

STUDIES ON CARBOHYDRATE METABOLISM IN PATIENTS WITH GASTRIC CANCER. DEFECTIVE HEPATIC GLYCOGENESIS; EFFECTS OF ADRENO-CORTICAL EXTRACT¹

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INTRODUCTION

A number of metabolic dysfunctions exist in patients with gastric cancer and may contribute to the malnutrition which often occurs in these patients in spite of an adequate diet (1-3). Thus there has been demonstrated an intractable hypoproteinemia which persists in the presence of body tissue repletion (4). Evidence also has been obtained for alterations in the water and electrolyte metabolism of these patients (5).

The present report deals with experiments designed to study carbohydrate metabolism in patients with gastric cancer. It was found that glucose administered by stomach tube to patients with gastric cancer is not transformed into hepatic glycogen and that this defective hepatic glycogenesis can be corrected by the administration of adrenal cortical extract.

PLAN OF STUDY

1) *Liver glycogen depletion after a 12-hour fast.* The concentration of hepatic glycogen was first measured in liver biopsies obtained at laparotomy from 38 patients with gastric cancer after a 12-hour fast. These findings were controlled by similar studies in 14 patients with benign gastric and duodenal lesions.

2) *Hepatic glycogenesis from administered dextrose.* In a second experiment, nine patients with gastric cancer were given 250 gm. of dextrose in water by stomach tube divided into five doses given at two-hour intervals for ten hours preceding the operation at which time a liver specimen was obtained for determination of glycogen. This procedure was repeated on 15 patients with benign gastric lesions.

3) *The effect of adrenal cortical extract on hepatic glycogenesis from administered dextrose.* Fourteen pa-

tients with gastric cancer were given dextrose as outlined above, and, in addition, received 10-30 ml. of Upjohn's aqueous adreno-cortical extract intramuscularly divided into five doses given every two hours during the ten hours preceding operation.

4) *The effect of insulin on hepatic glycogenesis from administered dextrose.* In six patients with gastric cancer, 5-12 units of insulin were given intramuscularly together with each of five doses of 50 gm. of dextrose administered by stomach tube prior to liver biopsy.

5) *Studies on regulation of blood sugar in patients with gastric cancer.* Intravenous glucose tolerance tests were performed on seven normal subjects and on 13 patients with gastric cancer. In three patients with gastric cancer, this was repeated three times at two-hour intervals. Intravenous insulin tolerance tests were done on five normal subjects and on five patients with gastric cancer.

The effect of a 62-hour fast on blood sugar and urinary nitrogen excretion was studied in three normal subjects and in four patients with gastric cancer. This fasting experiment was designed to test the stability of blood sugar concentration under stress as well as to give information on the extent of hepatic gluconeogenesis from endogenous sources.

METHODS

1. Preparation of patients and biopsies

In the ten hours preceding laparotomy, the patients were either fasted completely or received the medication mentioned (*vide supra*). The amount of residual dextrose solution in all cases was aspirated through the stomach tube at the time of operation, and was found negligible in those cases included in this series. In addition to the medications mentioned uniform pre-operative sedation was employed in all cases. Most of the cases were operated on under pentothal-ether preceded in a few cases by local and spinal anesthesia.

Liver biopsies⁵ were taken immediately upon entering the abdominal cavity and consisted of a piece of hepatic tissue weighing approximately 0.5-1.0 gm. taken from the edge of the right lobe of the liver. This tissue was immediately transferred into a tared dish, weighed and placed in 30 per cent potassium hydroxide for glycogen estimation.

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II. Determination of liver glycogen; methods of glucose and insulin tolerance tests; other chemical methods

The liver glycogen was determined by the method of Good, Kramer and Somogyi (6). The glucose tolerance tests were performed by the method of Thorn and associates (7). The dietary preparation periods ranged from three to 62 days. Capillary blood was taken for blood sugar determinations by the method of Somogyi, Shaffer-Hartmann (8) after protein precipitation according to Folin-Wu as modified by Van Slyke and Hawkins (9).

One-tenth of a U.S.P. unit of crystalline insulin per kg. of body weight was used in the intravenous tolerance tests (10).

In the balance studies, nitrogen was determined by a Kjeldahl method in diets and urine.

RESULTS

(1) Degree of liver glycogen depletion after a 12-hour fast

The values obtained for liver glycogen in the fasting patients were identical in the control and in the cancer group (Figure 1, Tables I and Ia).

(2) Hepatic glycogenesis from administered dextrose

The concentration of hepatic glycogen in patients with benign gastric and duodenal lesions following

TABLE I
Benign gastric lesions—no treatment

Liver glycogen gm./100 gm.	Hospital Case No.	Age	Sex	Diagnosis
0.4	56612	35	m	jejunal ulcer
0.4	77727	40	m	gastric ulcer
0.5	75594	52	f	gastric ulcer
0.9	79352	57	m	gastric ulcer
1.3	65722	58	m	gastritis
1.4	64874	63	f	gastritis
1.6	76358	69	m	duodenal ulcer
1.8	71505	51	m	duodenal ulcer
2.8	64784	57	f	peptic ulcers
2.8	76509	50	m	gastric ulcer
3.1	78661	18	m	duodenal cyst
3.6	69269	55	m	gastric ulcer
3.6	64791	60	m	gastric ulcer
4.2	79589	40	m	duodenal ulcer

2.0 average value.

the administration of 250 gm. of dextrose ranged from 4.6 gm./100 gm. of tissue to 9.7 gm./100 gm. of tissue and averaged 7.6 gm./100 gm. of tissue (Figure 1, Tables II and IIa).

In contrast to this, the concentration of hepatic glycogen in patients with gastric cancer under the same conditions ranged from 1.1 gm./100 gm. of tissue to 6.0 gm./100 gm. of tissue (Figure 1).

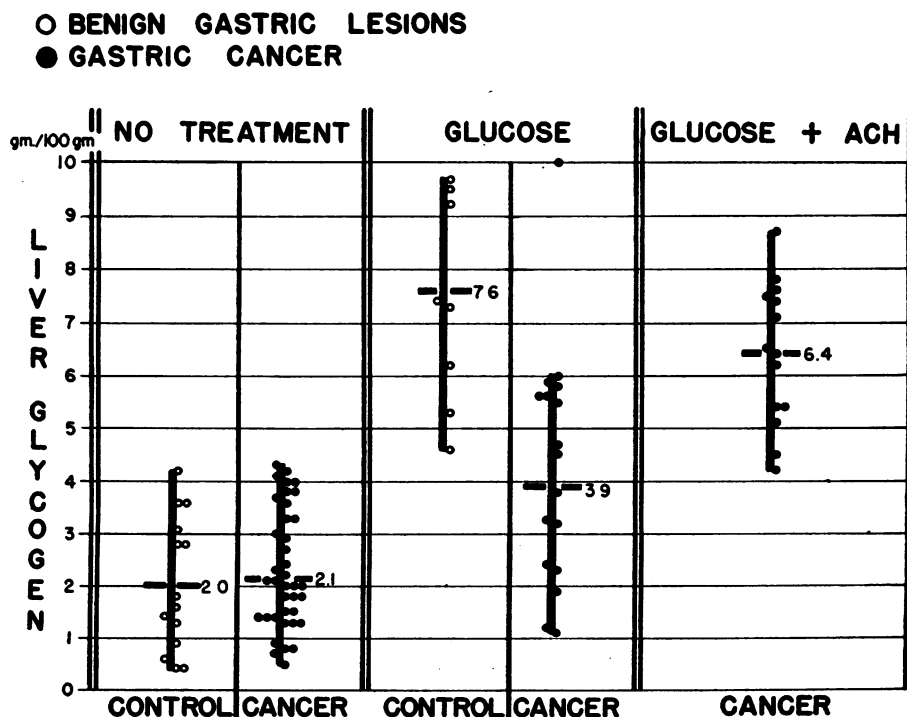


FIG. 1. CONCENTRATION OF LIVER GLYCOGEN IN PATIENTS WITH GASTRIC CANCER AND WITH BENIGN GASTRIC LESIONS

TABLE Ia
Gastric cancer—no treatment

Liver glycogen	Hospital Case No.	Age	Sex	Tumor*	Metastases†	
					Liver	Elsewhere
gm./100 gm.						
0.5	66224	53	m	o	—	+
0.7	77377	41	f	o	—	+
0.8	70734	53	f	o	—	+
0.8	68786	46	m	o	—	+
0.9	77532	45	m	o	—	+++
1.3	64441	60	m	i	—	+++
1.3	75766	64	m	o	—	+++
1.3	64910	58	m	o	—	+
1.4	68971	63	m	i	+	—
1.4	77529	35	f	o	—	+
1.4	64216	62	m	i	—	+++
1.5	71497	50	m	i	—	+++
1.5	65824	57	m	i	—	+++
1.8	64409	75	f	o	—	—
1.8	66457	37	m	i	—	+++
1.8	64331	59	m	i	+	+++
2.0	64866	66	m	o	—	+
2.0	64744	76	f	o	—	+++
2.0	65604	65	m	o	—	+++
2.1	68997	60	f	i	—	+
2.1	64518	65	m	i	+	+++
2.2	79195	58	m	i	+	+++
2.3	70528	50	f	i	+	+
2.4	64927	70	m	i	—	+
2.7	65198	54	m	i	—	+++
2.9	66545	54	m	i	+	—
3.0	64715	59	f	o	—	+
3.3	70748	62	f	o	—	+++
3.3	64821	63	m	o	—	—
3.6	64391	46	m	o	—	+++
3.7	68958	62	m	i	—	+++
3.8	77655	56	m	i	+	—
3.8	63706	48	f	i	—	+++
4.0	69689	43	m	i	—	+++
4.0	65407	56	f	o	—	+
4.1	70995	49	m	i	—	+++
4.2	65083	46	m	i	—	—
4.3	64618	48	f	i	—	+

2.1 average value.

* Tumor operable = o; tumor inoperable = i.

† Single or occasional metastasis = +; massive, wide-spread metastases = +++.

TABLE II
Benign gastric lesions—glucose

Liver glycogen	Number	Age	Sex	Diagnosis
gm./100 gm.				
4.6	71428	54	m	duodenal ulcer
5.3	69499	55	m	gastric ulcer
6.2	65622	59	m	duodenal ulcer
7.3				gastric ulcer
7.4	65821	63	f	abdominal aorta aneurysm
9.1	79862	59	f	duodenal ulcer
9.2	63450	49	f	gastric ulcer
9.5	68194	58	m	gastric polyposis, benign
9.7	75119	30	f	pancreatic cyst

7.6 average value.

TABLE IIa
Gastric Cancer—glucose

Liver glycogen	Hospital Case No.	Age	Sex	Tumor†	Metastases	
					Liver	Elsewhere
gm./100 gm.						
1.1	70702*	42	m	o	—	+
1.2	71443	64	m	o	—	+
1.9	70753	69	m	i	+	+++
2.3	68530	65	m	i	+	—
2.4	79930	71	m	i	—	+++
3.2	81158	69	m	i	—	+++
3.3	81115	58	f	i	+	+++
3.8	73025	64	f	o	—	—
4.5	65586	62	m	i	+	+
4.7	73406	70	m	i	—	+
5.5	71429	64	m	o	—	—
5.6	71017	53	m	i	—	+
5.8	81560	60	m	i	—	+++
5.9	65834	53	m	i	+	+
6.0	79157	58	m	i	+++	+

3.9 average value.

* Lymphosarcoma of stomach.

† Tumor operable = o; tumor inoperable = i.

(There was one exception with a value of 10 gm./100 gm. of tissue in a case of cancer of the esophageal end of the stomach in a woman of 28, the youngest in the entire series.) Excluding this one extreme value the average was 3.9 gm./100 gm. of tissue.

(3) *The effect of adrenal cortical extract on hepatic glycogenesis from administered glucose*

In 14 patients with gastric cancer who had received adrenal cortical extract together with dextrose, the hepatic concentration of glycogen ranged from 4.2 gm./100 gm. of tissue to 8.7 gm./100 gm. of tissue, with an average value of 6.4 gm./100 gm. of tissue (Figure 1 and Table III).

(4) *The effect of insulin on hepatic glycogenesis from administered dextrose*

The administration of insulin together with dextrose in six patients with gastric cancer resulted in an insignificant depression of their liver glycogen to an average value of 3.6 gm./100 gm. of tissue (Figure 2).

(5) *Studies on the regulation of blood sugar in patients with gastric cancer*

There were minor differences between the glucose tolerance curves in patients with gastric can-

TABLE III
Gastric cancer—glucose + ACH

Liver glycogen gm./100 gm.	Hospital Case No.	Age	Sex	ACH amount cc.	Tumor†	Metastases	
						Liver	Else-where
4.2	73016	49	m	20	o	—	—
4.5	73033	65	m	30	o	—	+++
5.1	72419	48	f	10	i	—	+++
5.4	72404	66	m	10	o	—	—
5.4	72985	64	m	30	i	—	+
6.2	73548*	59	m	30	o	—	+
6.4	72285	63	m	10	o	—	—
6.5	72615	57	f	20	o	—	+
7.1	72778	69	f	20	o	—	—
7.4	73396	49	m	30	o	—	—
7.5	72227	37	f	20	o	—	—
7.6	73457	70	m	30	o	—	+
7.8	72497	61	f	20	i	—	+++
8.7	72938	68	f	20	i	—	+++

6.4 average value.

* Epidermoid carcinoma of esophagus.

† Tumor operable = o; tumor inoperable = i.

cer and those of patients free of cancer. Thus the average value of the peak of the tolerance curve was 22 mg. per cent higher in the patients with gastric cancer. The slope of the disappearance curve was similar in both groups. The fasting blood sugar levels of patients with gastric cancer were on the average 12 mg. per cent higher than in the controls.

The response to a test dose of insulin was the same in a group of four patients with gastric cancer as in a control group of five normal subjects (Figure 3).

The response to repeated intravenous glucose tolerance tests (every two hours) was essentially

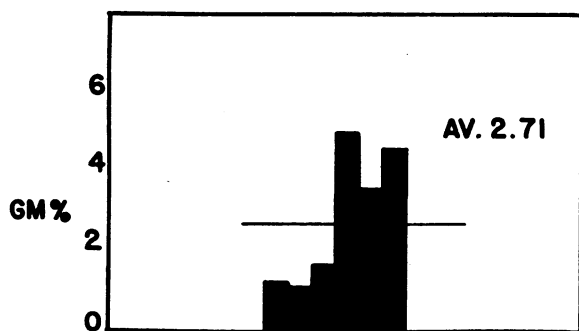


FIG. 2. THE CONCENTRATIONS OF GLYCOGEN IN THE LIVERS OF PATIENTS WITH GASTRO-INTESTINAL CANCER AFTER FEEDING OF 250 GM. GLUCOSE AND ADMINISTRATION OF 30-60 U OF INSULIN

EFFECT OF INSULIN (0.1 U/4g BW) ON BLOOD SUGAR

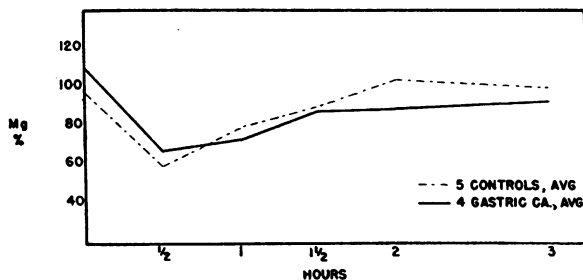


FIG. 3

EXAMPLES OF REPEATED GLUCOSE TOLERANCE TESTS IN A PATIENT WITH GASTRIC CANCER AND IN A NORMAL OF SAME AGE

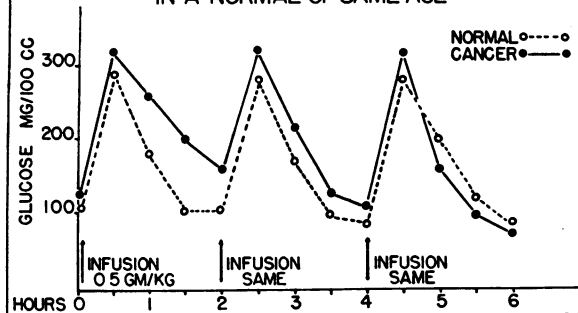


FIG. 4

FASTING EXPERIMENTS

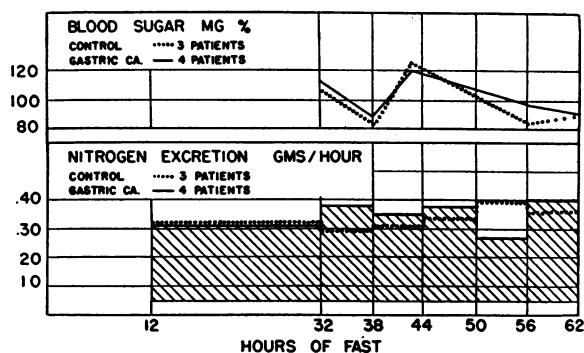


FIG. 5. NITROGEN EXCRETION IN CONTROLS AND GASTRIC CANCER PATIENTS

the same in patients with gastric cancer as in normals (Figure 4).

The blood sugar concentration in patients with gastric cancer during a 62-hour fast closely resembled that found in patients without gastric cancer under similar conditions. The nitrogen excretion in both groups was the same during the fast (Figure 5).

DISCUSSION

These results demonstrate that patients with gastric cancer fail to transform glucose given by stomach tube into hepatic glycogen at a normal rate. The administration of adrenal cortical extract corrects this abnormality. However, the defect is not similar to that prevailing in adrenalectomized animals or in patients with Addison's disease where blood sugar and hepatic glycogen as well as the urinary excretion of nitrogen are lowered by fasting (11, 12). Furthermore, such subjects exhibit marked insulin sensitivity.

The gluconeogenesis from endogenous sources in patients with gastric cancer proceeds normally as manifested by normal fasting concentrations of liver glycogen and by normal behavior of blood sugar and nitrogen excretion during a 62-hour fast (Figure 3). Furthermore, these patients responded normally to the separate intravenous injection of dextrose and insulin as well as to the repeated injection of test doses of dextrose at two-hour intervals. The slight differences in the fasting blood sugar levels and in the peak blood sugar levels during the glucose tolerance tests were satisfactorily explained by the age difference that existed between the control (young) and the cancer group (old) (13). There were no significant differences when individuals of equal age only were compared.

One is thus faced with a dysfunction of carbohydrate metabolism which, while corrected by adrenal hormones, is unlike the disturbance found in adrenalectomized animals. It would appear possible that glucose was poorly absorbed from the gastro-intestinal tract in patients with gastric cancer. However, a similar situation where intestinal malabsorption is ruled out prevails following the intraperitoneal administration of dextrose (14) in mice bearing Sarcoma 180.

The mechanisms of this defective hepatic glycogenesis from administered glucose are as yet poorly understood and call for further studies.

The abnormality is independent of the existence of tumor metastases in the liver or elsewhere and there is no relationship between the size of the total tumor mass and the severity of the disturbance.

The prompt amelioration of this defect by the simultaneous pre-operative administration of glu-

cose and adrenal cortical extract would seem to indicate the use of these measures to prepare patients for major abdominal operations, especially for surgery in gastric cancer.

SUMMARY

1. Patients with gastric cancer fail to transform into hepatic glycogen dextrose that has been given by stomach tube.
2. This metabolic defect is corrected by the injection of adrenal cortical extract.
3. Insulin has no effect on the disturbed hepatic glycogenesis from administered dextrose.
4. This hepatic glycogenesis from endogenous sources in a 12-hour fast is normal and no evidence of disturbed glycogenesis was obtained in a 62-hour fast. The regulation of the peripheral blood sugar and the sensitivity to insulin are normal in patients with gastric cancer.

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