ASCORBIC ACID, RIBOFLAVIN, THIAMIN, AND NICOTINIC ACID IN RELATION TO SEVERE INJURY, HEMORRHAGE, AND INFECTION IN THE HUMAN*

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CAREFUL STUDIES of ascorbic acid and of vitamin K in relation to surgical conditions have been reported in numerous publications during the last few years. Few similar studies of other vitamins have been made. In the meantime, all known vitamins are being used in the care of surgical patients with increasing frequency and in increasing doses. Recent work in the laboratory has shown that many vitamins play much more fundamental rôles in the animal organism than merely preventing or curing the well-known syndromes of scurvy, beri-beri, pellagra, or hypoprothrombinemia. For instance, thiamin and nicotinic acid both play fundamental rôles in the enzyme systems that control the metabolism of carbohydrates. Riboflavin is also important for the carbohydrate metabolism and, in addition, has a function associated with amino-acid metabolism. Ascorbic acid is said to have a fundamental rôle in the formation of adrenocortical hormone. These functions indicate that these four vitamins play important rôles in connection with recovery from shock, injury, and acute infections, since disturbances in the metabolism of carbohydrate, protein, and of adrenocortical hormones are caused by these conditions. Thus, Govier[1] has found the mortality of normal dogs exposed to a standardized type of hemorrhagic shock was reduced when thiamin was given in large doses before or after bleeding. In addition, dogs deficient in thiamin were particularly susceptible to death from hemorrhagic shock. Sayers, *et al.*[2] have found that there is a sudden fall in the ascorbic acid content and a slower fall in cholesterol content of the adrenal glands in hemorrhage and in hemorrhagic shock in rats and guinea-pigs. Uzbekov,[3] and Clark and Rossiter,[4] earlier, had found decreases

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in the ascorbic acid content of the adrenal cortex in burned guinea-pigs and rabbits, respectively.

Andreae, and his associates,[5] have studied the excretion of riboflavin in 23 cases of burns and injuries. It is not stated whether shock was encountered in any instance. This short preliminary report is quoted in full because of its importance.

"The 24-hour urinary excretion of riboflavin was followed in 23 patients who had suffered fractures and burn injuries and whose daily intake level of this vitamin was kept constant at 5.0 mg. by supplementation with crystalline riboflavin. Whereas about one-half of the ingested riboflavin is retained at this intake level in health, patients with acute injuries characteristically showed a marked retention during the initial three to five days after injury. This state was followed by a period of similar duration when there occurred an increased riboflavin loss as shown by the excretion rate. After about ten days following the injury, the riboflavin balance returned to normal. This would suggest that the vitamin retained during the first period was not utilized or destroyed, but was stored in some way and subsequently released. Observations made on these patients during convalescence demonstrated a retention of nitrogen. This correlation was statistically analyzed and found to be highly significant so that for each gram of nitrogen retained 0.30 mg. of riboflavin was retained over the normal base line."

The present study is concerned with the alterations in the blood level of ascorbic acid, and in the urinary excretion of ascorbic acid, thiamin, riboflavin, and of n-methyl-nicotinamide, in patients with severe injury, hemorrhage, or infection.

METHODS

The patients studied were cared for by the members of the "Burn Assignment" in a Metabolic Ward which was supplied with special nurses. The dietary calculations were made by a research dietitian. All hematologic and routine chemical determinations were by methods previously published from the Thorndike Memorial Laboratory.[6] Plasma ascorbic acid determinations were by the method of Mindlin and Butler.[7] The determinations of vitamin outputs were made in the Harvard Fatigue Laboratory using the field methods[8] developed there. These tests were made on timed morning specimens collected at least 14 hours subsequent to any vitamin administration. Vitamin supplements were given orally in the form of ascorbic acid tablets, and of "Multicebrin" capsules. These contain in each capsule: thiamin chloride, mg. 3.0; riboflavin, mg. 3.0; pyridoxine hydrochloride, mg. 1.5; pantothenic acid, mg. 5.0; nicotinamide, mg. 25; ascorbic acid, mg. 75; distilled natural tocopherols, mg. 10; vitamin A, 5,000 U.S.P. units; and vitamin D, 1,000 U.S.P. units. Vitamins were given intravenously in the form of single or multiple vitamin preparations. Saturation tests of vitamins were made as follows: The test doses were given after the collection of a fasting specimen of blood and a fasting hour specimen of urine. Specimens of blood and of urine were then collected at intervals of

one-half, one, two, three, and four hours. Two different test doses were used. One, named a "high test" contained not less than: ascorbic acid, one gram, thiamin chloride, 20 mg., riboflavin, 12 mg., and nicotinamide, 450 mg. The other, the "low test" contained ascorbic acid, 250 mg.; thiamin chloride, 5 mg.; riboflavin, 3 mg.; and nicotinamide, 50 mg. These "low" saturation tests have been used previously in studies of soldiers in all parts of the world.[8] Both "high" and "low" saturation tests have been studied on healthy laboratory personnel at the Boston City Hospital and the findings of these studies will be published shortly.[9]

Table I lists the patients with their diagnosis and the outcome of their treatment.

TABLE I

PATIENTS' DIAGNOSES AND OUTCOME OF TREATMENT

Case No.	Patient	Age	Sex	Shock	Diagnosis
1.	P. D.	24	M	0	Bullet wounds of jaw, neck, and abdomen with fractured jaw, perforated trachea, and perforated hepatic flexure. Operation—Death—Autopsy
2.	W. B.	33	M	+	Bilateral crush injuries both lower legs. Operation—Recovery
3.	P. J.	15	M	0	Bullet wounds of abdomen and chest, with lacerations of liver, perforated duodenum, ruptured right kidney, and hemopneumothorax. Operation—Death—Autopsy
4.	S. A.	58	M	+	Traumatic rupture right kidney, head injury, compound fracture both bones right lower leg. Operation—Recovery
5.	K. R.	56	M	+	Massive hematemesis, ? etiology. Operation—Recovery
6.	J. B.	46	M	+	Perforated gastric ulcer, peritonitis. No operation—Death—Autopsy

CASE REPORTS

CASE 1.—P. D., a 24-year-old white male, with a noncontributory past history, was admitted shortly after receiving bullet wounds of the jaw and abdomen. Examination on entry revealed a well-developed and well-nourished man. Blood pressure 115/80; pulse 132 of good quality; respirations 18. There was a small bullet hole on the right side of the lower jaw through which there was a fair amount of blood oozing. In addition, the patient was coughing up moderate quantities of blood. The lung fields were clear and resonant. Just above the right posterior iliac crest, about two inches from the midline, was another small bullet hole. Anteriorly, there was a small hematoma just to the left of the midline below the costal margin. The abdominal wall was rigid, and peristalsis was absent.

Fourteen hundred cubic centimeters of blood, 1,650 cc. of saline, and 1,000 cc. of 5 per cent glucose in water were administered intravenously in the first four hours after entry. The blood pressure and pulse remained good. At the end of this time, operation was performed.

Abdominal exploration revealed that the hepatic flexure had been perforated posteriorly and anteriorly. Resection of the damaged bowel was carried out and a primary end-to-end anastomosis made. The bullet was removed from the anterior abdominal wall. Exploration of the neck revealed that the second bullet had lodged in the right posterior lateral aspect of the larynx. It was removed and the resulting tracheal fistula packed with gauze. During the operative procedure, the patient was given 500 cc. of blood and 500 cc. of saline, and the blood pressure and pulse remained good. The urine output was satisfactory. Postoperatively, slight oozing of blood through the mouth continued and constant pharyngeal suction was carried out. The temperature varied from 100° to 102° F. rectally; the blood pressure and pulse re-

mained good, but there was sudden respiratory distress and asphyxia five hours postoperatively. Postmortem examination revealed the cause of death to have been aspiration of blood.

No vitamins were given at any time. The plasma ascorbic acid concentration at one and at three hours after entry was zero. At seven hours after entry it was 0.3 mg./100 cc. of plasma. Hourly excretion rates of the vitamins at 2.5 and 4.5 hours after entry were as follows: thiamin 0.3 and 10 micrograms per hour; riboflavin, 26 and 17 micrograms per hour; and the n-methyl-nicotinamide, 0.35 and 0.68 milligrams per hour.

COMMENT: A previously well-developed and well-nourished healthy male with major injuries but with no shock and with a good urine output. The plasma ascorbic acid was zero on two occasions prior to operation, but rose slightly during recovery from operation. The first determination of thiamin output was low but the second determination of thiamin and both determinations of riboflavin and of the n-methyl-nicotinamide were normal.

CASE 2.—W. B., a 33-year-old white male, with a noncontributory past history was admitted at 6 P.M., shortly after receiving crush injuries to both legs when he fell under a street car when intoxicated. Examination revealed a well-developed and well-nourished man, semiconscious. His skin was pale and cold, his blood pressure 70/50, pulse of fair quality. Both lower legs were crushed just below the knees and, in addition, there was a simple intracapsular fracture of the neck of the left femur. Leather belts had been applied as tourniquets at the scene of the accident. These were replaced by rubber tourniquets. He was given mg. 30 of morphine and an intravenous of saline, plasma, and of whole blood started. The blood pressure rose to 90/50 in 30 minutes and to 110/50 in the next one and one-half hours. His pulse was 100 at this time and of good quality. The urine output was good.

During the first six hours he was given a total of 1,000 cc. of plasma, 2,000 cc. of blood, and 2,000 cc. of saline. At this time, under cyclopropane anesthesia, bilateral, low thigh, guillotine amputations were done. The wounds were left open and dry pressure dressings applied. A Kirschner wire was inserted through the lower end of the left femur to serve as a means of applying traction to the fractured left femoral neck. During the operation he was given 1,000 cc. of additional blood. His blood pressure remained good until just after the operation, when it fell for a brief period to 70/50, at the time of a mild hemolytic transfusion reaction. Thereafter there were no further periods of shock. Penicillin, 20,000 units every two hours intramuscularly, was started on entry and continued for 15 days. The temperature which during the first few days rose as high as 102° F. rectally, became normal by the seventh day and remained normal thereafter. The wounds were secondarily revised and closed on the 17th and 28th days. During the first five days he was fed almost entirely intravenously with Amigen* and glucose in quantities sufficient to give him 20 Gm. of nitrogen and 3,000–4,000 calories daily. Subsequently he took food well by mouth. This diet contained approximately the same amounts of nitrogen and calories as given previously. The nitrogen output varied between 17 and 42 grams daily. The nitrogen balance and vitamin data are given in Charts 1 and 2.

COMMENT: The ascorbic acid concentration on three occasions during the first 12 hours was zero. At 16 hours, without any ascorbic acid having been given, the plasma level had risen to 0.3 mg. per 100 cc. At that time a "high" saturation test was performed. (See Chart 2.) The plasma response to this was lower than is seen in normal individuals. The excretion

* The Amigen was kindly supplied by the Mead-Johnson Corporation.

was also low, being less than 50 mg. The next day this test was repeated. The plasma curve was almost identical, but nearly 300 mg. was excreted. This is still below the usual excretion of a fully saturated individual. The

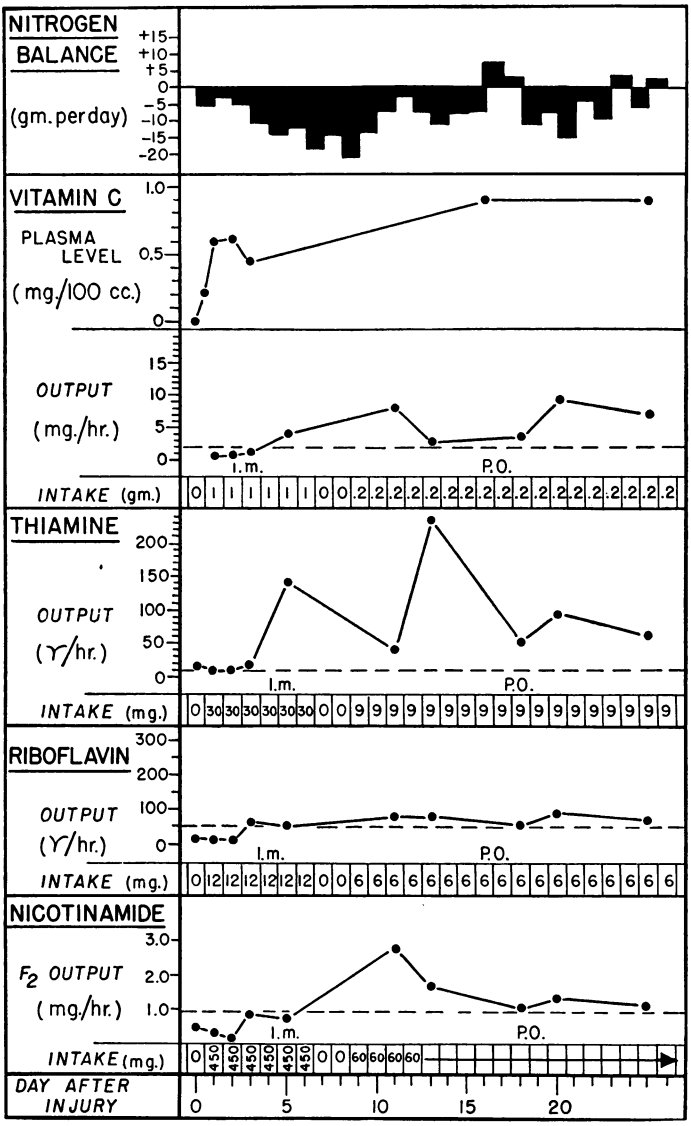

CHART I

The dotted lines indicate the *average* output of normal men on normal diets who are taking no supplementary vitamins.

fasting hour excretions of the three "B" vitamins and ascorbic acid were at low levels immediately after injury and, what is important, remained at these low levels for five days despite large doses given daily, as shown by Chart 1.

CASE 3.—P. J., a 15-year-old healthy high school boy, was admitted shortly after receiving a bullet wound of the abdomen. Examination revealed him to be well-developed and well-nourished. He was somewhat drowsy but fully conscious and rational. Blood pressure 90/40. His chest was clear and resonant throughout, and his abdomen was spastic, with absent peristalsis. Just above the umbilicus in the midline was the entrance wound of a bullet and posteriorly over the region of the right kidney was the exit wound. Both wounds were bleeding slowly.

He was given mg. 10 of morphine, and intravenous glucose in saline was started. After 400 cc. had been given in a period of a half hour, the blood pressure rose to 140/78. His pulse at this time was 108 and his respirations 20. In the next 1.5 hours he was given 500 cc. of blood, following which, under spinal anesthesia supplemented by cyclopropane, operation was carried out. It was found that the left lobe of the

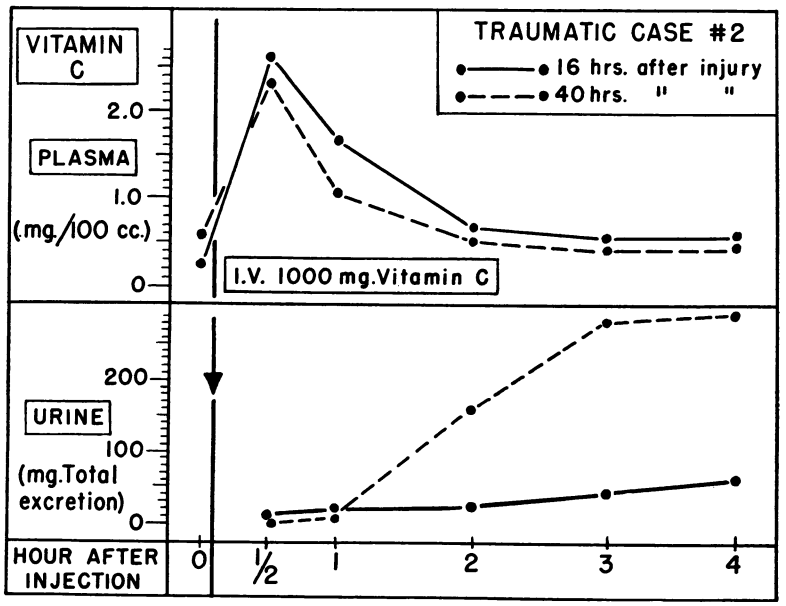

CHART II

Saturation test—Ascorbic Acid Intravenously

liver, the duodenum, the right lobe of the liver, the right kidney, and the right pleural cavity had all been perforated by the bullet. Crushed liver tissue was removed, the two perforations in the duodenum repaired, and the kidney removed. Drains were inserted down to the kidney bed and to the liver wound. The wound of entrance was excised and packed open with gauze. The wound of exit was also excised and was found to connect with the right pleural cavity. There was about one pint of blood in the pleural cavity and during exploration of the wound air was sucked in during inspiration. A gauze pack was inserted to control the aspiration of air. During the operation, the patient was given additional blood and saline. The blood pressure and pulse remained good, and thereafter there was no fall in blood pressure.

Postoperatively, he was given 25,000 units of penicillin every two hours for the first ten days. Five grams of sulfadiazine were given by clysis daily for the first three days and orally thereafter. Gastric drainage was instituted immediately after operation, and he was given 150 grams of protein hydrolysate and sufficient glucose intravenously to bring his caloric intake to 3,000 calories. Vitamins were started on the first postoperative day, as described below.

His postoperative course was satisfactory for the first week. He then began to run an afternoon fever of 102° F., but had no specific localizing signs. His urine output was three liters, or more, per day. On the 10th postoperative day, under cyclopropane anesthesia, the pack from the epigastric wound was removed, as was the drain from the liver and one of the drains to the kidney region. Culture of the wounds revealed *B. pyocyaneous.* The pack was taken out of the wound of exit, which was found to still connect with the pleural cavity. Consequently, a gauze pack was reinserted and the patient left the operating room in good condition. About ten hours after the dressing change the patient appeared considerably sicker and was markedly dyspneic. Examination revealed signs consistent with a pneumothorax in the right chest. The abdomen was soft and not tender. Roentgenograms confirmed the diagnosis of pneumothorax. Five hundred cubic centimeters of air were removed from

TABLE II

CASE 3: P. J.—BULLET WOUNDS OF LIVER, DUODENUM, AND KIDNEY

Days	0	1	2	3	4	5	6	7	8	9	10	11	12	13
Temperature		103°	102°	102°	101°	104°	101°	102°	101°	105°	102°	105°	105°	1 5°
Caloric intake	550	2950	2900	3050	3000	3000	3000	3000	3000	3000	3000	2500	1100	2250
Nitrogen intake (grams)	7	23	26	24	24	24	24	24	24	24	24	19	0	3
Nitrogen output (grams)		15	25	25	27	22	24	19	25	22	39	16	37	9
Plasma protein (grams/100 cc.)	5.7	4.7		5.6								6.8		
Plasma ascorbic acid (mg./100 cc.)	0.6	0.6		0.6		0.5			0.8		1.1			
Urine ascorbic acid (mg. per hour)		6		4		17		24			13			
Urine thiamin (micrograms per hour)		28		35		225		510			200			
Urine riboflavin (micrograms per hour)		105		17		57		64			68			
Urine n-methyl-nicotinamide (micrograms per hour)		0.3		0.6		3.2		2.6			1.4			

Vitamins were administered intravenously in the following daily doses from the 1st to the 13th day: Ascorbic acid, G 1.0; thiamin mg. 30; riboflavin, mg. 12; and nicotinamide, mg. 450.

the right chest, without significant effect on the dyspnea. His temperature had risen to 105°F. rectally. Penicillin which had been discontinued following the dressing, was resumed, and, in addition, sulfamerizine was begun, the sulfadiazine also having been omitted at the dressing change. Roentgenograms the following morning revealed the pneumothorax to be less and the lung fields to be clear except for some atelectasis of the right lower lobe. There was neither cyanosis nor dyspnea. The temperature continued high despite repeated alcohol sponges. Two lumbar punctures were negative. He gradually became weaker and died on the 14th day. Autopsy revealed no definite cause of death. The nutritional and vitamin data are given in Tables II and III.

COMMENT: This boy had a severe injury but was in excellent muscular training and nutritional condition. He did not go into shock at any time. Early, his ascorbic acid concentration in the plasma remained relatively high, being 0.6 mg. per 100 cc. of plasma on two occasions prior to any vitamin supplementation. He was given one gram of ascorbic acid; thiamin

30 mg.; riboflavin 12 mg.; and nicotinamide 450 mg. daily beginning on the first hospital day. On the first, third, seventh, and eighth days the vitamins were given in rapid injections for "high" saturation tests. On all other days they were given in a slow intravenous drip. The plasma ascorbic acid concentration remained between 0.5 and 1.1. The plasma levels of ascorbic acid in the first two tests were low but in the fourth test were normal. The four-hour urine excretions of ascorbic acid, thiamin, and riboflavin during the saturation tests were low on the third day, normal on the seventh day. The excretion of n-methyl-nicotinamide was normal on both occasions.

The "fasting hourly" excretions of ascorbic acid, thiamin, and n-methyl-nicotinamide were much lower on the first and third postoperative days than on the fifth and subsequent days. In the case of riboflavin, the first day excretion was higher than that on subsequent days.

TABLE III

CASE 3: P. J.—"HIGH" SATURATION TESTS

Days	Plasma Ascorbic Acid Milligrams Per 100 Cc. Hours					Urine—Output in Four Hours			
	Fasting	0.5	1	2	4	Ascorbic Acid (Milligrams)	Thiamin (Milligrams)	Riboflavin (Milligrams)	N-methyl-nicotinamide (Milligrams)
1.	0.6	1.9	1.7	1.5	1.0				
3.	0.6	1.4	1.3	1.3	0.6	108	4.0	0.6	23
7.						484	17	10	56
8.	0.8	3.1	2.9	2.7					

Saturation test doses: Ascorbic acid, G. 1.0; thiamin, mg. 30; riboflavin, mg. 12; and nicotinamide, mg. 450.

CASE 4.—S. A., a 58-year-old laborer, previously well, except for chronic bronchitis, was seen three hours after having been struck by an automobile. Examination on admission revealed a well-developed, well-nourished man with a compound fracture of both bones of the right lower leg and a laceration over the right eye. There were no external bruises elsewhere, and examination was otherwise negative. Blood pressure 80/50, pulse 90. During the next five hours he was given 900 cc. of plasma, 1,500 cc. of whole blood, 900 cc. of saline, and 50 grams of glucose. His blood pressure varied between 70/50 and 110/60, with his pulse remaining about 90. His abdomen, which had previously been soft, gradually became generally spastic and tender. Catheterization revealed grossly bloody urine. A spinal puncture revealed bloody fluid but a normal pressure of 160 mm.

Under spinal anesthesia, supplemented with cyclopropane, gas and ether, celiotomy was performed. There was about 200 cc. of blood in the peritoneal cavity but no injury to any interperitoneal organs. The blood had dissected up from the right retroperitoneal area where there was a large hematoma. The celiotomy wound was closed and a laparotomy exposed the right kidney, which was found to be ruptured completely across the pelvis. It was removed. The wound was packed and partially closed. During the operation the patient was given 1,000 cc. of whole blood; 1,200 cc. of saline and bicarbonate by clysis; and 50 grams of glucose intravenously. His

blood pressure, which was between 70/40 and 90/60 during the operation, rose immediately after the kidney was removed to 120/84. Thereafter there were no periods of shock.

The wound of the right lower leg was then irrigated and débrided. Kirschner wires were passed above and below the fracture line of the tibia and a plaster encasement was applied. The wound was not closed, even in part.

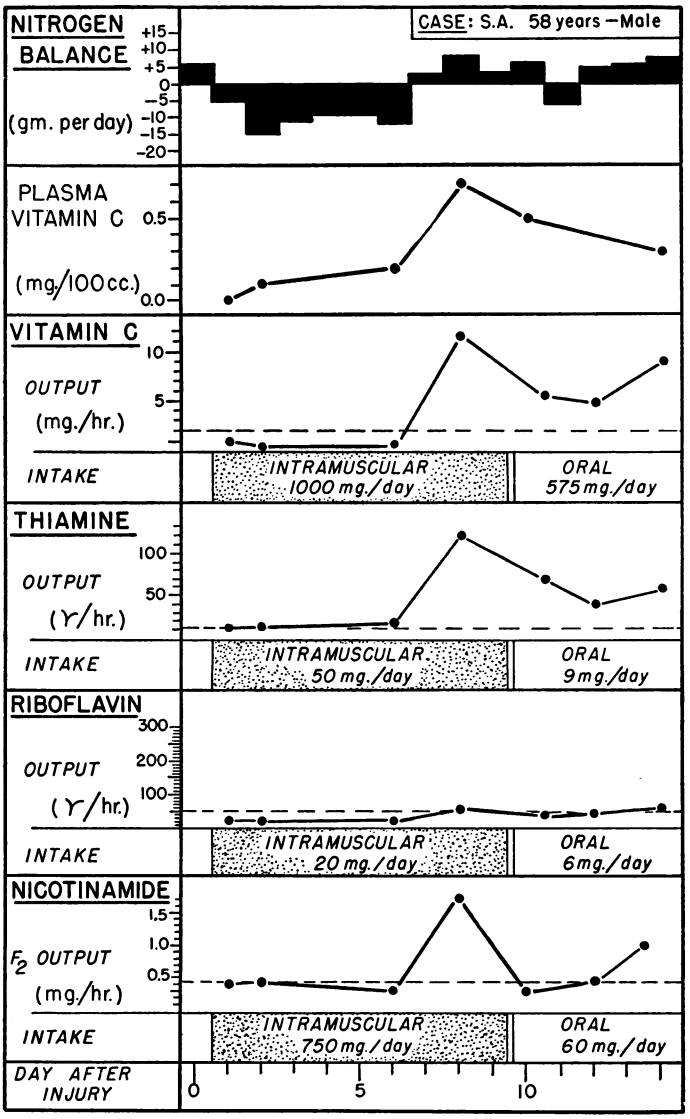

CHART III

Two hours postoperatively, 12 hours after injury, his temperature had risen to 106°F. rectally. Vigorous cold alcohol sponges were administered, and the temperature fell to 102.6° F. in the next one and one-half hours. At this time, a neurologic examination was negative. A second lumbar puncture revealed that the pressure had risen

to 300 mm. Repeated therapeutic lumbar punctures were performed during the next few days. After the sixth day the spinal fluid pressure and spinal fluid were normal.

Eighteen hours postoperatively, he became moderately dyspneic and cyanotic. A chest roentgenogram revealed diffuse mottling of the upper left lobe. Penicillin, 20,000 units, was given intravenously every two hours, and oxygen was administered by a tent. Within 36 hours he had improved, the dyspnea had disappeared, and only slight cyanosis remained. A chest film ten days later revealed the lung fields to be clear.

The clinical course after the second day was uncomplicated except for minimal infection of the kidney wound. The temperature ranged between 101° and 102°F. rectally until the 12th day, and after the 14th day was normal. Penicillin was discontinued on the 15th day. He was allowed to get out of bed daily after the seventh day, and felt very well. The hemoglobin which had been 90 per cent on entry fell gradually to 67 per cent by the eighth day. Two thousand cubic centimeters of whole blood was given in the next six days, the hemoglobin rising to 95 per cent.

During the first week he was given nourishment for the most part by the intravenous route. This consisted of plasma and glucose on the first day with Amigen and glucose for the next six days. The caloric intake ranged between 1,500 and 1,700 calories, with an average of 1,550. The nitrogen intake ranged from 14 to 17 grams, with an average of 15. The nitrogen output in the urine was 10 grams the first day, 30 grams the second and gradually decreased to 21 grams on the sixth, followed on the seventh day with an output of only 15 grams. There were no stools during this period. In the second week, oral feeding only was used, with an intake of from 2,700–4,100 calories, with an average of 3,100. The nitrogen intake ranged from 13 to 25 grams, with an average of 18. The nitrogen output ranged from 12 to 18 grams, with an average of 15.

The serum nonprotein nitrogen which was 50 mg. per 100 cc. on entry, rose to 70 the first day, came down to 60 on the second, and to 30 on the seventh day. The plasma albumin was 3.2 grams per 100 cc. on the first day, 1.35 on the seventh day, and 3.1 on the 16th day. The total plasma protein levels on the same days were 5.3, 5.3, and 6.7. The metabolic and vitamin data are presented on Chart 3.

COMMENT: This relatively old, but muscular laborer had extremely severe injuries, with a long period of shock. The blood level of ascorbic acid and the urinary excretion of all four of his vitamins remained extremely low in comparison to his enormous intakes until the eighth day when they all increased to excretion levels which were normal for his intake.

CASE 5.—K. R., a 56-year-old white male, was admitted because of repeated hematemeses for 24 hours. The day before entry, while at work, he suddenly vomited a cupful of bright red blood. Shortly thereafter he felt some vague abdominal pain, dull in character. The pain began in the midlower abdomen and extended up to the xiphoid; it did not radiate. During the next 24 hours the patient had at least ten episodes of vomiting blood. After the first few he began to feel dizzy, weak, and somewhat sweaty. The abdominal pain disappeared gradually about 18 hours after onset.

Until one year ago the patient was in good health but during the past year he had noticed a gradual weight loss, possibly as much as 25 pounds, and loss of appetite. There has been no nausea, vomiting, abdominal pain, constipation, diarrhea, jaundice, light stools, or dark urine, or melena. He had had varicose veins for many years with occasional edema of the feet.

Physical examination revealed a well-developed man with some evidence of recent weight loss. He was apathetic and sweating. His temperature was 97°F. rectally; pulse 120, and blood pressure 78/65. The pulse was weak and thready and his extremities were cold. Abdominal examination revealed generalized spasm but no

tenderness. The upper border of liver dullness was in the sixth interspace on the right. The lower edge of the liver could not be felt, but by percussion, dullness was present four fingers below the costal margin. Peristalsis was absent. There were no distended veins or venules on the abdomen. No masses could be felt. Rectal examination was negative except for the presence of dark red and black colored fecal material. His skin was clear. There were no telangiectases or jaundice. There were no obvious bleeding points in the mouth or throat. The chest was emphysematous, resonant, with some coarse bronchial râles. The heart was not enlarged, and its sounds were of poor quality. Its rhythm was regular, and there were no murmurs. The extremities were negative except for marked varicosities bilaterally.

Laboratory data on entry revealed a red count of 2.7, hemoglobin of 62 per cent, icterus index 3, white count 12,000, and prothrombin 100 per cent of normal. His N.P.N. was 71 mg. per 100 cc., and his serum protein 4.5 grams per 100 cc. of serum. The stools showed a strongly positive guaiac test and the urine was negative except for moderate traces of albumin.

Clinical Course: During the first three hours, the patient was given two liters of blood and 1,800 cc. of intravenous saline. The blood pressure rose to 120/70, the pulse dropped to 84, and the temperature rose to 100.6°F. At this time, under spinal anesthesia supplemented by cyclopropane, a subtotal gastrectomy was done. No definite bleeding point was found. During this procedure the patient received an additional 300 cc. of blood. The pulse remained of good quality, about 80, and the blood pressure rose to 150/80. Postoperatively, the patient was put on gastric suction. The following day he was given intravenous protein hydrolysate and glucose which was continued daily for the next ten days. He was started on water and milk by mouth on the fifth day and a soft diet on the sixth day. The details of his caloric and nitrogen intake, and nitrogen output for the first two weeks are given in Table 4. He was in negative nitrogen balance during the first week, and then in slight positive nitrogen balance on the second week. Nitrogen balance studies were discontinued at this time. The patient lost 12 pounds of weight. The plasma protein concentration was above six.

On the 16th day he developed calf tenderness and a positive Homan's sign bilaterally. Therefore, a bilateral femoral ligation was performed. His temperature rose during the next four or five days to 102° and 103°F. Repeated blood cultures were negative except for one which was reported showing an *alpha* streptococcus. His temperature subsided slowly, but continued to rise to 100°F. each afternoon for about a week. His course thereafter was normal and he was discharged ten days later. The laboratory data are detailed in Tables IV and V and Chart 4.

COMMENT: During the first two weeks he received vitamin supplements only on the first, sixth, and 13th days as test doses for "low" saturation tests. During this time the fasting concentration of ascorbic acid varied between zero and 0.7 mg./100 cc. plasma. The values after "low" saturation tests on the first, sixth, and 13th days were very low, as indicated in Chart 4. The four-hour urine excretion of ascorbic acid during these saturation tests were also very low, particularly on the 13th day when only 13 mg. were excreted. The fasting hourly excretion of ascorbic acid was also low at the end of the second week. During this first two-week period, and in fact, the entire period study, the fasting hourly excretions and the response to tests for thiamin, riboflavin, and n-methyl-nicotinamide were within normal range.

During the third week a supplement of 225 mg. of ascorbic acid, 9 mg.

TABLE IV

CASE 5: K. R. HEMATEMESIS WITH SHOCK.

Days	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28
Weight							143									137	133											131	
Temperature	97	104	103	103	100	100	100	100	103	101	100	101	101	101	100	100	102	103	103	103	102	101	101	100	100	101	100	100	99
Caloric intake	700	2600	1950	1900	3100	2900	2800	740	2350	2900	2100	1600																	
Nitrogen intake (grams)	11	14	12	12	18	22	10	7	22	26	16	17																	
Nitrogen output (grams)	11	9	18	18	24	23	16	16	23	23	15	16																	
Ascorbic acid intake (grams)	0	250	0	0	0	0	250	0	0	0	0	0	0	250	225	225	225	225	225	225	475	225	500	500	500	500	500	500	5,00
Plasma protein (grams per 100 cc.)					6.8							6.0																7.1	
Plasma ascorbic acid; (milligrams per 100 cc.)	0.3	0.0				0.5	0.0						0.8	0.0						0.2	0.0								0.8
Ascorbic acid output; (milligrams per hour)		1.2		2.1			1.3	2.5			0.8			0.7	0.4			1.2		1.3	3.1	2.1			2.1				4.3
Thiamin intake (milligrams per hour)		5					5							5	9	9	9	9	9	9	14	9	9	9	9	9	9	9	9
Thiamin output (micrograms per hour)	12		7				5	8			4			8	3			140		43	50	49			90				39
Riboflavin intake (milligrams per hour)		3					3							3	9	9	9	9	9	9	12	9	9	9	9	9	9	9	9
Riboflavin output (micrograms per hour)		40		70			65	1.8			1.0			54	52			184		150	300	85			250				75
Nicotinic acid intake; milligrams per hour)		50					50							50	75	75	75	75	75	75	125	75	75	75	75	75	75	75	75
N-methyl-nicotinamide output; (milligrams per hour)		0.6		0.5			0.5	0.3			0.2			0.4	0.2			0.5		0.4	1.0	0.5			1.3				0.5

each of thiamin and riboflavin, and 75 mg. of nicotinamide was given daily by mouth. The plasma ascorbic acid concentration both fasting, and after a "low" test on the 20th day, remained low as did the four-hour urinary excretion after injection of the test done.

CASE 6.—J. B., a 46-year-old white male, with a noncontributory past history, was admitted because of abdominal pain of 24 hours duration. He had been in good health until the day prior to entry, at which time he had sudden severe upper abdominal pain. Soon thereafter the pain reached to both shoulders, and he began vomiting, and vomited repeatedly until entry. There was no hematemesis or melena.

Examination revealed a fairly well-developed and well-nourished man who was dehydrated, apathetic, and in shock. His temperature was 97° F., and his pulse and blood pressure were unobtainable. The abdomen was spastic throughout, peristalsis was absent, and there was marked abdominal distention. The lung fields were clear.

TABLE V

CASE 5: K. R.—"LOW" SATURATION TESTS

	Excretion in Four Hours			
Day	Ascorbic Acid (Milligrams)	Thiamin (Milligrams)	Riboflavin (Milligrams)	N-methyl-nicotinamide (Milligrams)
1	24	0.8	0.9	7
6	21	1.2	0.4	9
13	13	1.3	0.9	11
20	50	1.7	1.1	8

The doses given were: Ascorbic acid, mg. 250; thiamin, mg. 5; riboflavin, mg. 3, and nicotinamide, mg. 50.

On entry, 1,500 cc. of saline were given intravenously within 40 minutes. The blood pressure rose to 100/65 and the pulse became of fairly good quality. An additional 3,000 cc. of saline were given in the next three and one-half hours; the blood pressure remaining between 92/60 and 108/90, and the pulse between 92 and 104. The temperature rose to 100.4°F. Whole blood was then started intravenously, 1,500 cc. being given in the next four hours. Thereafter he received a slow intravenous injection of 4 per cent Amigen and 15 per cent glucose.

Roentgenograms of the abdomen and chest revealed a large amount of free air under the right diaphragm, with some elevation of the right diaphragm and some clouding at the left lung base. Gastric drainage was started on entry. The abdominal distention increased gradually and led to marked impairment of the respiratory movements. An abdominal tap ten hours after entry yielded large amounts of gas and two liters plus of purulent yellowish-green fluid containing many gram-negative mobile rods. The respirations were much easier after the abdominal tap. The patient was placed in an oxygen tent and given penicillin, 20,000 units intravenously every two hours. The patient gradually became weaker, finally comatose, and died 36 hours after entry. The urine output had been low and during the last 24 hours he had intermittent periods of shock. The temperature rose to 103°F. An autopsy revealed an enormous opening in the stomach from a perforated ulcer.

Four hours after entry a saturation test was attempted. He was given ascorbic acid G 1.0, thiamin mg. 30, riboflavin mg. 12, and nicotinamide mg. 450. Unfortunately,

the urine output was negligible so that determination of vitamin outputs could not be made. The ascorbic acid plasma curve is shown in Chart 5.

COMMENT: A previously well, healthy male, with a neglected large perforation of a gastric ulcer, who entered the hospital in extreme shock. Although his blood pressure improved at times during treatment, he never reached a condition that seemed to warrant surgical intervention. His plasma ascorbic acid saturation curve showed a very low response to the test.

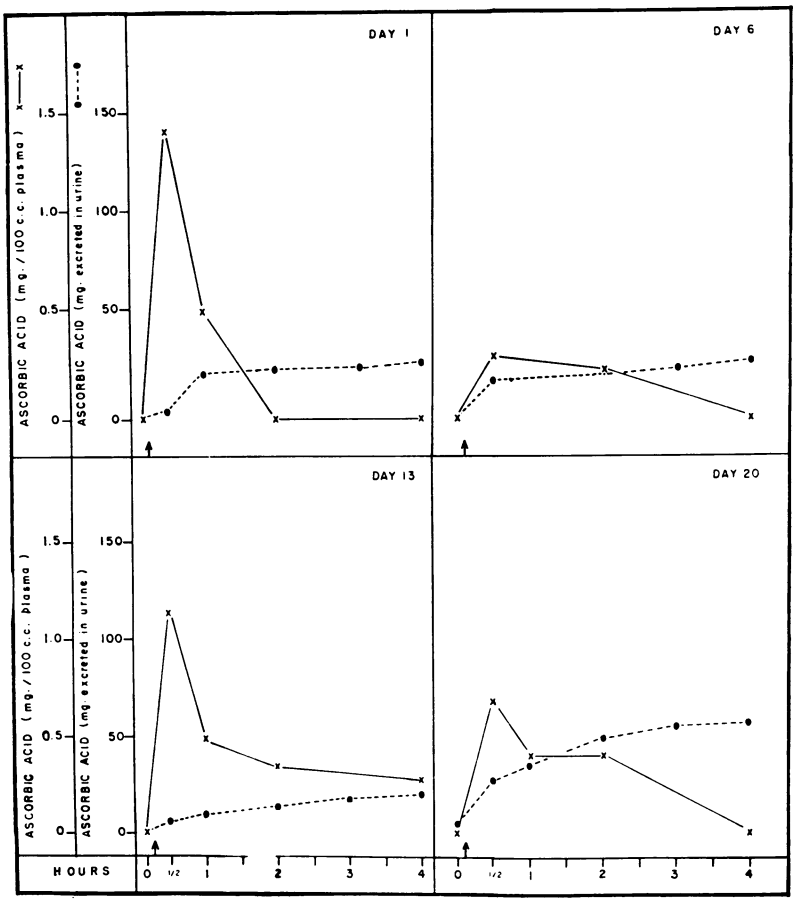

CHART IV

DISCUSSION.—The data presented demonstrate that six patients with severe injuries, hemorrhage, or infection had marked abnormalities in the metabolism of ascorbic acid, thiamin, riboflavin, and nicotinamide. These were evidenced by one or more of the following items: Low concentration of ascorbic acid in the plasma, fasting or after saturation tests, and low excretions of all four vitamins under the same two conditions. The abnormality is most marked when the patient is most sick; that is, when the metabolic

disturbances of the carbohydrates, proteins, and adrenocortical hormone are also most marked.

Theoretically, some or all of the findings might be accounted for by the following possibilities:

1. *Deficiencies before Injury.*—All of these patients had no recognizable signs or symptoms of deficiencies of these vitamins at the time of entry to the hospital. Several may have had less than fully saturated conditions of one or more of them. But the experiment of Crandon, Lund and Dill[10] showed that the plasma level fasting, and following therapy, and the excretion following therapy, rose much more rapidly after actual scurvy had been

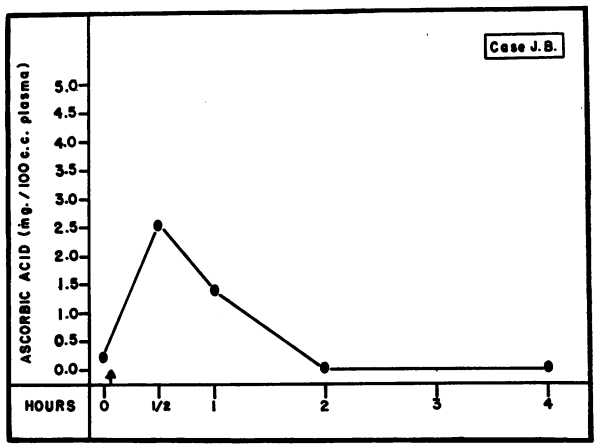

CHART V

treated with the same dose of ascorbic acid than these items rose in Patient 4 in this series. It does not seem possible that preëxisting deficiencies played any rôle in the findings in Patients 1, 2, 3, or 4 in this series, or more than a slight rôle in Cases 5 and 6.

2. *Inadequate Dosage.*—The dosage of vitamins administered varied from no dose to very large doses. Even the patients given the largest doses showed slight excretions during the acute phase of their illnesses but then showed very active excretions as soon as their metabolic disturbances were corrected.

3. *Failure of Absorption.*—Most of the vitamins were given intravenously. When they were given by mouth there were no instances of vomiting or diarrhea during the periods of mouth administration. Therefore, none of the results could have resulted from lack of opportunity for the vitamins to enter the blood.

4. *Excretion in the Sweat.*—That deficiencies might result from losses in the sweat has been postulated. Sargent, Robinson, and Johnson[11] have recently shown that sweating cannot cause important losses of these vitamins.

5. *Secretion in Exudates.*—Vitamins might be lost into exudates. Only one of the six patients (Case 6) had any important exudates.

6. *Storage.*—As noted in the introduction, Andreae, and his associates, interpret the evidence from their study of riboflavin excretion after injury as showing that riboflavin is stored early and excreted later. There is no data in the present study that confirms this finding for riboflavin. However, this difference in findings may be the result of differences in the technic of study. Andreae used the balance technic rather than the "fasting hour." At the same time, there is no evidence that any of the other vitamins react in this way.

7. *Destruction.*—It is possible that vitamins may be destroyed without performing any useful function during their destruction. This study contributes no evidence for or against such a postulate.

8. *Increased Utilization.*—Holt[12] has shown increased utilization of thiamin in conditions of stress such as increased basal metabolism and fever. As mentioned above, other stresses associated with acute hemorrhage or other medical or surgical illness, are followed by markedly increased turnover of protein and carbohydrate. Since the vitamins of the B group discussed here are intimately concerned with the metabolism of these substances, it is likely that the demand for, and utilization of them is increased. Similarly, it has been postulated that the demand for and utilization of ascorbic acid is increased due to its relation to the adrenocortical hormones.[2] The findings in the present study can best be explained by increased utilization.

It may be asked whether there is evidence in this study that administration of these vitamins was beneficial to these patients. Such evidence could only result from the study of large numbers of cases with comparable injuries or disease. Even the patients whose recovery was particularly gratifying (Cases 2, 4, and for the first eight days Case 3) and who were given large doses of vitamins had so many other powerful therapeutic agents used that we can have no opinion in answer to this question. On the other hand, the experimental work quoted above, and the demonstration of actual or apparent deficiency of ascorbic acid in the plasma and of all four vitamins in the urine under the conditions of the study, indicate that such treatment is reasonable as an attempt to aid the organism to achieve homeostasis.

If one accepts the possibility that these vitamins are useful in these conditions, do these results indicate any particular doses for such cases? It would seem reasonable to use doses of not less than one gram of ascorbic acid, 50 mg. of thiamin, 50 mg. or riboflavin, and 500 mg. of nicotinic acid per day during the period of acute stress and for two or three days afterward. Such doses will not result in any wastage of vitamins by excessive urinary secretion if they are given to patients with illness or injuries comparable to those of the patients studied. After this early period, the doses might well be reduced to 200 mg. ascorbic acid, 10 mg. of thiamin, 10 mg. of riboflavin, and 75 mg. of nicotinic acid until convalescence is well-established. This

study has not been carried into later convalescence so no estimate of the needs at that time can be given.

SUMMARY

1. Six patients with severe acute surgical conditions have been studied with respect to the plasma level of ascorbic acid and the excretion of ascorbic acid, thiamin, riboflavin, and nicotinic acid.

2. Abnormally small amounts of one or more of these substances have been found in many specimens from all cases during the period of the acute illness.

3. This study gives some further support to the idea that large doses of ascorbic acid, thiamin, riboflavin, and nicotinic acid may serve a useful purpose in the care of acutely ill people.

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