ASCORBIC ACID AND HUMAN WOUND HEALING*

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DURING the last few years, surgeons have been paying increasing attention to all the circumstances that play a part in the successful healing of operative and other wounds. The mechanical factors involved have been studied in great detail by two groups led, respectively, by Harvey,[1] and Whipple.[2, 3] Harvey, in particular, has shown how much strength can be expected in a given wound, at a given time, with a given type of suture material, properly placed. Eighty per cent of the disruptions that formerly occurred in Whipple's clinic have been avoided by changes in technic. Very widely over the country, there has been a steady shift in technic toward finer suture materials and especially toward fine silk and cotton, and to more suitable placing of sutures. With this change, better results are certainly being achieved.

During the same period of time, two chemical factors, plasma protein and ascorbic acid, that effect healing, have also come into prominent attention. Harvey showed an increased rate of healing on a high protein diet. Whipple,[4] Carrel,[5] and Ravdin,[6] have shown that a slight degree of lowering of the level of plasma protein may delay healing. A marked lowering will delay it enough so that even the most meticulous care in the type and placing of sutures may not result favorably.

More recently, the importance of ascorbic acid has been recognized in wound healing. Lanman and Ingalls,[7] Archer and Graham,[8] and Ingalls and Warren[9] made the earliest observations on surgical patients in which plasma ascorbic acid determinations were made. Lanman and Ingalls,[7] and also Taffel and Harvey[10] have studied the tensile strength of experimental wounds in animals with scurvy. Partial scurvy delays healing in animals. More recently, Wolfer and Hoebel,[11] Bartlett, Jones, and Ryan,[12] Holman,[13] Hartzell, Winfield, and Irwin,[14] and Lund and Crandon[15] have made further observations on man. All of these authors have found that many of their patients have subsaturation levels of ascorbic acid in the plasma. Some of them offer the opinion that a low plasma ascorbic acid level indicates a degree

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of deficiency that may cause failure of healing. Crandon, Lund, and Dill[16] showed that slight or even moderate deficiency in ascorbic acid reserves did not effect the healing of an experimental wound in a human. They also showed that plasma ascorbic acid determinations were not a good index of deficiency and that the plasma vitamin C level could be zero, and yet the patient might be far from having clinical scurvy, and his wound might heal quite normally. This indicates that the vitamin C reserves in the tissues or in the tissue cells and not the level in the plasma are the determining factor for healing. They also confirmed the finding of Butler and Cushman,[17] and showed that ascorbic acid determinations, made on leukocytes, gave a much more certain evidence of the degree of depletion of the body reserves of this substance. If the leukocyte level is below 4 mg. per 100 Gm., we consider the patient to be close to scurvy. (The normal value is 30–40 mg. per 100 Gm.)

Another method of studying the reserves of ascorbic acid is by saturation tests. Such tests may be carried out by measuring the plasma levels, the urinary excretion, or both, before and after test doses of the vitamin which may be given either by mouth or intravenously. Studies of the degree of ascorbic acid deficiency, by making saturation tests, have been made by many investigators. Wright, Lilienfeld, and MacLenathan,[18] Wright and MacLenathan,[19] and Portnoy and Wilkinson,[20] are among those whose data are very useful. Crandon, Lund, and Dill also performed a saturation test at the completion of their experiment, and determined the changes in the plasma and leukocyte ascorbic acid levels as scurvy was relieved. It is the authors' belief that one of the best and simplest saturation tests is performed by making daily plasma determinations 24 hours after daily doses of 1 Gm. of the vitamin given either intravenously or by mouth. Tested in this way, a moderately severe case of scurvy showed a zero level in the plasma the day after the first dose, 0.1 mg. per 100 cc.; after the second, 0.4 mg.; after the third, 0.6 mg.; after the fourth; and 0.8 mg., after the fifth dose. The leukocyte ascorbic acid determinations on the first four days showed 3, 15, 30, and 32 mg. per 100 Gm., respectively. Other cases studied by us failed to show any rise in the plasma level until after the fourth dose. Other laboratories have made similar findings. Provided intestinal absorption is normal it makes little difference whether the test dose is given by mouth or intravenously. Doses of ascorbic acid in smaller amounts may also be given. In some of our earlier work, various doses of less than 1 Gm. were tried. A good idea of the vitamin deficiency may be gained by such doses, but the period of testing is prolonged.

It is always preferable to know what the levels are before treatment is started, but if one is sure of the doses given one can sometimes calculate the degree of deficiency without such information. For instance, if a patient had a plasma level of 0.3 mg. per 100 cc. the morning after the third daily intravenous dose of 1 Gm. of ascorbic acid, one can be quite sure that a severe deficiency was present at the start of the treatment.

Another way of estimating the amount of deficiency is to calculate the amount of the vitamin taken by the patient in his food. This is less accurate, much more troublesome and more time-consuming than other methods, but has the great advantage of being available to any doctor and not necessitating any very delicate, expensive laboratory tests.

Dietary histories were taken on all the cases reported below. To evaluate such data the vitamin content of the foods must be estimated by calculation. These calculations were made from the data in Vitamin Content of Foods.[21] We believe that patients may maintain fair but not saturated reserves with an intake of 25 mg. of ascorbic acid per day,[16] but that when an intake below 10 mg. has prevailed for a long time that the reserves probably become severely depleted.

Two developments of the same general nature, but different in degree, occur as a result of poor healing after abdominal operations. One of these is postoperative hernia—due to failure of the fascia—and the other is disruption which is due to failure of all layers of the wall to heal. Both of these developments have been studied.

Postoperative Hernia Following Gallbladder Operations.—Lund and Crandon showed that various plasma vitamin C levels had no relation to the development of postoperative pulmonary complications. Fifty-eight of the same patients presented in that study, returned to the Follow-Up Clinic from three months to one year after discharge, and were studied for the presence of postoperative hernia by one of us (J. H. C.). Nine herniae were found. These patients were then tabulated in the same way they had been when the study of pulmonary complications was made (Table I).

TABLE I

VITAMIN C AND POSTOPERATIVE HERNIA FOLLOWING BILIARY OPERATIONS

Preoperative Plasma Ascorbic Acid—Mg. Per 100 Cc.	Average Preoperative Diet in Mg. Per Day			Total
	25	10–24	10	
0.5	1/11 = 9%	0/3 = 0%	0/0	1/14 = 7%
0.2–0.49	1/9 = 11%	0/11 = 0%	1/1 = 100%	2/21 = 9%
0.0–0.19	1/6 = 17%	1/6 = 17%	2/6 = 33%	4/18 = 22%
Unknown	1/2 = 50%	0/2 = 0%	1/1 = 100%	2/5 = 40%
Total	4/28 = 14%	1/22 = 5%	4/8 = 50%	9/58 = 15%

The numerators of each fraction indicate herniae. The denominators indicate total cases in each group.

It is seen from Table I that those cases with low plasma levels in the blood preoperatively showed a larger percentage of herniae than did those with high levels. Likewise, those with small amounts of the vitamin in their diet had a larger percentage than did those with fair or large amounts. However, these statistics, while we believe them to be of some significance, must be interpreted with great caution because of the fact that low plasma

values do not always mean depleted reserves, and patients who indicate a low intake on dietary history are perhaps not always telling the truth. However, *all* the patients in the higher brackets should heal, in so far as ascorbic acid is a factor in their healing. On the other hand, *some* of the patients in the lower brackets may be near enough to scurvy to interfere with their healing. With this reservation, and with the further reservation that the group of cases is small, it is believed that these statistics are sufficiently significant to indicate that cases with a low level of vitamin C in the plasma, if not corrected promptly, have more postoperative herniae than those with higher levels.

Disruption.—Twelve cases of wound disruption have now been studied from the standpoint of surgical technic and vitamin C reserves. The study is much more detailed than that undertaken on the cases of herniae. The estimation of the reserve supply of vitamin C was not made by the same method in all instances, so each case will be discussed briefly. Very few cases were studied early in the work as we did not then know how to interpret our plasma vitamin C values in postoperative cases. No studies of plasma protein were made, but transfusions were administered freely in certain of the cases that would have been likely to have low plasma values.

The cases were operated upon by several different surgeons and various different technics of wound suture were employed. In all cases, catgut was used and in many cases the catgut was of much larger caliber (Nos. 1 and 2

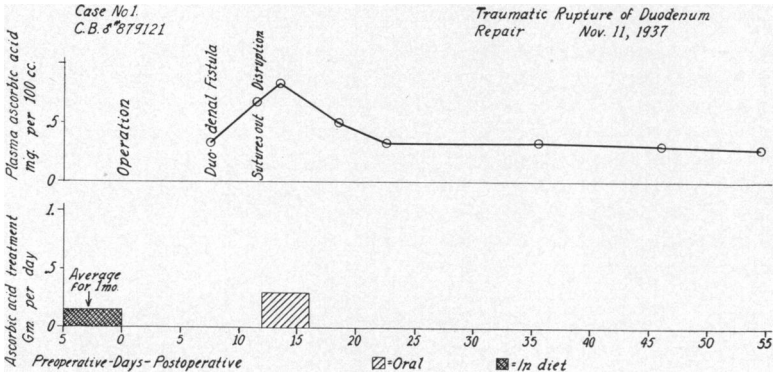

CHART 1.

chromic) than recommended by Whipple. Layer suturing, continuous to the peritoneum, and continuous or interrupted to the fascia, and silk or silkworm gut in the skin was the technic in all cases. A few silkworm stay-sutures were introduced in all cases. No overlapping or mattress sutures were used in the fascia. This technic in no way meets the standards set up by Whipple or Harvey, but the incidence of disruption was not believed to be excessive, although statistical studies to determine this incidence were not made. Three cases in this series have already been presented and discussed.[15] They are Cases 2, 4, and 6. Case 2 of the previous report is not presented again as

the peritoneum did not separate. In this report, only cases with complete separation of all layers are considered. The cases are presented in chronologic order.

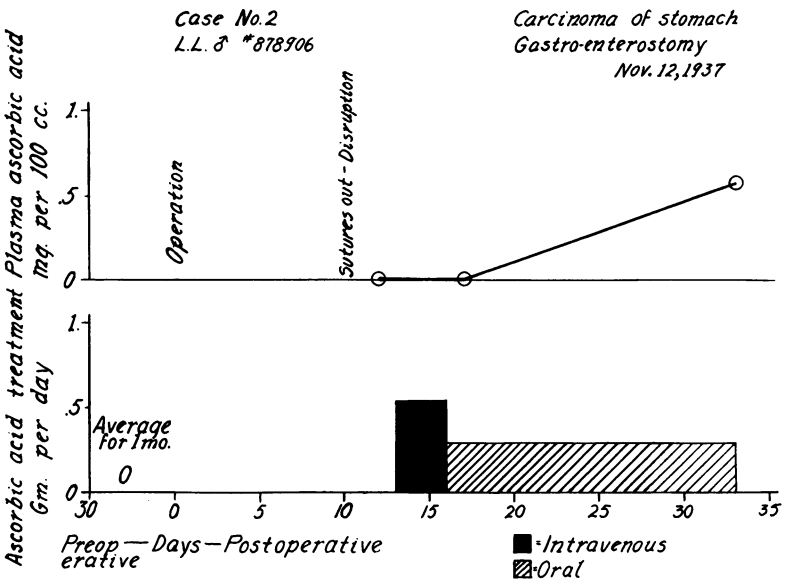

CHART 2.

Case 1.—*No Scurvy.* Hosp. No. 879121: C. B., a healthy high school boy, was injured playing football. He was brought to the hospital at once, and, at immediate operation, a traumatic retroperitoneal rupture of the duodenum was repaired with catgut. He had a stormy convalescence complicated by the early development of a duodenal fistula. Disruption occurred on the twelfth day, immediately after removing the stay-sutures. The wound was resutured. Chart 1 shows the intake and levels of plasma ascorbic acid. Calculations of the amount of ascorbic acid in the diet while in the hospital were not made as there was no possibility that this boy had scurvy. (See the high normal dietary intake before the accident.)

COMMENT.—Because of the high dietary intake and the plasma levels well above zero, we do not believe that vitamin C had anything to do with the disruption. Treatment of 0.3 Gm. per day was given because we did not then know that the levels determined were of no importance under these conditions. This disruption was due to technical factors and the chemical effect of duodenal secretion on the sutures. The boy eventually recovered.

Case 2.—*Near Scurvy.* Hosp. No. 878906: L. L., male, age, 59, had carcinoma of the stomach. His diet had contained very little, if any, ascorbic acid for months and he had lost 50 lbs. in weight. An exploration and anterior gastro-enterostomy were undertaken. Disruption occurred on the tenth day, shortly after removal of the stay-sutures. The wound was resutured and healed well.

COMMENT.—The preoperative diet was such that a condition close to scurvy was likely. After four days of 0.6 Gm. of ascorbic acid, intravenously,

the plasma level was still zero. After 17 further days of treatment by mouth, with daily doses of 0.3 Gm., the level was only 0.6 mg. per 100 cc. Inasmuch as there was no fever, sepsis or gastro-intestinal disturbance, these figures can only mean that this man probably had ascorbic acid deficiency of severe enough degree to contribute to this disruption.

Case 3.—*No Scurvy.* Hosp. No. 932411: T. A. D., male, age 45, with a gastro-jejunal ulcer of considerable duration. Vitamin deficiency was suspected and the ascorbic acid deficiency treated preoperatively, by giving 1.0 Gm. per day for three days. Determinations on two days showed a normal level. A difficult gastric resection and

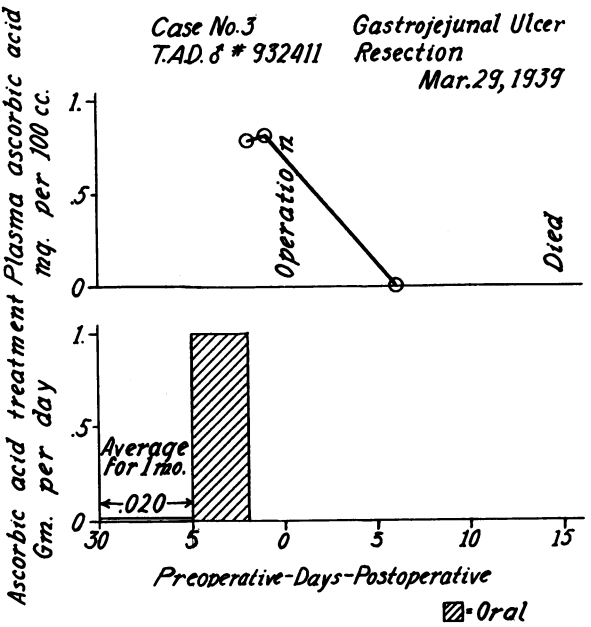

CHART 3.

repair was performed. On the third day, there was noted severe wound sepsis. Other complications followed, including hemorrhages from the wound and the stomach. Some delay occurred before treatment with vitamin K was given, as we did not, at that time, suspect that this deficiency was possible in such a case. In spite of treatment with vitamin K and many transfusions, the man died of peritonitis. Autopsy showed complete separation of the wound with a loop of intestine presenting just below the separated skin.

COMMENT.—Vitamin C played no part in this disruption, which was probably due, mainly, to effects of infection on the catgut sutures.

Case 4.—*Probably No Scurvy.* Hosp. No. 939296: R. F., male, had an appendix abscess. Until ten days before admission, and 20 days before operation he had had a diet fairly adequate in ascorbic acid (about 40 mg. a day). The operation consisted of drainage of the abscess through a right rectus incision. Disruption and protrusion of loops of intestine occurred 33 days after operation.

The data concerning vitamin C is relatively scanty. Two days before the operation,

and on the fifteenth day after it, the plasma level was zero. No vitamin C was given before the disruption. The convalescence was very stormy. Practically no food was taken for three weeks after the operation during which time Wangensteen drainage was constant. Fever was present from before admission to after the disruption. Eventually he recovered.

COMMENT.—No studies, that we know of, allow us to predict how long it takes for scurvy to develop in the presence of severe infection. All the evidence points toward the time being much shorter than without infection. The main cause of this accident was undoubtedly sepsis. Usually, in such cases

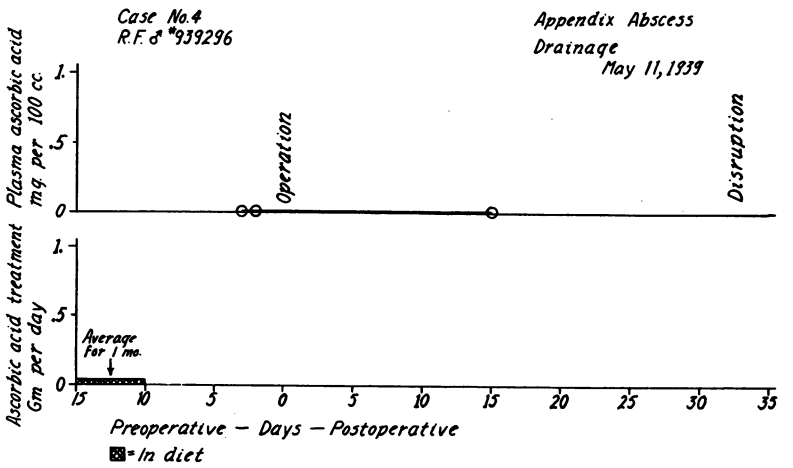

CHART 4.

firm adhesions prevent protrusion of the intestines, even if the wound breaks down. Possibly, there was a factor of vitamin C deficiency developing late in the infection, but the conservative position to take is that this case probably suffered from no important deficiency in spite of the zero plasma levels.

Case 5.—*No Scurvy.* Hosp. No. 944466: M. T., a male, had a ruptured gastric ulcer and was operated upon promptly. On the tenth day, the stay-sutures were removed and his wound disrupted a few hours later. Four days later, his ascorbic acid level was found to be 0.1 mg. per 100 cc. The morning after the first dose of 1 Gm. of ascorbic acid the level was 0.4 mg.

Comment.—This finding indicates that vitamin C was not a factor in this case of disruption.

Case 6.—*Near Scurvy.* Hosp. No. 970288: M. A. had had a duodenal ulcer for a long time, and severe obstruction for months. He had also been a heavy user of alcohol. He had been able to retain very little of the nourishment taken by mouth for some time before operation and he had lost 50 lbs. in weight. The surgical service had understood that plenty of ascorbic acid had been given before the operation, as preparation for it, but nobody realized how completely all food and vitamins taken by mouth had been vomited.

After operation, his stay-sutures were removed prematurely on the sixth day. The wound promptly disrupted. No tablets of ascorbic acid were used, but from the second day after the disruption over a pint of orange juice was taken daily along with his food and he retained it all. This was equivalent to about 200 mg. per day. The laboratory

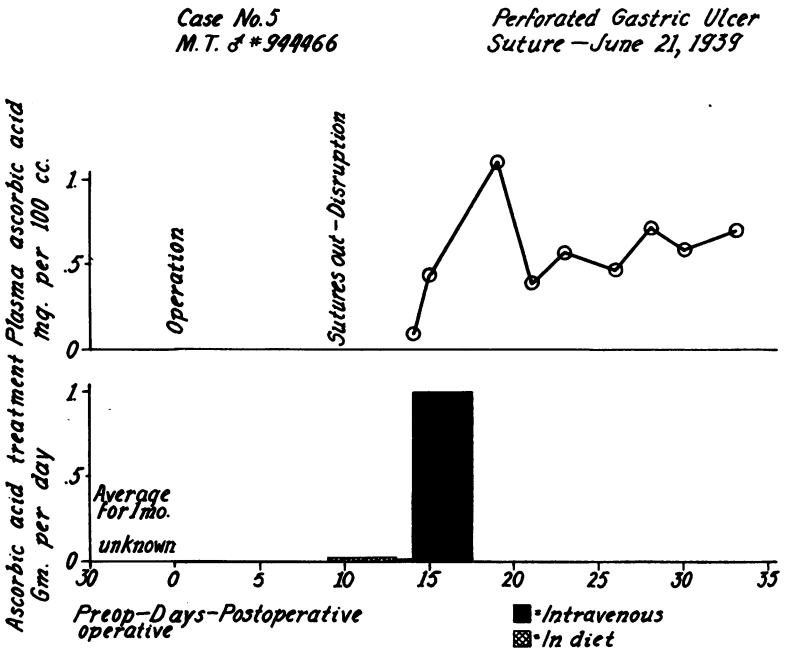

CHART 5.

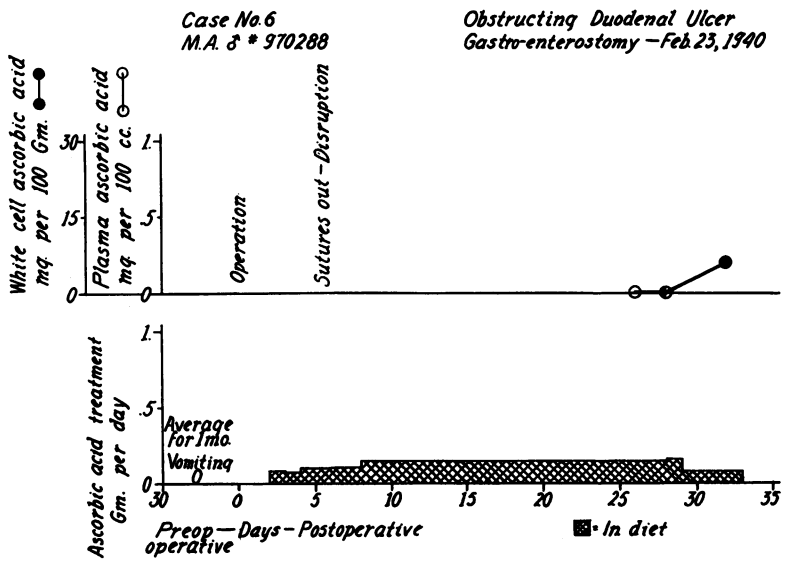

CHART 6.

did not have an opportunity to determine the blood levels until after 22 days of high orange juice diet. Even at this time the plasma and white blood cell levels were extremely low.

Comment.—This evidence points to a dangerous degree of scurvy. However, the removal of stay-sutures on the sixth day was inexcusable. The treatment of a man who vomits all his food should be by intravenous route.

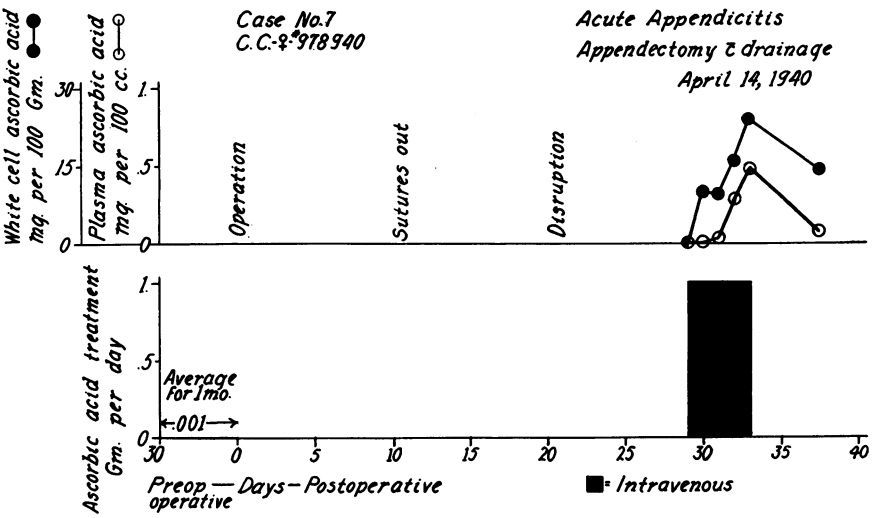

CHART 7.

Case 7.—*Near Scurvy.* Hosp. No. 978940: C. C., female, had acute appendicitis with peritonitis. Her diet before the illness had been very low in ascorbic acid containing foods. At operation, the appendix was removed, and the base of the cecum and the pelvis were drained. Stay-sutures were removed on the tenth day. The wound was moderately septic, and the patient was quite ill. Food was not taken well and no ascorbic acid given. On the twentieth day, a loop of intestine presented in the wound. This was replaced and held in by packing and strapping. Nine days later the patient was studied for scurvy and both the plasma and white cell levels were zero. The curve following the treatment proves a severe grade of deficiency.

Comment.—There can be little doubt that scurvy played a part in this late disruption.

Case 8.—*No. Scurvy.* Hosp. No. 981871: C. B., male, had a subacute cholecystitis and a chronic gastric ulcer. His diet contained a small amount (about 12 mg. of vitamin C) before entering the hospital. At operation the gallbladder was drained. The stay-sutures were removed on the eighth day, and he promptly disrupted. His wound was resutured. Some days later, the first vitamin C determinations showed none in the plasma, but about 6 mg, per 100 Gm. in the leukocytes. After test doses the levels rose rapidly.

Comment.—This evidence indicates that scurvy was not present.

Case 9.—*No Scurvy.* Hosp. No. 986160: E. McN., male, young, had a traumatic rupture of the intestine, this time of the jejunum. His history showed a small intake of

ascorbic acid before the injury. His stay-sutures were removed on the tenth day and he disrupted. He was resutured. Vitamin C determinations showed zero in the plasma and 12 mg. per 100 Gm. in the leukocytes. The test dose showed a rapid rise in both levels.

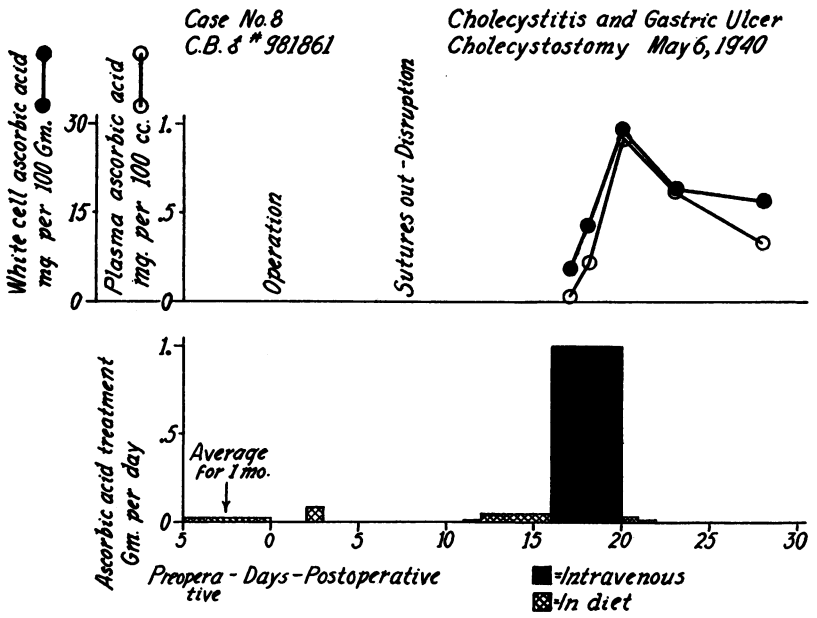

CHART 8.

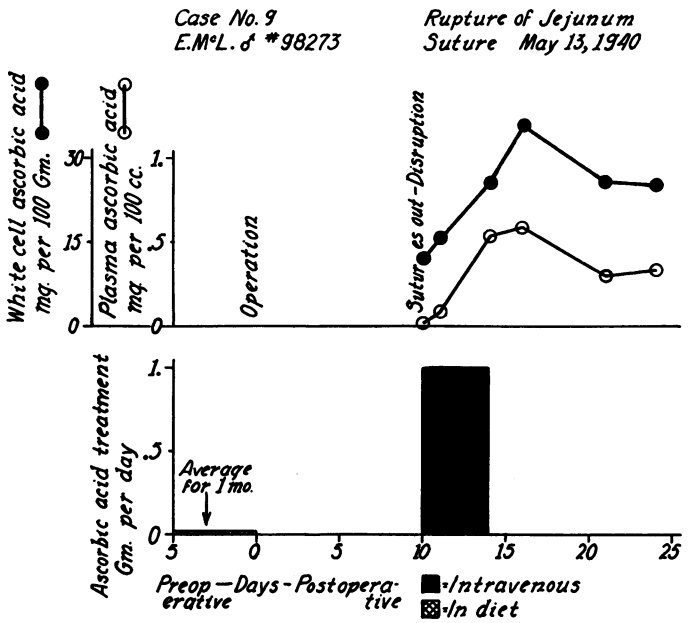

CHART 9.

Comment.—This finding, plus the response to test doses, proves the absence of scurvy.

Case 10.—*No Scurvy.* Hosp. No. 982674: J. M., male, had an obstructing duodenal ulcer. Although his preoperative leukocyte ascorbic acid was 14, he was given treatment intravenously with the results to the plasma and leukocyte levels shown on the chart. On the tenth day postoperatively the stay-sutures were removed and there was a small disruption. This was controlled by packing and strapping.

Comment.—Scurvy could have had no part in this accident.

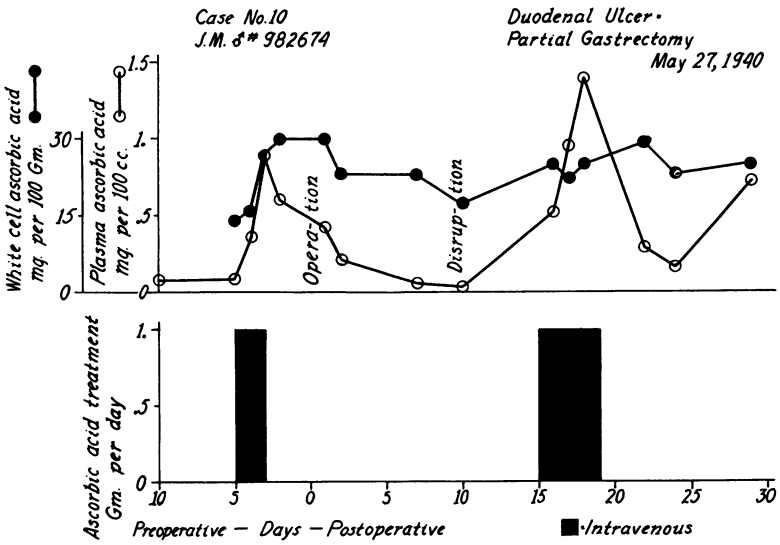

CHART 10.

Case 11.—*No Scurvy.* Hosp. No. 985945: P. B., male, rather feeble, with carcinoma of the sigmoid. He took a small amount of vitamin C in his food before operation. On the tenth day, his sutures were removed and he disrupted. His leukocyte level was eight. He was resutured and given vitamin C, but he died the next morning.

Comment.—With this leukocyte level the man could not have had a severe enough deficiency for it to be a factor in this disruption.

Case 12.—*No Scurvy.* Hosp. No. 995658: T. E. had a partial gastrectomy for duodenal ulcer. His preoperative diet had contained a small amount of vitamin C. On the sixth day, the stay-sutures were removed and the wound disrupted. It was resutured. The 0.5 Gm. doses of ascorbic acid were given for three days, after which the leukocyte level was 25 mg. per 100 Gm., and the plasma level 0.04 mg. per 100 cc.

Comment.—It is believed that the level of 25 mg. in the leukocytes, after only 1.5 Gm. of treatment, indicates that the wound was not affected by lack of vitamin C.

Discussion.—Twelve cases of disruption of abdominal wounds have been studied. Scurvy played no part in the accident in Cases 1, 3, 5, 8, 9, 10, 11, and 12. This statement is made in spite of the fact that most of these cases

had very low plasma vitamin C levels, at one time or another, during their illness. Cases 2, 6, and 7, had a severe depletion of their vitamin C reserves, and scurvy probably delayed, or prevented, the healing of their wounds. (Case 4 is doubtful.)

In none of the cases was the method of suturing up to the standards of technic set up by Whipple. On the other hand, it must be stated that these disruptions occurred among a very large number of abdominal operations,

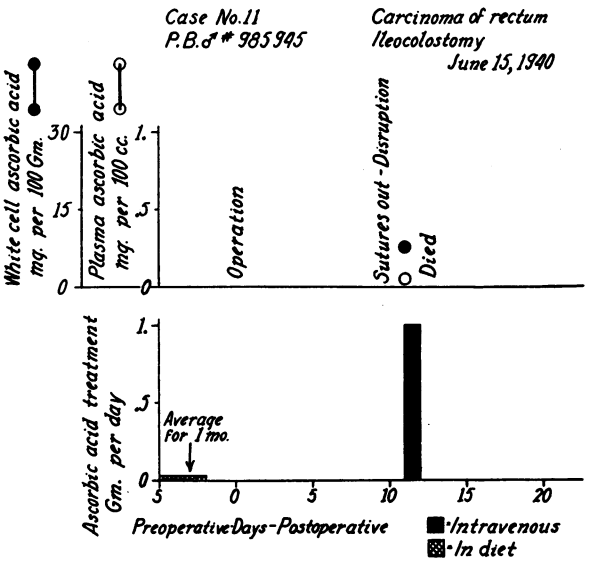

CHART II.

and the percentage of these accidents is low, showing that the methods of suturing used were, at least, reasonably good. Stay-sutures were used in all cases, and in some cases were removed much too early. If stay-sutures are put in for a purpose, the purpose must be to support the wound until natural healing has taken place sufficiently to make their presence superfluous. This makes it imperative that they remain, at least, until the twelfth or the fourteenth day.

It is obvious from the cases presented that a larger part of the problem of disruption will be solved by improved technic than by studies of or treatment with vitamin C. On the other hand, the fact that a few cases of disruption occur in patients with severe depletion of the vitamin C reserves, indicates that these reserves should be studied before operation. A series of gastric and duodenal ulcer patients who were in the hospital at the same time as those cases reported here, are also being studied and will be reported in another communication. Several of them had deficiencies comparable to that of Case 7, above. However, their deficiencies were corrected either just before or just after operation. If they had not been treated, the number of

cases disrupting from ascorbic acid deficiency might have been larger. Most surgical services have no facilities for such studies and such studies are extremely expensive. The authors are convinced that wide installation of such facilities are not necessary at present. In another communication, we hope, shortly, to prove that a few minutes spent in securing and analyzing a short dietary history will do as much or more to determine these reserves than ascorbic acid determinations. In such a history, special attention should be given to the amounts of certain foods that are eaten per day. About

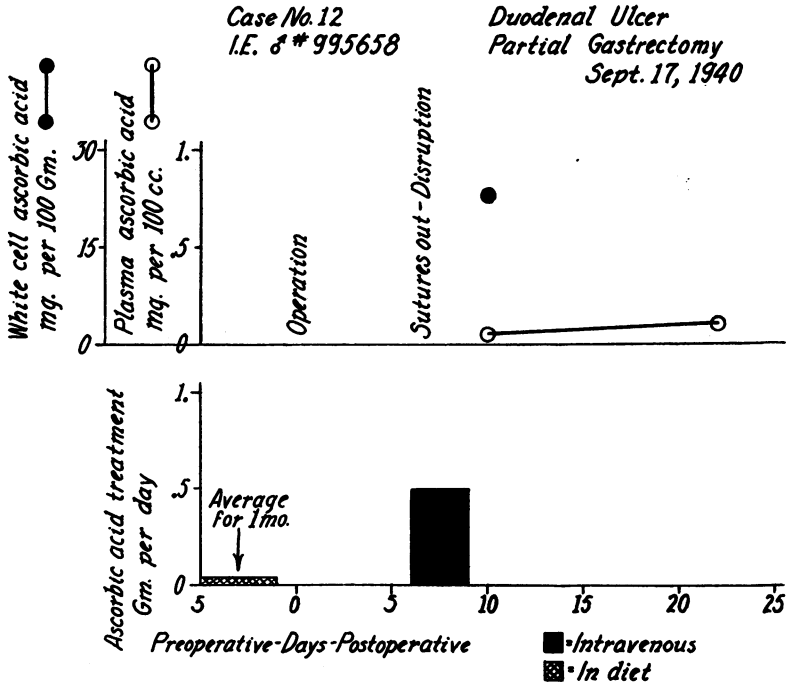

CHART 12.

75 mg. of ascorbic acid is generally accepted as an amount that will keep a well person saturated. We believe that even 20 mg. will keep sufficient reserves so that wounds will heal easily and well. Seventy-five mg. will be furnished by the amounts of food shown in Table II. Many other foods have

TABLE II

AMOUNTS OF CERTAIN FOODS NEEDED, DAILY, TO FURNISH 75 MG. OF ASCORBIC ACID, IF THE PARTICULAR FOOD IS THE ONLY SOURCE OF THE VITAMIN

Fresh citrus fruit or juice and fresh strawberries	150 Gm. or cc.
Canned citrus fruit	250 Gm. or cc.
Fresh or canned tomatoes or tomato juice	300 Gm. or cc.
Cooked liver	300 Gm.
Cooked potatoes (except fried)	300 Gm.
Raw apples, pears, other fruits and berries	1-5 Kg.

Lettuce, other greens, and most vegetables contain small amounts, and part of these small amounts may survive cooking.

small amounts of this vitamin, but grains and flour have none, and pasteurized milk very little.

Full data of this nature has been presented by Daniel, and Munsell,[21] and by many other students of diet.

Following the securing of data from the diet, those patients with very low reserves should be treated. The treatment should be given preoperatively in an "elective" case, and immediately postoperatively in an "emergency" case. Ascorbic acid is cheap and may be given by mouth, intramuscularly or intravenously (using different preparations). About 4 Gm. are needed to bring a severe case of scurvy up to saturation. This may safely be given in four days. Be sure, however, that the treatment be intramuscular or intravenous if there is likely to be vomiting or diarrhea, otherwise it makes no difference which way it is given.

SUMMARY AND CONCLUSIONS

(1) A study of preoperative diet and preoperative plasma vitamin C levels of patients having operations upon the biliary tract was made.

(2) Those with poor intake or low levels or both, had a higher percentage of postoperative herniae than those with better intakes or levels.

(3) A study of 12 cases of abdominal wound disruption shows that mechanical factors were more frequently the determining ones for disruption than depletion of vitamin C reserves in this series.

(4) Three cases, however, had sufficient degrees of ascorbic acid deficiency, so that this was an important factor in their disruptions. In a fourth case, depletion to a dangerously low level may have taken place, but the data are too incomplete to be sure.

(5) Two cases of depleted reserves were associated with lesions of the stomach, and two (including the doubtful one) with appendicitis.

(6) These studies indicate a need for improvement in surgical technic, and for routine study of vitamin C reserves by surgeons.

(7) Study of vitamin C reserves may be made by means of dietary histories and should be followed by preoperative, or early postoperative treatment of the few patients that probably have low reserves.

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