Partial Ileal Bypass for Hypercholesterolemia

20- to 26-year Follow-up of the First 57 Consecutive Cases

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Between 1963 and 1968, 57 patients underwent partial ileal bypass (PIB) at the University of Minnesota for primary hypercholesterolemia. Preoperative total plasma cholesterol (TC) was 363.3 ± 136.8 mg/dL (mean ± SD) in these patients. Baseline and follow-up TC results demonstrated highly significant ($p \leq 0.001$) TC reduction, 34% (n = 48), 28% (n = 49), 35% (n = 26), 35% (n = 11), and 30% (n = 25) at 1, 2 to 5, 6 to 10, 11 to 15, and more than 20 years, respectively, after PIB. In 21 patients with baseline, 1-year, and more than 20-year results, TC decreased 33% by 1 year and remained 29% less than baseline more than 20 years after surgery (p = NS *versus* 1 year). Plasma triglyceride results were available in fewer patients, and no statistically significant changes developed after PIB. Two patients (3.5%) underwent PIB reversal, one for intractable diarrhea and one for recurrent nephrolithiasis. In the 25 nonreversed, long-term survivors, no statistically significant weight change was noted. Twenty-four per cent had 0 to 2, 52% had 3 to 5, and 24% had more than 5 bowel movements per day. Subsequent cholecystectomy was required in eight patients, and nephrolithiasis developed in 10 (40%). During 20 to 26 years, most survivors developed clinically apparent atherosclerosis: angina (60%), myocardial infarction (16%), or coronary artery bypass (28%). Coronary heart disease was the predominant cause of death among nonsurvivors (80%). Overall survival rates were 95%, 88%, 75%, 59%, 53%, and 41% at 1, 5, 10, 15, 20, and 25 years, respectively, after PIB. Partial ileal bypass leads to highly significant TC reduction, which is sustained, essentially unchanged, more than 20 years after operation. In comparison to available epidemiologic and clinical trial data, these results support the hypothesis that TC reduction has a beneficial effect in patients with hypercholesterolemia.

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SINCE THE INITIAL induction of atherosclerosis by cholesterol feeding in rabbits by Anitschkow in 1913, the causal relationship between cholesterol and experimental atherosclerosis clearly has been established.[1] Epidemiologic analyses, including the Seven Countries Study,[2] the Framingham Study,[3] and the Pooling Project,[4] have confirmed this relationship in humans. The screening results of the Multiple Risk Factor Intervention Trial precisely related the total serum cholesterol level and the subsequent, 6-year coronary heart disease (CHD) mortality rate in 361,662 asymptomatic men.[5] Those with total serum cholesterol levels between 203 and 221 mg/dL had 1.7 times the 6-year CHD mortality risk, those with total serum cholesterol levels between 222 and 245 mg/dL had 2.2 times the 6-year CHD mortality risk, and those with total serum cholesterol levels greater than 264 mg/dL had more than four times the 6-year CHD mortality risk compared to men with total serum cholesterol levels less than 181 mg/dL. Despite modifications of CHD risk factors and improvements in medical care that have led to progressive decreases in annual CHD mortality rates, CHD remains the leading cause of death in the United States and in the western world, surpassing the number of deaths due to all forms of cancer combined.[6] Among the major, modifiable CHD risk factors, hypercholesterolemia, hypertension, smoking, and diabetes, the critical importance of hypercholesterolemia is evident. It is estimated that one fourth of the adult United States population, nearly 40 million people, have total plasma cholesterol levels greater than 240 mg/dL, placing them at significantly increased risk for death due to CHD.[7] Detection and treatment of hypercholesterolemia has become the focal point of recent public health initiatives to reduce the CHD mortality rate in this country and abroad.[8,9]

In May 1963, after completion of rabbit and swine experiments demonstrating that cholesterol and bile acid absorption from the intestinal tract, as well as plasma cholesterol levels, were significantly reduced, without concomitant weight loss, after diversion of substantial lengths of the distal small bowel,[10,11] we performed the initial partial ileal bypass (PIB) specifically for cholesterol reduction in humans.[12] Subsequently more than 600 PIB procedures have been performed worldwide.[13-18]

In 1989 we completed this review of the initial 57 patients undergoing PIB between 1963 and 1968 to examine the long-term effects of this operation on plasma lipid levels, nonatherosclerotic morbidity and mortality, and

Presented at the 110th Annual Meeting of the American Surgical Association, Washington, D.C., April 5–8, 1990.

Supported by grants HL-06314 and HL-11901 and by National Research Service Award HL-07586 (to Dr. Campos) from the National Heart, Lung and Blood Institute.

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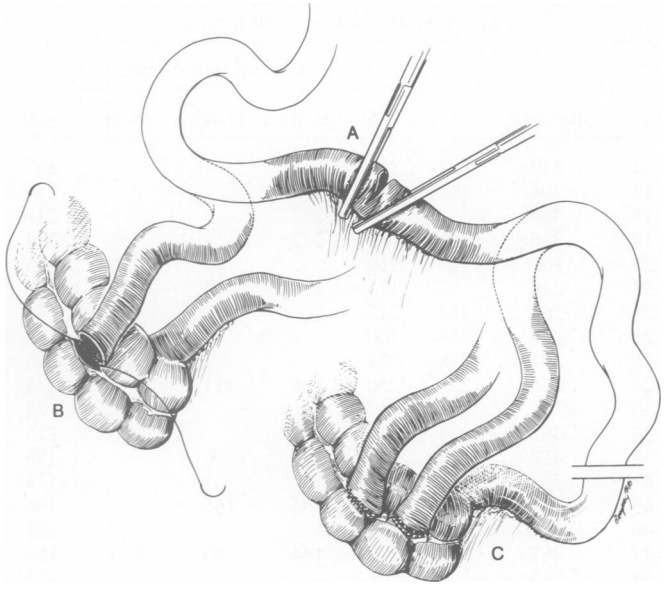
Accepted for publication April 12, 1990.

atherosclerotic morbidity and mortality. Although dietary and pharmacologic approaches have assumed the predominant role in the current management of hypercholesterolemia,[8] there is no report of the effects of any intervention to reduce cholesterol levels with follow-up extending beyond 20 years. Despite lack of a concurrent, randomized control group, the present analysis can provide insight into the potentially beneficial effects of long-term lipid intervention on the course of nonatherosclerotic and atherosclerotic disease in patients with hypercholesterolemia.

Methods

Operative Procedure

Between May 1963 and December 1968, 57 patients underwent PIB for the treatment of primary hypercholesterolemia. The operation was conducted in a similar manner in all patients (Fig. 1). Before operation intestinal preparation was begun, at least overnight, with a clear liquid diet, nonabsorbable oral antibiotics, and cathartics. Cleansing enemas were not used. The abdomen was entered through a transverse right lower quadrant incision approximately 2 cm below the umbilicus, unless a concomitant procedure such as a cholecystectomy was planned, in which case an upper transverse or a midline abdominal incision was used. After routine abdominal exploration, the total small bowel length was measured along the mesenteric border using a calibrated umbilical tape, allowing 25 cm for the duodenal length. The small bowel was transected 200 cm proximal to the ileocecal valve or at a point one third the total small bowel length proximal to the ileocecal valve if the total small bowel length was more than 600 cm. Although stapling instruments can be used, we have preferred clamps with hand-sewn, two-layer intestinal anastomoses and closures. The distal ileal segment was closed with a running inner absorbable layer and an interrupted outer nonabsorbable layer placed in Lembert fashion. The proximal small bowel segment was anastomosed, end-to-side, into the anterior taenia of the cecum approximately 6 cm distal to the inverted appendiceal stump using a two-layer technique. If present, the appendix was removed routinely. The cecum was chosen as the site of anastomosis to maximize the colonic, water-absorptive surface area. The anastomosis was made distal to the ileocecal valve to minimize ileal retention of chyme with absorption of cholesterol and bile acids. The previously closed end of the bypassed distal segment was tacked to the anterior taenia of the cecum between the anastomosis and the appendiceal stump to prevent intussusception of this segment. The small divisional and the large rotational mesenteric defects were closed to prevent internal herniation. The abdomen was copiously irrigated with antibiotic-containing normal saline solution and aspirated dry. After changing gowns and gloves, and using separate instruments, fascial closure was accomplished with interrupted, nonabsorbable sutures. The skin was reapproximated with interrupted, nonabsorbable sutures or with metal clips. Drains were not used routinely.



FIGS. 1A–C. Partial ileal bypass. (A) Division of the ileum 200 cm proximal to the ileocecal valve or one third of the total small bowel length proximal to the ileocecal valve if the total small intestinal length is greater than 600 cm. (B) End-to-side anastomosis of the proximal segment into the anterior taenia of the cecum, 6 cm distal to the appendiceal stump. (C) Tacking of the closed distal segment to the anterior taenia of the cecum midway between the anastomosis and the appendiceal stump.

Follow-up Analysis

In 1989 the medical records of all 57 patients were reviewed, and the vital status of each patient was ascertained from autopsy reports or death summaries in the medical record, or by telephone contact with the patient or with his or her survivors. Baseline and follow-up lipid values were abstracted directly from laboratory reports in the medical record. Many patients were referred by community physicians and did not receive their routine medical care at the University of Minnesota. Consequently their lipid results are sporadic. At baseline and throughout the follow-up period, the lipid profile was obtained after an overnight fast and included routine determination of the total plasma cholesterol (TC) level and occasional determination of the plasma triglyceride (TG) level by the clinical laboratory of the University of Minnesota Hospital using standard clinical methodology. In addition to these lipid results, all surviving patients contributed a 1989 plasma sample for analysis of TC, high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cho-

lesterol, very low-density lipoprotein (VLDL) cholesterol, TG, apolipoprotein A-I, and apolipoprotein B-100. After at least a 14-hour fast, plasma samples were obtained at the University of Minnesota or in community physicians' offices and shipped to Minneapolis overnight in refrigerated containers. The 1989 lipid analyses were performed in the Central Lipid Laboratory of the Program on the Surgical Control of the Hyperlipidemias (POSCH) at the University of Minnesota using previously described techniques.[19]

In addition to plasma lipid analysis, a standardized questionnaire was administered in 1989 during a personal interview or by telephone to all patients who had not undergone PIB reversal. Body weight, current medications, and the nature of postoperative hospitalizations were recorded. Cardiovascular, peripheral vascular, and cerebrovascular morbidities were noted. Follow-up nonatherosclerotic data, including the occurrence of gastrointestinal, renal, and musculoskeletal events, and the development of any malignancy, were collected. Postoperative complications, including development of an incisional hernia or occurrence of an intestinal obstruction requiring operation, were recorded.

Statistical Methods

Continuous data are presented as the mean ± one standard deviation (SD). Group means were compared using one-way analysis of variance and paired or unpaired Student's t tests when appropriate. Total plasma cholesterol and TG percentage changes were calculated for each patient and averaged to provide an overall group value. During intervals in which several TC or TG results were available, the determination closest to the end of the interval was chosen. Survival analysis was performed using actuarial methods with the date of operation as the starting point and with reversed patients censored at the time of PIB reversal. A two-sided p value of less than 0.05 was considered statistically significant.

Results

Thirty-eight male (66.7%) and 19 female (33.3%) patients, with a mean age of 42.2 ± 10.4 years (range, 12 to 60 years), underwent PIB between 1963 and 1968. Excluding two patients undergoing PIB reversal 5 and 6 years after operation, the mean age at operation of patients surviving more than 20 years (40.0 ± 11.7 years, n = 25) was slightly less than in patients surviving less than 20 years (44.3 ± 9.2 years, n = 30); however this difference was not statistically significant (p = 0.13).

The TC results are summarized in long-term survivors in Table 1A, and in nonsurviving and reversed patients in Table 1B. Preoperative TC levels were available in all 57 patients, and the mean value (363.3 ± 136.8 mg/dL) was significantly elevated (range, 200 to 1012 mg/dL). A follow-up TC level was available within the first postoperative year in 48 patients. Compared to the mean preoperative value in these patients, TC was significantly reduced (354.8 ± 139.7 mg/dL *versus* 231.1 ± 119.9 mg/dL, p = 0.0001), a 34.2% ± 17.7% reduction (p = 0.0001). A follow-up TC level was obtained between 2 and 5 years after surgery in 49 patients. This value was markedly reduced from the preoperative level (360.0 ± 133.4 mg/dL *versus* 257.7 ± 130.2 mg/dL, p = 0.0001), a decrease of 27.7% ± 21.7% (p = 0.0001). A 6- to 10-year follow-up TC level was available in 26 patients and was considerably lower than their preoperative values (324.9 ± 82.8 mg/dL *versus* 208.6 ± 73.4 mg/dL, p = 0.001), a reduction of 35.0% ± 16.6% (p = 0.0001). Between 11 and 15 years after operation, a TC level was determined in 11 patients and was significantly reduced compared to the preoperative value (355.5 ± 102.6 mg/dL *versus* 231.9 ± 118.1 mg/dL, p = 0.004), a decrease of 34.5% ± 24.9% (p = 0.001). A follow-up TC level was obtained in only five patients between 16 and 20 years after surgery, precluding meaningful statistical analysis.

Twenty-seven of the fifty-seven patients survived longer than 20 years. Excluding the two patients undergoing PIB reversal, the mean follow-up TC level obtained more than 20 years after operation was significantly reduced compared to the preoperative value (326.8 ± 88.1 mg/dL *versus* 219.0 ± 64.0 mg/dL, p = 0.0001), a 30.3% ± 19.6%

TABLE 1A. *Total Plasma Cholesterol Results (mg/dL) in Long-term Survivors After Partial Ileal Bypass*

		Follow-up Interval (years)					
Case	Baseline	1	2–5	6–10	11–15	16–20	>20
11	270	194	250	235			287
13	306	192	240	201			251
15	406		238	257			247
19	316		182	222			184
21	300	148	259				126
22	240		176	172	103		188
24	268	182	213			182	175
25	486	153	500				412
26	394	298	228				266
29	466	255	250	166	111		135
30	328	174	157				178
34	462	263					215
35	450	276	264				296
41	350	196					174
45	254	142		155	165		146
46	462		340				221
47	268	157	135	144	183	205	164
48	215	250					175
49	301	302	250				263
50	268	164	279				213
51	201	161	174	170			179
54	254	202	252	174	228		192
55	359	286	228	249	281	244	272
56	203	145	192				222
57	342	215	238				294

TABLE 1B. *Total Plasma Cholesterol Results (mg/dL) in Nonsurvivors and Reversed Patients After Partial Ileal Bypass*

		Follow-up Interval (years)				
Case	Baseline	1	2–5	6–10	11–15	16–18
1	558		297	332	315	
2	452	486	745	394	510	
3	378	313	268	416	292	274
4	402	195	186			
5	235	134	155	120		
6	333	192	189	207	127	170
7	404	250	260	172		
8	410					
9	364		145	137		
10	354	145	158	205		
12	298	123				
14	348	258	225	214	236	
16*	326		182			
17	270	174	172	169		
18	740	239				
20	314	158	140	140		
23	255	165	185	162		
27	432	288	290			
28	1012	878	815			
31	287	211	251	175		
32	468	290	405			
33	284	177	206	226		
36	368	170	184			
37	388	268	241			
38	353	378	327			
39*	200	155	207			
40	600		406			
42	540	360	292			
43	300	186	236			
44	340	188				
52	272	185	191	210		
53	254	170	222			

* Partial ileal bypass reversed.

decrease ($p = 0.0001$). In 21 of the 25 surviving, nonreversed patients, TC levels were available before operation, during the first postoperative year, and more than 20 years after surgery (Fig. 2). In these patients, the mean TC level decreased from 321.2 ± 87.6 mg/dL to 207.4 ± 54.2 mg/dL ($p = 0.0001$) within the first postoperative year, a decrease of 33.0% ± 18.1% ($p = 0.0001$). More than 20 years after surgery, the mean TC level was 220.7 ± 69.1 mg/dL, a decrease of 28.8% ± 20.4% *versus* the preoperative value ($p = 0.0001$). The TC level more than 20 years after operation remained significantly lower than the preoperative level ($p = 0.0001$), but was not significantly changed from the TC level within the first postoperative year considered as an absolute value ($p = 0.43$) or as a percentage change (11.1% ± 44.0%, $p = 0.26$).

To determine whether the TC change during the first year after PIB differentiates long-term survivors from nonsurvivors, the percentage change from the preoperative to the 1-year value was determined in long-term survivors (−33.0% ± 18.1%, $n = 21$) and in the nonsurvivors (−35.5% ± 17.7%, $n = 26$). These percentage reductions within the first postoperative year were not significantly different ($p = 0.63$).

The early and long-term TC results after PIB in male and female patients were examined (Table 2). During the first postoperative year, TC decreased significantly more in men than in women (38.2% ± 17.1% *versus* 27.5% ± 16.9%, $p = 0.04$). However, after the 20th postoperative year, the percentage reductions were similar in both sexes (30.5% ± 21.0% *versus* 31.6% ± 13.8%, $p = 0.90$). In the 21 nonreversed patients with TC levels before operation, within the first year, and more than 20 years after operation, no significant differences in the percentage reductions between the preoperative and 1-year TC level ($p = 0.79$), between the preoperative and the more-than–20-year TC level ($p = 0.70$), or between the 1-year and 20-year TC level ($p = 0.43$) were observed between male and female patients.

To determine whether the preoperative TC level influences the magnitude of TC change achieved by PIB, the TC results within the first postoperative year and more than 20 years after operation were examined in terciles

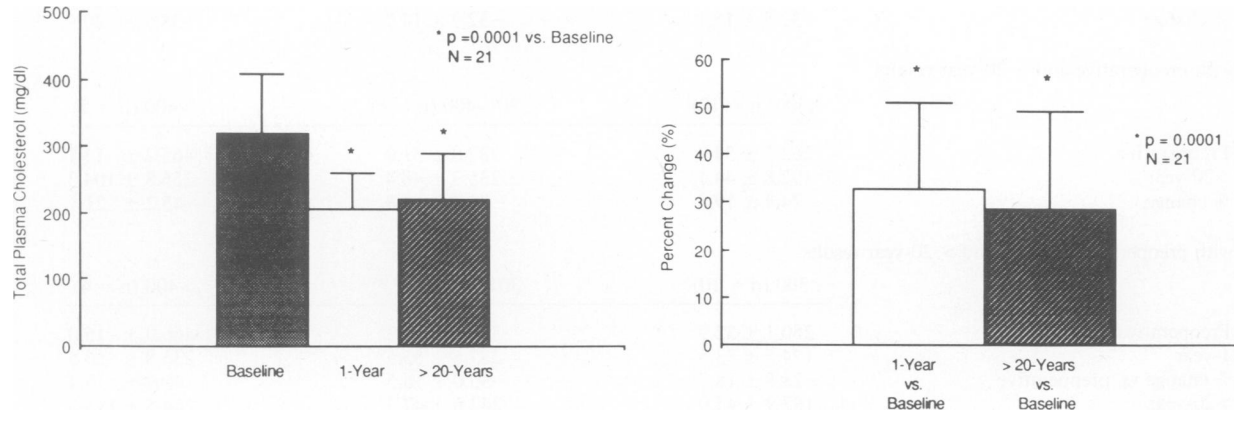


FIG. 2. Total plasma cholesterol results (mean ± SD) and percentage changes from baseline (mean ± SD) in 21 patients with baseline, 1-year, and >20-year results after partial ileal bypass.

TABLE 2. *Total Plasma Cholesterol Results (mg/dL) After Partial Ileal Bypass by Sex*

	Male (n = 30)	Female (n = 18)
Patients with preoperative and 1-year results		
Preoperative	348.4 ± 166.5	365.2 ± 80.5
1-year	210.8 ± 133.7	264.8 ± 85.3
% change	−38.2 ± 17.1*	−27.5 ± 16.9
Patients with preoperative and >20-year results		
	Male (n = 17)	Female (n = 8)
Preoperative	322.5 ± 98.8	335.9 ± 64.6
>20-year	214.6 ± 68.4	228.4 ± 56.6
% change	−30.5 ± 21.0	−31.6 ± 13.8
Patients with preoperative, 1-year, and >20-year results		
	Male (n = 13)	Female (n = 8)
Preoperative	312.2 ± 100.6	335.9 ± 64.6
1-year	195.0 ± 50.9	227.5 ± 56.7
% change *vs.* preoperative	−33.9 ± 20.0	−31.6 ± 15.9
>20-year	216.0 ± 77.5	228.4 ± 56.6
% change *vs.* preoperative	−28.0 ± 22.8	−31.6 ± 13.8
% change *vs.* 1-year	17.4 ± 54.4	1.4 ± 16.3

* p = 0.04.

based on the preoperative TC levels (Table 3). Although a tendency toward greater TC reduction in patients with the highest preoperative TC levels was evident within the first year and after the 20th postoperative year, no statistically significant differences were observed.

The impact of age at the time of surgery on the early and long-term TC results after PIB was examined in quartiles based on age at operation (Table 4). Within the first postoperative year, PIB led to a smaller TC reduction in younger patients (age less than 30 years). More than 20 years after surgery, this trend toward reduced TC lowering in younger patients continued; however none of these differences between age quartiles achieved statistical significance.

Plasma triglyceride levels were obtained less frequently than TC levels in these patients (Tables 5A and B). A TG level was available at the time of PIB and within 1 year of operation in 22 patients. The mean TG level decreased (378.1 ± 434.1 mg/dL *versus* 308.7 ± 370.3 mg/dL, p = 0.07); however the overall percentage change (1.8% ± 44.7%, p = 0.85) was not statistically significant. A TG level at operation and between 2 and 5 years after surgery was obtained in 23 patients. Mean TG decreased slightly (370.5 ± 426.0 mg/dL *versus* 298.0 ± 314.6 mg/dL, p = 0.12); however the 5.4% ± 50.0% change from baseline was not statistically significant (p = 0.61). A baseline and 6- to 10-year TG level was determined in 11 patients. Mean TG was somewhat lower (440.3 ± 441.3 mg/dL *versus* 238.3 ± 110.6 mg/dL, p = 0.10), and the mean percentage reduction from baseline (23.2% ± 38.8%, p = 0.08) approached statistical significance. Follow-up TG levels were available between 11 and 15 years and between 16 and 20 years after surgery in only five and three patients, respectively. This precluded meaningful statistical assessment.

A TG level at operation and 20 years or more after PIB was determined in 20 of the 25 surviving, nonreversed patients. Mean TG was somewhat lower (351.3 ± 444.9 mg/dL *versus* 229.3 ± 169.9 mg/dL, p = 0.22); however

TABLE 3. *Total Plasma Cholesterol Results (mg/dL) After Partial Ileal Bypass by Preoperative Total Plasma Cholesterol Level*

	≤300 (n = 20)	301–400 (n = 16)	>400 (n = 12)
Patients with preoperative and 1-year results			
Preoperative	257.8 ± 32.0	347.3 ± 27.1	562.2 ± 177.1
1-year	171.3 ± 29.3	233.3 ± 67.8	327.8 ± 192.1
% change	−32.5 ± 15.1	−32.9 ± 18.7	−38.6 ± 20.9
Patients with preoperative and > 20-year results			
	≤300 (n = 12)	301–400 (n = 8)	>400 (n = 5)
Preoperative	262.3 ± 54.3	337.0 ± 31.0	465.2 ± 13.1
>20-year	192.8 ± 44.1	235.3 ± 48.4	255.8 ± 104.3
% change	−24.4 ± 19.8	−29.9 ± 14.8	−45.2 ± 21.1
Patients with preoperative, 1-year, and > 20-year results			
	≤300 (n = 10)	301–400 (n = 7)	>400 (n = 4)
Preoperative	250.1 ± 32.9	340.0 ± 32.2	466.0 ± 15.0
1-year	174.5 ± 33.5	237.6 ± 55.5	236.8 ± 56.5
% change *vs.* preoperative	−28.8 ± 18.7	−30.0 ± 16.5	−48.9 ± 13.4
>20-year	187.9 ± 45.0	242.6 ± 47.3	264.5 ± 118.3
% change *vs.* preoperative	−23.3 ± 21.3	−28.2 ± 15.2	−43.5 ± 24.1
% change *vs.* 1-year	9.6 ± 26.7	4.3 ± 20.8	27.8 ± 96.9

TABLE 4. *Total Plasma Cholesterol Results (mg/dL) After Partial Ileal Bypass by Preoperative Age*

Patients with preoperative and 1-year results				
	<30 (n = 7)	30–39 (n = 9)	40–49 (n = 12)	≥50 (n = 11)
Preoperative	447.3 ± 264.3	356.1 ± 165.0	337.6 ± 88.1	327.3 ± 71.1
1-year	367.9 ± 248.1	205.0 ± 46.0	209.3 ± 64.6	206.9 ± 72.1
% change	−19.2 ± 18.8	−37.2 ± 15.3	−37.3 ± 12.1	−35.2 ± 24.2
Patients with preoperative and > 20-year results				
	<30 (n = 5)	30–39 (n = 4)	40–49 (n = 10)	≥50 (n = 6)
Preoperative	333.4 ± 94.0	320.0 ± 89.4	327.1 ± 84.9	352.2 ± 111.2
> 20-year	253.2 ± 33.7	256.5 ± 47.2	217.4 ± 77.5	168.2 ± 35.0
% change	−19.0 ± 22.8	−17.6 ± 17.3	−33.3 ± 13.4	−43.3 ± 20.9
Patients with preoperative, 1 year, and > 20-year results				
	>30 (n = 5)	30–39 (n = 4)	40–49 (n = 8)	≥50 (n = 4)
Preoperative	333.4 ± 94.0	320.0 ± 89.4	318.6 ± 91.0	312.3 ± 108.3
1-year	242.2 ± 63.5	216.0 ± 40.2	183.8 ± 49.1	202.5 ± 57.9
% change *vs.* preoperative	−25.8 ± 16.9	−31.1 ± 8.5	−39.8 ± 15.2	−30.3 ± 31.3
> 20-year	253.2 ± 33.7	256.5 ± 47.2	217.9 ± 86.2	150.0 ± 23.2
% change *vs.* preoperative	−19.0 ± 22.8	17.6 ± 17.3	−31.6 ± 14.6	−46.6 ± 22.9
% change *vs.* 1-year	10.8 ± 32.1	20.2 ± 23.7	23.1 ± 60.5	−21.9 ± 21.9

the overall percentage change from the preoperative value was not statistically significant (23.9% ± 111.1%, p = 0.35). Seventeen of the surviving, nonreversed patients had TG levels at the time of surgery, within the first postoperative year, and more than 20 years after operation (Fig. 3). Mean TG more than 20 years after surgery was

TABLE 5A. *Plasma Triglyceride Results (mg/dL) in Long-term Survivors After Partial Ileal Bypass*

		Follow-up Interval (years)					
Case	Baseline	1	2–5	6–10	11–15	16–20	>20
11	283		403	171			768
13			123	129			129
15			204	108			119
19	100		112	170			88
21	174	172	112				97
22			137	178	108		68
24	677	253	312			209	178
25		302	492				565
26	139	82	100				177
29	1632	1737	895	379	145		151
30	93	113	155				129
34	312	168					147
35	76	140	83				210
41		247					118
45	141	117		88	105		72
46	313		348				259
47	117	129	142	123	339	272	150
48	151	206					198
49	120	173	130				117
50	1524	966	1480				570
51	417	298	423	288			142
54	365	317	490	280	334		290
55	186	269	197	198	265	222	209
56	129	152	179				274
57	76	103	119				359

TABLE 5B. *Plasma Triglyceride Results (mg/dL) in Nonsurvivors and Reversed Patients After Partial Ileal Bypass*

		Follow-up Interval (years)				
Case	Baseline	1	2–5	6–10	11–15	16–18
1			375	179	160	
2			420	121	243	
3			177	196	181	60
4						
5			152	90		
6			254	520	85	315
7			206	147		
8						
9			75	87		
10			265	223		
12						
14		123	149	168	177	
16*			269			
17			239	119		
18	328	344				
20	372	263	179	179		
23			126			
27			158			
28	147		224			
31		558	289	245		
32		160	327			
33	448	188	154	295		
36		321	360			
37		168	219			
38			126			
39*	60	124	146			
40			258			
42		217	233			
43		95	66			
44		146				
52	782	478	269	450		
53	292		202			

* Partial ileal bypass reversed.

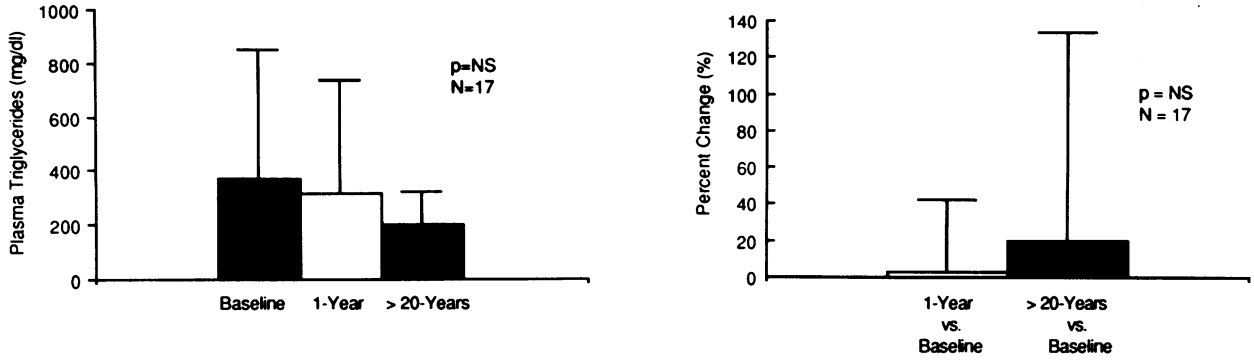


FIG. 3. Plasma triglyceride results (mean ± SD) and percentage changes from baseline (mean ± SD) in 17 patients with baseline, 1-year, and >20-year results after partial ileal bypass.

lower than either the preoperative level (372.3 ± 479.9 mg/dL *versus* 204.1 ± 119.0 mg/dL, p = 0.14) or the 1-year result (317.6 ± 418.1 mg/dL *versus* 204.1 ± 119.0 mg/dL, p = 0.26). The mean percentage changes between baseline and 1 year (3.2% ± 39.3%, p = 0.74), between baseline and more than 20 years (19.8% ± 114.4%, p = 0.49), and between 1 year and more than 20 years (8.8% ± 79.9%, p = 0.66) also failed to achieve statistical significance.

To determine whether TG change within the first year of operation influenced long-term survival after PIB, the percentage changes between the preoperative and 1-year TG levels in long-term survivors (3.2% ± 39.3%, n = 17) and in nonsurvivors (−20.6% ± 29.2%, n = 4) were compared. The difference in the TG response within the first postoperative year was not statistically significant (p = 0.27), although the number of determinations in nonsurvivors was limited.

The TG results within the first year and more than 20 years after PIB were assessed in terciles based on the preoperative TG level (Table 6). In patients with the lowest preoperative levels, mean TG tended to increase; whereas in patients with the highest preoperative TG levels, mean TG values decreased. The number of patients with elevated preoperative TG levels, however, was small.

In addition to TC and TG level determinations, a complete lipid profile was performed in the 25 surviving, nonreversed patients. More than 20 years after partial ileal bypass, HDL cholesterol was 45.4 ± 16.3 mg/dL, LDL cholesterol was 122.2 ± 50.4 mg/dL, VLDL cholesterol

TABLE 6. *Plasma Triglyceride Results (mg/dL) After Partial Ileal Bypass by Preoperative Plasma Triglyceride Level*

Patients with preoperative and 1-year results			
	≤200 (n = 12)	201–600 (n = 7)	>600 (n = 3)
Preoperative	121.8 ± 39.6	388.4 ± 61.3	1277.7 ± 523.0
1-year	148.3 ± 51.2	293.7 ± 104.1	985.3 ± 742.2
% change	28.5 ± 40.6	−24.3 ± 23.2*	−30.9 ± 34.9*
Patients with preoperative and > 20-year results			
	≤200 (n = 12)	201–600 (n = 5)	>600 (n = 3)
Preoperative	125.2 ± 35.4	338.0 ± 53.1	1277.7 ± 523.0
> 20-year	173.3 ± 83.6	321.2 ± 258.3	300.0 ± 234.5
% change	57.6 ± 117.3	2.9 ± 96.4	−75.7 ± 14.2
Patients with preoperative, 1-year, and > 20-year results			
	≤200 (n = 11)	201–600 (n = 3)	>600 (n = 3)
Preoperative	127.5 ± 36.2	364.7 ± 52.5	1277.7 ± 523.0
1-year	150.5 ± 53.1	261.0 ± 81.1	985.3 ± 742.2
% change *vs.* preoperative	21.4 ± 33.8	−29.3 ± 16.5*	−30.9 ± 34.9*
> 20-year	181.1 ± 83.0	193.0 ± 84.0	300.0 ± 234.5
% change *vs.* preoperative	63.9 ± 120.8	−46.5 ± 23.4	−75.7 ± 14.2
% change *vs.* 1-year	35.0 ± 87.2	−24.5 ± 24.2	−54.0 ± 32.8

* $p < 0.05$ *vs.* ≤ 200 mg/dL group.

was 50.2 ± 57.8 mg/dL, apolipoprotein A-I was 121.6 ± 38.6 mg/dL, and apolipoprotein B-100 was 96.6 ± 28.6 mg/dL.

In the surviving, nonreversed patients, nonatherosclerotic follow-up data were collected (Table 7). Excluding two reversed patients and two patients undergoing operation at the ages of 12 and 17 years, preoperative and follow-up weights more than 20 years after operation were available in 20 patients (three cases missing preoperative values). No significant change in weight after PIB was observed (72.8 ± 14.7 kg *versus* 68.1 ± 18.8 kg, p = 0.21). Six surviving patients (24%) reported 1 to 2, 13 patients (52%) reported 3 to 5, and 6 survivors (24%) reported more than 5 daily bowel movements. Only one patient required regular bowel-controlling medication, and no patient felt that bowel movement frequency necessitated a significant life-style modification. Six survivors (24%) experienced frequent postprandial bloating, and six patients reported excessive flatus. Eight patients required a cholecystectomy during the follow-up period; however the number of *in situ* gallbladders at the time of PIB could not be ascertained accurately from medical records or recalled by the patients with certainty. One patient was noted to have cirrhosis at the time of cholecystectomy. Ten patients (40%) developed nephrolithiasis, with two patients (8%) requiring operative stone removal. No kidney loss or decrease in renal function was reported. Two patients (8%) have undergone repeat operation for small bowel obstruction, and one patient (4%) has developed an incisional hernia. Three surviving patients have a diagnosed malignancy (1 prostate, 1 bladder, and 1 vocal cord), and 1 patient developed cataracts.

Clinically apparent atherosclerosis evolved in many of the surviving, nonreversed patients 20 or more years after PIB (Table 8). Sixty per cent of these patients have angina requiring at least occasional pharmacologic treatment, 16% of the survivors have sustained at least one myocardial infarction, and 28% have undergone coronary artery bypass surgery. Four survivors (16%) have lower-extremity claudication and four patients (16%) have undergone either abdominal aortic aneurysm repair or bypass surgery to the lower-extremity vasculature. One patient (4%) reported transient ischemic attacks; three patients (12%) suffered strokes, and two patients (8%) underwent carotid endarterectomy.

TABLE 7. *Nonatherosclerotic Follow-up in 25 Surviving, Nonreversed Patients After Partial Ileal Bypass*

Weight change (kg) *vs.* preop. (n = 20)	−4.7 ± 16.3
Percentage change *vs.* preop.	−5.4 ± 21.7
Bowel movements per day	
0–2	6 (24)
3–5	13 (52)
>5	6 (24)
Requiring regular bowel-controlling agents	1 (4)
Gas-bloat symptoms	6 (24)
Excessive flatus	6 (24)
Cholecystectomy	8
Cirrhosis	1
Nephrolithiasis	10 (40)
Requiring operation for extraction	2 (8)
Small bowel obstruction requiring operation	2 (8)
Incisional hernia	1 (4)
Cataract development	1 (4)
Malignancy (1 prostate, 1 bladder, and 1 vocal cord)	3 (12)

Values in parentheses are percentages.

TABLE 8. *Atherosclerotic Cardiovascular Disease Follow-up in 25 Surviving, Nonreversed Patients After Partial Ileal Bypass*

Cardiac	
Angina requiring medical therapy	15 (60)
Myocardial infarction	4 (16)
Coronary artery bypass surgery	7 (28)
Peripheral vascular	
Claudication	4 (16)
Abdominal aortic aneurysm repair	2 (8)
Peripheral vascular bypass	2 (8)
Cerebral	
Transient ischemic attack	1 (4)
Stroke	3 (12)
Carotid endarterectomy	2 (8)

Values in parentheses are percentages.

Mortality results are summarized in Table 9. One patient died of a myocardial infarction on the fourth postoperative day (operative mortality rate = 1.8%) and two additional patients died within the first postoperative year. Coronary heart disease was the cause of death in 80% of cases. Three patients (10%) died as a consequence of malignancy (two breast and one lymphoma). In one patient the cause of death could not be determined by medical record review and was unknown to her surviving relatives. Overall actuarial survival rates were 94.7% at 1 year, 87.7% at 5 years, 74.9% at 10 years, 58.5% at 15 years, 53% at 20 years, and 40.8% at 25 years after PIB (Fig. 4).

Discussion

Coronary heart disease remains the most frequent cause of death in the United States and in the western world.[6] In 1988 diseases of the heart accounted for 35.5% of all deaths in this country. Two thirds of these deaths were due to ischemic heart disease, the mortality rate (207.9 per 100,000) exceeding that observed in any other disease category, including all types of malignancy combined (198.6 per 100,000). Hypercholesterolemia clearly has been established as a major risk factor for the development of atherosclerosis and for death due to CHD.[3,20] The screening results of the Multiple Risk Factor Intervention Trial demonstrated that asymptomatic adult men with total serum cholesterol levels equal to or greater than 264 mg/dL had a 6-year CHD mortality rate of 13.05 per 1000, which is 4.13 times the rate observed in patients with total serum cholesterol levels less than 167 mg/dL.[5,21,22]

TABLE 9. *Mortality Results in 57 Patients After Partial Ileal Bypass*

30-day (operative) mortality	1 (1.8)
1-year mortality	3 (5.4)
Causes of death	
Coronary heart disease*	24 (42.1)
Ruptured abdominal aortic aneurysm	1 (1.8)
Ruptured cerebral aneurysm	1 (1.8)
Breast cancer	2 (3.5)
Lymphoma	1 (1.8)
Unknown	1 (1.8)
Total	30 (52.6)

Values in parentheses are percentages.
* Includes sudden death, myocardial infarction, and congestive heart failure.

Although the pantheon of lipid/atherosclerosis intervention trials using dietary or pharmacologic approaches to lower TC failed to demonstrate a beneficial effect of treatment on overall survival,[23-26] aggressive TC reduction has been shown to decrease the rate of new coronary artery lesion formation and to retard the rate of existing lesion progression assessed angiographically.[27,28] The incidence of clinical atherosclerosis events considered in combination, *i.e.*, CHD death or definite, nonfatal myocardial infarction, has also been reduced.[29] In the current clinical atmosphere, it appears prudent to advocate TC reduction in hypercholesterolemic patients, particularly in those with clinically evident atherosclerosis.

Beginning in 1962 experiments performed in our laboratory[10,11,30] and by others,[31,32] and retrospective analysis of patients undergoing ileal resections, demonstrated that both cholesterol and bile acid absorption from the intestine, and plasma cholesterol, were significantly reduced, without concomitant weight loss, after diversion of substantial lengths of the distal small intestine. Although the entire small intestine is capable of cholesterol absorption, preferential cholesterol uptake occurs in the distal half of the small intestine. The absorption sites for bile acids are less well defined; however our experiments demonstrated that bypass of the distal one third of the small intestine significantly interferes with the enterohepatic bile acid circulation and leads to a threefold increase in fecal bile acid excretion.[11] Thus the metabolic basis for PIB was defined. Total plasma cholesterol reduction results from (1) a direct cholesterol drain from increased fecal loss of normally absorbed exogenous (dietary) and endogenous (biliary and intestinally secreted) cholesterol, and (2) an indirect cholesterol drain from increased hepatic conversion of body cholesterol stores to bile acids to replenish the depleted bile acid reservoir.

Partial ileal bypass was introduced clinically at the University of Minnesota in May 1963.[12] Radioisotope studies in volunteers after operation confirmed the mechanism by which the significant TC reduction accomplished by PIB occurs.[33,34] Cholesterol absorption from the intestine was reduced by 60%. A 3.8-fold increase in total fecal steroid excretion occurred, with a 4.9-fold increase in bile acid excretion and a 2.9-fold increase in fecal neutral steroid losses. A compensatory 5.7-fold increase in the cholesterol synthesis rate developed. One year after surgery, the total exchangeable cholesterol pool was reduced by 33%, reflecting decreases in the freely miscible (plasma, red blood cells, liver, and intestinal mucosa) and in the less freely miscible (fat stores, muscle, solid organs, and vessel walls) cholesterol pools.

Since the introduction of PIB, more than 600 of these

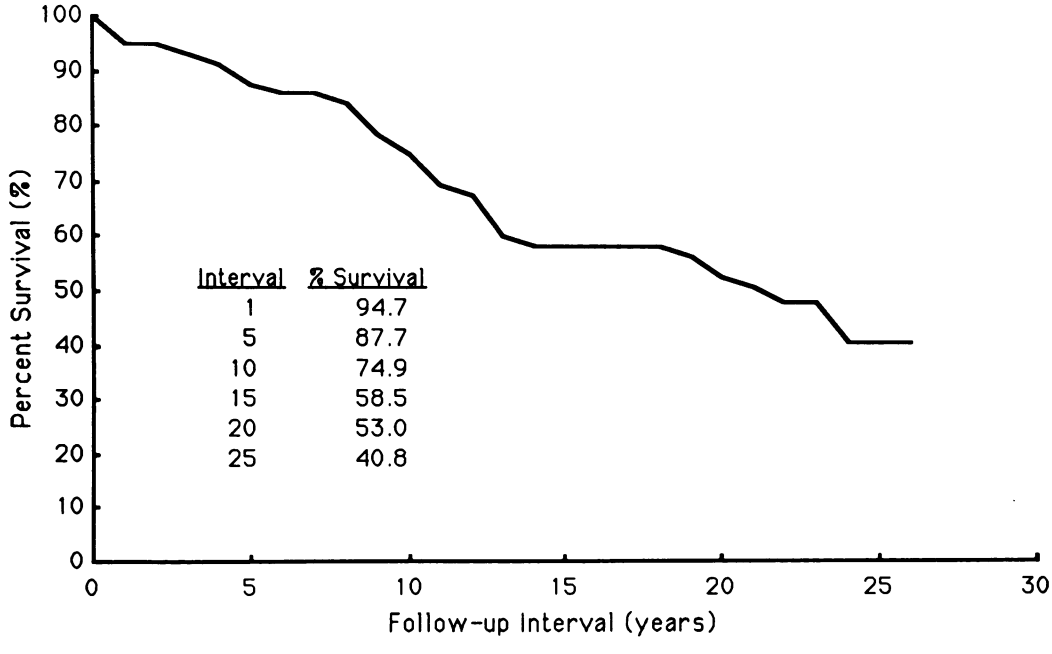


FIG. 4. Cumulative survival rates in the initial 57 hypercholesterolemic patients undergoing partial ileal bypass.

procedures have been performed at the University of Minnesota and at other centers in this country and worldwide.[13-18] The largest experience with this operation is within POSCH, a randomized, prospective, multicenter, secondary intervention trial testing the therapeutic arm of the lipid/atherosclerosis relationship, with PIB as the intervention modality.[19] The 5-year lipid results of PIB in 200 patients compared with those achieved by dietary fat and cholesterol restriction in 196 control patients have been published recently.[35-37] In 1974 we reported 9-year lipid results in patients undergoing PIB outside of POSCH; however the number of patients with long-term follow-up was small.[38] The present analysis of 57 patients undergoing operation between 1963 and 1968 is the largest collected series of PIB patients available with follow-up of more than 10 years. In this series all patients were followed for a minimum of 20 years after surgery.

In these patients PIB led to 34%, 28%, 35%, 35%, and 30% reductions in TC levels 1 (n = 48), 2 to 5 (n = 49), 6 to 10 (n = 26), 11 to 15 (n = 11), and more than 20 years (n = 25), respectively, after operation. In 21 patients baseline, 1-year, and more-than–20-year TC levels were determined (Fig. 2). In these patients TC was 33% lower than baseline in the first postoperative year and remained 29% less than baseline more than 20 years after operation. No significant difference between the percentage reductions from baseline at 1 year and after more than 20 years was observed, demonstrating that the TC-lowering effect of PIB occurs within the first year of operation and is sustained, essentially unchanged, more than 20 years after surgery. This relationship was confirmed in the 17 patients with baseline, 1-year (−34%), 2- to- 5–year (−23%), and more-than–20-year (−26%) TC levels; in the 8 patients with baseline, 1-year (−32%), 6- to- 10–year (−34%), and more-than–20-year (−28%) TC levels, and in the 7 patients with baseline, 1-year (−30%), 2- to- 5–year (−25%), 6- to- 10–year (−34%), and more-than–20-year (−26%) TC levels.

The TC reduction achieved within the first year after PIB did not differentiate long-term survivors from nonsurvivors. Male and female patients achieved comparable TC reduction after PIB. Greater TC reduction was induced in patients with the most elevated preoperative TC levels (Table 3). The operation, however, appeared to be less effective in younger patients (age less than 30 years) than in older individuals. This may have been due to the inclusion of several younger patients afflicted with homozygous, familial hypercholesterolemia in this analysis. These patients, with severely elevated TC levels, responded poorly to PIB.

Plasma triglyceride levels were less frequently obtained and demonstrated considerable variability when available. Compared to the preoperative TG value, PIB led to a 2% increase at 1 year (n = 22), a 5% increase at 2 to 5 years (n = 23), a 24% decrease at 6 to 10 years (n = 11), and a 23% increase in TG more than 20 years (n = 20) after surgery. None of these percentage changes from baseline were statistically significant. In the 17 patients with baseline, 1-year, and more-than– 20-year TG determinations, PIB led to a 3% increase from baseline within the first year and a 20% increase from baseline more than 20 years after surgery. Both of these percentage changes from baseline were not statistically significant. Analysis of the TG response after PIB according to the preoperative TG value demonstrated that TG levels increased significantly within 1 year of operation and continued to be increased more than 20 years after surgery in patients with low to normal preoperative TG levels. The mean TG level after 20 years in this subgroup, however, continued to be less than 200 mg/dL. Similar TG increases have been noted during oral bile acid sequestrant therapy.[39] In patients with moderately and severely elevated preoperative TG values, PIB led to significant reductions within the first year and more than 20 years after surgery. More than 20 years after operation, the mean TG level in patients with moderately elevated baseline levels was below 200 mg/dL. In patients with severely elevated preoperative TG levels, the mean TG level more than 20 years after surgery was 300 mg/dL. The number of postoperative TG determinations in patients with abnormal preoperative TG levels was small. However these results suggest that increases in TG may not be a uniform consequence of PIB, and plasma triglycerides may actually decrease in certain subgroups after surgery.

The adverse effect profile of PIB has been a major factor limiting clinical acceptance of this procedure into the hypocholesterolemic armamentarium. More than 20 years after PIB, no significant change in weight was noted in the surviving, nonreversed patients, clearly differentiating this operation from the more extensive jejunoileal bypass (JIB) formerly used in the management of morbid obesity. Vitamin B_{12} absorption is generally lost after PIB,[40] and all patients are advised to receive 1000 μg of vitamin B_{12} intramuscularly every 6 to 8 weeks. Frequent bowel movements are the rule following PIB; however not one surviving patient felt that this required any significant lifestyle modification. One quarter of surviving, nonreversed patients had normal bowel habits, one half had between three and five bowel movements per day, and one quarter had more than five bowel movements per day. Only one patient was regularly taking medication to limit bowel movement frequency, and only one patient (1.8%) underwent reversal of his PIB due to intractable diarrhea. Cholelithiasis appears to develop at an increased rate after PIB, and removal of an *in situ* gallbladder should be considered at the time of operation. One patient was noted to have subclinical hepatic cirrhosis of unknown etiology, at the time of cholecystectomy. This patient continues to

be asymptomatic. Our experience would indicate that cirrhosis and hepatic failure, sometimes seen after JIB, do not occur after PIB.[41] Nephrolithiasis occurs at an increased rate after bypass of the distal small intestine,[42] and 40% of surviving, nonreversed patients in this series developed calcium oxalate renal calculi during the follow-up period. In the era preceding ultrasonic and endourologic techniques for noninvasive fragmentation and removal of stones, two patients (8%) required operation for stone extraction. No kidney loss or decrease in renal function has been noted in the surviving, nonreversed patients. One patient (1.8%) underwent PIB reversal for recurrent nephrolithiasis. Preventive treatment with a low oxalate diet, increased fluid intake, and oral calcium supplementation has not had an appreciable impact on the incidence of nephrolithiasis in these patients. The potential effect of urine alkalization with oral potassium citrate is undergoing prospective, randomized, placebo-controlled evaluation in members of the PIB group in POSCH. Finally an increased risk for the development of gastrointestinal malignancy has been a concern in patients after PIB due to the markedly increased bile acid load delivered to the colon. In more than 20 years of follow-up, no gastrointestinal cancer has developed in these patients.

Analysis of the atherosclerosis morbidity and overall mortality results reveals that despite highly significant, sustained, TC lowering, most surviving, nonreversed patients have developed clinically apparent atherosclerosis during the 20-to-26-year follow-up period, and CHD remains their most frequent cause of death. This raises the issue of whether any real benefit has been achieved by aggressive, surgically induced TC lowering in these patients and calls into question the value of any long-term treatment to reduce TC in hypercholesterolemic patients. The absence of a randomized control group in this series does not allow a definite response to this question. However observational epidemiologic data from the Framingham Study suggest that a 2% reduction in CHD mortality is achieved for each 1% reduction in the TC.[43] Thus, although the long-term CHD mortality rate in the patients reported is significant, a far greater CHD mortality risk can be hypothesized if no total plasma cholesterol reduction had been accomplished. Evidence supporting a reduction in this projected mortality rate may be found by comparing the survival rate in this patient population (Fig. 4) with the 5-year and the 15-year survival experience in the placebo-treated group participating in the Coronary Drug Project.[44] In these adult, male survivors of a myocardial infarction, with a mean total serum cholesterol of 249 mg/dL, the overall mortality rate without hypocholesterolemic therapy was 20.9% at 5 years and 58.2% at 15 years. In the present series, the mortality rate was 12.3% at 5 years and 41.5% at 15 years, 41% and 29% lower, respectively. Although the patient populations in these two studies were dissimilar in mean TC levels and the prevalence of clinically apparent atherosclerosis at baseline, this comparison supports the hypothesis that intervention to reduce TC may have a beneficial impact on the course of CHD in hypercholesterolemic patients. Definitive evidence for such a conclusion, however, will be found in the results of prospective, randomized, controlled clinical trials, *e.g.*, POSCH, whose results will be available in October 1990.

References

1. Ross R. The pathogenesis of atherosclerosis—an update. N Engl J Med 1986; 314:488–500.
2. Keys A. Coronary heart disease in seven countries. Circulation 1970; 41(Suppl I):I1–I211.
3. Kannel WB, Castelli WP, Gordon T, McNamara PM. Serum cholesterol, lipoproteins, and the risk of coronary heart disease: the Framingham Study. Ann Intern Med 1971; 74:1–12.
4. The Pooling Project Research Group. Relationship of blood pressure, serum cholesterol, smoking habit, relative weight, and ECG abnormalities to incidence of major coronary events: final report of the Pooling Project. J Chronic Dis 1978; 31:201–306.
5. Martin MJ, Hulley SB, Browner WS, et al. Serum cholesterol, blood pressure, and mortality: implications from a cohort of 361,662 men. Lancet 1986; ii:933–936.
6. National Center for Health Statistics. Annual summary of births, marriages, divorces, and deaths: United States, 1988. Monthly Vital Statistics Report, Vol. 37, No. 13. Hyattsville, MD: Public Health Service, 1989.
7. The Lipid Research Clinics Program Epidemiology Committee. Plasma lipid distributions in selected North American populations: the Lipid Research Clinics Program prevalence study. Circulation 1979; 60:427–239.
8. The Expert Panel. Report of the National Cholesterol Education Program Expert Panel on detection, evaluation, and treatment of high blood cholesterol in adults. Arch Intern Med 1988; 148: 36–69.
9. Study Group, European Atherosclerosis Society. The recognition and management of hyperlipidaemia in adults: a policy statement of the European Atherosclerosis Society. Eur Heart J 1988; 9: 571–600.
10. Buchwald H, Gebhard RL. Effect of intestinal bypass on cholesterol absorption and blood levels in the rabbit. Am J Physiol 1964; 207:567–572.
11. Buchwald H, Gebhard RL. Localization of bile salt absorption in vivo in the rabbit. Ann Surg 1968; 167:191–198.
12. Buchwald H. Surgical operation to lower circulating cholesterol. Circulation 1963; 28:649–650.
13. Buchwald H, Campos CT. Partial ileal bypass for control of hyperlipidemia and atherosclerosis. *In* Sabiston DC Jr, Spencer FC, eds. Surgery of the Chest, 5th Edition. Philadelphia: WB Saunders, 1990, pp 1799–1820.
14. Koivisto P, Miettinen TA. Long-term effect of ileal bypass on lipoproteins in patients with familial hypercholesterolemia. Circulation 1984; 70:290–296.
15. Schouten JA, Beynen AC. Partial ileal bypass in the treatment of heterozygous familial hypercholesterolemia: a review. Artery 1986; 13:240–263.
16. Vaislic CD, Grondin PR, Bourassa MG, Campeau L. Partial ileal bypass in Type II familial hypercholesterolemia: eleven-year experience at the Montreal Heart Institute. Am Surg 1984; 501: 165–168.
17. Spengel FA, Jadhav A, Duffield RGM, et al. Superiority of partial ileal bypass over cholestyramine in reducing cholesterol in familial hypercholesterolaemia. Lancet 1981; i:768–770.
18. Van Niekerk JLM, Hendriks T, De Boer HHM. The treatment of familial hypercholesterolaemia by partial ileal bypass surgery. Neth J Med 1984; 27:18–23.

19. Buchwald H, Matts JP. Fitch LL, et al. Program on the Surgical Control of the Hyperlipidemias (POSCH): design and methodology. J Clin Epidemiol 1989; 42:1111–1127.
20. Grundy SM. Cholesterol and coronary heart disease. A new era. JAMA 1986; 256:2849–2858.
21. Kannel WB, Neaton JD, Wentworth D, et al. Overall and coronary heart disease mortality rates in relation to major risk factors in 325, 348 men screened for the MRFIT. Am Heart J 1986; 112: 825–836.
22. Stamler J, Wentworth D, Neaton JD, for the MRFIT Research Group. Is relationship between serum cholesterol and risk of premature death from coronary heart disease continuous and graded? JAMA 1986; 256:2823–2828.
23. Dayton S, Pearce ML, Hashimoto S, et al. A controlled clinical trial of a diet high in unsaturated fat in preventing complications of atherosclerosis. Circulation 1969; 40(Suppl II):II1–II63.
24. Leren P. The Oslo diet-heart study: eleven year report. Circulation 1970; 42:935–942.
25. Multiple Risk Factor Intervention Trial Research Group. Multiple Risk Factor Intervention Trial: risk factor changes and mortality results. JAMA 1982; 248:1465–1477.
26. Frick MH, Elo MO, Haapa K, et al. Helsinki Heart Study: primary prevention trial with gemfibrozil in middle-aged men with dyslipidemia. N Engl J Med 1987; 317:1237–1245.
27. Brensike JF, Levy RI, Kelsey SF, et al. Effects of therapy with cholestyramine on progression of coronary arteriosclerosis: results of the NHLBI Type II Coronary Intervention Study. Circulation 1984; 69:313–324.
28. Blankenhorn DM, Nessim SA, Johnson RL, et al. Beneficial effects of combined colestipol-niacin therapy on coronary atherosclerosis and coronary venous bypass grafts. JAMA 1987; 257:3233–3240.
29. Lipid Research Clinics Program. The Lipid Research Clinics Coronary Primary Prevention Trial results: I. reduction in incidence of coronary heart disease. JAMA 1984; 251:351–364.
30. Buchwald H. The effect of ileal bypass on atherosclerosis and hypercholesterolemia in the rabbit. Surgery 1965; 58:22–36.
31. Scott HW Jr, Stephenson SE Jr, Younger R, et al. Prevention of experimental atherosclerosis by ileal bypass: 20 per cent cholesterol diet and I^{131} induced hypothyroidism in dogs. Ann Surg 1966; 163:795–807.
32. Scott HW Jr, Stephenson SE Jr, Hayes CW, Younger RK. Effects of bypass of the distal fourth of small intestine on experimental hypercholesterolemia and atherosclerosis in rhesus monkeys. Surg Gynecol Obstet 1967; 125:3–12.
33. Moore RB, Frantz ID Jr, Buchwald H. Changes in cholesterol pool size, turnover rate, and fecal bile acid and sterol excretion after partial ileal bypass in hypercholesterolemic patients. Surgery 1969; 65:98–108.
34. Buchwald H, Moore RB, Varco RL. Surgical treatment of hyperlipidemia. Circulation 1974; 49(Suppl I):I1–I37.
35. Campos CT, Matts JP, Fitch LL, et al. Lipoprotein modification achieved by partial ileal bypass: five-year results of the Program on the Surgical Control of the Hyperlipidemias. Surgery 1987; 102:424–432.
36. Campos CT, Matts JP, Santilli SM, et al. Predictors of total and LDL cholesterol change following partial ileal bypass. Am J Surg 1988; 155:138–146.
37. Campos CT, Matts JP, Fitch LL, et al. Modification of plasma lipoproteins following partial ileal bypass. Five-year results of the Program on the Surgical Control of the Hyperlipidemias. *In* Crepaldi G, Gotto AM, Manzato E, Baggio G, eds. Atherosclerosis VIII: Proceedings of the 8th international symposium on atherosclerosis. Amsterdam: Elsevier Science Publishers, 1989, pp 769–774.
38. Buchwald H, Moore RB, Varco RL. Ten years clinical experience with partial ileal bypass in management of the hyperlipidemias. Ann Surg 1974; 180:384–392.
39. Beil U, Crouse JR, Einarsson K, Grundy SM. Effects of interruption of the enterohepatic circulation of bile acids on the transport of very low density lipoprotein triglycerides. Metabolism 1982; 31: 438–444.
40. Buchwald H. Vitamin B_{12} absorption deficiency following bypass of the ileum. Am J Dig Dis 1964; 9:755–759.
41. Schwartz MZ, Varco RL, Buchwald H. Liver function and morphology following distal ileal excision in the rabbit. Surg Forum 1971; 22:355–356.
42. Clayman RV, Buchwald H, Varco RL, et al. Urolithiasis in patients with a jejunoileal bypass. Surg Gynecol Obstet 1978; 147:225–230.
43. Cornfield J. Joint dependence of risk of coronary heart disease on serum cholesterol and systolic blood pressure. A discriminant function analysis. Fed Proc 1962; 21(Suppl 2):58–61.
44. Canner PL, Berge KG, Wenger NK, et al. Fifteen year mortality in Coronary Drug Project patients: long-term benefit with niacin. J Am Coll Cardiol 1986; 8:1245–1255.

Discussion

DR. ROGER GREENHALGH (London, England): This historical work we have heard from Dr. Buchwald is most courageous.

These patients were recruited during 1963 to 1968. It is well to recall the prevailing thought at the time. The aim was to lower cholesterol by a large amount and thus to bring about benefit in terms of arterial disease.

It was in the 1960s when the four major primary prevention studies for coronary artery disease were performed, and they showed collectively benefit from reduction of lipid levels in terms of development of the first cardiac event. In other words, for primary prevention there was benefit.

It was not until 1967 that Frederickson from the National Institutes of Health classified lipoproteins, and in 1969 Levy and Frederickson described the first controlled trial on angiographically documented coronary artery disease patients. They stressed the importance of the then so-called type II lipoprotein abnormality later referred to as type IIA.

In 1971, with Mr. Peter Martin and Dr. Barry Lewis, I described the first controlled trial of angiographically documented peripheral arterial disease patients in terms of banking serum lipid and lipoprotein levels.

It seemed at that time, 20 years ago, that it would only be a matter of time before the proof would be demonstrated of the value of the lipid lowering in terms of benefit for our vascular patients. But then one or two pieces of bad news followed.

The Coronary Drug Project showed negative results in many of the treatment groups. Then bad results were reported with atromids clofibromate. We knew this lowered fibrinogen and cholesterol and triglyceride, but the drug was discredited and withdrawn. Then in my own work in 1980 I was distressed to have to reveal that the lipid lowering conferred no benefit after arterial reconstruction whatsoever, but smoking was a factor that was of great importance.

More recently, in 1989 and 1990 from the femoropopliteal bypass study, a multicenter trial in the United Kingdom, we discovered that, for vein and prosthetic bypass, there was failure to demonstrate any relationship of cholesterol or triglyceride to outcome. The big factors were smoking and fibrinogen.

Therefore, back to the 1960s and the primary prevention situation and back to this paper, I wonder from these data, which are so valuable and have such an important place in history, whether the authors can give us any comfort that patients have had benefit from the primary prevention point of view, because we rather regret that from the secondary prevention point of view, lipid lowering at a rather late stage of the disease may have limited benefit.

DR. H. WILLIAM SCOTT, JR. (Nashville, Tennessee): In the early 1960s with Sam Stevenson and the help and strength of a large number of