University of Nebraska Medical Center
BREAKTHROUGHS FOR LIFE

University of Nebraska Medical Center
DigitalCommons@UNMC

MD Theses

Special Collections

1958

Beta sitosterol : a new therapeutic approach to the management of atherosclerosis

Leon Donald Wanek
University of Nebraska Medical Center

This manuscript is historical in nature and may not reflect current medical research and practice. Search PubMed for current research.

Follow this and additional works at: https://digitalcommons.unmc.edu/mdtheses

Recommended Citation

Wanek, Leon Donald, "Beta sitosterol : a new therapeutic approach to the management of atherosclerosis" (1958). *MD Theses*. 2359.
https://digitalcommons.unmc.edu/mdtheses/2359

This Thesis is brought to you for free and open access by the Special Collections at DigitalCommons@UNMC. It has been accepted for inclusion in MD Theses by an authorized administrator of DigitalCommons@UNMC. For more information, please contact digitalcommons@unmc.edu.

BETA SITOSTEROL - A NEW THERAPEUTIC APPROACH TO THE MANAGEMENT OF ATHEROSCLEROSIS

Leon Donald Wanek

Submitted in Partial Fulfillment for the Degree of

Doctor of Medicine

College of Medicine, University of Nebraska

April 1, 1958

Omaha, Nebraska

TABLE OF CONTENTS

INTRODUCTION

During the past several years a large number of experimental and clinical studies have appeared in the literature which seem to implicate disorders of lipid metabolism in the pathogenesis of atherosclerosis. The possibility that dietary factors may influence a process long considered an inevitable consequence of aging has presented scientists with a real challenge. The postulated relationship between dietary intake of fats, serum cholesterol, and the pathogenesis of atherosclerosis has been the basis for the prophylactic use of diets low in fat and cholesterol lowering factors.

The fat content of these diets must be extremely low if a significant lowering of the blood cholesterol and serum lipoprotein fractions is to be realized. However, such a rigid dietary regimen is difficult for a prolonged period because it can be relatively unpalatable and becomes quite monotonous. When a reduction of blood lipid concentration is desired, an easily administered preparation which could decrease the blood cholesterol and other serum lipids without dietary restriction would be preferable to a strict low fat regimen. Plant sterols or sitosterols have been investigated for their possible effect on lowering blood lipids. This paper will be a review of the literature dealing with the effect of sitosterol in both animal experiments and clinical trials.

REVIEW OF ATHEROSCLEROSIS

Before we discuss the merits or value of sitosterol, let us review atherosclerosis; its incidence, etiology and pathogenesis.

Atherosclerosis is one form of arteriosclerosis. In this form the larger and medium sized musculo-elastic arteries are affected. Of chief interest clinically are the aorta and coronary and cerebral vessels, atherosclerosis of which may be manifested by myocardial infarction, angina pectoris, cerebral thrombosis, chronic brain syndrome, and aortic aneurysm, to name a few. Pathologically, atherosclerosis is characterized by internal fibrosis and lipoidosis (1).

The ubiquity of atherosclerosis in the United States is generally agreed upon. Keys in 1954 maintained "the distinction between normal health and atherosclerosis is a matter of degree; differentiation being more quantitative than qualitative." (2)

Autopsies done on three hundred young soldiers killed in action in the Korean War with an average age of twenty-two years, showed gross evidence of coronary atherosclerosis in 77.3 per cent of the cases (3). According to the National Office of Vital Statistics, there were 1,528,717 deaths in the United States in 1955, a sizeable portion of which were

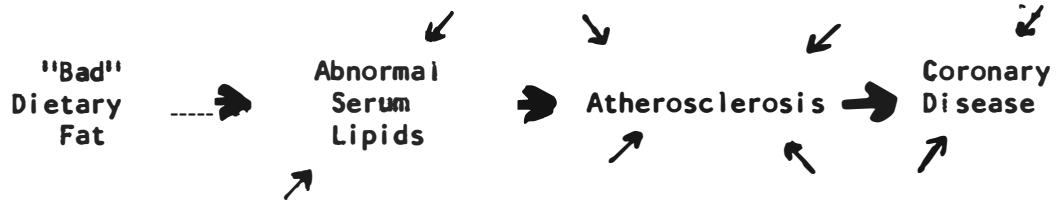
closely related to atherosclerosis and complications (4). The leading cause of death was 'diseases of the heart' which accounted for 584,620 (38%) deaths, followed in third place by 'vascular lesions a fecting the central nervous system' which accounted for another 174, 42 (11%) deaths, and in seventh place was 'generalized arteriosclerosis' which accounted for an additional 32,486 (1%) of all deaths.

Any disease process which is responsible for approximately 50% of the deaths in the United States each year has justifiably stimulated exhaustive research and varying ideas as to pathogenesis and etiology (5, 6). All that can be said with certainty about the etiology and pathogenesis of atherosclerosis is that the complete answer is not known, no more than we know of the etiology and pathogenesis of cancer.

Two main theories have been advocated concerning the etiology of atherosclerosis; first, the aging process and secondly, the metabolic theory. The latter is now generally accepted. The hypothesis that atherosclerosis is due to an alteration in lipid metabolism is made attractive by various lines of reasoning - pathological, clinical, and epidemiologic but there is serious lack of direct evidence substantiating this hypothesis. Pathologic evidence includes feeding of high cholesterol diets to animals with the production of atheroma along with analysis of atheroma in man (7, 8). These athero-

mata were found to be rich in cholesterol and cholesterol esters but low in neutral fats. Clinical evidence includes the higher incidence of coronary heart disease and atherosclerosis in patients with diabetes mellitus, myxedema, nephrosis and xanthomatosis, all of which are associated with hyperlipemia and hypercholesteremia. Although this association seems valid, the association of fat intake and hypercholesteremia has not been established (6). Epidemiologic evidence includes a lowered incidence of deaths attributable to atherosclerosis in the South African Bantu, Japanese and other societies, all of whose diets are low in total fat (9, 10).

Keys has stated that "no population characterized by low serum cholesterol values has yet been found to have a high incidence of atherosclerosis or coronary heart disease." (5) Ahrens and co-workers have postulated a simplified picture of atherosclerosis noting some of the unknown etiologic factors (11)



Each of the large arrows postulates cause and effect. The small arrows represent other contributing factors of varying magnitude, the unknown factor among them. Among the other

factors are, (a) heredity, (b) anatomy of the blood vessel wall, (c) arterial blood pressure and, (d) endocrine factors (6). One of the most difficult problems in the study of atherosclerosis is the inability to quantitively measure the extent of atherosclerosis during life. This difficulty not only complicates the evaluation of atherosclerosis in relationship to abnormal serum lipids in the diet, but also prevents the direct estimation of the effectiveness of any therapy that might reverse this process.

Another important question which arises is whether the atheromata are primary irritating events or secondary sequellae in the pathogenesis of the lesions (12). Even if the lipid deposits are primary, it remains to be established whether it is a localized disturbance in the arterial wall or if it is a local manifestation of systemic alteration of fat metabolism.

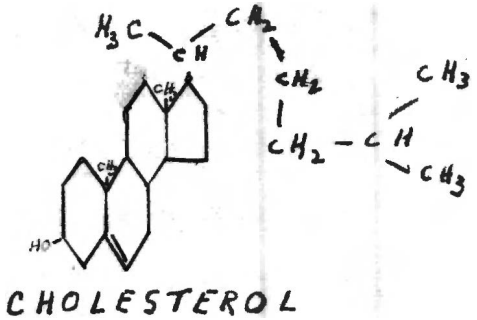
Since coronary heart disease is one of the most important clinical manifestat ons of atherosclerosis, let us glance at some of the various therapeutic approaches to the management of this disease so that we may better evaluate the place of sitosterol in the overall management of persons with clinical evidence of atherosclerosis. Friedberg (13) enumerates the various therapeutic approaches as follows: (a) weight reduction by low calorie diet, (b) low fat and/or low cholesterol diet, (c) plant sterols or sitosterol, (d) lipotrophic agents, (e) detergents,

(f) estrogen, and g) iodides and thyroid extract. Thus we can see that sitosterol is only one approach to the proposed management of patients with atherosclerosis.

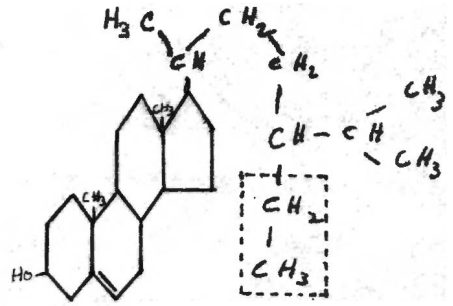
SITOSTEROL

Before studying the experimental effects of sitosterol, let us first consider the chemistry and pharmacology of sitosterol. The sitosterols are the most widely distributed of plant sterol or phytosterols (4). The average daily American diet contains one-fourth to one-half grams of sitosterol. This sterol fraction is now known to contain at least five components, alpha 1, alpha 2, alpha 3, beta and gamma sitosterol. Beta sitosterol is the main sterol of cotton seed oil, tall oil and wheat germ oil; gamma sitosterol is the principle sterol of soybean oil. Beta sitosterol has even been obtained from dried grapefruit pulp (15 . The sitosterols are white, odorless, tasteless, slightly waxy, crystalline solids which are insoluable in water (16). Davis states that sterols are "probably the most water-insoluable non-saponifiable substances occuring in biological systems." (17) Structurally beta sitosterol is closely related to cholesterol except for an ethyl group in the side chain at C-24 and a saturated ring system in the dihydrobeta derivative (18). Beta and dihydrobeta sitosterol are the sitosterols with which this paper chiefly deals. The for-

mulas of cholesterol and beta sitosterol are as follows:



CHOLESTEROL



BETA SITOSTEROL

Dihydrobeta without the double bond

The pharmacological action of sitosterols is due to interference with absorption of cholesterol from the intestine. The mode of action has presented many interesting theories. Peterson postulated that sitosterol must interfere with the absorption of cholesterol since sitosterol has been found to be practically inert and has been recovered in unmodified form in the feces of experimental animals (19). Gould using radioisotope techniques, demonstrated that a very small percentage of sitosterol may be absorbed but it is excreted at a much faster rate than cholesterol (20). Pollack suggested that sitosterol formed a mixed crystal with cholesterol in ratio of 1:1 which has much lower solubility than cholesterol alone (21). Davis confirmed this, stating that these "large" cystals were not as readily absorbed (17). Hernandez and associates used labeled cholesterol and postulated that sitosterol competes with cholesterol for the available esterase

essential for absorption of cholesterol (22). Swell and associates felt that bile and fatty acids along with esterase played a large portion in the mode of action of interference with cholesterol absorption (23, 24).

In view of the rather obscure and confusing theories on the etiology and pathogenesis of atherosclerosis, it is difficult to formulate any criterion for evaluation of the efficacy of beta sitosterol as a therapeutic agent in the management of atherosclerosis. Most investigators agree that plasma lipids and lipoprotein along with dietary fats play some part in the total picture of atherosclerosis. The plasma lipids include: (a) neutral fat, (b) phospholipids such as lecithin, spingomyelin and cephalin, and, (c) cholesterol, of which approximately 70% is in the ester form (13). Lipoproteins are plasma proteins, mainly alpha and beta globulins, which provide a means of transportation for the major portion of the blood lipids (25, 26). Cholesterol is essential in all lipoproteins but is abundant in some and less abundant in others. Only 25 to 30% of total serum cholesterol is present in alpha lipoproteins, whereas 70 to 75% is found in the beta lipoprotein fraction. Serum lipoproteins have been separated and classified by both ultracentrifuge and electrophoretic techniques Gofman and co-workers used the ultracentrifuge to class fy lipoproteins into four classes which

are designated by Svedberg flotation (Sf) numbers: (a) Sf 0-12, (b) Sf 12-20, (c) Sf 20-100, (d) Sf 100-400 (27). Using this grouping and from observations in patients who had survived myocardial infarctions, Gofman postulated an atherogenic index as a possible measure for predicting coronary atherosclerotic heart disease. He considers the Sf 12-20 class as the most atherogenic and feels that cholesterol levels can be misguiding when evaluating the effect of dietary changes on serum lipids. However, most investigators disagree with him. Lewis and Page analysed the lipoproteins by both ultracentrifuge and electrophoretic methods and classified them according to -S flotation fractions (28). They failed to implicate any specific fraction as atherogenic, however. Barr and associates reported a correlation between increased serum beta lipoprotein levels with increased incidence of atherosclerosis (29). An extensive joint research project over a three year period by Donner Laboratories, Cleveland Clinic, Pittsburg University and Harvard Laboratories, failed to show any advantage of ultracentrifuge measurement of lipoprotein fraction over the simple serum cholesterol measurements (30). In this study, serum lipids of approximately 15,000 subjects were studied in a period of three years. There were 4,914 men in the age group 40-59 who were judged to be clinically normal at the time of

entry into the project and on whom a follow-up was made in one or two years. In this latter group, eighty-two developed clinical manifestation of disease which could be attributable to atherosclerosis. This is about the number which might be expected in a random sampling of the population. In this study, atherosclerosis, as manifested by coronary artery disease, was associated with antecedent elevation of serum cholesterol, Sf 20-100 and slight elevations of Sf 12-20.

An elevated total cholesterol to lipid phosphorus ratio has been noted in association with atherosclerosis. (31) However, when the total cholesterol is reduced, the ratio returns to normal so that this measurement does not offer any additional information above that of total serum cholesterol determination.

Peters analysed serum of apparently normal persons over a period of ten years (32). The following table shows his results:

Substance	Numbers of Observations	Mean	Plus or Minus Deviations
Fatty acids (meq/l)	355	12.3	3.37
Cholesterol (mg %)	312	262.7	35.6
Lipid Phosphorus (mg %)	213	9.6	1.41
Ratio Chol: lipid Phos.	214	21.53	2.48
Free Fat	209	4.26	1.49

Now that we have noted some of the various determinations of serum lipids and lipoproteins, let us examine the effect of sitosterol ingestion in both animals and human subjects and the resultant serum changes.

D. W. Peterson in 1951, was among the first persons to experiment with sitosterol in conjunction with cholesterol (19). It was known at that time that although cholesterol was readily absorbed, plant sterols were not. Peterson showed that by the addition of sitosterols to a high cholesterol and cottonseed diet, markedly lower plasma and liver cholesterol levels were obtained in chicks, than when fed cholesterol and cottonseed diets alone. In 1953, Hernandez showed marked reduction in the absorption of cholesterol when sitosterols were added to the diets of rats. Similar results were noted in 1954 when a greater ratio of sitosterol was used. (33) Pollack in 1953, showed in rabbits that mixed sitosterols added to cholesterol diets in the ratio of 6:1 prevented any absorption of exogenous cholesterol (21). Rabbits fed the same diet but without sitosterol developed hypercholesteremia and atherosclerosis. Heptinstall and Porter found considerably less athersclerosis in rabbits with induced hypertension when sitosterol was added, in the ratio of 3:1 to a high cholesterol diet (34). Beher showed that beta sitosterol not only minimized hypercholester-emia in rabbits and retarded the rate of atherosclerotic

plaque formation, but could increase the rate and degree of regression of these atherosclerotic plaques (35). Rosenman failed to show any reduction in hypercholesteremia in the rat when sitosterol was fed in a 1:1 ratio with cholesterol (36).

Although the majority of animal experiments show favorable results, most clinical investigators feel that these results do not correlate well with human atherosclerosis. The location of the atheroma, lack of symptoms resulting from the atheroma, and production of these lesions by the addition of food foreign to the natural diet of these animals, all seem to negate the results of animal experiments (11).

Pollack, after noting the protection against hypercholesteremia when rabbits were fed sitosterols with their regular diet, attempted to duplicate his results in humans (37). He fed five to 10 grams of mixed sitosterols to twenty-six patients for periods of eight days to eight months. The fall in serum cholesterol was rather rapid at first, with stabilization at a basal level but never under 200 mg %. Pollack used patients with both elevated and normal cholesterol levels. The higher the origina cholesterol level, the easier it was to reduce it, but once basal level was obtained, continued sitosterol administration was necessary to maintain this lowered level. Pollack observed a definite lowering of the serum cholesterol with admin stration of sitosterol.

Barber and Grant studied twenty-six persons who had electrocardiographic evidence of myocardial infarction and serum cholesterols of greater than 230 mg % (38). Nine grams of beta sitosterol were given in divided doses before each meal. Diet was unrestricted. The mean serum cholesterol during control period was 304 mg % and during therapy was 283 mg %. Total serum lipid were 822 mg % initially with a rise to 913 mg % during therapy. Cholesterol-lipid phosphorus ratio was relatively unchanged at 27 mg %. Sitosterol produced a fall in serum cholesterol values in twenty-five of the twenty-six patients, but the decrease was minimal as compared with the wide variation in cholesterol determination. Moreover, one patient died of a myocardial infarct although showing a decreased cholesterol value. Barber and Grant felt that a nine gram daily dosage was insufficient and added a postscript stating that with higher doses of sitosterol, more significant results were obtained, but did not give further details.

Joyner and Kuo used the double blind method in studying the effect of different concentrations of sitosterols in seven patients on regula diets and in two patients on low fat, low cholesterol diets (39). The first group was composed of four women and three men, all with elevated serum cholesterol levels. Doses of six to fifteen grams of sitosterol were given for four week periods, followed by four weeks control periods. The mean

serum cholesterol levels for the seven patients on regular diets were as follows: first control period, 278 mg%; after sitosterol administration, 247 mg%; placebo administration, 278 mg%; and last control period, 272 mg%. The minimum effective dose was found to be ten grams per day. When sitosterol was fed to the two patients on low fat diet, further lowering of the serum cholesterol levels was noted above that which had been obta ned from the diet alone. Electrophoretic studies showed that the majority of cholesterol reduction was in the beta lipoprotein portion with little change in the alpha lipoprotein fraction. These lipoprotein changes occurred only with lowered serum cholesterol levels, but in one patient the beta lipoprotein fraction was reduced in greater degree than was the serum cholesterol.

Kuo in 1956, found that in seven patients with evidence of atherosclerosis, serum cholesterol, phospholipids and total lipid levels fell to nearly normal levels eight to twelve weeks after therapy was initiated (40). These patients were given thirty to forty-five grams of sitosterol in divided doses while on restricted fat diets. Three young males with angina were freed from symptoms within six months after starting treatment. Two patients with intermittent claudication also showed marked improvement in claudication time. Two other patients with abnormal ballistocardiograms showed improvement on the cardio-

grams as well as subjective improvement. Three additional patients were started in the original series but made only token efforts at cooperation and with no resultant improvement and are not included in the above series of seven patients.

Best and co-workers in 1954, administered beta sitosterol to nine patients two with normal serum cholesterol levels and seven with hypercholesteremia and clinical evidence of atherosclerosis (41). The diets were unrestricted and five grams of beta sitosterol was ingested before each meal. Double blind technique was used over the thirteen to twenty-nine weeks of study. An average of twenty-two weeks of treatment per patient included two periods of placebo administration and one or more periods of sitosterol administration. The effect of sitosterol was noted within one week and in all nine patients there was a reduction in the total serum cholesterol, ranging from 6.7% to 20% of the control. No tendency to escape was noted, even for periods of up to eighteen weeks of continuous administration of sitosterol. Apparent spontaneous fluctuations in serum cholesterol levels during both placebo and sitosterol administration emphasizes the necessity for repeated determinations in studies of this type. In three patients lipoprotein concentrations were determined by ultracentrifuge technique. Concentrations of Sf 10-30 and 30-100 classes at the end of sitosterol administration were approximately one half that of the placebo

period. The serum cholesterol-lipid phosphorus ratio was also decreased, but secondary to the changes in cholesterol levels. Similar results were obtained in 1955 in a series of fourteen patients (42). Twelve of these patients had hypercholesteremia and/or hyperlipemia, and two had normal cholesterol levels. Ten grams of sitosterol per day showed some effect, but a greater effect was noted when doses up to fifty grams per day were used. The twelve patients with elevated cholesterol levels showed a mean fall of 16% while the normals had a mean fall of 6.8%. A concomitant reduction of total lipids, neutral fats and to a lesser degree, lipid phosphorus, also occurred. No loss of weight was noted in any of the subjects, obviating dietary changes as the cause of the reduced cholesterol levels. A general tendency toward lower levels of Sf 3-10, 10-30, and 30-100 classes of lipoproteins also occurred, but the authors felt these changes secondary to lowered cholesterol levels.

A third series of twenty-four patients with abnormal lipid pattern were studied by the same authors (43). These patients included eleven persons with previous myocardial infarction. The other thirteen had hypercholesteremia and included four persons with essential hyperlipemia and xanthoma, three persons with renal disease, and five persons with hypothyroidism. Six to eight grams of sitosterol were given im-

mediately before the ingestion of food, the usual total daily dose being eighteen to twenty-five grams. There was no restriction as to type or amount of food in the diet. Average duration of treatment was 12.2 months, with average control time of 4.3 months A reduction, not only of serum cholesterol but also lipid phosphorus and total lipids, was noted. The mean reduction of serum cholesterol was 15.5%, phospholipids 9.4%, and total lipids 13.8%. A trend toward lowering of Sf 30-100 was noted, but this effect was less consistent than the reduction of serum cholesterol in the seven of twenty-four patients studied by ultracentrifuge technique. One of the eleven patients with history of myocardial infarction died of his third infarction after three months of sitosterol administration.

Farquhar in 1956, studied fifteen normotensive, non-dia-betic men between the ages of twenty-six and forty-five who had well documented histories of previous myocardial infarcts (44). These patients were divided into two groups: nine patients placed on fat restricted diets, and six patients given regular diets. Beta sitosterol was given orally immediately before meals in total daily doses of twelve to eighteen grams per day. A control group of fifteen apparently normal men, matched for age and weight had serum lipid measurement taken for baseline studies. See table below (44).

Number of Patients	Normal 15	Abnormal 15
Age	35	36
Weight	170	166
Total Protein (mg%)	6.6	7.0
Cholesterol (mg%)	213	291
Total Lipid (mg%)	965	1204
Alpha Lipid (mg%)	262	224
Beta Lipid (mg%)	419	557

It may be noted that the apparently normal men showed significantly lower mean values for beta lipoproteins, total lipids, and cholesterol. A prompt fall in serum cholesterol occurred during the first two to three weeks of sitosterol treatment with no tendency to return to pre-treatment levels even after sitosterol administration for periods up to three months. Within three weeks after withdrawal of the sitosterol or starting placebo administration, the serum cholesterol level returned almost to pre-treatment levels. Mean cholesterol pre-medication level was 293 mg%, with sitosterol 242 mg%, and 288 mg% with placebo administration. A lowering of beta lipoproteins, proportionate to that of serum cholesterol was also noted, along with a small increase in alpha lipoprotein fraction. It must be remembered that none of these patients had markedly elevated serum cholesterol levels at the onset of treatment.

Shipley in 1955 and 1957, reported several cases in

which reduction of cholesterol followed sitosterol administration (14, 45). He feels that the minimum daily dose for any benefit is nine grams, although much larger doses are readily tolerated.

Levkoff studied two children with essential familial hypercholesteremia (46). Both were given four grams of sitosterol before each meal and were unrestricted as to diet. Previous to this time they had been on restricted fat and cholesterol diets. Sitosterol lowered the serum cholesterol even more than had been accomplished by the strict dietary regimen.

Lesesne in 1955, reported serum cholesterol reductions of 13.2% in three women studied, and 16.4% in four men studied (47). All except one had hypercholesteremia. Three grams of sitosterol were fed before each meal over uninterrupted periods of three to eight months, with tendency to escape occurring in only one patient. Leseene proposed that sitosterols block the absorption of endogenous cholesterol as well as exogenous cholesterol.

Lehmann studied sixteen private patients, nine males and seven females, all ambulatory (48). Nine of these patients had a history of myocardial infarctions, six suffered from angina pectoris with abnormal electrocardiographs, and one patient had essential hypercholesteremia. No placebo or control groups were used, and the patients were treated on an outpatient basis with

no dietary restrictions. Beta sitosterol was administered in doses of six to eig t grams before each meal for an average daily dose of twenty grams. Rapid lowering of serum cholesterol levels took place within two weeks and remained lowered with no tendency to escape. The mean percentage drop was 16.8%. In two patients no lowering of serum cholesterol was obtained, but both were within normal limits before treatment was started. In eight patients lipoprotein determinations were performed with a mean lowering of Sf 0-12 fraction of 9.2% and a mean lowering of 24.7% in Sf 12-400 fraction. The atherogenic index (according to Gofman) was 124 units before treatment and dropped to 108 units after sitosterol administration. A 34-year-old male patient suffering from angina on effort obtained marked clinical improvement along with reversal of the S-T depression on Masters electrocardiograph. This patient showed a 21% drop in serum cholesterol and 35% drop in Sf 12-400 lipoprotein. Two other patients with angina noticed increased exercise tolerance.

Sachs and Weston reported the effect of nine grams of sitosterol per day on five clinically normal persons using the double blind technique over a four week period (49). The five normal persons showed an average mean fall in serum cholesterol of 13% with a maximum fall of 20.9%. The cholesterol levels returned to control evels after discontinuing therapy. In one

patient with xanthomatosis, administration of sitosterol suppressed the growth of a large xanthoma which showed increase in size upon secession of therapy. In two of the persons with abnormal serum lipids, after a transient fall, the serum cholesterol returned toward control levels despite continued sitosterol administration.

Wilkinson and co-workers studied patients with clinical evidence of atherosclerosis (50, 51). These patients had been on low fat, low cholesterol diets. When sitosterol administration began, gamma sitosterol and diet of choice failed to show any decrease in serum cholesterol values, even when doses of six grams before each meal were used. All lipoprotein values either returned to normal or increased. The authors felt that cholesterol values fluctuate so widely, even during control periods, that no serum cholesterol lowering could be attributed to the sterol emulsion.

Ripley studied thirteen patients, six ambulatory and seven hospitalized, all with clinical evidence of athersclerosis (52). The patients were given doses ranging from nineteen to fifty-two grams per day. In only one half of the trial periods was sitosterol thought to be effective in lowering serum cholesterol to a signi icant degree. With high serum levels of cholesterol, greater variations in serum cholesterol occur than in normal persons. One patient showed more advanced coronary

insufficiency while on sitosterol therapy. Patients with essential familial hypercholesteremia showed a tendency to return to control levels even though on continued therapy.

Wilkinson was the only observer who noticed any side effects, and that was with gamma sitosterol. He stated that his patients tended to get a diarrhea and gastric irritations. There have been no other contraindications or side effects noted. Since sitosterol is not absorbed, the stool may become bulky and light in color along with some laxative effect (16). After prolonged sitosterol administration, hemoglobin, white cell count, blood urea nitrogen, serum calcium, serum phosphorus, fasting blood sugar, bromsulphalein retention, total serum proteins, A/G ratio, prothrombin time, and urinary sediment were found to remain normal (47). No tendency for cholesterol level to rise above control levels was noted after termination of sitosterol administration.

SUMMARY

In summary, atherosclerosis was briefly reviewed from the standpoint of incidence, proposed etiology and pathogenesis. A large majority of persons in the United States are afflicted with this disease but the extent of the disease during life is not apparent until the advanced stages. Any attempt to evaluate the clinical efficacy of sitosterol in the management of

atherosclerosis is beset by many difficulties. There are no available criteria for accurate assessment of the degree of atherosclerosis in the living patient. Only when atherosclerosis has advanced to a point where there is interference with blood flow does it become manifest clinically. Even late complications are a poor index as they are dependent on the location of the atheroma. A single atheromatous plaque in the coronary artery may lead to coronary infarction, whereas extensive atherosclerosis in the aorta may be present without symptoms. Available information seems to point toward deranged lipid metabolism and dietary malpractices as contributing factors in the etiology and pathogenesis of atherosclerosis, but there are still many other elements which are not understood. Serum cholesterol determinations seem to be as good a guide in predicting complications from atherosclerosis as the more complicated and technically difficult lipoprotein determinations, although its value is purely speculative. Sitosterol administration with unrestricted diets was noted to be only one of the many approaches to the management of atherosclerosis. Beta sitosterol is the plant sterol considered in this paper, and is mainly derived from cottonseed oil and wheatgerm oil. Sitosterols are closely related to cholesterol in chemical formula and exert their effect by preventing the absorption of cholesterol from the intestine. Absorption of endogenous cholesterol

in the bile, as well as exogenous dietary cholesterol, is inhibited. Sitostero s are effective in doses of ten to twenty grams per day given in divided doses before meals. Cholesterol levels remain lowered only on prolonged and continuous ingestion of sitosterol, no tendency to escape has been noted however. No irritation or toxic side effects have been noted, even on high doses. Serum cholesterol levels have been lowered by most investigators, both in "normal" persons and in patients with hypercholesteremia. Reductions by as much as 20% have been noted. Reductions in Gofman's atherogenic Sf 12-20 fraction and beta lipoprotein levels have also been reported. Two investigators failed to show any lowering of either cholesterol or lipoprotein levels. In several patients suffering from angina pectoris, improvement, both subjectively and on the electrocardiograph, was noted. However, two persons with previous infarcts experienced fatal advancement of their disease, although on sitosterol therapy. Animal experiments do not seem to be of much value in the study of atherosclerosis and sitosterol therapy.

CONCLUSIONS

About the only conclusion which can be proposed from the review of the literature is that beta sitosterol does seem to have an effect on owering blood cholesterol levels. Whether this is of any significant value in the treatment of atherosclerosis has not been proven conclusively. Epidemiologic evidence

seems to make such an assumption tempting, however. Sitosterol is effective n maintaining lowered serum cholesterol levels only upon continuous administration. It has been found to be entirel free of any side effects or contraindications. Further investigation into the exact relationship between serum cholesterol and atherosclerosis is necessary before routine use of sitosterols is advocated.

BIBLIOGRAPHY

1. Anderson, W. A. D., Pathology, 2nd Edition, St. Louis, C. V. Mosby Company, p. 513.

2. Keys, A., Anderson, J. T., Relationship of the Diet in the Development of Atherosclerosis in Man, Symposium on Atherosclerosis, 388:181, 1955.

3. Enos, W. F., Holmes, H. A., Beyer, J., Coronary Disease Among United States Soldiers Killed in Action in Korea, J. A. M. A. 152:1090, 1953.

4. National Office of Vital Statistics, Vol. II, 1957. U. S. Department of Health, Education and Welfare.

5. Keys, Ancel, Diet and Epidemiology of Coronary Heart Disease, J. . M. A. 164:1912, (Aug. 24) 1957.

6. Page, I. H., Stare, F. J., Corcoran, A. C., Wilkinson, C. K. Jr., Atherosclerosis and Fat Control of the Diet, J. A. M. A. 64:2048, (Aug. 31) 1957.

7. Anitschkow, N. Experimental Arteriosclerosis in Animals, Arteriosclerosis, New York, Macmillan Company, 1933. p. 271.

8. Lehninger, A. ., Lipid Metabolism and the Atherosclerosis Problem, Symposium on Atherosclerosis, 388:129, 1955.

9. Bronte-Stewart, B., Keys, Ancel, Brock, J. F., Serum Cholesterol, Diet and Coronary Heart Disease: An Interracial Survey in the Cape Peninsula, Lancet 2:1103, 1955.

10. Keys, Ancel, Serum Cholesterol In Japanese Coal Miners, Am. J. Clin. Nutrition 5:245.

11. Ahrens, E. H., Hirsch, J., Insull, W. Jr., Tsaltas, T. T., Peterson, M. L., Dietary Control of Serum Lipids in Relationship to Atherosclerosis, J. A. M. A. 164:1905, (Aug. 24) 1957.

12. Hartroft, W. S., Thomas, W. A., Pathological Lesions Related to Disturbances of Fat and Cholesterol Metabolism in Man, J. A. M. A. 64:1899, (Aug. 24) 1957.

13. Friedberg, C. K., Diseases of the Heart, 2nd Edition, Philadelphia, W. B. Saunders Company, 1956. p. 415.

14. Shipley, R. E., Modern Treatment of Atherosclerosis, J. Ind. State Med. Assn. 50:1623, (Dec.) 1957.

15. Ma, R. M., Schaffer, R. S., Beta Sitosterol, D-glucoside and Beta Sitosterol from Commercially Dried Grapefruit Pulp, Arch. Biochem. 417:419, (Nov) 1953.

16. Eli Lilly Publication A-2254A, p. 6.

17. Davis, W. W., Physical Chemistry of Cholesterol and Beta Sitosterol Related to the Intestinal Absorption of Cholesterol, Trans. N. Y. Acad. Sci., Series II, 18:123, 1955.

18. New and Nonofficial Remedies, J. A. M. A. 160:670, (Feb. 25) 1956.

19. Peterson, D. W., Effect of Soybean Sterols in the Diet on Plasma and Cholesterol in Chicks, Proc. Soc. Exp. Biol. and Med. 78:143, 1951.

20. Gould, R. G., Absorbability of Beta Sitosterol, Trans. N. Y. Acad. Sci., Series II, 18:129, 1955.

21. Pollack, O. J., Successful Prevention of Experimental Hypercholesteremia and Cholesterol Atherosclerosis in the Rabbit, Circ., 7:696, 1953.

22. Hernandez, H. H., Peterson, D. W., Chaikoff, I. L., Dauben, W. G., Absorption of Cholesterol-4-C14 in Rats Fed Mixed Soybean Sterols and Beta Sitosterol, Proc. Soc. Exp. B ol. and Med. 83:498, 1953.

23. Swell, L., Bo tes, T. A., Field, H. Jr., Treadwell, C. R., Absorption of Plant Sterols and Their Effect on Serum and Liver Sterol Levels, J. Nutrition 58:385, (Mar.) 1956.

24. Swell, L., Boites, T. A., Fields, H. Jr., Treadwell, C. R., Esterification of Soybean Sterols in Vitro and Their Influence on Blood Cholesterol Level, Proc. Soc. Exper. Biol. and Med. 86:295, (Junel) 1954.

25. Cantarow, A., Trumpler, M., Clinical Biochemistry, 5th Edition, Philadelphia, W. B. Saunders Company, 1955. p. 111.

26. Fredrickson, D. S., Some Biochemical Aspects of Lipid and Lipoprotein Metabolism, J. A. M. A. 64:1894, (Aug. 24) 1957.

27. Gofman, J. W., Jones, H. B., Lindgren, F. T., Elliot, H. A., Lyon, T. P., Strisower, B., Blood Lipids and Human Atherosclerosis, Circ. 2:161, 1950.

28. Lewis, L. A., Page, I. H., Electrophoretic and Ultracentrifugal Analysis of Serum Lipoproteins of Normal, Nephrotic and Hypertensive Persons, Circ. 7:707, (May) 1953.

29. Barr, D. P., Russ, E. M., Eder, H. A., Protein Lipid Relationships in Human Plasma, Am. J. Med. 11:480, 1955.

30. Technical Committee, Evaluation of Serum Lipoproteins and Cholesterol Measurement as Predictors of Clinical Atherosclerosis, Circ. 14:691, (Oct.) 1956.

31. Gertler, M. M., Garn, S. M., Lerman, J., Interrelationships of Serum Cholesterol, Cholesterol Esters and Phospholipids in Health and Cornonary Artery Disease, Circ. 2:205, 1950.

32. Peters, J. P., Mann, E. B., The Interrelationship of Serum Lipids in Normal Persons, J. Clin. Invest. 22:707, (Sept.) 1943.

33. Hernandez, H. H., Chaikoff, I. L., Do Sterols Interfere With Absorption of Cholesterol? Proc. Soc. Exper. Biol. and Med. 86.541, 1954.

34. Heptinstall, R. H., Porter, K. A., Effect of Beta Sitosterol on Cholesterol-Induced Atheroma in Rabbits with High Blood Pressure, Brit. J. Exper. Path. 38:49, 1957.

35. Beher, W. T., Anthony, W. L., Baker, G. B., Effect of Beta Sitosterol on Regression of Cholesterol Atherosclerosis in Rabbits, Circ. Res. 2:485, (July) 1954.

36. Rosenman, R. H., Beyers, S. O., Friedman, M., Effect of Soybean Sterols on the Absorption of Cholesterol by the Rat, Clin. Res. 2:160, 1954.

37. Pollack, O. ., Reduction of Blood Cholesterol in Man, Circ. 7:702, (May), 1953.

38. Barber, J. M., Grant, A. P., The Serum Cholesterol and Other Lipids After Administration of Sitosterol, Brit. Heart J. 17:296, (July) 1955.

39. Joyner, C. Jr., Kuo, P. T., Effect of Sitosterol Administration on the Serum Cholesterol Level and Lipoprotein Patterns, Am. J. Med. Sci. 230:636, (Dec. 1) 1955.

40. Kuo, P. T., Effect of Lipemia on Tissue Oxygenation in Arteriosclerotic Patients, Circ. 14:964, (Nov), 1956.

41. Best, M. M., Duncan, C. H., Van Loon, E. J., Wathen, J. D., Lowering of Serum Cholesterol by Administration of a Plant Sterol, Circ. 10:201, (Aug.) 1954.

42. Best, M. M., Duncan, C. H., Van Loon, E. J., Wathen, J. D., Effect of Sitosterol on Serum Lipids, Am. J. Med., (July 1, 1955). p. 61.

43. Best, M. M., Duncan, C. H., Modification of Abnormal Serum Lipid Pattern in Atherosclerosis by Administration of Sitosterol, Ann. of Int. Med. 45;614, (Oct.) 1956.

44. Farquhar, J. W., Smith, R. E., Dempsey, M. E., Effect of Beta Sitosterol on the Serum Lipids of Young Men with Arteriosclerotic Heart Disease, Circ. 14:77, (July) 1956.

45. Shipley, R. E., Effect of Sitosterol Ingestion on Serum Cholesterol Concentration, Trans. N. Y. Acad. Sci. Series II, 18:111.

46. Levkoff, A. H., Knode, K. I., Treatment of Familial Hypercholesteremia with a Plant Sterol, Pediatrics 19: 88, (Jan.) 1957.

47. Lesesne, J. M., Castor, C. W., Hoobler, S. W., Prolonged Reduction in Human Blood Cholesterol Levels Induced by Plant Sterols, U. Mich. Med. Bull. 21:13, (Jan.) 1955.

48. Lehman, J. H., Clinical Experience with Beta Sitosterol, A New Anti-Cholesteremic Agent, Northwest Med. 56:43, (Jan) 1957.

49. Sachs, B. A., Weston, R. E., Sitosterol Administration in Normal and Hypercholesteremic Subjects, Arch. Int. Med. 97:201, (June) 1956.

50. Wilkinson, C. F. Jr., Boyle, E., Jackson, R. S., Benjamin, M. R., Effect of Varying the Intake of Dietary Fat and the Ingestion of Sitosterol on Lipids and Lipoprotein Fractions of Human Serum, Metabolism 4:302.

51. Wilkinson, C. F. Jr., Jackson, R. S., Bozian, R. C., Benjamin, M. R., Levere, A. H., Croft, G., Davidson, N. W., Clinical Experience with Sitosterols, Trans. N. Y. Acad. Sci. Series II, 18:119.

52. Ripley, F. P., Steiner, A., Effect of Sitosterol on the Concentration of Serum Lipids in Patients with Coronary Atherosclerosis, Circ. 16:723, (Nov.) 1957.