The influence of dietary fats on serum lipid levels in man

E. H. Ahrens, J. Hirsch, W. Insull, T. T. Tsaltas, R. Bloomstrand, M. L. Peterson

Lancet. 1957;1:943-953

One of the most striking aspects of this seminal paper is the quality of the research presented, and the profound questions that are raised about the fundamental influence of the quantity and quality of dietary fats upon the serum lipid profile. Therefore, this work provided the cornerstone for many of the investigations, which will be described later. A second remarkable feature is the fact that experiments were performed with human as opposed to animal subjects, and their rigorous basic design is replicated in much of the later work in this field.

The authors summarize a number of different studies to clarify the influences of dietary fat. Fundamental to all is the principle of each study subject consuming a liquid diet with varying proportions of protein (15%), fat (40%), and carbohydrate (45%), while maintaining a constant calorific intake and body weight throughout the study period, which varied from 4 to 6 months. By feeding the subjects on corn oil in the first part of their dietary regimen, a steady state of serum cholesterol level was achieved for any given individual, and was therefore used as a baseline for comparison.

The first of theses studies describes an investigation into why a diet of corn oil might be responsible for the observed reduction in total serum cholesterol. The first question asked is whether the fall is due to the absence of elevating factors or to the presence of lowering factors, but previous work by their group had established that the addition of extra-dietary cholesterol would not lead to a rise in serum cholesterol. Therefore, the next issue was to determine which constituent of the corn oil was the cholesterol-lowering factor. Studies manipulating the proportion of the nonsaponifiable, ie, nonglyceride fraction of corn oil without significant changes in the cholesterol-lowering effect led to the suggestion that the glycerides themselves were the cholesterol-lowering factors.

The next part of the investigation therefore focused on the components of the fatty acid fraction. The authors found that by varying the proportion of fats with a higher iodine value, ie, those with more double bonds (unsaturated fats), the lipid levels would show a good correlation, such that higher iodine values corresponded with lower cholesterol levels. However, what was less clear was whether the lipid-lowering effect was due to unsaturated fats in general or to a specific variety of unsaturated fat, because the study oils used were so heterogeneous, and pure fatty acid synthesis was prohibitively expensive. Pursuing a similar line of enquiry, however, using partially hydrogenated corn oil to produce a greater proportion of saturated fat, did not lead to firm conclusions in the 3 patients that were studied, although there was a tendency for the saturated fat diet to lead to higher serum cholesterol.

The next stage of investigation was based on the finding that the higher cholesterol levels were observed in the saturated fat-fed groups, but these fats also happened to have short to intermediate carbon chain lengths. Therefore, 2 subjects were fed butter and cocoa butter, containing short- and intermediate-length chains, respectively, but each having near-identical iodine values. The results suggested that the shorter carbon length properties of the butter diet led to higher serum cholesterol.

The authors concluded after these fascinating experiments that modification of food habits, even for those most at threat from atherosclerosis, was not recommended until a more complete understanding of dietary fat and serum cholesterol was obtained, as many aspects remained unexplained. However, the contribution of this study to focusing the direction of future investigations is unmistakable.

1957

The Pulitzer biography prize is awarded to John F. Kennedy for his book "Profiles in Courage"; Great Britain performs atmospheric nuclear tests at Christmas Island; and Joseph R. McCarthy, the driving force behind the anticommunist crusade in the US, dies

Prediction of serum cholesterol responses of man to changes in fats in the diet

A. Keys, J. T. Anderson, F. Grande

Lancet. 1957;2:959-966

This paper is remarkable for several reasons. Firstly, it sets out to achieve what at first sight appears to be a near-impossible task, that is, to demonstrate a method for predicting serum cholesterol changes from the dietary source. Secondly, where previous and subsequent studies had sought to compare formula (usually liquid) diets with each other, this study attempts to measure the effects of test fatty acids within so-called "ordinary" diets. Astonishingly, the test subjects include exclusively schizophrenic patients in the American arm of the study (whose consent to participate was obtained from their "nearest relative"), as well as coalminers of Japanese nationality in the second arm, bearing in mind that the Second World War had finished a little over 10 years previously. Finally, having expended considerable time and resources in the execution of the study, much of the discussion centers upon reasons why the "predictive" model serves very limited use outside the strict experimental parameters! The authors argue that lowering any type of fat ingested, whether animal or vegetable, may have significance.

Groups of between 12 and 27 men were given calorie-balanced diets, which were controlled so that each was maintained for 4 weeks on "normal" diets (composition not specified). They were subsequently fed for between 2 to 9 weeks on each of 2 to 6 diets that differed in their fat content (between 9% and 44% of total calorie value of the diet), with the experimental fats comprising approximately 75% of the total fat content. The study fats included butterfat, hydrogenated coconut oil, olive oil, cottonseed oil, corn oil, sunflower seed oil, safflower oil, sardine oil, and the mixed food fats of an "ordinary" American diet.

The authors are careful to indicate that an analytical method of predicting the cholesterol response will depend crucially upon the reliability of the assay used to measure cholesterol, and they provide a measure of the error by repeating the assay on duplicate samples for each blood test.

The results that follow are portrayed in a way that is less focused upon identifying components of a fat diet that may alter serum cholesterol, than they are in providing the means to construct equations that describe the relative influences of saturated, monoethenoid and polyethenoid fats upon serum cholesterol. Consequently, there is relatively little emphasis on the finding that saturated fatty acids (S) with carbon chains longer than 10 have nearly twice as much potential to raise serum cholesterol as the cholesterol-lowering effect of an equal mass of polyethenoid fats (P), and monoethenoids (M) are deemed to exert an almost neutral effect. Instead, there is a complicated, and occasionally baffling analytical process that results in a series of regression equations that describe a surprisingly linear relationship between the fatty acid variables mentioned expressed as calorific values and changes in serum cholesterol:

$$\Delta\text{Cholesterol} = 2.76\Delta S + 0.05\Delta M - 1.35\Delta P - 1.68.$$

However, with the intention of simplifying further the analysis of any particular diet to determine its effect upon serum cholesterol, a mathematical relationship is constructed using the total iodine value as a measure of the average saturated fat content of a diet, although the predictive value of the resulting regression equation is less than that achieved with the previous model when any individual participant's data is subjected to the equations; rather, these equations are better at predicting values for a group than an individual.

Although ultimately flawed, this study provided a benchmark for future attempts to create a regression model for predicting changes in serum cholesterol.

1957

The USSR launches Sputnik 2,
containing Laika, the dog;
the remains of Captain Bligh's ship
"The Bounty" are found off Pitcairn Island; and
Diego Rivera, the Mexican mural painter, dies

Quantitative effects of dietary fat on serum cholesterol in man

D. M. Hegsted, R. B. McGandy, M. L. Myers, E. J. Stare

Am J Clin Nutr. 1965;17:281-295

Both similarities and striking differences are to be found between this paper and previous studies seeking to discover a mathematical prediction of the effect of dietary lipids upon serum cholesterol. It is remarkable considering the nature of the patient cohort and the duration of the study. The participants consisted of 2 groups of 10 mostly schizophrenic men all selected from a psychiatric institution, who were furnished with experimental diets over a period of 2 years. They were fed a relatively low-fat diet (after a control period of 4 weeks eating a "usual" American diet) to which a wide variety of test fats of equal calorific value were added so that total dietary fat was 22% or 38% to 40% of total calorie intake, each test period lasting 4 weeks, and alternated with control diets of varying intervals. Dietary cholesterol was also varied by the addition of egg yolk. Despite the relatively small numbers, by using the same individuals throughout the study period, the authors infer that the conclusions drawn should be "strong."

They begin by describing the key findings of work published to date, including the correlation between the degree of saturation (iodine number) of a fat and serum cholesterol, the multiple regression equation of Keys linking serum cholesterol changes with calorific values of mainly saturated and polyunsaturated fats, the conflicting evidence for polyunsaturated fats and dietary cholesterol, and the relative lack of data for dietary phytosterols, carbohydrates, and proteins.

By collating the data and submitting them to an IBM machine (presumably the grandfather of modern computers), the investigators obtained 256 equations that represented, with varying degrees of accuracy, a model for predicting serum total cholesterol using each of 8 dietary variables (5 different saturated fatty acids, monounsaturated, polyunsaturated fatty acids, and dietary cholesterol.) As in previous studies, changes in the β-lipoprotein fraction paralleled changes in total cholesterol, although in contrast to earlier studies, the pretest cholesterol levels of individuals did not influence their response to the test diets.

A multiple regression equation was obtained which was adequate to explain 91% of total cholesterol changes, but using only the variables of myristic acid (14 carbon atoms, no double bonds, ie, a saturated fat; [14:0]), palmitic acid (16:0), polyunsaturated fats and dietary cholesterol; inclusion of other variables did not significantly alter the correlation. The most important of the fatty acid components affecting serum cholesterol was the saturated fat myristic acid, whereas palmitic (16:0) and stearic acids (18:0) did not exert a significant effect. Dietary cholesterol unsurprisingly showed a linear relationship with serum cholesterol, in line with most of the current studies, although this finding was at odds with one previous work. As previously shown, increasing the polyunsaturated portion lowered serum cholesterol. Interestingly, the amount of fat consumed, whether 22% or 40% of total intake, had no influence on serum cholesterol, but a more accurate prediction could be made from considering the proportions of different dietary fatty acids. The authors summarize by suggesting that practical means of lowering cholesterol by diet is to include fats with a relatively small proportion of myristic and palmitic acids and cholesterol, and a high proportion of polyunsaturated acids.

The authors conclude with a honest appraisal of the limitations of multiple regression equations, namely, that they are simply descriptions of the results obtained, and that the dietary oils act as though their specific fatty acids have the influence upon serum cholesterol proportional to their coefficient. However, they do not prove per se that the fatty acids have these effects.

1965

Folk rock is born when Bob Dylan is booed off stage at the Newport Folk Festival for using electric instruments; France's president De Gaulle and the Italian president Saragat officially open the Mount Blanc tunnel; and death of Japanese writer Junichiro Tanizaki

Serum cholesterol response to changes in the diet. IV. Particular saturated fatty acids in the diet

A. Keys, J. T. Anderson, F. Grande

Metabolism. 1965;14:776-787

Amidst the abundance of regression analyses and equation-solving that characterizes both this paper and the previous one from this group that is discussed in these summaries, there does appear to be at least one clear conclusion: dietary stearic acid does not have a serum cholesterol–raising effect. This conclusion is reached, however, not from a specific investigation into the effects of dietary stearic acid per se, but by an attempt to understand why the chosen formula relating serum cholesterol changes to dietary intake of fatty acids does not appear to provide a reliable estimate in many instances. This formula is:

$$\Delta \text{ Cholesterol} = 1.35\,(2\Delta S - \Delta P) + 1.5\Delta Z,$$

where S and P are the percentage of total calories provided by saturated and polyunsaturated fats, respectively, and Z^2= mg of dietary cholesterol per 1000 calories.

Previous work by this group led to a derivation of this formula from a rather specific patient population with specific test diets, as described above. The implication of the formula is that all saturated fats exert an equal effect upon dietary cholesterol, whereas the coefficient value of S was derived from mixtures of saturated fats, with possible different dietary effects. Even by exclusion of small carbon chain length fatty acids, which the authors argue have different physical properties and therefore different metabolic fates compared with their longer–chain length counterparts, the effect upon the discrepancies noted by using the formula to estimate serum cholesterol changes is negligible, presumably because such small-length chains do not occur in any normal diet.

Attention is then turned to experiments with cocoa butter, where the largest differences are seen between observed and expected results using the formula for any particular diet. The authors indicate that one distinguishing characteristic of this food is its high stearic acid content. Based on this observation, they suggest that there may be three explanations why stearic acid analysis leads to higher than expected errors, which are: (i) stearic acid has a neutral effect upon cholesterol and should be subtracted from the "S" value prior to calculation; (ii) stearic acid actually has a cholesterol-lowering effect; and (iii) stearic acid interferes with the cholesterol level–modifying properties of other fats. The authors then proceed to reanalyze 46 different lines of evidence from several different studies in order to explore these concepts further.

The remainder of the paper appears to be an exercise in justifying the validity of the original regression equation, albeit with sufficient modification to take into account the various stearic acid diets analyzed. The equations that lead to the most accurate prediction of serum cholesterol levels are those that exclude stearic acid from the calculation.

The authors conclude that stearic acid is not cholesterol-elevating and that, therefore, the other constituents of saturated fat, chiefly lauric, palmitic, and myristic acids, have the greatest influence upon raising cholesterol levels.

This paper once again demonstrates the shortfalls in ascribing too great an importance to regression analyses; each equation is ultimately a description of observed data, but if the data itself are limited, or if assumptions are made about the constituent parts of the data that cannot be validated reliably, then the predictions will be inaccurate.

1965

Rhodesian Prime Minister Ian D. Smith unilaterally proclaims independence from Britain; Ferdinand Marcos claims victory in the Philippines presidential election; and Joseph Mobutu deposes Congo President Joseph Kasavubu and installs himself as the head of state

The Seven Countries Study: 2289 deaths in 15 years

A. Keys, A. Menotti, C. Aravanis, H. Blackburn, B. S. Djordjevic, R. Buzina, A. S. Dontas, F. Fidanza, M. J. Karvonen, N. Kimura, et al

Prev Med. 1984;13:141-154

Epidemiological studies such as this rely on a long duration of follow-up (in this case 15 years) to obtain significant results, a period made all the more poignant in this case by the fact that two of the authors died before it reached publication. The primary goal was to investigate the causes of death in men apparently free of cardiovascular disease from the initiation of the study, and potentially use the data to predict and prevent deaths across various different populations.

There were 15 cohorts from 7 countries, grouped further into 4 regions (USA, Northern Europe, Southern Europe, and Japan). Several risk factors were examined to assess their contribution for both coronary and all-cause mortality; these were age at entry, serum cholesterol, systolic blood pressure, smoking, body mass index (BMI, termed "relative body weight"), and physical activity.

Several problems become immediately apparent with the study methods and design. Firstly, despite a study population of just over 11 500, no women were included. Secondly, the range of ages investigated is relatively narrow (40 to 59 years). Thirdly, information about arguably the most important data, the cause of death, was obtained variously from death certificates, insurance companies, and from friends and relatives of the deceased. The authors themselves point out the limitations of such methods, particularly in areas such as rural Japan where coronary artery disease–related death was a relatively new diagnosis, and could potentially be missed. Despite stipulating the intention to document causes of premature death, no mention is made of how this might be defined. Crucially, information is lacking about the method of describing how an individual was deemed to be free of cardiovascular disease before allowing entry into the study. Finally, the statistical method used to calculate the probability of death for the various risk factors was a multiple logistic model derived by an iterative method described nearly 20 years earlier, without any apparent validation.

So despite these limitations, several conclusions were drawn from the results. Of the 11 579 men deemed to be free from cardiovascular disease, 2289 died in 15 years, 618 of coronary disease. Systolic blood pressure appeared to be the only factor on entry to the study that explained differences in all-cause mortality, although the values of blood pressure are not specified. For variances among regions in coronary death, serum cholesterol and blood pressure had the most influence. As might be expected, the coronary mortality risk for individuals was significantly affected by age, serum cholesterol, blood pressure, and smoking (number per day unspecified), although somewhat surprisingly, BMI did not affect risk. Japan was the exception, where too few individuals died of coronary disease to make an evaluation. Physical activity only had an influence in Southern Europe. Similarly, for all-cause death, age, blood pressure, and smoking were significant, except in Japan, and BMI was now a negative risk factor, that is, the probability of death from all causes decreased with increasing BMI.

The investigators then used their findings to compare risk factors for coronary death among regions, and found that trends in mortality for the USA and northern Europe were closely correlated, but could be used to predict trends in Southern Europe, and vice versa. This final point, that different populations may have an intrinsic difference in their response to coronary risk factors, is perhaps the most important conclusion, but due to the various critical flaws of study design and methodology it is not clear if this, and other conclusions, are valid.

1984

Ingmar Bergman's classic film "Fanny and Alexander" wins the best foreign film award at the Oscars; British ice dancing team, Torvill and Dean, become the first skaters to receive 9 perfect 6.0s in world championships; and South-Africa and Mozambique sign a pact banning support for each other's internal foes

Comparison of effects of dietary saturated, monounsaturated, and polyunsaturated fatty acids on plasma lipids and lipoproteins in man

F. H. Mattson, S. M. Grundy

J Lipid Res. 1985;26:194-202

This study was published at a time when questions were being raised about the long-term safety of polyunsaturated fats, and as a result carbohydrates were being recommended as a replacement for saturated fatty acids in the diet. There were, however, even fewer data about monounsaturated fats, whose effect upon plasma lipids was thought to be neutral. This paper aimed to compare the effects of saturated, monounsaturated, and polyunsaturated fats upon the serum lipid profile, represented by palm oil, high oleic safflower oil, and high linoleic safflower oil, respectively. A small number of individuals (n=20) were given a rather daunting liquid diet of which 40% total calorific value was given by these fats, which represented the only fats in the diet. The relative proportions of carbohydrate and protein were 44% and 16%, respectively. Each diet was consumed for 4 weeks before switching to the next diet, and the order of the diets was randomized. All but two had elevated plasma total cholesterol at the beginning of the study, defined as greater than 200 mg/dL. Twelve had normal triglyceride levels, while the remaining 8 had elevated levels. These two groups were analyzed separately because of a presumed disturbance of lipid metabolism in hypertriglyceridemic individuals.

In the group as a whole, both monounsaturates and polyunsaturates produced almost identical reductions in low-density lipoprotein (LDL) cholesterol levels (17%) compared with saturates, but no changes in high-density lipoprotein (HDL) levels were observed. Similar reductions in total cholesterol were also observed in these groups compared with saturates, which was different from previous studies that had demonstrated a more marked reduction with polyunsaturates compared with monounsaturates. When normotriglyceridemic patients were considered separately, a significant reduction in HDL cholesterol was seen in the polyunsaturated group. Within the groups, however, there was marked variability in HDL cholesterol response, and the authors emphasize that the small patient numbers prevent firm conclusions from being drawn. Additionally, there was no significant reduction in total cholesterol level with polyunsaturates and monounsaturates. Once again, these results were in conflict from the earlier studies by Keys, who had produced a model for predicting the change in total cholesterol for a given increase in saturated fats (an increase in total cholesterol), as well as for a given increase in polyunsaturated fats (leading to a decrease in total cholesterol). These results, therefore, suggested that the earlier models were incomplete, and also that a nonlinear response in serum lipids to changes in dietary fats might exist.

When the 8 patients with hypertriglyceridemia were considered, a significant reduction in total cholesterol was observed in the polyunsaturate group, but not in the monounsaturate group. By contrast, the monunsaturate group, but not the polyunsaturate group, produced a fall in LDL cholesterol. None of the three fat varieties changed the level of HDL cholesterol in the hypertriglyceridemic group, although levels of HDL cholesterol were generally lower.

Therefore, the general conclusion from the paper was that monunsaturated fats have at least as important a role as polyunsaturated fats in reducing LDL cholesterol levels and total cholesterol, whereas a reduction in HDL cholesterol was seen in normotriglyceridemic patients taking polyunsaturates.

1985

Madonna's “Like a Virgin” album reaches number one in the USA and music charts worldwide; Desmond Tutu is enthroned as the first black Anglican Archbishop of Johannesburg; and Isobel Peron resigns as the head of the Peronist party in Argentina

Comparison of monounsaturated fatty acids and carbohydrates for lowering plasma cholesterol

S. M. Grundy

N Engl J Med. 1986;214:745-748

Unlike previous studies focusing upon the comparison between polyunsaturated and saturated fats, this is one of the first studies to compare the impact upon plasma lipids of diets rich in carbohydrate (consequently low in fat) with those rich in monounsaturated fats. This study investigated the relative influences of carbohydrates and monounsaturated fats upon the plasma lipid profile, in the context of the relatively low rates of atherosclerotic disease observed in epidemiological studies of Mediterranean diets, despite their relatively high intake of fats in the form of monounsaturated olive oil. Additionally, the study also provides a means of considering the established benefits of a low-fat diet (low rates of coronary heart disease, holding body weight down), against its potential disadvantages.

Remarkably small numbers of trial participants were involved (n=11), and with a ratio of 10 men to 1 woman, this study is thrown into stark relief by modern trials in which patient numbers run into several thousands with equal sex distribution before they are taken seriously. These brave individuals were selected to take part in the trial, which involved consumption of three different liquid diets of equal energy content, each over 4 weeks, selected in a random order for each individual. In two of the diets, 40% of the total energy came from fats and 43% from carbohydrate, and in the third diet just 20% was from fat, but 63% from carbohydrate (the so-called low-fat diet.) In the two fat-rich diets, the principal fat components differed between saturated and monounsaturated fats, respectively. The study was subdivided further into two further categories based upon whether the saturated fatty acids were composed of short chains (mainly coconut oils), or long chains (palmitic acid), but as there were no obvious differences in response compared with the monounsaturated group and the carbohydrate group, the saturated fats were considered as a whole for data comparison.

Interestingly, the monounsaturated diet and low-fat diets both lowered total cholesterol and low-density lipoprotein (LDL) significantly. In addition, the high monounsaturated fat group had a significantly lower level of total cholesterol compared with the LDL group. Unsurprisingly, the plasma triglycerides were raised with the low-fat, carbohydrate-rich diet, as had been demonstrated by earlier groups, although the authors argue that the observed fall in triglyceride levels seen in individuals who have a prolonged carbohydrate-rich exposure from previous studies was not seen possibly because the 4-week test diet period was too short. However, the low-fat diet also reduced the level of high-density lipoprotein (HDL) cholesterol compared with the other two diets, which had very little effect upon this factor. As a consequence, the LDL/HDL ratio was significantly higher in the low-fat group compared with the monounsaturated fat group.

The authors conclude that a high monounsaturated fat diet can lower the LDL and total cholesterol, together with a neutral effect on HDL. At the same time, however, this diet would have similar or more positive effects upon the plasma lipid profile as a high carbohydrate diet, as long as body weight does not change.

1986

Richard Manuel, rock vocalist and pianist with the "Band," commits suicide at the age of 40 years; Jacques Chirac becomes Prime Minister of the French government; and "Out of Africa" wins best film at the 58th Academy Awards

Effect of dietary stearic acid on plasma cholesterol and lipoprotein levels

A. Bonamone, S. M. Grundy

N Engl J Med. 1988;318:1244-1248

An important question regarding the relative effects of different saturated fats upon the serum lipid profile is addressed in this study: do all saturated fats have a deleterious influence? Two important reasons why this question needs to be asked at all is that saturated fats are present in many animal fats, present in most Western diets, and, secondly, they provide texture in many foods. This experiment could only have been performed without prohibitive costs in a more modern era where relatively inexpensive synthesis of specific fatty acids was made possible, which may explain why this issue was not conclusively dealt with before.

The key piece of evidence suggesting a nonelevating effect of stearic acid (18 carbon atoms, no double bonds [18:0]), found in a high proportion in fats, such as beef, upon cholesterol came from Ahrens in 1957, who observed this phenomenon in the naturally occurring stearic acid–rich cocoa butter. As other evidence has suggested a cholesterol-elevating effect of palmitic acid (16:0), and a lowering effect of oleic acid (18:1), these two fats were used as a comparison with stearic acid in 11 male inpatients of a metabolic ward. Each subject was given three different diets, respectively containing the three different oils, with the order of the diets randomized. Each test diet period lasted for 3 weeks, with a washout period between diets. As in previous studies, the relative proportions of calorific value were fixed among diets, such that 40% came from fats, 40% from carbohydrates, and 20% from milk protein, with a small, fixed cholesterol content of less than 100 mg. The authors are clear in pointing out that the study fats in each diet were not the only fats present, such that the stearic acid–rich diet also contained small amounts of palmitic acid, and the oleic and palmitic acid–rich diets each contained a small portion of stearic acid.

The results showed that the stearic acid diet not only significantly lowered plasma cholesterol, low-density lipoprotein (LDL), and the LDL/HDL (high-density lipoprotein) ratio, but also produced this effect with as much potency as the oleic acid–rich diet, with a tendency for being even more effective, although this latter finding was not statistically significant. Triglycerides and HDL levels were unchanged with the oleic acid–rich diet when compared with the other two diets. As expected, the palmitic acid–rich diet led to higher total and LDL cholesterol compared with the other two groups.

The investigators also measured the fatty acid composition of plasma triglycerides and cholesterol esters, and discovered that both the oleic acid–rich and the stearic acid–rich diet intriguingly led to a rise in oleic acid in plasma compared with the palmitic acid–rich diet, and yet the stearic acid level in plasma remained unchanged. Some suggestions are made as to why cholesterol is not elevated in the stearic acid–rich diets. One is that this fatty acid may be less well absorbed, but this is unlikely as the subjects did not lose weight while on this diet, and animal studies have suggested otherwise. Secondly, they hypothesize that stearic acid is rapidly converted into oleic acid.

The investigators conclude by pointing out the major flaws in this study, principally that men, but not women, were enrolled, and, secondly, that the effects observed in artificially created dietary fats should not be extrapolated to include naturally occurring foods. Thus, the investigation provides a useful insight both into underlying metabolic fates of certain fats, and also into potential methods of modifying manufactured foods to lessen the impact upon serum lipids.

1988

Chet Baker, the jazz trumpeter,
falls to his death from a hotel window, aged 59;
the Edgar Degas statue "Danseresje van Veertien"
sells for $10 120 000 at auction; and
Soviets begin their phased withdrawal
from Afghanistan

Effects of dietary *trans* fatty acids in high-density and low-density lipoprotein cholesterol levels in healthy subjects

R. P. Mensik, M. B. Katan

N Engl J Med. 1990;323:439-445

Prior to the publication of this paper, there were reports that drew conflicting conclusions about the influences of dietary fatty acids upon serum lipids. This study was designed to investigate the influence of different varieties of fatty acid components of a diet. Particular attention is given to the distinction between *cis* and *trans* isomers of oleic acid. Both contain one double bond, and are by definition monounsaturated, but because the *cis* isomer has carbon chains that are oriented in the same direction around the double bond, crystallization of the molecules is less likely than with the *trans* isomer whose chains are pointing in opposite directions. The differences between the isomers extend beyond mere molecular geometry, however. Most naturally occurring fats and oils contain *cis* isomers, with the exception being milk fats, which are predominantly *trans* isomers. Synthetic oils, by contrast, which are produced by hydrogenation of unsaturated compounds such as margarines, adopt a *trans* configuration. Particular interest is drawn to the distinction between isomers because the investigators quote an average daily *trans* fatty acid intake as being 6% to 8% of total fat intake in the US diet. They argue that the pressure to decrease the intake of saturated fat in the diet based on previous studies leads to a greater consumption of *trans* fatty acids, as they are the most suitable alternative for the food industry for producing semisolid and solid fats.

The study investigators recruited 59 students who were willing to enter a trial in which they would follow three diets for 3 weeks each, with no washout period between diets. One diet was high in oleic acid (a monounsaturated acid with the *cis* configuration), the second one high in *trans* isomers of oleic acid, and the third high in saturated fats. Interestingly, the experimental design allowed just 10% of the overall energy intake of the diets to be controlled in terms of the fat composition. The remainder of the energy intake was similar across diets for total calorific value, as well as proportions of carbohydrate, protein, fiber, alcohol, and cholesterol. The participants were categorized in 6 groups according to sex, and use of oral contraceptives (for women), so that each group had near-identical numbers in each category. Then each group followed the three diets in different orders, working on the investigators' assumption that serum lipoprotein levels stabilize within 2 weeks after a dietary change.

The results would lead to a striking conclusion—that all classes of fatty acids that are substituted for carbohydrates in the diet do not necessarily increase high-density lipoprotein (HDL) cholesterol levels. Indeed, *trans* isomers in this study actually produced a reduction in HDL cholesterol levels to a degree greater than carbohydrates alone would have produced. Additionally, due to an increase in low-density lipoprotein (LDL) cholesterol levels with *trans* isomers (an effect also seen with the saturated fats diet, but to a greater degree), the LDL/HDL ratio increase was more pronounced in the *trans* isomer group compared with the saturated fats group. Both the *trans* fatty acid and saturated fat diets led to an increase in serum triglyceride levels.

What was not clear, however, was whether the relationship between intake of *trans* fatty acids and serum lipid levels was linear. Additionally, the authors were keen to emphasize that the results should not be extrapolated to fatty acids containing a higher number of carbon atoms than oleic acid, or even to *trans* fatty acids of any variety other than oleic acid. However, given the emerging evidence, they recommended that patients with atherosclerosis should reduce their intake of *trans* fatty acids.

1990

Blues guitarist Stevie Ray Vaughan dies in a helicopter crash aged 35; Iraqi forces invade Kuwait ; and Benazir Bhutto is fired as prime minister of Pakistan and her government dissolved

Effects of a dietary portfolio of cholesterol-lowering foods vs lovastatin on serum lipids and C-reactive protein

D. J. Jenkins, C. W. Kendall, A. Marchie, D. A. Faulkner, J. M. Wong, R. de Souza, A. Eman, T. L. Parker, E. Vigden, K. G. Lapsley, et al

JAMA. 2003;290:502-510

Jenkins et al investigate the intriguing hypothesis that dietary modification may have comparable benefits to a first generation statin (lovastatin) in altering low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol, and C-reactive protein (CRP) levels. The study is framed in the context of the Adult Treatment Panel III (ATP III) of the National Cholesterol Education Program (NCEP), recommending diets low in saturated fats and high in plant sterols and viscous fibers, and the American Heart Association (AHA) drawing attention to potential benefits of soy proteins and nuts. The authors indicate that previous studies examining the reduction in cholesterol by dietary manipulation had resulted in a relatively small reduction in cholesterol compared with statin use. However, there were no studies to date examining the impact of a more robust attack upon dietary fat intake incorporating the food items mentioned above.

Forty-six hyperlipidemic individuals with a mean body mass index (BMI) of 27.6 (range 20.5 to 30.5) were recruited and randomized to one of three vegetarian diets: a control group with a low–saturated fat and high-fiber content including skimmed milk, fat-free cheese; another group with the same low–saturated fat content, but with the addition of lovastatin 20 mg; and a third group taking the so-called combination dietary portfolio, incorporating viscous fibers, soy protein, plant sterols, and almonds. The nonlovastatin groups were given placebo controls. Prior to starting on this diet, there was a 4 week "run-in" period in which each participant followed their own low-fat diet, and any that were taking statins prior to the study diet were asked to stop at least 2 weeks beforehand. The study participants then started on their diets with a 7-day rotating menu plan, while their compliance was monitored using weekly checklists and return of uneaten foods. The use of the statin was double blinded, although the diet regimen was not blinded to the dieticians who were responsible for the patient diets and checking dietary records.

Compliance was surprisingly good in all 3 groups (93% for control, 95% for statin, and 94% for dietary portfolio), although one must bear in mind that the participants were potentially more motivated to comply than a randomly selected group. The results indicated that although the control group managed a small, but significant, reduction in LDL cholesterol compared with baseline (2.1%, P=0.002), there was no difference in the LDL/HDL ratio, or in CRP levels. However, in both the statin and dietary portfolio group, there was a greater reduction in LDL cholesterol levels (3.6% and 3.2%, respectively), LDL/HDL ratio (4.2% and 3.2%), and in CRP levels (8.3% and 10.8%). Moreover, there was no significant difference in the level of improvement between the statin-treated and dietary portfolio–treated groups.

The authors suggest that there is an additive effect of the components of the dietary portfolio because of their different modes of action resulting in marked benefits vs the control group. Bile acid excretion is promoted by viscous fibers, cholesterol absorption is reduced by plant sterols, soy proteins reduce hepatic synthesis of cholesterol and increase LDL receptor levels, and almonds contain plant sterols and monounsaturated fatty acids that reduce LDL cholesterol levels. This was also the first study to demonstrate a reduction in CRP levels by dietary modification.

This study offers an alternative lipid-lowering technique to individuals intolerant of statins, or those who are reluctant to take them, although strong motivation and a penchant for nuts and soy beans is recommended!

2003

A fireworks factory in China explodes, killing 29 people; "Kuno the Killer," a giant 5-ft, 77-lb catfish that terrorized bathers at a German lake after swallowing a dachshund puppy whole, washes up dead; and after 20 days with no new case of SARS in Taiwan, the WHO declares the outbreak to be contained