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RESEARCH FORUM

The Development of the Subtotal Ileal Bypass Operation
as a Therapeutic Approach to Hypercholesterolemia
and Atherosclerosis: A Review*

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The association of atherosclerosis with circulating blood lipids and with cholesterol in particular, has been fairly widely accepted after the epidemiologic and experimental work of the last few decades. Most physicians who deal with the manifestations of atherosclerosis today measure the serum cholesterol, and if it is elevated, they advise their patients of means of reducing the circulating lipids. Cholesterol reduction by drugs has at present proved to be either ineffectual or dangerous. Dietary regulation, in particular a reduction of saturated fat intake, has been able to lower circulating cholesterol to some degree, but is often not at all or only negligibly successful in patients with extremely high blood levels—the very persons for whom maximum therapeutic endeavor is indicated. This paper reviews the development of surgical means that have proved successful in markedly lowering circulating cholesterol and other lipid fractions and which may show some early promise of being beneficial in the treatment of atherosclerosis.

Jankau,1 in 1892, first demonstrated that cholesterol is absorbed in the intestinal tract. Mueller,2 in 1914, showed that absorbed cholesterol is transported by the lymphatics and enters the circulation via the thoracic duct. There have since been numerous papers elucidating the factors influencing cholesterol absorption, i.e., bile salts, pancreatic secretions, dietary cholesterol intake, saturation status and volume of accompanying fatty acids, etc.2** There has been, however, only a minimal amount of work published on the localization of cholesterol absorption and excretion and the relationship of transit time and cholesterol absorption.

Since the early work of Chevreul,3 in 1824, we know that cholesterol is secreted in the bile. Papers of Sperry4 and of Shoeneheimer and Sperry5 showed that cholesterol can be directly secreted into the intestinal lumen through the intestinal wall as well. Siperstein, Hernandez and Chaikoff5 gave evidence of an enterohepatic cycle, comparable to, though not as efficient as, the enterohepatic bile salt cycle. Localization of the site of reabsorption of this endogenous cholesterol and the ingested exogenous cholesterol (both handled in an identical fashion by the body) has been approached in only two publications, prior to the work presented herein. In 1926, Yama- kawa and associates6 presented data showing cholesterol is not absorbed in the large
bowel. Byers, Friedman and Gunning concluded that, in rats, cholesterol absorption takes place in the small intestine and not in the colon, and that the more distant the segment from the pylorus, the greater the absorption with maximum absorption in the distal ileum. The animal preparations used were all acute, with maximal survival time of 24 hours.

We have attempted to determine in a chronic animal preparation the site of cholesterol absorption and the effect of transit time on cholesterol absorption. Bypass of the ileum in the rabbit was seen to result in maximum cholesterol absorption reduction and concomitant lowering of blood cholesterol levels. This finding was then tested in the pig and in an indirect retrospective study in man. When the rabbit findings were substantiated, we embarked, in May of 1963, on our clinical trial of ileal bypass specifically as a therapeutic effort in patients with hypercholesterolemia and atherosclerosis. The effect of the sustained marked lowering of cholesterol levels in experimental animals and in our human patients has been and is being evaluated. The proposed rationale of this approach is to provide a direct drain on the body cholesterol pool by fecal excretion of normally absorbed and reabsorbed cholesterol. If ileal bypass reduces bile reabsorption as well, an indirect or metabolic drain on the cholesterol pool is also established, since bile salts can only be synthesized from hepatic cholesterol.

The site of cholesterol absorption and the effect of transit time on cholesterol absorption

The first series of experiments involved the study of the site of cholesterol absorption and the effect of transit time thereon in a physiologically intact chronic rabbit preparation. The effect of ileocecal valve destruction, bypass of the upper half of the small intestine, or bypass of the lower half of the small bowel, on circulating cholesterol levels was determined as well. Four experimental groups of ten rabbits each were compared: (1) normal controls, (2) animals which had undergone ileocecal valvuloplasty, only, (3) rabbits subsequent to upper small intestinal bypass and ileocecal valvuloplasty, and (4) rabbits with lower small intestinal bypass (including the ileocecal valve, to insure equal transit time with group 3). The operated rabbits were included in their respective test group on the basis of full uncomplicated recovery from surgery and resumption of normal feeding pattern. They all regained their preoperative weight and the individual variation of weight among the rabbits in all four groups at the time of the feeding of labeled cholesterol was small but, nevertheless, corrected for.

Cholesterol absorption capacity was measured by six-day blood radioactivity levels subsequent to a standard force-fed test dose of cholesterol 4-C14, 10 mg, 0.4 μc/mg. The Abell method of saponification and extraction of cholesterol into petroleum ether, bp 30-60° C, was utilized throughout. Radioactivity was determined by a Packard automatic Tri-Carb liquid-scintillation spectrometer with 0.3 per cent 2,5-diphenyloxazole in toluene as the fluor. A modified Liebermann-Burchard reaction, with color intensity analysis in a Coleman junior spectrophotometer, was used to determine milligrams of cholesterol in the sample.

The ileocecal valvuloplasty rabbits had 21.3 per cent less cholesterol absorption than the control group (P=.098) and no reduction in whole blood cholesterol. The upper bowel bypass group had an 81.0 per cent reduction in absorption (P<.0005) and a 15.2 per cent lowering of whole blood cholesterol (P=.018). The lower bowel, or ileal, bypass group had an 86.1 per cent decrease in absorptive capacity (P<.0005) and 27.7 per cent reduction in whole blood cholesterol (P<.0005). Comparison of the upper and lower bypass groups to each other shows a difference in counts per minute per milliliter whole blood of 27.1 per cent (P=.148) and a difference in whole-blood cholesterol levels of 14.7 per cent (P=.031).
Analysis by combination of parameters, utilizing the P value of the difference in counts/min/ml and the P value of the difference in mg/100 ml cholesterol, yields on a "X^2" table a P value of .026 significance for the functional difference between the ileojejunal bypass and the lower ileal bypass groups.

The conclusions arrived at from these data are that the entire small intestine is capable of absorbing cholesterol, that bypass of either the upper or the lower half of the small intestine results in a marked reduction in the blood radioactivity subsequent to the oral test dose, and that there is a functional difference between the upper and the lower small intestinal bypass groups. Transit time in the small intestine appears to play a role in the amount of cholesterol absorbed. To achieve both marked lowering of cholesterol absorption and circulating cholesterol levels, the most efficacious surgical site of bypass of the small intestine is the ileum.

Verification of the ability of ileal bypass to reduce cholesterol absorption and lower circulating cholesterol levels in three different species

Three separate experiments, involving rabbits, pigs and human subjects, independently showed marked, statistically significant and apparently permanent lowering of cholesterol absorption and circulating cholesterol levels following distal ileal bypass. The rabbit data obtained were essentially identical to the results outlined above. Four of the animals were kept for follow-up study for up to two years. The greatly reduced absorptive capacity remained unchanged, showing failure of the remaining bowel to assume the absorptive role of the ileum in regard to cholesterol. The blood cholesterol levels remained depressed as well, demonstrating lack of an effective compensatory synthesis mechanism in the rabbit.

The procedure and results in the pigs were comparable, with the exception that the eight animals employed were used as their own controls. That is, blood levels and absorptive capacity were tested with labeled cholesterol before and after bypass in the same animal. Weight correction factors were employed to correct for the weight gain of these growing animals.

The seven human study patients had had ileal resection for causes other than carcinoma. They were age and sex-matched with physiologically normal, mentally retarded patients at a state hospital. All subjects in both groups received identical doses of oral C-14 labeled cholesterol (50 mg, 0.2 µc/mg) and subsequently had their plasma level of radioactivity and plasma cholesterol levels compared. The control group's average plasma cholesterol was 183 mg per cent (low for subjects on a standard American diet), that of the operated group 136 mg per cent. By combination of parameters analysis, the significant value of P=0.01 is obtained when the absorptive and plasma levels of the two groups are compared. Several years have elapsed since most of the patients in the study test group had ileal surgery. The maintenance of circulating cholesterol at levels that must be regarded as far below the accepted normal values would seem to indicate an absence of a compensatory body response (absorptive or synthetic).

Initiation of a therapeutic trial of ileal bypass in patients with hypercholesterolemia and atherosclerosis

On the basis of the above information, in May, 1963, in association with Dr. Richard L. Varco, an experimental therapeutic program of subtotal ileal bypass in patients with hypercholesterolemia and atherosclerosis was started. Twenty-seven patients to date have had this operation at the University of Minnesota Hospitals. Patients have been selected for operation on the basis of severity of hypercholesterolemia, clinical evidence of atherosclerosis and a family history of early and severe atherosclerotic disease. We have not accepted patients over the age of 60 and prefer those in their 30's and 40's. At least three months before the operation, the patient is given a moderately stringent low saturated-fat, low-
cholesterol diet. His average plasma cholesterol at the end of this period is used as the preoperative baseline to which postoperative values are compared. After operation, the patient remains on the same diet.

The entire small intestine is measured along the mesenteric border with a piece of calibrated tape. The usual intestinal length is about 500-600 cm from the ileocecal valve to the ligament of Treitz. The bowel is transected 200 cm from the ileocecal valve or one-third the length of the small bowel, whichever is larger. The upper segment of small intestine is anastomosed end-to-side to the cecum and the lower bowel closed by inversion. The cecum has been selected as the site for re-establishing continuity in order to retain as much of the colonic water absorbing surface as possible. The closed end of the bypassed segment is tacked down to prevent intussusception and the mesenteric defect is closed.

Cholesterol absorption has been determined after feeding five grams of butter containing 50 mg of cholesterol-4-C-14 (specific activity 0.2 μc/mg). Plasma cholesterol radioactivity (CPM/ml) was measured during the next four days. The average four-day values obtained before ileal bypass and about three months after surgery were compared. An average plasma cholesterol value (mg %) for the five-day absorption test period was taken as the preoperative baseline value and compared to the five-day plasma cholesterol average three months after surgery.

In addition to routine chemical data obtained before and after surgery, the following tests have been reported periodically and compared to the preoperative baseline evaluation: lipid profiles (total lipids, triglycerides, phospholipids and cholesterol), blood sugars, serum electrolytes, serum proteins, electrocardiograms, vectorcardiograms, double Master’s exercise tolerance tests and femoral and iliac arteriograms. Recently we have started routinely to employ selective coronary angiography as a means of atherosclerotic plaque evaluation.

Comparison of cholesterol absorption curves before and after surgery shows a reduction of cholesterol absorption capacity that averages 60 per cent (range 37 per cent-95 per cent). An average reduction of 40 per cent from the preoperative plasma cholesterol baseline, determined only after at least three months on a low saturated-fat, low-cholesterol diet, has been achieved. The average preoperative post-diet plasma cholesterol has been over 300 mg per cent; the average postoperative cholesterol about 200 mg per cent. Approximately 60 per cent of the operated patients have cholesterol levels below 200 mg per cent. The ileal bypass operation has not been associated with any significant weight loss or nutritive malabsorption with the exception of vitamin B₁₂, which subsequent to surgery is given parenterally.

The fall in total lipids, phospholipids and triglycerides is comparable to the cholesterol drop. Blood electrolytes, proteins, hemoglobin, etc., remain unchanged.

Clinical evaluation of the effect of this lowering on the atherosclerotic process has been characterized by uniform subjective lessening in anginal symptoms; objective evidence of xanthomata regression and apparent nonprogression of arterial disease as determined by coronary and femoral angiography. These findings are preliminary and will require much more substantiation.

The effect of ileal bypass on atherosclerosis and hypercholesterolemia in the rabbit

Concurrently with the clinical work, a long-term study on the effect of ileal bypass, prophylactically and therapeutically in rabbit atherosclerosis was begun in the laboratory. White New Zealand rabbits were divided into four groups: Group I (controls) fed standard rabbit pellets for four months; Group II was fed a 2 per cent cholesterol diet for four months; Group III was fed a 2 per cent cholesterol diet for four months subsequent to ileal
bypass surgery; and Group IV was subjected to ileal bypass after four months on the 2 per cent cholesterol diet and then continued on the diet and followed for periods over two years.

Group I rabbits exhibited no hypercholesterolemia or atherosclerosis. Group II animals had an average blood cholesterol level of 1,265 mg per cent and were severely atherosclerotic, as shown by a 50 per cent myocardial infarction rate. (Demonstration that atherosclerosis of coronary vessels to a degree severe enough to cause histologically true myocardial infarction in rabbits strictly on a dietary basis was first demonstrated in our laboratory.9) Group III rabbits retained cholesterol values below that of the controls and showed no evidence of atherosclerosis. Group IV animals, if permitted to survive six months or longer after a lowering in cholesterol levels, often to below 100 mg per cent, showed no progression of acute atherosclerosis. They evidenced regression of liver, spleen and kidney foam cell and cholesterol accumulations; and fibrosis of established intimal plaques, with a total aorta cholesterol content per residue weight 33.8 per cent lower than that of Group II, and possibly fewer plaques than at the height of their atherosclerosis.

Conclusions that can be reached from this experiment are: (a) ileal bypass will prevent hypercholesterolemia and atherosclerosis in rabbits on a severely atherogenic 2 per cent cholesterol diet for four months; (b) ileal bypass in rabbits with established hypercholesterolemia and atherosclerosis will reverse the hypercholesterolemia and organ cholesterol accumulations, despite continuation of the 2 per cent cholesterol diet; and (c) ileal bypass in rabbits will arrest the atherosclerotic process and may possibly, in time, partially reverse established atherosclerotic lesions.

DISCUSSION

In dealing with the subject of therapy for hypercholesterolemia and atherosclerosis, certain basic questions must be considered by the researcher in regard to his own efforts.

Is hypercholesterolemia dangerous? I shall make no effort herein to review the mountains of papers showing that it would appear to be. Skeptics will point out the patient with severe early atherosclerotic cardiovascular disease and a cholesterol level in the 100 mg per cent range, or the patriarch of a family with familial hypercholesterolemia who is alive and free of any of the manifestations of arterial disease in his 70's despite a serum cholesterol over 700 mg per cent. These patients are, however, the exceptions, and, in general, the average person with a relatively high circulating cholesterol level is more prone to develop atherosclerosis than is the average person with a relatively low circulating cholesterol level. We must also consider the fact that our American norms are probably higher than the ideal physiologic cholesterol level, as evidenced by the prevalence of atherosclerotic cardiovascular disease in this country. Also, there may be varying cholesterol tolerance levels in a population, and what for one person may be a "safe" cholesterol level may be for another etiologically atherogenic.

What means can be used to lower the circulating cholesterol (and other lipid modalities) and are these means worth the risks and inconveniences? A subtotal ileal bypass operation has been shown, by the data reviewed in this article, to cause a marked and sustained lowering of circulating cholesterol and the other blood lipids. To date we have had two acute myocardial infarcts in the immediate postoperative period in our patients. One ended fatally; the other patient made an uneventful recovery. This operative mortality between 4-5 per cent is perhaps brought into better focus when compared with the fact that three patients scheduled for bypass surgery, but still in the process of undergoing their preoperative baseline battery of tests succumbed to myocardial infarctions. Surgery, in the case of such high risk patients, requires not only the routine meas-
ures of quick efficient operation, avoidance of hypotension and hypoxia, etc., but also the use of possibly valuable adjuncts, e.g. intravenous dextran drip before, during, and after surgery.

Besides the pain, time loss and discomfort associated with an intra-abdominal procedure, there are two side effects of subtotal ileal bypass. The patients undergo a transient period of increased bowel activity, which after several months generally is autoregulated and our patients subsequently have one to three formed stools daily. The site of vitamin B₁₂ absorption is effectively bypassed by this operation and we have maintained our patients on parenteral supplements (1,000 µg every two to three months). With the exception of the desired impairment of lipid absorption capacity, there are no other known nutritive absorptive deficiencies. It should be stressed that this operation is not a weight losing procedure and should not be confused with the massive jejuno-ileal bypass employed for that purpose. Our patients regain and maintain their preoperative weights without difficulty.

Given a patient with an elevated cholesterol level, will sustained lowering of his circulating cholesterol be beneficial to him with respect to his atherosclerosis? This is a different question from the one considering a causal association of hypercholesterolemia and atherosclerosis. This question grants the association and asks if a modification of one abnormality will influence the progress of the other. It is possible to discuss this influence in terms of three different mechanisms: (1) retardation of a progressive disease once well initiated; (2) arrest of the further development of the disease with maintenance of the status quo, or, what is essentially the same effect further back in the time course, the prevention of the accumulation of arterial deposits; and, (3) actual reversal of established arterial plaques. As for our own results in regard to these criteria, we can say that in the rabbit subtotal ileal bypass retards, arrests, prevents and possibly reverses the plaque lesions of atherosclerosis. It is too early to draw any definitive conclusions from our human data.

**Summary**

This is a review paper giving the highlights of the development, in our laboratory and in the hospital, of subtotal ileal bypass surgery as a feasible therapeutic approach to the treatment of atherosclerosis in patients with hypercholesterolemia. Detailed data, with accompanying charts, graphs and pictures, can be found in the original publications referred to in the paper and listed in the reference section.

**Resumen**

El autor revisa los aspectos más salientes en el desarrollo, en el laboratorio y la clínica, de una operación de exclusión ilial subtotal, como medida terapéutica factible en el tratamiento de la arteriosclerosis en sujetos con hipercolesterinemia.

La información detallada con datos clínicos, gráficos e ilustraciones, puede ser obtenida en las publicaciones originales, a las que se hace referencia en el trabajo y que aparecen en la bibliografía del mismo.

**Résumé**

Revue des principaux points du développement, dans notre laboratoire et à l'Hôpital, de la chirurgie de dérivation sub-totales de l'intestin grêle, comme thérapeutique possible pour le traitement de l'athérosclérose chez le malade ayant une hypercholestérolémie. Le résultat détaillé, avec des figures, graphiques et illustrations, peuvent être trouvées dans les publications originales auxquelles l'article fait allusion, et citées dans la liste des références.

**Zusammenfassung**

Übersicht über die Hauptmerkmale der Entwicklung der subtotalen Kurzschluß-Operation im Bereich der Beckenarterien als ein möglicher therapeutischer Weg zur Behandlung der Arteriosklerose bei Patienten mit Hypercholesterinämie, wie er in unserem Laboratorium und im Krankenhaus entwickelt ist. Detaillierte Angaben zusammen mit graphischen Darstellungen, Tabellen und Bildern können in den Originalpublikationen eingesehen werden, auf die in dieser Mitteilung Bezug genommen ist und die im Literaturverzeichnis aufgenommen sind.

**References**

GIANI DIAPHRAGMATIC Hernia

A woman, age 49, is reported, in whom mass miniature radiography revealed hypertranslucency of the major part of the left lung: cystic lung was suspected. The patient was admitted to the Medical Academy Hospital in Krakow. Examinations, including barium meal ingestion, showed a giant diaphragmatic hernia. The stomach and a considerable part of the large intestine were situated in the left pleural space as high as the left clavicle. The patient had no complaints whatever while performing her every-day work as a charwoman.