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THE EFFECT OF BETAINE ON HUMAN SERUM LIPOPROTEINS

EDWARD H. STRISOWER, M.D., PH.D., JOHN W. GOFMAN, M.D., PH.D., PAUL ELMLINGER, M.D., BEVERLY STRISOWER, A.B. AND CLETUS L. KRAG, M.D.

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THE EFFECT OF BETAINE ON HUMAN SERUM LIPOPROTEINS*

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The Donner Laboratory of Medical Physics, Lawrence Radiation Laboratory, University of California, Berkeley, California and the Napa State Hospital, and Stockton State Hospital of the California Department of Mental Hygiene

ABSTRACT

The effect of long-term administration of betacyamine, a mixture of betaine and guanidoacetic acid, on the concentration of serum lipoproteins was studied in 6 out-patients. A similar controlled study was made of the effect of betaine on the concentration of serum lipoproteins in 3 groups of institutionalized chronic psychiatric patients. A definite hyperlipoproteinemic and hypercholesterolemic effect of betaine was discovered, involving all low-density serum lipoproteins (except the $S_f^0$100–400 class) and the major high-density serum lipoprotein class, HDL-3. The largest increases were observed in the $S_f^0$0–12 class. The increased levels of low-density serum lipoprotein resulted in concomitant elevations in atherogenic index values. Female patients showed significantly greater elevations in the concentrations of $S_f^0$0–12 and $S_f^0$12–20 serum lipoproteins and total cholesterol than did male patients. The association of high atherogenic index values with an increasing incidence of morbidity and mortality from coronary artery disease contraindicates the use of hyperlipoproteinemic agents such as betaine in the treatment of patients with coronary artery disease. Biochemical mechanisms by which betaine may produce its hyperlipoproteinemic effect are discussed.

REPORTS that betaine lowers the level of total serum cholesterol (1) and that it is beneficial in the treatment of human coronary atherosclerosis in man led to the present study of the effect of betaine on the concentration of human serum lipoproteins.

CLINICAL MATERIAL AND METHODS

Out-patients (betacyamine)

Six patients (3 males and 3 females) were seen on an out-patient basis for periods ranging from eleven to thirty-six months, during which time from 30 to 60 blood specimens were obtained on each. Table 1 contains a summary of the clinical data. All blood

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samples were analysed for concentration of serum lipoproteins and total serum cholesterol by methods previously reported (2, 3).

The preparation administered was betacyamine, a mixture of betaine and guanidoacetic acid (glycocyamine). Blood samples were obtained before treatment, during the course of treatment, and following cessation of treatment. Betacyamine was administered orally in gradually increasing doses (increments of 5 Gm. for betaine and of 1 Gm. for glycocyamine), until a total daily maintenance dose of 25 Gm. of betaine and 5 Gm. of glycocyamine was reached.

Hospitalized patients (betaine)

The effect of betaine without glycocyamine was studied in 3 different groups of chronic ambulatory psychiatric patients hospitalized in 2 state mental institutions.

Group 1 consisted of 13 male and 3 female patients ranging in age from 25 to 63 years, hospitalized in institution A. The men received betaine daily for a period of one month, the women for sixteen weeks. All received a total daily dose of 15 Gm. of betaine administered in fruit juice in three fractional doses of 5 Gm. each. Blood samples were obtained after two and four weeks of this medication in the men, and after two, four, seven, ten and twelve weeks in the women. Weight and blood pressure were recorded each time. Three blood samples spaced one week apart were obtained on all patients before administration of betaine, and 2 samples were obtained at varying intervals following cessation of betaine therapy. Lipoprotein and serum cholesterol determinations were made on all blood specimens.

Group 2 consisted of 24 male patients ranging in age from 29 to 74 years, hospitalized in institution B. Of these, 5 (mean age 53 years) were studied concurrently as control subjects not receiving any medication. The remaining 19 (mean age 56 years) received 15 Gm. of betaine daily divided into two equal doses, for a period of twenty weeks. Blood samples were obtained serially during this 20-week period, as well as before and after treatment. Seventeen samples were obtained from each treated and control patient over a period of fourteen months. Thus the data on Group 2 are based on the analysis of 408 (17×24) blood specimens.

The results in Groups 1 and 2 suggested that female patients receiving betaine show a greater increase in the concentration of serum lipoproteins than do male patients. To test this impression, 17 female chronic psychiatric patients ranging in age from 24 to 60 years, hospitalized in institution A, were studied for a period of thirty-one weeks. They were designated Group 3, and included 7 controls (mean age 44 years) and 10 patients receiving betaine (mean age 44 years). The former received no medication; the latter ingested 15 Gm. of betaine daily in two equal doses, for a period of sixteen weeks. Nineteen blood samples were obtained from each patient—4 during the four-week pre-treatment period, 11 during the sixteen weeks of treatment, and 4 during the ten-week post-treatment period. Thus the data on Group 3 are based on the analysis of 323 (17×19) blood specimens.

RESULTS

In both the out-patient and in-patient studies it was found that administration of betaine produced an elevation in the concentration of certain of the low-density serum lipoproteins and of total serum cholesterol. Statistical analyses of the data showed that the elevation in the levels of $S_f^0$0–12 and $S_f^0$12–20 serum lipoproteins and of total serum cholesterol was

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highly significant, that the elevation of the $S_f^{\circ}20$–100 lipoprotein level was less consistent, and that there was no significant change in the level of $S_f^{\circ}100$–400 lipoproteins.

Tables 1 and 2 contain summaries of the data (and their statistical significance) obtained in the out-patient and in-patient study, respectively. Figure 1 shows mean serum lipoprotein concentrations charted in terms of weeks of betaine therapy in the 10 treated female patients of Group 3. A detailed discussion of the changes observed in each band of serum lipoproteins follows.

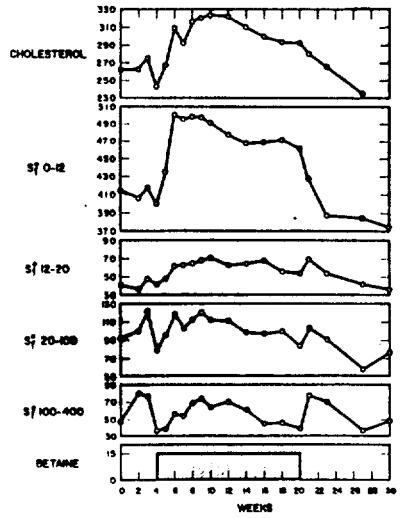

FIG. 1. Curves of the concentrations of serum lipoproteins and total cholesterol (mg. per 100 ml.) in relation to time of therapy (weeks) in 10 female patients receiving 15 Gm. of betaine daily.

Changes in $S_f^{\circ}0$–12 serum lipoprotein levels

In the out-patient study with betacyamine, 3 of the 6 patients (B.H., M.F. and M.J.) showed pronounced elevations (significant at the 0.1 per cent level) in the concentration of $S_f^{\circ}0$–12 lipoproteins, and 2 (G.R. and L.H.) showed somewhat smaller increases (significant at the 5 and 2 per cent level, respectively). It is of interest that the latter 2 patients initially had the abnormally elevated $S_f^{\circ}20$–100 lipoprotein levels characteristic of xanthoma tuberosum (4, 5). No definite statement can be made about the $S_f^{\circ}0$–12 values in the sixth patient (E.M.) because of the extremely elevated initial levels associated with xanthoma tendinosum (4, 5) which did not permit accurate partition between the $S_f^{\circ}0$–12 and $S_f^{\circ}12$–20 bands. Therefore the effect of betacyamine had to be evaluated on the combined bands of $S_f^{\circ}0$–20, which showed a pronounced elevation, significant at the 0.1 per cent level. This finding suggests that an extremely high initial concentration of $S_f^{\circ}0$–12 lipoproteins per se does not obviate the effect of betacyamine in raising the level of $S_f^{\circ}0$–20 lipoproteins.

A statistically highly significant and fairly large increase in $S_f^{\circ}0$–12 serum lipoprotein concentration was observed in all 3 groups of institutionalized patients (Table 2). Thus 15 of 16 treated patients in Group 1, 15 of 19

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TABLE 1. SUMMARY OF RESULTS IN 6 OUT-PATIENTS TREATED WITH BETACYAMINE (BETAINE + GLYCOCYAMINE)

Patient. Sex. Age. Diagnosis	S_f0–12			S_f12–20			S_f20–100			S_f100–400			Atherogenic index			Cholesterol		
	No treat.*	Treat.**	Change† & signif.	No treat.	Treat.	Change & signif.	No treat.	Treat.	Change & signif.	No treat.	Treat.	Change & signif.	No treat.	Treat.	Change & signif.	No treat.	Treat.	Change & signif.
B.H.—M55 Myocard. infarct (old)	350	425	+75 P <0.001	41	60	+19 P <0.001	70	78	+ 8 N.S.‡	22	22	0 N.S.	58	71	+13 P <0.001	227	266	+ 39 P <0.001
M.F.—F60 Hypertension, CVA	353	439	+86 P <0.001	43	60	+17 P <0.01	109	115	+ 6 N.S.	63	53	− 10 N.S.	73	84	+11 P <0.02	234	265	+ 31 P <0.01
M.J.—M64 Hypertension, CVA	460	540	+80 P <0.001	41	72	+31 P <0.001	74	112	+ 38 P <0.001	27	59	+ 32 P <0.001	71	97	+26 P <0.001	255	309	+ 54 P <0.001
G.R.—M48 Xanthoma tuberosum	109	148	+39 P <0.05	80	114	+34 P <0.02	561	628	+ 67 N.S.	826	572	−254 P <0.01	267	245	−22 N.S.	593	484	−109 P <0.01
L.H.—F47 Xanthoma tuberosum	151	178	+27 P <0.02	118	132	+15 N.S.	356	368	+ 12 N.S	47	73	+ 26 N.S.	106	118	+12 N.S.	270	278	+ 8 N.S.
E.M.—F52 Xanthoma tendinosum	1165	1649	+484 P <0.001	=S_f0–20			29	166	+137 P <0.01	0	14	+ 14 N.S	142	221	+79 P <0.001	651	783	+132 P <0.001

* The mean of all pre- and post-treatment values.
** The mean of all values obtained during treatment with betacyamine.
† Change is the difference between the mean of the values during treatment and the mean of the values before and after treatment.
‡ Not significant.
Note S_f0–12, S_f12–20, S_f20–100 and S_f100–400 lipoprotein and cholesterol values are expressed in mg./100 ml. of serum; atherogenic index values are expressed in units.

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TABLE 2. SUMMARY OF RESULTS IN 3 GROUPS OF HOSPITALIZED PATIENTS TREATED WITH BETAINE

	S_f0-12		S_f12-20		S_f20-100		S_f100-400		Cholesterol		Atherogenic index		HDL-1		HDL-2		HDL-3		Body weight	
	No trest.*	Trest.**	No trest.	Trest.	No trest.	Trest.	No trest.	Trest.	No trest.	Trest.	No trest.	Trest.	No trest.	Trest.	No trest.	Trest.	No trest.	Trest.	No trest.	Trest.
Group 1 (hosp. A) 13 males, 4 wks.	331	367 +36† P~0.02‡	38	46 + 8 P<0.01	79	110 +31 P<0.02	39	65 +26 n.s.§	213	238 +25 P<0.001	60	76 +16 P<0.01	23	35 +10 n.s.	41	50 +9 P<0.10	203	241 +38 P<0.001	141.8	141.9 +0.1 n.s.§
3 females, 16 wks.	371	500 +129	43	78 +35	63	74 +11	13	20 + 7	207	312 +105	58	80 +22	23	35 +12	85	89 +4	213	245 +32	100.3	101.2 +0.9
Group 2 (hosp. B) 19 males, 20 wks.	336	366 + 30 P<0.01	41	45 + 4 P<0.05	83	104 +21 P<0.01	38	47 + 9 n.s.	215	237 +22 P<0.001			25	28 + 3 n.s.	73	83 +10 P<0.01	144	210 +66 P<0.01	153.3	151.7 −1.6 n.s.
5 male controls	409	406 − 3	52	47 − 5	103	106 + 3	46	52 + 6	242	246 + 4			27	23 − 4	49	50 +1	179	188 + 9	153.9	153.3 −0.6
Group 3 (hosp. A) 10 females, 16 wks.	404	480 + 76 P~0.001	48	62 + 14 P<0.01	95	107 + 12 P~0.05	64	57 − 7 n.s.	265	306 + 41 P<0.001			28	37 + 9 P<0.001	98	89 − 9 P<0.01	227	251 + 24 P<0.01	136.8	137.0 +0.2 n.s.
7 female controls	352	358 + 6	44	45 + 1	61	64 + 3	18	14 − 4	233	243 +10			25	27 + 2	110	110 0	236	250 +14	126.8	127.1 +0.3

* The mean of all pre- and post-treatment values.
** The mean of all values obtained during treatment with betaine.
† Change is the difference between the mean of the values during treatment and the mean of the values before and after treatment.
‡ Significance of the change.
§ Not significant.
Note: All low and high density serum lipoprotein and cholesterol values are expressed in mg./100 ml. of serum; atherogenic index values are expressed in units; and body weight in pounds

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TABLE 3. SUMMARY OF DATA OBTAINED IN INDIVIDUAL PATIENTS IN GROUP 2 (19 MALES RECEIVING BETAINE FOR 20 WEEKS)

Patient	S_f°0-12			S_f°12-20	S_f°20-100			S_f°100-400	Cholesterol		
	No treatment*	Δ**	Signif. of Δ	Δ**	No treatment*	Δ**	Signif. of Δ	Δ**	No treatment*	Δ**	Signif. of Δ
B.A.	326	16	N.S.†	− 9	81	4	N.S.	4	203	−2	N.S.
C.A.	345	55	P <0.01	3	76	10	N.S.	− 3	226	24	N.S.
C.H.	326	38	P <0.05	1	94	19	P <0.05	− 5	230	20	P <0.01
D.E.	300	−77	P~0.02	13	185	94	P <0.01	112‡	215	8	N.S.
E.S.	207	−11	N.S.	− 3	63	15	N.S.	− 1	204	2	N.S.
F.R.	365	77	P <0.01	28‡	103	20	P <0.02	−15	214	47	P <0.01
F.U.	378	74	P <0.02	20‡	93	42	P~0.02	38‡	230	54	P <0.01
J.O.	336	4	N.S.	0	100	8	N.S.	−31	199	6	N.S.
J.O.S.	382	− 4	N.S.	− 7	88	15	N.S.	11	235	8	N.S.
K.R.	304	0	N.S.	− 2	81	7	N.S.	2	225	−4	N.S.
M.E.	226	50	P~0.01	−10	70	21	N.S.	26	162	31	P <0.02
P.A.	308	19	N.S.	− 8	82	26	P <0.05	10	212	17	N.S.
P.I.	512	73	P <0.01	−11	64	3	N.S.	− 1	328	33	P~0.02
S.C.	332	51	P <0.02	11	85	12	N.S.	8	206	34	P <0.01
S.H.	401	50	P <0.01	12	70	5	N.S.	−17	218	25	P~0.02
T.I.	330	56	N.S.	21‡	98	48	P <0.01	27	203	26	N.S.
W.A.	363	85	P <0.05	− 1	67	19	N.S.	0	225	55	P <0.01
W.I.	230	2	N.S.	4	58	19	N.S.	− 1	164	8	N.S.
W.I.L.	332	6	N.S.	− 2	24	− 5	N.S.	0	194	9	N.S.

* The mean of all pre- and post-treatment values (7-8 samples per patient).

** Difference between the mean of the values during treatment (8 samples per patient) and the mean of the values before and after treatment.

† Not significant.

‡ Statistically significant changes (P=0.05 to P=0.01).

Note: S_f°0-12, S_f°12-20, S_f°20-100 and S_f°100-400 lipoprotein and cholesterol values are expressed in mg./100 ml. of serum.

treated patients in Group 2, and all 10 treated patients in Group 3 showed increases in the serum level of this class of lipoproteins.

In Table 3 the individual changes in the 19 treated patients of Group 2 are listed. It may be seen that in 9 of the 19 there were statistically significant increases in the S_f°0–12 lipoprotein level and in only 1 was there a significant *decrease*. This patient (D.E.) initially had abnormally elevated levels of S_f°20–100 and S_f°100–400 serum lipoproteins. It is of interest that in the only other patient (Group 1) with a decrease in S_f°0–12 lipoprotein concentration there was also a marked elevation in the initial levels of S_f°20–100 and S_f°100–400 lipoproteins. Lack of sufficient information concerning factors regulating individual serum lipoprotein classes in individual subjects prevents interpretation of the peculiar reaction to betaine in these 2 patients.

Changes in S_f°12–20 lipoprotein levels

In the out-patient group of 6 subjects, the pattern of the S_f°12–20 serum lipoproteins reflected quite closely that of the S_f°0–12 lipoproteins. Thus the smaller elevations of S_f°12–20 occurred in the 2 patients with xanthoma

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tuberosum; in G.R. they were significant at the 2 per cent level, and in L.H. they were not statistically significant. Three of the remaining 4 patients (B.H., M.F. and M.J.) showed marked elevations in $S_f^{\circ}12$–20 concentration, significant at the 0.1, 1 and 0.1 per cent level, respectively. The high level of $S_f^{\circ}0$–20 lipoproteins in the patient with xanthoma tendinosum (E.M.) has already been mentioned.

In the hospitalized patients, there was a small though statistically significant increase in the mean level of $S_f^{\circ}12$–20 lipoproteins, with the women (Group 3) showing by far the largest mean increase (Table 2). In Table 3 it may be seen that for the individual male patients of Group 2 there were about equal numbers of plus and minus signs for the $S_f^{\circ}12$–20 value, though for 3 men (F.R., F.U. and F.L.) there was a statistically significant increase in Δ values, and no significantly negative Δ values were noted. In 12 of 13 male patients in Group 1 there were positive Δ values for $S_f^{\circ}12$–20; the single negative Δ value was not significant.

Changes in $S_f^{\circ}20$–100 lipoprotein levels

Only 2 of the 6 out-patients showed significant elevations in the serum concentration of $S_f^{\circ}20$–100 lipoproteins, namely, Patient E.M. with xanthoma tendinosum, and Patient M.J. with hypertension and a history of a cerebrovascular accident. No significant changes could be demonstrated in the remaining 4 subjects.

Among the institutionalized patients, statistically significant increases (about 20–30 mg. per 100 ml.) were observed in the mean $S_f^{\circ}20$–100 levels in the 2 male groups but not in the female group. Inspection of the individual responses of patients in Group 2 (Table 3) shows that 18 of 19 patients had positive Δ values for $S_f^{\circ}20$–100 lipoproteins, 6 of which were statistically significant.

Changes in $S_f^{\circ}100$–400 serum lipoprotein levels

Only 2 of the 6 out-patients showed significant changes in this lipoprotein band —— Patient M.J. in whom there was an increase significant at the 0.1 per cent level, and Patient G.R. with xanthoma tuberosum, in whom there was a decrease. This was the only decrease in any serum lipoprotein band observed in the out-patient group.

No significant changes in the concentration of $S_f^{\circ}100$–400 lipoproteins occurred in the 3 groups of hospitalized patients. In only 2 (D.E., Group 2; E.F., Group 1) of a total of 45 betaine-treated patients in Groups 1–3 were large increases noted in the values for this class of lipoproteins. It is of interest that these 2 patients initially had high levels of $S_f^{\circ}20$–100 lipoproteins and were also unique in responding to betaine with a *decrease* in the concentration of $S_f^{\circ}0$–12 lipoproteins.

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Inspection of the individual responses of the patients in Group 2 (Table 3) shows a fairly even distribution of plus and minus signs, and only 2 significant Δ values for $S_f^0$100–400 lipoproteins, both positive.

Changes in the atherogenic index (A.I.) and in total serum cholesterol levels

In 4 of the 6 out-patients, A.I. values were significantly elevated, but remained unchanged in the 2 patients with xanthoma tuberosum. The level of total serum cholesterol rose markedly in the same 4 patients; however, in the 2 patients with xanthoma tuberosum, it remained unchanged in one (L.H.) and was only moderately elevated in the other (G.R.).

In the 3 groups of hospitalized patients, marked elevations in A.I. values and in serum cholesterol levels were observed, significant at the 1 and 0.1 per cent level, respectively.

Changes in body weight

Body weight remained fairly stable in the 3 groups of hospitalized patients. An effect of betaine on body weight is clearly excluded by the weight data summarized in Table 2.

DISCUSSION

The data show that betaine has a definite effect on serum lipoprotein concentrations, producing increases in all except the $S_f^0$100–400 low-density classes. The largest and most consistent elevations occurred in the $S_f^0$0–12 class. Statistically significant increases were also observed in the HDL-3 class, the major high-density lipoprotein component. As expected, along with these increases in serum lipoprotein concentrations, there were distinct elevations in the level of total serum cholesterol and in the atherogenic index.

Some quantitative differences in the response to betaine were noted between the male and female hospitalized patients. These differences are summarized in Table 4. It may be seen that there were significantly greater increases in the levels of $S_f^0$0–12 and $S_f^0$12–20 lipoproteins and total cholesterol in the female group. The levels of $S_f^0$20–100 and $S_f^0$100–400 lipoproteins were increased less in the female than in the male patients on the average, but these differences were not statistically significant. The reason for this sex difference in response to betaine is unknown.

Analysis of all the data failed to demonstrate any relationship between the initial level of serum lipoprotein and the subsequent change produced by betaine.

That betaine rather than glycocyamine is the effective agent in betacyamine is shown by 1) the results of the in-patient study in which only betaine was used, and 2) the fact that in 3 (G.R., L.H. and M.J.) of the 6

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TABLE 4. DIFFERENCES BETWEEN MALE AND FEMALE PATIENTS IN THE RESPONSE TO BETAINE

	S_f^*0–12			S_f^*12–20			S_f^*20–100			S_f^*100–400			Cholesterol			Atherogenic index		
	No treat.*	Treat.**	Δ†	No treat.	Treat.	Δ	No treat.	Treat.	Δ	No treat.	Treat.	Δ	No treat.	Treat.	Δ	No treat.	Treat.	Δ
13 female patients‡ (16 wks.)	401	436	+35	43	66	+23	93	100	+ 7	53	49	− 4	250	309	+59	73	86	+13
13 male patients (4 wks.)	331	367	+36	38	46	+ 8	79	110	+31	39	65	+26	213	238	+25	60	75	+15
Difference between values (F-M)			49			15			−24			−30			+34			− 2
Significance of difference in Δ values			P<0.05			P<0.05			P<0.10			n.s.§			P<0.02			n.s.§

* Mean of pre-betaine values.
** Mean of values during treatment with betaine.
† Difference between the mean of the values during treatment and the mean of the values before treatment.
‡ The 10 female patients of Group 3 and the 3 female patients of Group 1.
§ Not significant.
Note: S_f^*0–12, S_f^*12–10, S_f^*20–100 and S_f^*100–400 lipoprotein and cholesterol values are expressed in mg./100 ml. of serum; atherogenic index values are expressed in units.

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out-patients, betaine produced the same effect as did betacyamine. Our findings are in distinct contrast to those of Morrison (1), who reported that betaine produced a marked lowering of total serum cholesterol concentration in a group of patients with coronary atherosclerosis. However, direct and detailed comparison of the 2 studies is difficult because Morrison's patients were maintained with a low-fat, low-cholesterol diet and also had received previous treatment with choline and inositol.

The practical clinical application of our findings derives directly from the statistical relationship of the atherogenic index to mortality and morbidity from coronary artery disease (6, 7). The definite increase in the atherogenic index produced by betaine implicates betaine as a potentially dangerous substance for use in the treatment of patients with coronary artery disease. Furthermore, it would seem wise to reconsider the free and indiscriminate use of other "lipotropic" agents (*e.g.*, choline) until their effects on serum lipoprotein levels are known.

The mechanism by which betaine increases the concentration of serum S_f^0–20 lipoproteins and total cholesterol is by no means clear. The biochemical pathways of betaine metabolism are known in some detail and have been reviewed by Mackenzie (8). The known metabolic products of betaine are n-dimethylglycine, n-methylglycine, glycine, an active one-carbon intermediate of the oxidation state of formaldehyde plus small and variable quantities of formaldehyde, and serine formed by condensation of glycine with the one-carbon intermediate. Betaine is also a methyl donor in the transmethylation reaction forming methionine from homocysteine. In the absence of clinical evidence for the accumulation of formaldehyde, the only potentially toxic and unphysiologic compound in the foregoing sequence, it appears unlikely that the effect of betaine on serum lipoproteins is mediated via any of the remaining metabolites along the known metabolic pathways of betaine. The role of choline as a lipotropic agent has been reviewed in detail (9). It seems unlikely that the effect of betaine on serum lipoproteins can be explained on the basis of "lipotropic action" in patients who maintain their weight while receiving a diet presumably adequate in protein and lipotropic agents. Mobilization of depot fat by betaine or choline also does not offer an adequate explanation, for the same reasons. It has been shown that choline accelerates synthesis of hepatic phospholipid (10) but the possible relationship of this finding to an increase in the concentration of low-density serum lipoproteins is not clear, even though a relationship between *serum* phospholipid and serum cholesterol levels has been suggested recently (11).

Desiccated thyroid (12–14), thyroxine (15) and triiodothyronine (16) each cause a marked lowering of the S_f^0–20 serum lipoprotein level, and vitamin B_{12} has been shown to prevent weight loss and sometimes death

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due to thyrotoxicosis in young rats (17–19); the suggestion has also been made that thyrotoxicosis is primarily a deficiency of vitamin B_{12} (20). A vitamin B_{12} deficiency has been postulated to explain the decreased rate of methylation of nicotinamide observed in hyperthyroid rats (21), and the requirement of vitamin B_{12} for the synthesis of methyl groups is well known, though transmethylation reactions probably do not require this vitamin (22, 23).

Furthermore, in rats, a deficiency of dietary betaine produced by ingestion of ethanolamine may be compensated for by an increase in methyl synthesis following administration of vitamin B_{12} (24). Low plasma B_{12} levels have been reported in strict vegetarians (25), and low serum cholesterol and $S_f^{\circ}0$–20 lipoprotein levels have been repeatedly observed in human subjects and animals receiving low animal-fat or vegetarian diets (26–29). These diverse observations are consistent with the hypothesis that low levels of vitamin B_{12} are in some way related to low levels of $S_f^{\circ}0$–20 serum lipoproteins, and high levels of vitamin B_{12} to high levels of $S_f^{\circ}0$–20 serum lipoproteins and cholesterol.

An effect of betaine on the absorption of fats or of some nutrient involved in the regulation of fat metabolism represents another mechanism by which betaine might cause the observed changes in serum lipoprotein concentration. However, the absence of a significant weight loss makes a defect in fat absorption an unlikely explanation.

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