

Contents

1	Emergence of Coronary Heart Disease as a Diagnosis	1
1.1	In Osler's Textbook (1904)	1
1.2	First Reports of Coronary Thrombosis with Survival	2
1.3	Papers Appear in British Journals	3
1.4	Added to International List of Causes of Death (1930)	4
2	Experimental Pathology in St. Petersburg	5
2.1	Atherosclerosis Introduced as a Pathological Term	5
2.2	Pioneering Experimental Work 1908–1913 Feeding Cholesterol to Rabbits in St. Petersburg	5
2.3	Anitschkow Described His Work Further in 1933 American Monograph	6
2.4	Anitschkow's Early Rabbit Work Confirmed in Other Countries	7
2.5	Rabbits' Arterial Lesions Compared with Human Atherosclerosis	7
3	Is Plasma Cholesterol Raised with Human Atherosclerosis?	9
3.1	Cholesterol Characteristic in Human Atherosclerosis	9
3.2	At First Not Clear If Plasma Cholesterol Raised with Human Atherosclerosis	9
3.3	Improved Statistical Design Shows Average Plasma Cholesterol Higher with CHD	10
3.4	It Is Low-Density Lipoproteins that Are Associated with CHD	10
3.5	"Normal" Cholesterol Level in Affluent Countries May Not Be Healthy Cholesterol	11
3.6	Serum Cholesterols Lower in Naples and Madrid ... and Hunter Gatherers	11
4	Diet <i>Can</i> Have Worthwhile Effects on Human Plasma Cholesterol	13
4.1	Dietary Cholesterol	13
4.2	Dietary Fat Has More Effect than Dietary Cholesterol	14

4.3	And the Type of Dietary Fat	14
4.3.1	Saturated and Polyunsaturated Fats, Rather than Animal or Vegetable Fats	14
4.3.2	Repeated Tests by Keys' Group with Different Fats and Oils	16
4.3.3	Not All Saturated Fatty Acids Have the Same Effect on Serum Cholesterol	17
4.4	How Does It Work? Could It Be by Changing Cholesterol Excretion?	18
4.5	Discovery of the Low Density Lipoprotein Receptor	18
5	A New Type of Observational Epidemiology	21
5.1	Invention of Prospective, Cohort Studies	21
5.1.1	The Framingham Study, Started 1949	21
5.2	Results Emerge from Framingham and Subsequent Cohort Studies	22
5.2.1	Big Three Risk Factors: Serum Cholesterol, Smoking and Blood Pressure	22
5.3	Tentative Recommendations to High Risk Patients Start in 1960s	23
6	Serum Triglycerides? Another Risk Factor	25
6.1	Endogenous and Exogenous Serum Triglycerides	25
6.2	Early Claims that Serum Triglycerides Predict Risk of CHD	25
6.3	Fasting Serum Triglycerides Not a Strong Independent Risk Factor	26
7	Fredrickson's Classification of the Hyperlipoproteinaemias	29
7.1	Five Types of Hyperlipidaemia, and Three Types of Low Serum Lipoproteins	29
7.2	Further Developments of Fredrickson's Types	31
8	The Seven Countries Study (7CS)	33
8.1	Setting Up	33
8.2	Methods	35
8.2.1	Results	35
8.2.2	Dietary Results	36
8.3	Implications from the 7CS	37
8.4	Longer Follow Up	38
9	Sucrose – An Alternative Dietary Hypothesis	39
9.1	Yudkin's Proposal	39
9.2	Reactions	40
10	HDL-Cholesterol Is Protective	41
10.1	Early Observations	41
10.2	The Millers' Hypothesis	42
10.2.1	It Ran Against the Grain	42

10.3	Epidemiological Support	42
10.4	HDL ₂ or HDL ₃ ?	43
10.5	In Developing Countries?	43
10.6	In Women	43
10.7	Diet Affects HDL-Cholesterol Quite Differently	44
11	Critics and Sceptics	45
11.1	Sir John McMichael, London	45
11.2	Dr George Mann, USA	46
12	Thrombosis on and in Atheroma	49
12.1	Thrombosis a Separate, Acute Process	49
12.2	Tests for Liability to Thrombosis Are Indirect	49
12.3	Or Can Mural Thrombosis Become Atheroma?	50
13	Dietary Cholesterol <i>May</i> Affect Plasma Cholesterol	51
13.1	Keys Had Asserted Dietary Cholesterol Does Not Raise Plasma Cholesterol	51
13.2	Other Early Studies Inconclusive	51
13.3	Keys' Group and Hegsted's Group Re-examine	52
13.4	Metabolism of Labelled Cholesterol	52
13.5	Many Human Experiments with Dietary Cholesterol 1960s and 1970s	53
13.6	Are Some Individuals Responsive to Dietary Cholesterol, Not Others?	54
13.7	Effect of Basal Cholesterol Intake	55
13.8	Different Recommendations by Advisory Committees	56
14	First Controlled Trials	57
14.1	First Two Randomised Dietary Trials, 1965	57
14.2	Two More Dietary Trials	58
14.3	The Los Angeles VA Trial, Reported 1969	59
14.4	Helsinki Mental Hospitals	59
14.5	Drugs Trials	61
14.5.1	Early Trials with Cholesterol-Lowering Drugs	61
14.5.2	More Promising Drugs Followed	61
14.5.3	"Atromid" or Clofibrate	62
14.5.4	Cholestyramine Resin	62
15	Dietary Fibre	63
16	Obesity	65
16.1	Desirable Weight for Height	65
16.2	Body Mass Index	66
16.3	Waist Circumference – Visceral Adiposity	69
16.4	At the End of the Century the Cardiac Risk of Overweight Remained Variable for Moderate Overweight	70

17	Thrombosis Treated Early	71
	17.1 Acute Phase Coronary Angiography	71
	17.2 Clotting Factors in a Prospective Study	72
	17.3 Platelet Function	73
	Box 17.1 What's a Normal Plasma Cholesterol?	74
18	Fish Oil	77
	18.1 Traditional Eskimos: High Fat Diet but CHD Uncommon	77
	18.2 Eicosapentaenoic Acid Reduces Platelet Aggregation	78
	18.3 Epidemiological Studies: Fish Consumption and CHD	79
	18.4 Polyunsaturated Oils Prevent Dangerous Arrhythmias in Rats	80
	18.5 Human Prevention Trials with Fish Oil	81
19	Alcohol	83
	19.1 Impressions at Post-mortem Examination	83
	19.2 Negative Association with CHD in 1974 Case-Control Study	84
	19.3 Epidemiological Studies Build Up the Case	84
	19.4 Alcohol Only Benefits Health of Older People in Developed Countries	86
	19.5 Which Type of Alcoholic Drink?	87
	19.6 How Does Alcohol Reduce the Risk of CHD?	88
	19.6.1 Serum HDL-Cholesterol (HDL-c)	88
	19.6.2 Haemostatic Effects	89
	19.6.3 Polyphenolic Antioxidants in the Beverage	89
	19.7 The French Paradox	89
20	Coffee	91
	20.1 Coffee and Caffeine	91
	20.2 Coffee and CHD (Direct) Epidemiology	92
	20.2.1 Coffee and Serum Cholesterol: Human Experiments	93
	20.2.2 It's Cafestol and Kahweol in Coffee that Raise Serum Cholesterol	94
	20.3 And Tea?	95
21	Trans-Fatty Acids	97
	21.1 Hydrogenation of Liquid Oils to Make Solid Margarines	97
	21.2 Human Experiments: Trans Fatty Acids and Serum Cholesterol	98
	21.3 Epidemiological Studies	101
	21.4 Conclusion	102
22	Antioxidants	103
	22.1 LDL Oxidation and Atherosclerosis – Hypothesis	103
	22.2 α -Tocopherol the Major Antioxidant Inside LDL	104
	22.3 Vitamin E and CHD in Cohort Studies	104

22.4	Randomised Controlled Prevention Trials with Vitamin E	105
22.5	Trials with Beta-Carotene	105
22.6	Why Didn't Alpha Tocopherol or Beta Carotene Work?	106
	Box 22.2 Fruit and Vegetables – Part of Favourable Dietary Patterns .	106
23	More Controlled Dietary Trials	109
23.1	Further Dietary Trials in Table 23.1	109
23.2	Two Large Multi-Factorial Trials	112
23.3	Four Dietary Trials Assessed by Coronary Angiography	113
23.4	The Lyon Diet Heart Study	114
24	Trials of Better Drugs	115
24.1	Cholestyramine (1984)	115
24.2	Gemfibrozil (1987)	116
	24.2.1 Statins Arrive	116
	24.2.2 Implications of Statins	118
25	Linoleic Acid Is Protective	121
25.1	Cohort Studies Accumulate	121
25.2	Mechanism(s) of Action	123
25.3	Linoleic (18:2) Not the Usual Source of Arachidonic Acid (20:4)	123
25.4	Recommendations	123
26	Plant Sterols Fade and Return	125
26.1	Phytosterols Not Absorbed	125
26.2	The Pharmaceutical Phase	126
26.3	Sitosterolaemia	127
26.4	The Food Additive Phase	127
27	Soy Proteins Versus Casein	129
27.1	An Animal Protein Effect on Serum Cholesterol in Rabbits . .	129
27.2	In Humans Soy Protein Compared Against Casein: Variable Results	130
27.3	Isoflavones May Contribute	131
28	High Homocysteine Associated with Cardiovascular Diseases . . .	133
28.1	Homocystinuria and Arterial Disease	133
28.2	Raised Plasma Homocysteine and Arterial Disease	134
28.3	Environmental Influences on Plasma Homocysteine	135
28.4	Plasma Homocysteine Lowered by Folic Acid and/or Vitamin B-12	136
29	And Salt Should Be Included	139
29.1	Discovery of Essential Hypertension	139
29.2	Early Diets for Hypertension	140
29.3	Is Salt a Cause of Essential Hypertension?	142
29.4	Thiazides and Sceptics	144
	Box 29.1 Potassium and Blood Pressure	144

29.5	Answers to the Sceptics; the Salt Case Develops	145
29.5.1	Moderate Sodium Restriction	145
29.5.2	Remote Communities	146
29.5.3	Regression Dilution Bias	147
29.5.4	INTERSALT	147
29.5.5	Chimpanzee Experiments	148
29.5.6	Cardiac Effects of Salt Reduction	149
Box 29.2	Higher Blood Pressures in African Americans	149
29.6	Baby Food Manufacturers Take the Lead	150
29.6.1	And for Adults	151
29.6.2	Dietary Goals for the US	151
29.6.3	Subsequent Official Recommendations	152
29.7	Most Salt We Eat Was Put in by Food Processors	152
29.8	How Does BP Increase in Salt-Sensitive Individuals	153
29.8.1	Kidneys	153
29.8.2	Arterioles	153
29.8.3	Humoral Inhibitor of the Sodium Pump	154
29.9	Into the Next Century	155
30	How It Adds Up	157
30.1	American Heart Association, 2000	157
30.2	In “ABC of Nutrition”, 1999	158
31	The Big Picture	161
31.1	USA and Canada	161
31.2	Australia and New Zealand (Fig. 31.4)	164
31.3	Nordic Countries	166
31.4	British Isles (Fig. 31.6)	167
31.5	Western Europe	168
31.6	East European Countries	169
32	End Notes	173
32.1	What Happened	173
32.2	On the Research Front	174
32.3	Inertia and Opposition	175
32.4	In the Public Arena	176
32.5	What Happened Further	177
32.6	Hypothesis and Variations	178
	References	181
	Index	221