International Journal of Obesity (1993) 17, 579–583

Improvement in arterial stiffness during hypolipidaemic therapy is offset by weight gain

P.G. Matthews,[1] M.L. Wahlqvist,[2] S.J. Marks,[2] K.A. Myers[1] and J.M. Hodgson[2]

Departments of [1]Surgery and [2]Medicine, Monash Medical Centre, Melbourne, Australia

Summary

Fourteen patients with familial hypercholesterolaemia were managed with dietary advice and simvastatin for 12 months. Either nicotinic acid or cholestyramine resin was added to the regimen if serum cholesterol was not less than 5.5 mmol/l within 18 weeks. After dietary advice but before commencing pharmacotherapy for hyperlipidaemia, arterial stiffness was measured in the common carotid and common femoral arteries. These studies were repeated after 12 months on pharmacotherapy. The primary objective of this study was to determine whether arterial stiffness could be altered with total cholesterol and low density lipoprotein (LDL) cholesterol lowering. Over the 12 month interval, serum total cholesterol, LDL cholesterol and triglycerides fell significantly, whereas high density lipoprotein (HDL) cholesterol and body mass index (BMI) rose significantly. Mean supine blood pressure did not change significantly. Arterial stiffness in the common carotid artery decreased from $1.04 \pm 0.21 \times 10^5$ N/m^2 to $0.63 \pm 0.06 \times 10^5$ N/m^2 ($T = -2.67$, $P < 0.01$) over the interval. Stiffness of the common femoral artery decreased from $2.10 \pm 0.57 \times 10^5$ N/m^2 to $0.83 \pm 0.15 \times 10^5$ N/m^2 ($T = -2.73$, $P < 0.01$). The change in arterial stiffness was not directly related to changes in circulating lipids or supine blood pressure. Increase in BMI, however, correlated with change in arterial stiffness in the common femoral artery ($R_s = 0.53$, $P < 0.05$) but not in the common carotid artery. An increase in BMI was associated with a smaller decrease in common femoral arterial stiffness. Aggressive hypolipidaemic therapy was therefore associated with a favourable effect on arterial wall stiffness. However, in the common femoral artery this was offset by weight gain.

Keywords: body mass index, weight change, arterial stiffness, hypolipidaemic therapy, simvastatin

Introduction

Complications of atheromatous vascular disease are responsible for the majority of morbidity and mortality in Western communities. Epidemiological data over many years have associated these complications with so-called risk factors which may be predictive of disease. On the assumption that complications such as ischaemic symptomatology and infarction are a consequence of prior atheromatous pathological change, attempts to modify risk factors, either by behavioural or pharmacological means, have been adopted in an attempt to reduce the likelihood of development of disease, its progression or subsequent complications.[1–4] Recently, techniques have become available to monitor atheromatous lesions in arterial walls.[5–10] Observations suggest that progressive pathological changes associated with atheromatous vascular disease can be influenced.

Epidemiological data also suggest that the atheromatous process may begin at an early age and that processes for modification of vascular disease, if they are to be effective, should be instituted early in life.[11,12] At such an early stage of the disease, satisfactory end-points for assessing the outcome of such intervention are not widely developed. Techniques such as angiography or angioscopy are invasive and not appropriate for the demonstration of early pathology or for repeated assessment. High resolution non-invasive ultrasound techniques allow good visualization of the arterial wall and they are quantitative and reproducible.[13–15] As such, they offer an opportunity to study vessel wall characteristics serially, *in vivo*.

An ultrasound technique has been used to measure arterial stiffness in individuals who have undergone a combined non-pharmacological and pharmacological approach to controlling one of the major risk factors for atherosclerosis, namely hypercholesterolaemia. This has provided the opportunity to determine whether lowering of

Correspondence to: M.L. Wahlqvist, Monash University Department of Medicine, Monash Medical Centre, 246 Clayton Road, Clayton, Victoria 3168, Australia.
Received 17 September 1992; accepted 16 March 1993

serum total and LDL cholesterol is associated with reduced arterial stiffness. The range of BMI and arterial stiffness changes further provided the opportunity to examine the interaction between arterial stiffness and body fatness change over 12 months. Body fatness is a potential determinant of arterial pathology.

Methods

Fourteen individuals (nine males and five females) were included in the study on the basis of persistently elevated serum total cholesterol levels despite dietary and other approaches (excluding HMG CoA reductase inhibitors) to modify this. All had familial hypercholesterolaemia demonstrated by raised cholesterol levels, family history of hypercholesterolaemia and premature arterial disease in a first degree relative. Subjects currently smoking or with diabetes mellitus were not included.

After an interview and dietary documentation, patients were advised to follow a regimen of low saturated fat intake, one or two servings of fish per week and a prominent fruit, vegetable and whole grain cereal intake during a six week run-in phase. Over this time, hypolipidaemic pharmacological therapy was withheld and usual activity levels were maintained. At the end of the run-in period, a seven day food diary was completed, the dietary advice was reinforced, and initial measurements of arterial stiffness, blood pressure, serum lipids, height and weight were performed.

Following the first ultrasound examination, simvastatin was commenced at 10 mg per day. If the serum cholesterol was not less than 5.5 mmol/l after six weeks therapy, the dose was increased to 20 mg per day. If the serum cholesterol level was not less than 5.5 mmol/l after 12 weeks therapy, the dose was increased further to 40 mg per day. If the serum cholesterol was not less than 5.5 mmol/l after 18 weeks, either nicotinic acid (750–1500 mg per day) or cholestyramine resin (12–24 mg per day) was added for the remainder of the period of observation.

Dietary review and reinforcement of dietary advice was performed at each visit, a total of six times in all. Serum lipid measurements were also performed at each visit. Repeat measurements of arterial stiffness, blood pressure, serum lipids and height and weight were performed 12 months after commencing simvastatin.

The brachial blood pressure was monitored after five minutes supine rest, at one minute intervals, using a Dinamap Vital Signs Monitor (Critikon Inc, Tampa, Florida, USA). The mean blood pressure was read directly from the instrument. Using M mode ultrasound imaging, the internal diameter (lumen/intimal interface) of the vessel under examination was measured electronically at maximum systolic and minimum diastolic diameter on at least seven occasions. Each estimate took approximately one minute. The coefficients of variation of these measurements range from 4–8%. These observations were used to determine the arterial stiffness according to the formula: $Y = dP/(dD/D)$ where Y = arterial stiffness (N/m^2), dP = pulse pressure (N/m^2), dD = change from the diastolic to the systolic diameter (mmHg), D = diastolic diameter (mmHg). Observations were made 1 cm proximal to the flow divider at each site. If there was any evidence of atheroma at this site on B mode imaging, the sampling was performed at least 1 cm proximal to the most proximal extent of the lesion, and the site recorded for future comparison. If this was not possible within 5 cm of the flow divider, the left side vessel was used.

Fasting blood samples were drawn from the antecubital fossa vein into evacuated glass tubes. The blood was allowed to clot, and the serum was separated by centrifugation. Total cholesterol, triglycerides and HDL cholesterol were measured on fresh serum. Total cholesterol and triglycerides were measured enzymatically with commercial kits (Trace Scientific Pty Ltd, Clayton, Victoria, Australia; Catalogue Numbers 13225 and 22203, respectively). HDL cholesterol was measured enzymatically as for total cholesterol following the precipitation of apolipoprotein B-containing lipoproteins using equal volumes of 20% polyethylene glycol 6000 and serum. LDL cholesterol was estimated by calculation using the Friedewald formula adapted to SI units.[16] Cholesterol and triglyceride measurements were performed on a KONE Progress random access analyser (KONE Instruments Corporation, Espoo, Finland).

Dietary nutrient composition was determined using Nutritionist III.[17] Body weight was measured to the nearest 0.1 kg using a standard beam scale (Seca, Hamburg, Germany). Height was measured to the nearest 0.5 cm using a fixed stadiometer (Seca).

Statistical analyses were performed using SAS.[18,19] The Wilcoxon signed ranks test was used to compare data at 12 months with results for the pre-treatment period. The possible influences of serum lipids, blood pressure and body mass index (BMI) on changes in arterial wall stiffness were also considered. Spearman's correlation coefficient (R_s) was used to assess the degree of association between arterial wall stiffness and serum lipids, blood pressure and BMI.

Results

Characteristics of the subjects involved in the study are presented in Table 1. The seven day food diary analysis in nine subjects showed a 6.3% decrease in average weekly calorie intake over the 12 month interval (Table 2). Table 2 also indicates the percentage distribution of energy intake, which remained essentially stable across the study period. The polyunsaturated:saturated (P:S) ratio of the fat component showed the anticipated trend towards a lower contribution from saturated fats. Serum lipid values changed dramatically (Table 3) with significant falls in total cholesterol, LDL cholesterol and triglycerides, and a significant rise in HDL cholesterol. Body mass index in the 14 participants increased over the 12 month period. Mean supine blood pressure did not change significantly.

The changes in arterial stiffness are shown in Figure 1. In the common carotid artery, arterial stiffness fell from $1.04 \pm 0.21 \times 10^5$ N/m^2 to $0.63 \pm 0.06 \times 10^5$ N/m^2 ($T = -2.67$, $P < 0.01$). Corresponding values for the common femoral artery were $2.10 \pm 0.57 \times 10^5$ N/m^2 and $0.83 \pm 0.15 \times 10^5$ N/m^2 ($T = -2.73$, $P < 0.01$). These significant falls in arterial stiffness were not directly related to changes in

Table 1 Subject characteristics

Number	Age (years)	Sex	Entry smoking status	History			
				HT	IHD	PVD	CVD
1	70	F	−	+	+	−	−
2	63	F	*	+	−	−	−
3	65	M	−	−	+	+	+
4	31	M	−	−	−	+	−
5	35	M	*	−	−	−	−
6	53	M	*	−	−	−	−
7	55	F	−	−	+	−	−
8	51	M	*	−	−	−	−
9	47	M	*	−	+	−	−
10	36	M	−	−	−	−	−
11	39	M	−	−	−	−	−
12	44	M	−	−	−	−	−
13	49	F	*	−	−	−	−
14	54	F	−	+	+	−	−

HT = hypertension; IHD = ischaemic heart disease; PVD = peripheral vascular disease; CVD = cerebrovascular disease.
*+ current; − never; * ex-smoker.*

Table 2 Energy intake*

	Baseline	12 months
Total energy		
kcal/week	13521	12666
kJ/day	8070	7560
Percentage distribution		
Protein	19	17
Carbohydrate	48	47
Alcohol	6	6
Fat (P:S ratio)	27 (0.46)	30 (0.60)

* *Assessed over one week in nine individuals.*

serum lipids or mean supine blood pressure. On the other hand, a positive correlation existed between change in BMI and change in arterial stiffness. However, this was significant only with respect to the common femoral artery (R_s = 0.53, $P < 0.05$). These results are presented in Figure 2. An increase in BMI was associated with a smaller decrease in common femoral arterial stiffness.

Discussion

This study, similarly to other published data, demonstrates the effectiveness of the HMG CoA reductase inhibitor simvastatin, in conjunction with other hypolipidaemic therapy, in producing a marked reduction in serum total cholesterol and LDL cholesterol levels. The 14 subjects demonstrated an average reduction of 39% and 49% respectively. The more novel and striking finding, however, was the alteration in arterial wall characteristics which accompanied this change in circulating lipid levels. The arterial wall stiffness measured here relates a level of force applied to the arterial wall to its resultant distortion within the range of stresses induced by cyclical blood pressure changes. After treatment for one year, the force required to produce a given amount of arterial wall distortion was dramatically reduced in both the common carotid and common femoral arteries, by 39% and 60%, respectively. In considering the sequence of events in the arterial wall in the development of atherosclerosis, these changes, which have been demonstrated in segments of the vessels unaffected by visible atheroma, presumably represent modifications at a pre-atheromatous stage of the disease. The difference in arterial wall stiffness between the common carotid and femoral arteries just proximal to their respective flow dividers is not explained in this study but supports the findings of van Merode *et al.*[20]

The main objective of this study was to determine whether arterial wall stiffness could be altered in a group of subjects with familial hypercholesterolaemia if both serum total and LDL cholesterol approached normal levels. Large

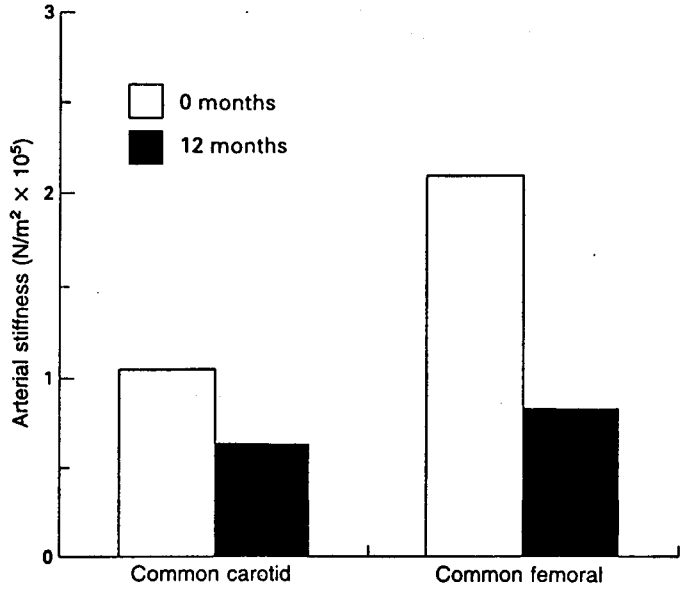

Figure 1 Changes in arterial stiffness over a 12 month period of aggressive treatment of hyperlipidaemia.

Table 3 Mean values (± s.e.m.) for serum lipids, mean blood pressure and BMI

	Baseline	12 months	T*	P
Total serum cholesterol (mmol/l)	10.8 ± 0.4	6.6 ± 0.3	−3.30	<0.001
Serum triglycerides (mmol/l)	2.0 ± 0.2	1.5 ± 0.4	−2.51	<0.05
Low density lipoprotein cholesterol (mmol/l)	8.7 ± 0.5	4.4 ± 0.3	−3.30	<0.001
High density lipoprotein cholesterol (mmol/l)	1.15 ± 0.08	1.48 ± 0.09	3.30	<0.001
Mean supine blood pressure (mmHg)	94 ± 3	88 ± 2	−1.45	n.s.
BMI (kg/m²)	24.9 ± 0.7	25.6 ± 0.8	2.00	<0.05

* *T = Wilcoxon signed ranks statistic.*

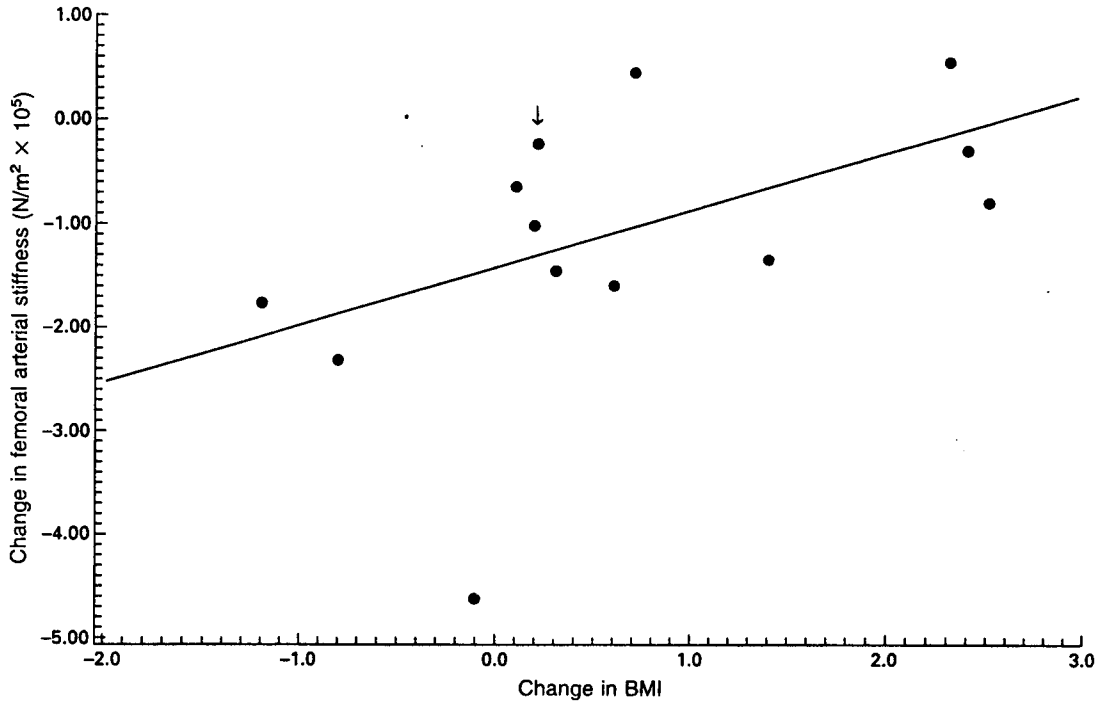

Figure 2 The relationship between change in BMI and change in stiffness of the common femoral arterial wall. Note: a positive change in BMI implies an increase in body fatness. $R_s = 0.53$; $P < 0.05$. $n = 14$, two points superimposed, marked by arrow.

reductions in arterial stiffness and serum total and LDL cholesterol were seen. Changes in serum lipid values could not be related to changes in arterial wall characteristics. The marked improvement in plasma lipid values may have at least played a permissive role, and one explanation for the lack of a relationship may be that all subjects showed a similar reduction in LDL cholesterol and there is little opportunity for relationship to be observed.

Body mass index increased over 12 months despite a 6.3% decrease in average energy intake in a subset of these individuals (Table 2). There are several possible explanations for this observation and it must be emphasized that dietary changes are only one part of the energy balance equation. It is not known how much changes in physical activity or energy utilization efficiency contributed to the increase in BMI. On an individual basis, change in BMI was variable. This together with the variable changes in arterial stiffness for individuals provided the opportunity to examine the relationship between change in BMI and change in arterial stiffness. An increase in BMI was associated with a smaller decrease in common femoral arterial stiffness. The lack of demonstration of a similar relationship in the common carotid artery may be explained by a different interplay between lipid lowering therapy and body fatness/metabolic phenomena at this site. Risk factor profiles, for example, demonstrate different emphasis for differing arterial circulations.[21] A larger sample size may be required to demonstrate the relationship in the less stiff segments of the arterial tree, such as the common carotid artery as opposed to the common femoral artery.

There are several potential mechanisms for the observed relationship between body fatness and arterial stiffness. The effects of body fatness on the arterial wall may be mediated via insulin resistance, glycaemic status or other risk factors for arteriosclerosis. Obesity has been associated with several risk factors for arteriosclerosis, including insulin resistance,[22] glucose intolerance,[23] plasma cholesterol,[24] and blood pressure.[25] The results from this study do not provide evidence for any of the proposed mechanisms. However, measures of insulin resistance and glycaemic status were not included in this study.

High resolution real-time ultrasound was used in this study to assess arterial wall characteristics. Arterial wall stiffness was reduced with hypolipidaemic treatment of subjects with familial hypercholesterolaemia. The improvement in common femoral arterial wall characteristics was offset by weight gain. Body mass index was used to assess body fatness. Future studies should also include measures of body fat distribution. These results draw attention to the clinical importance of monitoring body fatness in the course of management of macrovascular disease.

Acknowledgements

We would like to acknowledge the expert technical assistance of Mr Robert Ziengenbein who performed the vascular ultrasound investigations.

References

1 Strandberg, T.E., Salomaa, V.V., Naukkarinen, V.A., Vanhanen, H.T., Samma, S.J. & Miettinen, T.A. (1991): Long term mortality after 5 year multifactorial prevention of cardiovascular diseases in middle aged men. *JAMA* **266**, 1225–1229.

2 Blankenhorn, D.H., Nessim, S.A., Johnson, R.L., Sanmarko, M.E., Azen, S.P. & Cashin-Hemphill, L. (1987): Beneficial effects of combined colestipol-niacin therapy on coronary atherosclerosis and coronary venous bypass grafts. *JAMA* **257**, 3233–3240.

3 Arntzenius, A.C., Kromhout, D., Barth, S.D., Reiber, J.H., Bruschke, A.V., Buis, B., Van Gent, C.M., Kempen-Voogd, N., Strikwerda, S. & van der Velde, E.A. (1985): Diet, lipoproteins, and the progression of coronary atherosclerosis: the Leiden intervention trial. *N Engl J Med* **312**, 805–811.

4 Lipid Research Clinics Program (1984): The Lipid Research Clinics Coronary Primary Prevention Trial results. I. Reduction in incidence of coronary heart disease. *JAMA* **251**, 351–364.

5 Selzer, R.H., Hagerty, C., Asen, S.P., Seibes, M., Lee, P., Shircore, A. & Blankenhorn, D.H. (1989): Precision and reproducibility of quantitative coronary angiography with applications to controlled clinical trials. A sampling study. *J Clin Invest* **83**, 520–526.

6 Blankenhorn, D.H., Chin, H.P., Conover, D.J. & Nessim, S.A. (1988): Ultrasound observation on pulsation in human carotid artery lesions. *Ultrasound Med Biol* **14**, 583-587.

7 Erikson, V., Helmius, G., Hemmingsson, A., Ruhn, G. & Olsson, A.G. (1988): Repeat femoral arteriography in hyperlipidaemic patients. A study of progression and regression of atherosclerosis. *Acta Radiol* **29**, 303–309.

8 Wahlqvist, M.L., Lo, C.S., Myers, K.A., Simpson, R.W. & Simpson, J.M. (1988): Putative determinants of arterial wall compliance in NIDDM. *Diabetes Care* **11**, 787.

9 Lo, C.S., Relf, I.R.N., Myers, K.A. & Wahlqvist, M.L. (1986): Doppler ultrasound recognition of preclinical changes in diabetic subjects: compliance and pulse-wave damping. *Diabetes Care* **1**, 27–31.

10 Bond, M.G., Wilmoth, S.K., Gardin, J.F., Barnes, R.W. & Sawer, J.K. (1985): Non-invasive assessment of atherosclerosis in non-human primates. *Adv Exp Med Biol* **183**, 189–195.

11 Laron, Z. (1991): Atherosclerosis starts in childhood – fact, myth or insinuation? *Z Gerentol* **24**, 70–72.

12 Roy, C.C. & Galeano, N. (1985): Childhood antecedents of adult degenerative disease. *Pediatr Clin North Am* **32**, S17–S33.

13 Pignoli, P., Tremoli, E., Poli, A., Oreste, P. & Paoletti, R. (1986): Intimal plus medial thickness of the arterial wall. A direct measurement with ultrasound imaging. *Circulation* **74**, 1399.

14 Pignoli, P. & Longo, T. (1988): Evaluation of atherosclerosis with B-mode ultrasound imaging. *J Nuclear Med Allied Sci* **32**, 166.

15 Pignoli, P. & Longo, T. (1986): Ultrasound evaluation of atherosclerosis. Methodological problems and technical developments. *Eur Surg Res* **18**, 238–253.

16 Friedewald, W.T., Levy, R.I. & Fredrickson, D.S. (1972): Estimation of the concentration of low-density lipoprotein cholesterol in plasma without the use of the preparative ultracentrifuge. *Clin Chem* **18**, 499–502.

17 N-squared computing (1988): *Nutritionist III*, Version 4.0. Silverton, Oregon: N-squared computing.

18 SAS Institute Inc (1985): *SAS Introductory Guide for Personal Computers: Statistics*, Version 6 Edition. Cary, North Carolina: SAS Institute Inc.

19 SAS Institute Inc (1985): *SAS Users Guide: Statistics*, Version 5 Edition. Cary, North Carolina: SAS Institute Inc.

20 Van Merode, T., Hick, P.J.J., Hoeks, A.P., Smeets, F.A. & Reneman, R.S. (1988): Carotid artery wall properties in normotensive and borderline hypertensive subjects of various ages. *Ultrasound Med Biol* **14**, 563.

21 Myers, K.A., Matthews, P.G., Wahlqvist, M.L. & Lo, C.S. (1991): The management of occult atherosclerosis in arteries of the lower limbs. In *Occult Atherosclerotic Disease*, eds A.M. Salmasi & A.N. Nicolaides, pp. 243–267. London: Kluwer Academic Publishers.

22 Kolterman, O.G., Insel, J., Saekow, J. & Olefsky, J.M. (1980): Mechanisms of insulin resistance in human obesity. Evidence for receptor–post-receptor defects. *J Clin Invest* **65**, 1272–1284.

23 Wilson, P.W.F., McGee, D.L. & Kannel, W.B. (1981): Obesity, very low density lipoproteins and glucose intolerance over fourteen years: the Framingham Study. *Am J Epidemiol* **114**, 697–704.

24 Egan, E.B., Bassett, D.R. & Block, W.D. (1991): Comparative effects of overweight and obesity on cardiovascular risk in younger *versus* older men. *Am J Cardiol* **67**, 248–252.

25 Van Itallie, T.B. (1985): Health implications of overweight and obesity in the United States. *Ann Intern Med* **103**, 983–988.