Niacin: Antipellagra Factor, Hypcholesterolemic Agent

Model of Nutrition Research Yesterday and Today

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Niacin, the antipellagra factor, which was found recently to be a hypcholesterolemic agent, serves as well as a prototype of the trends in nutrition research in the present century. When Joseph Goldberger initiated his studies of the etiology of pellagra in 1914,1,2 the concept that disease could be due to deficiency of a nutritional factor was relatively new and had not gained wide acceptance. His brilliant epidemiological studies, culminating in the experimental production of pellagra in a group of prisoners by dietary restriction, proved that pellagra was due to nutritional deficiency.3,4 Search for the missing dietary factor required more than 20 years. Goldberger5 participated in this search and suggested at one time that amino acid deficiency might be involved but later concluded that vitamin deficiency was probably responsible.

Nutrition research during the 25 years following Goldberger’s early work was directed primarily toward determination of essential dietary substances for animals and man and delineation of the deficiency syndromes resulting from an inadequate supply of essential nutrients, particularly vitamins. The clinical and pathological changes in deficiency states were described, and, in the latter part of this period, attention was directed toward elucidation of the role of nutrients in metabolism. This evolution of nutrition research is illustrated by investigations leading to discovery of the antipellagra factor6 (Table 1). A dietary-deficiency disease, known as blacktongue, that appeared to be the canine analogue of human pellagra, was produced in dogs. This experimental approach, used with other nutrients also, was of great assistance in the search for pellagra-preventive vitamin. In 1935, niacinamide was found to be a part of two coenzymes, one obtained from erythrocytes, triphosphopyridine nucleotide, and the other, a substance needed for the alcoholic fermentation of carbohydrate by yeast, diphosphopyridine nucleotide. Niacinamide was isolated from heart muscle and then from liver by Elvehjem and associates.7,8 These workers administered niacin and its amide to dogs with blacktongue and found that it cured the disease. Shortly after this, niacin was administered to patients with pellagra by a number of investigators and shown to be therapeutically effective.

The remarkable advances in biochemistry, particularly since 1940, were applied widely in nutrition research and made possible delineation of the exact role of many nutrients at the cellular and molecular levels. The use of radioisotopes permitted tracing of the metabolic pathways of nutrients from ingestion through utilization to breakdown and excretion. The requirements of a number of nutrients, especially vitamins, were determined. Niacin may again be utilized to illustrate these trends in research.

Our interest in niacin began in the early 1940’s after this vitamin had been shown to be the antipellagra factor and when methods were being developed to assay some of the urinary exception products of niacin metabolism. At this time, it was thought that the problem of the etiology of pellagra had been solved completely. However, further studies uncovered findings that could not be explained satisfactorily. Diets in some parts of the world in which pellagra was not encountered contained less niacin than did corn diets which were associated with pellagra. Furthermore, certain pellagra-preventive foods, such as milk, were low in niacin. Investigations at the University of Wisconsin assisted in solving the problem. Krehl and as-

Table 1.—Highlights in Niacin Research, 1915-1940

| Pellagra—A deficiency disease |
| Blacktongue in dogs—Canine pellagra |
| Niacin—A coenzyme and tissue constituent |
| Niacin—The antipellagra factor |

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associates\textsuperscript{11} observed that when rats were fed diets containing 40\% corn, there was cessation of growth. Administration of either niacin or tryptophan restored growth to normal. The rationale for tryptophan administration was that one of the proteins in corn, zein, is low in this amino acid. Shortly after this, Rosen and associates\textsuperscript{12} found that administration of tryptophan to rats led to a marked increase in the urinary excretion of the niacin metabolite, N\textsuperscript{1}-methyl nicotinamide (N\textsuperscript{1}-Me). The findings suggested that tryptophan might be a precursor of niacin (Table 2).

About this time we initiated studies in human subjects and found that the administration of tryptophan led to an increase in excretion of N\textsuperscript{1}-Me in the urine.\textsuperscript{13} Similar findings were reported by Perlzweig and associates.\textsuperscript{14} Subsequently, Vilter et al\textsuperscript{15} and our group found that the administration of tryptophan in large amounts was effective in the treatment of pellagra. It appeared likely that tryptophan was converted in the body to niacin. Studies of many investigators using neurospora and several animal species elucidated the pathway of this conversion\textsuperscript{9} (Fig 1).

At one time it was suggested that tryptophan might catalyze the synthesis of niacin by intestinal bacteria rather than being converted to niacin in the tissues. However, it was shown that in the enterectomized rat the administration of tryptophan was followed by an increased urinary excretion of niacin compounds. In human subjects we found that the conversion of tryptophan to niacin was not affected by oral administration of streptomycin in amounts that largely inhibited the growth of intestinal microorganisms. Finally, the conversion of tryptophan to niacin was demonstrated unequivocally by several groups of investigators using radioisotope techniques.\textsuperscript{8} Administration of tryptophan labeled with radioactive carbon (\(^{14}\)C) was followed by recovery of niacin in the urine with the isotope in the carboxyl group. When the indole nucleus of tryptophan was labeled with tritium, the label appeared in the ring nitrogen of niacin derivatives in the urine. The conversion of tryptophan to niacin is a rather inefficient process. Data obtained in human subjects by Horwitt et al\textsuperscript{16} and in our laboratory\textsuperscript{7} indicated that an average of about 60 mg of tryptophan can be converted to 1 mg of niacin. Thus, two centuries after pellagra was first described by Casal in Spain, this disease was shown to be due to deficiency of a vitamin, niacin, and its precursor, the amino acid tryptophan.

In the 1940’s, proteins and their constituent amino acids became a prominent area of nutrition research. Rose\textsuperscript{18} determined minimum requirements of amino acids in rats and in man. The estimation of minimum tryptophan requirement for the maintenance of nitrogen balance made possible the formulation of diets containing little excess tryptophan and set the stage for determination of human niacin requirements. With this objective, studies were initiated in our laboratory\textsuperscript{19,20} and in that of Horwitt and associates.\textsuperscript{16} In our studies, niacin deficiency was induced in 15 of 19

![Table 2.—Highlights in Niacin Research, 1940-1955](image)

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<th>Tryptophan—A niacin precursor</th>
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<td>Human Niacin Requirement—4.4 mg/1,000 calories</td>
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<td>Corn diets—Relationship to pellagra</td>
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long-term experiments in adult human subjects. Practically all of the characteristic manifestations of pellagra were observed. The diets that resulted in pellagra furnished 3.4 to 5.4 mg of niacin and 151 to 207 mg of tryptophan daily. Twelve of the subjects who developed pellagra received diets containing corn as the principal cereal, whereas three received diets containing wheat. In Horwitt’s studies, none of 15 subjects developed evidence of niacin deficiency. His diets provided 5.2 to 7.0 mg of niacin and 238 to 318 mg of tryptophan. The diets contained no corn, although 6 gm of zein was included. The potential total niacin values of the diets furnished by Goldsmith and Horwitt and their associates can be calculated by assuming that approximately 60 mg of tryptophan is equivalent to 1 mg of niacin. Such calculations showed that diets that resulted in experimental pellagra furnished 5.9 to 8.8 mg of niacin equivalent, whereas the diets that did not induce deficiency furnished 9.2 to 12.3 mg. From these data, minimum niacin requirement for the prevention of pellagra appeared to be about 9 mg/day.

Calculation of the niacin equivalent of the diets used by Goldberger and Wheeler in 1915 in the production of pellagra indicated a value of about
12 mg. The caloric intake of Goldberger’s diet was much higher than that of diets used by Horwitt or Goldsmith. Horwitt analyzed all data available and concluded that the minimum amount of niacin that would prevent pellagra, including that formed from tryptophan and assuming a conversion factor of 60 to 1, was 4.4 mg/1,000 calories, except at low levels of caloric intake, when at least 8.8 mg was required.

**Pellagragenic Effect of Corn.**—Other studies in our laboratory, with diets containing a constant amount of tryptophan (200 mg) and varying amounts of niacin, indicated a significant change in the percentage of dietary niacin excreted in the urine as metabolites when the niacin content of the diet approached 8 to 10 mg daily. Assuming that 60 mg of tryptophan will supply 1 mg of niacin, the total niacin furnished by these diets was 11 to 13 mg. These and other studies of niacin-tryptophan relationships and niacin requirement indicate that the pellagragenic effect of corn diets may be explained in large part by the low niacin and tryptophan content of corn. They also illustrate an area of interest in nutrition research in recent years, namely, interrelationships among nutrients. Another illustration of such interrelationships was the development of angular stomatitis and cheilosis in our subjects in whom experimental pellagra was induced. These findings are usually attributed to riboflavin deficiency. The diet contained adequate riboflavin, and the signs disappeared when niacin or tryptophan was administered.

Factors other than the niacin and tryptophan content of corn may play a role in the pellagraenic effect of this cereal. Most of the niacin in corn has been shown to be present in bound forms which is unavailable to the experimental animal. It can be made available by treatment with alkali. It was suggested that treatment of corn with lime, a practice common in Central America, might be a partial explanation for the relatively low incidence of pellagra in this area, in which corn supplies about 80% of the caloric value of the diet. Experiments in our laboratory indicated that pellagra could be produced as readily with lime-treated as with untreated corn. However, corn products furnished only 15% to 20% of the caloric intake. In the process of treating corn with lime in Central America, there is an overall loss of niacin of about 20%. If release of bound niacin is responsible for a pellagra-preventive effect of lime-treated corn, the amount of niacin made available must be large enough to more than compensate for the overall loss. This might be the case.

Amino acid imbalance has been suggested as another factor in the relationship of corn diets to pellagra. Corn has a high leucine content as has another cereal, jowar (Indian millet). Gopalan and Srikantia reported that administration of leucine caused an increase in the urinary excretion of N'-Me. They suggested that excess leucine caused amino acid imbalance which resulted in loss of niacin from the tissues. Studies in our laboratory failed to confirm these findings.

For many years it was thought that corn contained a toxic or inhibitory factor. Woolley concluded from experiments in mice that such a substance was present in corn. In our investigations, we found that pellagra seemed to develop more rapidly and to be more severe with corn than with wheat diets of similar niacin and tryptophan content. In addition, pellagra was induced more rapidly with whole corn than with degerminated corn. These findings might be explained by the presence of some inhibitory substance in corn, particularly in the bran and germ layers, which affects requirement or utilization of niacin. However, there are other possible explanations for the findings. If an inhibitory factor is present in corn, it appears to have a minor role in the development of human pellagra.

Methods for the evaluation of niacin nutrition by estimation of urinary excretion of niacin metabolites have been developed through studies of normal subjects and of patients with experimental and endemic pellagra. The two principal metabolites of niacin found in the urine are N'-Me and the 6-pyridone of N'-Me. In pellagra the combined excretion of these two metabolites in the urine is usually less than 2 mg in 24 hours. In mild deficiency, slightly larger quantities are excreted. Normal subjects receiving good diets excrete in the neighborhood of 5 to 8 mg of N'-Me and 7 to 10 mg or more of pyridone daily.

**Functions of Niacin.**—The functions of niacin have been widely studied in recent years. Niacin or one of its derivatives is required by all living cells. It is an essential component of two coenzymes, diphosphopyridine nucleotide or coenzyme I (nicotinic adenine dinucleotide [NAD]) and triphosphopyridine nucleotide or coenzyme II (nicotinic adenine dinucleotide phosphate [NADP]). More than 40 biochemical reactions dependent on these enzymes have been identified. The major function of NAD and NADP is the removal of hydrogen from certain substrates in cooperation with dehydrogenases and the transfer of hydrogen or electrons to another coenzyme in the hydrogen transport series or to another substrate which is correspondingly reduced.

The many reactions in which NAD and NADP are involved include glycolysis, pyruvate metabolism, pentose biosynthesis, and the process by which high-energy phosphate bonds are synthesized. They also function in lipid, amino acid, and protein metabolism and in photosynthesis. The exact reactions and mechanisms involved in many of these complex systems remain unknown.

**Niacin Deficiency in Various Disease States.**—In recent years, the effects of various diseases and of chemotherapeutic agents on the nutritional status of the patient has received increased attention (Table 3). Nutritional deficiency may occur as a complication of pathological states in which food
intake is restricted, in which there is interference with absorption or utilization of nutrients, or in which nutrient requirements are increased. Most of the pellagra in the United States at the present time occurs in association with chronic alcoholism. It may be encountered also in patients with cirrhosis of the liver, chronic diarrheal diseases, diabetes mellitus, neoplasia, prolonged febrile illnesses, and thyrotoxicosis or after parenteral feeding without niacin supplementations. Signs of lack of niacin have been reported in patients with malignant carcinoid tumors. In this instance, as much as 60% of the body’s tryptophan may be converted to 5-hydroxytryptamine instead of a normal 1%. This may result in less tryptophan being available for synthesis of niacin.

Modern methods of therapy occasionally lead to the development of deficiency states. Pellagra has occasionally been observed during therapy with isonicotinic acid hydrazide which is a pyridoxine (vitamin B₆) antagonist and may cause pyridoxine deficiency. Pyridoxine is needed in one of the steps of the conversion of tryptophan to niacin and in severe deficiency this conversion may be curtailed.

Nutrition research has become concerned with inborn errors of metabolism. An hereditary disease characterized by a pellagra-like skin rash, severe but reversible cerebellar ataxia, and psychological disturbances has been described in families and termed Hartnup disease. Gross aminoaciduria of renal origin and abnormalities of tryptophan metabolism are characteristic. It has been suggested that there is defective transport of tryptophan across the cells of the jejenum and proximal renal tubules. Tryptophan is found in the feces, which is not the case in normal subjects. Kynurenine excretion in the urine is decreased. Presumably there is a decrease in the conversion of tryptophan to formylkynurenine. This would result in a decrease in the conversion of tryptophan to niacin. Niacin will relieve the pellagra-like symptoms of this disease.

Dietary Factors and Atherosclerosis.—Currently, there is wide interest in the role of nutrition in diseases that are not considered to be primarily nutritional in origin. Extensive investigation has indicated a relationship between a number of dietary factors and the development of atherosclerosis. Fats have received particular attention, but proteins, carbohydrates, vitamins, and minerals have been implicated as well. Some years ago, a causal relationship was postulated between dietary fat, serum cholesterol concentrations, and atherosclerosis on the basis of epidemiologic and clinical studies in man and investigations in several animal species. Many dietary manipulations, including changes in the amount and kind of dietary fat, have been shown to influence the levels of cholesterol and other lipids in the serum, but the role that serum lipids play in atherogenesis is still uncertain.

Effects of Niacin on Cholesterol Level.—Many pharmacological agents have been shown to influence serum lipid concentrations, among them niacin. In 1955, Altshul first observed that the administration of large doses of niacin lowered serum cholesterol levels in human subjects. Administration of the niacinamide was without effect. This observation was confirmed by Parsons et al and by investigations in our laboratory. Our interests have been centered primarily on elucidation of mechanisms that control serum lipid concentrations and determination of the mode of action of various dietary factors and pharmacological agents. Serum lipids can be reduced by (1) decreasing the quantities supplied by the diet, (2) limiting absorption, (3) inhibiting tissue synthesis, (4) increasing degradation or excretion, or (5) affecting lipid transport or distribution with an increase in tissue lipids at the expense of those in the circulating blood. The concentration of serum cholesterol is known to be the result of the amount ingested and absorbed, plus the amount synthesized in the body, as related to the amount excreted in the bile as cholesterol or bile acids (to which cholesterol is degraded) and the amount utilized or stored in the tissues. Some of the bile acids and cholesterol are reabsorbed from the intestine and act as a feed-back mechanism influencing the amount of cholesterol synthesized and degraded. Details of the feed-back mechanism are being gradually elucidated.

Niacin in large doses, 3 to 6 gm daily, causes a reduction in the concentrations in serum of cholesterol, both free and esterified fractions, triglycerides, and, to a lesser extent, phospholipids. In our investigations of the mechanism of action of niacin, the first hypothesis was that it might increase fecal excretion of lipids. Subjects were placed in a metabolism ward on controlled diets, high in saturated or unsaturated fat, and niacin was administered. Fecal excretion of fats, sterols, and bile acids was determined. Niacin was found to have no effect on excretion of these compounds. Subsequent studies showed that the action of niacin was not related to depletion of methyl groups in the body. Administration of methionine with niacin had no influence on its action in lowering serum lipid levels. Since both methionine and choline influence lipid transport, these data suggested that niacin did not influence lipid transport indirectly through methionine.

It appeared possible that the action of niacin might be related to an increased demand for the production of aminoacetic acid (glycine). Niacin is conjugated with aminoacetic acid to form nicotinuric acid, which is a major excretry product.

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<td>Niacin deficiency induced by drugs</td>
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The same type of condensation occurs in the case of bile acids which are excreted in conjugated form. Niacin might compete with bile acids for aminoacetic acid. To test this possibility, sodium benzoate, which also requires aminoacetic acid for detoxification, was administered to human subjects, being substituted for equimolar amounts of niacin. It was not effective in lowering serum lipid levels. In other studies, when niacin was given in association with diets high in unsaturated fat as compared with those high in saturated fat, smaller amounts of nicotinuric acid were excreted in the urine during the unsaturated-fat regimen. The excretion of methylated products of niacin was the same with both diets. Unsaturated fat may lower serum cholesterol in part by increasing the fecal excretion of sterols and bile acids, although this remains controversial. The administration of unsaturated fat may have reduced formation of nicotinuric acid by the liver when bile acid excretion increased, as both substances require conjugation with aminoacetic acid. These data suggest a possible competition for aminoacetic acid. Although this does not explain the mechanism of action of niacin in lowering serum lipids, it might explain the retention of sulfobromophthalein (Bromsulphalein) that occurs in some patients receiving niacin. This substance also requires aminoacetic acid conjugation prior to excretion. When niacin is administered, large amounts of nicotinuric acid are excreted in the urine, whereas none is excreted when niacinamide is given. At one stage in our investigations, some data suggested that nicotinuric acid might be the metabolite of niacin responsible for lowering serum cholesterol concentration. Subsequent experiments failed to substantiate this hypothesis.

In experiments using rat-liver mitochondria, Kritchevsky and associates\(^7\) reported that niacin caused an increased oxidation of cholesterol to bile acids by the liver and suggested this might be responsible for its hypcholesterolemic effect. This seems unlikely in view of our failure to find an increase in fecal excretion of bile acids. The most probable mechanism of action of niacin is an effect on the biosynthesis of cholesterol and perhaps of other lipids. It has been reported that liver slices from rats fed niacin converted more acetate \(^1^4\)C to carbon dioxide and less to cholesterol and fatty acids than did liver slices from control rats.\(^8\) Parson's studies in human subjects indicated that less acetate \(^1^4\)C was converted to cholesterol when patients were receiving niacin. Studies in our laboratory showed that the decrease in total cholesterol esters during therapy with niacin was the result of proportionately equal lowering of cholesteryl linoleate, arachidonate, oleate, stearate, and palmitate.\(^9\) This might be interpreted as indicative of a decreased synthesis of cholesterol, since the decrease in cholesterol esters resulting from administration of unsaturated fat or of neomycin did not result in proportionate lowering of cholesterol esters. If niacin inhibits cholesterol synthesis, the failure to find any other sterol in the serum of patients treated with niacin is consistent with the view that it inhibits the sequence of reactions prior to the cyclization of squalene to form lanosterol.

Studies in rabbits have shown that niacin therapy tends to protect against atherosclerosis or reduce its severity. Whether niacin has a similar influence in man remains unknown. Lipid deposits in the skin have disappeared in patients during niacin therapy.\(^1^0\)

Niacin, when administered in large doses, has a number of side effects. These include cutaneous flushing, which may be severe but often disappears after a few weeks of therapy. The action of niacin in lowering serum lipids does not seem to be related to cutaneous vasodilatation, since the same effect is observed in the absence of the flush reaction. Niacin may cause gastrointestinal symptoms, dryness of the skin, and, in some instances, brown pigmentation. Hepatic dysfunction may be observed with impairment of sulfobromophthalein excretion, and an increase in alkaline phosphatase and glutamic-oxalacetic transaminase levels in serum, but histological findings on liver biopsy are usually normal. Prolonged use of niacin may occasionally result in histologic changes, including fibrosis and cholangiolitis. Glucose tolerance may decrease with niacin therapy, and there is a tendency for serum uric acid levels to rise slightly. Practically all of these findings are reversed rapidly when therapy is discontinued.

Effects of Neomycin Administration.—Another pharmacological agent that lowers serum lipid levels, neomycin, has been studied in our laboratory.\(^\text{19-10}\) Neomycin was administered in amounts of 0.5 gm four times daily to subjects on controlled diets high in saturated or in polyunsaturated fat. When the diet was changed from saturated to unsaturated fat, a decrease in cholesterol, total esters, and phospholipids in serum was observed. In association with this decrease, we found an increase in the fecal excretion of bile acids and neutral sterols. There was also a change in the ratio of cholestane to coprostanol compounds; the latter are indicative of the activity of the intestinal flora. The ratio changed from 1:8 when the diet furnished saturated fat to 1:4 when it furnished unsaturated fat. This decrease in conversion of cholesta to coprostanol supported the thesis that the type of fatty acid furnished by the diet influenced the intestinal flora.

The administration of neomycin with either the saturated- or unsaturated-fat regimen caused a decrease in serum cholesterol concentration of 10% to 30%. This was accompanied by a several fold increase in fecal excretion of bile acids. The excretion of sterols was not increased, but only cholesterol compounds were present in the feces. There was failure of conversion of cholic acid to deoxycholic acid. Neomycin has a profound effect on the intestinal flora but does not completely sterilize.
the gut. In most instances, coliform organisms are absent or markedly reduced, as are other enteric organisms with the exception of enterococci and Clostridium welchii, which tend to become more abundant. During neomycin administration, the taurine and glycine conjugates of bile acids are split to free acids. This action has been shown by Danielsson et al to be carried out by clostridia. Cholic acid is usually the predominant bile acid found in the feces after oral administration of neomycin, but occasionally large amounts of 7-ketodesoxycholic acid are found. The conversion of cholic acid to this compound is accomplished by coliform organisms. The bacteria that convert cholesteryl to coprosterol were inhibited by neomycin except in one instance. All samples have shown complete inhibition of the conversion of cholic acid to desoxycholic acid. The organism that converts cholic to desoxycholic acid has not been identified.

Little is known about the absorption of bile acids from the large intestine, but, since both lithocholic and desoxycholic acids have been shown to be formed by intestinal bacteria and both of these acids appear in significant amounts in the bile, absorption is obviously significant. It has been suggested that neomycin has its effect on serum lipids by causing a "malabsorption syndrome." In several studies in which large doses of neomycin (8 to 12 gm daily) were administered, this has been the case. In studies of Leveille et al and in our laboratory, fecal fat excretion increased slightly during administration of small doses of neomycin, ie, amounts up to 2 gm/day. The average in Leveille's series was a rise from 2.5 gm to 5.5 gm of fecal fat per day when 2 gm of neomycin was administered.

De Somer et al, in a study of chicks, reported findings that support the hypothesis that basic substances such as neomycin interfere with intestinal absorption of fats, cholesterol, and bile acids by disturbing the emulsification of lipids in the intestine or by complexing bile acids. Although the mechanism by which neomycin lowers serum cholesterol is still the subject of some difference of opinion, findings in our studies and those of others indicate a reciprocal relationship between the amount of bile acids excreted and the level of serum cholesterol. This could be part of a mild "malabsorption syndrome," but such terminology is not very satisfactory. The malabsorption appears to be medically inconsequential, whereas the decrease in serum cholesterol is significant. The increase in fecal excretion of bile acids may be due to changes in the intestinal flora which in turn influence the structure of bile acids (and steroids), thus affecting their absorption. Cholesterol synthesis and degradation may be increased during neomycin administration, but there is an overall loss of cholesterol from the body. Neomycin is a useful tool in studying mechanisms that control serum lipid levels but is not advocated as a therapeutic agent in hypercholesterolemia.

Failure of desoxycholic acid formation during neomycin therapy prompted us to administer desoxycholic acid to a patient who was receiving neomycin. Serum cholesterol concentration decreased to still lower levels, and fecal excretion of cholic acid and cholesterol increased. There was a disappearance of coprostanol from the stools at first, but this was followed by a marked increase. In view of this response, desoxycholic acid was given alone in amounts of 1.5 to 3 gm daily to seven subjects who received constant diets consisting of ordinary foods or liquid formula and containing predominantly saturated fats. Serum cholesterol concentration decreased significantly in all subjects. Although diarrhea developed frequently, fecal fat excretion was not altered appreciably. The excretion of cholic acid and cholesterol in the stools increased markedly, almost no coprostanol was formed, and total neutral sterol excretion increased (Fig 2).

It was decided to compare the administration of desoxycholic acid with administration of ox bile concentrate, 3 gm daily (Fig 2). In three subjects who received the latter medication, there was slight or no depression of serum cholesterol, although fecal sterol excretion increased considerably and coprostanol was virtually absent. Both whole bile and desoxycholic acid appear to influence the intestinal flora and increase excretion of neutral sterols, largely cholesterol, whereas only desoxycholic acid markedly lowers serum cholesterol concentration. The mechanism of action of desoxycholic acid requires elucidation. Findings to date suggest that it may decrease the absorption of cholesterol and cholic acid. It may also, by a feed-back mechanism, influence cholesterol degradation or inhibit cholesterol synthesis or have an effect on both mechanisms. Fimognari and Redwell have shown that certain bile salts inhibit biosynthesis of mevalonate, and hence of cholesterol, from acetate-2C in normal rat-liver homogenates. Desoxycholate was more inhibitory on a molar basis than cholate or taurocholate. The evidence suggests that bile salts may be cholesterol metabolites responsible for physiological regulation of cholesterol synthesis.

These studies of niacin and other hypocholesterolemic agents exemplify one of the current areas in nutrition research of great importance to human health, namely, the role of nutrition in the pathogenesis of atherosclerosis and its complications. This avenue of research has led to a great increase in knowledge of the metabolism of lipids. Today, nutrition research is delving into many unsolved metabolic problems and yet nutritional deficiency is of paramount importance in all of the developing countries of the world.

This brief review of niacin as an antipellagra factor and hypocholesteremic agent has attempted to point out trends in nutrition research in the past half century. The advance in nutrition knowledge since the time of Goldberger has been tremendous.
2. Desoxycholic acid and ox bile effects on serum cholesterol concentration and fecal excretion of fat, cholic acid, and neutral sterols.

and, as information has accumulated, research has turned to new areas. The future is bright, with new tools and techniques and the imagination engendered by the space age. Nutrition is an integral part of the current molecular biological era of science. Yesterday, interest was concentrated on the description of disease and methods of diagnosis as well as the search for etiologic factors and understanding of pathogenesis. While this search continues, it is at a different level. Modification of molecular reactions and configurations may dominate the nutritional and medical horizon of tomorrow but always with the aim of improvement in human health.

References