Effect of Low Caloric Diet on Endogenous Carbon Monoxide Production: Normal Adults and Gilbert's Syndrome (37603)

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In 1906 Gilbert (1) observed that caloric deprivation produced an elevation of serum bilirubin concentration. Recently this observation has been confirmed (2–4) and various mechanisms have been suggested for the indirect hyperbilirubinemia that occurs (2, 3). Studies by Bloomer *et al.* (3) showed that fasting-induced hyperbilirubinemia was secondary to impaired hepatic clearance.

Since the catabolism of heme yields carbon monoxide (CO) and bilirubin in equimolar amounts (5, 6), measurement of endogenous CO production therefore reflects heme turnover (7) and bilirubin production (5, 6). Because of the possibility that fasting itself produces an increase in heme turnover (and therefore CO and bilirubin production), we studied the effect of caloric deprivation on the endogenous production of CO.

Subjects and Methods. Five normal volunteers (two male and three female) and nine patients with Gilbert's syndrome (all male) were studied. All subjects were carefully screened to preclude intake of any drugs or diagnostic agents known to influence the metabolism of bilirubin or CO. Informed consent was obtained from all participants in this study. Serum bilirubin concentration (8) and endogenous CO production were determined before and after the subjects had consumed a 400 calorie diet/24 hr for 48 hr. The diet contained approximately 46 g of carbohydrate, 16.5 g of protein, and 14.5 g of fat/24 hr. In three of the patients with Gilbert's syndrome, additional studies were performed after 18 to 24 hr of caloric deprivation. Endogenous CO production was measured utilizing a closed rebreathing system (9). The CO content of venous blood was analyzed by the gas chromatographic technique of Collison, Rodkey and O'Neal (10). Standard hematologic and liver function studies were performed prior to the onset of the caloric restriction, and included serum lactic acid dehydrogenase, alkaline phosphatase, transaminase, and total and direct bilirubin (Table I). Additional studies on the patients with Gilbert's syndrome included hemoglobin electrophoresis (11), red blood cell glucose-6-phosphate dehydrogenase, 6-phosphoglyconate dehydrogenase, pyruvate kinase (12)[2] and osmotic fragility (13). Liver biopsies performed in four of the nine patients with Gilbert's syndrome proved normal.

The diagnosis of Gilbert's syndrome was made in the presence of persistent unconjugated hyperbilirubinemia with normal concentration of serum conjugated bilirubin as determined by the investigations listed above (14).

Results. In the control subjects the serum bilirubin concentration rose from 0.44 ± 0.15 to 0.78 ± 0.40 mg/100 ml after the low caloric diet (mean increase of 77%; $p = 0.07$), while the rate of CO production did not change significantly ($p > 0.3$) (Table II). The subjects with Gilbert's syndrome had a mean rise of serum bilirubin concentration of 138% ($p < 0.001$) but no significant change in CO production (0.41 ± 0.12–0.47 ± 0.12 μmoles/kg/hr; $p > 0.1$)

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[2] Performed through the courtesy of Dr. Bertil Glader.

TABLE I. General Laboratory Data in Control and Gilbert's Syndrome Subjects.

Subjects	Sex	Age	Hemoglobin (g/100 ml)	Hematocrit (%)	Reticulocytes (%)	LDH (Wrob. units/ml)	SGOT (Karmen units/ml)
Control							
D.C.	F	23	14.3	43	1.1	285	18
J.M.	M	24	14.5	43	1.2	300	20
R.D.	F	23	12.9	38	0.9	275	17
J.L.	M	23	14.7	46	1.0	225	13
A.A.	F	24	13.0	39	1.3	275	19
Mean			13.9	42	1.1	272	17
±			0.9	3	0.2	28	3
Gilbert's syndrome							
J.K.	M	25	16.3	48	1.3	250	25
J.L.	M	25	17.0	44	1.1	215	12
A.I.	M	21	15.4	42	1.4	250	22
C.I.	M	21	14.9	42	1.3	270	13
J.B.	M	19	14.2	41	1.1	255	9
M.B.	M	21	14.0	42	0.3	295	18
F.W.	M	22	13.6	43	1.3	—	—
T.T.	M	34	14.5	43	1.2	250	20
W.H.	M	22	15.0	42	1.3	270	21
Mean			15.0	43	1.1	257	18
±			1.1	2	0.3	23	6

(Table III).

Discussion. These studies indicate that the increase in the level of serum unconjugated bilirubin after caloric restriction is not due to an increase in heme turnover. While Bloomer *et al.* (3) suggested that an increase in heme turnover may make a small contribution to the observed increase in plasma

TABLE II. Normal Subjects: Bilirubin and CO Production Studies Before and After 400 Calorie Diet Restriction for 48 hr.

Subject	Study	Total serum bilirubin concn (mg/100 ml)	CO		Hemoglobin (g/100 ml)	Reticulocytes (%)
			Production (μmoles/hr/kg body wt)	Space (ml)		
D.C.	Baseline	0.3	0.41	878	14.3	1.1
	After 48 hr, 400 cal	0.5	0.42	858	13.3	1.2
J.M.	Baseline	0.6	0.32	1056	14.5	2.2
	After 48 hr, 400 cal	0.6	0.44	1158	13.7	1.7
R.D.	Baseline	0.6	0.33	816	13.3	0.9
	After 48 hr, 400 cal	1.3	0.29	752	13.1	1.0
J.L.	Baseline	0.4	0.36	1110	14.7	1.0
	After 48 hr, 400 cal	1.1	0.79	1152	15.7	1.3
A.A.	Baseline	0.3	0.28	622	13.0	1.3
	After 48 hr, 400 cal	0.4	0.32	556	14.3	1.4
Before		0.44 ± 0.15	0.34 ± 0.05	896 ± 196	14.0 ± 0.8	1.3 ± 0.5
After		0.78 ± 0.40	0.45 ± 0.20	895 ± 261	14.0 ± 0.1	1.3 ± 0.3
p		$=0.07$	$=0.3$	>0.5	>0.5	>0.5

TABLE III. Gilbert's Syndrome Subjects: Bilirubin and CO Production Studies Before and After 400 Calorie Diet Restriction for 48 hr.

Subject	Study	Total serum bilirubin concn (mg/100 ml)	CO Production (μmoles/hr/kg body wt)	CO Space (ml)	Hemoglobin (g/100 ml)	Reticulocytes (%)
J.K.	Baseline	0.9	0.48	875	14.0	2.0
	After 24 hr, 400 cal	1.8	0.56	868	16.3	1.9
	After 48 hr, 400 cal	2.4	0.65	886	15.5	1.8
J.L.	Baseline	1.3	0.46	961	17.0	1.8
	After 48 hr, 400 cal	3.6	0.63	923	16.7	1.1
A.I.	Baseline	2.6	0.55	740	15.4	2.4
	After 48 hr, 400 cal	3.6	0.47	758	16.2	1.5
C.I.	Baseline	1.4	0.59	711	15.2	1.7
	After 48 hr, 400 cal	4.6	0.55	719	14.9	2.3
J.B.	Baseline	1.4	0.49	530	14.2	0.9
	After 48 hr, 400 cal	3.9	0.44	549	14.0	1.1
M.B.	Baseline	0.9	0.30	529	13.0	0.6
	After 48 hr, 400 cal	2.1	0.36	522	13.6	0.3
F.W.	Baseline	1.1	0.30	608	13.5	2.4
	After 48 hr, 400 cal	2.7	0.39	637	13.6	—
T.T.	Baseline	0.8	0.31	688	13.4	1.5
	After 18 hr, 400 cal	1.0	0.39	656	13.9	1.6
	After 48 hr, 400 cal	1.6	0.46	586	14.2	1.8
W.H.	Baseline	1.7	0.26	829	15.3	2.0
	After 24 hr, 400 cal	3.1	0.39	818	14.8	2.2
	After 48 hr, 400 cal	3.7	0.32	740	15.0	2.0
	Before	1.3 ± 0.55	0.41 ± 0.12	719 ± 150	14.6 ± 1.3	1.6 ± 0.6
	After 48 hr	3.1 ± 0.98	0.47 ± 0.12	702 ± 191	14.9 ± 1.1	1.5 ± 0.6
	p	<0.001	$=0.11$	$=0.3$	>0.2	>0.5

bilirubin concentration, the differences in the rates of CO production in their five subjects both before and after caloric restriction was not significant ($p > 0.05$). Our results thus support their conclusion that impaired bilirubin clearance is the primary mechanism involved.

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