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## ASCORBIC ACID ECONOMY IN SURGICAL PATIENTS AS INDICATED BY BLOOD ASCORBIC ACID LEVELS\*

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**T**ODAY, ascorbic acid is well recognized as having an important role in the preoperative and postoperative nutrition of surgical patients. Nevertheless, information on the requirements and total physiologic action of this vitamin is scanty. The result frequently has been either shotgun therapy or none at all.

This study has centered around the requirements of ascorbic acid, the effects of deficiency and the significance of blood acid levels in adult surgical patients exclusive of those suffering burns or severe trauma. The classic work of Bartlett, Jones and Ryan,<sup>1</sup> in 1942, suggested that in the adult, plasma ascorbic acid levels below 0.2 mg. per 100 ml. were indicative of serious deficiency. From a clinical appraisal of surgical patients we must concur that plasma levels below 0.2 mg. per 100 ml., together with a buffy-coat ascorbic acid below 8 mg. per 100 gm., indicate serious deficiency of this vitamin.

Early in the investigation, determinations of urinary ascorbic acid were found to be so variable and inconsistent that this approach to the study of vitamin C economy in surgical patients was discarded as worthless.

### ORIENTATION

All analyses in this study were performed immediately by the Roe-Kuether<sup>2</sup> method, using Butler-Cushman tubes to separate the buffy coat by cen-

trifugation. For buffy-coat determinations, at least 10 ml. of unhemolyzed blood was required.

Figure 1 presents the various categories of ascorbic acid economy that may be encountered, as determined by blood analyses. The buffy-coat or white-cell and platelet ascorbic acid is small in relation to the amount in the plasma, but it is an important index of body economy since it absorbs and releases its ascorbic acid much more slowly than the plasma, which rises and falls rather quickly in response to fluctuation in intake. In the saturated person, the plasma ascorbic acid ranges above 1 mg. per 100 ml. whereas the buffy coat measures above 30 mg. per 100 gm. In the normal subject, the plasma ascorbic acid averages about 0.7 mg. per 100 ml., and the buffy-coat value 15 mg. or more per 100 gm. In the deficient patient, the plasma level is under 0.2 mg. per 100 ml., and the buffy-coat level is less than 8 mg. per 100 gm. In the scorbutic patient, the plasma ascorbic acid is generally under 0.1 mg. per 100 ml., and the buffy-coat value under 4 mg. per 100 gm. In the deficient patient who has recently received ascorbic acid, the buffy-coat level may remain relatively low whereas the plasma value, owing to rapid uptake of the vitamin, may be high in relation to actual tissue economy of ascorbic acid.

### WOUND DEHISCENCE

Over a four-year period immediate blood ascorbic acid determinations were performed at the Boston City Hospital on 47 patients suffering wound dehiscence postoperatively (Table 1). Of these patients, 19 were found to have deficient levels of blood ascorbic acid according to our concept. The average blood levels of the group deficient in ascorbic acid were, for plasma, 0.1 mg. per 100 ml. and, for buffy coat, 4 mg. per 100 gm. Comparable levels were observed among 15 clinical scorbutic patients entering the medical wards over this period. On the other hand, among the 28 patients suffering dehiscence and showing sufficient blood levels of the vitamin, the average ascorbic acid was slightly greater than

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the average for 100 consecutive surgical patients, and approached the mean for 20 normal controls. Of the patients with low blood ascorbic acid 16 were found to have cough, vomiting, distention or wound infection or a combination of these, which may have been contributing or actual causative factors for their evisceration.

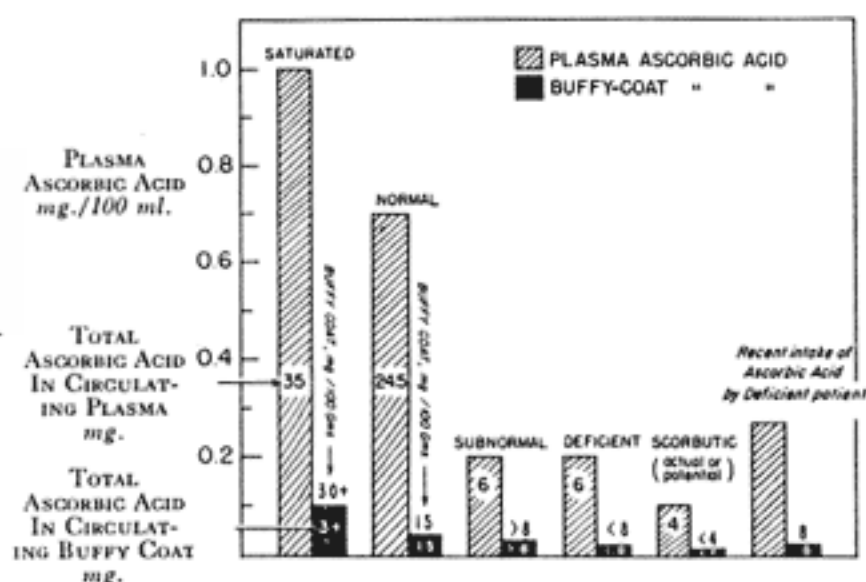


FIGURE 1. Relative Estimated Amounts of Ascorbic Acid in the Circulating Blood of Saturated and Deficient Adult Patients (Roe-Kuether Method<sup>2</sup>).

Buffy-coat ascorbic acid (in mg. per 100 gm.) has been transposed to the equivalent in mg. per 100 ml. of plasma for comparison of relative amounts of each.

Five patients suffering dehiscence had wound biopsies subjected to pathological study and tissue analysis for ascorbic acid. Microscopical studies were unsatisfactory in each case because of the presence of

TABLE 1. Blood Ascorbic Acid of Patients with Wound Dehiscence Requiring Resuture or Strapping, July, 1950, to July, 1954.\*

GROUP	PLASMA LEVEL mg./100 ml.	BUFFY-COAT LEVEL mg./100 gm.
Entire group suffering dehiscence	0.37	12.1
Low group	0.10	4.0
15 clinical scorbutic patients (medical)	0.08	3.6
High group	0.47	16.4
100 consecutive Boston City Hospital surgical patients	0.33	12.6
20 ambulatory normal controls	0.69	15.2

\*Determination performed at time of dehiscence in each case. Total dehiscences, 47; patients with low blood ascorbic acid (plasma, < 0.2 mg./100 ml., & buffy-coat, < 8 mg./100 gm.), 19; number in low group with cough, vomiting, distention or wound infection, 16.

inflammatory reaction. Tissue analysis revealed an adequate fascial ascorbic acid in 3 of the 4 patients showing high blood levels of the vitamin (Table 2). In the fourth patient (J.L.) the tissue analyzed was necrotic. The 1 patient with low blood ascorbic acid levels having wound-tissue analysis showed 0.0 mg.

per 100 gm. of ascorbic acid in the fascia and 0.2 mg. per 100 gm. in the muscle layer.

Three patients in the low group had blood determinations before dehiscence—2 at original operation. None of them received ascorbic acid postoperatively. All 3 patients showed a drop in the already low blood ascorbic acid levels to practically 0 at the time of evisceration or shortly thereafter (Table 3).

Five patients in the low group were given ascorbic acid in known amounts parenterally before or after dehiscence (Table 4). One patient (H.L.) had received 100 mg. of ascorbic acid intramuscularly for ten days before evisceration, 1 (D.G.) had received 100 mg. of ascorbic acid for five days before evisceration, and 1 (J.D.) had received 100 mg. of vitamin C intramuscularly for four weeks before definitive operation, but not thereafter. In spite of this ascorbic

TABLE 2. Tissue Analysis of Dehisced Wounds in 5 Patients.

PATIENT	DISEASE OR PROCEDURE	PLASMA ASCORBIC ACID mg./100 ml.	BUFFY-COAT ASCORBIC ACID mg./100 gm.	FASCIA ASCORBIC ACID mg./100 gm.	MUSCLE ASCORBIC ACID mg./100 gm.
D.F.	Carcinoma of cecum (exploratory laparotomy)	0.32	23.0	1.9	4.0
J.M.	Appendectomy	0.70	11.5	8.0	6.0
J.L.	Carcinoma of rectum (Miles's resection)	0.31	11.8	0.05	
F.B.	Cholecystoduodenostomy	0.62	13.9	5.0	
S.M.	Cholecystostomy	0.04	2.9	0	0.2

acid therapy the blood levels of these 3 patients were very low at the time of evisceration. After dehiscence 2 patients (J.E. and M.B.) received 200 mg. of ascorbic acid intramuscularly daily for six days, at the end of which the blood levels were still low but showed slight improvement. The patient with the lower blood level had a severe Meleney infection of the abdominal wall, which at autopsy was shown to involve the entire abdominal fascia.

#### MAINTENANCE STUDIES

In maintenance studies on 26 patients it was found that when the inflammatory reaction was not great, even though the patient was initially quite deficient and the magnitude of the surgery quite marked, maintenance could be carried out on 100 mg. of ascorbic acid a day. Thus, a sixty-year-old Chinese showing marked deficiency of ascorbic acid by blood analyses and undergoing partial gastrectomy for carcinoma of the stomach experienced a completely uneventful recovery on maintenance of only 100 mg. of ascorbic acid daily (Table 5). His abdominal

wound gave no evidence of weakness when checked a year later. When the magnitude of surgery was more marked, and particularly if there was inflammatory

ments. Postoperatively, he was placed on only 100 mg. of ascorbic acid a day. With this supplement the plasma ascorbic acid was kept somewhat above the

TABLE 3. *Predehiscence Blood Ascorbic Acid Studies in 3 Deficient Patients.*

PATIENT	AGE	OPERATION	BLOOD ASCORBIC ACID BEFORE DEHISCENCE		ASCORBIC ACID INTAKE	BLOOD ASCORBIC ACID AT TIME OF DEHISCENCE		REMARKS
			PLASMA	BUFFY COAT		PLASMA	BUFFY COAT	
	yr.		mg./100 ml.	mg./100 gm.		mg./100 ml.	mg./100 gm.	
H.C.	52	Exploratory laparotomy for chronic volvulus	0.03 (1 day before dehiscence)	7.8	0	0.06	0	Distention & cough Patient died
H.I.	65	Exploratory laparotomy for strangulated hernia	0.14 (at operation 4 days before dehiscence)	7.1	0	—	1.0	Cough Patient died
L.Mc.	55	Perforated ulcer	0.11 (at operation 10 days before dehiscence) Three days after dehiscence	7.8	0	0.19 0	4.5 1.6	Cough & wound infection Patient recovered

reaction in the wound, a daily supplement of 100 mg. of ascorbic acid was insufficient. This was shown in a patient undergoing total gastrectomy with splenec-

level that we consider to mark borderline deficiency, and the buffy-coat value hovered around borderline levels. In this patient consideration was not taken of

TABLE 4. *History before and after Dehiscence in 5 Deficient Patients.*

PATIENT	AGE	DISEASE & OPERATION	ASCORBIC ACID BEFORE & AFTER DEHISCENCE	BLOOD ASCORBIC ACID AT TIME OF DEHISCENCE		SUBSEQUENT BLOOD ASCORBIC ACID		REMARKS
				PLASMA	BUFFY COAT	PLASMA	BUFFY COAT	
	yr.			mg./100 ml.	mg./100 gm.	mg./100 ml.	mg./100 gm.	
H.L.	84	Carcinoma of stomach; gastrectomy (7/26).	100 mg. intramuscularly/day from day of operation to evisceration (10 days)	0.19	(Not done)*	Patient died		Autopsy showed subacute peritonitis from leaking suture line
J.D.	62	Carcinoma of ascending colon; right-sided colectomy (10/24).	100 mg. intramuscularly/day for 4 wk. before operation; none thereafter for 13 days to evisceration.	0.12	6.4†	Patient died		Clinical evidence of peritonitis; delirium tremens; no autopsy.
D.G.	58	Volvulus of sigmoid; exteriorization (1/26).	100 mg. intramuscularly/day from 3/5 to evisceration (5 days)	0.15	0‡	Patient died		Clinical evidence of peritonitis; no autopsy.
J.E.	69	Cholecystitis; cholecystectomy & common-duct exploration (4/30).	200 mg. intramuscularly/day from day after evisceration (5/10)	0	0‡	0.09 (5/13) 0.21 (5/17)	1.38 7.8§	No autopsy; clinical evidence of bronchopneumonia; patient died on 5/21.
M.B.	58	Bleeding duodenal ulcer, diabetes & shock; emergency gastrectomy (4/22).	500 mg. intravenously on day of operation (5/1); 200 mg. daily beginning on 5/5.	0.11	4.0§	0.14 (5/11)	5.6	Patient died on 5/14; autopsy showed extensive Meleney infection of entire abdominal wall.

\*10th postoperative day.

†13th postoperative day.

‡11th postoperative day.

§9th postoperative day.

||After ascorbic acid for 6 days.

tomy for carcinoma who was initially markedly deficient in ascorbic acid (Table 6). He successfully weathered his operation without vitamin supple-

the fact that the parenteral ascorbic acid was being absorbed into the plasma before it reached the tissues and that therefore the plasma levels did not truly

reflect his tissue economy of ascorbic acid. On the thirteenth postoperative day, at approximately the time that a bilateral femoral-vein ligation was necessary for phlebitis, a draining sinus showing no growth on culture developed in the wound. Shortly thereafter the plasma and buffy-coat ascorbic acid levels fell. Although this patient had no cough or dis-

TABLE 5. Maintenance Studies in a Seriously Depleted Patient Undergoing Partial Gastrectomy for Carcinoma of the Stomach.\*

DATE	BLOOD ASCORBIC ACID†	
	PLASMA mg./100 ml.	BUFFY COAT mg./100 gm.
Jan. 9	0.03	0.0
Jan. 15‡	0.13	1.2
Jan. 15§	0.04	0.0
Jan. 18	0.09	0.0
Jan. 22	0.34	0.0
Jan. 29	0.41	9.7
Jan. 30¶		

\*L.M., 60-yr.-old Chinese, who had been on diet low in fruits & vegetables.

†With patient on 100 mg. of ascorbic acid/day.

‡Before operation.

§After operation.

¶Patient discharged — no complications.

tion postoperatively it was soon apparent that a total, large incisional hernia was developing that in our opinion was entirely due to inadequate ascorbic acid intake. This patient should probably have received 200 rather than 100 mg. of ascorbic acid per day.

Among all 26 patients subjected to maintenance studies the maximal ascorbic acid requirement per day was seen in a patient with severe enterocolitis (Table 7). This patient was followed closely both for dietary intake and for blood ascorbic acid levels during his entire hospital course. He was discharged to his home after ileostomy and staged colectomy on oral vitamin supplements, which subsequently were not taken. During the latter part of his severe illness he re-entered the hospital with recurrent disease in the small bowel, multiple fistulas and evidence of peritonitis. Parenteral administration of ascorbic acid supplements was then recommenced at 100 mg. per day. The blood ascorbic acid levels, which were already low, continued to fall until the ascorbic acid supplements were increased to 300 mg. per day, which had been the maintenance dose during the previous hospital stay. Although with this amount of parenteral supplement the plasma ascorbic acid was kept relatively high, the buffy-coat value remained at borderline levels. Therefore, we must conclude that this patient was actually utilizing close to 300 mg. of ascorbic acid per day near the termination of his illness.

### IMMEDIATE EFFECT OF SURGERY

Studies of blood ascorbic acid levels immediately before and after operation were made on 105 patients. There was generally a fall, as reported by Lund<sup>3</sup> for the plasma in 1939. No correlation between degree of drop in blood ascorbic acid and duration or type of either surgery or anesthesia could be found. For the over-all group, the average plasma fall was 17 per cent, and the average buffy-coat fall 20 per cent. In general the greatest fall was seen in patients who had high or saturated blood

TABLE 6. Maintenance Studies in a Seriously Depleted Patient Undergoing Total Gastrectomy and Splenectomy.\*

CONDITION OF PATIENT	PERIOD OF ASSAY	PLASMA ASCORBIC ACID mg./100 ml.	BUFFY-COAT ASCORBIC ACID mg./100 gm.	REMARKS
No hypotension during operation—8 hr. in duration; 4 blood transfusions given.	Immediately before operation	0.12	3.1	Thoracoabdominal approach
	1st hr. of operation	0.15	3.7	Total gastrectomy with splenectomy & enteroenterostomy
	3rd hr. of operation	0.10	7.5	
	Immediately after operation	0.10	9.3	
	1st postoperative day	0.13	6.2	100 mg. of ascorbic acid intramuscularly/day
Phlebitis developed; temperature 102°F., & pulse 100; chlortetracycline intramuscularly begun.	3d postoperative day	0.26	7.5	Wangensteen suction
	5th postoperative day	0.27	9.0	Eosinophil count dropped to 6/cu. mm.
	7th postoperative day	0.30	9.3	Wangensteen suction discontinued
Draining sinus developed in wound; culture showed no growth; bilateral femoral-vein ligation.	10th postoperative day	0.25	7.9	Soft-solid diet free of vitamin C begun
	13th postoperative day	0.28	11.1	
	18th postoperative day	0.20	4.4	
	25th postoperative day	0.23	7.2	

\*P.K., 52-yr.-old man, who had had epigastric distress for 7 mo. & had been on diet containing no fruit or vegetables.

levels of the vitamin (Fig. 2). Among 22 patients with initial low blood ascorbic acid levels, the fall was much less pronounced (Fig. 3). In a few cases, some of considerable magnitude, there was a slight rise. Among these 105 patients subjected to operations, some lasting for five or six hours, the average fall in plasma ascorbic acid was only 0.072 mg. per 100 ml. (Table 8). This would represent an estimated total loss of approximately only 2.5 mg. of

ascorbic acid from the circulating plasma, provided no ascorbic acid entered the plasma from the tissues during this time. This drop is considered statistically significant. Among the 22 deficient patients in this group, the fall in plasma ascorbic acid averaged only 0.019 mg. per 100 ml. (Table 9), which according to

TABLE 7. Data in a Patient Suffering from Severe Enteritis Requiring 300 Mg. of Ascorbic Acid Per Day.\*

STAGE OF DISEASE, OPERATIONS, THERAPY & COMPLICATIONS	INTERVAL AFTER 1ST ILEOSTOMY	ASCORBIC ACID INTAKE	ASCORBIC ACID	
			PLASMA mg./100 ml.	BUFFY COAT mg./100 gm.
Fecal fistula, left flank; inanition.	-4	Ascorbic acid, amount unknown, given parenterally	0.65	12.0
Ileostomy & right-sided colectomy; bland diet without fruit or fruit juices; mashed potato twice daily; total intake of ascorbic acid by mouth estimated at no more than 10 mg. daily.	0 (pre-operative)	300 mg. daily	0.56	35.0
	0 (post-operative)		0.64	13.4
	7		0.97	clot
	42	1000 mg. intravenously	0.76	47.0
	49		0.88	19.5
	61		0.95	21.0
	70	300 mg. daily	0.89	28.6
	73			
	74		0.60	15.1
	87		0.49	19.1
Patient re-entered hospital with profuse ileal discharge & cramps & perineal fistulas	464			
	466	100 mg. daily	0.10	6.6
Conservative supportive therapy; intravenous infusion of fluids; transfusions every 2 days; cortisone, 50 mg. every 6 hr. for 6 days.	470	200 mg. daily	0.15	3.4
	473	300 mg. daily	0.06	0.0
	476		0.12	6.5
Resection of diseased small bowel, with new ileostomy; oxytetracycline given.	479		0.31	9.5
	483		0.39	8.3
Signs of peritonitis & pelvic abscess	497		0.64	7.8
Death on operating table	515			

\*H.C., 37-yr.-old man, admitted to hospital on 9/6/50, discharged on 12/23/50 & readmitted on 1/2/52, dying on 2/22/52.

statistical analysis is not significant. Among the entire group of 105 patients, the average fall in the buffy-coat ascorbic acid was 3.3 mg. per 100 gm., whereas in the 22 deficient patients the fall was 1.58 mg. per 100 gm. Although these falls represent an

estimated total loss of only 0.33 mg. and 0.15 mg. respectively from the entire circulating blood, they are considered significant statistically. For the entire group of plasma analyses, the 95 per cent confidence limit was  $\pm 0.07$  mg. per 100 ml. preoperatively and  $\pm 0.05$  mg. per 100 ml. postoperatively. For the entire group of buffy-coat analyses the 95 per cent confidence limit was  $\pm 2.05$  mg. per 100 gm. preoperatively and  $\pm 1.5$  mg. postoperatively.

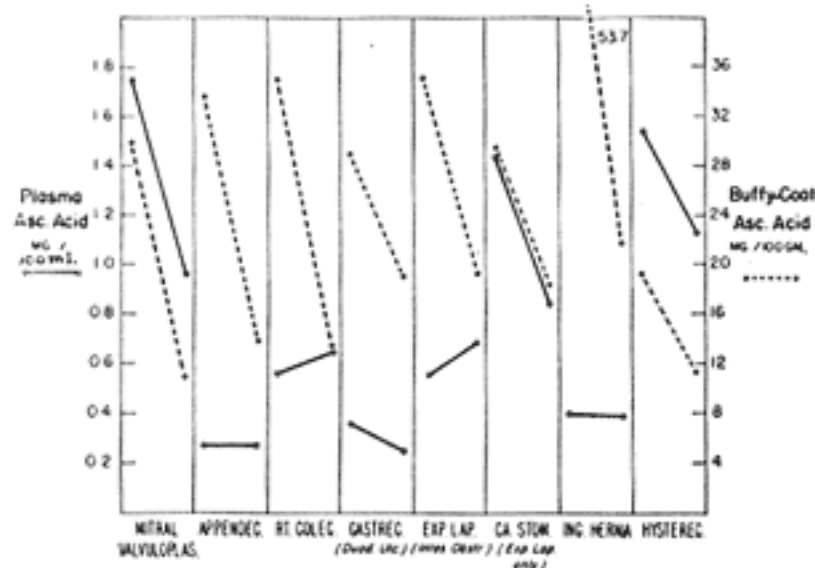


FIGURE 2. Changes in Plasma and Buffy-Coat Ascorbic Acid during Operations on 8 Saturated Patients.

Thirteen more patients had preoperative and postoperative blood ascorbic acid determinations with intravenous administration of ascorbic acid during surgery. Among 4 patients receiving 500 mg. of vitamin C intravenously during surgery the plasma ascorbic acid averaged 0.44 mg. per 100 ml. higher after operation, and the buffy-coat analyses 5.1 mg. per 100 gm. lower. In each of these patients the plasma ascorbic acid rose whereas buffy-coat ascorbic acid fell. An explanation of this phenomenon of

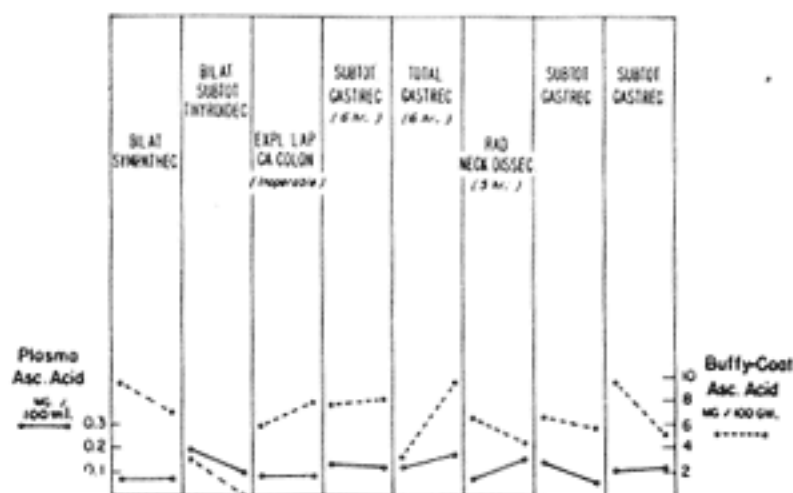


FIGURE 3. Changes in Plasma and Buffy-Coat Ascorbic Acid during Operations on 8 Deficient Patients.

paradoxical fall in buffy-coat ascorbic acid with plasma rise in these 4 patients could be that it resulted from a combination of two factors: inability of the buffy coat to absorb ascorbic acid rapidly and dilution of the preoperative buffy coat by new white

cells and platelets less rich in this vitamin. Among 9 patients receiving 1000 mg. of ascorbic acid intravenously during the operation, both plasma and buffy-coat ascorbic acid levels rose in each case, the over-all average rise for the plasma being 1.72 mg. per 100 ml., and that for the buffy coat 3.4 mg. per 100 gm.

after test doses of L-tyrosine was reported in human scorbutic patients by Rogers and Gardner<sup>5</sup> in 1949. On the other hand, Steele et al.<sup>6</sup> failed to find increased tyrosyl excretion after test doses of tyrosine among experimentally deficient volunteers whose plasma ascorbic acid had been reduced to 0.2 mg. per 100 ml. but no lower.

TABLE 8. *Effect of Operation on Plasma Ascorbic Acid.*

DATUM		PLASMA ASCORBIC ACID				
		PREOPERATIVE VALUE	POSTOPERATIVE VALUE	DIFFERENCE		
		mg./100 ml.	mg./100 ml.	mg./100 ml.		
All cases	n = 105					
Mean		0.428	0.356	-0.072	t = 4.93	p < 0.01 (significant)
Standard error of mean		0.0356	0.0280	0.0146		
95% confidence limits		0.36 to 0.50 ± 0.07	0.30 to 0.41 ± 0.055	-0.10 to -0.04		
"Low" group (plasma < 0.2, buffy coat < 8)	n = 22					
Mean		0.110	0.091	-0.019	t = 1.46	p > 0.05 (not significant)
Standard error of mean		0.0107	0.0116	0.0130		
95% confidence limits		0.09 to 0.13 ± 0.02	0.07 to 0.12 ± 0.025	-0.05 to +0.01		
"High" group (plasma > 0.2, buffy coat > 8)	n = 83					
Mean		0.512	0.426	-0.086	t = 4.80	p < 0.01 (significant)
Standard error of mean		0.0402	0.0310	0.0179		
95% confidence limits		0.43 to 0.59 ± 0.08	0.37 to 0.49 ± 0.06	-0.12 to -0.05		

#### CORRELATION OF BLOOD ASCORBIC ACID WITH OTHER LABORATORY FINDINGS

Throughout this study persistent efforts were made to correlate deficient blood ascorbic acid levels with other laboratory findings such as wound biopsy at the time of evisceration to substantiate the validity of our blood values; wound biopsy was invariably unsatisfactory, owing to the presence of obscuring inflammatory response. In 1 deficient patient with an indolent granulating wound of an amputated extremity the typical microscopical picture of scorbutus was seen (Fig. 4). This patient's blood levels at the time of biopsy were as follows: plasma, 0.12 mg. per 100 ml.; and buffy coat, 6.0 mg. per 100 gm. Tissue analyses were made in 70 patients at time of operation, and in all but 3 of 26 patients with low levels of fascia ascorbic acid, the plasma was below 0.2 mg. per 100 ml.; these 3 had been receiving ascorbic acid before testing. These findings were the subject of a previous report.<sup>4</sup>

More recently we have found what we believe to be a good correlation between deficient blood levels of ascorbic acid and increased excretion of urinary "tyrosyl" after a 30-gm. test dose of L-tyrosine (Table 10). A marked increase in tyrosyl excretion

The tyrosyl derivatives or intermediate breakdown products of tyrosine were measured by means of the reaction of Medes.<sup>7</sup> It is essential that no aspirin be given during testing since this results in falsely high values owing to the presence of phenol rings. After a 30-gm. test dose of L-tyrosine we have found in resting surgical patients, who are sufficient in ascorbic acid according to their blood ascorbic acid levels, an average three-day excretion of 1957 mg. of tyrosyl. This compares with an average three-day excretion of 3086 mg. in 7 normal controls, whose larger excretion may have been due to increased metabolism. Among 4 scorbutic patients tested on the medical wards during the study the three-day urinary excretion averaged 5726 mg. of tyrosyl. Among our borderline depleted surgical patients, as indicated by blood ascorbic acid levels, the average was 3744 mg. during a three-day period, whereas among our depleted surgical patients this average rose to 4940 mg. Administration of ascorbic acid resulted in reversal of the three-day tyrosyl excretion to an average of approximately 1900 mg. in the depleted patients so tested.

To 18 patients having sufficient ascorbic acid, according to their blood levels, a 30-gm. test dose of

L-tyrosine was given on the night before operation. Many of the surgical procedures to which the patients in this group were subjected were of considerable magnitude: aortic grafts, gastrectomies and other operations lasting up to eight hours. The average three-day tyrosyl excretion for this group was 2666 mg. (Line 7, Table 9). A study of the tyrosyl

requirement of ascorbic acid found among patients in this study was 300 mg. daily, it is conceivable that in the patient with generalized peritonitis or severe burns the requirement would be even higher.

Analysis of immediate preoperative and postoperative blood ascorbic acid levels in 105 patients undergoing surgical procedures, many of considerable mag-

TABLE 9. *Effect of Operation on Buffy-Coat Ascorbic Acid.*

DATUM		BUFFY-COAT ASCORBIC ACID				
		PREOPERATIVE VALUE	POSTOPERATIVE VALUE	DIFFERENCE		
		mg./100 gm.	mg./100 gm.	mg./100 gm.		
All cases	n = 105					
Mean		16.34	13.04	-3.30	t = 5.48	p < 0.01 (significant)
Standard error of mean		1.034	0.764	0.602		
95% confidence limits		14.29 to 18.39 ± 2.05	11.53 to 14.55 ± 1.50	-4.49 to -2.11		
"Low" group (plasma < 0.2, buffy coat < 8)	n = 22					
Mean		5.99	4.41	-1.58	t = 2.12	p < 0.01 (significant)
Standard error of mean		0.851	0.637	0.744		
95% confidence limits		4.22 to 7.76	3.09 to 5.73	-3.13 to +0.03		
"High" group (plasma > 0.2, buffy coat > 8)	n = 83					
Mean		19.08	15.32	-3.76	t = 5.16	p < 0.01 (significant)
Standard error of mean		1.108	0.778	0.729		
95% confidence limits		16.89 to 21.27	13.78 to 16.86	-5.20 to -2.32		

excretion in borderline depleted patients subjected to surgery is in progress.

### DISCUSSION

Investigation of the hospital records of the patients suffering wound dehiscence in this study indicates that, among those showing low blood ascorbic acid levels (19), the administration of supplementary ascorbic acid postoperatively had been overlooked in all but 3 patients, none of whom had received over 100 mg. of the vitamin per day in spite of the presence of severe inflammatory processes in wound or peritoneum. All patients in this low group had poor dietary histories, and before dehiscence the majority had peritonitis or wound infection or both, which are known to require increased utilization of the vitamin. Two such patients gave indication of utilizing 200 mg. of ascorbic acid or more daily after evisceration.

In maintenance studies on 26 patients it was found that in general the daily requirement of ascorbic acid varied with the degree of inflammatory response. In this phase of the study it was reaffirmed that when parenteral administration of ascorbic acid is being given daily, the plasma ascorbic acid may be misleadingly high and may not reflect the true deficiency of the tissues for ascorbic acid. Although the maximal

nitide, indicated an over-all 17 per cent drop in plasma and a 20 per cent drop in buffy-coat ascorbic acid. This fall was most marked in patients having high blood levels; in patients with low blood ascorbic acid the fall became so slight as to be insignificant statistically for plasma. In view of these facts the question arises whether a considerable factor in the observed fall in blood ascorbic acid during operation may not be the dilution of the circulating blood with new plasma, white cells and platelets less rich in ascorbic acid.

It will be noted that several patients extremely deficient in ascorbic acid underwent major surgical procedures without untoward incident. We do not mean to imply from these findings that major surgery in the deficient patient is not hazardous. Hypotension bordering on shock has been noted in clinical scorbutic patients on the occasion of their simply standing upright from the supine position in bed. Moreover, we have previously described 2 patients markedly deficient in ascorbic acid who did poorly during surgery and died twenty-four and seventy-two hours respectively after operation.<sup>3</sup> One showed focal necrosis of the myocardium similar to that seen in scorbutic guinea pigs at autopsy, and the other had massive oozing into his wound. On the other hand,

the ability of some patients seriously deficient in ascorbic acid to withstand operations of great magnitude, as indicated by this study, together with the relatively small drop in blood ascorbic acid of such patients during these operative procedures, raises serious doubt in our minds whether such operations

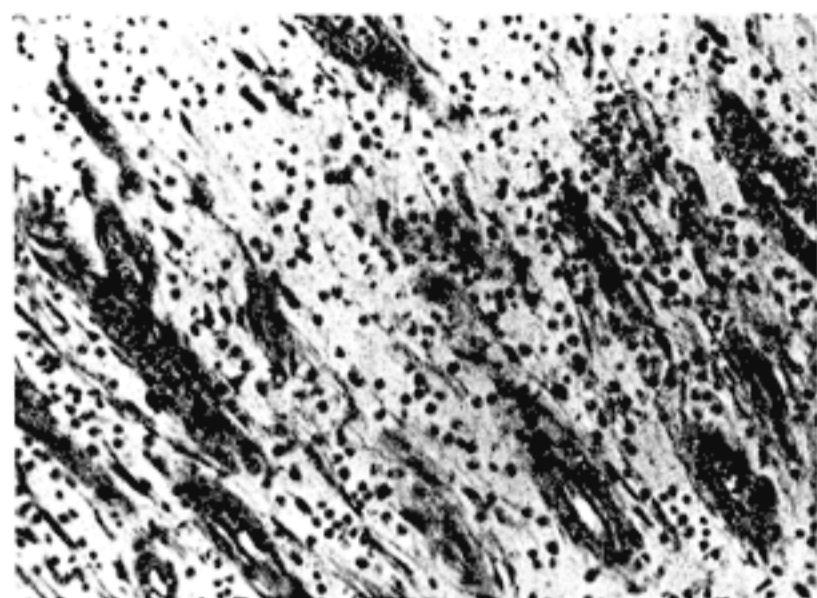


FIGURE 4. Photomicrograph, Showing the Typical Scorbutic Appearance.

per se always immediately produce an acute stress reaction or, if they do so, whether acute stress per se necessarily causes a markedly increased utilization of

ascorbic acid therapy, it has been noted that at least three days of therapy have been necessary to institute reversal of the increased tyrosyluria. Whereas the resting patient with sufficient ascorbic acid showed an average three-day tyrosyl excretion of 1957 mg., the operated patient sufficient in ascorbic acid showed an average three-day excretion of 2666 mg., a value roughly midway between that shown by the resting sufficient patient and that of the active ambulatory normal person. In each patient urinary output over the three-day postoperative period was considered adequate. In the patients subjected to test dosing and surgery there was thus an average increased tyrosyl excretion of 709 mg., apparently the result of the surgical procedure, over the average shown by the resting surgical patient sufficient in ascorbic acid. The clinical scorbutic patient, on the other hand, showed an average tyrosyl excretion of 3769 mg. more than that of the resting surgical patient sufficient in ascorbic acid after test dosing with 30 gm. of L-tyrosine.

#### SUMMARY AND CONCLUSIONS

Plasma ascorbic acid levels below 0.2 mg. per 100 ml., together with buffy-coat levels below 8 mg. per 100 gm., are indicative of serious ascorbic acid deficiency.

In a large general hospital 19 of 47 patients suffer-

TABLE 10. Correlation of Blood Ascorbic Acid with Increased Three-Day Tyrosyl Excretion after a 30-Gm. Test Dose of Tyrosine.

GROUP	n	AVERAGE BLOOD ASCORBIC ACID		MEAN TYROSYL	STANDARD ERROR OF MEAN	DIFFERENCE BETWEEN NORMAL & GROUP MEAN	STATISTICAL EVALUATION
		PLASMA mg./100 ml.	BUFFY COAT mg./100 gm.				
Ambulatory normal controls	7	0.83	30.0	3086	178		
Resting saturated patients	7	0.45	18.0	1957	134	-1129	Significant
Clinical scorbutic patients	4	0.07	4.0	5726	688	+2640	Significant
Borderline depleted patients	14	0.15	8.08	3744	192	+658	Questionable
Depleted patients	5	0.13	6.67	4940	336	+1854	Significant
Depleted patients after vitamin C	3	0.53	14.9	1709	273	-1377	Significant
Saturated patients after operation	18	0.40	19.4	2666	222	-420	Not significant
Borderline depleted patients after operation	5	0.15	10.8	4049	196	+963	Significant

ascorbic acid in human beings, as it apparently does in the rat.

The finding of "tyrosyluria" among patients deficient in ascorbic acid after a 30-gm. test dose of L-tyrosine is still under study. The deficient patients with the greatest inflammatory processes have to date shown the greatest increase in tyrosyl excretion after test dosing. Although a return to normal levels of excretion has been found in each case retested after

ing wound dehiscence were found to have serious ascorbic acid deficiency as indicated by their blood levels.

Surgical patients suffering severe inflammatory processes were observed to require 300 mg. of ascorbic acid daily.

Among 105 patients there was an average fall of 17 per cent in the plasma and 20 per cent fall in the buffy-coat ascorbic acid during operation. Among



patients with an initially low blood ascorbic acid, the fall in blood ascorbic acid was much less marked.

A significantly increased tyrosyluria after a test dose of 30 gm. of L-tyrosine is reported among surgical patients with deficient blood levels of ascorbic acid. This increased excretion is abolished by administration of ascorbic acid.

As judged by this simple tyrosyl excretion test, the patient sufficient in ascorbic acid who has been subjected to major surgery does not act biochemically like the scorbutic patient.

We are indebted to Drs. Mildred Jefferson and Richard Lennihan for their assistance, Ben H. Amdur, M.A., for his valuable technical advice, the entire staff of Boston City Hospital, particularly the First and Third Medical Services,

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## INTERNAL-MAMMARY-ARTERY LIGATION FOR CORONARY INSUFFICIENCY\*

### An Evaluation

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THIS report is a summary of observations made in an attempt to evaluate internal-mammary-artery ligation as a method of therapy for coronary insufficiency. Angina pectoris, myocardial ischemia and infarction, and major arrhythmias are regarded in this study as variable sequelae to inadequate coronary-artery inflow.

#### CASE REPORTS

CASE 1. M.B., an 80-year-old woman, had a 6 months' history of increasingly severe anginal pain radiating from the precordium to the left shoulder, accompanied by regurgitation of frothy mucus. Fluoroscopically, the heart was grossly enlarged, with pulsations barely visible, and there was variable cardiospasm of the distal esophagus. An electrocardiogram gave evidence of hypertrophy and strain of the left ventricle, with sagging of ST segments. Respirometry studies confirmed the absence of pulmonary disease. Tests during exercise had to be stopped because anginal pain appeared in the precordium and arms.

Bilateral internal-mammary-artery ligation was done on April 29, 1957. Anginal pain with exertion continued postoperatively. Esophageal regurgitation ceased and had not recurred in the 5 months since operation. The patient continued to have angina pectoris, on effort, but emphasized the fact that she was much improved by the operation. At review of all tests on September 6, there was no change from preoperative observations in the heart size, amplitude of pulsations or respirometry studies. There had been no further trouble from cardiospasm. Angina pectoris had persisted, and 4 or 5 nitroglycerin tablets were taken daily. Follow-up exercise tests were precluded by the onset of angina when the tests were attempted. An electrocardiogram showed less sagging of the T segments in Leads aVL and V<sub>4</sub> through V<sub>6</sub>.

This very intelligent woman rearranged multiple

minutiae of her sedentary and solitary life to avoid having pain in the left arm and precordium (above the line of the incision on the anterior thoracic wall but not below it). She commented, with piercing insight, that she was able to do this rearranging of her activities because she lived alone, was completely her own boss and was able to pay to have done what she could not do for herself. Simultaneously, she expressed thanks for the diminution in pain below the level of incision. One cannot understand anatomically why this might be so. She was grateful for the interest taken in her case, and for the symptomatic improvement sustained. The subjective improvement was believed to reflect a desire to succeed in her ambition to get better; there was an obvious relation between lessened activity and fewer symptoms. Psychologically and symptomatically, she was better. Objectively, no benefit from the internal-mammary-artery ligation could be recognized.

CASE 2. E.R., a 72-year-old woman, had severe angina pectoris, associated with arteriosclerosis and chronic mild congestive heart failure of at least 3 years' duration. Cholecystectomy, with removal of gallstones, in March, 1957, failed to cause improvement of anginal pain, although she recovered successfully from the surgical procedure.

By May, angina pectoris was so severe that she had to take nitroglycerin before she could walk from her bed across the room to use toilet facilities. Even as heart-failure signs again appeared in early May, at home, her anginal symptoms increased. The question arose whether ligation of the internal mammary arteries might bring about increased myocardial circulation and, if so, whether the angina might be benefited. There were standard clinical signs of myocardial failure and supportive electrocardiographic changes interpreted as showing myocardial ischemia, strain and ventricular hypertrophy. Angina was induced in the precordium and both arms if she sat up and down twice on an examination table. Changes in pulmonary ventilation before and after this brief exercise test were not of detectable

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