Paper, revised and resubmitted 8/9/76

[Pathology]

Supplemental Ascorbate in the Supportive Treatment of Cancer:

1. Prolongation of Survival Times in Terminal Human Cancer *

(vitamin C, ascorbic acid)

EWAN CAMERON and LINUS PAULING

Vale of Leven District General Hospital, Loch Lomondside, G83 0UA, Scotland

and

Linus Pauling Institute of Science and Medicine, 2700 Sand Hill Road, Menlo Park, California 94025, U.S.A.

Contributed by Linus Pauling 1976

*Publication no. from the Linus Pauling Institute of Science and Medicine

ABSTRACT Ascorbic acid metabolism is associated with a number of mechanisms known to be involved in host resistance to malignant disease. Cancer patients are significantly depleted of ascorbic acid, and in our opinion this demonstrable biochemical change (in cancer) indicates a substantially increased requirement and utilization of this substance to energize these various host resistance factors.

The results of a clinical trial are presented in which 100 terminal cancer patients were given supplemental ascorbate as part of their routine management. Their progress is compared to that of 1000 similar patients treated identically, but who received no supplemental ascorbate. The mean survival time is 4.06 times as great for the ascorbate subjects (204 days) as for the controls (50 days).

The results clearly indicate that this simple and safe form of medication is of definite value in the treatment of patients with advanced cancer.

The nature of the study

The study involved a treated group of 100 patients with terminal cancer of various kinds and a control group of 1000 untreated and matched patients. (No patients with lung cancer were included; they are treated in another hospital.) The treated group consists of 100 patients who began ascorbate treatment, as described by Cameron and Campbell[4] (usually 10 g per day, by intravenous infusion for about 10 days and orally thereafter), at the time in the progress of their disease when in the considered opinion of at least two independent clinicians the continuance of any conventional form of treatment would offer no further benefit. (There is one exception, Case 80, who is Case 45 of Ref. 4 and the subject of Ref. 5. As is explained in these papers, he was started on the ascorbate treatment while waiting for high-energy radiation therapy, and has received no treatment other than ascorbate.) Fifty of the treated subjects are those described in Ref. 4 (with, however, different case numbers) and the other fifty were obtained by random selection from the alphabetical index of ascorbate-treated patients in Vale of Leven District General Hospital, where treatment of some terminal cancer patients with ascorbate had been begun in November 1971. We believe that the ascorbate-treated patients represent a random selection of all of the terminal patients in this hospital, even though no formal randomization process was used. Four of the treated patients (Cases 17, 59, 80, and 84) were in Hairmyres Hospital; they are included because they had been included in the group described in Ref. 4, and it seemed unwise to us to omit them. In the

random selection three patients were excluded because supplemental ascorbate treatment had been discontinued by order of another physician and five were excluded because matching controls could not be found for them. Patients known to have voluntarily discontinued ascorbate treatment have been retained in the group, as have those who died from some cause other than their cancer. No patient was excluded because of short survival time. The survival times of the 19 patients marked with a ~~star~~ plus sign correspond to the date 10 July 1976, on which they were still alive.

Ten control cases for each treated case were selected by random search of the index for the last ten years in Vale of Leven Hospital. All ten control cases match the treated case as to kind of cancer, sex, and age of the patient (to within five years). The case of pseudomyxoma (91) was difficult to match, requiring search of the records for 20 years; this case was included, despite this difficulty, because of its inclusion in Ref. 4. Selection of the 1000 control cases was made by Frances Meuli, M.B., Ch.B. (Otago), who was given the sex and age of the patient and the type of cancer for each of the 100 treated cases, but who had no knowledge of their survival times. She determined from the records the date at which each control patient was classified as untreatable, from the establishment of inoperability at laparotomy, the abandonment of any definite form of cancer treatment, or the final date of admission for "terminal care." We thank Dr. Meuli for her valuable contribution to

this investigation.

Even though no formal process of randomization was carried out in the selection of our two groups, we believe that they come close to representing random subpopulations of the population of terminal cancer patients in Vale of Leven Hospital. There is some internal evidence in the data in Table 1 to support this conclusion.

The Results of the Study

The results of the study are given in Table 1 and summarized in Table 2, in which values for different kinds of cancer represented by 7 or more patients treated with ascorbate (70 or more controls) are shown. For each of the eight categories the ratio of average days of survival (ascorbate/controls) is greater than unity, the range for the eight categories being from 2.5 to 7.4, with 4.06 for all 100 patients. The ratios are somewhat uncertain; for example, omitting the patient with longest survival in the colon group would decrease the ratio from 7.4 to 5.2. At the present time we cannot conclude that ascorbate has less value for one kind of cancer than for others. Our conclusion is that the administration of ascorbic acid in amount about 10 g per day to patients with advanced cancer leads to about a four-fold increase in their life expectancy, in addition to an apparent improvement in the quality of life. This great increase in survival time results from the much larger numbers of the ascorbate patients than of the controls who live for long times, as is shown in Figure 1. Sixteen percent of the patients treated with ascorbic

acid survived for more than a year, fifty times the value for the controls (0.3%).

Statistical analysis shows that the null hypothesis that the treatment with ascorbate has no benefit is to be rejected for each of the categories in Table 2. The results of a simple statistical test are given in the table. A reasonable dividing line, the average survival time for all subjects, is given in column E, and the percentages exceeding this value are given in columns F and G. Column H contains the values of χ^2 obtained by a two-by-two calculation, and I gives the corresponding values of $\underline{P}$ (one-tailed). Similar values are obtained by non-parametric methods.

The fraction of survivors at time $\underline{t}$ after the initial date (determination of nontreatability) is given to within ± 0.01 by the expression $\exp(-\alpha \underline{t})$, in which $\underline{t}$ is the survival time in days and α has the value $0.021\ d^{-1}$. This expression corresponds to a constant mortality rate for this group of untreated patients with terminal cancer, and its validity suggests that for them a single random process, occurring with a probability independent of time, leads to death. For the group of patients treated with ascorbate the same expression with α about $0.007\ d^{-1}$ approximates the fraction of survivors up to about 100 days, after which a larger fraction of survivors is found, reaching about 0.07 beyond 600 days. A simple interpretation of these facts is that the administration of ascorbate to the patients with terminal cancer has two effects. First, it increases the effectiveness of the natural mechanisms of resistance to such an extent as to lead to an

increase by 3 in the average survival time for all patients; 3 is the ratio of the two values of α, 0.021 and 0.007. Second, it has another effect on about 7 percent of the patients, such as to cause them to live a much longer time. This effect might be such as to "cure" them; that is, to give them the life expectancy that they would have had if they had not developed cancer. On the other hand, it might only set them back one or more stages in the development of the cancer, in which case their life expectancy would be somewhat less than that corresponding to complete elimination of the effect of their having developed cancer. This uncertainty may be eliminated in the course of time, as the survival times of the 19 patients in the ascorbate-treated group who were still living in 10 July 1976 become known.

Conclusion

In this study the times of survival of 100 ascorbate-treated cancer patients in Scotland (measured from the day when the patient was pronounced to have cancer untreatable by conventional methods) have been discussed in comparison with those of 1000 matched controls, 10 for each of the ascorbate-treated patients. The data indicate that deaths occur for about 93 percent of the ascorbate-treated patients at one third the rate for the controls, so that for this fraction there is a threefold increase in survival time, measured from the date when the cancer was pronounced untreatable. For the other 7 percent of the ascorbate-treated patients the survival time is not known with certainty, but it is indicated by the values in Table 1 to be more than 22 times the average for the untreated patients. The value 4.06 (Table 2) for the ratio

of average survival times expresses the resultant of these two effects (note that 93 percent of 3 plus 7 percent of 22 equals 4.33).

We conclude that there is strong evidence that treatment of Scottish patients with terminal (untreatable) cancer with about 10 g of ascorbate (ascorbic acid, vitamin C) per day increases the survival time by the factor 3 for most of them and by at least 22 for a few (about 7 percent). It is our opinion that a similar effect would be found for untreatable cancer patients in other countries. Larger amounts than 10 g per day might have a greater effect. Moreover, we surmise that the addition of ascorbate to the treatment of patients with cancer at an earlier stage of development might well have a similar effect, changing life expectancy after the stage when ascorbate treatment is begun from, for example, five years to twenty years. We have begun studies along this line.

This study was supported by research grants from The Secretary of State for Scotland and The Educational Foundation of America.

References

1. Cameron, E. & Pauling, L. (1973) "Ascorbic acid and the glycosaminoglycans: An orthomolecular approach to cancer and other diseases", Oncology 27, 181-192.

2. Cameron E. & Pauling, L. (1974) "The orthomolecular treatment of cancer. I. The role of ascorbic acid in host resistance", Chem.-Biol. Interactions 9, 273-283.

3. Cameron, E. (in press) "Biological function of ascorbic acid and the pathogenesis of scurvy: a working hypothesis", Medical Hypotheses.

4. Cameron, E. & Campbell, A. (1974) "The orthomolecular treatment of cancer. II. Clinical trial of high-dose ascorbic acid supplements in advanced human cancer", Chem.-Biol. Interactions 9, 285-315.

5. Cameron, E., Campbell, A., & Jack, T. (1975) "The orthomolecular treatment of cancer, III. Reticulum cell sarcoma: double complete regression induced by high-dose ascorbic acid therapy", Chem.-Biol. Interactions 11, 387-393.

Table 1

Comparison of time of survival of 100 cancer patients who received ascorbic acid and 1000 matched patients with no treatment[a]

Case No.	Primary Tumor Type	Sex	Age	Survival time (days) Ten matched controls										Mean	Test case	Test case mean
1.	STOMACH	F	61	12	41	5	29	85	124	8	54	21	36	38.5	121	314%
2.	STOMACH	M	69	8	6	3	9	4	26	8	114	15	14	20.7	12	58%
3.	STOMACH	F	62	15	1	72	19	19	27	35	99	76	111	47.4	9	19%
4.	STOMACH	F	66	4	87	7	11	3	13	12	6	34	35	21.2	18	85%
5.	STOMACH	M	42	8	1	74	358	9	84	14	16	16	128	70.8	258	368%
6.	STOMACH	M	79	45	4	12	1	9	6	12	130	4	11	23.4	43	184%
7.	STOMACH	M	76	22	19	12	9	14	7	15	3	5	14	12.0	142	1183%
8.	STOMACH	M	54	24	26	21	61	27	48	7	26	2	221	46.3	36	78%
9.	STOMACH	M	62	14	23	13	89	4	11	4	4	36	27	22.5	119+	528%
10.	STOMACH	F	69	6	19	55	2	21	8	53	11	103	17	29.5	142+	481%

1.	STOMACH	M	45	17	24	7	57	128	16	44	64	110	78	54.5	82	150%
2.	STOMACH	M	57	19	13	8	11	39	29	41	17	170	5	36.9	64	173%
3.	BRONCHUS	M	74	16	56	29	27	67	41	25	26	6	40	33.3	39	117%
4.	BRONCHUS	M	74	21	2	27	30	18	1	31	1	21	16	16.8	427	2542%
5.	BRONCHUS	M	66	47	94	7	39	3	53	5	4	82	9	34.3	17	50%
6.	BRONCHUS	M	52	35	4	70	21	126	8	46	272	39	75	69.6	460	661%
7.	BRONCHUS	F	48	11	33	30	5	6	1	45	24	81	57	29.3	90	307%
8.	BRONCHUS	F	64	7	1	26	13	71	14	4	30	103	2	27.1	187	690%
9.	BRONCHUS	M	70	24	8	20	7	62	20	5	41	19	49	25.5	58	227%
10.	BRONCHUS	M	78	32	19	39	40	24	21	43	103	2	21	34.4	52	151%
11.	BRONCHUS	M	71	5	53	7	30	2	5	20	39	31	16	20.8	100	481%
12.	BRONCHUS	M	70	3	2	33	24	25	35	25	62	2	63	27.4	170+	620%
13.	BRONCHUS	M	39	42	31	74	5	88	45	28	3	15	70	40.1	42	105%
14.	BRONCHUS	M	70	24	1	30	2	5	42	46	41	7	57	25.5	167	655%
15.	BRONCHUS	M	70	8	34	29	24	5	4	32	129	20	51	40.7	33	81%
16.	OESOPHAGUS	M	72	12	21	19	14	81	26	59	21	28	33	57.4	50	87%
17.	OESOPHAGUS	F	80	2	29	6	45	48	24	13	238	56	2	46.3	43	93%
18.	COLON	F	76	2	2	18	5	20	22	1	1	4	1	7.6	57	750%
19.	COLON	F	58	56	39	31	15	9	11	8	10	6	62	24.7	32	130%
20.	COLON	M	49	35	122	107	28	30	13	78	65	46	56	58.0	201	347%
21.	COLON	M	69	48	9	7	15	30	90	26	94	38	15	37.3	1267	4343%
22.	COLON	F	70	64	102	13	82	8	51	33	144	17	11	52.5	144	274%
23.	COLON	F	68	9	15	40	11	17	217	163	59	18	38	38.5	170	441%
24.	COLON	M	50	7	108	7	18	17	14	51	69	16	(32)	33.8	428	1266%
25.	COLON	F	74	11	45	50	6	18	26	40	11	88	23	31.8	127+	399%
26.	COLON	M	66	13	7	224	31	72	11	1	4	11	14	38.8	58	149%
27.	COLON	F	76	23	129	8	63	60	21	28	3	15	70	43.8	93+	212%
28.	COLON	F	56	24	1	30	2	5	42	46	41	7	57	25.5	861	3376%
29.	RECTUM	F	56	51	406	74	36	41	106	30	82	82	98	100.6	62	61%
30.	RECTUM	F	75	3	40	46	58	7	9	19	68	16	178	44.4	223	502%

41. RECTUM	M	56	3	18	52	36	34	7	49	3	6	(13)	22.2	18	81%
42. RECTUM	F	57	9	73	11	19	98	82	(184)	(97)	(89)	(47)	70.9	223	314%
43. RECTUM	M	68	11	11	91	47	18	23	4	13	79	84	38.1	110+	289%
44. RECTUM	M	54	52	36	10	127	18	98	6	73	11	19	45.0	198	440%
45. RECTUM	M	59	15	2	78	8	98	30	140	54	233	(14)	67.2	759	1129%
46. OVARY	F	49	36	5	117	29	31	22	101	140	94	73	64.8	226	349%
47. OVARY	F	68	41	39	18	37	67	3	91	40	6	13	35.5	33	93%
48. OVARY	F	49	53	15	38	122	68	33	841	18	21	40	124.9	183	146%
49. OVARY	F	67	19	36	22	2	10	32	48	132	21	97	41.9	210+	501%
50. OVARY	F	56	49	39	22	85	160	1	86	106	99	107	75.4	93+	123%
51. BREAST	F	56	1	65	26	6	2	15	19	102	71	131	43.8	4	9%
52. BREAST	F	57	3	28	15	4	14	16	14	48	61	15	21.8	22	101%
53. BREAST	F	53	33	183	6	190	45	29	16	45	109	34	69.0	576	835%
54. BREAST	F	66	22	12	94	55	7	38	2	10	76	12	102.8	342	333%
55. BREAST	F	68	107	41	69	19	17	251	101	81	50	52	78.8	567	720%
56. BREAST	F	53	8	2	2	42	31	17	96	231	42	20	49.1	86	175%
57. BREAST	F	75	45	175	12	91	27	5	20	11	63	73	74.2	590	795%
58. BREAST	F	74	12	2	35	6	18	33	30	107	85	47	37.5	8	21%
59. BREAST	F	49	3	16	62	44	1	17	93	73	5	57	37.1	35	94%
60. BREAST	F	50	31	29	28	40	265	14	31	24	104	229	82.6	1614+	1954%
61. BREAST	F	53	105	73	193	159	8	127	126	167	71	42	107.1	143+	134%
62. BLADDER	M	93	17	47	21	12	2	18	21	46	133	48	36.5	241	660%
63. BLADDER	F	70	39	9	126	52	26	97	10	8	7	79	45.3	253	556%
64. BLADDER	F	73	1	23	52	30	38	38	25	13	45	24	28.9	110	381%
65. BLADDER	F	77	3	52	48	142	118	34	33	10	38	26	50.4	34	67%
66. BLADDER	M	44	6	9	36	48	10	21	8	52	42	16	24.8	34	137%
67. BLADDER	M	62	47	118	85	76	19	58	127	72	10	15	62.7	639+	1019%
68. BLADDER	M	69	39	5	66	26	25	267	85	12	13	27	56.5	30	53%
69. GALLBLADDER	F	71	7	8	56	22	91	44	30	22	47	14	34.1	22	64%
70. GALLBLADDER	M	67	20	159	4	212	73	60	94	31	16	91	76.0	209	275%

71. KIDNEY (Ca)	F	71	6	2	17	83	81	55	14	114	60	106	53.8	176	327%
72. KIDNEY (Ca)	F	63	68	76	8	31	26	5	8	69	29	49	36.9	89	241%
73. KIDNEY (Ca)	F	51	16	82	27	41	65	29	8	125	(95)	(117)	60.6	147	243%
74. KIDNEY (Ca)	M	53	7	15	7	49	95	21	91	35	19	76	41.5	58	140%
75. KIDNEY (Ca)	M	55	15	13	12	16	45	48	89	95	6	83	42.2	659	1561%
76. KIDNEY (Ca)	M	73	25	11	209	19	30	198	31	7	30	50	61.0	293	480%
77. KIDNEY (Ca)	M	45	91	35	19	77	64	12	127	74	34	82	61.5	3	5%
78. KIDNEY (Pap)	M	69	67	74	(24)	(37)	87*	43*	21*	82*	14*	41*	49.0	24	49%
79 KIDNEY (Pap)	M	74	57	67	51	(491)	(127)	324	174	126*	179*	97*	169.3	1524+	900%
80 LYMPHOMA	M	40	144	41	53	29	16	20	41	279	302	103	102.8	986+	961%
81 LYMPHOMA	M	65	28	68	51	56	117	138	10	36	51	142	69.7	82	118%
82 PROSTATE	M	47	24	14	22	23	101	53	157	123	16	80	82.3	136+	165%
83. UTERUS	F	56	25	11	7	67	130	126	30	18	185	61	66.0	68	103%
84. CHONDROSARCOMA	M	63	20	25	3	17	136	17	31	23	19	157	44.8	9	20%
85. 'BRAIN'	M	49	1	85	56	(187)	57	24	13	29	1	95	54.8	37	67%
86. PANCREAS	M	77	11	25	19	38	91	78	13	41	40	94	45.0	317	704%
87. PANCREAS	M	67	112	6	55	36	256	25	91	76	67	52	77.6	21	27%
88. PANCREAS	F	60	11	42	23	49	57	69	122	253	89	59	77.4	16	21%
89. FIBROSARCOMA	F	54	13	1	171	10	30	64	(101)	(9)	(25)	(17)	44.1	22	50%
90. TESTICLE	M	42	11	10	56	46	39	102	17	(19)	(29)	(87)	41.6	15	36%
91. PSEUDOMYXOMA	M	47	35	16	1	19	(37)	(27)	(12)	(15)	(87)	(162)	41.1	132	321%
92. CARCINOID	F	68	19	12	45	8	31	12	18	15	82	(38)	28.0	132+	471%
93. LEIOMYOSARCOMA	F	32	31	74	66	(28)	(87)	(121)	[21]	[44]	[27]	[242]	74.1	423+	571%
94. LEUKAEMIA	F	59	6	36	183	6	36	32	44	36	112	63	55.4	400+	722%
95. STOMACH	M	55	34	34	12	78	5	253	77	79	72	49	69.3	27	39%
96. OVARY	F	51	70	13	76	31	65	216	62	140	62	40	77.5	82	106%
97. BRONCHUS	M	69	92	30	90	160	43	147	32	20	135	125	87.4	31	35%
98. BRONCHUS	F	67	93	20	29	90	97	68	185	8	37	26	65.3	138	211%
99. COLON	M	77	8	69	80	14	30	9	57	68	14	21	37.0	15	40%
00. COLON	M	38	3	41	78	17	58	40	66	98	42	(80)	52.3	122+	233%

(Footnote to Table 1)

[a] The sign + following the survival time of the patients treated with ascorbic acid means that the patient was alive on 10 July 1976.

Parantheses ( ) indicate that the matched patient had the same sex, same kind of tumor, and same dissemination, but had an age difference greater than 5 years.

Brackets [ ] indicate opposite sex, same tumor, same dissemination, age difference greater than 5 years.

*Diffuse urinary tract papillomatosis. The test cases (78 and 79) had lesions in both kidney and bladder. The nine control cases indicated by the asterisk had tumor of identical histology, but with their disease confined to bladder mucosa.

Table 2

Ratios of Average Survival Times for Ascorbate Patients and Matched Controls, with Statistical Significance

A	B	C	D	E	F	G	H	I
Bronchus (15)	134d	38.5d	3.48	47d	47%	8.7%	24.5	<<0.0001
Colon (13)	275	37.0	7.42	59	54%	20%	7.63	<0.003
Stomach (13)	94.3	37.9	2.49	43	46%	17%	6.41	<0.006
Breast (11)	362	64.0	5.66	91	55%	22%	5.74	<0.026
Kidney (9)	330	64.0	5.16	88	67%	22%	8.35	<0.002
Bladder (7)	192	43.6	4.39	57	57%	20%	4.90	<0.028
Rectum (7)	222	55.5	4.00	71	86%	33%	7.57	<0.003
Others (25)	158	60.2	2.62	72	44%	28%	2.64	<0.052
All (100)	204.2	50.3	4.06	64	61%	25%	57.66	<<0.0001

A. Type of cancer and number of ascorbate patients. Ten matched controls for each ascorbic acid patient.

B. Average days of survival for ascorbate patients.

C. Average days of survival for controls.

D. The ratio B/C.

E. Average days of survival for all subjects in group.

F. Fraction of ascorbate patients surviving longer than E.

G. Fraction of controls surviving longer than E.

H. Value of χ^2 for F and G (two-by-two calculation).

I. Corresponding value of P (one-tailed).

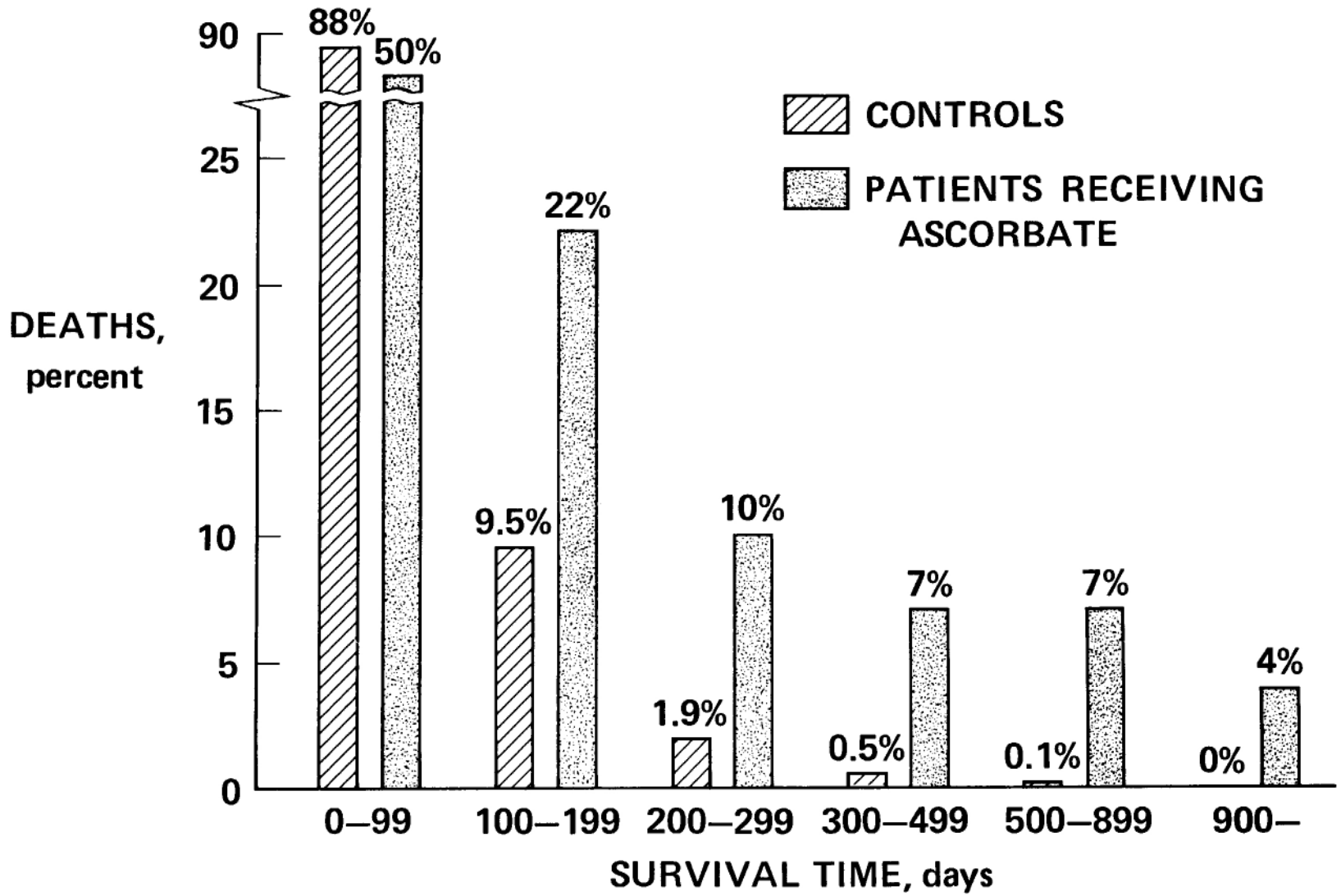

Figure 1

L. Pauling

Legend for figure

Figure 1. The percentages of the 1000 controls (matched cancer patients) and the 100 patients treated with ascorbic acid who survived by the indicated number of days after being deemed untreatable.