Summary. 1. In numerous healthy individuals and normal experimental animals hypoglycemia entails hyperglycemia in the post-absorptive state, irrespective of the experimental conditions which initiated the hypoglycemia. The phenomenon is interpreted as the result of a delay in the adjustment between the reaction velocities of glycogen breakdown and glycogen formation in the liver. 2. In the diabetic the same physiologic process takes place on a greatly magnified scale. Hypoglycemias, caused by overdoses of insulin, entail in the diabetic patient excessive degrees of hyperglycemia and glycosuria. Recurrence of this sequel over considerable periods of time progressively increases the instability of the patient and aggravates the disease.

9737

Vitamin C Saturation—Kidney Retention after an Intravenous Test Dose of Ascorbic Acid.

IRVING S. WRIGHT AND ELIZABETH MACLENATHEN.

From the Department of Medicine of the New York Post-Graduate Medical School and Hospital, Columbia University.

Following the observation that Vitamin C was not uniformly absorbed from the intestinal tract it was natural that the intravenous route of administration should be adopted for the test dose* and for therapy when utilization by the oral route was unsatisfactory. This method of studying the Vitamin C saturation of the body was described by the authors,[1, 2] using 1000 mg. doses and later by others[3, 4] with smaller dosage. When the 1000 mg. test dose in 10 cc. of physiologic solution of sodium chloride was given intravenously the normal urinary excretion during the 24 hours following was found to be not less than 500 mg. In deficient states the body uses more of the vitamin and the excretion is less. In saturated states the excretion may be markedly increased. Fever and the use

* The ascorbic acid used was supplied through the courtesy of Merck and Company, Rahway, N. J.

1 Wright, Irving S., *Am. J. Med. Sci.*, 1936, **192**, 719.

2 Wright, Irving S., Lilienfeld, Alfred, and MacLenathen, Elizabeth, *Arch. Int. Med.*, 1937, **60**, 264.

3 Ralli, E. P., Friedman, G. J., and Kaslon, M., PROC. SOC. EXP. BIOL. AND MED., 1937, **36**, 52.

4 Finkle, Philip, *J. Clin. Invest.*, 1937, **16**, 587.

of certain drugs may influence metabolism and excretion. At whatever level studied it was found that 80% or more of the amount excreted in the 24 hours was excreted in the first 5 hours.[2] Exceptions to this were very rare and we have never seen a reading below 75%. This was the basis of the 5-hour test after an intravenous test dose, the normal excretion, therefore, being not less than 400 mg. More than 200 such tests have confirmed our original studies and the conclusion that this represented the most satisfactory test for Vitamin C saturation suggested up until that time. The advantages of 5-hour studies over 24-hour studies are obvious if equally accurate. Single observations of the blood content of Vitamin C are too dependent upon intake or lack of intake of the vitamin during the preceding 48 hours. Urinary excretion studies without a test dose had proven very unreliable and the smaller doses for the intravenous method appear to us to be too markedly influenced by the immediately preceding diet.

There was, however, a weakness in this and all similar tests which we pointed out.[2] Having overcome the factor of faulty absorption from the gastro-intestinal tract we were still confronted with the possible factor of faulty elimination through the kidneys. We suggested that a parallel blood curve determined during the 5-hour test would probably enable us to derive the information regarding kidney excretion and provide a more completely satisfactory saturation test. We have, therefore, proceeded with such studies as follows:

The patient was permitted his normal diet with no increase in citrus fruits (since the amount of Vitamin C taken in the ordinary diet in 24 hours does not appreciably alter the findings when 1000 mg. doses are used) but fasted on the morning of the test. All possible urine was voided and discarded. Control specimens of blood were taken and 1000 mg. of ascorbic acid in 10 cc. of physiologic saline was injected intravenously. Specimens of blood and urine were collected and analyzed for Vitamin C content at 15 minutes, 1½ hours, 3 hours and 5 hours after the injection respectively.†

We had previously reported[2] typical blood curves following such a procedure with individuals in varying states of Vitamin C sat-

† The vitamin C in the urine was determined by a modification of Tillman's 2.6-dichloraphenolindophenol method[5] and in the blood by the method of Farmer and Abt.[6].

[5] Tillman, J., Hirsch, P., and Jackisch, J., *Z. f. Untersuch d. Libersmith*, 1932, **63**, 241.

[6] Farmer, C. J., and Abt, A., PROC. SOC. EXP. BIOL. AND MED., 1935, **32**, 1625.

TABLE I.

Intravenous 1-gram Test for Vitamin C Saturation. Typical Blood and Urine Figures in Patients with and without Renal Disease.

	History	Control Blood mg. %	15 min. Blood mg. %	15 min. Urine mg.	1½ hr. Blood mg. %	1½ hr. Urine mg.	3 hr. Blood mg. %	3 hr. Urine mg.	5 hr. Blood mg. %	5 hr. Urine mg.	Total Urine mg. C
M.A.	C intake excellent. No renal disease	1.2	8.6	64.5	4.4	440.3	3.0	189.7	2.4	75.2	789.7
H.R.	C intake poor. No renal disease	.33	3.3	10.0	1.3	112.7	.86	78.0		1.8	131.3
C.D.	C intake good, Glom. neph. No nitro. retention	.88	4.7	110.4	2.4	273.0	1.6	89.6	1.4	51.1	524.1
M.T.	C intake excellent. Malig. Hyper. N.P.N. 75 mg.	1.5	4.6	2.1	4.1	26.3	4.1	23.7	2.2	26.0	78.1
F.D.	C intake poor. Glom. neph. N.P.N. 53 mg.	Broke in centrifuge	6.1	6.8	2.6	19.4	1.6	10.8	1.4	5.3	42.3

uration but with no evidence of retention at the kidney threshold. These curves were confirmed and we then performed the same tests in patients with several types of renal disease to see whether retention of this vitamin occurred as a result of certain types of kidney damage. In cases illustrating some of the possible types of results the findings were as shown in Table I.

The curves of patients M. A. and H. R. were selected as being typical of those seen in individuals without renal retention of Vitamin C. The 15-minute blood reading is always the highest and there is a fairly sharp drop with the blood level returning well toward the control level within 5 hours. The general form of the curve is similar whether the patient is unsaturated or saturated with Vitamin C, the main difference being in the height of rise. The urinary excretion curve is also similar in form regardless of degree of saturation of the individual in that the peak is reached in 1½ hour specimen followed by a rapid return toward the control level. Again the difference rests in the height of the rise.

Patient C. D., a typical case of glomerulonephritis, had a good dietary history for Vitamin C. There was no nitrogenous retention. Both the blood and urinary curves for Vitamin C were typical for individuals with normal saturation and no renal retention of Vitamin C.

Patient M. T. was suffering from advanced malignant hypertension with kidney damage and nitrogenous retention in the blood (N.P.N. 75 mg. per 100 cc. One week later 125 mg. per 100 cc.). In spite of the preceding excellent dietary history for Vitamin C the low urinary excretion would lead one to believe that the body was very low in the vitamin unless a blood curve were also followed. The blood figures show a retention of the Vitamin C in the blood stream probably because of faulty renal excretion. This avoids an error of interpretation inevitable with the urinary excretion studies alone.

Patient F. D. was suffering from glomerulonephritis with nitrogenous retention in the blood. (N.P.N. 53 mg. per 100 cc. One week later 75 mg. per 100 cc.) The dietary history for Vitamin C was only fair. In this patient the blood curve would appear to be normal in form without renal retention but the urinary curve demonstrates that this was not due to excretion through the kidneys. The most likely explanation rests in the probability of very rapid utilization by the tissues due to their previous dietary depletion.

Thus far we have obtained evidence of Vitamin C renal retention in cases with nitrogenous retention only, but not in all such patients.

Further studies may show that this phenomenon may occur under other conditions also.

Conclusions. 1. The intravenous test dose method for the determination of Vitamin C saturation in the body by the study of the urinary excretion eliminates the factor of uncertain absorption of the ascorbic acid from the gastro-intestinal tract, but the problem of faulty kidney elimination remains. 2. In order to properly evaluate this factor a study of the blood curve for possible renal retention is essential. 3. A test is outlined which permits a more complete study of Vitamin C saturation. 4. Results illustrating certain types of curves obtained with and without renal retention are presented and interpreted. Thus far retention of Vitamin C has been noted in patients with marked nitrogenous retention only. 5. All patients with nitrogenous retention do not have Vitamin C retention, but renal retention of Vitamin C may occur. To our knowledge this has not been demonstrated before.

9738

Sexual Abnormalities in an Inbred Strain of Mice.

ELIZABETH FEKETE. (Introduced by C. C. Little.)
Roscoe B. Jackson Memorial Laboratory, Bar Harbor, Maine.

An interesting sexual abnormality was observed in the Little-Murray dilute brown strain of mice. To date this abnormality has been observed in 10 animals, and is evidently hereditary. All the abnormal individuals were descendants of the same pair of mice, the ancestors of which were inbred by brother to sister matings for many generations. A pedigree chart (Table I) gives further details.

Mouse No. 6 was 23 months old when killed. Externally the animal was a normal female. Internally no female sex organs were present. A large nodule was found in the peritoneal cavity. Microscopical sections showed that the nodule was surrounded by a fibrous capsule. A few definitely recognizable but atrophic seminiferous tubules were present near the periphery. The rest of the tissue was composed of diffusely distributed large cells, of embryonal type, and was diagnosed as embryonal carcinoma of the testis (Fig. 1).

Mouse No. 323 was 20 months old when killed. At autopsy a large, yellow, necrotic nodule was found on the right side, half way between the kidney and the bladder. On the left side a small oval