relation between smoking per se and atherosclerosis. In the seven-country study[22] there was no significant association between CHD incidence and smoking in the different countries, and in the prospective necropsy series of the Oslo study a significant correlation between prevalence of coronary raised atherosclerotic lesions and smoking could not be shown.[23,24]

On the other hand it is possible that smoking intervention might be effective only when tobacco consumption is reduced to zero. This point may be relevant to our study, because most of the participants reduced their consumption but did not stop totally.

If this had been a diet trial only, the difference in MI incidence in the two groups would probably not have reached statistical significance. However, the chosen design for the study, which examines a combination of two important life-style factors, demonstrates clearly the effects of intervention and is also more relevant to usual medical practice.

Financial support from the City of Oslo and from the Norwegian Council of Cardiovascular Diseases is gratefully acknowledged.

Correspondence should be addressed to Dr I. Hjermann, The Oslo Study, Medical Outpatient Clinic, Ullevaal Hospital, Oslo 1, Norway.

REFERENCES

1. Carlson L, Lindstedt S. The Stockholm prospective study. *Acta Med Scand* 1968; Suppl. 493. 1–135.
2. Stamler J. Epidemiology of coronary heart disease. *Med Clin North Am* 1973; 57: 5–46.
3. Westlund K, Nicolaysen R. Ten-year mortality and morbidity related to serum cholesterol. *Scand J Clin Lab Invest* 1972; 30: (Suppl. 127): 1–24.
4. Wilhelmsen L, Wedel H, Tibblin G. Multivariate analysis of risk factors for coronary heart disease. *Circulation* 1973; 48: 950–58.
5. Holme I, Helgeland A, Hjermann I, Leren P, Lund-Larsen PG. Four and two-thirds years incidence of coronary heart disease in middle-aged men: The Oslo Study. *Am J Epidemiol* 1980; 112: 149–60.
6. Reid DD, Hamilton PJS, McCartney P, Rose G. Smoking and other risk factors for coronary heart disease in British civil servants. *Lancet* 1976; ii: 979–84.
7. Pooling Project Research Group. Relationship of blood pressure, serum cholesterol, smoking habits, relative weight and ECG abnormalities to incidence of major coronary events. Final report of the Pooling Project. *J Chronic Dis* 1978; 31: 201–306.
8. Leren P. The effect of plasma cholesterol lowering diet in male survivors of myocardial infarction. *Acta Med Scand* 1966; Suppl. 466 1–92.
9. Dayton S, Pearce ML, Hashimoto S, Dixon WJ, Tomiyasn M. A controlled clinical trial of a diet high in unsaturated fat. Monograph no 25. New York: The American Heart Association Inc., 1969.
10. Miettinen M, Turpeinen O, Karvonen MJ, Elusuo R, Paavalainen E. Effect of cholesterol-lowering diet on mortality from coronary heart disease and other causes: a twelve-year clinical trial in men and women. *Lancet* 1972; ii: 835–38.
11. Veterans Administration Cooperative Study Group on Anti-hypertensive Agents. Effects of treatment on morbidity in hypertension. *JAMA* 1970; 213: 1143–52.
12. McFate Smith W. Treatment of mild hypertension. Results of a ten-year intervention trial. *Circ Res* 1977; 40 (Suppl. 1): 98–105.
13. Rose G, Hamilton PJS. A randomised controlled trial of the effect on middle aged men of advice to stop smoking. *J Epidemiol Commun Hlth* 1978; 32: 275–81.
14. Leren P, Askevold EM, Foss OP, et al. The Oslo study, cardiovascular disease in young and middle aged Oslo men. *Acta Med Scand* 1975; Suppl. 588: 1–38.
15. Foss OP. The Oslo Study. The quantitative determination of cholesterol, triglycerides and glucose in blood serum. Laboratory protocol no 2. Central laboratory, Ullevaal hospital, Oslo, 1975; 1–92.
16. Hjermann I. Smoking and diet intervention in healthy coronary high risk men. Methods and 5-year follow-up of risk factors in a randomised trial. The Oslo Study. *J Oslo City Hosp* 1980; 30: 3–17.
17. Hjermann I, Enger S Chr, Helgeland A, Holme I, Leren P, Trygg K. The effect of dietary changes on high density lipoprotein cholesterol. The Oslo study. *Am J Med* 1979; 66: 105–09.
18. Kay R. Proportional hazards regression models and the analysis of censored survival data. *Appl Statist* 1977; 26: 227–37.
19. Holme I. On the separation of the effect of antismoking and lipidlowering diet on incidence of acute myocardial infarction in high risk men. The Oslo study. *J Oslo City Hosp* (in press).
20. Ahrens EH. Dietary fat and coronary heart disease: unfinished. *Lancet* 1979; ii: 1345–48.
21. Werkö L. Diet, lipids and heart attacks. *Acta Med Scand* 1979; 206: 435–39.
22. Keys A. Coronary heart disease in seven countries. Monograph no. 29. New York: The American Heart Association Inc., 1970.
23. Holme I, Enger S Chr, Helgeland A, et al. Risk factors and raised atherosclerotic lesions in coronary and cerebral arteries. A statistical analysis. The Oslo study. *Arteriosclerosis* 1981; 1: 250–56.
24. Solberg LAa, Enger S Chr, Hjermann I, et al. Risk factors for coronary and cerebral atherosclerosis in the Oslo study. In: Gotto AM, Smith LC, Allen B, eds. Proceedings of the fifth International Symposium of Atherosclerosis, Houston Texas. New York, Heidelberg, Berlin: Springer-Verlag, 1980.

# TOWARDS AN IMPROVED LIPID-LOWERING DIET: ADDITIVE EFFECTS OF CHANGES IN NUTRIENT INTAKE

B. LEWIS, F. HAMMETT, M. KATAN, R. M. KAY, I. MERKX, A. NOBELS, N. E. MILLER, A. V. SWAN

*Department of Chemical Pathology and Metabolic Disorders, St Thomas's Hospital, London; and the Department of Human Nutrition, Agricultural University, Wageningen, Netherlands; and Department of Surgery, University of Toronto, Toronto, Canada*

***Summary*** To identify diets that are more effective than existing ones in reducing lipoprotein-mediated risk of atherosclerotic heart disease, the serum lipid and lipoprotein response to three modified diets was studied in twelve normal men living in an institution. The "Western" reference diet (40% energy from fat, P/S ratio 0·27) was compared in Latin square design with a fat-modified diet (diet B, 27% energy from fat, P/S 1·0, reduced cholesterol content); with a fat-modified diet supplemented with fruit, vegetable, and cereal fibre (diet C); and with a diet providing 40% energy from fat, having P/S ratio 1·0 and supplemented by fibre (diet D). The effects of fat modification and fibre-supplementation (diets C and D) were strongly additive—a fall in serum cholesterol by 24–29%, in low-density-lipoprotein (LDL) cholesterol by 31–34%, and in serum triglyceride by 21–26%; and the reduction, by diet C, of the ratio of serum cholesterol to high-density-lipoprotein (HDL)-cholesterol by 21%, and that of LDL-cholesterol to $HDL_2$-cholesterol by 26%. The additive effects of multiple changes in nutrient intake, each moderate in extent, permits the design of diets which are remarkably effective in reducing serum-cholesterol level.

## Introduction

THERE is now much evidence that a raised serum-cholesterol concentration is a causal factor in atherosclerotic heart disease (AHD),[1–3] and a large body of data supports the view that it is desirable to reduce cholesterol levels in AHD-prone populations as a means of reducing risk from this disease.[1,2,4] All proposals involve changes in diet.[2,4–7] Increased physical activity is usually recommended, and for patients with major primary hyperlipidaemias drug treatment is often indicated.[7] Each method of controlling hyperlipidaemia must be assessed for its efficacy, safety, cost, and acceptability for long-term use. Conventional dietary management of hypercholesterolaemia alone (without measures for reducing obesity) comprises restriction of intake to 25–35% of dietary energy and reduction of cholesterol intake to 150–250 mg per day.[7] Most recommendations also include partial substitution of saturated fat by polyunsaturated fatty acids; recent guidelines propose a ratio of polyunsaturated fatty acids to saturated fatty acids (P/S ratio) of 1, though ratios of 1·5–2 were typical of earlier lipid-lowering diets.

The effects of dietary change on serum lipids is influenced not only by the composition of the diet but also by individual responsiveness,[8] the type and genetic basis of the lipoprotein abnormality, and compliance and palatability. The 8–16% reductions in serum cholesterol achieved in clinical practice and in large-scale trials[6,7,9–11] are smaller than those achieved in metabolic wards.

Many nutrients other than dietary lipids influence serum cholesterol levels. Some forms of dietary fibre, predominantly those derived from fruit and vegetables, such

as pectins, reduce serum cholesterol by 4–12% when consumed in large quantity.[12–14] In a careful trial, replacement of proteins of animal origin by a vegetable protein, soy protein,[15] reduced serum cholesterol by 6%.[16] Several minerals and vitamins have also been said to lead to minor changes in serum cholesterol.

This report concerns attempts to identify diets that are more effective than existing ones in reducing serum-cholesterol levels, and thus in potentially reducing lipoprotein-mediated risk of ischaemic heart disease. Hence, detailed measurements of lipoprotein classes have been made. We have tested the hypothesis that the effects of various changes in nutrient intake on cholesterol metabolism are at least partly additive, as is the case for changes in fatty acid and cholesterol intake[17] and probably so for fat and fibre consumption.[18] We have also compared diets of differing fat content and fatty acid composition.

## Methods

The dietary studies were carried out at the Maria Toevlucht Abbey at Zundert in the Netherlands. Twelve monks, aged 24 to 60 years, mean 45·1, volunteered to participate. They lived in the monastery, and apart from eating the prepared diets and undergoing regular blood tests and faecal collections, they did not change their daily pattern of work and devotions. Their relative body weights ranged from 0·79 to 1·19, mean 0·98. That all were in good health was supported by baseline routine biochemical findings, including serum thyroxine levels. No intercurrent illness occurred during the study. The twelve participants were selected from a larger number of volunteers on the basis of their having the highest plasma-cholesterol levels within our reference range (up to 6·5 mmol/l), normal triglyceride levels, and very low alcohol intake.

Blood samples were drawn, with minimal stasis, after an overnight fast. Serum was separated and disodium edetate (EDTA) was added (1 mg/ml); samples were promptly cooled to 0–4°C and sent to St Thomas's Hospital, London, where analyses began within 10 h of venesection. Very low density lipoprotein (VLDL) was isolated by preparative ultracentrifugation at d=1·006 g/ml.[19,20] High density lipoprotein (HDL) was isolated by heparin-manganese precipitation;[21] a portion of the supernatant was ultracentrifuged at d=1·125 g/ml to yield the $HDL_2$ subclass.[19] Cholesterol and triglyceride concentrations in serum and lipoprotein fractions were manually measured by standard enzymatic methods (Boehringer-Mannheim catalogue nos. 187313 and 166448, respectively) with duplicate analyses at the end of each period. Usual quality control procedures were followed, and the coefficients of variation for cholesterol and triglyceride measurement were 1·8% and 2·7%. Apolipoproteins B, AI, and AII were assayed by rocket immunoelectrophoresis.[22]

A computer data bank of Dutch food composition was used to design four diets providing the nutrient intakes shown in the accompanying table. Normally available foods were selected, single batches being purchased when practicable. Duplicate portions of the diets were directly analysed at the University of Wageningen to check their conformity with the planned nutrient intakes. The types of food were restricted to those allowed by Trappist rules. The major foods making up the reference diet A were cheese, whole milk, white bread, butter, diet margarine (linoleic acid 60% of fatty acid content), eggs, rice, fruit, vegetables, semolina, cream, Dutch honey cake, golden syrup, sucrose, and an "instant" pudding. The fat-modified diet B differed from diet A in the proportions of these constituents, and in substitution of skimmed milk for whole milk and of a diet margarine for most of the butter. The fibre-enriched fat-modified diet C had greater amounts of apples, oranges, and bananas than diet B, and partial substitution of whole-wheat bread for white bread; brown beans were included and intake of other vegetables was greater. The high-fat, fat-modified, fibre-enriched diet D included less bread and potato, but more whole milk and diet margarine, than did diet C.

NUTRIENT COMPOSITION OF THE REFERENCE DIET A AND THREE EXPERIMENTAL DIETS

| Nutrient | A | B | C | D |
|---|---|---|---|---|
| Protein (% of energy) | 14 | 14 | 14 | 14 |
| Vegetable protein (% of protein) | 34 | 34 | 52 | 49 |
| Fat (% of energy) | 40 | 27 | 27 | 40 |
| Linoleic acid (% of energy) | 4·6 | 8·1 | 8·4 | 12·4 |
| Polyunsaturates (% of energy) | 5·2 | 8·5 | 8·7 | 12·8 |
| P/S ratio | 0·27 | 1·01 | 1·00 | 1·01 |
| Cholesterol (mg/2500 kcal)* | 617 | 245 | 252 | 245 |
| Available carbohydrates (% of energy)† | 46 | 59 | 59 | 47 |
| Dietary fibre (g/2500 kcal)* | 19 | 20 | 55 | 43 |
| Pectin (g/2500 kcal)* as polygalacturonate | 1·2 | 1·8 | 6·3 | 6·5 |

Alcohol intake was negligible. *Energy intakes varied from 1550 to 4250 kcal/24 h. †Monosaccharides and disaccharides contributed 18–20% energy in all four diets.

Two dieticians prepared the individual diets each day in a separate area in the monastery kitchen. The diets were planned so as to be precisely isocaloric with the estimated energy intake of the participants as assessed by 24 h dietary recall. The subjects' energy intake ranged from 1550 to 4250 (mean 2937) kilocal/day and was given as three meals per day plus snacks;in a few cases a change was made in the course of the study on grounds of inappropriate hunger or satiety or because of weight trends. In addition, four batches of gruel were prepared daily, of composition conforming to the diets in the table; participants were instructed to eat portions of this, if necessary, to provide satiety. The dietary schedule made it possible for all subjects to maintain body weight within ± 1 kg except in the first 2 weeks, when most subjects lost 1–2 kg.

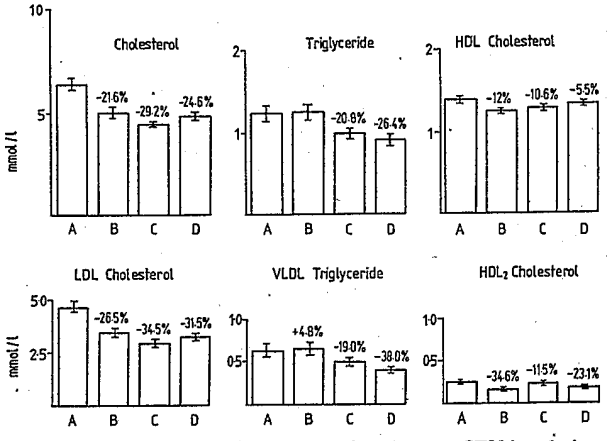
Diet A, the reference diet, was designed as a typical "Western" diet, providing 40% energy as fat with a P/S ratio of 0·27, and 617 mg of cholesterol in a 2500 kcal diet. Diet B was representative of a conventional but fairly strict fat-modified or "prudent" diet for reduction of plasma cholesterol (27% energy from fat, P/S 1·0, cholesterol 245 mg, pectin 1·8 g). Diet C was closely similar to diet B except in two respects: it provided 3–4 times more dietary fibre, with emphasis on fruit and vegetable fibre, and half instead of a third of the protein was of vegetable origin. Diet D differed from diet C only in that there was no restriction of total fat; the P/S ratio (1·0), cholesterol content (245 mg at 2500 kcal), and fibre, pectin, and vegetable protein content of diets C and D were similar, but the fat content of diet D (40% of energy) resembled that of the Western diet A.

Each feeding period lasted 5 weeks. Every participant consumed all four experimental diets; the subjects were divided into four groups of three, each group receiving one of the four diets in turn in Latin square design, in the sequence ABCD, BCDA, CDAB, or DABC. The data of the Latin square were analysed by regression techniques to perform the analysis of variance, with the computer package GLIM.[23] Since there was a reasonably steady state from the end of week 3, we treated values from weeks 3 to 5 as within-subject replicates in most cases.

## Results

Lipid and lipoprotein levels at the end of each feeding period are illustrated in the accompanying figure. Compared with those during diet A, serum-cholesterol levels were lower during the three modified diets ($p<0·01$); the reductions during consumption of the fat-modified fibre-rich diets C (−29·2%) and D (−24·6%) were greater than that during the conventional fat-modified diet B (−21·6%; $p<0·01$, $p<0·05$, respectively). Similarly, serum-triglyceride concentration was significantly lower on diets C and D than on diet A or B ($p<0·05$ and $p<0·01$, respectively). Serum cholesterol was lowest during consumption of the fibre-rich fat-modified diet C, in which fat comprised 27% of food energy and carbohydate 59%, while diet D (40% energy from fat, 47% from carbohydrate) was associated with the lowest serum-triglyceride levels (−26·4%).

LDL-cholesterol changes paralleled those of total serum cholesterol, decreasing by 26·5% on diet B, 34·5% on diet C, and 31·5% on diet D ($p<0·01$ for each, compared with the




**Serum lipid and lipoprotein concentrations (mean ± SEM in relation to type of diet.**

Nos. given at top of columns refer to changes in levels. Cholesterol/HDL cholesterol ratio was 4·49 for diet A, 4·02 for diet B, 3·56 for diet C, and 3·56 for diet D. LDL cholesterol/$HDL_2$ cholesterol ratio was 17·7 for diet A, 19·9 for diet B, 13·1 for diet C, and 15·8 for diet D.

reference diet). The reduction was greatest with diet C; LDL-cholesterol levels were lower during diets C and D than during diet B ($p<0·01$ and $p<0·05$, respectively). Serum-triglyceride levels reflected changes in VLDL-triglyceride which decreased by 19% on diet C and by 38% on diet D.

HDL-cholesterol, and to a smaller extent $HDL_2$-cholesterol, were lowered by diets B, C, and D, compared with diet A. The decrease in HDL-cholesterol with diet D (−5·5%) was small but those on diets B and C were significant ($p<0·01$). Diet C resulted in the smallest decrease in the $HDL_2$ subclass (11·5%, NS) while diets B and D reduced $HDL_2$-cholesterol concentration significantly ($p<0·01$ and $p<0·05$, respectively). On diet C the ratio of total serum-cholesterol to HDL-cholesterol fell by 21%, and that of LDL-cholesterol to $HDL_2$-cholesterol fell by 26%.

No untoward effects were reported during consumption of the four diets.

## Discussion

A major purpose of this study was to define diets that are more effective than existing ones in reducing serum cholesterol concentration, and hence likely to have a better potential for decreasing AHD risk. Because the various classes of plasma lipoproteins differ in their physiology and pathological associations,[7] it is necessary to consider the effects of these diets on individual lipoproteins. LDL, which transports 60–70% of circulating cholesterol, is strongly implicated in the pathogenesis of AHD on epidemiological[2,4,24] and experimental[2,4] grounds. The role of VLDL, the main vehicle for plasma triglyceride of endogenous origin, is more controversial: although clearly a risk factor for AHD,[25] its predictive power may not be independent of that of other lipoproteins.[26] HDL-cholesterol levels are inversely and independently predictive of AHD risk,[26,27] and a recent study indicates that levels of the small $HDL_2$ subclass of HDL, but not of $HDL_3$, discriminate between groups of patients with and without severe coronary atherosclerosis.[28] VLDL and HDL metabolism are closely linked,[7,29] and are partly controlled by common determinants.[30]

The three experimental diets were compared with diet A, a reference diet similar to habitual food patterns in the U.K., U.S.A., and most of Western Europe. Diet B was typical of a conventional, fairly strict "fat-modified", lipid-lowering diet. Under the controlled conditions of this study, diet B resulted in lower serum and LDL-cholesterol levels than did diet A; HDL-cholesterol, especially the $HDL_2$ subclass, was also reduced. Diets C and D were designed to answer the following questions: (1) Since plasma-cholesterol levels are reduced by a diet low in saturated fat and with an increased P/S ratio, and also by diets supplemented with gel-forming fibre such as pectins,[12,14] were the effects of these dietary modifications additive? (2) If so, was the effectiveness further influenced by the level of fat intake, i.e., 27% of dietary energy typical of many Mediterranean diets[3] vs 40%, the level typical in Western Europe and North America? Diet C (27% fat, fibre-enriched) was the most effective in reducing cholesterol levels in serum and in LDL, the latter remarkably by 34·5%; VLDL and serum triglyceride levels also fell, HDL-cholesterol decreased as with diet B, but $HDL_2$ cholesterol did not change significantly. Diet D (40% fat, fibre-enriched) was of intermediate effectiveness in reducing serum cholesterol and LDL-cholesterol and of greatest potency in decreasing VLDL-triglyceride (by 38%); it did not reduce HDL-cholesterol significantly, though it reduced the $HDL_2$ subclass more than did diet C. Although the experimental design does not permit quantitative assessment of the interaction between the modified fat and cholesterol intake and the supplementation with fibre (i.e., whether these modifications were fully or partly additive or synergistic), it is clear that diets C and D, particularly the former, are very effective in reducing LDL-cholesterol, in decreasing the LDL/HDL and LDL/$HDL_2$ ratios, and in reducing serum triglyceride. From the epidemiological associations and physiological functions of these lipoproteins,[2,7,24–28] diets such as C and D might be expected to reduce the lipoprotein-mediated component of AHD risk substantially.

Probably more than one characteristic of diet C contributed to the greater fall in serum-cholesterol produced by this diet than by diet B. Diet C was enriched with dietary fibre. When consumed as fruit and vegetables or as pectin or hemicellulose,[12,13,31] fibres, mainly those classified as non-cellulosic polysaccharides, reduce serum cholesterol by 0·17–0·8 mmol/l in normal subjects. In one study on hypercholesterolaemic patients, 40–50 g pectin reduced cholesterol levels by 1 mmol/l.[13] Diets C and D also had higher ratios of vegetable protein to total protein compared with diets A and B. Complete substitution of soybean protein for other dietary proteins has been reported to reduce serum-cholesterol by 6–24% in different studies, varying with the baseline serum-lipid levels and the degree of dietary control.[15,16,32]

In the present investigation, soy protein was not used, and only partial substitution of vegetable proteins for animal proteins was introduced. The vegetable protein contents of diets C and D were 52% and 45%, compared with about 34% in diets A and B.

In practice, dietary recommendations do not reduce mean serum-cholesterol concentrations in free-living people to levels associated with minimum AHD risk within Western populations (5–5·5 mmol/l),[33] and still less to those of communities in which AHD is uncommon (4–5 mmol/l).[34] Regression of experimental atherosclerosis in primates occurs at cholesterol levels of about 5 mmol/l.[35] Hence nutritional patterns of improved effectiveness, such as the multifactorial dietary changes in this study, seem desirable.

The choice of institutional residents for the study was justified because it meant that all meals could be prepared and served in the subjects' normal environment, and that participants could continue with their habitual level of physical activity, and were likely to show very good

compliance with the diets. They were willing to take part in a prolonged nutritional investigation. Nevertheless, because of the special features of the environment and the Trappist dietary rules, further studies in other, free-living subjects are necessary; this is now in progress.

The diets given in this study will require longer-term and more extensive investigation both of efficacy and safety. One important index of the safety of dietary recommendations for AHD-prone communities or individuals is their similarity to the long-standing habitual diets of populations that have lower total and disease-specific mortality rates.[36] Total fat availability is directly related to mortality from carcinomas of the colon and breast[37] and that from AHD,[34] and fibre intake may be inversely related to colon cancer[38] and AHD rates.[39] Judging by these relationships diet C has desirable characteristics—low total fat and high fibre content (containing cereal fibre as well as that of fruit and vegetable origin). Comparative studies of the four diets (Kay et al. in preparation) show that the faecal bile acid concentrations during consumption of diets C and D are 40–50% lower than those during diets A and B. Since there is increasing epidemiological and experimental evidence[40-42] implicating high faecal bile acid concentrations as a risk factor for cancer of the large intestine, the high fibre diets have the advantage of influencing faecal steroids in a direction compatible with a reduced risk of this largely Western disease.

M. K. is an established investigator of the Netherlands Heart Foundation.

Correspondence should be addressed to B. L., Department of Chemical Pathology and Metabolic Disorders, St Thomas's Hospital, London SE1 7EH.

REFERENCES


1. Marmot MG. Epidemiological bases for the prevention of coronary heart disease. *Bull Wld Hlth Org* 1979; **57**: 331–47.
2. Lewis B. Dietary prevention of ischaemic heart disease—a policy for the 80's. *Br Med J* 1980; **281**: 177–80.
3. Stamler J. Population studies. In: Levy R, Rifkind B, Dennis B, Ernst N (eds). Nutrition, lipids and coronary heart disease. New York: Raven Press, 1979: 25–88.
4. Stamler J. Lifestyles, major risk factors, proof and public policy. *Circulation* 1978; **58**: 3–19.
5. Joint Working Party of Royal College of Physicians of London and British Cardiac Society. Prevention of coronary heart disease. *J Roy Coll Phycns* 1976; **10**: 1–63.
6. Mann JI, Marr JW. Coronary heart disease prevention. Trials of diets to control hyperlipidaemia. In: Miller NE, Lewis B (eds). Lipoproteins, atherosclerosis and coronary heart disease. Amsterdam: Elsevier, 1981: 197–210.
7. Lewis B. The hyperlipidaemias: Clinical and laboratory practice. Oxford: Blackwell Scientific, 1976.
8. Mistry P, Miller NE, Laker M, Hazzard WR, Lewis B. Individual variation in the effects of dietary cholesterol on plasma lipoproteins and cellular cholesterol homeostasis in man. *J Clin Invest* 1981; **67**: 493–502.
9. Rose G, Heller RF, Tunstall Pedoe H, Christie DGS. Heart disease prevention project: a randomised controlled trial in industry. *Br Med J* 1980; **280**: 747–51.
10. Ernst N, Fisher M, Bowen P, Schaefer EJ, Levy RI. Changes in plasma lipids and lipoproteins after a modified fat diet. *Lancet* 1980; ii: 111–13.
11. Leren P. The effect of plasma cholesterol lowering diet in male survivors of myocardial infarction. *Acta Med Scand* 1966; suppl 466: 5–92..
12. Kay RM, Truswell AS. Effect of citrus pectin on blood lipids and fecal steroid excretion in man. *Am J Clin Nutr* 1977; **30**: 171–75.
13. Miettinen RA, Tarpila S. Effect of pectin on serum cholesterol, fecal bile acids and biliary lipids in normolipidemic and hyperlipidemic individuals. *Clin Chim Acta* 1977; **79**: 471–77.
14. Stasse-Wolthuis M, Albers HFF, van Jeveren JGC, et al. Influence of dietary fiber from vegetables and fruit, bran or citrus pectin on serum lipids, fecal lipids and colonic function. *Am J Clin Nutr* 1980; **33**: 1745–56.
15. Sirtori CR, Agradi E, Conti F, Mantero O, Gatti E. Soybean protein diet in the treatment of the type-II hyperlipoproteinaemia. *Lancet* 1977; i: 275–77.
16. Carroll KK, Giovanetti PM, Huff MW, Moase O, Roberts DCK, Wolfe BM. Hypercholesterolemic effect of substituting soybean protein for animal protein in the diet of healthy young women. *Am J Clin Nutr* 1978; **31**: 1312–21.
17. Brown HB, Diets that lower blood cholesterol in man. In: RJ Jones, (ed). Atherosclerosis. Proceedings of the Second International Symposium. Berlin: Springer-Verlag 1970: 426–35.
18. Anderson JI, Grande F, Keys A. Cholesterol lowering diets. *J Am Diet Assoc* 1973; **62**: 133–42.
19. Havel RJ, Eder HA, Bragdon JH. The distribution and chemical composition of ultracentrifugally separated lipoproteins in human serum. *J Clin Invest* 1955; **34**: 1345–53.
20. Lewis B, Chait A, Wootton IDP, et al. Frequency of risk factors for ischaemic heart disease in a healthy British population. *Lancet* 1974; i: 141–46.


*References continued at foot of next column*

# CONTROLLED TRIAL OF ARGON LASER PHOTOCOAGULATION IN BLEEDING PEPTIC ULCERS

C. P. SWAIN S. G. BOWN
D. W. STOREY J. S. KIRKHAM
T. C. NORTHFIELD P. R. SALMON

*Norman Tanner Gastroenterology Unit, St James' Hospital; and Department of Gastroenterology, University College Hospital, London*

***Summary*** The efficacy of argon laser photocoagulation in the endoscopic control of haemorrhage from peptic ulcers was tested in a controlled trial at two centres in London. Of 330 patients consecutively admitted with acute upper gastrointestinal tract haemorrhage, 76 were seen at endoscopy to have a peptic ulcer accessible to laser therapy and stigmata of recent haemorrhage. These patients were included in the trial. Identification of the exact source of haemorrhage within the ulcer crater was achieved by use of standard endoscopes with careful washing. Patients were stratified into three groups: ulcers with a visible vessel (52 total, 11 actively spurting); those without a vessel (17); and those with an overlying clot persisting after washing (7). Of the 52 patients with a visible vessel, 8 of 24 treated with the laser and 17 of 28 control patients had a further haemorrhage. 7 control patients died after an episode of rebleeding, but no treated patients. Treated and control patients were well

PROFESSOR LEWIS AND OTHERS: REFERENCES—*continued*


21. Albers JJ, Warnick GR, Wiebe D, et al. Multilaboratory comparison of three heparin-$Mn^{2+}$ precipitation procedures for estimating cholesterol in high-density lipoprotein. *Clin Chem* 1978; **24**: 853–56.
22. Laurell CB. Electroimmunoassay. *Scand J Clin Lab Invest* 1972; **29** (suppl 124): 265–75.
23. Baker RT, Nelder JA. The GLIM system manual for Release 3. Oxford: Numerical Algorithms Group, 1978.
24. Gordon T, Castelli WP, Hjortland MC, Kannel WB, Dawber TR. Predicting coronary heart disease in middle-aged and older persons. The Framingham study. *JAMA* 1977; **238**: 497–99.
25. Carlson LA, Bottiger LE, Ahfeldt PE. Risk factors for myocardial infarction in the Stockholm prospective study. *Acta Med Scand* 1979; **206**: 351–60.
26. Gordon T, Castelli WP, Hjortland MC, Kannel WB, Dawber TR. High density lipoprotein as a protective factor against coronary heart disease. The Framingham study. *Am J Med* 1977; **62**: 707–14.
27. Miller NE, Førde OH, Thelle DS, Mjøs OD. The Tromsø Heart Study. *Lancet* 1977; ii: 965–68.
28. Miller NE, Hammet F, Saltissi S, et al. Relation of angiographically defined coronary artery disease to plasma lipoprotein subfractions and apolipoproteins. *Br Med J* 1981; **282**: 1741–44.
29. Chajek T, Eisenberg S. Very low density lipoprotein. Metabolism of phospholipids, cholesterol and apolipoprotein C in the isolated perfused rat heart. *J Clin Invest* 1978; **61**: 1654–65.
30. Nicoll A, Miller NE, Lewis B. High density lipoprotein metabolism. *Adv Lipid Res* 1980; **17**: 53–106.
31. Kies C, Fox HM. Dietary hemicellulose interactions influencing serum lipid patterns and protein nutritional status of adult men. *J Food Sci* 1977; **42**: 440–43.
32. Descovich GG, Gaddi A, Manning G, et al. Multicentre study of soybean protein diet for outpatient hypercholesterolaemic patients. *Lancet* 1980; ii: 709–12.
33. Intersociety Commission for Heart Disease Resources. Primary prevention of the atherosclerotic diseases. *Circulation* 1970; **42**: A55–A95.
34. Keys A. Seven countries. Cambridge: Havard University Press, 1980.
35. Wagner WD, St. Clair RW, Clarkson TB. A study of atherosclerosis regression in Macaca Mulatta. 11. *Am J Pathol* 1980; **100**: 633–45.
36. Stamler J. The fat-modified diet: its nature, effectiveness and safety. In: Lauer RM, Shekelle RB (eds). Childhood prevention of atherosclerosis and hypertension. New York: Raven Press, 1980: 387–403.
37. Carroll KK. Lipids and carcinogenesis. *J Env Pathol Toxicol* 1980; **3**: 253–71.
38. Burkitt DP. Epidemiology of cancer of the colon and rectum. *Cancer* 1971; **28**: 3–13.
39. Trowell H. Ischaemic heart disease and dietary fiber. *Am J Clin Nutr* 1972; **25**: 926–32.
40. Hill MJ. Colon cancer: A disease of fibre depletion or of dietary excess? *Digestion* 1974; **11**: 289–306.
41. Weisburger JH, Reddy DVM, Hill P, Cohen A, Wynder EL, Spingarn NE. Nutrition and cancer—On the mechanisms bearing on causes of cancer of the colon, breast, prostate, and stomach. *Bull NY Acad Med* 1980; **56**: 673–96.
42. Carroll KK. Lipids and carcinogenesis. *J Env Pathol Toxicol* 1980; **3**: 253–71.