Treatment of Hypercholesterolemia with Nicotinic Acid


Nicotinic acid was administered orally to 33 patients with hypercholesterolemia in doses varying from 1.5 to 6.0 Gm. per day for periods of 3 months to 1 1/2 years. Significant, sustained, and reproducible decreases in the concentration of cholesterol and total lipids in the plasma and of serum beta-lipoprotein cholesterol were observed in a majority of patients. This form of therapy appears to be effective, practical, and probably free from serious harmful effects.

In 1955 Altschul and co-workers reported a decrease of serum cholesterol in normal and hypercholesterolemic individuals following the ingestion of 1 to 4 Gm. of nicotinic acid over a 24-hour period. Altschul has also described significant decreases of serum cholesterol in hypercholesterolemic rabbits when nicotinic acid was administered for 90 days, and in addition observed that in a majority of animals so treated expected atherosclerotic lesions were either absent or lessened in severity.

These interesting observations led us, with Parsons, to investigate the long-term effects of large daily doses of nicotinic acid given orally to persons with hypercholesterolemia. The findings from this preliminary study were sufficiently encouraging to warrant continued investigation employing a greater number of patients over an even longer period. The purpose of this paper is to report our experience to date regarding the use of nicotinic acid as a means of lowering increased concentrations of blood lipids.

Methods

Individuals were selected for this study if their concentration of plasma cholesterol was consistently higher than 250 mg. per 100 ml. before treatment with nicotinic acid. All those selected were observed as outpatients at the clinic, where they were seen at monthly intervals or more frequently if necessary. At each visit pertinent observations were recorded and necessary examinations made. Upon completing 1 year of treatment, each patient underwent a complete physical and laboratory examination. Each was instructed to continue during the study whichever diet (unrestricted or low in fat) and medications he had employed prior to treatment. Therefore, in each case the only change in management was the addition of nicotinic acid.

Initially, all patients were given 3 Gm. of nicotinic acid daily. This amount was usually taken on the schedule of 2 capsules (1 Gm.) 3 times daily with meals. Whenever possible, changes in dosage were made only after a study period of at least 3 months in order for the effects of a given dose to become stabilized. After each patient had completed 6 months of treatment, placebo capsules identical in appearance to those containing nicotinic acid were substituted in the same dosage schedule for an additional 3 months. Following this, another 3-month period of nicotinic acid therapy was reinstituted, thus completing a year of study. At this time, a change was made in either the dosage of the drug or the

One patient had a pretreatment concentration of plasma cholesterol that averaged 234 mg. per 100 ml.

The nicotinic acid and placebo preparations were kindly supplied by the Eli Lilly Company, Indianapolis, Ind. Except for the placebo, each capsule contained 0.450 Gm. of nicotinic acid and 0.050 Gm. of lactose. For purposes of calculating total dosage, the approximation of 500 mg. of nicotinic acid per capsule was used.
Table 1.—Decreases in Concentration of Blood Lipids Following Treatment with Nicotinic Acid

<table>
<thead>
<tr>
<th>Patients</th>
<th>Study period and change</th>
<th>Plasma cholesterol*</th>
<th>Cholesterol/phospholipid ratio</th>
<th>Total plasma lipides†</th>
<th>Serum beta lipoprotein cholesterol†</th>
<th>Beta/alpha ratio†</th>
</tr>
</thead>
<tbody>
<tr>
<td>All</td>
<td>With lipoprotein studies</td>
<td>33 19</td>
<td>337</td>
<td>1.15</td>
<td>874</td>
<td>238</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0-3 mo.</td>
<td>282</td>
<td>1.08</td>
<td>729</td>
<td>197</td>
</tr>
<tr>
<td></td>
<td></td>
<td>% decrease</td>
<td>16</td>
<td>6</td>
<td>17</td>
<td>17</td>
</tr>
<tr>
<td></td>
<td></td>
<td>21 18</td>
<td>339</td>
<td>1.09</td>
<td>899</td>
<td>238</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3-6 mo.</td>
<td>282</td>
<td>1.08</td>
<td>719</td>
<td>203</td>
</tr>
<tr>
<td></td>
<td></td>
<td>% decrease</td>
<td>17</td>
<td>1</td>
<td>20</td>
<td>15</td>
</tr>
<tr>
<td></td>
<td></td>
<td>17 16</td>
<td>322</td>
<td>1.08</td>
<td>809</td>
<td>216</td>
</tr>
<tr>
<td></td>
<td>Pretreat.</td>
<td>6-9mo. (placebo)†</td>
<td>322</td>
<td>1.13</td>
<td>824</td>
<td>234</td>
</tr>
<tr>
<td></td>
<td>% change</td>
<td></td>
<td>0</td>
<td>+4</td>
<td>+2</td>
<td>+8</td>
</tr>
<tr>
<td></td>
<td>9-12 mo.</td>
<td></td>
<td>323</td>
<td>1.15</td>
<td>822</td>
<td>234</td>
</tr>
<tr>
<td></td>
<td>% decrease</td>
<td></td>
<td>16</td>
<td>3</td>
<td>13</td>
<td>22</td>
</tr>
</tbody>
</table>

* Values are averages of all determinations on all patients treated for period indicated.
† Concentrations are in milligrams per 100 ml.
‡ Beta-lipoprotein cholesterol/alpha-lipoprotein cholesterol.

content of fat in the diet. The effects of any such change were also observed for 3 months before any additional alteration in management was initiated.

Samples of blood for analysis were obtained at weekly intervals for the first 4 weeks of treatment and every 2 weeks thereafter for the first year. After 1 year, specimens were taken at intervals of 4 weeks. Venipunctures and determination of blood lipids were done in the clinic laboratory as a routine part of the usual work load without special labeling or distinction. This procedure ensured complete separation of clinical management of the patients from determination of the concentration of their blood lipids. Plasma cholesterol was determined by the method of Bloor; plasma phospholipids by the Maclay modification of the Gomori method; and total lipids, by the method of Bloor. Cholesterol in the serum lipoprotein fractions was determined concurrently in 16 patients during the first year of treatment by the procedure previously described.

Results and Comment

At the time of this writing 44 persons have begun the program of study previously outlined. Six individuals have not yet completed 3 months of study. Three additional patients stopped treatment shortly after it was started because of gastrointestinal effects, which will be discussed later. Two other persons moved from the city and subsequently have had infrequent return visits. Data from the remaining 33 patients, who have been observed closely for 3 months or longer, form the basis of this report.*

Effect of Treatment on Concentration of Plasma Lipids. Following the administration of 3 Gm. of nicotinic acid daily for 3 months, the concentration of plasma cholesterol decreased an average of 16 per cent from pretreatment values (table 1). There was also a similar decrease (17 per cent) in the concentration of total plasma lipids, and a lesser decline (6 per cent) in the cholesterol-phospholipid ratio. The various ranges of diminution in concentration of plasma cholesterol are shown in table 2. During the second 3-month period of treatment (3 to 6 months) the decrease in plasma lipids was the same or slightly greater. This improvement may be partly explained by the fact that the average dose of nicotinic acid per person during this second 3-month period was 0.5 Gm. more than the original starting amount. During

*Tabular data on the individual patients are available from the authors to those with special interest in the subject.
the third 3-month period of study (6 to 9 months), when a placebo was administered, concentration of plasma lipids increased so that the average values were remarkably similar to those obtained prior to treatment (Table 1). Following the placebo period, treatment with nicotinic acid was reinstated with the original dose of 3 Gm. per day being used for an additional interval of 3 months, which then completed 1 year of study. The concentration of plasma lipids was again decreased, with the degree of diminution closely approximating that obtained during the initial 3 months of treatment.

Of the 33 patients, 19 had pretreatment concentrations of cholesterol of more than 300 mg. per 100 ml. of plasma. Following treatment for 3 months with nicotinic acid, 13 of these 19 had a decrease in plasma cholesterol of 15 per cent or more, while only 4 of the remaining 14 persons with pretreatment levels of less than 300 mg. had a similar response. This suggests that persons with higher initial concentrations of plasma cholesterol usually obtain a greater response to treatment with nicotinic acid than do those with lower pretreatment levels.

Of the 33 patients treated for at least 3 months, only 1 failed to achieve a decrease in the concentration of plasma lipids; in this instance the levels during treatment were slightly increased from those noted before treatment and during placebo administration. Thus far, 23 patients have maintained concentrations of plasma cholesterol that have averaged less than 260 mg. for at least 1 3-month period of treatment with nicotinic acid.

**Effect of Treatment according to Sex, Age, and Diagnosis.** An effort was made to determine whether various groups of patients showed significant differences in response to therapy. The women had only slightly higher pretreatment concentrations of plasma cholesterol than did the men, yet their response to treatment was nearly twice as great. Although patients 48 years of age or older had a greater decrease in concentration of plasma cholesterol than did those less than 48, half the older group were women. Hence, the more favorable response to treatment exhibited by the older age group is probably related to the greater proportion of women in this group. The grouping of patients into those with familial hypercholesterolemia, those with disease of the coronary arteries, and those with arterial hypertension did not reveal any significant differences in response to treatment from that obtained by the entire group. As more information was obtained regarding relatives of the patients in this study, more of them could be classed as having familial hypercholesterolemia. It seems likely that if sufficient data were available the hypercholesterolemia of nearly all our patients might be termed "familial," and therefore such distinction serves no useful purpose.

**Effect of Increased Dosage on Concentration of Plasma Lipids.** The effects on plasma lipids when the dose of nicotinic acid was increased were studied on 17 occasions, with the results shown in Table 3. With the exception of 4 occasions, each increase in the daily amount of nicotinic acid produced a definite further decrease in the average concentration of cholesterol and total lipids in the plasma as compared with values resulting from the lesser dose. Decreases in the cholesterol-phospholipid ratio also occurred, but these were small. As seen in Table 2, 48 per cent of all patients treated initially with 3 Gm. of nicotinic acid daily for 3 months obtained

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### Table 2—Percentage Decrease in Concentration of Plasma Cholesterol from Placebo or Pretreatment Values Following Therapy with Nicotinic Acid

<table>
<thead>
<tr>
<th>Average decrease in plasma cholesterol, %</th>
<th>Patients treated for indicated period with indicated average dose (Gm./day) of nicotinic acid</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0-3 mo. (3 Gm.)</td>
</tr>
<tr>
<td>Increased</td>
<td>1</td>
</tr>
<tr>
<td>0-14</td>
<td>16</td>
</tr>
<tr>
<td>15-29</td>
<td>13</td>
</tr>
<tr>
<td>30-44</td>
<td>3</td>
</tr>
<tr>
<td>Total</td>
<td>33</td>
</tr>
</tbody>
</table>

* During the third 3-month period (6-9 mo.) a placebo was given.
a lowering of plasma cholesterol by 15 per cent or more. When the average daily dose per person was 3.5 Gm., 67 per cent of the patients achieved a similar decrease in the plasma cholesterol. Following the period of placebo administration, 3 Gm. per day of nicotinic acid was again given for another 3-month period, and again one half of the patients obtained a decrease of 15 or more per cent in the level of plasma cholesterol. Subsequently, an average daily dose of 5 Gm. of nicotinic acid was administered for 3 additional months, which resulted in a reduction in the concentration of plasma cholesterol of 15 or more per cent in 82 per cent of the patients. From these observations it appears that most patients who fail to obtain a satisfactory decrease in cholesterol when treated with nicotinic acid in daily doses of 3 Gm. or less will respond further to increased doses of the drug.

**Diet.** At the beginning of the study 16 of the 33 patients were eating diets without restriction of fats, 8 avoided "extra fat" in their meals but did not follow any precise diet, 7 were attempting to adhere to diets that contained 40 Gm. or less of fat per day, and 2 were following diets low in calories for reduction of body weight. Although the patients were instructed to continue on these same dietary programs during the study, it became apparent that many did not do so, especially those with diets severely restricted in fat content. Because of these variations in diet and because it was not practical for our patients to eat diets uniform in fat content prepared at a diet kitchen, we could not accurately assess the effect of diet in this study. However, since the pretreatment values for plasma lipids were very similar to those obtained during placebo administration, it is believed that dietary variations did not influence significantly the results obtained. This is supported further by the finding that 16 patients experienced little change in weight during treatment for 1 year, 6 gained a combined total of 37 pounds, 9 lost a combined total of 37 pounds, and 1 had no change.

**Effect of Treatment on Concentration of Lipoprotein Cholesterol in Serum.** Determinations of lipoprotein cholesterol in the serum were carried out in 19 patients of whom 16 were observed for 1 year (table 1). The percentage decrease of serum beta-lipoprotein cholesterol following treatment with nicotinic acid closely paralleled the percentage decrease of total plasma cholesterol during each period of therapy. Simultaneously, there was a similar percentage increase in the concentration of the serum alpha,-lipoprotein cholesterol. These changes resulted in considerable decrease in the ratio of beta-lipoprotein cholesterol to alpha,-lipoprotein cholesterol, hereinafter referred to as the "beta/alpha, ratio." Previous data have shown that 95 per cent of normal young women have beta/alpha, ratios of less than 3.8. This value, or less, was attained during some period of treatment with nicotinic acid in 11 of 18 patients whose ratios were greater than 3.8 before treatment or during placebo administration.

It is clear that further study is needed in order to establish what, if any, practical advantages are to be gained from a knowledge of the serum lipoprotein fractions. Our experience indicates that variations in total plasma cholesterol are nearly always associated with similar changes in the beta-lipoprotein cholesterol, but with the alpha,-lipop-
protein cholesterol varying in the opposite direction. We believe that an accurate determination of total blood cholesterol is adequate in most instances and offers the most practical method for planning and assessing the results of therapy in patients with hypercholesterolemia.

**Symptoms and Signs during Therapy.** Symptoms and signs associated with the administration of nicotinic acid are shown in table 4 for all 44 persons who started treatment. The complaints of cutaneous flushing, pruritus, and mild urticaria were noted by all patients at the onset of treatment and were of moderate to marked severity in 91 per cent. An interesting feature of this reaction was the rapid decrease in severity noted by most patients so that after 3 days of treatment only 43 per cent had severe reactions, and after 2 weeks only 14 per cent noted similar effects. Several persons had severe skin flushing and itching with only the first 1 or 2 doses. Of the 30 patients who had persistence of flushing or pruritus after 2 weeks of treatment, 18 experienced this effect only after the first morning dose. Most patients noted that the degree of flushing was lessened considerably by taking the nicotinic acid with meals, and this procedure was usually recommended. Following reinitiation of therapy after administration of the placebo or after lapses in taking the medication, flushing again became prominent and followed the original pattern of reaction. When doses of nicotinic acid were increased there was rarely any increase in flushing, and 6 persons flushed less while taking the increased dose. In no instance was treatment with the drug discontinued because of these cutaneous side-effects.

Anorexia, nausea, and occasionally frequent soft stools were complained of by 18 per cent of the patients during the first 2 weeks of nicotinic acid therapy. Three women felt that these complaints were sufficiently disagreeable to discontinue treatment altogether. After 2 weeks of therapy only 3 additional people (7 per cent) experienced gastrointestinal complaints to any appreciable degree, and therapy was not stop-

<table>
<thead>
<tr>
<th>Signs and symptoms</th>
<th>Initial effects, 1-14 days (44 patients)</th>
<th>Late effects (41 patients)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Patients</td>
<td>%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cutaneous flushing, burning, and pruritus</td>
<td>Severe</td>
<td>29</td>
</tr>
<tr>
<td></td>
<td>Moderate</td>
<td>11</td>
</tr>
<tr>
<td></td>
<td>Mild</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>None</td>
<td>0</td>
</tr>
<tr>
<td>Anorexia and nausea</td>
<td>8*</td>
<td>18</td>
</tr>
<tr>
<td>Increased hair growth (?)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Herpes simplex</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Pityriasis rosea</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Dry taste in mouth</td>
<td>1</td>
<td>2</td>
</tr>
</tbody>
</table>

* Three patients stopped study as a result of symptoms.
† One patient had esophagitis which subsided.
ped in these instances. In 1 woman who had a previously known diaphragmatic hernia, esophagitis developed while she was taking 6 Gm. of nicotinic acid daily, but this subsided following appropriate treatment and reduction of the medication to 4.5 Gm. per day.

Herpes simplex, pityriasis rosea, and a questionable increase in growth of facial hair were noted in 2 instances each during the treatment period, but these could not be definitely attributed to therapy with nicotinic acid.

While receiving treatment with nicotinic acid many patients reported subjective improvements in well-being which were not observed during the period of placebo administration, but there did not appear to be any consistent relationship between subjective reactions and objective findings. It is apparent that the taking of a drug with such an obvious effect on the patient (cutaneous flushing and itching) as well as the continued interest shown by sympathetic physicians must exert a considerable psychologic effect. For this reason it is difficult to make any firm conclusions based on subjective evaluation. With this in mind, it can be said that none of the patients with angina pectoris had any increase in their symptoms while being treated with nicotinic acid, and most of them considered that they were improved in this regard. In contrast, it must be pointed out that 1 patient sustained an acute myocardial infarction during treatment. He has continued to take the drug, however, and his recovery has been uneventful. Two additional patients died suddenly and unexpectedly while taking the placebo following 6 months of therapy with nicotinic acid. Necropsy revealed extensive coronary atherosclerosis as the cause of death in both patients. It seems unlikely that treatment with nicotinic acid had any part in the deaths of these patients, but the possibility cannot be entirely excluded.

After 1 year of study all patients underwent a complete physical and laboratory examination including electrocardiograms and tests of hepatic and renal function in a further attempt to evaluate the effects of treatment with nicotinic acid. No untoward results were noted.

**Mechanism of Action.** The mechanism by which nicotinic acid reduces the concentration of blood lipids is not known. Altschul and co-workers have suggested that intracellular oxidation might be enhanced with a greater formation of oxycholesterols, and that this form may be more readily excreted than cholesterol.

**Summary**

On the basis of our observations on 33 patients with hypercholesterolemia, it appears conclusively established that in most instances large doses of nicotinic acid administered orally for periods of 3 months to 1½ years significantly decrease the concentration of plasma cholesterol, total lipids, and serum beta-lipoprotein cholesterol. This decrease can be maintained for periods exceeding 1 year, but disappears when treatment is stopped. The degree of response to treatment varies widely but is reasonably reproducible for each individual.

A distinct relationship between dose and effect has been demonstrated for individual patients as well as for the group in which changes in dose were studied. Increasing the daily dose of nicotinic acid resulted in further lowering of concentration of the blood lipids from those values obtained following administration of a lesser dose. This result was reversed when the amount of nicotinic acid was decreased. By using nicotinic acid in amounts of 3 Gm. per day and by increasing this dose as needed, three fourths or more of patients with hypercholesterolemia obtained a satisfactory decrease of their blood lipids. Thus far, 6 Gm. of nicotinic acid daily is the largest amount we have used.

Those persons with higher initial concentrations of cholesterol in the plasma usually obtained a greater response to treatment than did those whose values were lower before treatment. As a group, women had a considerably better result than did men. The
diets of the patients were not changed during the study, and the data suggest that diet remained a rather constant factor which did not appreciably influence the results.

Side reactions to treatment, while frequent, did not create any marked problems of management. Severe cutaneous flushing and pruritus occurred in nearly all patients when treatment with nicotinic acid was started, but this usually subsided rapidly. Many persons experienced mild flushing subsequently, but this did not constitute an appreciable limitation to therapy. Anorexia and nausea occurred much less frequently than did the cutaneous effects, but were sufficiently disagreeable in 3 women to cause them to discontinue treatment permanently. Thorough physical and laboratory examinations revealed no evidence of other untoward effects from treatment.

Nearly all patients experienced subjective improvement in well-being that seemed unrelated to any objective findings. No increase in severity of angina pectoris was noted by patients who had this symptom, and many experienced less angina during treatment. Two patients died suddenly as a result of atherosclerotic heart disease during the period of placebo administration, and another sustained an acute myocardial infarction while on treatment with nicotinic acid. Therefore, while this form of treatment appears safe, further observations will be necessary to verify this impression.

It is not within the scope of this paper to discuss whether or not therapy designed to lower abnormally increased concentrations of blood lipids is an effective form of treatment or prophylaxis for atherosclerosis. However, if such a goal is desired, then large oral doses of nicotinic acid appear to offer yet another means by which blood lipids may be decreased. In our experience this method has been highly effective, very practical to carry out, and is probably quite safe. Further investigation, especially comparative studies with other forms of therapy, is needed before the proper role can be assigned to such use of nicotinic acid.

**Summario in Interlingua**

Super le base de nostre observationes in 33 patientes con hypercholesterolemia, il pare definitivemente estabili que in le majoritate del casos grande doses de acido nicotinic administrate oralmente durante periodos de inter 3 menses e 1½ annos effectua reduciones significative in le concentration del cholesterol in le plasma, del lipidos total, e del cholesterol de lipoproteina beta in le sero. Iste reduction pote esser mantenite durante periodos de plus que un anno, sed illo dispere quando le tractamento es interrupite. Le grado del responsa al tractamento varia grandemente ab un paciente al altere, sed illo es satis reproducibile in un subjecto individual.

Un distincte relation inter le magnitude del dose e su effecto esseva demontrate in patientes individual e etiam in grupplos in que variationes de dosage esseva studiate. Augmentos del dose diurne de acido nicotinic resultava in reductiones additional del concentration de lipidos del sanguine in comparation con le valores jam obtenite per le administration de doses plus micre. Iste resultato se revertava quando le quantitate del acido nicotinic administrate esseva reducite. Per le uso de acido nicotinic in doses de 3 g per die, sequite per augmentos de dosage in tanto que indicate, tres quartos o plus del patientes con hypercholesterolemia obteneva reductiones satisfactori del lipidos in lor sanguine. Usque al tempore presente, 6 g de acido nicotinic per die es le maximo unquam usate.

Patientes con plus alte concentrationes initial de cholesterol in lor plasma obteneva usualmente plus pronunciate responsas sub le tractamento, comparare con patientes in qui le valores esseva minus elevate ante le institution del therapia. Considerate como grupo total, feminas monstrava considerabilemente melior resultatos que homines. Le dieta del patientes non esseva alterate durante le tractamento. Le datos colligite reflecte le facto que le dieta esseva un factor satis constante que non exerceva ulle considerable influentia super le resultatos.
Le reazione del lato provocate per le terapie esibivano numerose sed non rappresentavano importanti problemi terapeutici. Severi gradi di rubore cutaneo con prurito si osservavano in quasi tutti i pazienti quando le terapie con acido nicotinico venivano iniziate, sed in le majorità del casi il fenomeno si manifestava rapidamente. Minus pronunciati gradi di rubore esibivano esperienze subseguentemente per molti dei pazienti, sed isto non costituiva un serio ostacolo al trattamento. Anorexia e nausea si osservavano molto meno frequentemente che le effetti cutanei, sed i loro effetti side effetti disgradabili si osservavano in malgrado la paziente a interrompere le terapie permanentemente in 3 casi. In omne isto il trattamento di farmaci. Meticoloose esibivano mutuli segni di altere effetti: avere di iste forma di trattamento.

Quasi omne le pazienti experimentivano un migliorare subjective di ben-esser che pareva esser in relazione a un significativo obiettivo. Nulla aumento del severità di angina del pectore esibivano notate per pazienti che avevano iste symptomatologia, e multe esibivano minus angina durante le terapie therapeutic. Due pazienti morivano subitemente in conseguenza di atherosclerotic morbo cardiae durante un periodo di administration di un medicina fictitiae. Un altere paziente sussurrava un acut infarcimento myocardial durante le curso di acido nicotinico. Per conseque, ben che il pare che iste forma de trattamento es disproviste de riso, observationes additional es requirete pro confermare iste impression.

Il non es parte del objectivos del presente reporto de discuter si o non un trattamento che visa a reducere anormalmente alte concentrazione de lipidos in le sanguine es un efficace forma de terapia o de prophylaxe contra le occurrentia de atherosclerosis. Tamen, si le effectuation de tal reductiones es desirete, grande doses de acido nicotinico esibivano apparentemente un medio additional pro reducere le livello del lipidos in le sanguine. In nostre experientia iste metodo ha essite efficacissime, multo practico in sua application, e apparentemente satis libero de riso. Investigationes additional, specialmente studios comparative con altere formas de terapia, es requirite ante che le rolo definitivo de iste maniera de usar acido nicotinico pote esser determinate.

REFERENCES
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RICHARD W. P. ACHOR, KENNETH G. BERGE, NELSON W. BARKER and BERNARD F. MCKENZIE

_Circulation_. 1958;17:497-504
doi: 10.1161/01.CIR.17.4.497
_Circulation_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

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