

THE ORTHOMOLECULAR TREATMENT OF CANCER*
II. CLINICAL TRIAL OF HIGH-DOSE ASCORBIC ACID SUPPLEMENTS IN
ADVANCED HUMAN CANCER

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SUMMARY

This communication reports the clinical response of fifty consecutive advanced cancer patients to the continuous administration of large doses of ascorbic acid. It concludes that this simple and safe form of medication is of definite value in the palliation of terminal cancer. The findings suggest that it should be employed as a standard supportive measure to reinforce established methods of treatment in the general management of earlier and more favorable cases.

INTRODUCTION

The concept that ascorbic acid might have specific value in the prevention and treatment of cancer has evolved over a number of years¹⁻⁴, and the general arguments in favor of its use are set out in the preceding article⁵. This communication describes the clinical responses of fifty consecutive advanced cancer patients to this form of treatment.

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Abbreviations: AA, ascorbic acid; ESR, erythrocyte sedimentation rate; GSR, ground substance depolymerization residues from tumor stroma; PHI, physiological hyaluronidase inhibitor.

DESIGN OF THE STUDY

Since November 1971, large doses of ascorbic acid have been administered to a number of cancer patients attending Vale of Leven and Hairmyres Hospitals. These patients fall into three main groups:

Group 1. Bladder papilloma and carcinoma

Following the reports by SCHLEGEL and his associates that ascorbic acid appeared to have some protective effect against bladder cancer⁶, the majority of patients coming under our care suffering from this anatomical variant of neoplasia have received ascorbic acid *in addition to* standard methods of treatment. The results in this group are not included in the present report, but they have enlarged our experience in the use and problems associated with long-term high-dose ascorbic acid therapy.

Group 2. Other cancers treated by standard methods supplemented by ascorbic acid

In a number of our patients, ascorbic acid has been prescribed as a *supplement to* established forms of cancer treatment, such as after surgery, irradiation or endocrine ablation, or in combination with orthomolecular doses of hormones, and in a very small number in conjunction with cytotoxic agents. These patients are also excluded from the present report.

Group 3. Advanced cancer treated by ascorbic acid alone

In every clinical practice in the cancer field, terminal situations are encountered in which all forms of conventional treatment have been tried and failed; in others they cannot even be applied at the time of first diagnosis because of widespread dissemination of the disease, or are precluded by other major constitutional factors. We have administered ascorbic acid as the only form of definitive treatment in this advanced group, in whom no hopeful treatment by conventional methods could be suggested, and this report presents a summary of the clinical responses of the first fifty patients in this category.

ETHICAL AND OTHER CONSIDERATIONS

Investigating the possible value of any new treatment in such a difficult area as advanced human cancer poses many familiar problems.

Ethics rightly prohibit anything approaching "experimentation" on human subjects, particularly those in the distressing terminal stages of a lethal disease. Every patient in the series here reported was examined by at least one independent clinician, and a patient was only included in the series if all clinicians agreed that no form of conventional treatment had the least prospect of success. This principle has had an important consequence tending to introduce a bias against our findings. Some patients, initially regarded as "hopeless" improved sufficiently on ascorbic acid alone for established forms of cancer treatment to be initiated at a later date; this improvement

and their transition from Group 3 to Group 2 automatically excludes them from the present report. Those remaining are, by the very nature of their selection, those least likely to show any benefit from any form of treatment.

We have made no attempt to conduct a double-blind clinical trial for two reasons. Because of all the variables involved in the progress of human cancer, it would be quite impossible for us to obtain anything like "exactly matched pairs" for comparison within our own clinical practice, and in any case the usual course of untreated terminal cancer is well enough known. Moreover, as our clinical experience increased, we felt it to be ethically wrong to withhold ascorbic acid in otherwise hopeless situations, merely for the sake of obtaining observations of dubious significance for statistical comparison. In conducting this pilot study, we agree with FEINSTEIN⁷ that uncontrolled clinical observations can still advance medical progress and that "our best approach to many problems in therapy will be to rely upon the judgements of thoughtful people who are familiar with the total reality of human ailments". This statement seems to us to be particularly applicable to the terminal stages of human cancer.

From the onset, we have been well aware that our results might be distorted by "placebo effect" on the part of our patients and their relatives, and by "anticipation effect" on our own part, acting as both therapists and observers. These potential sources of error have been particularly difficult to eliminate. Following Scottish custom, no patient in the series was directly informed that he or she was suffering from incurable terminal cancer, but we have little doubt that the great majority, having endured the gamut of major surgery, radiotherapy and all the rest, without lasting benefit, were only too well aware of the true diagnosis and imminent prognosis.

All patients were treated routinely in general surgical or medical wards and not in a special unit. As outpatients they attended routine consultative clinics along with many other non-cancerous patients, and we took special care to avoid giving any impression of special interest. All close relatives were fully informed as to the true diagnosis and usual outcome. To both patients and their close relatives, ascorbic acid was always described as a medication "which might help a little" and never as a definitive form of treatment.

We are convinced that the general awareness of failure of standard treatment regimes produced a strong "reverse placebo effect" in many of these patients entering the trial. We believe that all these factors have tended to minimize "placebo and anticipation effects", but we accept that they can not be entirely excluded.

TREATMENT REGIMES

(a) Intravenous ascorbic acid

In many of the patients here reported, treatment was initiated in hospital by the continuous intravenous infusion of ascorbic acid for periods up to 10 days. Ringer's Lactate Solution was used as the "carrier" and infused at a standard rate of 2 l per day. (Ascorbic acid in isotonic dextrose tends to induce a chemical phlebitis.) "Sterile Parenteral Ascorbic Acid Solution" purchased commercially in 500-mg ampoules

TABLE I
RESPONSE OF FIFTY ADVANCED CANCER PATIENTS TO CONTINUOUS LARGE DOSES OF ASCORBIC ACID

Case No., sex, age	Diagnosis	Previous treatment and condition on entry to ascorbic acid trial	Ascorbic acid regime: i.v. (g/day, days); oral (g/day, days) (total AA administered)	Outcome	Category of response and comments
1 F 74	Carcinoma of breast with widespread metastases	None: terminal situation at first diagnosis	10 × 2; (80 g)	10 × 6	Died on day 8 1. No response
2 M 69	Carcinoma of stomach with hepatic and sub- cutaneous metastases	None: terminal situation at first diagnosis	10 × 6; (110 g)	10 × 5	Died on day 12 1. No response
3 F 62	Carcinoma of stomach with diffuse intra- peritoneal spread	None: irresectable at laparotomy; profuse obstructive vomiting	10 × 9; (90 g)	0 × 0	Died on day 9 1. No response
4 F 71	Carcinoma of bile duct with obstructive jaundice	None: irresectable mass in porta hepatis with direct liver infiltration	10 × 5; (210 g)	10 × 16	Died on day 22 1. No response
5 M 65	Reticulum cell sarcoma of ileum with widespread metastases	Palliative resection for intestinal obstruction	10 × 10; (820 g)	10 × 72	Died on day 82 1. No response
6 F 66	Carcinoma of stomach with peritoneal and hepatic metastases	None: irresectable at laparotomy; short history and rapid progression	5 × 1; 23 × 1; 45 × 3; (193 g)	10 × 3 — —	Died on day 18 1. No response
7 M 78	Carcinoma of bronchus with mediastinal spread; in cardiac failure	None: irresectable at time of first diagnosis	5 × 6; (440 g)	10 × 41	Died on day 52 1/2. No response Subjective benefit

TABLE I (Continued)

Case No., sex, age	Diagnosis	Previous treatments and condition on entry to ascorbic acid trial	Ascorbic acid regime: i.v. (g/day, days); oral (g/day, days) (total AA administered)	Outcome	Category of response and comments
8 F 57	Advanced carcinoma of breast concealed for 12 years	None: massive infiltration of chest wall ulcerating through to pleural involvement and gross lymphedema of arms	10 × 8; (220 g) 10 × 14	Died on day 22	1/72. No response Some subjective benefit
9 F 58	Adenocarcinoma of colon with local recurrence	Posterior pelvic exenteration; massive pelvic recurrence with abscess and intestinal fistulae	45 × 4; (180 g) *not tolerated 0 × 0*	Died on day 32	1. No response
10 F 76	Adenocarcinoma of the colon with hepatic metastases	Palliative sigmoid colectomy; liver metastases present	0 × 0; (220 + g) *oral intake thereafter reduced by patient, eventually to zero. 10 × 20+*	Died on day 57	1/2. No clear response Ingestion of AA evoked right subcostal pain
11 F 54	Post-radiation fibrosarcoma 13 years after mastectomy and irradiation for carcinoma of breast	None: massive malignant ulceration of chest wall and shoulder girdle; in intolerable pain	0 × 0; (190 g) 10 × 19	Died on day 22	1/2. No clear response Better control of pain by opiates
12 F 56	Carcinoma of rectum with pelvic spread	Posterior pelvic exenteration; early development of deep pelvic recurrence	10 × 10; (580 g) 10 × 48	Died on day 62	1/6. No clear response Brisk terminal illness with "explosive" tumor growth
13 M 71	Carcinoma of bronchus with mediastinal spread	None: untreatable at time of first diagnosis	0 × 0; (960 g) 10 × 96	Died on day 100	1/2. No clear response Subjective benefit
14 M 70	Carcinoma of bronchus infiltrating esophagus with hepatic metastases	None: untreatable at time of first diagnosis; quite terminal	0 × 0; (580 g) 10 × 58	Died on day 58	1/2 ? Benefit Lived in comfort beyond expectation

TABLE I (Continued)

Case No., sex, age	Diagnosis	Previous treatment and condition on entry to ascorbic acid trial	Ascorbic acid regime: i.v. (g/day, days); oral (g/day, days) (total AA administered)	Outcome	Category of response and comments
15 F 71	Renal adenocarcinoma with skeletal metastases	Nephrectomy; irradiation of spinal metastases on day 150 for pain relief; became paraplegic terminally	10 × 9; (871 g) 5 × 163	Died on day 176	1/2. ? Benefit Stable for months then brief terminal illness
16 F 64	Carcinoma of bronchus with visceral and skeletal metastases	None: untreatable at time of first diagnosis; terminal	0 × 0; (1820 g) 10 × 182	Died on day 187	1/2. No clear response ? Stable for months then brief terminal illness
17 F 49	Cystadenocarcinoma of ovary with hepatic metastases	Hystero-salpingo-oophorectomy; returned with massive malignant hepatomegaly	0 × 0; (2240 g) 10 × 224	Died on day 226	1/2. No clear response Stable for months then brief terminal illness
18 M 47	Pseudomyxoma peritonei	Diagnosed at laparotomy; ascites requiring frequent paracentesis	0 × 0; (650 g) 5 × 130	Died on day 132	2. Beneficial Control of ascites. Sudden "unexpected" death from intestinal obstruction
19 F 53	Carcinoma of breast with visceral and skeletal metastases	Mastectomy, radiotherapy, hormones; terminal situation, in severe pain requiring opiates	5 × 7; (595 g) 8 × 70	Died on day 86	2. Beneficial Complete relief of bone pain and need for opiates
20 M 73	Renal adenocarcinoma multiple pulmonary and hepatic metastases	None: regarded as untreatable at time of first diagnosis	10 × 5; (2860 g) 10 × 281	Died on day 293	2/3. Beneficial Changed from terminal care situation. Steady improvement for months then sudden terminal deterioration

TABLE I (Continued)

Case No., sex, age	Diagnosis	Previous treatment and condition on entry to ascorbic acid trial	Ascorbic acid regime: i.v. (g/day, days); oral (g/day, days) (total AA administered)	Outcome	Category of response and comments
21 M 44	Poorly differentiated transitional cell carcinoma of bladder with skeletal metastases	Cystodiathermy, partial cystectomy, radiotherapy, chordotomy; quite terminal; in intense pain inadequately controlled by morphine sulfate 30 mg i.v. three-hourly	10 × 10; (348 g)	Died on day 34	2/ ? 4. Beneficial Dramatic relief from bone pain and no further need for opiates. Sudden death from intestinal obstruction
22 F 61	Carcinoma of stomach with peritoneal and hepatic metastases	None; untreatable at first diagnosis; ascites requiring frequent paracentesis.	10 × 6; (948 g)	Died on day 121	2/ ? 3. Beneficial Control of ascites then very brief terminal phase
23 F 49	Disseminated carcinoma, primary unknown, but histologically consistent with primary in breast	None; presented in terminal state with anemia and severe bone pain; skeletal survey demonstrated innumerable osteolytic metastases	10 × 7; (340 g)	Died on day 35	2/3. Beneficial Complete relief from bone pain. Became unexpectedly alert and ambulant. Sudden death in coma.
24 F 73	Invasive carcinoma of the bladder	Radiotherapy: very distressed by constant hematuria, dysuria and intense frequency	10 × 10; (1030 g)	Died on day 110	2/3. Beneficial Complete symptomatic relief for months
25 F 68	Carcinoma of colon with peritoneal and hepatic metastases	Colectomy, then one year later widespread recurrence; quite terminal	14 × 1; 30 × 1; 45 × 8; (1914 g)	Died on day 170	2/4 Beneficial Fluctuating course, but prolonged survival
26 F 48	Carcinoma of bronchus with mediastinal infiltration	Inoperable; palliative R/T given with benefit, then progressive deterioration into terminal state	10 × 4; (840 g)	Died on day 90	2/3. Beneficial Reversal of terminal trend for 2 months, months, then "explosive" tumor growth

TABLE I (Continued)

Case No., sex, age	Diagnosis	Previous treatment and condition on entry to ascorbic acid trial	Ascorbic acid regime: i.v. (g/day, days); oral (g/day, days) (total AA administered)	Outcome	Category of response and comments
27 M 49	"Brain tumor" of unknown histology; autopsy refused; carotid angiogram: a large, definitely malignant tumor of right temporal lobe	None: presented in moribund state with intolerable headache, anorexia and projectile vomiting; bilateral papilledema. Opiates and corticosteroids given without benefit	10 × 11; (360 g) 10 × 25	Died on day 37	2/3. Beneficial Quite striking relief from headache and vomiting. Sudden death in coma after definite reversal of clinical trend
28 F 57	Carcinoma of rectum with extensive pelvic spread	Inoperable; large fixed tumor mass in pelvis, constant diarrhea, gross weight loss; cachectic and anemic with life expectancy of weeks	0 × 0; (2840 g) 10 × 284	Died on day 287	3. Beneficial Gradual but sustained clinical improvement with weight gain. No appreciable change in tumor mass and diarrhea persisted. Rapid terminal illness
29 M 67	Carcinoma of gallbladder with direct liver invasion	None: irresectable at dia- gnostic laparotomy; deepening jaundice and gross hepatomeg- aly; general condition good	10 × 9; (1658 g) 8 × 196	Died on day 209	3/4. Beneficial Jaundice cleared completely with steady clinical improvement for 4 months, then slow deterioration
30 F 77	Papillary transitional cell carcinoma of bladder; in cardiac failure	None: definitive treatment precluded by cardiac state; large "solid" ulcerating bladder tumor evident on cystoscopy and measurable on cystography; very distressed by constant strangury and hematuria	5 × 5; (257 g) 8 × 29	Died on day 34	3/4. Beneficial Complete relief of all bladder symptoms, with apparent reduction in tumor size. Death from pulmonary embolus

TABLE I (Continued)

Case No., sex, age	Diagnosis	Previous treatment and condition on entry to ascorbic acid trial	Ascorbic acid regime: i.v. (g/day, days); oral (g/day, days) (total AA administered)	Outcome	Category of response and comments
31 M 52	Carcinoma of bronchus with mediastinal involvement and paresis of left vocal cord	None; untreatable at first diagnosis; multiple pathology, diabetes, gout, rheumatoid arthritis, peripheral vascular disease	0 × 0; — ; (5340 g)	Died on day 460	3/4/5. Beneficial Early subjective improvement with relief of cord paresis. No increase in size of lung tumor for 18 months. Died from peripheral vascular disease and infection
32 M 70	Differentiated transitional cell carcinoma of bladder	Repeated cystodiathermy for years, megavoltage radiotherapy, cytotoxics; massive bladder recurrence, unfit for total cystectomy; distressing hematuria, strangury and increased micturition frequency; terminal	0 × 0; (805 g) *discontinued because of nausea	Died on day 252	3. Beneficial Symptomatic relief and change in cystoscopic appearance from "red fleshy" to "white sloughing" tumor Death from uremia
33 M 42	Carcinoma of stomach with extensive recurrence	Partial gastrectomy; early recurrence causing intestinal obstruction; palliative ileal resection; deteriorating	10 × 5; (2530 g) *discontinued because of vomiting	Died on day 258	3. Beneficial Interruption of rapid downhill course. "Static" for months, then brief terminal illness
34 F 68	Carcinoma of breast with pleural metastases	Mastectomy; radiotherapy; hormones; terminal cancer situation; anemic, confined to bed; on pethidine 50 mg four-hourly; Horner's syndrome; death imminent	0 × 0; (5500 g)	Died on day 567	3/4. Beneficial Pain relief and slow general improvement for over a year, then slow terminal deterioration

TABLE I (Continued)

Case No., sex, age	Diagnosis	Previous treatment and condition on entry to ascorbic acid trial	Ascorbic acid regime; i.v. (g/day, days); oral (g/day, days) (total AA administered)	Outcome	Category of response and comments
35 F 75	Carcinoma of rectum with pelvic and hepatic metastases	None: untreatable at first diagnosis; innumerable large hepatic metastases present; rectal bleeding, tenesmus and diarrhea for one year; steadily deteriorating	5 × 7; (1085 g) 5 × 210	Died on day 223	3/4. Beneficial "Static" for many months, then 48-h terminal illness with death in coma
36 F 70	Carcinoma of caecum with multiple hepatic metastases	Right hemicolectomy for Ca caecum; returned with deepening jaundice; second laparotomy confirmed many large hepatic metastases; rapidly deteriorating	10 × 10; (960 g) *discontinued because of nausea	Died on day 144	3/4/5. Beneficial Malignant jaundice cleared by day 18. Remained "well" for over 2 months, then steady deterioration with terminal melena
37 F 49	Carcinoma of ovary with malignant ascites	None: rapid presentation with tense malignant ascites requiring frequent paracentesis (4-5 l per week); large irregular fixed mass in pelvis with malignant hepatomegaly; terminal	45 × 10; (1180 g) *discontinued because of nausea	Died on day 183	3/4. Beneficial Striking subjective response with complete control of ascites for 4 months, then (stopping AA) ascites recurred with death in 6 months
38 M 93	Well-differentiated transitional cell carcinoma of bladder	Repeated cystodiathermy for years; partial stectomy; radiotherapy; massive recurrence with constant hematuria and stranguary	0 × 0; (1200 g) 5 × 240	Died on day 241	3. Beneficial Complete relief within 2 months, after years of symptoms. Sudden death from cerebral hemorrhage

TABLE I (Continued)

Case No., sex, age	Diagnosis	Previous treatment and condition on entry to ascorbic acid trial	Ascorbic acid regime: i.v. (g/day, days); oral (g/day, days) (total AA administered)	Outcome	Category of response and comments	
39 M 74	Diffuse urinary tract papillomatosis	Bladder papilloma successfully treated by repeated cystodiathermy, but hematuria persisted requiring repeated transfusion; pyelography demonstrated bilateral renal papillomatosis; not terminal but untreatable by conventional methods	0 × 0; — (6510+ g)	5 × 20 10 × 641+ (6510+ g)	Alive and well	4. Beneficial No significant hematuria for 18 months, and no need for further transfusion. Improvement in pyelogram
40 F 56	Carcinoma of colon with hepatic metastases	Palliative sigmoid colectomy for obstructing adenocarcinoma; liver metastases present	0 × 0; (5730+ g)	10 × 573+ (5730+ g)	Alive and well	4. Beneficial Right subcostal pain after ingestion of AA for some months, but now symptom-free
41 F 66	Carcinoma of breast with pleural metastases	Mastectomy with axillary clearance; radiotherapy; emergency readmission with massive malignant pleural effusion requiring repeated thoracentesis	10 × 8; (6350+ g)	10 × 627+ (6350+ g)	Alive and well	4. Beneficial Clinically static, with no reaccumulation of pleural effusion or evidence of progressive disease
42 F 68	Carcinoma of ovary with peritoneal and hepatic metastases	None: untreatable terminal cancer (see text)	5 × 7; (155 g)	5 × 24 (155 g)	Died on day 33	5. Regression (see text)
43 M 77	Carcinoma of pancreas with obstructive jaundice	Irresectable; palliative hepatico-duodenostomy; recurrent untreatable obstructive jaundice	0 × 0; (1575 g)	5 × 315 (1575 g)	Died on day 317	5. Regression (see text)

TABLE I (Continued)

Case No., sex, age	Diagnosis	Previous treatment and condition on entry to ascorbic acid trial	Ascorbic acid regime: i.v. (g/day, days); oral (g/day, days) (total AA administered)	Outcome	Category of response and comments
44 M 55	Carcinoma of kidney with skeletal metastases	Nephrectomy plus excision of one skeletal metastasis	0 × 0; — ; (9140 g)	Died on day 659	5. Regression (see text)
45 M 40	Reticulum cell sarcoma	None: generalised reticulosis (see text)	10 × 10; (1100+g)	Alive and well	5. Regression (see text)
M 69 46	Carcinoma of colon with liver metastases	Recurrence after palliative resection (see text)	8 × 3; — ; (9994+g)	Alive and well	5. Regression (see text)
47 M 66	Carcinoma of bronchus with metastases	None; untreatable at first diagnosis	10 × 6; (120 g)	Died on day 17	6. Harmful (see text)
48 M 63	Chondrosarcoma of ilium with metastases	Palliative radiotherapy	10 × 3*; (30 g)	Died on day 9	6. Harmful (see text)
49 M 42	Teratoma of testis with metastases	Orchidectomy; radiotherapy	8 × 3*; (24 g)	Died on day 15	6. Harmful (see text)
50 M 45	Carcinoma of kidney with metastases	Nephrectomy; hormones; cytotoxic chemotherapy; palliative radiotherapy	0 × 0; (15 g)	Died on day 3	6. Harmful (see text)

*discontinued ascorbic acid because of adverse reaction

from Antigen International of the Republic of Ireland, was added to the carrier solution immediately before administration (5 ampoules per 0.5 l bottle) to give a standard infusion rate of 10 g of ascorbic acid per day. Variations in individual dose regimes are outlined in Table I, some few patients receiving up to 45 g i.v. per day without complication, but without any clear therapeutic advantage.

(b) Oral ascorbic acid

The great majority of patients received oral ascorbic acid usually at a standard dose of 10 g per day, either as their sole treatment, or commencing immediately after the intravenous regime. Individual variations are outlined in Table I. Initially we used a number of proprietary formulations but found them not only unduly expensive but also unpalatable for terminal cancer patients in the dose range desired. The most acceptable form for oral medication in these circumstances proved to be the simple "Ascorbic Acid Mixture" devised by our senior pharmacists, Miss Meikle and Miss Vowles:

<i>R.</i> ,	
Ascorbic acid	100 g
Sodium bicarbonate	48 g
70 % Sorbitol syrup	200 ml
Distilled water to	600 ml

Dose: 15 ml (2.5 g ascorbic acid) four times a day after meals. The mixture to be continued indefinitely.

Dispensed in dark brown bottles, this mixture has a shelf life of at least two weeks. At the time of writing, one patient has taken this mixture continuously for over 2.5 years, and several others for more than 2 years, without, in their case, any significant ill-effects.

Current treatment policy

At the commencement of this study, our standard treatment regime was an initial period of intravenous administration, followed by oral medication continued indefinitely as described above. With increasing experience, we now tend to believe that the intravenous regime is probably unnecessary as a routine measure, and need only be employed in clinical situations, where vomiting, anorexia, or other complications of malignancy preclude oral administration.

SIDE EFFECTS OF ASCORBIC ACID IN ADVANCED CANCER

Ascorbic acid tends to be regarded as a completely innocuous chemical compound which can be given in very large amounts without harmful side effects. Although we agree with its general safety, we consider that it is not completely harmless in the particular clinical context of advanced cancer.

Ascorbic acid is alleged to possess diuretic activity, but this has not been notice-

able with the formulations we have employed; indeed, if anything, our experience has been rather the reverse. The majority of our patients have developed some degree of fluid retention and gravitational edema. Although this side effect occurs without any consistent change in serum electrolyte levels, it appears to be due to sodium overload in the particular clinical context of the frail, ill, cachectic, and usually elderly patient dying from disseminating cancer. Both the intravenous and the oral formulations we have used contain 57 mequiv. of sodium per daily 10 g of ascorbic acid. However, gravitational edema is a relatively minor and perfectly acceptable side effect in these particular circumstances.

More important from the point of view of practical therapeutics is the development or aggravation of dyspeptic symptoms such as heartburn, nausea, acid regurgitation and actual vomiting, which may follow ingestion of these high-dose ascorbic acid mixtures, particularly in patients with upper alimentary tract carcinomatosis. This effect has been severe enough to cause voluntary discontinuation of further oral medication in a number of patients, as noted in Table I.

In concurrent studies with normal healthy volunteers (increasing oral ascorbic acid intake by increments of 1 g per day in successive weeks) symptoms of flatulent distension, transient colic and diarrhea have been a fairly frequent occurrence when the 3 to 4 g per day level is reached. We have observed this side effect in only one cancer patient, which may be an observation of some significance, indicating a state of increased requirement and absorption in cancer relative to normal health. Diarrhea was the presenting symptom in a few patients with lower alimentary tract malignancy. In them, ascorbic acid by mouth, did not appear to aggravate this symptom.

The regular ingestion of large amounts of ascorbic acid results in an increase in urinary oxalate excretion, particularly in certain individuals⁸. However changes in oxalate output can only be detected in most people when the daily ascorbic acid intake exceeds 4 g, and even then the changes are said to be minimal⁹. We believe that the danger of oxalate urolithiasis exists, but consider it an acceptable risk in this particular clinical situation. No patient in this trial has suffered any complication of this nature.

In a few patients, the oral ingestion of ascorbic acid was followed within the hour by transient discomfort at the site of known metastases. In a significant proportion of patients in the series, we appear to have observed a "rebound effect" of explosive tumor acceleration producing a very brief terminal illness, after a measurable period of comparative well-being and apparent tumor quiescence. In a few patients with very rapidly proliferating and widely disseminating tumors, the administration of ascorbic acid appeared to precipitate widespread tumor hemorrhage and necrosis with disastrous consequences.

All these observations indicate that large doses of ascorbic acid, although comparatively safe, are neither completely innocuous nor totally free from side effect in the particular clinical context of advanced human cancer, and must be prescribed with some caution.

RESULTS

As EDELSTYN AND MACRAE have strongly emphasized¹⁰, it is extremely difficult to try and assess the value of any new form of cancer treatment, when its initial trial use has to be confined to only those hopeless patients in the terminal stages of the disease. However if we could demonstrate that the administration of ascorbic acid could produce a favourable tilt in the host/tumor relationship in even a few of these terminal cancer patients (in whom all other treatments had been tried and failed, and all host defensive mechanisms are exhausted), it would be reasonable to expect that the same form of treatment would have even greater therapeutic value, when used in the adjuvant management of earlier and more favorable patients. We are convinced that our results demonstrate precisely this encouraging indication.

In assessing these results, it is important to remember, not only the potential benefits, but also the theoretical limitations, of this form of therapy⁵. Terminal cancer is a complex situation with progress of the disease at any one point in time depending upon the delicate balance reached between tumor growth-promoting factors on the one hand and various defensive mechanisms on the other, with an overall trend towards accelerating tumor dominance. If one could introduce into this complex equilibrium, *one* further factor capable of enhancing host defense in a safe and physiological way, one could logically predict a whole spectrum of therapeutic response:

- (1) No response (or at least a therapeutic response so slight as to be unrecordable)
- ↓
- (2) Minimal response
- ↓
- (3) Growth retardation
- ↓
- (4) Cytostasis (or "standstill effect")
- ↓
- (5) Tumor regression
- ↓
- (6) Tumor hemorrhage and necrosis

It will be appreciated that in describing such a therapeutic spectrum, each individual category is somewhat arbitrary, with each shading imperceptibly into its neighbor. Moreover, because of the complexity and interdependence of all the other factors involved, this would be a dynamic situation, with patients tending to move from one category of response to another at different periods in time. To complicate the problems of clinical assessment even further, death in cancer does not occur when some critical end-point in the tumor/host ratio has been reached, but is determined by the almost chance involvement of some vital organ or function. For instance, a small annular constricting carcinoma of the colon, therapeutically induced into carcinostasis or even mitotic regression, would still cause quite rapid death from intestinal obstruction.

Despite these obvious difficulties, it is still possible to ascertain a general pattern of therapeutic trends. Our first fifty consecutive advanced cancer patients are classified according to their predominant clinical response in Table I. We now present illustrative examples in each category.

CATEGORY 1: NO RESPONSE (17 patients)

Case No. 5: Male, aged 65 years—Reticulum cell sarcoma of ileum

Emergency admission on April 19th, 1972 with acute intestinal obstruction, superimposed on a 4-month history of anorexia, progressive weight loss, and bowel irregularity. Palliative right hemicolectomy performed, on day of admission, for large obstructing tumor mass in terminal ileum with innumerable irresectable metastatic deposits throughout mesentery, peritoneum and liver. Histology of resected tumor—reticulum cell sarcoma. Uneventful recovery from emergency resection. Intravenous ascorbic acid (10 g per day for 10 days) commenced on 4th post-operative day, followed by oral regime of 10 g per day. Transient relief of acute symptoms from surgery and intravenous fluid replacement. Readmitted on 45th day for nursing care. Thereafter, in spite of oral ascorbic acid, rapid clinical deterioration with increasing hepatomegaly, progressive weight loss, malignant subcutaneous infiltration in the right flank, terminal bilateral pleural effusion and pulmonary collapse. Death from generalised sarcomatosis on 82nd day after commencing treatment, with no suggestion of any therapeutic benefit.

Case No. 17: Female, aged 49 years—Serous cyst-adenocarcinoma of ovary

In May 1969, total hysterectomy and bilateral salpingo-oophorectomy performed for serous cyst-adenocarcinoma of ovary, without, at that time, any obvious evidence of intra-abdominal spread. Returned in January 1972 with gross hepatomegaly extending to the umbilicus, and isotope liver scan confirmed multiple hepatic metastases. General condition fair and deteriorating. Commenced on ascorbic acid (10 g orally per day) with some subjective evidence of benefit. General condition remained fairly static for over 7 months until August 1972, thereafter very rapid deterioration with swiftly deepening jaundice, ascites, bilateral leg edema from caval compression, and terminal appearance of multiple pulmonary metastases. Died on 226th day after commencing ascorbic acid with no clear evidence of any therapeutic benefit.

CATEGORY 2: MINIMAL RESPONSE (10 patients)

Case No. 19: Female, aged 53 years—Adenocarcinoma of breast

Presented in March 1970 with a 3 cm diameter ulcerative lesion of the right inframammary fold. Wide local excision performed, and histology confirmed mammary adenocarcinoma. Within weeks complained of backache and skeletal survey demonstrated metastatic destruction of lumbar vertebrae. Palliative irradiation given to breast and spine with good symptomatic relief and patient commenced on androgens.

By June 1971 had developed large malignant mass in upper outer quadrant of right breast and numerous infiltrated cervical lymph nodes (biopsy positive). Further local irradiation given to prevent fungation and androgen dosage increased, but general condition steadily deteriorated.

Readmitted on December 10th, 1971 for terminal nursing care. Miserable and bed-ridden, and in constant pain requiring heavy opiate sedation. Large palpable tumour mass in right breast and right axilla, extensive supraclavicular and cervical malignant lymphadenopathy and innumerable subcutaneous metastases. Skeletal survey showed numerous metastases in ribs, thoraco-lumbar spine and pelvis. Ascorbic acid commenced on December 13th, 1971 (5 g i.v. per day for 7 days, 8 g per day orally thereafter). Quite dramatic subjective and objective improvement. Complete relief of bone pain by 4th day with cessation of opiate requirement. Became alert and ambulant, and contrary to usual clinical expectation, was able to return home and manage her own domestic affairs, but without any obvious change in the size or number of her obvious metastases. Readmitted on February 9th, 1972 with nausea and visual disturbance. Steady deterioration thereafter with steadily disseminating tumor. Death in coma on 86th day after commencing ascorbic acid. Autopsy confirmed innumerable visceral, subcutaneous, intracranial and skeletal metastases.

Case No. 26: Female, aged 48 years—Carcinoma of bronchus

First attended in July 1972 with a 4-month history of rapid weight loss, persistent cough and increasing dyspnea. Swelling of face noticed for two weeks, with full clinical picture of superior vena caval obstruction. Chest X-ray showed right hilar carcinoma with widening of mediastinum by direct tumor infiltration. A course of palliative radiotherapy was given with relief of caval obstruction, but no real benefit to respiratory function, or arrest of general clinical deterioration. Emergency readmission on September 16th, 1972 in semi-comatose condition following epileptiform convulsions; fractional improvement without any specific treatment, but remained disorientated and mentally confused and very distressed by respiratory stridor. Repeat chest X-ray showed increase in size of right hilar mass with lymphatic infiltrative changes, now involving right middle and right upper lobe with mediastinal enlargement. EEG indicated multiple brain metastases. Accepted as terminal cancer. situation with life expectancy measurable in days or, at most, weeks. Intravenous ascorbic acid was commenced on September 21st, 1972 (10 g/day for 4 days) followed by 10 g/day orally. Initial response was quite dramatic. Within days, patient became quite rational and claimed to feel "quite well" with complete relief of respiratory stridor. In contrast to admission expectation, she became fit enough to leave hospital on October 5th, 1972. Clinical improvement was sustained at home for approximately two months, then very rapid terminal illness with "explosive" appearance of innumerable subcutaneous metastases. Died quite suddenly in coma 86 days after commencing ascorbic acid.

CATEGORY 3: GROWTH RETARDATION (11 patients)

Case No. 29: Male aged 67 years—Adenocarcinoma of gallbladder

Presented in December 1971 with painless obstructive jaundice of some three weeks' duration, anorexia and rapid weight loss. Irresectable carcinoma of the gallbladder with direct liver infiltration diagnosed at laparotomy on December 21st, 1971, and surgery perforce limited to confirmatory biopsy. Uneventful post-operative recovery but steadily deepening jaundice. Readmitted on February 24th, 1972 with serum bilirubin of 15 mg/dl, gross hepatomegaly and clinical suspicion of early ascites, but general condition still remarkably good. However progress of disease indicated that, without effective treatment, would almost certainly have died within a few weeks from obstructive hepatic failure.

Ascorbic acid commenced on February 24th, 1972 (10 g/day i.v. for 9 days) followed by 8 g/day orally thereafter). Subjective evidence of benefit was apparent within a week, with return of appetite, weight gain and slow but steady resolution of obstructive jaundice pattern (serum bilirubin had dropped to 1.9 mg/dl by April 26th, 1972). Slow but sustained clinical improvement continued for some 4 months, then equally gradual reversal and deterioration with development of chylous ascites requiring paracentesis, but no recurrence of jaundice, clinically or biochemically. Died at home on September 29th, 1972, 209 days after commencing ascorbic acid.

Case No. 33: Male, aged 42 years—Adenocarcinoma of stomach

In December 1971, fairly rapid onset of anorexia, lassitude, weight loss and upper abdominal pain. On February 3rd, 1972, high partial gastrectomy performed for large but mobile tumor of pyloric antrum, without obvious dissemination. Histology of resected specimen reported as invasive anaplastic carcinoma with glandular involvement. Within weeks developed right sided abdominal pain of increasing severity culminating in acute intestinal obstruction requiring second laparotomy on June 3rd, 1972; widespread peritoneal, hepatic and glandular metastatic deposits discovered with malignant ascites. Palliative ileal resection performed to relieve intestinal obstruction and histology confirmed metastatic spread. Surgery relieved obstructive symptoms but general condition steadily deteriorating into terminal phase.

Ascorbic acid commenced on June 29th, 1972 (10 g/day i.v. for 5 days, 10 g/day orally thereafter). General condition slowly improved with return of appetite and weight gain. Returned to work. Transient episode of intestinal obstruction in mid-December 1972 which resolved spontaneously. Remained generally well until relatively brief final episode of intestinal obstruction with death on March 10th, 1973, 258 days after commencing ascorbic acid. Autopsy permission not obtained.

CATEGORY 4: CYTOSTASIS (3 patients)

Case No. 40: Female, aged 56 years—Adenocarcinoma of colon

Presented in November 1972 with a 4-month history of lower abdominal colic,

weight loss, bowel irregularity, and a large palpable mass in the left iliac fossa. Palliative sigmoid colectomy performed for adenocarcinoma; many hepatic metastases present. Uneventful recovery from surgery.

Ascorbic acid (10 g/day by mouth) commenced as outpatient on December 20th, 1972. Within 1 h of ingesting ascorbic acid mixture, experienced discomfort in right sub-costal region (*cf.* Case No. 10), but encouraged to persevere with medication and this side effect resolved within about 2 months. Now, some 18 months later, remains clinically well, with no evidence to suggest progressing malignancy.

Case No. 41: Female, aged 66 years—Adenocarcinoma of breast

Presented in September 1971 with centrally placed adenocarcinoma of the right breast with axillary gland involvement, and a right pulmonary opacity of dubious significance on pre-operative radiological screening. Right simple mastectomy with axillary clearance performed followed by a full course of post-operative radiotherapy. Emergency readmission for terminal care on October 28th, 1972, acutely dyspneic with massive right pleural effusion. 4.5 l of bloodstained fluid aspirated from right pleural cavity on October 31st, 1.5 l on November 13th, 1.5 l on November 17th, 1.5 l on December 6th, none since.

Ascorbic acid commenced on November 15th, 1972 (10 g/day i.v. for 8 days, 10 g/day orally thereafter). Immediate subjective improvement with rapid reduction in the rate of reaccumulation of malignant pleural effusion and transition from a "dying" to a "recovering" state. Present condition some 20 months later remains reasonably good. She is frail but active and free of symptoms apart from some dyspnea on exertion. Serial chest X-rays show malignant infiltration of the right pleura, but no significant change, progression or regression, over the last 20 months.

CATEGORY 5: TUMOR REGRESSION (5 patients)

Case No. 42: Female, aged 68 years—Adenocarcinoma of ovary

Presented in late September 1971 with a 6-month history of lower abdominal discomfort, increasing abdominal distension and very marked weight loss. Ascites present with large fixed mass in the left pelvis easily palpable on abdominal and vaginal examination. Diagnostic laparotomy performed on December 13th, 1971. The whole pelvis was full of solid tumor with widespread peritoneal, omental and hepatic metastases. Surgery limited to an omental biopsy reported as "adenocarcinoma with papillary structure in places, consistent with primary in ovary".

Readmitted for terminal care in late November 1971. Terminal cancer situation under heavy opiate sedation. Tense malignant ascites with superimposed intestinal obstruction and distressing "fecal" vomiting. Abdominal paracentesis performed with some symptomatic relief, but revealing many palpable abdominal masses, including one large fixed mass in the left iliac fossa and irregular hepatomegaly.

Ascorbic acid commenced on December 8th, 1971 (5 g/day i.v. for 7 days, 5 g/day orally thereafter) with quite dramatic response. Subjective benefit obvious by 5th day. Intestinal obstruction resolved, vomiting ceased and appetite returned. Pain

subsided and opiate requirement diminished to zero. Palpable abdominal masses gradually diminished in size and eventually became impalpable, a finding confirmed by a number of independent clinicians. Steady transformation from a terminal state into a "recovering" situation quite contrary to all clinical expectation.

After 1 month of steady improvement, patient suddenly developed severe abdominal colic, profuse vomiting and profound hypotension, and died within a matter of hours on January 9th, 1972, 33 days after commencing ascorbic acid.

Autopsy was performed. In striking contrast to the laparotomy and pre-treatment clinical findings, the abdominal cavity contained no tumor "masses" as such, and in particular the pelvic organs looked surprisingly normal. There were innumerable intra-peritoneal fibrinous adhesions responsible for terminal mechanical intestinal obstruction. The adrenal glands appeared normal in all respects. There were innumerable small tumor nodules and plaques scattered throughout the peritoneum and the pleura, and in particular over the liver capsule. Histological examination of these tumor nodules, and sections from the "normal-looking" ovaries, showed neoplastic tissue with mitotic figures and some interstitial calcification.

Case No. 43: Male, aged 77 years—Carcinoma of pancreas

In 1960, papilloma of bladder successfully treated by cystodiathermy. Cholecystectomy performed elsewhere for gallstones in 1969. Presented in September 1971 with painless obstructive jaundice and steady weight loss of several months' duration. At laparotomy in September 1971, a large irregular tumor mass was discovered replacing head of pancreas and infiltrating porta hepatis with extensive glandular involvement. The operative findings left no room for doubt that the primary pathology was an infiltrating carcinoma arising from the head of pancreas, and this opinion was confirmed by the routine operative cholangiogram which showed irregular common bile duct distortion leading to complete obstruction. Regrettably in view of subsequent developments, the operative diagnosis was so obvious that no confirmatory biopsy was taken. The tumor was clearly irresectable, and a palliative hepatico-duodenostomy was performed. Recovery was uneventful with steady resolution of obstructive jaundice.

However, jaundice recurred by January 1972 with accelerating weight loss, progressing relentlessly into a terminal situation. At that time serum bilirubin was 13 mg/dl and rising.

Ascorbic acid commenced on February 9th, 1972, at 5 g orally per day. The general clinical response was gradual but sustained and far exceeded normal expectations. Within a matter of weeks, subjective evidence of benefit became obvious, with increased sense of well being, return of appetite and weight gain. In very general terms, coincident with the administration of ascorbic acid, this cachectic, jaundiced, confused, "dying" elderly man was converted from a terminal nursing care situation into an alert ambulant active member of the community, and this clinical improvement was sustained for 9 months. His jaundice slowly cleared completely.

He developed a very brief, dramatic, and undiagnosed terminal illness, presenting with visual disturbance, progressing very rapidly to mental confusion, anasarca,

"cushingoid facies", intense generalised pruritus, and brown skin pigmentation, without recurrence of jaundice. He died, within 4 days of manifestation of these terminal symptoms, on the 317th day after commencing ascorbic acid.

Autopsy was performed. The immediate cause of death was ascribed to bilateral hypostatic pneumonia with myocardial ischemia. The liver was unremarkable. The adrenal glands appeared normal both macroscopically and microscopically. In quite striking contrast to the operative findings, the pancreas was notably small and fibrous. Histologically sections showed only "chronic sclerosing pancreatitis with no evidence of malignancy".

Case No. 44: Male, aged 55 years—Adenocarcinoma of kidney

Presented in October 1971 with short-duration painful swelling of right 8th rib. General condition good and in active employment. Rib biopsy indicated "hypernephroma" metastasis. Skeletal survey otherwise negative. On November 4th, 1971, right nephrectomy performed for 6 cm diameter "clear cell adenocarcinoma of the kidney", combined with excision of right eighth rib. Uneventful immediate post-operative recovery and progress. Returned in March 1972 complaining of increasing discomfort in right shoulder and left hip. Not yet in severe pain requiring opiates but unable to work. Skeletal survey demonstrated osteolytic metastases in right humerus (Fig. 1a) and right ilium (Fig. 2a).

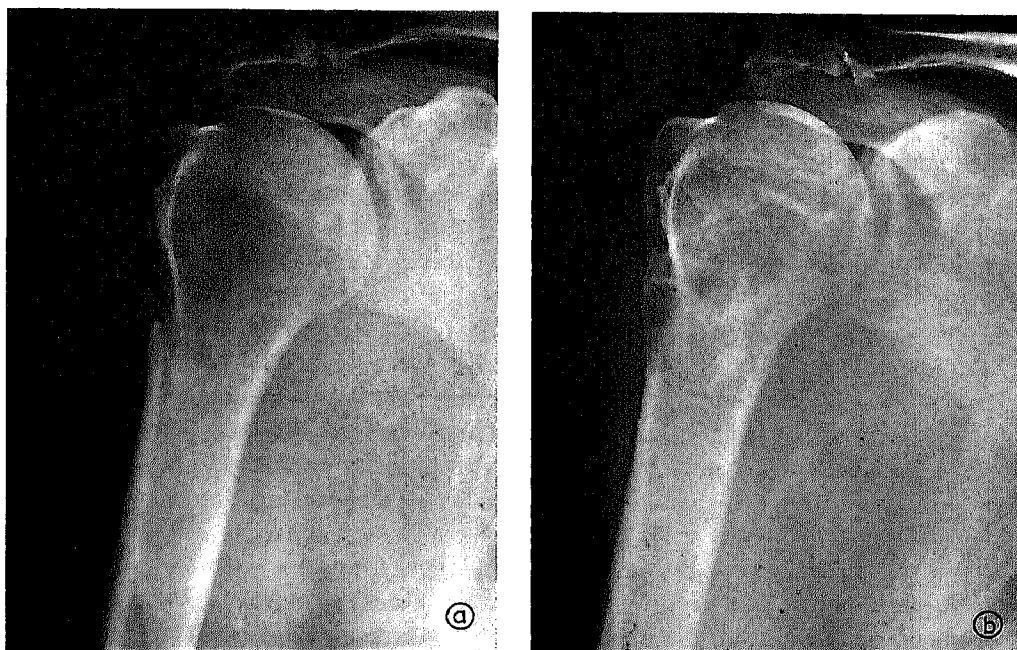


Fig. 1. (a) Case 44: osteolytic metastasis in right humerus with erosion of cortex before administration of ascorbic acid. (b) Case 44: regression of humeral metastasis, with evidence of retrabeculation and recalcification of cortex, 220 days after commencing ascorbic acid.

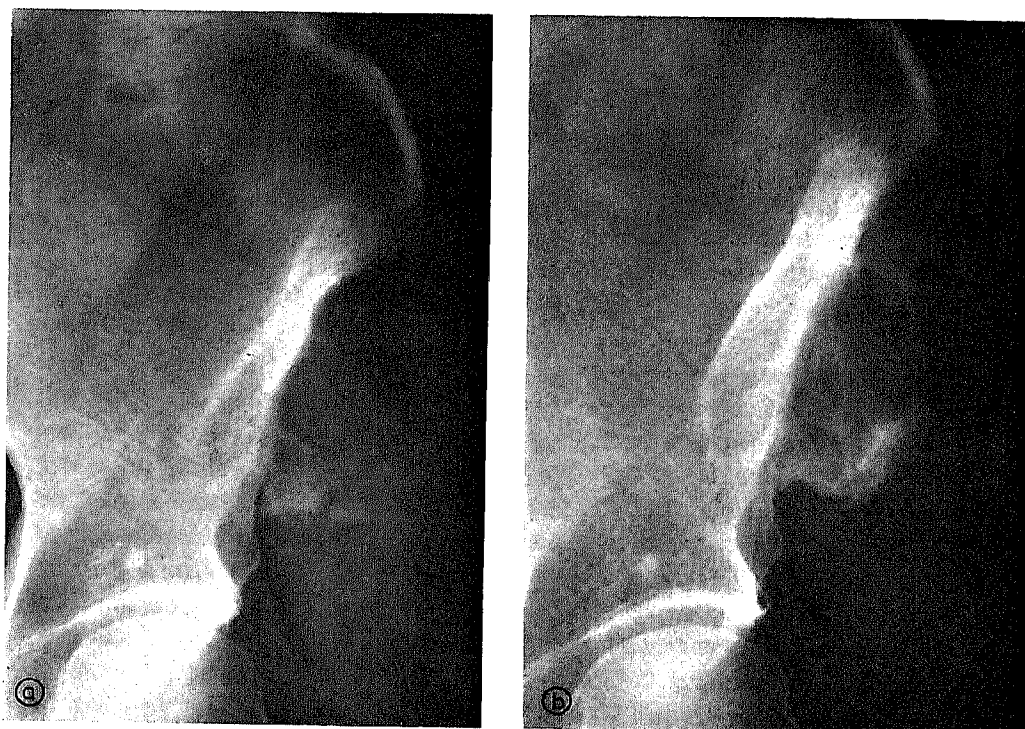


Fig. 2. (a) Case 44: poorly calcified expanding metastasis arising from ilium, before administration of ascorbic acid. (b) Case 44: calcification and evidence of trabeculation in iliac metastasis 395 days after commencing ascorbic acid.

Ascorbic acid commenced on April 10th, 1972 at an initial dose regime of 10 g/day orally. Steady and sustained symptomatic improvement with pain relief, return to active employment, and radiological evidence of resorption and re trabeculation of osteolytic metastases (Figs. 1b and 2b). Remained "well" for over a year, then gradual increase in ESR and seromucoid indicated malignant reactivity. Ascorbic acid intake increased to 20 g/day on May 11th, 1973 with further symptomatic and "biochemical" remission for months, then very rapid deterioration (Figs. 3a and 3b). Radiotherapy given to right shoulder and pelvis in November 1973 to avert the risk of pathological fracture. No systemic benefit. Despite continuing ascorbic acid therapy very rapid change from an ambulant outpatient to a bed-fast terminal invalid with evidence of disseminating visceral and skeletal metastases leading to paraplegia and death in coma on January 25th, 1974, 659 days after commencing ascorbic acid.

Case No. 45: Male, aged 40 years—Reticulosis

Presented in October 1973 with a 4-month history of right pleurodynia, night sweats, increasing lethargy and sharp weight loss. Marked right cervical lymphadenopathy with right axillary lymphadenopathy. Easily detectable hepatomegaly and splenomegaly. Chest radiograph showed mediastinal enlargement with right pleural effusion (Fig. 4a). Right cervical gland biopsy (October 26th, 1973) reported as

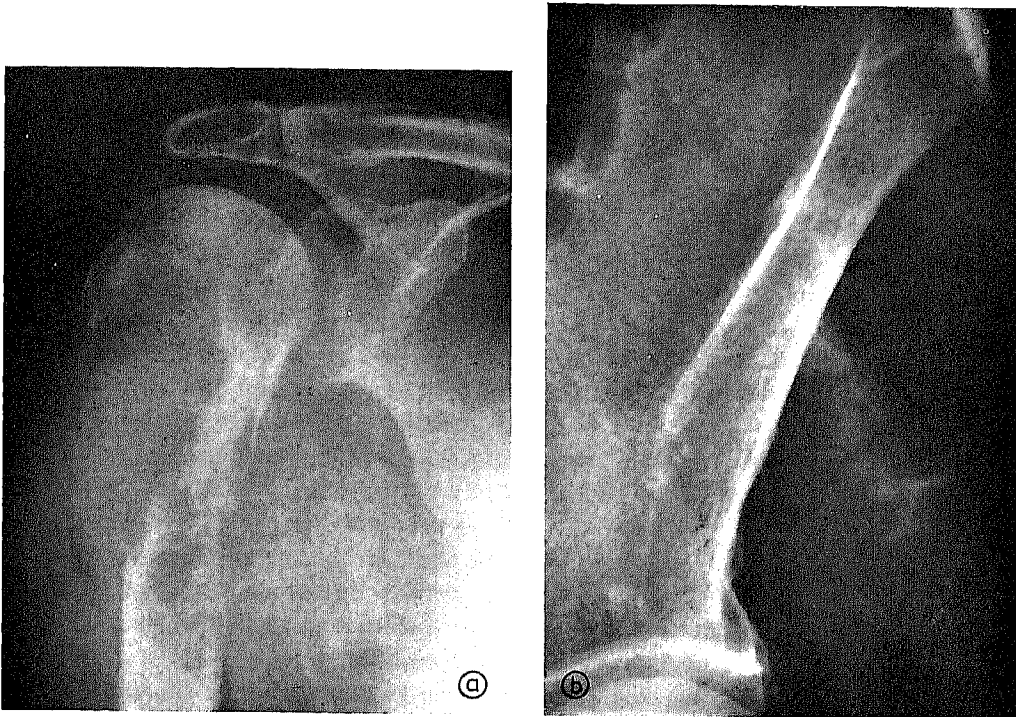


Fig. 3. (a) Case 44: humeral metastasis "uncontrolled" 550 days after commencing ascorbic acid. (b) Case 44: iliac metastasis "uncontrolled" 550 days after commencing ascorbic acid.

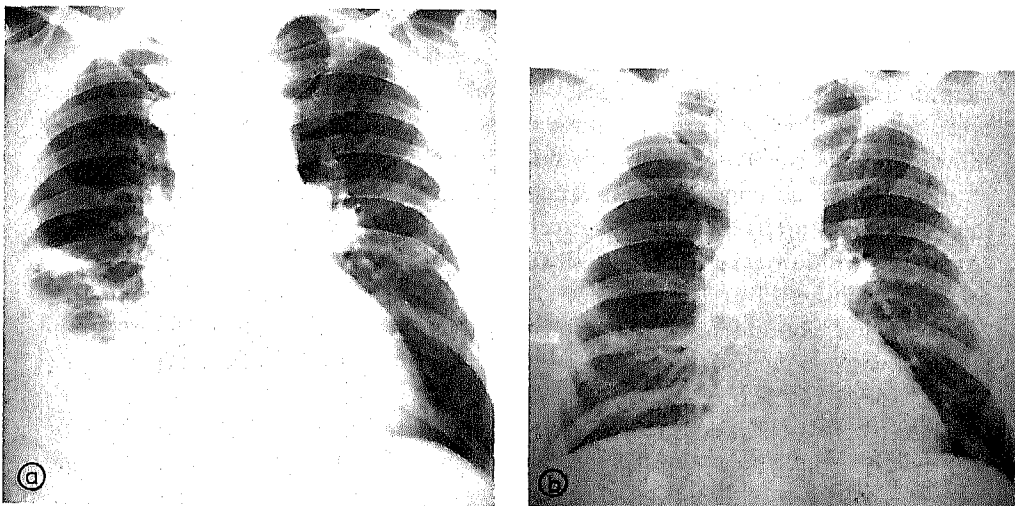


Fig. 4. (a) Case 45: Chest X-ray showing mediastinal and hilar gland enlargement with right basal collapse and effusion, before administration of ascorbic acid. (b) Case 45 Normal chest X-ray, 70 days after commencing ascorbic acid.

"malignant lymphoma with many reticulum cells—reticulum cell sarcoma". Accepted for palliative radiotherapy, but because of administrative delay, course of ascorbic acid prescribed.

Ascorbic acid commenced on October 28th, 1973 (10 g/day i.v. for 10 days, 10 g/day orally thereafter). Very dramatic response. By November 4th, 1973, spleen clinically impalpable, liver barely palpable and cervical and axillary lymphadenopathy rapidly regressing. Repeat cervical lymphadenobiopsy on November 8th, 1973 reported as "hyperplasia only without reticulum cell predominance". Steady clinical improvement with return of chest X-ray to normal 70 days after commencing ascorbic acid (Fig. 4b).

(This particular patient's ascorbic acid intake was gradually reduced over the next few months and by early May 1974 after 4 weeks on no supplemental medication, chest X-rays showed evidence of malignant reactivity. At the time of writing, the recommencement of ascorbic acid 10 g/day appears to be inducing a second regression. If this continues, this particular patient will be reported in detail elsewhere.)

Case No. 46: Male, aged 69 years—Carcinoma of colon

Presented in May 1969 with a 4-month history of constant abdominal pain of increasing intensity, steady weight loss, bowel irregularity, and a large palpable mass in the epigastrium extending into the left hypochondrium. At laparotomy on 2 June 1969 a palliative "en-masse" excision was performed of a large tumor mass involving transverse and descending colon, omentum and an infiltrated loop of ileum. Good recovery and remained reasonably well apart from mild myocardial infarction in late 1970. Readmitted in January 1972 with a 4-month history of upper abdominal pain and backache, steady weight loss, and jaundice first noticed by patient only a few weeks before admission.

General condition not terminal, but cachectic and deteriorating. Jaundiced with serum bilirubin of 8.6 mg/dl and liver function test profile consistent with hepatic metastases. Hard irregular "malignant" hepatomegaly with liver edge three finger-breadths below the costal margin. Intravenous cholangiogram (when jaundice cleared) showed no abnormality of the biliary duct system.

Ascorbic acid commenced on January 29th, 1972 (8 g/day i.v. for 3 days, 8 g/day then 10 g/day orally thereafter). Excellent subjective response. Jaundice cleared completely within weeks, and all "liver function test parameters" returned to normal within 6 months. Liver became clinically impalpable within 10 weeks. More than 2.5 years later, continues with his ascorbic acid and remains fit, active and well in all respects, with no clinical or biochemical indication of neoplastic disease.

CATEGORY 6: TUMOR HEMORRHAGE AND NECROSIS (4 patients)

Case No. 47: Male, aged 66 years—Carcinoma of bronchus

Presented in August 1972 with increasingly severe pain in right shoulder for 6 weeks. A chronic bronchitic with increasing dyspnea for over a year. Tender tense soft tissue swelling noted over apex of right shoulder. X-Rays demonstrated inoperable

right hilar carcinoma infiltrating mediastinum, with metastases in right shoulder girdle and spine. Gravely ill and bed-fast requiring heavy sedation.

Ascorbic acid commenced on August 19th, 1972 (10 g/day i.v. for 6 days, then 10 g/day orally until discontinued 6 days later). Very transient subjective response with relief of bone pain by 3rd day, but by 6th day, hyperpyrexia with necrotic tumor breakdown and rapid skin ulceration over shoulder metastasis. Increasing mental confusion and brisk deterioration into death in coma on September 4th, 1972, 17 days after commencing ascorbic acid.

Case No. 48: Male, aged 63 years—Chondrosarcoma of ilium

Presented in June 1972 with pain in right hip and progressive weakness of right leg of a few weeks' duration. Diagnosis at first uncertain, but by August 1972 had developed a large palpable mass in the right iliac fossa showing patchy calcification on X-ray. Laparotomy demonstrated a large solid irresectable chondrosarcoma growing from right ilium into pelvic cavity, confirmed by biopsy. A course of palliative irradiation was given without appreciable benefit in September 1972. At the time of entry into present trial, general condition deteriorating with a large fixed mass in the right iliac fossa and paresis and edema of right leg. In constant pain requiring regular opiates, and although gravely ill, not moribund.

Ascorbic acid commenced on October 4th, 1972 (10 g/day i.v. discontinued after 3 days). Within 72 h of institution of ascorbic acid, became acutely distressed with intolerable pain in the right hip and right lower abdomen, with increasing mental confusion, rising fever and the clinical picture of congestive cardiac failure with pulmonary edema. Infusion immediately discontinued and symptomatic treatment instituted, but rapid downhill course with death in hyperpyrexial coma on October 12th, 1972, 9 days after commencing ascorbic acid.

Autopsy showed "an enormous partially necrotic chondrosarcoma replacing the right ilium, with extensive para-aortic dissemination and "uncountable" pulmonary and sub-capsular hepatic metastases; numerous metastases also present in the muscles of both thighs". The striking feature of the examination was that both the primary tumor and its innumerable secondary deposits all showed extensive hemorrhage and necrosis.

Case No. 49: Male aged 42 years—Teratoma of testis

Presented in late August 1971 with painless enlargement of the left testis of 3 weeks' duration. Left orchidectomy performed on September 7th, 1971 for malignant teratoma showing areas of hemorrhagic necrosis. Surgery followed by a course of radiotherapy to para-aortic and left inguinal lymph nodes. At completion of course, chest X-ray previously clear showed many "cannon-ball" metastases to be present throughout both lung fields. Readmitted in late December 1971 with a large fleshy metastasis growing into mouth from left upper alveolus. Repeat chest X-ray showed increase in both number and size of pulmonary metastases, but in spite of this, general condition was still remarkably good.

Ascorbic acid commenced on December 28th, 1971 (8 g/day i.v. until discon-

ted 3 days later). A catastrophic deterioration in clinical state occurred within 72 h of initiating ascorbic acid. The alveolar metastasis "sloughed out" with continuous intra-oral hemorrhage, requiring repeated blood transfusion. Hemoptysis became a feature by the following day and the patient became mentally confused, restless, hyperpyrexial with signs of meningismus. Thereafter rapid deterioration into terminal coma with death on January 12th, 1972, 15 days after commencing ascorbic acid.

Autopsy was performed. Innumerable metastatic deposits were present throughout the brain, in the dura, throughout both lungs, in both kidneys, in the liver, in the spleen, in the left adrenal and elsewhere. The striking autopsy finding was that all these metastatic deposits showed quite remarkable hemorrhage and necrosis, and could quite literally be "scooped out as amorphous necrotic mush" from each affected site.

Case No. 50: Male, aged 45 years—Adenocarcinoma of kidney

On August 31st, 1967, left nephrectomy performed for 4 cm diameter "clear cell renal adenocarcinoma". Uneventful recovery and remained well until hemoptysis in July 1968, when radiology demonstrated a few small pulmonary metastases. Responded to hormone therapy for over a year, then relapsed. Course of cytotoxic chemotherapy then given with benefit and further "standstill effect" for appreciable period of time. However by late 1971, general condition steadily deteriorating with malignant hepatomegaly and numerous skeletal metastases. Local palliative radiotherapy given for painful pelvic and thoracic cage metastases with symptomatic relief.

Emergency readmission on February 5th, 1972 following melena. Transfused with benefit. At this stage, this cachectic but mentally alert and still ambulant patient was clearly "doomed" by all conventional prognostic standards, but by these same standards, death was not thought to be imminent.

Ascorbic acid was commenced on February 7th 1972 (10 g/day by mouth) just prior to planned hospital dismissal. Within 36 h, patient developed epileptiform convulsions with steadily rising fever and signs of subarachnoid hemorrhage. Catastrophic deterioration to death in deep coma on February 9th, 1972, 3 days after commencing ascorbic acid. Autopsy permission refused. However, the clinical sequence of events, in this particular patient known to have innumerable metastases, strongly suggests that the administration of ascorbic acid precipitated tumor hemorrhage and necrosis with catastrophic consequences and accelerated death from intracranial bleeding.

FEATURES OF THE THERAPEUTIC RESPONSE

Certain features of the response to high dose ascorbic acid supplements in advanced human cancer deserve special mention.

Survival times

In the absence of untreated and exactly matched controls for comparison, we have no statistical information to claim that the administration of ascorbic acid alone

produced a significant increase in survival times in the terminal cancer patients studied. However it is our opinion that most clinicians familiar with the practical realities of terminal cancer, perusing Table I, would be inclined to agree that many of these patients survived much longer than reasonable clinical expectation.

Subjective evidence of benefit

The great majority of patients treated experienced some degree of subjective benefit usually first noticeable about the 5th to 10th day after commencement. This subjective improvement was noted in even the most unfavorable situations (*e.g.* Cases 8 and 11). Subjective evidence of benefit is notoriously difficult to measure and to substantiate, but it is still the prime object of any therapeutic regime, and should never be ignored. Any agent which can make, or even appear to make, the burden of terminal cancer more tolerable, deserves further study. We, our patients, their relatives, our nursing staff, and many of our medical colleagues (initially understandably utterly sceptical) are now quite convinced that ascorbic acid has this effect.

Objective evidence of benefit

In the particular clinical context of disseminating terminal cancer, it is still difficult to find indices capable of demonstrating objective benefit apart from recording dramatic instances of induced regressions. The series contains a significant number of such examples. However, certain patterns of clinical response, though less dramatic, are also clear indications of some objective benefit.

(1) *Pain from skeletal metastases.* In many patients with disseminating cancer, pain from expanding bone metastases is a particularly distressing feature. In a number of patients in this series, the administration of ascorbic acid produced quite dramatic relief from pain and opiate dependence in a matter of days¹¹. The only logical explanation we can offer for this dramatic effect is that the medication produced some retardation of expansile metastatic growth relative to their rigid skeletal containment.

(2) *Relief of other pressure effects.* The one patient in the series with an intracranial tumor (Case 27) obtained quite striking relief from headache. The Horner's syndrome in Case 34 resolved completely for over a year, as did the recurrent laryngeal nerve paresis in Case 31.

(3) *Malignant ascites and malignant pleural effusions.* Widespread peritoneal, omental and hepatic metastases are familiar features of terminal cancer, usually presenting as "malignant ascites" and requiring increasingly frequent paracentesis for control. Similarly malignant deposits in the pleura present as "malignant pleural effusions" and require repeated thoracocentesis. As a result of ascorbic acid treatment alone, a significant reduction in the rate of reaccumulation of such effusions was observed in a number of patients as detailed in Table I.

(4) *Hematuria.* The series contains a number of patients with malignant disease of the urinary tract presenting with hematuria, and in whom for a variety of reasons, conventional methods of treatment could not be employed, or had already been employed and failed. All patients in this group experienced quite a significant reduction in the degree of hematuria, and where applicable, relief of strangury and distressing urgency of micturition.

(5) *Malignant hepatomegaly and malignant jaundice.* Quite extensive involvement of liver substance by metastatic deposits can occur without significant disturbance of hepato-cellular function. Eventually, however, through a combination of biliary duct obstruction and liver cell replacement, liver function deteriorates to produce the all too familiar terminal cancer picture of steadily enlarging liver, relentlessly deepening jaundice, accelerating cachexia and a very limited prognosis. The series contains many such examples. Of these, Cases 2, 4, 5, 6, 10 and 14 appeared to receive no benefit whatsoever. Of the remainder, the most that could be claimed for Cases 17, 20, 22, 25, 35 and 40, was that some retardation of tumor growth had been achieved. However, in Cases 29, 36, 37, 42, 43 and 46, there is indisputable clinical and biochemical evidence to show that reversal of terminal malignant jaundice was induced for significant periods of time.

(6) *Changes in the erythrocyte sedimentation rate.* Elevation of the ESR is an "acute-phase reactant" and a non-specific test of neoplastic activity. In progressive untreated cancer, the ESR tends to show a steady rise throughout the course of the disease. We present in Fig. 5, serial estimations of the ESR in a number of patients in the series, showing that the administration of ascorbic acid usually halts and very often reverses the relentlessly rising ESR of terminal cancer.

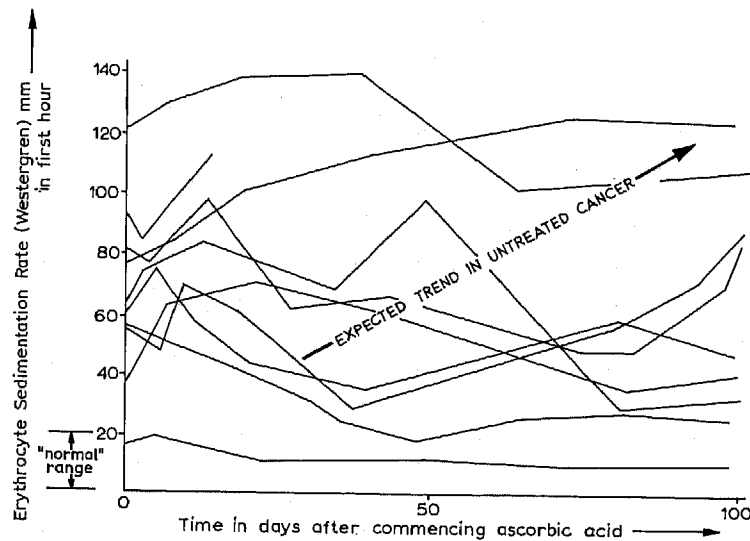


Fig. 5. Changes in the ESR in cancer patients receiving large doses of ascorbic acid.

(7) *Changes in serum seromucoid concentration.* The estimation of serum seromucoid concentration has been a routine diagnostic and prognostic test in our laboratories for over 15 years¹, and something of the order of 25 000 such estimations have now been performed. On the basis of this expanding experience, we would reiterate our original statement that the seromucoid concentration remains within a relatively narrow normal range in health, and rises in any condition in which excessive cellular proliferation is taking place. In untreated progressive cancer, the serum sero-

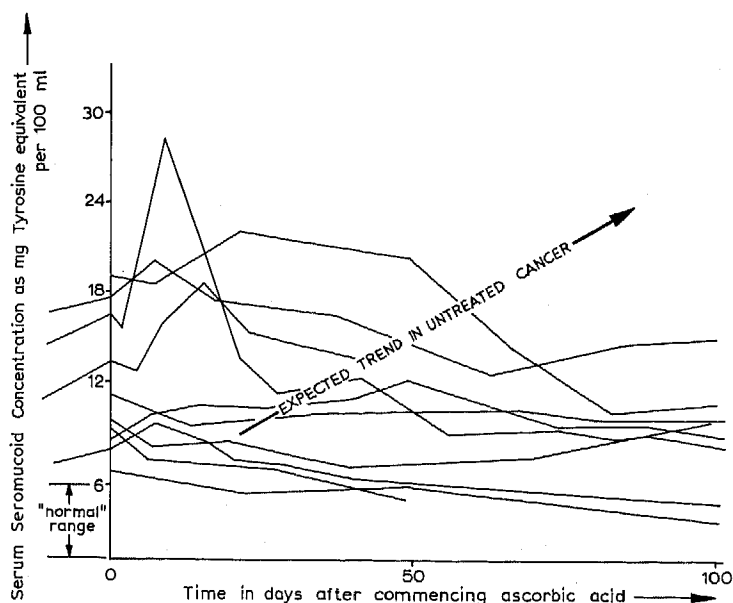


Fig. 6. Changes in the serum seromuroid level in cancer patients receiving large doses of ascorbic acid.

muroid concentration steadily rises. We present in Fig. 6, serial seromuroid estimations in a number of patients in the series, showing that the administration of ascorbic acid usually halts, and very often reverses, the steadily rising seromuroid levels of progressive disseminating cancer.

(8) *Changes in plasma ascorbic acid concentration, total leukocyte and lymphocyte ascorbic acid concentrations, changes in serum hyaluronidase, and changes in serum hyaluronidase inhibitor concentrations.* These estimations will be presented in separate publications. The results are in general agreement with the working hypothesis⁴.

DISCUSSION

Table I summarizes the individual responses of fifty consecutive "untreatable" cancer patients to the continuous administration of large doses of ascorbic acid. Their collective response could be presented in a variety of ways. To oversimplify, it could be stated that, while the majority of these patients have died, some have survived well beyond reasonable clinical expectation, or in other words, that the administration of ascorbic acid can bring about a fractional, albeit significant, improvement in cancer morbidity and cancer mortality.

Although we agree with the truth of this statement, we believe that such an interpretation ignores many important facets of the collective response. We believe that the different patterns of clinical response can only be properly understood when viewed against the background of our basic working hypothesis⁴.

If the progression of cancer simply depended upon the continuous release of

hyaluronidase (creating a constant micro-environment of ground substance depolymerisation, and "autonomous" release from proliferative and invasive restraints²), and if this progression was only countered by the chance or therapeutic availability of ascorbic acid to fuel an intrinsic feed-back control³, then the very best we could hope to achieve from this form of treatment would be some generalised restraint of malignant invasive growth⁴. Viewing this particular defense mechanism in isolation, it is apparent that, irrespective of the availability of ascorbic acid, the yield of the vital PHI would always tend to lag behind a suppressive maximum, because its rate of production is also controlled by the availability of depolymerized ground substance residues from the peri-tumoral tissues, in accordance with the provisional equation:

$$\text{PHI} = \text{GSR} + \text{AA}$$

However (and perhaps fortunately from the point of view of practical therapeutics) cancer is a far more complex situation, with many other factors involved in the conflict between tumor dominance and tumor suppression⁵. The potentiation of PHI production, by the continuous provision of an abundance of ascorbic acid, could therefore produce a whole spectrum of therapeutic response as categorized in Table I.

The important feature of this categorization is not the somewhat arbitrary distinction between Groups 1, 2 and 3 and even 4, but the fact that the administration of ascorbic acid was able to induce tumor regression in a few patients (Group 5) and provoke tumor hemorrhage and necrosis in a few others (Group 6). This latter response, although quite catastrophic in these particular patients because of the widespread nature of the disease, is in fact a manifestation of a very strong defense reaction, and would certainly be regarded as a very favorable response indeed in patients suffering from earlier and more localized lesions.

We should now like to describe what we have come to recognize as the standard response to large-dose ascorbic acid supplements in patients with advanced cancer. Subjective evidence of benefit is usually apparent by about the 5th to 10th day of treatment, and in many patients this response can be very striking indeed. The patient then enters a stage of increased well-being and general clinical improvement, and during this phase objective evidence accumulates to confirm that some retardation of tumor growth has been achieved. The objective evidence of benefit varies with the individual clinical presentation, but may take the form of relief of particularly distressing pressure symptoms such as pain from skeletal metastases, a slowing down of the rate of reaccumulation of malignant effusions, a trend towards improvement in malignant jaundice, or relief from respiratory distress, and is accompanied by a slow fall in the ESR and the serum seromucoid concentration. This phase of clinical improvement may be very transient, or it may last for weeks or months, and in a few patients may be so prolonged and accompanied by such convincing evidence of objective benefit as to indicate that permanent regression has been induced.

However, in this study where the treatment is only introduced in the terminal phase of the illness, the majority of patients are not so fortunate. After a variable period of sustained clinical improvement, malignant activity reasserts itself, and the

patient dies from his original disease. In many of these patients the mode of death is in itself unusual. After a period of comparative well-being and apparent tumor quiescence, the patient may very suddenly enter a rapid terminal phase with a precipitous downhill course and death within a matter of days from fulminating cancer. We are unable to offer any explanation for this "rebound effect" of abrupt transition from apparently restrained to totally uncontrolled "explosive" dissemination. We have observed this particular sequence of events in a significant number of patients in this series, and have come to recognize the general pattern as something distinct from the usual steady downhill course of terminal cancer.

CONCLUSION

Our clinical findings support the general contention that large doses of ascorbic acid enhance natural resistance to cancer. We have found this form of medication to have definite palliative value in the management of terminal "untreatable" human cancer. We would therefore expect it to have even greater value when used in the treatment of earlier and more favorable patients. We believe that, in time, ascorbic acid supplementation will come to be accepted as a standard supportive measure in most, if not all, forms of cancer treatment. We conclude that large scale clinical trials along such lines are now clearly indicated.

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