Summary. 1. The glucose assimilation curve in cases of hyperinsulinism due to tumor of the islands of Langerhans is frequently of the diabetic type.

2. Normal glucose tolerance tests were obtained in 3 patients in whom three-quarters of the pancreas had been removed. There was no obvious difficulty with food digestion or absorption.

3. Normal fat absorption is possible when no pancreatic juice enters the intestine.

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VITAMIN C IN THE TREATMENT OF DIABETES.*

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In our studies of possible vitamin deficiencies among diabetic patients, it was thought advisable to investigate vitamin C. The chemical function of vitamin C has been better understood in plant than in animal metabolism. In plants, it is generally agreed that ascorbic acid forms part of a cellular oxidation-reduction system; while most workers agree that in animal tissues glutathione occupies a rôle analogous to ascorbic acid, and that the vitamin has no part in cellular oxidation.[13] Even though there is no proof that vitamin C enters into the cellular oxidation of carbohydrates, various experiments indicate some effect on carbohydrate metabolism in general. Since diabetes is primarily a disturbance of carbohydrate metabolism, which secondarily causes disturbances in metabolism of other foodstuffs as well, any agent which might regulate the handling of carbohydrates assumes great clinical importance.

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In a previous study at the Diabetic Clinic, Cincinnati General Hospital, a survey of 125 diabetic patients was made with respect to their vitamin C status.[9] No relation was found between vitamin C and the diabetic state of the patient. This present paper covers the results of ascorbic acid administration in various dosages to controlled diabetic patients in all states of vitamin C nutrition, in order to observe what effects it may have on subjective complaints and the severity of the disease.

Stepp, Schroeder and Altenburger[12] found that 300 mg. of ascorbic acid given intravenously to 17 patients, both diabetic and otherwise, invariably produced a drop in the blood sugar, in some instances as much as 20% of the starting level. Oshima[7] demonstrated this fall in diabetic individuals only; in normal people the blood sugar remained the same. Guinea-pigs on a C-deficient diet developed a diabetic type of glucose tolerance which was corrected when vitamin C was again added to the diet.[11] Clinically, Pfleger and Scholl[10] and others have found that when ascorbic acid is given orally, the urinary sugar of diabetics is reduced and less insulin is required.

Hirsh[5] administered vitamin C to guinea-pigs and produced an increase in liver glycogen; furthermore, this vitamin offsets the glycogenolytic activity of thyroid extract. Bartelheimer has also stated that glycogen storage in experimental animals is increased after vitamin C.[1] This is of particular interest in relation to diabetes, since many physiologists believe that the primary defect in the diabetic individual is an inability to form and store glycogen. Any agent that promotes glycogenesis and has an action similar to that of insulin might be of practical importance.

Most of the work done on the relation of vitamin C to carbohydrate metabolism has been either to measure the immediate effects of a single intravenous or oral dose, or to follow the effects of vitamin C on diabetics who have come under recent control. One group of workers whose work is widely quoted administered ascorbic acid to a group of uncontrolled diabetics at the same time that a diabetic regimen was started. They disregarded the fact that the tolerance of any diabetic patient improves under treatment, and attributed the beneficial effects to the use of the vitamin. Small laboratory animals have also been used to test the effects of ascorbic acid; but these animals are notoriously prone to show a variety of manifestations, when placed on deficient diets, which would tend to upset their carbohydrate metabolism and make estimation of the results difficult. Since many authors have intimated that vitamin C may be of some practical benefit in the treatment of diabetes mellitus, and since few reports concerning the efficacy of the vitamin appear in the literature, it is the purpose of this paper to discuss the practical benefit actually derived from the administration of various dosages of vitamin C to diabetics over a considerable period of time.

Method of Study. A group of 16 out-patients from the Diabetic Clinic of the Cincinnati General Hospital were taken for this study. Selection was made from those who were willing to coöperate and follow dietary instructions. One colored and 15 white patients were chosen. The average age was 50.8 years, the extremes being 32 and 60 years. All were taking insulin. The observations extended from February to June, 1940.

All of the patients had been controlled in the clinic for 2 to 8 years, with the exception of 2 relatively new patients who had been followed for only 4 and 6 months respectively. They were included since they were quite stable at the time the study was started. It was felt that the selection of these 16 patients eliminated the variable factor of the natural tendency of diabetics to show improvement and decreased insulin requirement early in the period of diabetic control. The length of control was discussed in a previous paper,[8] and its importance cannot be overemphasized.

The diet allowed during the study was the same as had been prescribed for a considerable time previous to the test period. The calories ranged from 1430 to 2300 daily, and the carbohydrate from 100 to 180 gm. Each patient was asked to keep a daily record of all the food eaten, both with respect to type and amount of vegetable, fruit, or meat. The sizes of portions were recorded in common household measurements, and the diets were evaluated first for *dependable* sources of vitamin such as citrus fruits, tomato juice, and raw vegetables, and then for *uncertain* sources such as cooked fruits and vegetables. The table compiled by Bessey[2] was used for estimating the vitamin C content of the various foods. Dependable and uncertain sources were calculated separately and then divided by the number of days the diet was observed, so that the final figures represent the average daily intake from all sources. The theoretical amount of vitamin C that any one diet would allow by proper selection of foods was also calculated, so that two dietary vitamin C figures were available for analysis: 1, the amount that could reasonably be obtained from the diet allowed; 2, the amount actually eaten by the patient.

Before any specific medication was given, a physical examination was made with particular attention to the presence of any signs of scurvy. Examination of the gums and capillary resistance tests were made. Two of the patients had generalized arteriosclerosis with hypertension; 4 had retinitis, and 8 out of the 16 had cataracts, either operated or unoperated. In no case was there a severe infection.

At the beginning of the period, a 1000-mg. 5-hour intravenous saturation test was done. This test was described by Ludden and Wright[6] and was designed to measure the 24-hour output of vitamin C after an intravenous test dose, based on the calculation of the 1½- and 5-hour urinary excretion. Initial blood ascorbic acid level was also measured. The method of Harris was used[4] for the determination of the urine C, and all values were reported in milligrams.

Patients were seen in clinic every 2 to 3 weeks during the time the ascorbic acid was being given. They were weighed at each clinic visit, so that it was possible to follow weight curves during the vitamin administration; and any change in subjective complaints were elicited without the use of leading questions.

Blood sugar determinations were made at the beginning of the study and found to be within reasonable limits. The control of the diabetic state of these patients was observed by examination of the usual 4 daily routine specimens, and by measurement of the blood sugar whenever it was felt necessary. All of the patients remained under good control, as is evidenced by the fact that only 2 showed more than a 2+ sugar during the period of observation. Both instances resulted from glucose ingestion taken to correct mild insulin reaction. The urines of most of the patients were negative except for an occasional trace of sugar after meals, a finding which we consider normal in patients taking protamine insulin. Changes in the

insulin requirement were watched carefully, as this was one of the indices used to measure the effect of the vitamin.

Ascorbic acid tablets were given 3 times a day before meals,* 300, 600, and 1200 mg. being taken daily. The blood levels of ascorbic acid were examined on each clinic visit. No ascorbic acid tablets or foods that contained any appreciable amount of vitamin C were allowed on the morning of blood level determination. The method of Farmer and Apt was used for the blood ascorbic acid level.[3]

Results and Discussion. *Diet Analysis for Vitamin C Content.* Dietary values for carbohydrate, protein, and fat for each patient, theoretical amounts of vitamin C that the diets might reasonably be said to contain, and amounts of C actually eaten by the patients are given in Table 1. If proper selection were made, the dependable sources of vitamin C citrus fruits, tomato juice, and raw vegetables were alone sufficient to cover the daily needs. When the amount

TABLE 1.—ANALYSIS OF CARBOHYDRATE, PROTEIN AND FAT AVAILABLE AND ACTUAL VITAMIN C CONTENT OF DIETS.

	Diet.				Total vitamin C (mg.).			
					Available.*		Actually eaten.	
Patient.	Carbohydrate (gm.).	Proteins (gm.).	Fats (gm.).	Calories.	Dependable.	Uncertain.	Dependable.	Uncertain.
1	165	85	125	2125	100	40	41	57
2	160	70	80	1740	100	40	45	30
3	150	80	100	1820	90	25	0	46
4	150	75	60	1440	90	25	64	61
5	180	80	140	2300	100	40	24	38
6	120	70	115	1795	50	20	80	40
7	130	70	70	1430	50	20	3	20
8	150	75	75	1575	90	25	40	30
9	130	75	85	1585	50	20	80	75
10	160	70	60	1560	100	40	0	19
11	150	80	60	1560	90	25	65	35
12	135	70	100	1700	50	20	0	60
13	160	80	80	1680	100	40	0	25
14	140	60	70	1430	90	25	76	25
15	150	85	140	2190	90	25	40	45
16	100	65	90	1470	50	20	76	35

* Average figures for the common fruits and vegetables.

that is inconstantly present in cooked fruits and vegetables was added, there was a considerable margin of safety. It is entirely possible to design diabetic diets having an adequate amount of vitamin C, if foods with a high natural content of C are chosen. In all but three instances in which the diet was analyzed, the theoretical amount of vitamin the prescribed diet could reasonably contain was higher than the amount eaten. Since all patients received regular instruction about selection of foods, in order that the greatest value per dollar could be obtained, we feel that dietary lack of vitamin C was mainly dependent on likes and dislikes of the patient or improper handling and cooking of foods.

Weight Changes. Of the 16 patients who were on 300 mg. of ascorbic acid daily, 2 lost 5 pounds over a period of 3 weeks, and

* The ascorbic acid for this study was supplied through the courtesy of Parke, Davis & Co.

1 gained 5 pounds over a period of 5 weeks. With the larger doses of 600 and 1200 mg., 1 gained 3 pounds and 1 lost 3. These observations failed to demonstrate any consistent weight change.

The insulin requirement was followed very carefully, because reports in the literature state that the administration of ascorbic acid lessens the insulin need. An effort was made to keep constant all variable factors such as diet, exercise, worry, and infections. During the whole period of observation, only 2 patients needed a significant change in insulin dosage: 1 needed an increase of 8 units, and 1 a decrease of 10. It seems safe to say that ascorbic acid does not consistently alter the insulin requirement in previously well-controlled diabetic patients, as long as their dietary intake remains constant.

Ascorbic acid saturation tests and blood ascorbic acid determinations were made on each patient at the beginning of the period of administration to determine their state of vitamin C nutrition. Although no signs of scurvy were found among any of the patients, 7 of the 16 were found to have fasting blood ascorbic acid values below the so-called scurvy level of 0.4 mg. per 100 cc. Two had levels between 0.4 and 0.8 mg. per 100 cc., and the remaining 7 had levels over 0.8 mg. per 100 cc. A fairly close correlation was found between the blood ascorbic acid level and the milligrams excreted after an intravenous test dose. Of the patients with chemical scurvy, all but 1 had a urinary output of less than 400 mg. after an intravenous test dose of 1000 mg. Of those with blood levels over 0.4 mg. per 100 cc., only 1 failed to excrete less than 400 mg. Since such a close parallel existed between the blood ascorbic acid and the urinary output in the saturation tests, the patients were subsequently followed by measurement of the blood levels alone.

Effect of 300 Mg. Ascorbic Acid on the Blood Levels. In every instance the blood levels rose after the administration of 300 mg. ascorbic acid daily. Whereas a striking increase was found among patients who started with low levels, many of those with a good state of saturation also showed a marked rise. The greatest single increase was found in a patient who started with a blood ascorbic acid of 1 mg. per 100 cc. (Table 2, No. 13). A prolonged accumulative effect from the administration of the vitamin could not be demonstrated. Those who took 300 mg. of ascorbic acid daily for longer than 3 weeks showed lower levels of blood ascorbic acid at the end of the period than those who took it for less than 3 weeks. In observing patients from week to week, the highest levels were found on the first visit after the medication was started; there would then be a slow, progressive fall, even though administration was continued in the same dosage.

The Effect of 600 and 1200 Mg. Ascorbic Acid on the Blood Levels. Ascorbic acid was increased to 600 or 1200 mg. daily immediately after the 300-mg. dosage was discontinued. In spite of the fact that the amount was doubled or quadrupled, no significant changes

could be demonstrated. Six patients showed a rise in blood ascorbic acid levels, 7 showed a drop, and 2 stayed the same. These results indicate that a state of saturation can be reached with a comparatively small dose, and that once it is reached, no further increase in the blood level can be attained. Excretion then matches ingestion.

TABLE 2.—EFFECT OF VARIOUS DOSAGES OF VITAMIN C ON WEIGHT,* INSULIN REQUIREMENT, AND NON-SPECIFIC SYMPTOMS.

Patient.	Sex.	Age.	Weight, pounds.		Insulin, units.		Vitamin C.						Non-specific symptoms.
							Saturation test.		Blood, mg. per 100 cc.				
			Beginning.	End.	Beginning.	End.	Blood, mg. per 100 cc.	Total excreted in urine, mg.	Beginning.	End.	Daily dosage, mg.	Weeks given.	
							300 MG. DAILY DOSAGE.						
1	F	53	114	115	25	22	0.05	296	0.05	1.11	300	3	+
2	F	41	146	146	30	35	0.15	238	0.15	1.15	300	3	0
3	M	48	130	130	70	70	0.15	377	0.15	1.27	300	4	−
4	M	60	139	139	100	100	0.19	260	0.19	1.07	300	3	0
5	M	58	140	135	35	35	0.22	196	0.22	1.04	300	3	−
6	M	58	139	120	17	17	0.31	413	0.31	1.08	300	5	0
7	F	53	138	136	22	22	0.37	291	0.37	0.98	300	3	+
8	F	56	132	132	40	40	0.48	405	0.48	1.24	300	3	+
9	F	60	126	127	34	34	0.50	760	0.50	1.30	300	7	+
10	M	36	174	169	60	60	0.80	653	0.80	1.22	300	3	+
11	M	40	146	144	30	30	0.81	708	0.81	0.94	300	3	+
12	M	57	115	120	22	22	0.96	712	0.96	1.33	300	5	+
13	F	56	119	117	25	25	1.00	588	1.00	2.56	300	2	+
14	F	58	116	118	16	16	1.00	734	1.00	1.10	300	8	+
15	M	32	124	123	50	50	1.13	372	1.13	1.24	300	3	+
16	F	57	128	130	12	12	1.56	744	1.56	2.15	300	3	+
							600 MG. DAILY DOSAGE.						
11	M	40	144	144	30	30			0.94	0.80	600	2	
7	F	53	136	136	22	30			0.98	0.88	600	4	
5	M	58	135	134	35	32			1.04	1.27	600	4	
4	M	60	139	139	100	100			1.07	1.24	600	2	
6	M	58	129	127	17	17			1.08	1.42	600	4	
14	F	58	118	119	16	16			1.10	0.65	600	3	
10	M	35	169	169	60	60			1.22	1.56	600	4	
9	F	60	127	127	34	34			1.30	1.24	600	2	
12	M	57	120	117	22	22			1.33	1.33	600	4	
3	M	48	130	130	70	60			1.37	1.22	600	5	
16	F	57	130	133	12	10			2.15	1.10	600	4	
							1200 MG. DAILY DOSAGE.						
2	F	41	146	147	35	38			1.15	1.15	1200	1	
15	M	32	123	123	50	50			1.24	1.68	1200	1	
9	F	60	127	126	34	34			1.24	1.15	1200	1	
8	F	56	132	134	40	40			1.24	1.68	1200	2	

* For diet see Table 1.

Analysis of Subjective Complaints. Since there were no signs of ascorbic acid deficiency, only subjective indices of a general nature could be measured. Nine patients felt better after taking the medication, 5 felt the same, and 2 felt worse. Of the 9 that felt better, 1 who had cataracts noticed an improvement in vision; the remaining 8 noticed an increase in body strength and endurance. It was felt that this improvement had nothing to do with the specific medication, because the greatest improvement was found among those who started with a good state of vitamin C nutrition. Among those patients with chemical scurvy in whom the greatest improvement could be expected, 2 felt better, 3 noticed no change, and 2 felt worse after taking ascorbic acid.

In spite of the fact that there is experimental evidence to show that ascorbic acid has a beneficial effect on the ability of the normal and diabetic individual to metabolize glucose and store glycogen, no practical benefit resulted from its administration. We feel that the best way to assure adequate intake of vitamin C in diabetic patients is by instruction in the proper selection of foods having a high natural content. Supplemental additions of ascorbic acid appear to have no beneficial effect on the diabetic state.

Summary. 1. Ascorbic acid was administered in 300, 600 and 1200 mg. daily doses to 16 diabetic patients in various states of vitamin C nutrition. All patients had been under good control, and were kept as stable as possible during the period of observation.

2. No constant objective improvement resulted from the ascorbic acid administration in any dosage or for any length of time. There was no weight gain or significant change in the insulin requirement. The disease severity remained unchanged.

3. Some subjective improvement, consisting of increased strength and endurance, was found in 9 of the 16, but the least improvement was found among those who started with a poor state of vitamin C nutrition.

4. Regardless of the initial state of vitamin C nutrition, ascorbic acid administration has no effect on the severity of the diabetic state.

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SOME EFFECTS OF IRON ON HEMOGLOBIN FORMATION.

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Although the efficacy of simple iron salts in the treatment of iron deficiency hypochromic anemias is well recognized there are