THE HYPOCHOLESTEROLEMIC EFFECT OF NICOTINIC ACID AND ITS RELATIONSHIP TO THE AUTONOMIC NERVOUS SYSTEM*

By

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INTRODUCTION

NICOTINIC acid, well known physiologically and chemically as a vitamin if administered in small quantities, has many interesting additional properties when given in relatively large amounts. Altschul (2, 3) found that it markedly decreased the levels of cholesterol in rabbits made hypercholesterolemic by diet, and Altschul, Hoffer and Stephen (4) found that in divided dosages of three grams per day this vitamin produced appreciable decreases in the cholesterol levels of healthy young subjects and in patients from a general hospital. The decrease was related linearly to the initial cholesterol levels while the percentage decrease increased as the initial cholesterol levels were elevated. The incorporation of nicotinic acid into atherogenic diets inhibited the development of arteriosclerosis in rabbits (Altschul (2)). Of seventeen animals tested, two showed intense arteriosclerosis, six showed mild change, and nine showed no arteriosclerosis. Without nicotinic acid, at least thirteen of the rabbits would have had severe arteriosclerosis on the basis of many previous studies by Altschul (2) and by many other investigators.

Altschul and Hoffer (5) found similar decreases in the serum cholesterol levels of young volunteers. After two weeks of treatment with nicotinic acid, there was a 22 per cent. decrease in the mean values. During the same period, the B.M.R. increased significantly but to a minor degree. The decrease in cholesterol levels depended upon the initial cholesterol levels and upon body weight. The regression equation calculated from their data gives the equation:

$$Y = 0 \cdot 95x - 0 \cdot 39z - 90$$

where Y is the decrease in cholesterol, mg.
x is the initial cholesterol value, mg. and
z is the initial body weight, lbs.

The multiple correlation coefficient is 0·83.

Recently Parsons, Achor, Berge, McKenzie and Barker (16) confirmed the hypocholesterolemic effect of nicotinic acid. O'Reilly, Demay and Kotlowski (15) found similar decreases. A group of twenty-seven patients without arteriosclerosis and ten patients with clinical evidence of arteriosclerosis showed a decrease in mean cholesterol levels from 217 mg. per 100 ml. to 183 mg. in one

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week and to 173 mg. after six weeks of treatment (a decrease of 44 mg. or 20 per cent.). During the same interval, there was no change in the mean cholesterol levels in ten control patients not treated with nicotinic acid.

For some years, nicotinic acid has been used as part of a therapeutic programme for the treatment of schizophrenia (Hoffer, Osmond, Callbeck and Kahan (13)). Certain aspects of schizophrenic metabolism are different from normal controls. For this reason, cholesterol levels were determined before and after treatment in order to study the relative response of cholesterol levels to nicotinic acid of schizophrenic patients and to compare this to the response of non-schizophrenic patients as reported by others. Schizophrenic patients show different autonomic responses from other patients (Hoffer (12)). The relationship to the autonomic nervous system was therefore examined.

Method

All the patients tested were schizophrenic patients diagnosed and treated in psychiatric wards of two general hospitals. Diagnosis was based upon the clinical examination of the patient according to criteria originally described by Bleuler (6) and by Lewis and Piotrowski (14). The patients were admitted to the hospital directly from the community and as a rule were well nourished. In hospital, they received standard hospital diets.

Before receiving treatment, the patients were tested by the mecholyl test developed by Funkenstein (9) and by the atropine test of Hoffer (12). All mecholyl tests were conducted at 1.30 p.m. using a standardized procedure. Reliability of the test was shown by Weckowicz (20). The patients were classified into three groups, i.e. "hypo" where the systolic pressure did not return to the original level within twenty-five minutes after the injection of 10 mg. of mecholyl, "normal" where the original level was regained, and "hyper" where the original level was exceeded. The response to epinephrine was not determined. The results of the atropine tests were rated according to Hoffer (11) into two groups—(1) those scoring between 0 and 4 and (2) those scoring between 5 and 11.

The patients were randomized into two groups (1) those given three grams of nicotinic acid per day in three doses, and (2) those given placebo. A fasting serum cholesterol determination was made using a Lieberman-Burchard reaction, just before treatment, two weeks after treatment had started, and five days or more after treatment was discontinued. The B.M.R. was determined in twenty-two of these patients before and after two weeks treatment.

All the patients were actively treated for their psychiatric disorder and therefore received either electroconvulsive therapy, sedation (including tranquillizers) or psychotherapy in various combinations. The same psychiatric treatments were given to each group. Nicotinic acid treatment was randomized with placebo. Both groups are comparable for cholesterol determination as the only variable was nicotinic acid treatment.

Results

The mean ages and standard deviations for the various sub-samples of the patients are shown in Table I.

None of the means are significantly different from each other. All the standard deviations are not different from each other with the exception of the S.D. for the "normal" mecholyl group which was the smallest of all the groups.

TABLE I

Description by Age of the Patient Groups

Group	Number	Mean Age	Age Range	S.D. of Mean Age
Placebo	24	29·8	16–51	9
Nicotinic acid	33	31·2	16–53	9
Unimproved	9	29·1	17–53	11·6
Improved	19	31·1	16–50	8·4
Atropine score 0–4	9	33·2	18–53	12·1
Atropine score 5–11	20	29·6	16–43	7·5
Mecholyl-hypo	9	36·8	22–53	10·2
Mecholyl-normal	7	27·6	24–38	4·6
Mecholyl-hyper	13	28·2	16–43	8·5

Relationship of Initial Values and Responses to Nicotinic Acid

The cholesterol levels before treatment, after one day of treatment, after two weeks of treatment and a few days after the treatment had been discontinued are shown in Tables II and III and in Figure 1.

TABLE II

Effect of Nicotinic Acid on Cholesterol Levels

Patient	Sex	Age	Weight (lbs.)	Serum Cholesterol				
				Before Treatment	24 Hours Nicotinic Acid	2 Weeks Nicotinic Acid	Percentage Change	After Treatment
1	F	43	160	225	185	200	−11	170
2	M	39	176	235	200	190	−19	—
3	M	19	135	232	187	180	−14	260
4	F	38	135	260	255	255	−2	260
5	F	53	142	440	407	400	−9	363
6	F	34	98	255	312	180	−29	295
7	M	29	130	205	—	185	−10	355
8	M	28	160	300	215	260	−13	225
9	M	40	190	125	—	155	+24	180
10	F	34	130	190	—	190	0	260
11	M	18	152	190	—	150	−21	150
12	F	17	111	250	—	130	−48	135
13	M	34	170	235	—	250	+6	225
14	M	22	155	195	—	200	+2	165
15	F	24	120	240	—	105	−56	105
16	M	16	156	150	—	110	−27	150
17	F	30	205	225	—	100	−56	200
18	F	28	146	235	—	—	—	225
19	M	31	172	210	—	235	+12	210
20	F	38	135	230	245	—	—	—
21	F	27	137	200	170	—	—	—
22	F	24	129	160	168	125	−22	175
23	M	30	163	260	220	152	−3	140
24	F	27	116	195	180	130	−33	230
25	M	22	173	195	190	175	−10	255
26	M	25	146	150	—	130	−13	155
27	F	25	160	160	155	130	−19	135
28	F	40	165	200	175	140	−30	170
29	M	37	145	175	—	190	+8	—
30	F	24	116	212	203	105	−50	—
31	F	50	115	205	235	175	−15	—
32	M	38	162	170	152	195	+15	—
33	M	45	224	175	175	—	—	—
Means				215	212	176	−18	206

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TABLE III

Effect of Nicotinic Acid (24 hours) and Placebo (2 weeks) on Cholesterol Levels

Patient	Sex	Age	Weight	Serum Cholesterol, mg.%				
				Before Treatment	24 Hours Nicotinic Acid	2 Weeks Placebo	Percentage Change	5 Days After Treatment
34	F	51	160	310	295	325	5	335
35	F	20	100	215	230	230	7	310
36	F	16	125	222	250	260	18	285
37	M	25	125	215	240	245	14	225
38	F	35	125	220	235	242	10	205
39	M	28	166	205	187	200	−2	233
40	F	22	105	200	224	260	15	265
41	F	21	103	225	—	245	9	330
42	F	26	114	175	—	200	14	230
43	M	34	162	210	185	—	—	245
44	F	35	135	245	220	195	−20	245
45	F	33	150	175	165	155	−11	220
46	M	46	153	215	—	—	—	220
47	F	22	119	160	—	245	53	235
48	F	33	143	220	—	220	0	185
49	F	23	95	165	160	170	3	210
50	M	47	177	165	145	160	−2	180
51	M	23	150	180	167	195	8	200
52	F	33	120	213	200	275	29	235
53	F	19	122	150	125	180	20	205
54	M	26	147	125	125	190	52	160
55	F	29	135	180	195	170	−6	197
56	F	23	139	130	165	200	54	215
57	F	46	162	245	180	235	−4	—
Mean				199	194	219	+10	233

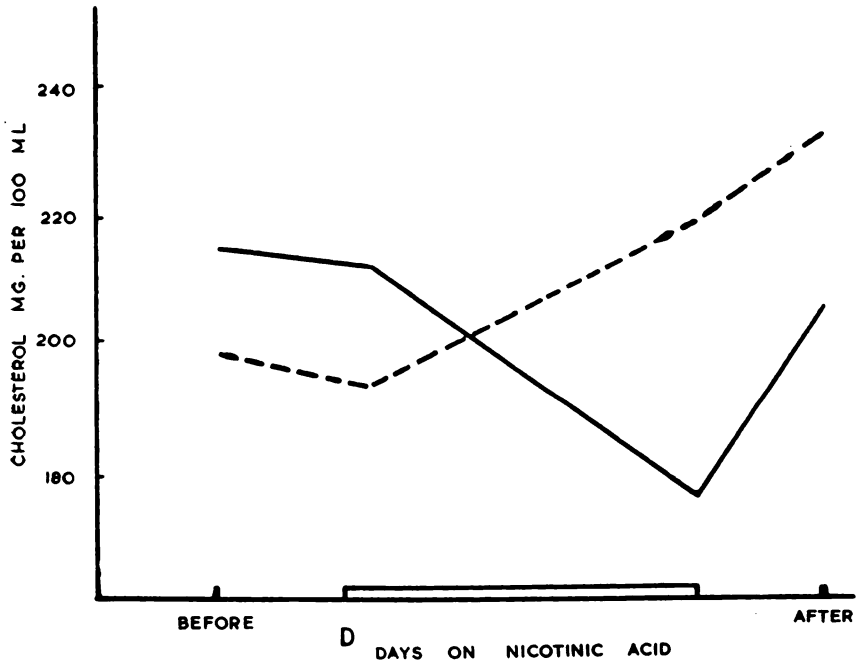

FIG. 1.—Effect of nicotinic acid on cholesterol levels (solid line) and of placebo on patients (broken line).

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The mean of the 57 initial values was 208 mg. per 100 ml. (S.D.=6·5 mg.). After treatment of 38 patients with nicotinic acid for one day, the serum cholesterol decreased from 212·6 to 203·2 mg. This decrease, although slight, is statistically significant (t=4·7, p lower than 1 per cent.). This compares with a decrease of 6·4 per cent. reported for 43 subjects having an initial value of 203 mg. (Altschul, Hoffer and Stephen (4)).

After two weeks treatment with nicotinic acid, the cholesterol level had decreased to 176 mg. Five days after treatment, the cholesterol level had returned almost to the original value. In the group on placebo, the initial value was lower than for the nicotinic acid group but there was an increase after two weeks and a further increase after sham treatment. The final value, 233 mg., was significantly higher than was the initial value. The increase may have been due to several factors including hospital diet, psychiatric therapy, etc. The decrease produced by nicotinic acid compares well with that reported by Altschul and Hoffer (5).

The decrease in cholesterol levels was significantly correlated with the initial cholesterol value before treatment (r=0·59, t=5·8). The decrease in cholesterol for the schizophrenic patients of this study did not differ from the cholesterol response reported by O'Reilly *et al.* (15). The data from the O'Reilly study was therefore incorporated with this data in order to offer a larger sample and thus obtain a more reliable regression equation relating expected decrease to the initial cholesterol value. The expected decrease is given:

$$Y=0\cdot52x-71$$

where x is the initial cholesterol level

Y is decrease in cholesterol, mg.

According to this equation, negative decreases (an increase) will be predicted when the initial cholesterol value is below 136 mg. per cent. When the initial value is much below the normal range, nicotinic acid produces an increase in the level. Out of this series of 64 patients 13 showed an increase. The mean cholesterol value for this sample of 13 was 178 mg. with a mean increase of 34 mg. or 13 per cent.

The decrease in cholesterol levels after one day of treatment with nicotinic acid shows a similar relationship to the initial value. The correlation between decrease and initial value was 0·76, for the study reported by Altschul, Hoffer and Stephen (4) and 0·59 (t=5·8) for this study. The regression equation for the one-day treatment effect is:

$$Y=0\cdot68x-122$$

Both regression lines are shown in Figure 2.

In this study, the dosage of nicotinic acid was uniform for each patient irrespective of initial body weight and sex. Of course, body weight might play a role since heavier patients might have a lesser effective nicotinic acid concentration in the blood. The relationship of body weight to decrease of cholesterol is shown in Table IV.

For the two-week treatment period, the greatest response was achieved with the lighter patients. This did not depend upon a relationship between body weight and initial levels since they were constant for mean weights varying from 105 lbs. to 175 lbs. The majority of patients under 140 lbs. were female. However, the increased response of the patients in the low weight range does not appear to be due to sex. Of 29 patients receiving nicotinic acid for two weeks, 16 were male. Of these, 6 responded with an increase in cholesterol.

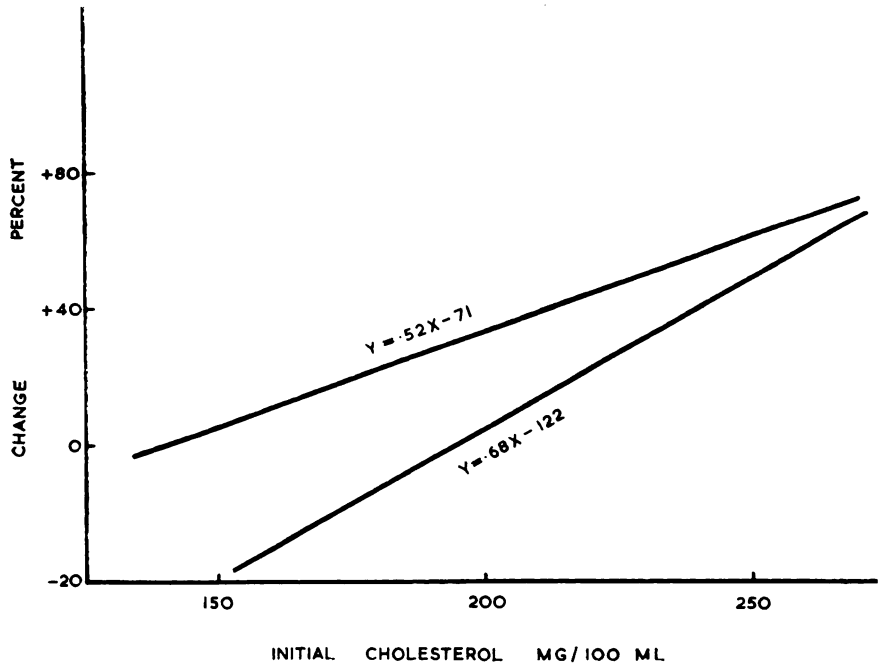

FIG. 2.—Regression equations showing relationship between initial cholesterol level and expected response to nicotinic acid medication.
(1) 2 weeks $Y = \cdot 52x - 71$
(2) 1 day $Y = \cdot 68x - 122$

TABLE IV

Relationship of Body Weight and Hypocholesterolemic Effect of Nicotinic Acid

Weight Range	Nicotinic Acid (one day) N	Mean Weight	Initial Cholesterol (mg.)	Change Per cent.	Nicotinic Acid (fourteen days) N	Mean Weight	Initial Cholesterol (mg.)	Change Per cent.
90 to 119	8	105	201	5	6	108	213	−33
120 to 139	13	131	204	1	6	130	214	−19
140 to 159	5	150	229	−8	7	151	218	−10
160 to 209	12	171	223	−12	10	174	216	−11

Out of 13 female patients, only 1 did not increase in cholesterol. These ratios are not significantly different (chi square=2·0). The mean response of all the male patient group reported by O'Reilly *et al.* (15) was of the same order as the total group discussed in this study. A comparison of the various studies is shown in Table V.

TABLE V

Comparison of Hypocholesterolemic Effect of Nicotinic Acid of Various Authors

Study Reference	Number	Mean Initial Value	Dosage grams	Effect, Days 1	7	14	42	Regression Equation
15	37	217	3	—	—	—	173	
4	43	203	1–3	190	—	—	—	
4	25	284	1–3	222	—	—	—	
5	12	205	3	207	172	161	—	$Y = \cdot 95x - \cdot 39z - 90$
Present	33	215	3	212	—	176	—	$Y = \cdot 28x - \cdot 43z + 53$

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The correlation for body weight and cholesterol decrease calculated from the data of Altschul and Hoffer (5) was 0·82. This is not significantly different from the correlation for the present study.

The regression equation relating expected decrease to both body weight and initial cholesterol level is:

$$Y=0\cdot28x-0\cdot43z+53$$

where Y is the expected decrease
x is the initial cholesterol value, and
z is the body weight.

The multiple correlation coefficient is 0·43 (t=2·65). The data of Altschul and Hoffer (5) yields a different equation:

$$Y=0\cdot95x-0\cdot39z-90$$

with a multiple correlation coefficient of 0·83. This is significantly higher than for this series of schizophrenic patients.

Relationship of Autonomic Tests and Cholesterol Response to Nicotinic Acid

The relationship of the mecholyl and atropine tests and the response of cholesterol to nicotinic acid is shown in Table VI. The starred values differ significantly at the 1 per cent. level from the total values.

TABLE VI

Relationship of Autonomic Tests to Cholesterol Response to Nicotinic Acid

Group	Number	Initial Cholesterol Mean	Ratio	Expected Ratio
Total	57	208	−·16	
Mecholyl-hyper	13	216	−·17	−·19
Mecholyl-normal	7	182*	−·25*	−·13
Mecholyl-hypo	9	242*	−·13*	−·23
Atropine 0–4	9	233*	−·25*	−·22
Atropine 5–11	20	207	−·14	−·18

* Statistically significant.

The hypo mecholyl respondents had higher initial cholesterol values and decreased least when given nicotinic acid. The normal mecholyl respondents had the lowest original cholesterol values and showed the greatest decrease to nicotinic acid. Patients in the 0 to 4 atropine group, i.e. normal sympathetic activity, had higher initial values with an increased response to nicotinic acid. Patients in the 5 to 11 atropine group (the expected response for schizophrenics) had normal initial cholesterol values but responded less than the total group to nicotinic acid.

Relationship of Clinical Response to Therapy and Cholesterol Response to Nicotinic Acid

Patients receiving nicotinic acid were divided into two groups (1) where the psychiatric response to treatment was good and (2) where there was a poor clinical response. These evaluations were based upon discharge evaluation and upon follow-up investigation in the community after discharge. The group of 9 patients who did not respond well clinically had a higher initial cholesterol level which decreased less than would be expected. The patients who responded

well to therapy had normal initial cholesterol levels with a slightly stronger hypocholesterolemic response to nicotinic acid.

TABLE VII

Relationship of Clinical Response and Cholesterol Decrease

Group	Number	Initial	Ratio	Expected Ratio
Total	57	208	−·16	
Improved	19	205	−·20*	−·17
Unimproved	9	243*	−·14*	−·23

* Statistically significant.

Relationship of B.M.R. to Hypocholesterolemic Responses to Nicotinic Acid

B.M.R.s were determined before and two weeks after treatment. Nicotinic acid significantly elevated the B.M.R. in both normals and schizophrenics. This was more pronounced in the schizophrenic group.

TABLE VIII

Relationship Between Diagnosis, B.M.R. and Cholesterol Response to Nicotinic Acid

Diagnosis	Treatment	Number	Initial B.M.R.	B.M.R. After Two Weeks	Change in B.M.R.
Schizophrenia ..	Nicotinic acid ..	12	−1·58	13·3	14·88*
Schizophrenia ..	Placebo	10	−5·80	−5·50	0·30
Normals (1) ..	Nicotinic acid ..	12	−9·75	−3·30	6·45*

(1) Altschul and Hoffer (1957).
* Statistically significant.

DISCUSSION

Nicotinic acid is hypocholesterolemic for patients who have elevated cholesterol levels and tends to be hypercholesterolemic for patients who have abnormally low cholesterol values. Values which deviate toward either extreme are brought toward the normal range.

Paolantonio (17) reported that ultraviolet irradiation following the method described by Altschul (1) decreased cholesterol levels within four weeks. Examination of this response indicates that the magnitude of response of the Italian patients to ultraviolet is of the same order as was the response to nicotinic acid in our series. A similar study by Altschul (1) with a larger series of patients shows that the cholesterol decrease for the Canadian series given ultraviolet was less pronounced than the response of the Italian series and less pronounced than the nicotinic acid response. The total range of cholesterol values in the Italian series was much lower than the Canadian series of Altschul (1). Both sets of ultraviolet data are shown in Table IX.

The regression equation relating decrease to only initial cholesterol value works reasonably well for the range of cholesterol values below 229 mg. but predicts decreases much greater than was found with ultraviolet. Apparently nicotinic acid is a more effective hypocholesterolemic substance for Canadian patients as reported in the study of Altschul (1) and this study. In the Italian series where in general cholesterol values are lower, ultraviolet was as effective as nicotinic acid in the Canadian series.

TABLE IX

The Response of Cholesterol to Ultraviolet Irradiation

A.—Study of Paolantonio (17)

Range	Number	Initial	Final	Predicted from Regression Equation
110–129	3	131	135	134
130–149	7	143	146	140
150–169	10	160	149	148
170–189	7	182	149	158
190–209	10	199	173	166
210–229	8	219	175	176
230–279	4	260	223	196
B.—Study by Altschul (1)				
110–129	1	111	135	124
130–149	2	141	129	139
150–169	7	160	181	148
170–189	5	178	158	156
190–209	13	200	181	167
210–229	13	222	194	178
230–249	8	242	206	187
250–269	12	259	231	195
270–289	8	278	246	205
290–329	5	304	288	217
330–470	4	368	334	248

The agreement between the response to ultraviolet and nicotinic acid is reasonably good. Apparently, both factors have a similar action upon cholesterol metabolism and perhaps they normalize the same metabolic pathway.

The mechanism whereby nicotinic acid decreased elevated cholesterol levels is not known. If the action were only hypocholesterolemic, one might postulate some interference with absorption of lipid or some increase either in overall utilization or an increase in excretion. It is more likely that nicotinic acid plays a more fundamental role by normalizing cholesterol metabolism. Since nicotinamide, the constituent of DPN, has so far not been proven to lower cholesterol levels, the response to nicotinic acid is not dependent upon the respiratory enzyme *per se*.

The relationship of the cholesterol response to the autonomic tests may depend upon the secretion of norepinephrine and epinephrine. Epinephrine, according to Raab (18), is fundamentally related to arteriosclerosis. He states that all arterial walls contain epinephrine derived from sympathetic nervous endings and from the adrenal medulla. Injections of epinephrine produce media necrosis, thickening of the intima (which may be secondary) and increased deposition of cholesterol in the intima. In animals (Raab (18)), excessive treadmill exercise (which promotes catecholamine discharge) greatly accelerates the deposition of cholesterol in the coronary vessels. Epinephrine also alters plasma lipid ratios. Dury (7) reported that injections of epinephrine into rabbits markedly increased the serum content of total lipids, phospholipids and neutral fat. These values reached a maximum after 48 hours and remained high for five days. Cholesterol levels were also at a maximum after 24 hours and remained elevated for five days.

The mecholyl test (Funkenstein (9)) measures central sympathetic reactivity

(Gellhorn (10)). Funkenstein (9) has shown that patients who show a hypo-mecholyl response tend to over-secrete epinephrine rather than norepinephrine. This group is, according to Funkenstein, characterized by an increased peripheral output of epinephrine and by a decreased reactivity of the sympathetic nervous system. The patients in this study who were hypo-reactive were much higher in initial cholesterol values and reacted very sluggishly to the administration of nicotinic acid. Patients with normal and hyper-mecholyl responses, according to Funkenstein (9), tend to over-secrete norepinephrine. These groups had a normal or decreased initial cholesterol level and either over-reacted or reacted normally to nicotinic acid. There is therefore a consistent relationship between the apparent over-secretion of epinephrine or norepinephrine and the initial cholesterol levels and their response to nicotinic acid.

The atropine test is a measure of sympathetic reactivity (Hoffer (12)). Patients with scores between 0 and 4 have normal response to atropine and presumably are able to respond to additional stimulus. With this group, the hypocholesterolemic response to nicotinic acid was greater than one would expect from the mean response of this study. Patients with scores between 5 and 11 are not able to respond to further stimuli. Their cholesterol response to nicotinic acid was below normal.

The schizophrenic patients who did not respond to therapy were higher in initial cholesterol levels and the decrease to nicotinic acid was sluggish. Thus, it appears that schizophrenics from this group with relative over-secretion of epinephrine as indicated by the mecholyl response and by the initial higher cholesterol levels have not as good a prognosis clinically.

There apparently is some relationship between epinephrine metabolism and cholesterol levels. This data provides some confirmation for the observations of Schmidtmann and Huttich (19) and Westphal and Hermann (21) relating epinephrine to cholesterol metabolism. Nicotinic acid which is useful for the treatment of early schizophrenia (Hoffer, Osmond, Callbeck and Kahan, 1957) may decrease the production of epinephrine by producing a relative deficiency of methyl groups. This might be an explanation for its hypocholesterolemic effect. Against this concept is the lack of hypocholesterolemic effect of nicotinamide when administered for twenty-four hours. Perhaps there is some relationship to glycine. Nicotinic acid is excreted primarily as nicotinuric acid whereas nicotinamide is excreted mainly as N-methyl nicotinamide.

Summary

Nicotinic acid tends to normalize cholesterol levels in schizophrenics, normals and non-schizophrenic patients in the same way. The change is partially dependent upon the initial cholesterol values and upon body weight. The change can be predicted by regression equations. There is some relationship between the hypocholesterolemic response and autonomic tests.

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Bibliography

1. Altschul, R., "Lowering of serum cholesterol by ultraviolet irradiation," *Geriatrics*, 1955, **10**, 208–213.
2. *Idem*, "Die Beeinflussung des Blutcholesterinspiegels und der experimentellen Atherosklerose durch Nikotinsäure," *Zeit. für Kreislaufforschung*, 1956, **45**, 573–576.
3. *Idem*, "Influence of nicotinic acid on cholesterol metabolism," Meeting Amer. Soc. for Study of Arteriosclerosis, 1956. November 11–12.
4. *Idem*, Hoffer, A., and Stephen, J. D., "Influence of nicotinic acid on serum cholesterol in man," *Archives Biochem. and Biophysics*, 1955, **54**, 558–559.
5. *Idem* and Hoffer, A., *Effect of nicotinic acid on cholesterol levels and B.M.R. of normal volunteers*, 1957. (In press.)

6. BLEULER, E., *Dementia Praecox or The Group of Schizophrenias*, Transl. 1950. New York: International Universities Press.
7. DURY, A., "Effects of epinephrine on lipid partition and metabolism in the rabbit," *Circ. Res.*, 1957, **5**, 47–53.
8. ELLES, S., "The metabolic effects of epinephrine and related amines," *Pharm. Reviews*, 1956, **8**, 485–562.
9. FUNKENSTEIN, D. H., GREENBLATT, M., and SOLOMON, H. C., "A test which predicts the clinical effects of electro-shock treatment on schizophrenic patients," *Amer. J. Psychiatry*, 1950, **106**, 889–901.
10. GELLHORN, E., *Physiological foundation of neurology and psychiatry*, 1953. Minneapolis: The University of Minnesota Press.
11. HOFFER, A., "Objective criteria for the diagnosis of schizophrenia," *Confinia Neurologica*, 1954, **14**, 385–390.
12. *Idem*, "Effect of atropine on blood pressure of patients with mental and emotional disease," *Arch. Neur. and Psychiat.*, 1954, **71**, 80–86.
13. *Idem*, OSMOND, H., CALLBECK, M. J., and KAHAN, I., "Treatment of schizophrenia with nicotinic acid and nicotinamide," *J. Clin. and Exper. Psychopathology*, 1957. (In press.)
14. LEWIS, N. D., and PIOTROWSKI, Z., *Depression*, 1954. Edited by P. H. Hoch and J. Zubin. New York: Grune and Stratton, Inc.
15. O'REILLY, P. O., DEMAY, M., and KOTLOWSKI, K., 1957. Private communication.
16. PARSONS, W. B., ACHOR, R. W. P., BERGE, K. G., MCKENZIE, B. F., and BARKER, N. W., "The effect of large doses of nicotinic acid on the plasma and serum lipids of human beings with hypercholesterolemia," *Proc. Staff Meeting, Mayo Clinic*, 1956, **31**, 377–390.
17. PAOLANTONIO, V., "Atti Dell Accademia Medico Chirurgica Di Perugia," *Nvova Sene*, 1953–54, Vol. 5, Fasc. 5.
18. RAAB, W., "Adrenergic cholinergic control of cardiac metabolism and function," *Advances in Cardiology*, 1956. New York: S. Karger.
19. SCHMIDTMANN, M., and HUTTICH, M., "Die Bedeutung der Gefasswandreaktion fur die Arteriosklerose," *Virchow's Arch. path. Anat.*, 1928, **267**, 601–624.
20. WECKOWICZ, T. E., "Reliability of mecholyl test," *Arch. Neur. and Psychiatry*, 1956, **76**, 109–111.
21. WESTPHAL, K., and HERMANN, F., "Pathogenese der essentiellen Hypertonie," *Ztschr. Klin. Med.*, 1925, **101**, 566–583.