Chapter 3

VITAMIN C AND INFECTIOUS DISEASE: A REVIEW OF THE LITERATURE AND THE RESULTS OF A RANDOMIZED, DOUBLE-BLIND, PROSPECTIVE STUDY OVER 8 YEARS

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Library of Congress Cataloging in Publication Data

Main entry under title:
Recent vitamin research.

Includes bibliographies and index. 1. Vitamins —
Physiological effect. 2. Vitamin therapy. I. Briggs,
Michael H. [DNLM: 1. Vitamins

International Standard Book Number 0-8493-5618-0
Library of Congress Card Number 83-7093
Printed in the United States

B. Methods and Materials

The basis of the study was to randomize carefully screened volunteers between two identical products, one containing 50 mg and the other 1000 mg L-ascorbic acid. The obvious solution appeared to be to pack these weights of AA into identical opaque gelatin capsules (dark brown) and to make up the weight difference with some other white crystalline powder, of similar acidic taste, but lacking vitamin C activity. Citric acid was selected (950 mg to each 50 mg AA capsule).

In order to ensure this mixture with citric acid did not either interfere with the absorption or pharmacokinetics of AA, studies were made in 10 volunteers who received capsules of 50 mg A A alone and 50 mg A A + 950 mg citric acid on a double-blind, cross-over basis. Measurements were made of plasma AA at 1-hr intervals for 8 hr, and a 24-hr urine was collected and examined for A A and metabolites.

There were no significant differences between the preparations with or without citric acid for all of these parameters.

Vitamin C capsules stored at room temperature in bottles with silica gel bags showed similar mild deterioration (98 ± 2% S.D. stability) after 100 days, irrespective of the presence of citric acid.

Capsules were packed in brown bottles (100 capsules per bottle). Each bottle was labelled with an adhesive patch with a code number, depending upon the date of manufacture and packaging. Bottles of capsules of the two types were separately crated (each clearly marked A or B).

The criteria for inclusion in the study are set out in Table 15 which summarizes the complete protocol of the study. Volunteers were assigned to product A or B by the use of

Table 15
PROTOCOL FOR THE COMPARATIVE STUDY OF HIGH- AND LOW-DOSE VITAMIN C

1. Adults (either sex) in full-time employment (aged 18+ years)
2. Cigarette intake <10 daily
3. No oral contraceptive use
4. No regular use of other drugs
5. Not pregnant or lactating
6. At least 6 months postpartum
7. No other vitamin supplements (fruit juices were not excluded)
8. No contraindications to high-dose vitamin C
9. No history of nasopharyngeal pathology
10. No history of asthma, chronic bronchitis, pneumonia, etc.
11. Vegetarians excluded
12. Judged to be intelligent and well-motivated
13. Capsules for 100 days supplied: bottle to be returned for residual count and replacement; further return at 6 months
14. Only subjects returning at 3 or 6 months included in study: total subjects divided for analysis by total known duration of treatment
15. No current illness: at least 3 months since previous illness (no chronic disease)
16. Volunteers assigned to 1 of the 2 products using random number tables
17. One product contained 1000 mg AA the other 50 mg A A plus 950 mg citric acid (both in identical brown gelatin capsules): products identified by code numbers on label
18. Instructions were to take 1 capsule daily and increase to 4 capsules daily at first signs of a cold and continue 4 while symptoms persisted
19. Code broken only after subject dropped from study (3 or 6 months completed)
20. Re-entry into the study was not allowed
21. Subjects asked to rate severity of any cold by 7 symptoms, each graded severe, moderate, or mild (see Table 2); record card supplied
22. The symptoms were explained to each subject with care until the interviewer was satisfied that the subject understood how to grade each symptom accurately
23. Subjects supplied written informed consent
24. Selected subjects supplied 24-hr dietary histories (by recall), 5 m€ blood by venepuncture (for ascorbate analysis), and 24-hr urine collections (for ascorbate and oxalate analysis)

random number tables and neither the physician nor the volunteer was aware of the composition of the capsules prescribed.

Clinical criteria for the classification of colds were based on those of Abbott et al. (1968) and are shown in Table 16. The record card completed by each subject is shown in Table 17.

Dietary histories were obtained from some subjects (using the 24-hr recall method) during the return visits after 3 or 6 months. These subjects also brought with them a 24-hr urine collection and supplied 5 m€ of nonfasting blood (collected by venepuncture of the antecubital vein). Urine was analyzed for total ascorbate (using the method of Roe and Kuether, 1943) and oxalate (using the enzymic method of Costello et al., 1976). Heparinized blood was separated into plasma, platelets, and leukocytes, which were separately analyzed for total AA (methods of Albanese et al., 1975 and Briggs, 1973).

C. Results and Discussion

In all, 528 persons took part in this study (160 men and 368 women). Distribution of both sexes between the two doses of vitamin C was close (see Table 18). Low-dose A A was received by 263 persons (186 women and 77 men), while the 1000 mg dose was taken by 265 persons (182 women and 83 men).

Of the total group (528 persons), 237 completed only a single 3-month course (45%),

Table 16
CLINICAL CRITERIA FOR SYMPTOMS[2]

Symptom	Grade*	Criteria
Sore throat	1	Red and inflamed throat
		Sore all day long
		Pain on swallowing
		Requiring analgesics
	2	Less red and inflamed throat
		Sore mainly in mornings and on eating
		Requiring only occasional analgesics
	3	Sore only for short time first thing in mornings
Stuffy nose	1	Both nostrils completely blocked, resulting in mouth breathing
		Blockage present more often than it is not
		Nostrils cannot be cleared by blowing
	2	Intermittent obstruction of nostrils
		Obstruction may be one-sided
		Nostrils sometimes cleared by blowing
	3	Nostrils not blocked and nose-breathing possible
		Blowing necessary to keep nostrils clear
Sneezing	1	More or less continuous throughout the day
	2	Bouts on and off throughout the day
	3	Occasional (usually early mornings only)
Watery nasal discharge	1	All day long
		Continuous use of handkerchief
	2	Bouts on and off throughout the day
		Intermittent use of handkerchief
	3	Short time only (usually mornings)
		Occasional use of handkerchief
Purulent nasal discharge	1	Thick and purulent
	2	Less thick and less purulent
	3	Muco-purulent
Headache	1	Continuous analgesics required
	2	Occasional analgesics required
	3	Ache present but no analgesics required
		Not inconveniencing in any way
Aching back and limbs	1	Continuous analgesics required
	2	Occasional analgesics required
	3	Aches present, but analgesics not required
		Not inconveniencing in any way

* Grades: 1-severe; 2-moderate; 3-mild

while 291 (55%) completed the double course of 6 months. The sex distributions were as follows:

50 mg	Men completing 3 months	= 29	77	(38% total)
	Men completing 6 months	= 48		(62% total)
	Women completing 3 months	= 89	174	(51% total)
	Women completing 6 months	= 85 → 97	186	(49% total)
1000 mg	Men completing 3 months	= 34	83	(41% total)
	Men completing 6 months	= 49		(59% total)
	Women completing 3 months	= 85	182	(47% total)
	Women completing 6 months	= 97		(53% total)
Both doses	Men completing 3 months	= 118 → 63	263 → 160	(45% total)
	Men completing 6 months	= 145 → 97		(55% total)
	Women completing 3 months	= 174	368	(47% total)
	Women completing 6 months	= 194		(53% total)
Both doses	M, F completing 3 months	= 237	528	(45% total)
	M, F completing 6 months	= 291		(55% total)

compare p. 60 & Table 18

Table 17
RECORD CARD

DATE OF NEXT APPOINTMENT: _____
(Please bring this card with you)
NAME: _____

Write the date for each day with cold symptoms and evaluate yourself for the severity of each of the seven symptoms (check the appropriate boxes). Try to fill in the record daily, rather than rely on memory. Leave a blank where a symptom is not present.[a]

Dates of colds	Sore throat			Stuffy nose			Sneezing			Watery nasal discharge			Purulent nasal discharge			Headache			Aching back and limbs		
	1	2	3	1	2	3	1	2	3	1	2	3	1	2	3	1	2	3	1	2	3

[a] Scored 4 in the analysis.

Generally speaking, significantly more men entering the study completed the 6-month course than women, who had a higher drop-out rate at the 3-month stage.

Table 19 lists the annual and cumulative days of treatment with the two preparations. Over the 8-year period the total number of treatment days for both doses combined was 25,079; 12,349 days with the 50 mg dose and 12,730 days with 1000 mg dose. Men used the 50 mg dose for 3781 days (30.6% of total for that dose), while women used 50 mg for 8568 days (69.4%). For the 1000 mg dose, men used this for 4220 days (33.1% of total for that dose) and women for 8510 days (66.8%).

A detailed breakdown of reported cold symptoms is given in Table 20. Over the period of study there was a total of 246 colds, of which 121 (49.2%) occurred in the 50 mg dose group and 125 (50.8%) in the 1000 mg dose group. This is not significantly different. The number of days on which cold symptoms occurred was 792, of which 402 (50.8%) were with the 50 mg dose and 390 (49.2%) with 1000 mg. Again, these are not significantly different.

The mean duration of cold symptoms was 3.3 days with 50 mg and 3.1 days with 100O mg.

These data are presented in Table 21 as percentages of the total groups (by year and cumulative). Only occasional individuals reported more than one cold during the trial period. Figures 1 to 5 graphically present the data presented in the above tables.

Estimates of the severity of colds are given in Table 22, where the six major symptoms were separately assessed by subjects during each cold episode. There are clearly major differences in certain symptoms during particular years. For example, aching back and limbs were much less frequent in 1977 through 1981 than in 1974 and 1975. Similarly, stuffy nose was less severe in 1977 and 1979 than in most other years. Sore throat and sneezing, however, were relatively constant throughout the 8-year study period.

When the average scores for each symptom are compared between the 50 mg and 1000 mg treatment groups, it is immediately apparent that differences between the scores for stuffy nose, headache, and aching back are very small and statistically insignificant.

For the other symptoms (sore throat, sneezing, and watery nasal discharge), the 1000 mg

Table 18
ANNUAL AND CUMULATIVE TREATMENTS

		Subjects						Cumulative					
		Men		Women		Total		Men		Women		Total	
Year[a]		50	1000	50	1000	50	1000	50	1000	50	1000	50	1000
1974	T	11	13	17	20	28	33	—	—	—	—	28	33
	3	5	6	7	11	12	14	—	—	—	—	12	17
	6	6	7	10	9	16	16	—	—	—	—	16	16
1975	T	12	10	22	29	34	39	23	23	39	49	62	72
	3	6	4	11	14	17	18	11	10	18	25	29	35
	6	6	6	11	15	17	21	12	13	21	24	33	37
1976	T	16	18	43	26	59	44	39	41	82	75	121	116
	3	6	9	21	12	27	21	17	19	39	37	56	56
	6	10	9	22	14	32	23	22	22	43	38	65	60
1977	T	9	9	30	31	39	40	48	50	112	106	160	156
	3	3	4	12	13	15	17	20	23	51	50	71	73
	6	6	5	18	18	24	23	28	27	61	56	89	83
1978	T	8	8	22	20	30	28	56	58	134	126	190	184
	3	3	4	10	9	13	13	23	27	61	59	84	86
	6	5	4	12	11	17	15	33	31	73	67	106	98
1979	T	11	8	29	29	40	37	67	66	163	155	230	221
	3	3	2	14	11	17	13	26	29	75	71	101	100
	6	8	6	15	18	23	24	41	37	88	84	129	121
1980	T	8	6	19	17	27	23	75	72	182	172	257	244
	3	2	3	12	10	14	13	28	32	87	81	115	113
	6	6	3	7	7	13	10	47	40	95	91	142	131
1981	T	2	11	4	10	6	21	77	83	186	182	263	265
	3	1	2	2	4	3	6	29	34	89	85	118	119
	6	1	9	2	6	3	15	48	49	97	97	145	146

[a] T = total; 3 = 3 months; 6 = 6 months.

Table 19
ANNUAL AND CUMULATIVE DAYS OF TREATMENT

	Men		Women		Total		
Year	50	1,000	50	1,000	50	1,000	50 + 1,000
1974	512	695	818	879	1,330	1,574	2,904
	—	—	—	—	—	—	—
1975	541	609	997	1,333	1,538	1,942	3,480
	1,053	1,304	1,815	2,212	2,868	3,516	6,384
1976	784	815	1,959	1,218	2,743	2,033	4,776
	1,837	2,119	3,774	3,430	5,611	5,549	11,160
1977	453	426	1,451	1,490	1,904	1,916	3,820
	2,290	2,545	5,225	4,920	7,515	7,465	14,980
1978	395	368	1,029	939	1,424	1,307	2,731
	2,685	2,913	6,254	5,859	8,939	8,772	17,711
1979	575	426	1,332	1,440	1,907	1,866	3,773
	3,260	3,339	7,586	7,299	10,846	10,638	21,484
1980	428	272	796	728	1,224	1,000	2,224
	3,688	3,611	8,382	8,027	12,070	11,638	23,708
1981	93	609	186	483	279	1,092	1,371
	3,781	4,220	8,568	8,510	12,349	12,730	25,079

Table 20
SUBJECTS AND DAYS WITH REPORTED COLD SYMPTOMS

	Subjects													
	Men				Women				Totals				Mean cold duration	
	50		1000		50		1000		50		1000			
Year	S	D	S	D	S	D	S	D	S	D	S	D	50	1000
1974	5	16	8	27	8	25	11	36	13	41	19	63	3.2	3.3
	—	—	—	—	—	—	—	—	—	—	—	—	—	—
1975	5	21	6	24	12	49	14	56	17	70	20	80	4.1	4.0
	(10	37)[a]	(14	51)	(20	74)	(25	92)	(30	111)	(39	143)	(3.7	3.7)
1976	8	20	6	17	13	46	13	38	21	66	19	55	3.0	2.9
	(18	57)	(20	68)	(33	120)	(38	130)	(51	177)	(58	198)	(3.5	3.4)
1977	4	7	3	7	12	23	15	29	16	30	18	36	0.9	2.0
	(22	64)	(23	75)	(45	143)	(53	159)	(67	207)	(76	294)	(3.1	3.1)
1978	5	21	4	26	7	28	7	19	12	49	11	45	3.9	4.1
	(27	85)	(27	101)	(52	171)	(60	178)	(79	256)	(87	279)	(3.2	3.2)
1979	6	28	4	21	15	62	9	39	21	90	13	60	4.3	4.6
	(33	113)	(31	122)	(67	233)	(69	217)	(100	346)	(100	339)	(3.5	3.4)
1980	4	14	4	8	13	37	10	28	17	51	14	36	3.0	2.6
	(37	127)	(35	130)	(80	270)	(79	245)	(117	397)	(114	375)	(3.4	3.3)
1981	1	2	5	6	3	3	6	9	4	5	11	15	1.2	1.3
	(38	129)	(40	136)	(83	273)	(85	254)	(121	402)	(125	390)	(3.3	3.1)

Note: S = subjects; D = days.

[a] Numbers in parenthesis indicate cumulative totals.

Table 21
PERCENTAGE SUBJECTS AND DAYS WITH COLDS: ANNUAL AND CUMULATIVE

	Men				Women				Total			
	50		1000		50		1000		50		100	
Year	S	D	S	D	S	D	S	D	S	D	S	D
1974	45	3.1	61	3.9	47	3.1	55	4.1	46	3.1	58	4.0
	—	—	—	—	—	—	—	—	—	—	—	—
1975	41	3.9	60	3.9	54	4.9	48	4.2	50	4.5	51	4.1
	(43	3.5)[a]	(61	3.9)	(51	4.1)	(51	4.2)	(48	3.9)	(54	4.1)
1976	50	2.5	33	2.1	30	2.3	50	3.1	36	2.4	43	2.7
	(46	3.1)	(51	3.2)	(40	3.2)	(51	3.8)	(42	3.1)	(50	3.6)
1977	44	1.5	33	1.6	40	1.6	48	1.9	41	1.6	45	1.9
	(46	2.8)	(48	2.9)	(40	2.7)	(50	3.2)	(42	2.7)	(49	3.1)
1978	62	5.3	37	7.1	54	2.7	75	2.0	53	3.4	64	3.4
	(48	3.2)	(40	3.5)	(34	2.7)	(42	3.0)	(35	2.9)	(41	3.2)
1979	54	4.9	50	4.9	52	4.6	31	2.7	52	4.7	35	3.2
	(49	3.5)	(47	3.6)	(41	3.1)	(44	3.0)	(43	3.2)	(45	3.2)
1980	50	3.3	66	2.9	68	4.6	59	3.8	63	4.2	61	3.6
	(49	3.4)	(49	3.6)	(44	3.2)	(46	3.1)	(45	3.3)	(47	3.2)
1981	50	2.1	45	1.0	75	1.6	60	1.9	66	1.8	52	1.4
	(49	3.4)	(48	3.2)	(45	3.2)	(47	3.0)	(46	3.3)	(47	3.1)

Note: S = subjects; D = days.

[a] Numbers in parenthesis indicate cumulative totals.

treatment group is slightly better than the 50 mg group to the extent of approximately + 6% in each case. By the χ^2 test, however, this difference fails to reach statistical significance.

It should be stressed that if years are considered in isolation, occasional statistically significant differences between the two treatment groups can be found (e.g., stuffy nose in 1980, sore throat in 1975, aching back and limbs in 1978). These differences, however, disappear when the complete 8-year treatments are pooled. As the common cold viruses are subject to frequent mutations, it might be argued that vitamin C is effective against certain strains, but not others. While this possibility cannot be discounted, it would be almost impossible to investigate by clinical trials other than on a massive scale with detailed identification of strains by viral immunology and electron microscopy.

The distribution of AA between blood plasma, platelets, and leukocytes for 34 persons taking 50 mg vitamin C and for 36 taking 1000 mg is shown in Table 23. While plasma levels were slightly higher in the 1000 mg group, the difference is not statistically significant. A A concentrations in platelets and leukocytes were also not significantly different between the two treatment groups, nor between the sexes, either within a group or between groups.

Finally, Table 24 gives the estimated dietary vitamin C intake of 143 persons in the 50 mg dose group and 151 in the 1000 mg group. As expected, the mean urinary A A excretion per 24 hr was highly significantly greater for the 1000 mg group than for the 50 mg group ($p < 0.001$). While 24-hr urinary oxalate values overlapped between the two groups, the mean value in the 1000 mg group was significantly higher than in the 50 mg group ($p < 0.01$).

D. Conclusions

1. A total of 528 carefully selected individuals were randomized between either 50 mg

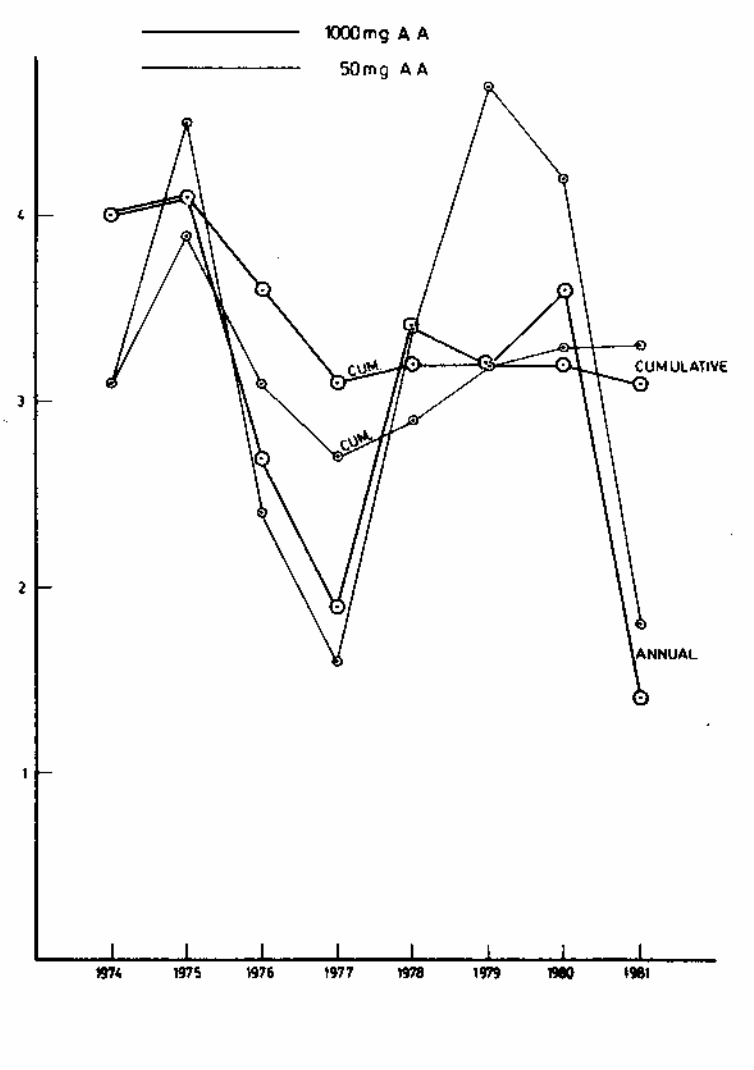

FIGURE 1. Total percentage days with colds

or 1000 mg vitamin C daily for 3 or 6 months. There were no significant differences between the two groups for the number of colds, their severity, or duration. The concentrations of A A in blood plasma, platelets, and leukocytes were not significantly different between the two groups, but those receiving 1000 mg daily excreted much more A A in 24-hr urine specimens. The high-dose group also excreted significantly more oxalic acid, though there was considerable overlap between the two groups.

The present study suggests that a daily large intake of vitamin C (1000 mg increasing to 4000 mg during a cold) is no more helpful in reducing the incidence, severity, or duration of colds than a much smaller dose (50 mg increasing to 200 mg during a cold). Although the increase in urinary oxalate with the high dose is small, this may increase the risk of urinary stones in predisposed individuals. High doses of vitamin C should not, therefore, be used for mass self-medication.

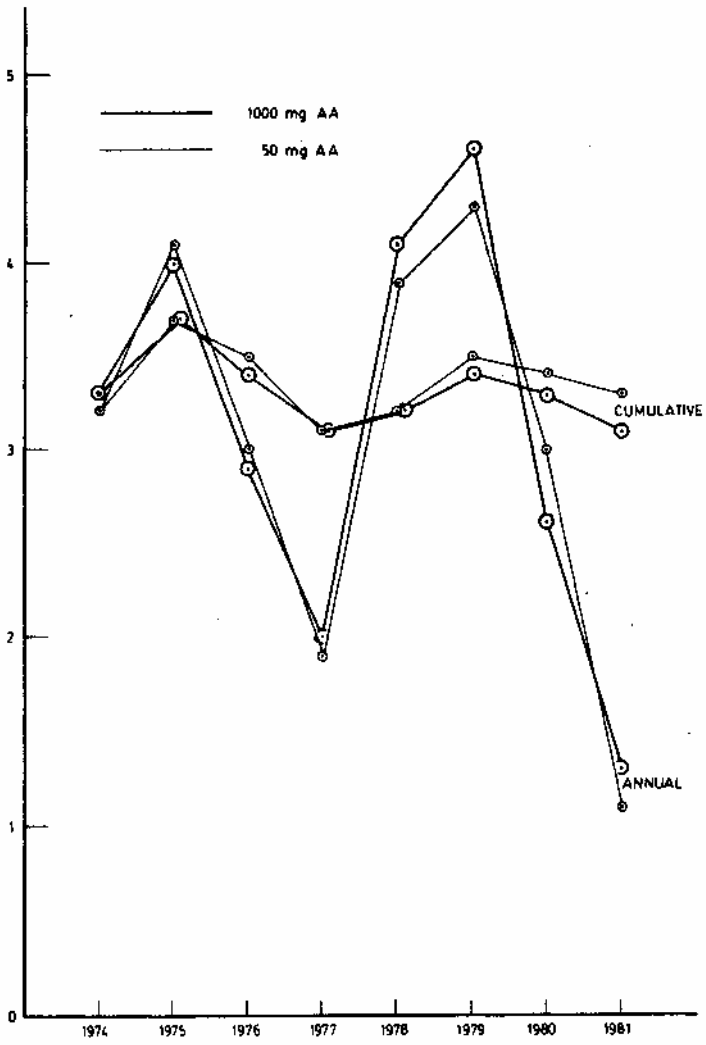

FIGURE 2. Duration of colds (mean days)

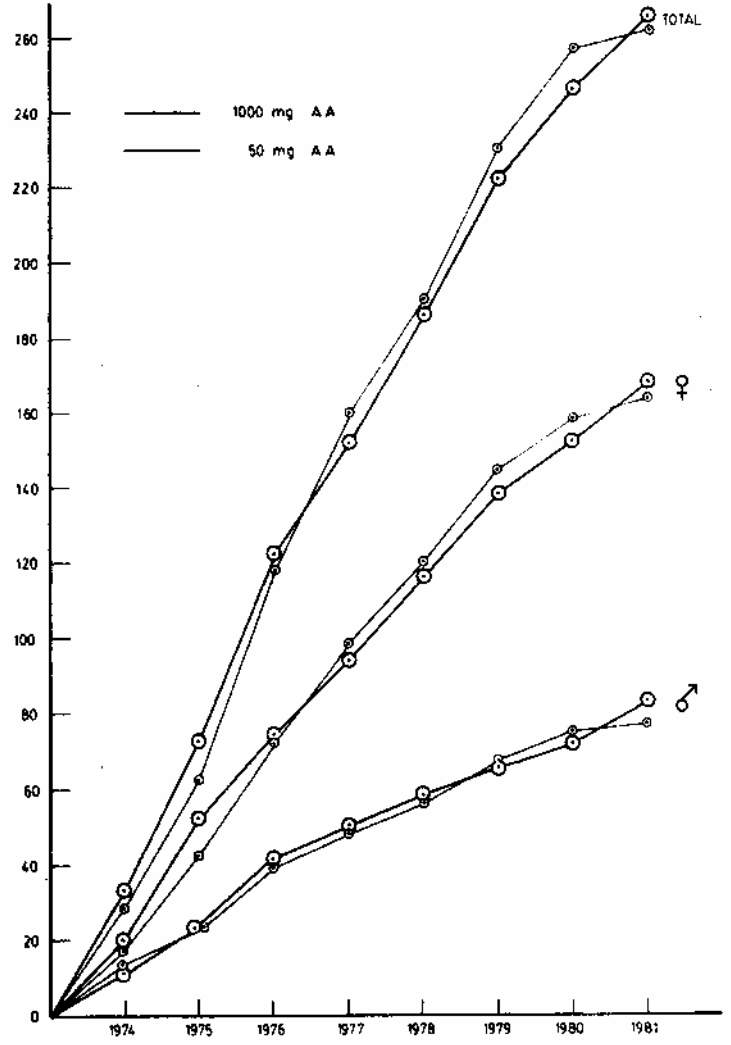

FIGURE 3. Progressive recruitment (subjects).

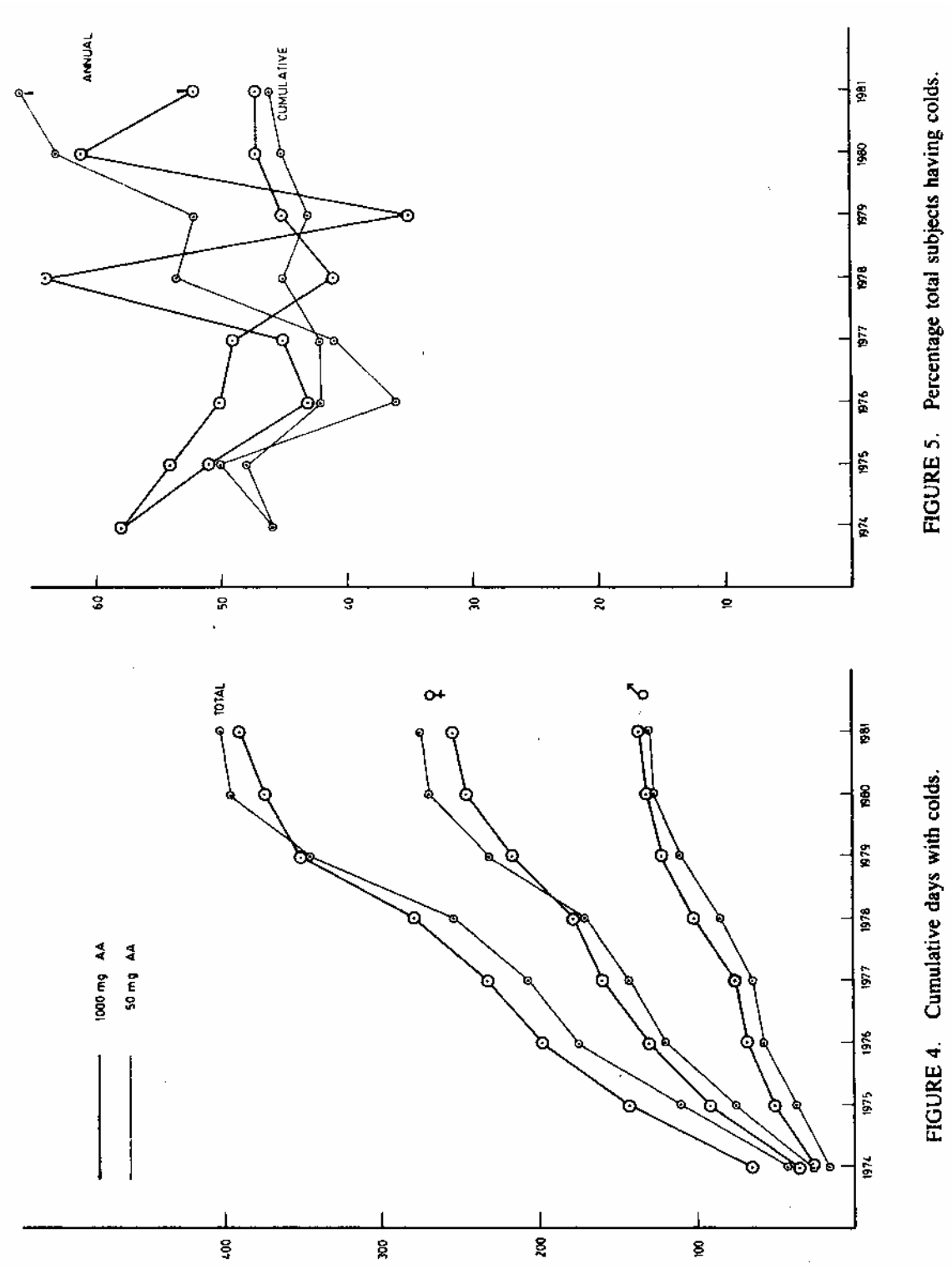

FIGURE 4. Cumulative days with colds.

FIGURE 5. Percentage total subjects having colds.

Table 22
SEVERITY OF COLDS: SYMPTOM SCORES[a]

Year	Dose (mg)	Sore throat		Stuffy nose		Sneezing		Watery nasal discharge		Headache		Aching back	
		Total	Average/cold	Total	Average/cold	Total	Average/cold	Total	Average/cold	Total	Average/cold	Total	Average/cold
1974	50	23	1.80	55	4.21	21	1.62	76	5.81	116	8.91	95	7.31
	1000	31	1.61	76	3.98	31	1.65	128	6.72	168	8.87	141	7.40
1975	50	24	1.40	62	3.62	35	2.05	65	3.81	152	8.93	119	7.01
	1000	41	2.05	80	4.02	42	2.10	81	4.06	180	8.65	147	7.02
1976	50	34	1.61	62	2.95	64	3.06	60	2.86	178	8.51	188	8.95
	1000	30	1.59	57	3.01	49	2.57	72	3.79	163	8.57	168	8.85
1977	50	17	1.09	75	4.70	20	1.28	32	2.01	131	8.16	154	9.65
	1000	21	1.15	83	4.62	34	1.90	46	2.57	158	8.75	175	9.72
1978	50	20	1.68	37	3.05	25	2.06	70	5.86	116	9.63	103	8.50
	1000	21	1.91	31	2.85	24	2.15	69	6.31	106	9.61	106	9.68
1979	50	26	1.26	89	4.26	39	1.86	86	4.11	199	9.49	187	8.91
	1000	17	1.31	63	4.82	25	1.90	65	5.01	111	8.51	129	9.89
1980	50	33	1.98	71	4.16	30	1.76	66	3.86	150	8.83	169	9.95
	1000	22	1.61	87	6.21	28	2.00	28	2.00	139	9.90	125	8.93
1981	50	8	2.01	9	2.38	8	2.00	4	1.00	35	8.75	39	9.65
	1000	20	1.85	24	2.16	33	3.00	12	1.11	91	8.30	102	9.29
Total	50	185	1.53	490	4.05	242	2.00	459	3.79	1077	8.90	1053	8.70
	1000	203	1.62	501	4.01	266	2.13	501	4.01	1116	8.93	1093	8.74

[a] Severity scores for all cold episodes in each group. It should be noted that severity of each symptom is *inversely* proportional to the score.

Table 23
AA IN BLOOD (MEAN VALUES ± S.D.)

Group (mg)	Sex	No.	Blood fractions: Plasma mg/ℓ	Platelets mg/g wet wt.	Leukocytes μg/10⁸
50	♂	15	11 ± 3	0.27 ± 0.10	34 ± 6
	♀	19	12 ± 3	0.29 ± 0.11	33 ± 5
	Both	34	11 ± 3	0.28 ± 0.10	33 ± 5
1000	♂	14	12 ± 3	0.29 ± 0.09	32 ± 6
	♀	21	13 ± 3	0.27 ± 0.11	34 ± 5
	Both	36	13 ± 3	0.28 ± 0.10	33 ± 5

Table 24
MEAN URINARY EXCRETIONS (± S.D.)

Group (mg)	No.	Food AA[b]	Urinary oxalate and ascorbate[a] (mg/24 hr): Oxalate Mean ± S.D. (range)	Ascorbate Mean ± S.D. (range)
50	143	85 ± 5	46 ± 11 (22—105)	28 ± 9 (19—51)
1000	151	78 ± 8	89 ± 15 (41—151)	705 ± 35 (612—855)

[a] Subjects provided urine specimens after 3 months treatment: oxalate-rich foods were excluded for 7 days prior to urine collection.

[b] Estimated from recall and dietary tables.