non-specific immunological stimulant, and use of this agent is considered adjuvant immunotherapy, similar to the use of BCG.

The data presented here do not completely support this hypothesis. In fact, shortly after *C. parvum* administration (within 24 hr) most patients experienced side-effects of fever and nausea accompanied by a strong shift to the left in the white blood cell differential count and a severe depression in the numbers of circulating lymphoid cells. By 8 days after injection, the blood picture returned to normal (Table 1).

One method of evaluating immunological changes is to enumerate changes in T- and B-lymphocyte numbers, since these cells are responsible respectively for cell-mediated and humoral immune responses. Interestingly, the percentage of T cells was not altered, even during the 24 hr drop in total lymphocyte count. B-cell numbers appeared variable but low; no correlation is evident between B-cell numbers and the ability to produce complement-fixing anti-*C. parvum* antibody (Tables 2 and 3).

T-cell function and the general status of the cell-mediated immune system can be gauged by the response of these cells to the mitogen phytohaemagglutinin (PHA). This reaction was depressed at 24 hr, but rebounded by day 8. In several patients, hyperresponsivity was demonstrated, with no associated clinical findings.

From these results it appears that intravenous administration of *C. parvum* at the surface area adjusted dose used here produces a temporary marked immunological depression, which returns to essentially normal values in 8 days. The return to normal may be accompanied by resolution of the endotoxin-like syndrome of side-effects. Further studies will determine how quickly these values return to normal.

The immunological anti-tumour benefits of *C. parvum* therapy may require multiple treatments, as does BCG. It is important, therefore, to study carefully the changes in immune parameters in patients receiving this therapeutic agent. This information is important not only from the stand-point of detecting enhancement of the anti-tumour immunological response, but bears upon the ability of the patient to maintain immunological protection from internal and/or environmental agents hazardous to general health. We look forward to further reports of human immune reaction associated with the use of *C. parvum*.

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