Partial Ileal Bypass in the Treatment of Hypercholesterolemia

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Partial ileal bypass is a surgical method of lowering circulating cholesterol levels. This article outlines the history of the partial ileal bypass operation and compares the efficacy, durability, compliance, safety, and cost of this operation with currently available diet and drug therapy for hypercholesterolemia. Partial ileal bypass patients have been followed for up to 26 years, and the procedure is employed currently throughout the United States and Europe. Partial ileal bypass has moved beyond the research stage and can be performed in community hospitals by competent general surgeons.

Key words: Partial ileal bypass; hypercholesterolemia; cholesterol, dietary; drug therapy; atherosclerosis.

History and Technique

The PIB procedure was introduced clinically for the management of hypercholesterolemia at the University of Minnesota in 1963. The metabolic basis for PIB consists of: (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. Radioisotope studies in hypercholesterolemic patients who have undergone PIB have confirmed these mechanisms.

Since the clinical introduction of PIB, more than 600 procedures have been performed at the University of Minnesota and at other centers. Over 55 papers on the clinical use of PIB have been published by authors other than the Minnesota group. It is erroneous to consider this operation a new or an experimental procedure; PIB has been in clinical use for nearly 30 years, and its results have been well documented in the peer-reviewed scientific literature. Partial ileal bypass has, in fact, been evaluated far more extensively, and for a longer time, than any pharmacologic hypocholesterolemic agent.

The partial ileal bypass operative technique has been previously described and is depicted in Figure 1. Before the operation, intestinal preparation is begun, at least overnight, with a clear liquid diet, nonabsorbable oral antibiotics, and cathartics. Cleansing enemas are not used. After administration of an intravenous antibiotic (usually a second-generation cephalosporin) and skin preparation with a povidone-iodine solution, the abdo-
Partial Ileal Bypass

Program on the Surgical Control of the Hyperlipidemias

The Program on the Surgical Control of the Hyperlipidemias (POSCH) was a randomized clinical trial designed to test whether cholesterol lowering induced by the PIB operation would affect the prognosis of postmyocardial infarction patients. The study population consisted of 838 patients (417 in the control group and 421 in the surgery group), both men (90.7%) and women, with an average age of 51 years, who had survived a single myocardial infarction. The mean follow-up period was 9.7 years.

In POSCH, the diet-plus-PIB intervention group, in comparison with the diet-only control group, attained a 23.3% lower total plasma cholesterol level \( (P < .0001) \), a 37.7% lower low-density lipoprotein (LDL) cholesterol level \( (P < .0001) \), a 4.3% higher high-density lipoprotein (HDL) cholesterol level \( (P = .02) \), reduced concentration of the atherogenic apolipoprotein B-100 \( (P < .0001) \), and higher levels of the protective HDL2 subfraction \( (P < .0001) \) and apolipoprotein A-1 \( (P < .0001) \) after 5 years of follow-up. The triglyceride level was 19.8% higher \( (P = .003) \), and the very low-density lipoprotein cholesterol level was 18.3% higher \( (P = .02) \) in the surgery group. These overall favorable lipid modifications were associated with significant reductions in the following: overall mortality (36%) in the subgroup.
of PIB patients with a normal (≥50%) left ventricular ejection fraction (P = .021); death from atherosclerotic coronary heart disease or confirmed nonfatal myocardial infarction (35%, P < .001); clinical peripheral vascular disease (27%, P = .038); and the incidence of postrandomization coronary artery bypass surgery or percutaneous transluminal coronary angioplasty (61%, P < .0001). Associated with these clinical findings was an overwhelming demonstration of decreased progression (P < .001) of atherosclerotic lesions on the accompanying coronary arteriograms performed at baseline and 3, 5, 7, and 10 years after randomization, as well as increased regression of existing lesions on the 5-year and 7-year arteriograms (P < .01). Overall mortality and mortality due to coronary heart disease showed a trend toward reduction that did not achieve statistical significance during the formal trial tenure (overall deaths, control vs surgery, 62 vs 49, P = .164; deaths due to coronary disease, control vs surgery, 44 vs 32, P = .133).

Efficacy of Partial Ileal Bypass

How effective is PIB in comparison with diet or drug intervention? The findings from international epidemiologic analyses support the conclusion that certain diets (eg, the Mediterranean diet), initiated early in life, can result in a low mean total plasma cholesterol level in a population.12 What, however, can be achieved if dietary therapy is undertaken in adult life? If we limit discussion to the dietary results from randomized controlled clinical trials, the Oslo Diet Heart Study achieved a net 14% decrease in total plasma cholesterol,13 the Veterans Administration Unsaturated Fat Study showed a net total plasma cholesterol reduction of 13%,14 the British Corn Oil Study yielded no significant change in the cholesterol concentration,15 the British Research Committee Soya-Bean Oil Study demonstrated a 12% difference in the total plasma cholesterol level between groups,16 the British Research Committee of London Diet Study reported a 9% difference between the diet-treated and the control group,17 the Minnesota Coronary Survey had a mean 13% difference between groups,18 and the Multiple Risk Factor Intervention Trial (MRFIT), the most ambitious of all diet-intervention studies, achieved only a 2% greater reduction in total plasma cholesterol in the intervention group compared with the control group.19 Apart from the failure of all of these trials to demonstrate a significant impact of dietary therapy on atherosclerosis incidence or progression, none of these diet-intervention studies is overly encouraging with regard to the efficacy of dietary therapy in reducing elevated cholesterol levels.

Randomized controlled trials employing hypocholesterolemic drugs have been no more rewarding, until the findings from trials employing multidrug regimens are considered. In the Scottish Physicians Clofibrate Study, the total plasma cholesterol reduction was 16%.20 In the Newcastle Upon Tyne Clofibrate Study, the net total plasma cholesterol reduction was 9%.21 The net reduction of total plasma cholesterol was 6.5% in the clofibrate group and 9.9% in the nicotinic acid group in the Coronary Drug Project.22 In the European Cooperative Clofibrate Study, the average total plasma cholesterol reduction was 9%.23 In the Upjohn Colestipol Hydrochloride Study, the mean difference in the total plasma cholesterol concentration between groups was 7%.24 In the National Heart, Lung, and Blood Institute (NHLBI) Type II Coronary Intervention Study, there was a 16% net reduction in the total plasma cholesterol level induced by cholestyramine.25 In the Lipid Research Clinics—Coronary Primary Prevention Trial (LRC-CPPT), the net total plasma cholesterol concentration difference between the cholestyramine group and the control group was only 8.5%.26 In the Helsinki Heart Study, the overall total plasma cholesterol reduction in the gemfibrozil group was limited to 9%.27

With the use of double-drug therapy, greater total plasma cholesterol lowering has been achieved. In the Cholesterol Lowering Atherosclerosis Study, which employed a combination of colestipol and nicotinic acid, the net reduction of total plasma cholesterol for the intervention group was 22%.28 The recently reported Familial Atherosclerosis Treatment Study used two double-drug treatment arms: lovastatin with colestipol, and niacin with colestipol.29 The net reduction in total plasma cholesterol in the lovastatin-coles­tipol group was 28%, with an accompanying LDL cholesterol lowering of 34%. In the niacin-colestipol group, the net reduction in total plasma cholesterol was 17%, with an LDL cholesterol reduction of 20%. Finally, a recent study reported by Kane and associates showed a net 22% reduction in the total plasma cholesterol level and a 29% lowering of the LDL-cholesterol level with triple-drug therapy employing colestipol, niacin, and lovastatin.30

The randomized controlled clinical trial data from POSCH clearly demonstrate that PIB, as a single intervention modality, is as effective as, or even more effective than, double- or triple-drug regimens. In combination with a cholesterol synthesis inhibitor, PIB should induce an even greater total plasma cholesterol reduction than PIB therapy alone. The relative efficacy of dietary, pharmacologic, and surgical therapy, as determined by randomized controlled clinical trials, is summarized in Table 1.
Table 1. Relative Efficacy of Therapy for Hypercholesterolemia: Randomized Clinical Trial Data

<table>
<thead>
<tr>
<th>Therapy/Clinical Trial</th>
<th>Net Reduction (%)*</th>
<th>Cholesterol</th>
<th>LDL-Cholesterol</th>
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<tbody>
<tr>
<td><strong>Dietary</strong></td>
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<tr>
<td>Oslo Diet Heart Study</td>
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<tr>
<td>VA Unsaturated Fat Study</td>
<td>13</td>
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<tr>
<td>British Corn Oil Study</td>
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<tr>
<td>British Research Committee Soya-Bean Oil Study</td>
<td>12</td>
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<tr>
<td>British Research Committee of London Diet Study</td>
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<tr>
<td>Minnesota Coronary Survey</td>
<td>13</td>
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<tr>
<td>Multiple Risk Factor Intervention Trial</td>
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<tr>
<td><strong>Pharmacologic</strong></td>
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<tr>
<td>Scottish Physicians Clofibrate Study</td>
<td>16</td>
<td></td>
<td>21</td>
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<tr>
<td>Newcastle Upon Tyne Clofibrate Study</td>
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<tr>
<td>Coronary Drug Project (clofibrate)</td>
<td>7</td>
<td></td>
<td>10</td>
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<tr>
<td>Coronary Drug Project (nicotinic acid)</td>
<td>10</td>
<td></td>
<td>10</td>
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<tr>
<td>European Cooperative Clofibrate Study</td>
<td>9</td>
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<tr>
<td>Upjohn Colestipol Hydrochloride Study</td>
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<td>7</td>
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<tr>
<td>NHLBI Type II Coronary Intervention Study (cholestyramine)</td>
<td>16</td>
<td></td>
<td>21</td>
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<tr>
<td>Lipid Research Clinics—Coronary Primary Prevention Trial (cholestyramine)</td>
<td>9</td>
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<td>13</td>
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<tr>
<td>Helsinki Heart Study (gemfibrozil)</td>
<td>9</td>
<td></td>
<td>9</td>
</tr>
<tr>
<td>Cholesterol Lowering Atherosclerosis Study (cholesteryl and nicotinic acid)</td>
<td>22</td>
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<td>38</td>
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<tr>
<td>Familial Atherosclerosis Treatment Study (lovastatin and colestipol)</td>
<td>28</td>
<td></td>
<td>34</td>
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<tr>
<td>Familial Atherosclerosis Treatment Study (nicotinic acid and colestipol)</td>
<td>17</td>
<td></td>
<td>20</td>
</tr>
<tr>
<td>Familial Hypercholesterolemia Combined Drug Regimen Study (cholesteryl, nicotinic acid and colestipol)</td>
<td>22</td>
<td></td>
<td>29</td>
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<tr>
<td><strong>Surgical</strong></td>
<td></td>
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<td></td>
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<tr>
<td>Program on the Surgical Control of the Hyperlipidemias (partial ileal bypass)</td>
<td>23</td>
<td></td>
<td>38</td>
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*Percent net reduction is the difference between the control group and the intervention group during the trial. When these data were not cited in the referenced article, the net percentage reduction was calculated according to the formula: 

\[
\text{Net Reduction} = \frac{\text{Placebo group cholesterol} - \text{intervention group cholesterol}}{\text{Placebo group cholesterol}} \times 100
\]

Durability

The medical literature is scant in the documentation of the long-term efficacy of dietary and drug hyperlipidemia management. Follow-up in the diet-intervention trials ranges from 2 to 8 years, and ranges from 2.5 to 7 years in the drug studies. Interestingly, in the Helsinki Heart Study, the numerical data in the published text reflect the hypolipidemic effects observed at less than 1 year; whereas the graph accompanying the text clearly shows a diminution of the cholesterol-lowering efficacy of gemfibrozil intervention over 5 years. Since compliance with drug therapy was essentially constant over this 5-year period, this difference may reflect a lack of drug-effect durability.

In contrast, PIB-induced lipid changes have been carefully evaluated for up to 26 years. In a recent report reviewing the findings in 57 patients who underwent PIB, the lipid changes induced by this procedure were shown to be sustained, essentially unchanged, for more than 20 years after the operation. There is no dietary therapy or pharmacologic agent for which there are durability data comparable to the long-term results achieved with PIB.

Compliance

Compliance with dietary and drug therapy over the long term, ie, 5 years or longer, has been uniformly poor. In the Coronary Drug Project, maximum dose adherence at 5 years for clofibrate was 77.1%; for nicotinic acid, 66.3%; and even for placebo, 77.8%. The NHLBI Type II Coronary Intervention Study reported 73.7% adherence to the placebo and 79.7% adherence to cholestyramine at 5 years. In the LRC-CPPT, compliance was expressed as the mean number of packets of cholestyramine or placebo taken daily out of the six packets prescribed. At 1 year, these values were 4.2 for cholestyramine and 4.9 for placebo; at 7 years, they were 3.8 and 4.6, respectively. During each of the 5 years of follow-up in the Helsinki Heart Study, adherence to gemfibrozil was 85%, 85%, 84%, 84%, and 82%, respectively, and adherence to placebo was 85%, 86%, 86%, 86%, and 83%, respectively. Partial ileal bypass therapy is obligatory, as long as the operation is not reversed. In the POSCH study, 94% of patients undergoing the operation had not had a reversal after an average of 9.7 years. The compliance experience in several randomized, controlled clinical trials is summarized in Table 2.
Table 2. Compliance with Therapy for Hypercholesterolemia: Randomized Clinical Trial Data

<table>
<thead>
<tr>
<th>Clinical Trial/Therapy</th>
<th>Compliance (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coronary Drug Project22</td>
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</tr>
<tr>
<td>Clofibrate</td>
<td>77.1</td>
</tr>
<tr>
<td>Nicotinic acid</td>
<td>66.3</td>
</tr>
<tr>
<td>Placebo</td>
<td>77.8</td>
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<tr>
<td>NHLBI Type II Coronary Intervention Study25</td>
<td></td>
</tr>
<tr>
<td>Cholestyramine</td>
<td>79.7</td>
</tr>
<tr>
<td>Placebo</td>
<td>73.7</td>
</tr>
<tr>
<td>Lipid Research Clinics–Coronary Primary Prevention Trial26</td>
<td></td>
</tr>
<tr>
<td>Cholestyramine</td>
<td>63.3</td>
</tr>
<tr>
<td>Placebo</td>
<td>76.7</td>
</tr>
<tr>
<td>Helsinki Heart Study27</td>
<td></td>
</tr>
<tr>
<td>Gemfibrozil</td>
<td>82.0</td>
</tr>
<tr>
<td>Placebo</td>
<td>83.0</td>
</tr>
<tr>
<td>Program on Surgical Control of the Hyperlipidemias1</td>
<td></td>
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<tr>
<td>Partial Ileal Bypass</td>
<td>94.0</td>
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</tbody>
</table>

Safety

The side effects and complications of PIB have been more thoroughly documented than those of any pharmacologic agent prescribed for lipid modification. In recent publications, the side effects and complications of PIB are fully outlined for up to 14.8 and 26 years.1,11

In POSCH, there were no immediate in-hospital deaths after PIB. The 30-day mortality after surgery was limited to two deaths: one caused by an atherosclerotic coronary heart disease event, and the other secondary to complications of a postoperative bowel obstruction. The only other death attributable to PIB in POSCH patients was from intra-abdominal sepsis after reversal of the operation.

Wound infections, pneumonia, pulmonary emboli, or other serious postoperative complications requiring hospitalization for more than 1 week have occurred in only 2% of patients. All patients are discharged on parenteral vitamin B12 supplementation; no case of clinically evident vitamin B12 deficiency following PIB has been reported. It is essential to differentiate the PIB operation from the far more extensive jejunoileal bypass procedure formerly employed for the treatment of morbid obesity.31 No significant changes in serum electrolytes follow PIB, nor have nutrient malabsorption or hepatic changes been reported.

The principal side effect of PIB is diarrhea. At each POSCH follow-up visit, the surgery group patients reported an average of more than three bowel movements per day; however, this increase in stool frequency was well tolerated by nearly all of the patients. In addition to more frequent bowel movements, the PIB patients had stools of looser consistency. Excessive, foul-smelling flatus and a gas-bloat syndrome are occasionally encountered after PIB. These symptoms generally respond to oral metronidazole therapy.

The POSCH trial clearly demonstrated that kidney stone and gallstone formation were consequences of PIB therapy. The incidence rate of kidney stones was approximately 4% per year in the surgery group, compared with approximately 0.7% per year in the control group. The difference between groups in the 5-year rate of gallstone formation was also significant (14 control group patients vs 54 surgery group patients). As expected with an intervention requiring a celiotomy, symptoms of bowel obstruction have occurred in the PIB population. In POSCH, 3.6% of the surgery group patients required operative intervention for the management of this complication.

The PIB operation is reversible. In POSCH, 23 patients underwent reversal of their bypass procedure between 2 and 11 years postoperatively. Seventeen bypasses were reversed because of diarrhea, three for nephrolithiasis, and one each for excessive weight loss, carcinoma of the cecum, and lymphoma of the small bowel. The overall and gastrointestinal malignancy rates were similar between the control and the surgery groups. There was a 5 kg (11 lb) weight loss attributable to PIB at 5 years in the POSCH trial.

The standard dietary guidelines for hyperlipidemia management appear to be safe. Certain excesses in the recommendations of specific food products may be detrimental, however, as illustrated by the increased incidence of colorectal cancer possibly associated with the ingestion of large amounts of polyunsaturated fatty acids.14 All of the lipid-modifying drugs are toxic to some degree. The principal pharmacologic agents currently available for the treatment of hypercholesterolemia include cholestyramine, colestipol, nicotinic acid, gemfibrozil, probucol, and lovastatin.

Cholestyramine and colestipol are bile acid sequestrants that are difficult to administer because of unpalatability, frequent side effects, and numerous drug interactions.32 The major side effects of these agents are gastrointestinal and include constipation, bloating, nausea, and flatulence. These resins bind concomitantly administered drugs such as digitalis, phenobarbital, thiazide diuretics, warfarin, thyroxine, tetracycline, and beta blockers, leading to unpredictable absorption of these drugs. Decreased absorption of fat-soluble vitamins and of folic acid has also been noted.

Nicotinic acid (niacin), in therapeutic doses, is infrequently tolerated over a prolonged period.33 Flushing and pruritis, the result of prostaglandin-mediated capillary dilation, occur within 1 hour of drug administration in 10% to
15% of patients. Elevations of liver function tests and gastritis have also been seen, requiring monitoring of liver function tests and contraindicating use of this agent in patients with a history of peptic ulcer disease. Other documented side effects include hyperpigmentation, impaired glucose tolerance, and hyperuricemia.

Gemfibrozil is associated with nausea, gastrointestinal discomfort, myositis, and impaired glucose tolerance. Gemfibrozil can also potentiate the anticoagulant effects of warfarin and increase biliary lithogenicity.

Probucol use has been associated with gastrointestinal symptoms including diarrhea, flatulence, abdominal pain, and nausea occurring in approximately 5% of patients. Probucol may prolong the Q-T interval and should not be used in patients with electrocardiographic evidence of ventricular irritability, in patients with a prolonged Q-T interval, or in patients taking medications that might also prolong the Q-T interval. This particular agent not only lowers the LDL cholesterol level but also lowers the HDL cholesterol level by approximately 20% to 25%. This latter effect raises concern, as HDL cholesterol appears to be protective against atherosclerosis.

Lovastatin is a member of a newly developed class of competitive inhibitors of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase, the enzyme controlling the rate-limiting step in cholesterol biosynthesis. Lovastatin received approval from the Food and Drug Administration in August 1987, and by 1988 was the most frequently prescribed cholesterol-lowering drug in the United States. Reported side effects of lovastatin include changes in bowel function, headaches, nausea, fatigue, insomnia, and skin rashes. Approximately 2% to 3% of patients develop increases in hepatic transaminase levels that require discontinuation of this agent. Careful monitoring of liver function is recommended. Myositis of uncertain etiology, with greatly elevated creatinine phosphokinase and potassium levels, has been encountered. Rhabdomyolysis leading to acute renal failure has occurred in patients treated with lovastatin in combination with immunosuppressive therapy after cardiac transplantation and in patients treated with a combination of lovastatin and gemfibrozil.

Cost

The cost of therapy is of increasing concern to insurers, to physicians, and, certainly, to patients. Hypocholesterolemic diet management would seem to pose little or no financial burden. The same is not true for the pharmacologic management of hypercholesterolemia. The immediate cost of the PIB operation and the average 7 days of required hospitalization is still far greater than the initial cost of any drug therapy. However, how does drug therapy over 5, 10, or 20 years compare with the cost of surgery? If the treatment of hypercholesterolemia is successful, the time-span for this form of therapy can be expected to exceed one or more decades.

In Table 3, the current retail costs of a daily regimen of 40 mg and 80 mg of lovastatin (the most effective hypocholesterolemic drug available today) are compared with the cost of PIB. The PIB cost is based on the average expenses incurred by a PIB patient at the University of Minnesota Hospital and Clinic. When these costs are projected for 5, 10, and 20 years, several interesting comparisons become evident. After the first year, PIB costs 8.93 and 4.46 times the cost of 40 mg and 80 mg of lovastatin, respectively. By 5 years, however, the cost of PIB is only approximately twice that of 40 mg of lovastatin daily and about the same as 80 mg of lovastatin daily. By 10 years, PIB costs less than either dose of lovastatin. Over 20 years, the cumulative cost of 40 mg of lovastatin daily is $25,500, and 80 mg of lovastatin daily is $51,000. In comparison, the cost of PIB is $11,393. These numbers are simplistic and do not take into account follow-up costs, which can be assumed to be identical for nonsurgical and surgical therapy, and the cost of the management of complications, which will be higher for PIB therapy. At the same time, if these numbers were projected for the cost per mg/dL reduction of total plasma cholesterol or LDL cholesterol, the cost-effectiveness of PIB would be even more dominant over time.

Clinical Role

This appraisal does not deviate from the established principle that diet is the primary lipid intervention modality, even though dietary therapy, as demonstrated in randomized controlled clinical trials, often lacks efficacy and is associated with poor long-term compliance. Furthermore, this review of lipid-lowering therapies follows orthodox guidelines and recommends pharmacologic intervention when dietary treatment fails. What this analysis advocates is that surgical management by PIB is indicated either after failure of drugs or, occasionally, in lieu of drugs. Drug failure, as a precedent for the em-
employment of PIB, should be reasonably defined, and not allow for the procrastination of changing from drug to drug, from dose to dose, and from drug combination to drug combination. At the same time, young patients with severe hyperlipidemia who have good cardiac function merit consideration for early operative intervention, without the prerequisite of having failed pharmacologic therapy.

A balanced examination of the available trial and other well-documented patient series would allow for the increased use of PIB in clinical practice. The procedure appears to be effective in acquired hypercholesterolemia and in most forms of familial hypercholesterolemia. Patients with overt atherosclerotic cardiovascular disease warrant consideration for PIB if, after nonoperative therapy, their total plasma cholesterol level is over 220 mg/dL, or their total plasma cholesterol level is between 200 and 219 mg/dL and their LDL-cholesterol level is greater than 140 mg/dL. For patients with no clinical evidence of atherosclerotic cardiovascular disease, a total plasma cholesterol level after nonoperative management greater than two standard deviations above the mean for age and sex may be a reasonable level at which to consider operative intervention. The operation may well be warranted in the adolescent and pediatric population. Age over 65 years, the presence of end-stage cardiac disease, or evidence of other imminent life-threatening problems are contraindications for PIB.

Certainly, PIB has now moved beyond the research stage and can be performed in community hospitals by competent general surgeons. The resources and techniques required for the preoperative evaluation, operative procedure, and postoperative follow-up of patients undergoing PIB are well within the scope of the community hospital and the primary care physician and surgeon. The operative technique is uncomplicated and is based on fundamental principles of gastrointestinal surgery. Although a large published series reporting the outcome of hypercholesterolemic patients treated by PIB in the community setting is not available, over 600 partial ileal bypass procedures have been performed at the University of Minnesota and elsewhere, and the results obtained in the United States and worldwide since the introduction of this procedure in 1963 have been very positive.

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