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Dockets Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, Maryland 20852

**Re: Food Labeling: Health Claims; Plant Sterol/Stanol Esters
and Coronary Heart Disease (Docket Nos. 00P-1275 and
00P-1276)**

Dear Sir or Madam:

We are submitting this comment on behalf of our client, GFA Brands, Inc. (GFA), on the above referenced Food and Drug Administration (FDA) interim final rule on health claims regarding plant sterol/stanol esters and reduced risk of coronary heart disease. Although the formal comment period for this rule has closed, we are specifically writing in reference to health claims regarding phytosterols, which were referenced in a more recent related correspondence from FDA in February 2003 and for which a separate final rule is expected to be published in the future. ^{1/}

GFA applauds the agency's efforts to approve this important health claim. GFA manufactures and markets Smart Balance, a line of products containing a patented blend of natural vegetable oils developed to help improve the cholesterol ratio (lowering "bad" LDL cholesterol while maintaining "good" HDL cholesterol) and help provide a balanced fat diet, which can reduce the risk of heart disease. Smart Balance products include buttery spreads, cheese products and other foods, as well as a total eating plan designed to provide a healthy diet with the right balance of polyunsaturates, mono-unsaturates and saturates – including, a favorable balance between Omega-6 and Omega-3 polyunsaturates.

^{1/} Letter from Christine L. Taylor, Director, Office of Nutritional Products, Labeling and Dietary Supplements, FDA, to Fred L. Shinnick, Cargill Health & Food Technologies (Feb. 14, 2003), accessed on June 2, 2004, at <http://www.cfsan.fda.gov/~dms/ds-ltr30.html> ("February 2003 letter").

00P-1276

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The interim health claim allows the use of a cardiovascular health claim on foods containing phytosterols if, amongst other factors, the food meets the requirements for “low saturated fat” and “low cholesterol.” 2/ The February 2003 letter confirmed that “FDA intends to consider the exercise of enforcement discretion, pending publication of the final rule, with respect to certain requirements of the health claim” based on additional scientific evidence and a preliminary review of comments received. GFA’s Smart Balance Plus® spread provides 450 mg of phytosterols per serving and meets all of the criteria for using a phytosterol health claim except that it is not low in saturated fat.

GFA believes that there is significant scientific agreement supporting the use of the phytosterol health claim on products, like GFA’s, that exceed the low saturated fat limit, but more importantly, provide a balanced ratio of fats with a saturated fat: monounsaturated fat: and polyunsaturated fat ratio of approximately 1:1:1 (or more specifically, 1:1.3:1). In this comment we summarize the extensive data supporting the ability of diets with a balanced fat ratio to have beneficial impact on lowering bad cholesterol levels while maintaining good cholesterol levels. GFA, therefore, believes that FDA should similarly exercise its enforcement discretion and allow the use of the phytosterol health claim in products that provide a balanced level of fats.

In fact, FDA has not required other products to meet the “low saturated fat” and “low fat” requirements when making cardiovascular claims. Recently, the agency approved a qualified health claim for walnuts even though walnuts are not low in saturated fat or low fat “because walnuts have a good ratio of unsaturated fat to saturated fat and may contain other potentially beneficial substances such as dietary fiber and phytosterols.” 3/ This same reasoning should be equally applied to other foods, like GFA’s, that contain phytosterols and have similar beneficial ratios of fats.

2/ 65 Fed. Reg. 54686, Food Labeling: Health Claims; Plant Sterol/Stanol Esters and Coronary Heart Disease, Docket Nos. 00P-1275 and 00P-1276 (Sept. 8, 2000); 21 C.F.R. § 101.62(c)(2) and (d)(2).

3/ Letter from Laura M. Tarantino, Acting Director, Office of Nutritional Products, Labeling, and Dietary Supplements, FDA, to Sarah E. Taylor, Covington & Burling (March 9, 2004).

During an October 2003 meeting with FDA staff to discuss this issue, we mentioned a variety of research and studies that support a finding that the phytosterol health claim is appropriate for products containing a certain balance of fats because they have the positive effect of lowering LDL and raising HDL cholesterols. GFA has extensive data establishing that the fat blend in Smart Balance Plus, when consumed as part of a health diet and exercise program, is effective in improving the LDL/HDL cholesterol profile.

Research Findings

Dr. K.C. Hayes at the Foster Biomedical Research Laboratory of Brandeis University has conducted in-depth research and written extensively on the subject of dietary fat and heart health. The information below was compiled from materials developed by Dr. Hayes incorporating numerous studies conducted by various parties.

Healthy fat intake. Current National Cholesterol Education Plan (NCEP) and American Heart Association (AHA) Dietary Guidelines encompass the best and most relevant guide for fat and cholesterol intake. They recommend limiting fat to 30-40% of total dietary calories (%en) with the prudent recommendation at the low end because 40%en, common in the North American diet, tends to have the undesirable consequence of raising total cholesterol (TC) and low density lipoprotein (LDL). Decreasing fat to 20% or less can also be troublesome because, although LDL may decline, high-density lipoprotein (HDL) may also fall even though triglycerides tend to rise. This combination typically leads to more dense LDL particles, likely due to the distorted balance between saturated fatty acids (SFA or S), monounsaturates (MUFA or M), and polyunsaturates (PUFA or P) at 20%en. At this intake level, PUFA can easily become limited, thereby distorting lipoprotein (LP) metabolism and the LP profile.

Fatty acid balance. The original AHA Step I diet fat recommendations recognized the significance of the fatty acid balance at approximately 1:1:1 for SFA:MUFA:PUFA. Careful review of numerous published reports has revealed the importance of this balance in generating the best LDL/HDL ratio. Furthermore, the balance appears to be critical at any level of fat intake if one wishes to avoid adversely affecting the LP profile.

Within the concept of "balance" among classes of fatty acids, certain specific fatty acids have been found to be more beneficial than others. Many studies have suggested that SFA raise TC, LDL, and HDL and that PUFA lower them, but

certain SFA (as consumed in the diet) are better in terms of their impact on the LDL/HDL ratio than others. Fats rich in 12:0+14:0 (milk fat, coconut oil, palm kernel oil) raise LDL the most. Stearic acid (18:0) is not prevalent in saturated fats, but it is neutral in its effect on blood cholesterol when consumed in natural fats. The most common SFA is palmitic acid (16:0), (so named because it represents the major SFA in palm oil). The 16:0 SFA is present to some degree in essentially all fats and is by far the most prevalent SFA in our diets. Considering the influence on the LP profile, 16:0 is intermediate, i.e. it can be neutral when placed on a triglyceride molecule with MUFA, PUFA or 18:0, or cholesterol-raising when attached along with 12:0+14:0. In high amounts 16:0 can even raise TC and LDL when substituted for 18:0 MUFA, or PUFA in people who already have elevated TC or who eat large amounts of cholesterol. Accordingly, the general advice has been to remove as much SFA from the diet as possible. This is often not practical because the manufacture of many food products requires SFA, or some facsimile thereof, such as trans fatty acids. Moreover, extreme removal of dietary SFA is not recommended because their deletion from the diet surprisingly exerts an adverse effect on the LDL/HDL ratio.

What is the best approach to saturated fats? In recent years, one mistaken answer has been to utilize synthetic SFA manufactured by "hardening" vegetable oils through hydrogenation. This process makes a stiff, plastic fat this is rich in so-called trans fatty acids (TFA). However, studies now show that these TFA can be worse than any of the individual natural SFA because they not only raise LDL but also lower HDL, leading to an exaggerated increase in the LDL/HDL and in cardiovascular risk. TFA also increase a highly atherogenic lipoprotein in the LDL fraction called Lp(a). An alternative to the harmful effects of TFA is to provide a reasonable level of SFA in our diet by careful selection of naturally available SFA. Brandeis University's research with monkeys and humans indicates that the guidelines are best tempered by the original AHA Step I diet (30%en from dietary fat and 1:1:1 for SFA:MUFA:PUFA) and that the best SFA are 16:0 and 18:0 from *natural* fats. This conclusion comes from carefully analyzing all aspects of the NCEP-AHA recommendations coupled with analysis of the available LP data in relevant studies involving the controlled intake of dietary fat in humans (and experimental animals).

What is the best approach to PUFA? In selecting PUFA, the issue of whether to include linoleic acid (18:2n-6) or linolenic acid (18:3n-3), or longer n-3 like EPA and DHA, must be considered. Both n-6 and n-3 families are essential fatty acids (needed in the diet because the body cannot synthesize them) and both are important to health, especially cardiovascular health. The linoleic acid (n-6)

level has the greatest impact on regulating the LDL/HDL ratio, whereas linolenic acid (n-3) and its longer derivatives have a major influence on clotting mechanisms, as well as stabilizing the heart against abnormal beating, called arrhythmias, that can lead to sudden death. Diets enriched in 18:3n-3, or even better, 22:6n-3 (DHA) have been shown to exert a significant anti-coronary heart disease effect in humans, both in clinical and epidemiological studies. Smart Balance® contains a good balance (7:1) of linoleic (n-6) to (n-3) linolenic acids. This balance is unlike partially hydrogenated margarines, in which most of the linolenic acid has been destroyed by processing, and is also unlike most vegetable oils, which contain only a small amount of this important fatty acid (soybean and canola oils being exceptions).

Dietary Cholesterol. Dietary cholesterol is very important in the equation, as evidenced by the NCEP-AHA diet recommendations to reduce daily intake below 300mg or even 200mg, depending on individual risk. In fact, dietary cholesterol increases the body's sensitivity to SFA, so that maximizing its removal can substantially reduce much of the negative influence of SFA on the LP profile. Polyunsaturated fatty acids, on the other hand, are the major fatty acid able to actually offset the negative impact of dietary cholesterol because linoleic acid (18:2n-6) increases the removal of plasma LDL, the main LP that is increased by dietary cholesterol.

Monounsaturates. From the Brandeis researchers' results and the analysis of others, monounsaturated fatty acids have been found to be essentially neutral in terms of the LP profile, and thus, perhaps, are the best source of fatty acids to use as extra "filler" in the dietary fat load. Nevertheless, the critical issue is how much SFA and PUFA should be consumed to achieve the best LDL/HDL ratio. As Hayes' comparison between olive oil and balanced fat revealed in cynomolgus monkeys, a high MUFA intake at the expense of PUFA and SFA does not counter the presence of dietary cholesterol very well and leads to an increased LDL/HDL ratio relative to a balanced SFA:MUFA:PUFA ratio that allows for a higher PUFA intake. Thus, for example, fat blends like Smart Balance® incorporate a better fatty acid balance than olive oil alone.

The LDL/HDL ratio. An elevated cholesterol level (TL >180mg/dl, LDL >110mg/dl) begins to increase risk for coronary heart disease (CHD). Most of any increase above 180mg/dl arises in the LDL pool, and this lipoprotein is the one that is deposited during arterial cholesterol build-up. On the other hand, people (and essentially all animals) with naturally high levels of HDL do not develop CHD, primarily because this lipoprotein transports cholesterol back to the liver for excretion in bile. HDL in the arterial wall also blocks LDL deterioration, thereby

preventing the local damage induced by LDL accumulation. Thus, the "bad" and "good" cholesterol connotations for these two LPs become apparent and the justification for maintaining the lowest LDL and highest HDL (i.e. best LDL/HDL ratio) possible for any given TC value.

The Brandeis-PORIM research and GFA products. A novel finding from collaborative nutritional research at Brandeis University and the Palm Oil Research Institute of Malaysia (PORIM) resulted in technology to produce fat blends free of trans fatty acids and a Brandeis patent that was licensed to GFA Brands. The patent defines a means to produce the 1:1:1 balance in fatty acids recommended for many years by the AHA and adjusted by trial and error to approximately 1:1.3:1 through Brandeis-PORIM experiments and product development by GFA. Adequate intake of natural fats blended to approximate this fatty acid balance consistently elicits the best LP profile in animals and humans. This seems to be true for all levels of fat intake normally consumed in Western diets (20-40% of total calories). Significant deviation from a balanced ratio between SFA:MUFA:PUFA, such as too low SFA or too high MUFA or PUFA, induces a less than ideal LP profile, even if the total plasma cholesterol is lower.

Licensing of the Brandeis-PORIM technology by GFA Brands, Inc., resulted in Smart Balance® / Earth Balance margarines and a family of related products for use in a total diet program specifically designed to approximate this 1:1.3:1 fatty acid balance from blends of natural oils, thereby removing all trans fatty acids. Several human studies and epidemiologic reports indicate that trans fatty acids are more harmful than the saturated fatty acids they were designed to replace. In fact, some of the deleterious effects attributed to saturated fatty acids over the years were probably the result of their substitution by trans fatty acids when assessed by direct comparison with specific fatty acids, trans fatty acids proved worse than the saturated fatty acids they were designed to replace.

Substantiation from Studies & Reports

The following conclusions are made in published reports and studies, described below, which provide substantiation for the information contained in GFA's comments.

- **Fatty acid balance is more critical than the amount of fat.** 4/

This report evaluated the importance of dietary fatty acid balance on the lipoprotein profile in 22 nuns (aged 22-55, mostly post-menopausal) who had mildly elevated TC (224mg/dl at entry). They were fed three dietary fats for 6 weeks each: first, a high-level, saturated fat (42%en, P/S= 0.16); or second, that same level of fat with a balanced fatty acid profile (P/S, 1.0), which was accomplished by decreasing SFA (exact fatty acid profile not provided) and increasing PUFA. The third fat was close to the original AHA Step I (32%en with a 1:1:1 balanced fatty acid profile) and similar to the S:M:P balance in the second fat rotation. The results suggest that if one begins with a very unfavorable PUFA/SFA ratio (only 0.16 because PUFA was too low) in a high-fat diet (42%en), balancing the P/S ratio along AHA guidelines improves TC and the LDL/HDL ratio. (See Fig. 4.) The new balance between SFA and PUFA decreased LDL and increased HDL slightly.

However, dropping fat intake to 32%en with the AHA balance in place did not improve TC or the LDL/HDL ratio further. Significantly, in the 30-40%en range, a balance (adequate PUFA, adequate SFA) seems more critical than total fat. Although the exact SFA profile was not described, other studies have found that decreasing 12:0+14:0 is more important than decreasing 16:0+18:0 if the best LDL/HDL ratio is to be achieved at a lower SFA intake. 5/ Thus, the approximately equal balance of S:M:P (1:1.3:1) as recommended by NCEP-AHA is an important basic consideration *at any fat intake* for maintaining the best LDL/HDL ratio.

4/ Weisweiler, P., Janetschek, and Schwandt, P., *Influence of polyunsaturated fats and fat restriction on serum lipoproteins in humans*, *Metabolism* 34, 83-87 (1985).

5/ See *infra* n.13.

- **Both SFA and PUFA are required for the best LDL/HDL ratio.** 6/

This report tested the hypothesis that providing either too few SFA or PUFA in the diet (i.e. an imbalance between them) would be detrimental to the HDL or LDL level, respectively. Three fats were fed in whole-food diets, providing 2/3 of the daily fat load from the supplemented oil in each diet (with 31% of daily calories as fat) for 23 young men with normal cholesterol values. The diet fat was initially balanced as AHA Step I recommends with a 10:13:8 ratio of SFA:MUFA:PUFA in the final diet followed by a high-MUFA, low-SFA (6:17:8) or a high-SFA, low-PUFA (13:14:4) diet. The first fat represented a blend of soybean oil:palm oil:canola oil, whereas the other two fats were supplied as canola oil or palm olein alone. All three fats produced about the same normal total cholesterol value, but the AHA blend produced the highest HDL and lowest LDL, so that the LDL/HDL ratio was significantly enhanced by the AHA balanced blend of SFA:MUFA:PUFA. (See Fig. 1.) Thus, neither too low SFA nor too low PUFA was adequate, and MUFA were no substitute for either. Rather, one needs a balance of PUFAs (to lower LDL) and SFA (to raise HDL) for the best TC and LDL/HDL profile, at least when following an AHA Step I diet at 30%en from fat. The 9:12:9 balance for SFA:MUFA:PUFA inherent in the current NCEP and AHA recommendations for 30%en from fat appears to be the best advice for the average individual.

- **Fatty acid balance selectively lowers LDL but not HDL.** 7/

This report addressed the issue of whether simply improving the fatty acid balance in the diet of 30 normolipemic men fed a typical Western diet fat intake (37%en) would enhance the lipoprotein profile, even after 3 months of comparison feeding and even if not including the typical goal of reducing fat intake to 30%en. The hypothesis was tested by switching from a P/S fatty acid ratio of 0.3 to a ratio of 1.0, thus adopting an AHA balance in S:M:P of 1:1.3:1. The average entry TC was upper-normal (200mg/dl), and the level of PUFA intake (5.6%en) is

6/ Sundram, K., Hayes, K. C. and Siru, O. H., *A balance between dietary 18:2 and 16:0 may be required to improve the serum LDL/HDL cholesterol ratio in normocholesterolemic me*, J.Nutr. Biochem. 6,179-87 (1995).

7/ Schwandt, P., Janetschek, P., and Weisweiler, P., *High density lipoproteins unaffected by dietary fat modification*, Atherosclerosis 44, 9-17 (1982).

very typical of the U.S. today. Balancing the P/S to 1.0 by shifting 6%en from SFA to PUFA caused a significant decline in TC and LDL without depressing HDL. (See Fig. 3). This resulted in significant improvement in the LDL/HDL ratio. A design flaw was the failure to designate the specific type(s) of SFA removed. Thus, similar to a subsequent trial^{8/}, balancing the dietary fatty acid intake over a significant period of time is beneficial. Balancing fatty acid is important if one wants to lower LDL without depressing HDL, even when consuming a somewhat elevated level of dietary fat (37%en) in normolipemic subjects.

- **Too high PUFA or too low fat depresses both LDL and HDL.** ^{9/}

This report demonstrates what happens to LDL and HDL in normolipemic (n=11) and hyperlipemic (n=19) subjects fed a very saturated, high-fat diet (P/S 0.2, 40%en) or a very polyunsaturated, high-fat diet (P/S 2.0, 40%en). Subjects were then compared to an almost fat-free saturated fat diet (P/S 0.2, 3%en). Two questions were addressed: (1) Does the response of people with normal cholesterol differ from those with high cholesterol? and (2) Does the LDL/HDL profile benefit more from a high polyunsaturated fat approach to diet modification or is it better to drastically reduce the fat intake by eating a high-carbohydrate (low-fat) diet without concern for the fatty acid balance?

The results show that a high-PUFA diet (P/S 2.0) decreased both LDL and HDL in all subjects. (See Fig. 5.) Removing essentially all the fat (low-fat) decreased both LDL and HDL even further. The LDL/HDL ratio did not improve with either tactic and the general response was similar for both groups of subjects, i.e. normolipemics and hyperlipemics. Thus, a very high-PUFA or an essentially fat-free diet will both decrease TC and LDL in both normolipemic and hyperlipemic subjects, but the decline in HDL is also substantial. The LDL/HDL ratio does not improve. As shown, if one wishes to maintain the HDL while selectively lowering LDL and thereby improve the LDL/HDL ratio, a balance between dietary SFA and PUFA is important. The same decrease in LDL obtained with very high PUFA can

^{8/} See *supra* n.3.

^{9/} Schaefer, E.J., Levy, R.I., Ernst, N.D., Van Sant, F.D., and Brewer, H.B. *The effects of low-cholesterol, high-polyunsaturated fat, and low fat diets on plasma lipid and lipoprotein cholesterol levels in normal and hypercholesterolemic subjects*, Am. J. Clin. Nutr. 34, 1758-1763 (1981).

be achieved by simply balancing S:M:P, and this balanced approach does not depress HDL.

- **Fatty acid balance is especially critical in low-fat diets.** 10/

The objective of this study was somewhat similar to the Jones study 11/, emphasizing the importance of balance at any level of fat intake. Specifically, it determined whether the TC and lipoprotein profile would be altered by decreasing fat intake from a high level (39%en) to a low level (22%en) if the P/S ratio were held constant and balanced at about 1.0. Most studies show that switching to a high-carbohydrate (low-fat) diet lowers TC, including both LDL and HDL. 12/ Nine normolipemic males were evaluated in a carefully monitored metabolic ward, but the S:M:P ratios were not totally balanced and were 1.2:1.5:1.0 (hi-fat) and 1:1.4:1 (low-fat), providing P/S ratios of 0.8 and 1.0, respectively. The results reveal that the TC, LDL, and HDL were not significantly affected by the fat load, although they tended to be slightly lower during the low-fat period without affecting the LDL/HDL ratio. (See Fig. 6.) Thus, a low-fat diet (22%en) does not necessarily mean that HDL will decline during a high carbohydrate intake, provided that the balance between SFA and PUFA is maintained. However, the tendency toward slightly lower HDL at 22%en suggests that 30%en from fat might better sustain HDL 13/ or that the MUFA intake was allowed to drift up too far relative to SFA and PUFA for this low fat intake.

The results suggest that the dietary P/S ratio is important at any fat intake, but is especially critical for maintaining the best LP profile during low-fat intake (<20-25%en) because it dictates the absolute intake of 18:2. At low-fat intakes, a low P/S ratio (<0.5) greatly limits the 18:2 needed to meet metabolic requirements for normal LP metabolism, especially for lowering the LDL, but also

10/ Nelson, G.J., Schmidt, P.C., and Kelley, D.S., *Low-fat diets do not lower plasma cholesterol levels in healthy men compared to high-fat diets with similar fatty acid composition at constant caloric intake*, *Lipids* 30, 969-976 (1995).

11/ See *infra* n.17.

12/ See *supra* n.8.

13/ As shown in the Sundrum study. See *supra* n.5.

for sustaining HDL. As pointed out in other references, a dietary S:M:P ratio of 1:1.3:1 generally appears to be best.

- **Progressive removal of SFA lowers both LDL and HDL. 14/**

This carefully executed first DELTA study examined the effect of a two-step selective removal of SFA (at 4.5%en each step) from a human diet containing 34%en as fat, while keeping MUFA and PUFA constant. Even though the P/S ratio increased to 1.0 in the process, MUFA intake equaled the other two fatty acid classes combined in the low-fat diet (containing 25%en as fat). This progressive removal of 9%en as SFA decreased LDL by 12%, but HDL was depressed proportionally. (See Fig. 10.) Thus, the indiscriminant removal of SFA (individual SFA not identified) lowers TC without improving the LDL/HDL ratio, at least when MUFA intake substantially exceeds that of SFA or PUFA.

- **SFA are best represented by 16:0 and 18:0. 15/**

The most recent NCEP and AHA diets recommend a fat intake of about 30%en with a balance of approximately 7:15:8 %en for S:M:P. As indicated by the Mustad study above, this fat profile typically means reducing SFA in the average diet, but does it matter which of the major 4 SFA are removed? The Brandeis/Hayes' study data from cebus and rhesus monkeys reveal that removal of fats containing 12:0+14:0 (leaving 16:0+18:0-rich fats) leads to a greater reduction in TC and LDL and results in a better LDL/HDL ratio, especially if the overall fatty acid profile is balanced instead of simply removing the SFA. (See Fig. 9.) The preference for 16:0+18:0 reflects the fact that 12:0+14:0-rich fats tend to increase LDL more than HDL. Thus, when balancing the S:M:P ratio in a fat blend, it is

14/ Mustad, V.A., Etherton, T.D., Cooper, A.D., Mastro, A.M., Pearson, T.A., Jonnalagadda, S.S., and Kris-Etherton, P.M., *Reducing saturated fat intake is associated with increased levels of LDL receptors on mononuclear cells in healthy men and women*, J. Lipid Res. 38:459-468 (1997).

15/ Pronczuk, A., and Hayes, K.C., *Ideal LDL/HDL ratio requires precise balance in dietary saturated and polyunsaturated fatty acids in cebus monkeys*, FASEB J. 6: A561 (1999); Khosla, P., Hajri, T., Pronczuk, A. and Hayes, K.C., *Decreasing dietary lauric and myristic acids improves plasma lipids more favorably than decreasing dietary palmitic acid in rhesus monkeys fed AHA Step 1 diets*, J. Nutr. 127:525S-530S (1997).

preferable to utilize a natural 16:0+18:0-rich fat (e.g. palm oil, beef tallow) rather than one rich in 12:0+14:0 (e.g. milk fat, coconut oil, palm kernel oil) in terms of generating the best LDL/HDL ratio.

- **Trans fatty acids are worse than saturated fatty acids in humans. 16/**

Trans fatty acids are generated when vegetable oils are hardened by hydrogenation in order to replace naturally saturated fat in the diet. Since they typically are monounsaturated, it was thought that trans exerted a neutral effect on cholesterol metabolism and other biological functions. However, more recent data suggests that they have a negative influence on lipoproteins and possibly other functions, as well.

To examine this point more directly, trans 18:1n9 (elaidic acid) was compared head-to-head with the most cholesterol-raising saturated fatty acids and the neutral, cis 18:1n9 (oleic acid) in humans. The four fats representing these fatty acids were tested in natural diets of normocholesterolemic subjects who each consumed all 4 diets over a 16-week period. The data reveal that trans fatty acid proved as cholesterol elevating as the worst SFA (12:0+14:0), and that trans had the most detrimental impact on LDL (greatest increase) while uniquely depressing HDL. (See Fig. 13.) Again, note that the 16:0-rich fat was neutral and comparable to the cis18:1-rich fat. Thus, when assessed by direct comparison with specific fatty acids, trans fatty acids proved worse than the saturated fatty acids they were designed to replace.

- **High MUFA is not as favorable as a low MUFA diet. 17/**

The original AHA recommendation called for an even balance between S:M:P at 30%en from fat. Recently, AHA has recommended approximately 50% more MUFA at the expense of SFA and PUFA, especially as fat intake rises above 30 %en. However, a human study in 8 normolipemic males demonstrates the

16/ Sundram, K., Ismail, A., Hayes, K.C., *Trans (elaidic) fatty acids adversely affect the lipoprotein profile relative to specific saturated fatty acids in humans*, J.Nutr. 127:514s-520s (1997).

17/ Chang, N.W. and Huang, P.C., *Effects of dietary monounsaturated fatty acids on plasma lipids in humans*. J. Lipid Res. 31, 2141-2147 (1990).

potential downside of exaggerating the M:P ratio, feeding either 0.5 or 3.0 M:P ratios in two diets in which the P/S ratio would be considered ideal and constant at 1.0. The high-MUFA diet produced a TC that was identical to the low-MUFA diet, but the LDL was elevated ($p < 0.05$) when SFA and PUFA intake became too low; the HDL was also lower (n.s.), so that the LDL/HDL ratio was significantly increased by high MUFA. (See Fig. 8.) In addition, the high-MUFA diet induced a 20% rise in triglycerides. Thus, the high-MUFA diet proved inferior to the low-MUFA intake, indicating that a proper balance of all three fatty acid classes (S:M:P) is important for generating the best LDL/HDL ratio. Even though keeping the P/S ratio about 1.0 may be the most critical relationship, it would appear that MUFA should not exceed 1.5 times their relative abundance of PUFA and SFA.

- **High MUFA is inferior to a balanced S:M:P fatty acid ratio. 18/**

The objective of this study in cynomolgus monkeys more precisely explored the relative importance of the S:M:P balance in the regulation of TC and LDL/HDL ratio when consuming 30%en and less than 300mg/day cholesterol human equivalent (i.e. AHA Step I diets). Similar to the human results just cited 19/ and compared to an American fat blend derived from butter and canola oil, an unfavorable imbalance developed in the LDL/HDL ratio when dietary SFA and PUFA were about equal, but too low relative to MUFA. (See Fig. 9.) Specifically, AHA Step I diets (Diets 1X and 1H) with P/S ratios close to 1.0 represented blends of four and three oils, respectively. The third test diet was olive oil alone with a fairly favorable P/S ratio of 0.75. The TC response, as well as the LDL/HDL ratio, were much improved when the relative intake of S:M:P was fully balanced in the two AHA diet blends. Thus, while the dietary P/S ratio is a rough indicator of how a fat will affect the plasma LDL/HDL ratio, it would appear that an approximate balance between all three fatty acid classes (S:M:P) is also critical, at least at 30%en fat intake.

18/ Hayes, K.C. et al., *Lipoprotein response of cynomolgus monkeys fed AHA Step I diets having different fatty acids profiles* (unpublished data).

19/ See *supra* n.10.

- **HDL can increase when total fat intake decreases. 20/**

It is generally agreed that replacing fat with carbohydrate is associated with a decline in TC, but HDL also tends to decrease. In retrospect, one of the first studies to show that this need not occur was a subgroup from the Oslo Study, which basically applied the AHA Step I diet approach to a large population. In actual practice, reductions in total fat, especially saturated and monosaturated, and dietary cholesterol to slightly less than 30% and less than 300mg/day, respectively, greatly reduced TC and LDL without decreasing HDL in 18,000 men. To examine this response more closely, 23 diet-responders from the original study were subsequently compared with 23 controls who continued to eat the high-fat baseline diet. Both groups had identical, elevated blood lipid values initially. The test group was taught how to lower dietary fat from 44% to about 30% by focusing on removal of saturated fat. In the process, a good balance in S:M:P was achieved, decreasing from an imbalanced 18:19:7 to 8:12:8. The data demonstrate sharp declines in TC, LDL and TG (200 vs. 129 mg/dl) with an equally robust *increase* in HDL (42 vs. 50mg/dl). (See Fig. 7.) Thus, removing both SFA and MUFA from a high-fat diet to improve the overall FA balance can decrease LDL sharply, but may also increase HDL if the P/S ratio approximates 1.0 and total balance S:M:P approximates 1:1.3:1.

- **PUFA intake is critical for the best LDL/HDL ratio. 21/**

Another study addressed two questions: 1) whether a low-fat diet (20% fat calories) would improve relatively normal TC values in 31 adult women, and 2) whether it matters much if dietary fatty acids are balanced between SFA:MUFA:PUFA in either a high-fat (40% en) or a low-fat (20% en) diet situation, i.e. considerably above or below the AHA Step I diet objective of 30% fat energy, and with or without the 9:12:9 balance in S:M:P which an AHA diet would support. Several results were apparent. (See Fig. 2.) The dietary P/S ratio was only 0.3 in group I (n=15) and 1.0 in group II (n=16) women. Fatty acid balance had little

20/ Hjermann, I., Enger, S.C., Helgeland, A., Holme, I., Leren, P. and Trygg, K, *The effect of dietary changes on high density lipoprotein cholesterol: The Oslo Study*, Am. J. Med. 66:105-109 (1979).

21/ Jones, D.Y., Judd, J.T., Taylor, P.R., Campbell, W.S. and Padmanabhan, P.N, *Influence of caloric contribution and saturation of dietary fat on plasma lipids in premenopausal women*, Am. J. Clin. Nutr. 45, 1451-6 (1987).

effect on LDL or HDL at 40%en, primarily because the basal (group I) intake of PUFA (6%en) was close to the amount of 18:2 required for normal lipoprotein (LP) metabolism given the circumstances of these normolipemic women. But the superior balance (P/S 1.0) did tend to improve the LDL/HDL ratio slightly at this high-fat intake. However, when consuming the low-fat diet, balance in fatty acids was especially important because a balanced 1:1:1 ratio (group II) prevented the substantial decline in HDL seen with group I, where the typical American Fat imbalance (P/S, 0.3) resulted in higher LDL and lower HDL with a much improved LDL/HDL ratio. The undesirable impact on LDL and HDL in group I occurred primarily because the absolute intake of PUFA (at 3%en) was too low for adequate lipoprotein metabolism when total fat supplied only 20%en. Thus, the LDL/HDL ratio was much improved by feeding the 1:1:1 fatty acid balance at the low-fat intake (group II) because the 6%en from PUFA was now adequate in absolute terms (in total grams of 18:2/day).

Accordingly, with dietary fat somewhere between 40%en and 20%en a proper balance in fatty acid intake becomes exceedingly important for generating an optimal LDL/HDL ratio, i.e. the lowest LDL and highest HDL values. Like the 1995 Sundram study 22/, it would appear that a controlled intake of PUFA (18:2) is required to allow for the greatest decline in LDL without also lowering HDL. The particular type of SFA fed in this study was not specified, although an amount of total SFA equal to the PUFA resulted in a very favorable LDL/HDL response.

* * * * *

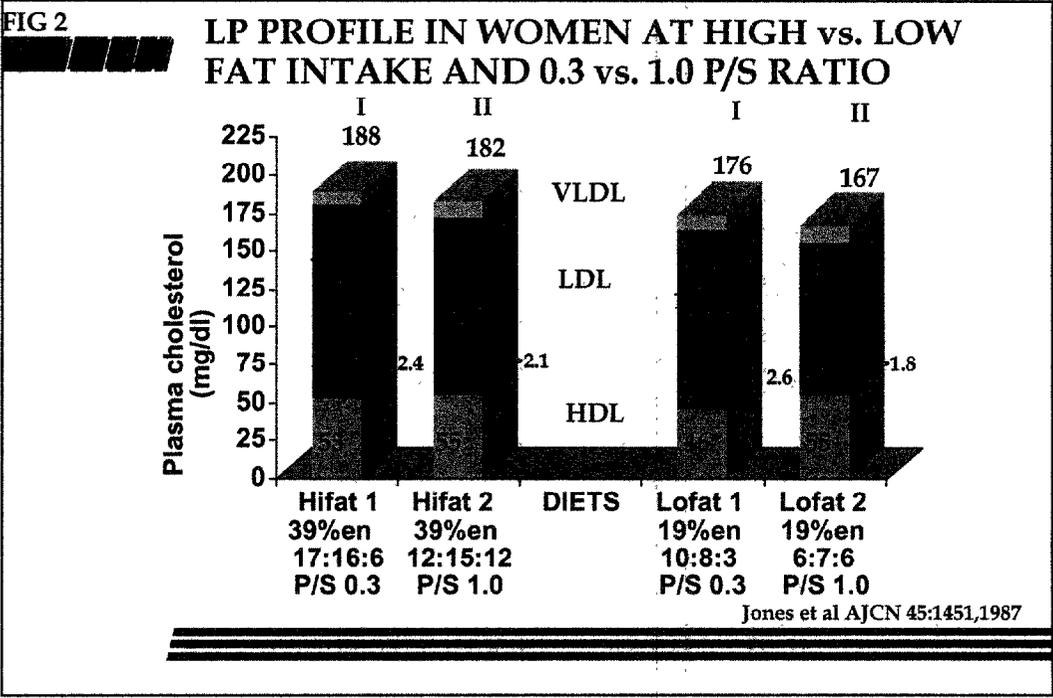
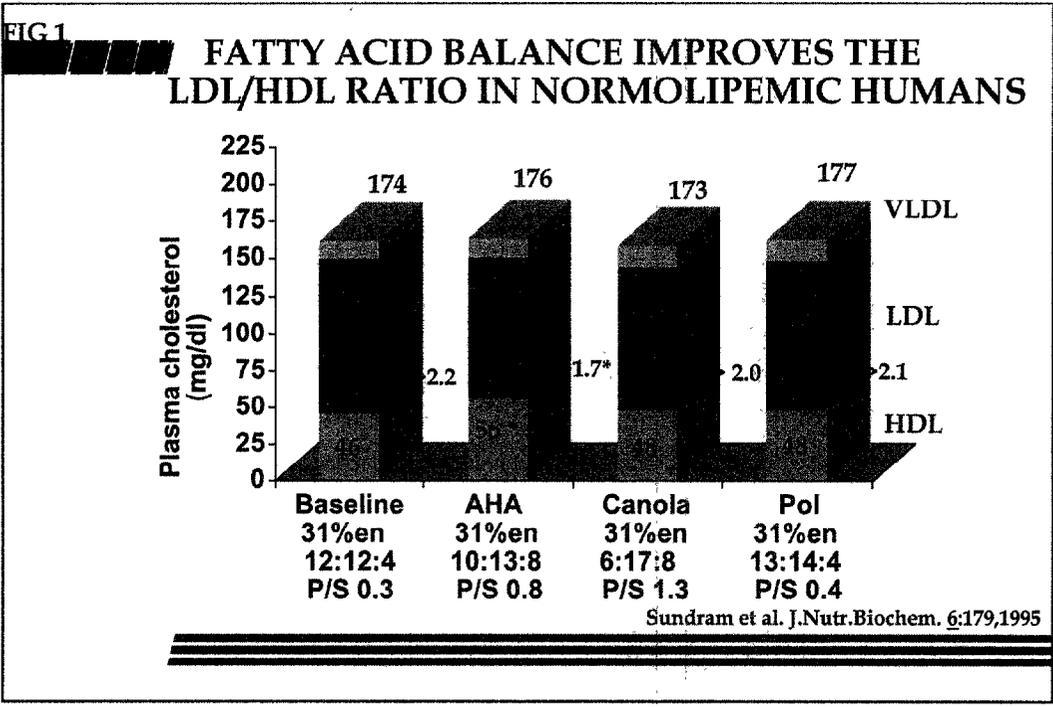
Based on the above information, GFA believes there is a strong basis for eliminating the low in saturated fat requirement for using phytosterol health claims on products such as Smart Balance Plus® that have a balanced level of saturated and polyunsaturated fatty acids and were designed specifically to be heart healthy. GFA appreciates your consideration of this issue and looks forward to working with the agency in the future. We would be pleased to discuss further with FDA staff any of the points made in these comments.

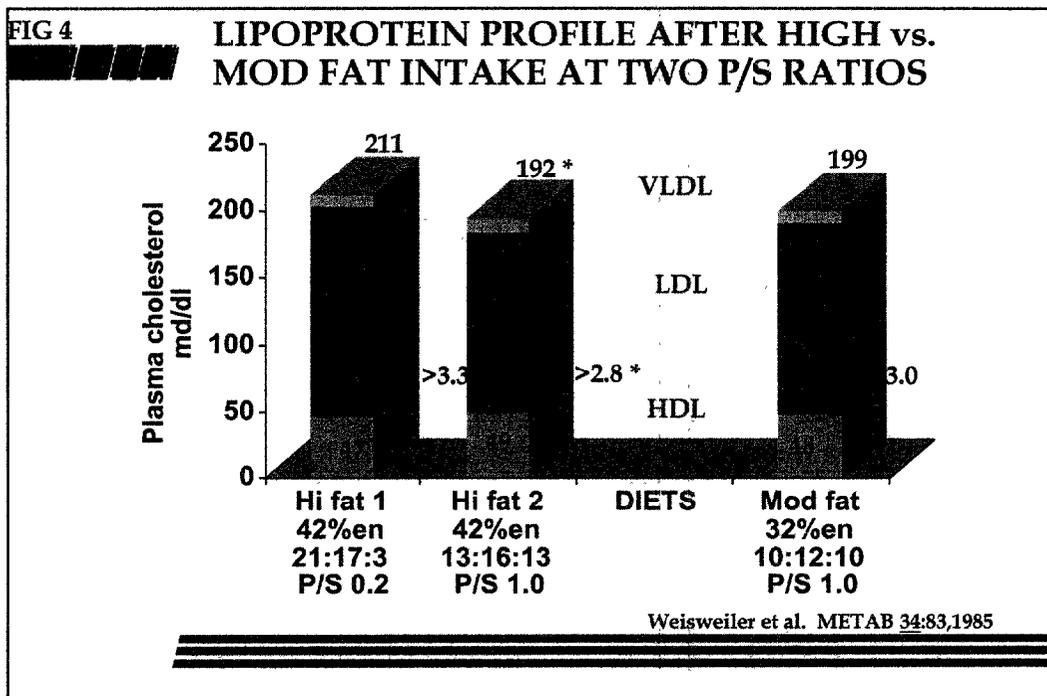
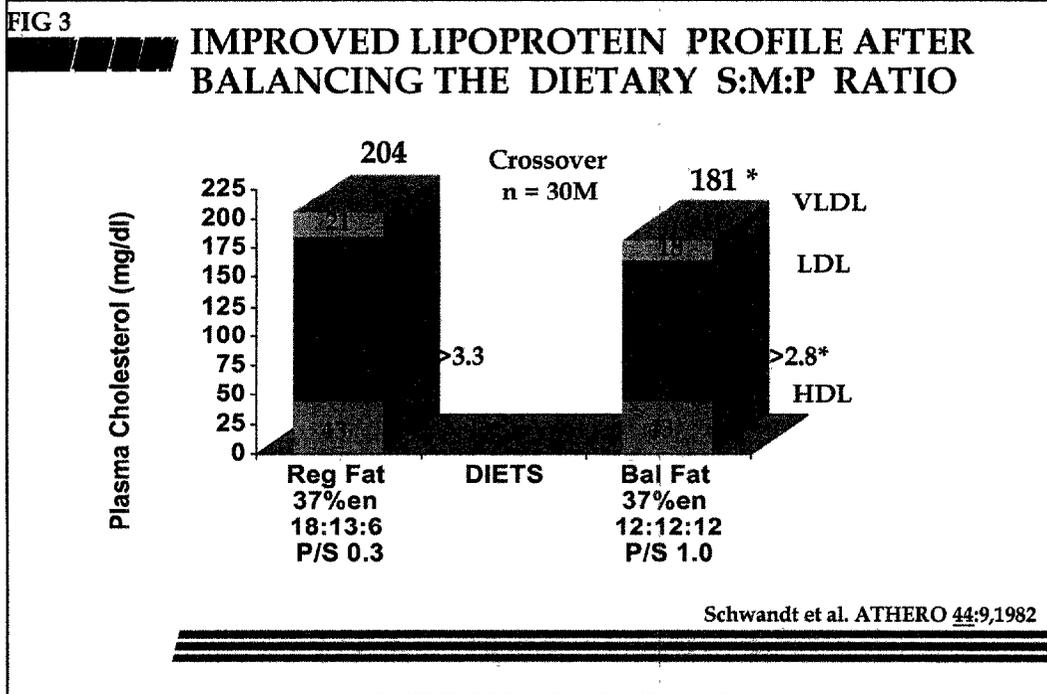
Sincerely,


Martin J. Hahn

Enclosures

22/ See supra n.4.





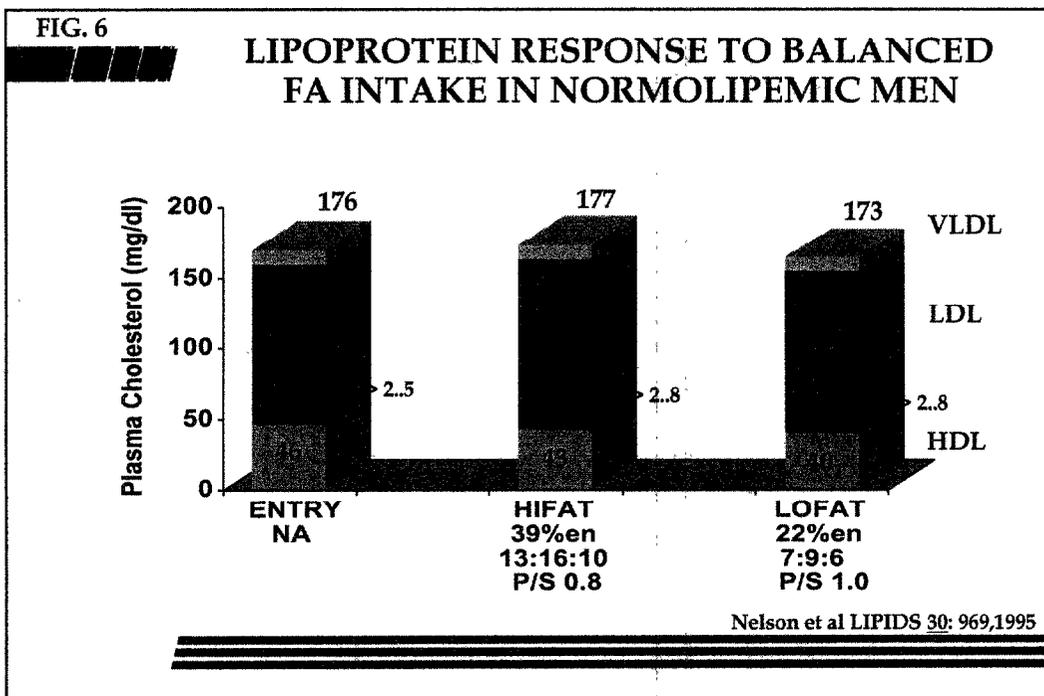
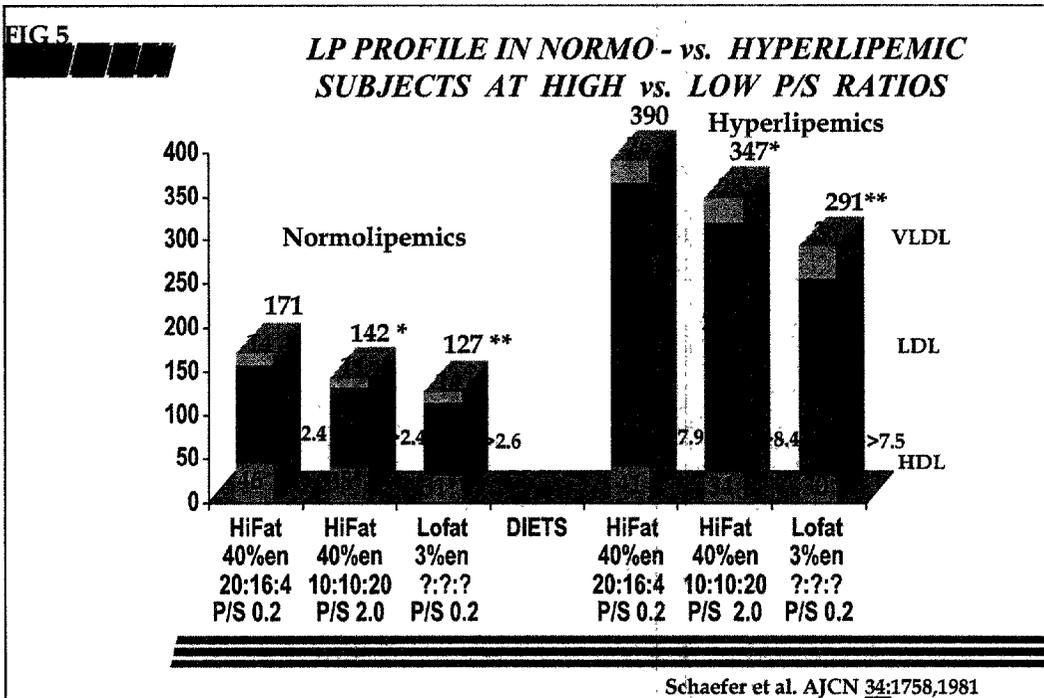
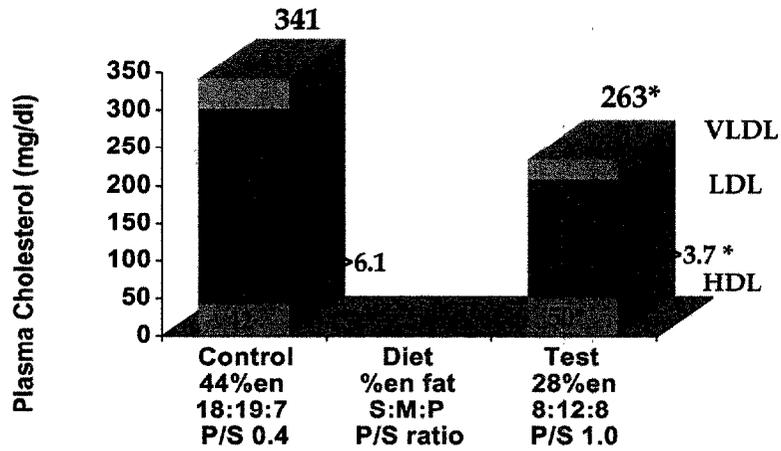


FIG 7

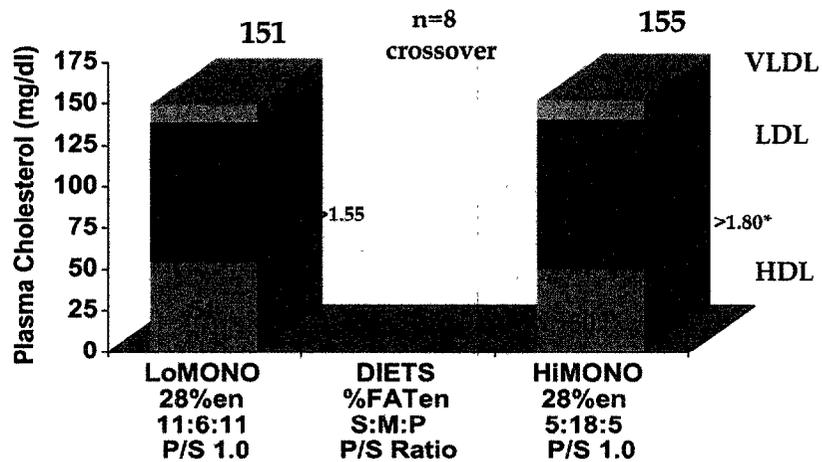
AHA STEP I DIET IMPROVES THE LIPOPROTEIN PROFILE OF HYPERCHOLESTEROLEMIC MEN



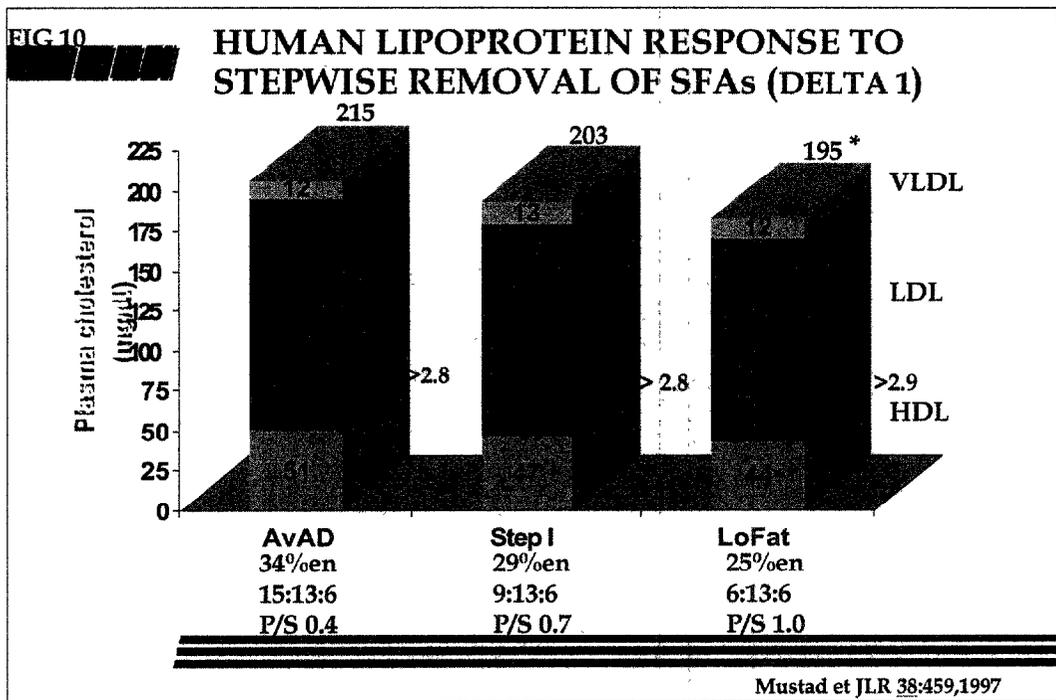
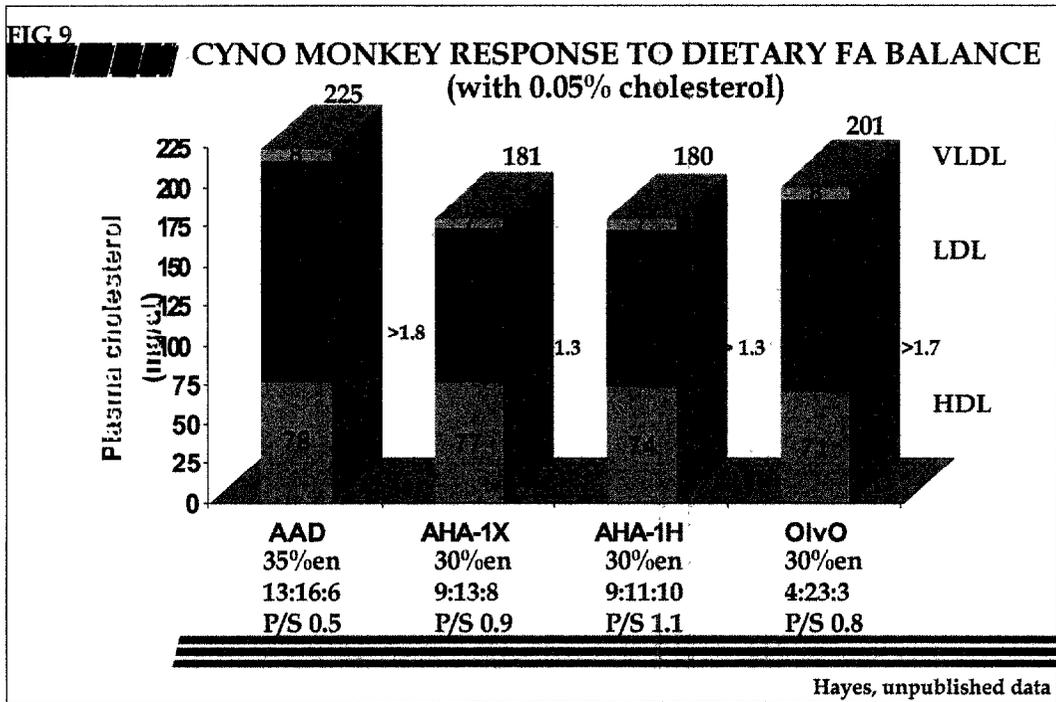
Oslo Study. Am J Med 66:105,1979

FIG. 8

HUMAN LIPOPROTEIN RESPONSE TO A LOW-MONO OR HIGH-MONO DIET



Chang JLR 31:2141,1990



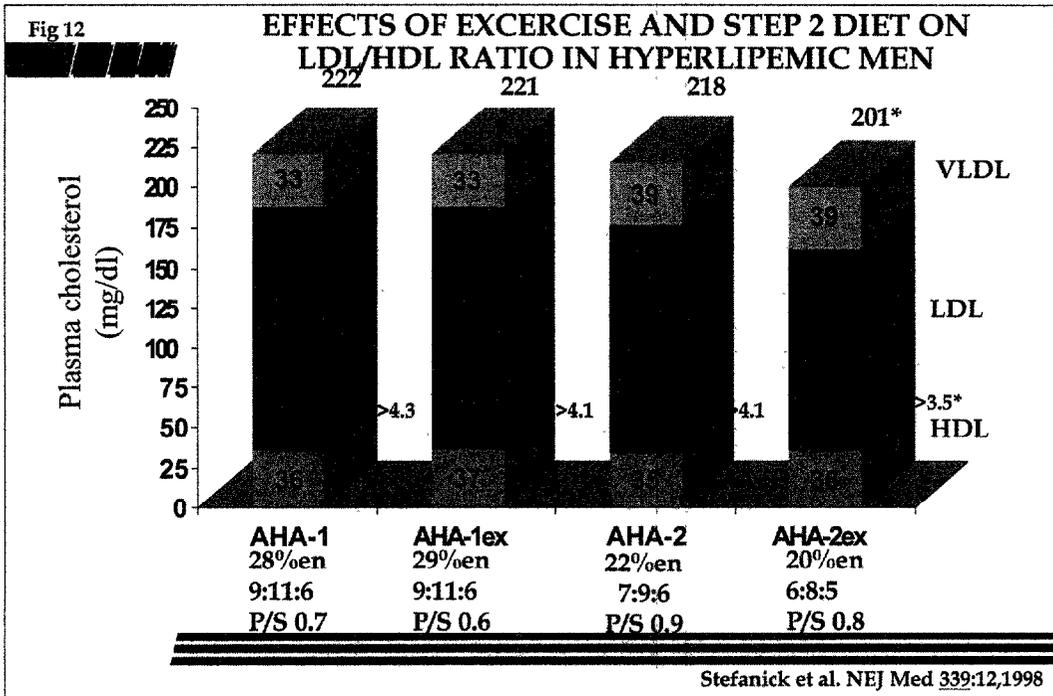
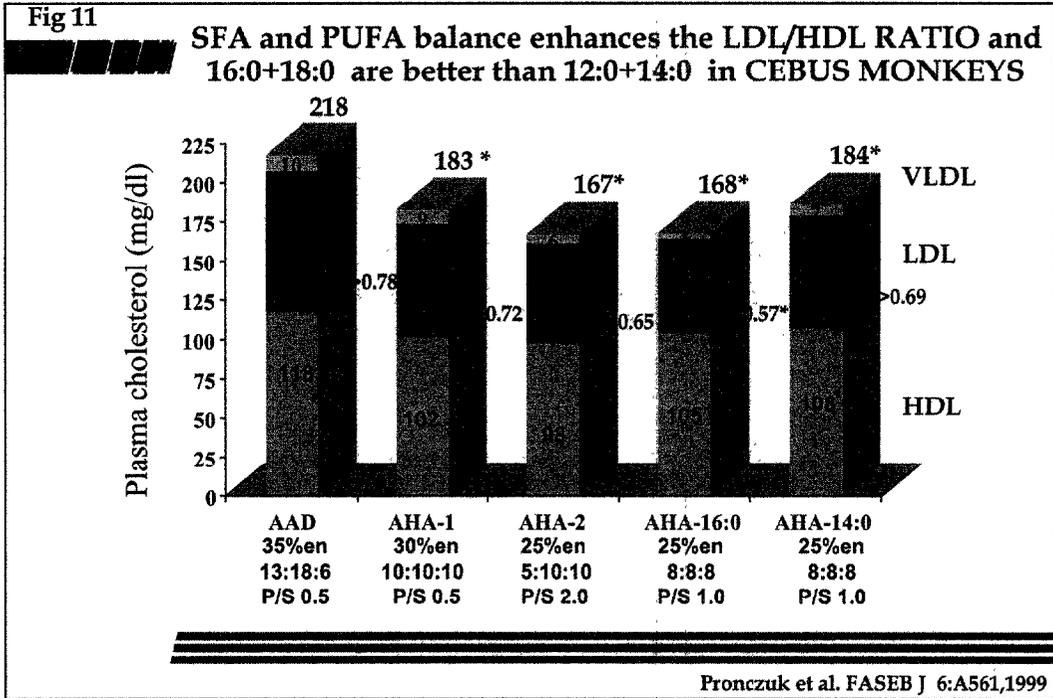
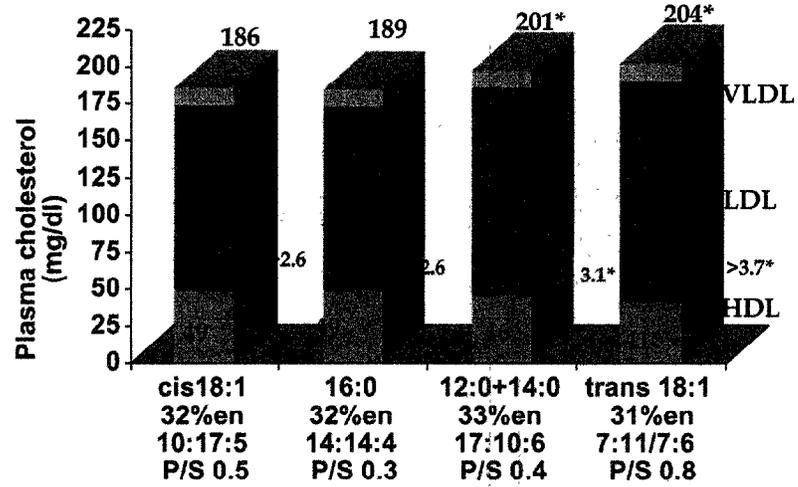


FIG.13

COMPARISON BETWEEN *cis* 18:1, 16:0, 12:0+14:0, AND *trans* 18:1 IN NORMOLIPEMIC HUMANS



Sundram et al. J.Nutr.127:514s,1997