Hypercholesteremia: Effects of Treatment with Nicotinic Acid for Three to Seven Years*

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Because of the clinical, experimental, and epidemiologic evidence that altered lipid metabolism is an important factor in human atherosclerosis, various regimens of diet and medication have been designed to lower abnormally elevated levels of lipids in the blood. Methods of treatment that we have evaluated include diets low in total fats with and without the addition of polyunsaturated fatty acids, and the use of estrogenic substances, thyroid analogues, triparanol (MER/29), and nicotinic acid. Although none of the many programs of treatment that we have tried has been entirely satisfactory, the use of nicotinic acid in large oral doses of 1.5 to 6.0 gm. daily has been the most uniformly effective method. Results of our earlier studies seemed favorable enough to warrant long-term investigational use of this agent.†

Data on 20 patients who have received treatment with large doses of nicotinic acid for periods of three to seven years form the basis of this report.

Materials and Methods

Patients were selected according to the following criteria: (1) presence of hypercholesteremia, as evidenced by a mean pretreatment concentration of plasma cholesterol greater than 250 mg. per 100 ml. (Zak method),* (2) absence of diabetes, myxedema, nephrosis, serious hepatic or biliary disease, or any other debilitating chronic illness, and (3) availability of the patient for close follow-up investigation for long periods.

The general plan of study was as follows: (1) a complete general physical and laboratory examination of each patient initially and annually, (2) no change in the usual diet or in medication given before the study, (3) return visits and determinations of the concentration of plasma cholesterol at least monthly, (4) administration of nicotinic acid†† in divided doses with meals for three months before any change in dosage, (5) use of a placebo for three months after nine to 12 months of treatment with nicotinic acid, and (6) additional studies or examinations when indicated.

Results

By July, 1962, the course of 20 patients meeting the above criteria had been followed for three years or longer. There were ten men and ten women ranging in age from 17 to 66 years with a mean age of 48 years. Pertinent additional diagnoses for these patients were as follows: familial hypercholesteremia in nine; ischemic heart disease in 11; arteriosclerosis obliterans in three; tendinous xanthoma in six; cutaneous xanthoma in six; and arterial hypertension in four.

Effects of Treatment on Hypercholesteremia. The changes in concentration of plasma cholesterol for the 20 patients treated for at least three years are shown in Fig. 1. The mean concentration of plasma cholesterol during the first year of treatment, in which a mean dosage of nicotinic acid of 3.5 gm. per day was given, was

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††Tablets and capsules of nicotinic acid (plain) used in this study were supplied by G. C. Chiu, M.D. of Eli Lilly and Company, Indianapolis, Indiana.
241 mg. per 100 ml., a decrease of 26 per cent from the mean pretreatment level of 327 mg. The hypocholesteremic effect of the medication was indicated further by the prompt increase in the mean concentration of plasma cholesterol to 311 mg. when the placebo was substituted for nicotinic acid. During the second year, the mean value for cholesterol decreased to 222 mg. with the mean dosage of nicotinic acid at 4.2 gm. daily. In the third year, the mean level of cholesterol was 217 mg. with a mean daily dose of 3.9 gm. The mean body weight during the three years did not change significantly.

Eight of the 20 patients have completed more than five years on this program of treatment (Fig. 2). The results in this group are similar to those just described; the hypocholesteremic effect of nicotinic acid was maintained throughout the five-year period. The mean concentration of plasma cholesterol for these eight persons decreased from the pretreatment value of 322 mg. per 100 ml. to 240 mg. for the first year, a decrease of 25 per cent, when the mean dosage of nicotinic acid was 3.3 gm. daily. There was a prompt increase in mean concentration of plasma cholesterol to 313 mg. when a placebo was substituted for nicotinic acid. During the next four years, the annual mean concentrations of plasma cholesterol ranged from 204 to 220 mg. with a dosage of nicotinic acid which averaged from 3 to 4 gm. daily. There was no escape from the hypocholesteremic effect during the five years despite the fact that the mean daily dose of nicotinic acid was decreased by 1 gm. during this interval. There was no appreciable change in mean body weights.

After prolonged use of the large doses of nicotinic acid, a greater responsiveness to its hypocholesteremic action was noted in several patients, and at times an intolerance to the medicament was observed. One patient, who has completed seven years on this program, illustrates this point (Fig. 3).
During the prolonged treatment, there was a reduction in mean dosage of nicotinic acid from 4.5 to 1.3 gm. daily with maintenance of the concentration of plasma cholesterol at a satisfactory level of 250 mg. per 100 ml. or less. Persistent gastrointestinal symptoms developed in this patient late in the course of the treatment; these were alleviated during the sixth and seventh years by an interrupted plan of treatment whereby the patient took 1.5 gm. of nicotinic acid six days a week.

Side Effects. Cutaneous flushing accompanied by burning, pruritus, and, at times, urticaria occurred initially in all patients treated with nicotinic acid. After the first four to seven days, these symptoms usually became mild and transitory, and it was seldom necessary to decrease the dosage of or temporarily discontinue the medication.

Gastrointestinal irritation with anorexia, nausea, vomiting, or diarrhea, with or without abdominal pain, was a more troublesome side effect. Unlike the cutaneous symptoms, these complaints were more frequent and of greater severity after three or more years of treatment. Nine (45 per cent) of the 20 patients experienced such delayed side effects. The substitution of capsules for tablets of nicotinic acid brought about prompt and complete relief in three of the nine patients, and the interrupted form of treatment referred to earlier alleviated the symptoms in three additional patients. In the other three patients, delayed intolerance to nicotinic acid led to withdrawal of treatment, following which the symptoms promptly subsided.

Tests of Hepatic Function. Tests of hepatic function were performed in all patients at regular intervals. In eight patients (40 per cent) all tests gave normal results. Six patients (30 per cent) were found to have mild, transitory abnormalities in one or more tests during the course of treatment. The remaining six patients (30 per cent) had significant abnormalities in one

![Figure 2](http://journal.publications.chestnet.org/pdfaccess.ashx?url=/data/journals/chest/21408/ on 06/26/2017)
or more tests during some period of the therapy with nicotinic acid. In order of frequency, abnormalities occurred in the following tests of liver function: cephalin cholesterol flocculation in six patients; serum glutamic oxalacetic transaminase activity in four; sulfobromophthalein retention in four; and alkaline phosphatase activity in three. In none was the concentration of serum bilirubin abnormal. Although treatment was continued in all patients, the abnormalities were persistent in only two, and neither of these had subsequent evidence of serious injury to the liver.

Carbohydrate Metabolism. The level of fasting “true” blood sugar was determined periodically in 19 patients during treatment with nicotinic acid. The values were normal (65 to 90 mg. per 100 ml.) in seven patients (37 per cent), in the equivocal range (91 to 110 mg. per ml.) in eight (42 per cent), and definitely elevated (111 to 131 mg. per ml.) in four (21 per cent).

Oral glucose tolerance studies were done in 17 patients during the treatment period, and 11 (65 per cent) had abnormal glucose tolerance curves which simulated those seen in patients with diabetes (more than 150 mg. per 100 ml. of blood at one hour and more than 110 mg. at two hours). Treatment was discontinued temporarily in eight of these 11 patients, and serial tests were subsequently repeated. In seven of the eight patients the result of the glucose tolerance test reverted to normal within four to 18 days; in the eighth patient, it was abnormal for four months.

Uric Acid and Gout. Hyperuricemia (uric acid 6 mg. or more per 100 ml. of serum) was present on at least one occasion in 12 of 17 patients (71 per cent) so tested during treatment and remained elevated during the more than three years of treatment in three. However, only one patient in this group, a woman, experienced acute gout, and she had only one episode. She has been free from attacks since that time, although therapy with nicotinic acid has been continued for three years.

Summary and Conclusions

In 20 persons with hypercholesteremia, nicotinic acid has been given in orally administered dosages of 1.5 to 6.0 gm. daily for periods of three to seven years. Observations on these patients may be summarized as follows:

1. It is practical to give large doses of nicotinic acid over a period of years.
2. Such treatment is effective in decreasing the concentration of plasma cholesterol to less than 250 mg. per 100 ml.

![Figure 3: Mean concentrations of plasma cholesterol in a patient treated with nicotinic acid for seven years.](http://journal.publications.chestnet.org/pdfaccess.ashx?url=/data/journals/chest/21408/)

<table>
<thead>
<tr>
<th>Year</th>
<th>Mean plasma cholesterol (mg./100 ml.)</th>
<th>Mean body weight (lb.)</th>
<th>Mean dosage niacin (gm./day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>235 (-10%)</td>
<td>134</td>
<td>3.9</td>
</tr>
<tr>
<td>2</td>
<td>253 (-10%)</td>
<td>128</td>
<td>4.5</td>
</tr>
<tr>
<td>3</td>
<td>257 (-10%)</td>
<td>121</td>
<td>3.0</td>
</tr>
<tr>
<td>4</td>
<td>237 (-10%)</td>
<td>121</td>
<td>2.1</td>
</tr>
<tr>
<td>5</td>
<td>217 (-10%)</td>
<td>118</td>
<td>2.5</td>
</tr>
<tr>
<td>6</td>
<td>218 (-10%)</td>
<td>120</td>
<td>1.3</td>
</tr>
<tr>
<td>7</td>
<td>218 (-10%)</td>
<td>120</td>
<td>1.3</td>
</tr>
</tbody>
</table>
in approximately 80 per cent of hypercholesteremic patients.

3. There is no tendency for the hypercholesteremic effect to diminish with prolonged treatment; rather, the effect can frequently be maintained with a lesser dose of nicotinic acid.

4. Cutaneous manifestations such as flushing, itching, or urticaria occurred in all patients at the start of treatment but diminished rapidly and were rarely a decisive factor in influencing therapy.

5. Gastrointestinal distress, which was occasionally present throughout all periods of treatment with nicotinic acid, became a major problem in nearly half of the 20 patients after three or more years of treatment.

6. Most patients had abnormalities in tests of liver function, which were generally mild and transitory, at some time during the course of treatment. To date, none has had evidence of serious or permanent liver damage.

7. Abnormalities in the level of blood sugar and in glucose tolerance tests which simulated those seen in diabetes mellitus occurred at some time during treatment in half of the patients.

8. Mild elevation of the concentration of serum uric acid occurred during treatment in more than two thirds of the patients.

The mechanism by which nicotinic acid decreases the concentration of plasma cholesterol or causes the aforementioned side effects is not yet clearly understood, and there is still no definite evidence that this treatment affects the development of atherosclerosis in humans. Therefore, such therapy must continue to be regarded as investigational.

**Resumen**

En 20 personas con hipercolesterolemia se dio por vía oral ácido nicotínico de 1.5 a 6.0 g. diariamente por periodos de tres a siete años. Se puede resumir la observación como sigue:

1. Es practicable el dar dosis alta de ácido nicotínico por años.

2. Tal proceder es efectivo para decrecer la concentración del plasma en colesterol, a menos de 250 mg. por 100 ml. en aproximadamente 80 por ciento de los casos hipercolesterolémicos.

3. No hay tendencia a que disminuya el efecto hipocolesterolémante con el tratamiento prolongado; más bien, el efecto puede ser mantenido frecuentemente con una dosis más baja de ácido nicotínico.

4. Las manifestaciones cutáneas, tales como bochornos, prurito o urticaria se presentaron en todos los enfermos al principio del tratamiento, pero disminuyeron con rapidez y rara vez fueron decisivos sobre el tratamiento.

5. Los trastornos gastrointestinales fueron ocasionales a través de todos los periodos del tratamiento con ácido nicotínico y fueron un problema mayor en casi la mitad de los enfermos después de tres o más años de tratamiento.

6. La mayoría de los enfermos tenían anormalidades en las pruebas de la función hepática, que fueron en general moderadas y transitorias en alguna época del tratamiento. A la fecha ninguno tiene evidencias de daño hepático grave y permanente.

7. En la mitad de los enfermos apareció anormalidad en el nivel de glucosa en sangre que simuló lo visto en diabetes y esto ocurrió alguna vez durante el tratamiento.

8. Se observó moderada elevación del ácido úrico en el suero en más de dos tercios de los enfermos. Aún no se sabe el mecanismo por el que el ácido nicotínico hace descender la concentración del colesterol plasmático y tampoco hay evidencia clara de que este tratamiento actúe sobre el desarrollo de la aterosclerosis humana. Por tanto, deberá continuarse y considerarse aún como en periodo de investigación.

**Zusammenfassung**

Bei 20 Patienten mit Hypercholesterinaemia wurde Nikotinsäure in oral verabfolgten Dosierungen von 1,5 bis 6 g täglich gegeben über Zeitspannen von 3 bis 7 Jahren. Beobachtungen an diesen Patienten können wie folgt zusammengefaßt werden:

1. Es ist durchaus möglich und praktisch, große Dosen von Nikotinsäure über jahrelange Zeitspannen zu geben.

2. Solche Behandlung ist von Wirksamkeit für die Herabsetzung der Plasmacholesterolkonzentration bis auf weniger als 250 mg per 100 ml in ungefähr 80% der hypercholesterinämischen Patienten.

4. Kutane Manifestationen wie Rötung, Juckreiz oder Urtikaria erzeugten sich bei allen Patienten zu Beginn der Behandlung, gingen jedoch rasch zurück und waren selten ein wesentlicher Faktor bei der Beeinflussung der Behandlung.

5. Gastrointestinalen Störungen, zu denen es gelegentlich während der gesamten Behandlungsperiode mit Nikotinsäure kam, waren zu einem Hauptproblem in nahezu der Hälfte der 20 Patienten nach 3 oder mehr Behandlungsjahren geworden.

6. Die meisten Patienten hatten Veränderungen in den Leberfunktionsproben, die aber im allgemeinen mild und flüchtig waren und zu irgendeiner Zeit während des Behandlungsablaufs auftraten. Gegenwärtig findet sich in keinem Fall ein Anhaltspunkt für einen ernsthaften oder dauernden Leberschaden.


**References**


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**CLINICAL AND BIOCHEMICAL EVALUATION OF DIURETIC EFFECTS OF HYPOTHIAZIDE**

Data on the application of hypothiazide in treating edema of cardiac and renal etiology are presented. Hypothiazide is a powerful diuretic, efficient both in conditions of acidosis and alkalosis. The effect of a single dose of the drug commences within three to six hours and continues for about 24 hours. In edema of various etiology, the administration of hypothiazide increases the excretion of water, sodium and chlorine which is particularly intensive during the first days of its application. During the second half of the therapeutic course, the diuresis and saluresis somewhat decrease, the initial level being restored shortly after the cessation of treatment. The excretion of potassium increases less drastically, but maintains the high level for a longer period sometimes even after the treatment is over. Hypothiazide treatment causes no essential changes in the levels of sodium, chlorine and alkalai reserves of plasma, whereas the concentration of potassium in plasma, even after a short-term application of the average doses of the preparation decreases as compared with the initial level, a fact which is statistically reliable. Potassium of plasma returns to the normal concentration already several days following the cessation of the hypothiazide treatment. The authors recommend repeated courses of the hypothiazide therapy (six to eight days with intervals of four to six days) combined with the administration of sufficient amounts of potassium (3-4 gm. of potassium chloride per 24 hours).


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**TREATMENT OF PLEURAL EFFUSION**

Radioactive colloidal gold (Au198) is an effective agent for the treatment of neoplastic pleural effusions. Eighty-five patients, of whom 73 had metastatic carcinoma of the breast, were treated for recurrent pleural effusion. Seventy per cent of the patients with cancer of the breast showed improvement to initial therapy, and when the treatment was repeated in 52 failures, this figure was 87 per cent. Periods of relief lasted from a few months to over two years. Despite the disadvantages of expense and radiation hazard, Au198 remains one of the best methods of treating malignant pleural effusions caused by carcinoma of the breast.