Protection against atherogenesis with the polymer drag-reducing agent Separan AP-30

FERRUKH I. FARUQUI, MAUREEN D. OTTEN, B.S.C., AND PHILIP I. POLIMENI, PH.D.

ABSTRACT The inhibitory effect of Separan AP-30, an anionic polyacrylamide, on atherosclerotic plaque formation in aortas of rabbits on a high (2%) cholesterol diet was tested over a period extending from 37 to 170 days. Atherogenesis was quantified morphometrically by application of a computer-assisted image analysis of histologic cross sections of the aorta. The area of vessel wall–atheroma interface, fraction of lumen occluded, and other indexes of atherogenesis were measured in each of 26 segments of aorta excised from the animals, half of which were administered injections (intravenous) of Separan three times a week. Regression analysis of the morphometric data indicates that the polyelectrolyte exerts a powerful antiatherogenic effect in all regions of the aorta, inhibiting the formation of plaque mass to less than half in the aortic arch and about one-fifth in the descending aorta as compared with the aortic plaque masses in untreated rabbits. Results are compatible with the suggestion that a novel hemodynamic principle in vivo, polymer drag reduction, might be effectively applied against atherosclerosis.


The addition of certain linear macromolecules to flow can under certain conditions greatly reduce frictional resistance by polymer drag reduction, an effect also known among hydrodynamicists as the “Toms phenomenon.” Flow can thus be increased by threefold or more without alteration of the driving pressure.1–3 The effect occurs only in the presence of disturbed or turbulent flow, and it is associated with a laminarization of the flow. This phenomenon has also been observed in pipe blood flow with at least four different drag-reducing polymers,4–7 including the anionic polyacrylamide Separan AP-30.

Application of the polymer drag-reduction principle to blood flow in vivo was first attempted independently at two laboratories in the mid-1970s.5–11 In one of these laboratories, Mostardi et al.8 demonstrated with hot-film anemometry that poststenotic flow disturbances in the dog were diminished subsequent to intravenous injection of Separan AP-30. They postulated10 that it might be feasible to inhibit atherogenesis with drag-reducing polymers given the evidence that atheromas tend to form preferentially at vascular bifurcations, branches, and other regions of disturbed flow.12 Accordingly, aortas of rabbits on a high-cholesterol diet, some of which had been administered Separan AP-30, were examined and compared. Based on a visual and photographic inspection of the inner walls of aortas slit lengthwise, it was concluded that the Separan-treated animals were markedly less atherosclerotic than the untreated ones. Similar results were obtained in White Carneau pigeons fed an atherogenic diet.13

Despite the profound theoretical and therapeutic implications of Mostardi’s hypothesis and pictorial evidence, the experiments were never repeated and the report was virtually ignored. The specific objective of our research was to test the claimed antiatherogenic effects of Separan, applying a computer-assisted image analysis of the contours of histologic cross sections obtained from aortas of Separan-treated and untreated atherosclerotic rabbits. This study is part of our more general objective of testing the hypothesis that a hydrodynamic principle known to dampen flow disturbances

From the Departments of Physiology and of Pharmacology and Therapeutics, University of Manitoba Faculty of Medicine, Winnipeg, Manitoba, Canada.

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Address for correspondence: Dr. P. I. Polimeni, Department of Pharmacology and Therapeutics, University of Manitoba, Faculty of Medicine, 770 Bannatyne Avenue, Winnipeg, Manitoba, Canada R3E OW3.

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and turbulence is applicable against a pathologic process known to be associated with such unstable flows.

Materials and methods

Experimental protocol. Female New Zealand white rabbits were ranked for body weight and organized into weight-matched cohorts, each consisting of a control (n = 8, 2.736 ± 0.498 kg), a Separan-treated (n = 8, 2.681 ± 0.480 kg), and in most cohorts a normal (n = 6, 2.519 ± 0.812 kg) rabbit. The normal group received 100% commercial rabbit chow (ICN Biochemical Canada Ltd., Montreal, Quebec); both control and Separan-treated groups received the same diet containing in addition 2% cholesterol. Separan treatment consisted of the injection into the marginal ear vein of a 0.2% (weight/weight) Separan AP-30 (Dow Chemical Co., Midland, MI) solution three times a week. Treatment was initiated at the same time that the high-cholesterol diet was started. The volume injected was adjusted so that the dose would result in a blood polymer concentration of about 60 ppm. The rabbits were housed in individual cages with access to chow and water ad libitum. The criteria for killing a cohort were persistent weight loss or signs of illness in any member. This protocol of termination was adopted, instead of fixed intervals, to maximize plaque mass in each cohort while keeping the total number of “sick days” to a minimum. An animal was considered to be ill when it became obviously listless. In all cases termination was necessitated by the illness, or in two cases unexpected death, of the control cohort member; one control rabbit was excluded (see below).

Preparation of Separan solution. To prepare the Separan solution the polymer powder was dissolved in 0.9% NaCl solution by agitating for 2 or more days on a rotary (60 rpm) shaker. The polymer solution was dialyzed (Spectrapor 2, molecular weight cutoff at 12,000 to 14,000 daltons, Spectrum Medical Industries Inc., Los Angeles) exhaustively over a 5 day period against a solution containing 154 mM NaCl, 1 mM CaCl₂, and 10 mM HEPES buffer (solution adjusted to pH 7.8). According to the manufacturer the polymer molecular weight ranges approximately between 1·10⁶ and 5·10⁷ daltons, with the “average” weight estimated to be 4·10⁶ daltons. The average molar concentration of polymer injectate was thus calculated to be about 0.5 μM and it was further diluted in vivo to about 15 nm/liter of blood.

Excision and sampling of aorta. Each rabbit was anesthetized with 60 mg/kg sodium pentobarbital via a marginal ear vein. A combined midline thoracotomy and laparotomy exposed the heart; 8 ml blood was withdrawn from the right atrium into a heparinized syringe. The hematocrit was determined and the remaining blood was centrifuged at 600 g for 20 min, and plasma was removed and frozen at −20°C for later cholesterol and triglyceride analyses. The abdominal cavity was examined for the presence of ascites and for gross abnormalities of the liver and other organs. A medial lobe liver biopsy sample was taken for histologic examination after the lungs and viscera had been photographed in situ. The heart and aorta extending to the iliac bifurcation, with stubs of its major branches left attached for purposes of orientation, were dissected free and photographed. The aorta was then divided into 5 or 10 mm segments, as shown in figure 1.

Morphometric assessment of aortic atherosclerosis. Each aortic segment was cleansed of blood clots and immersion fixed in ice-cold 2% glutaraldehyde dissolved in 25 mM Na-cacodylate, 4.7 mM KCl, 2.5 mM CaCl₂, 2H₂O, and 0.8 mM MgCl₂ at pH 7.35. After 48 hr at 4°C the fixative was decanted, each tissue specimen was rinsed three times with the cacodylate vehicle adjusted with NaCl to maintain osmolality, dehydrated in graded ethanol solutions, and infiltrated overnight in vacuo at 23 ± 1°C in a glycol methacrylate solution catalyzed with benzoyl peroxide (PolySciences Inc.). Each sample was embedded in a catalyzed glycol methacrylate solution polymerized with polyethylene glycol 400 and N,N-dimethylaniline. Sections 2 μM thick from the anterior face of each segment were stained with Lee’s methylene blue–basic fuchsin, coded, and examined at 25-fold magnification with a Leitz-Wetzler microscope fitted with a drawing tube. The morphometric analysis of the aorta and its atherosclerotic lesions is described in some detail elsewhere, but a brief description of the protocol follows below.

The vessel wall and any plaques that were present were traced first on paper and then on a digitizing tablet. The image of the vessel, usually partially collapsed, in cross section, was transformed by a microcomputer program to a circular shape amenable to geometric analysis. The linear and areal variables, derived values, and both original and transformed images were recorded (figure 2). Derived values included the percentages of atherosclerotic plaque area covering the inner vessel wall and of luminal occlusion. With the use of geometric calibration figures with cross-sectional contours similar to those of atherosclerotic aortas to assess the accuracy of the computer analysis, the mean

![SEGMENTS:](image-url)

**FIGURE 1.** Dissection of rabbit aorta into regional subdivisions (triangular markers) and segments for histologic cross sections.
errors for the calculations of plaque-wall interface area and luminal occlusion obtained by five observers were estimated to be 5% and 13%, respectively, with 95% confidence limits.15 A primary consideration in this comparative study was to avoid psychological and operational biases with respect to the two major groups (Separan-treated and untreated rabbits on an atherogenic diet). This was mainly accomplished by double-blind coding of the more than 500 histologic slides and rearranging them in slide boxes randomly. The code was broken after all contours and morphometric data were on paper and only then were the data collated and assessed.

Statistical analysis. The specific statistical tests applied are described in the Results section. All values are expressed as the mean ± SD unless otherwise indicated. Changes or differences are considered to be statistically significant when p < .05.

Results

To assess comparability of dietary intake between the cholesterol-fed controls and Separan-treated animals, mean daily body weight gain and plasma cholesterol and triglyceride levels were determined. Plasma cholesterol levels (mmol/liter plasma) in the three groups just before death were as follows: normal, 3.3 ± 2.6; control, 30.9 ± 13.3; and Separan-treated, 24.0 ± 13.3. Applying a one-way analysis of variance (ANOVA) with Duncan’s new multiple-range (NMR) test and p < .05, a statistical difference was established between the normal values and the values from the two cholesterol groups, but there was no statistical difference between the control and Separan-treated groups. There also appeared to be no relationship between prolonged exposure to dietary cholesterol and plasma cholesterol concentration. Plasma triglyceride levels (mmol/liter plasma) were not significantly different among the three groups (normal, 0.68 ± 1.89; control, 1.54 ± 0.98; and Separan-treated, 2.21 ± 1.89). Hematocrits for the same groups were 41 ± 5, 34 ± 2, and 25 ± 1, respectively. The microvolumetric method used to measure hematocrit is not considered to be technically reliable for tests on blood obtained from atherosclerotic animals because of a poorly defined lipid phase in the hematocrit microtubes. However, the low hematocrit values obtained for rabbits on a high-cholesterol diet are comparable to those previously reported.10, 16

The mean daily weight gains of the high-cholesterol groups were not statistically different, but both groups gained less weight than rabbits on a normal diet (figure 3). The fact that the Separan group gained at least as much weight as the control group suggests that the polymer-treated animals ingested at least as much chow and cholesterol as their control partners. Although it was difficult to quantify, it was our impression that in the later stages of the experiment the Separan-treated animals appeared distinctly less lethargic than the control rabbits. Fatty infiltration of the liver did not seem to be diminished by Separan treatment. Both high-cholesterol groups became jaundiced, but the jaundice appeared to develop less rapidly in the Separan-treated group. One rabbit was excluded from the control (114 days) group because of strong evidence that it had become chronically ill and its food intake apparently had been markedly reduced over a 3 week period before termination. This evidence included loss of body weight (observed in only one other animal, which died), the lowest plasma cholesterol level found in any cholesterol-fed animal, and all organs nearly free of fat, which was in contrast to the case in all other animals in the control and Separan-treated groups.

After quantification of the atheromas in 26 segmental samples of each aorta, the data were organized to show the mean value obtained from n samples in each aortic subdivision: arch (n = 4), descending thoracic (n = 8), celiac (n = 4), renomesenteric (n = 4), and suprailiac (n = 6). No plaques were found anywhere
in the aortas of the rabbits on a conventional diet. Figure 4, A, shows a comparison of data on luminal occlusion in aortic subdivisions (%) from rabbits, matched for duration of diet, in the control and Separan-treated groups. In such a comparison the points would be expected to cluster along the identity line if the polymer had no effect on atherogenesis. In fact, 16 of 23 points fell below the line when the luminal occlusion was less than 20% and all 12 points fell below the line when occlusion was greater than 20%. This skewing suggests that Separan tended to inhibit atherogenesis in all subdivisions of the aorta. A plot of all data from the two groups, ranked for percent occlusion in each group and rank-paired, is shown in figure 4, B. Wilcoxon's signed-ranks test of the hypothesis that the occlusions in the two groups had the same mean ranks indicated that the ranks were significantly different. The plot suggested generally that in the presence of Separan the onset of plaque formation was delayed and its rate inhibited.

A two-way ANOVA with \( p < .05 \) was applied to the data from the control and Separan groups to assess the plaque formations in the five aortic subdivisions. This test indicated that plaque formation in the aortic arch was greater than anywhere else in both groups, when the atheromas were assessed either in terms of vessel wall–plaque interface area or luminal occlusion. Application of Duncan's NMR test showed no differences among the remaining four subdivisions in the control group, but the protective effect of Separan was not the same for all subdivisions of the descending aorta.

An analysis of covariance (ANCOVA) was performed for each of the five aortic subdivisions comparing the two regression lines describing the relationship between the area of vessel wall covered by plaque and the duration of high-cholesterol diet. The slope for the control group was significantly greater than the slope for the Separan group in both the aortic arch and the suprailiac subdivision. This indicates that Separan reduced the rate of atherogenesis in these two regions of the aorta. When the four subdivisions of the descending aorta were analyzed as a single entity, the slope of the pooled data was still significantly lower for the Separan-treated group (table 1).

An ANCOVA comparing the percentage of lumen occluded in aortas from control and sepan-treated rabbits during the high-cholesterol diet showed that the slopes were different in each pair of the five aortic subdivisions (table 2). Figure 5 shows the regression lines for luminal occlusion as a function of days on a high-cholesterol diet in the aortic arches from the control and Separan groups. The comparable regression lines for the descending aorta are shown in figure 6. As with the wall-plaque interface data, two-way ANOVA indicated that the aortic arch was most susceptible to plaque formation, with no differences among the remaining segments of the same aorta.

The protective effect of Separan treatment is indicated in figure 7, which summarizes and compares the atherogenesis in the presence and absence of polymer predicted by regression analysis after 170 days of a high-cholesterol diet. The fractions (expressed as percentages) of vessel wall covered with plaque and lumen occluded by plaque in control and test groups are illustrated in the solid-line histograms by the relative heights and areas, respectively; the widths of the histo-
FIGURE 4. A, A plot of the mean (± SE) percentage of lumen occluded in the five subdivisions of each aorta from seven pairs of rabbits matched for their length of time on a high-cholesterol diet. The subdivisions, with their respective symbols and segment sample numbers in parenthesis, are the arch (solid circle, 4), descending thoracic (open circle, 8), celiac (open diamond, 4), renomesenteric (open square, 4), and suprailiac (solid square, 6) aorta. The lack of variance bars on some symbols signifies that the SE is less than the width or height of the symbol. The point coordinates for the values from control and Separan-treated pairs are indicated on the abscissa and ordinate, respectively, and the identity line consists of points of equal paired values. The coordinate scales are expanded for all values under 20%. All data from the two groups, irrespective of aortic subdivisions, are plotted in B after pairing of ranked occlusion values. The open circles are single pair values and the closed circles represent the mean of 10 such values, where the SE never exceeds the dimensions of the symbol.

### TABLE 1
Effect of Separan AP-30 on aortic atheromas in cholesterol-fed rabbits: wall-plaque interface area

<table>
<thead>
<tr>
<th>Aortic subdivisions</th>
<th>C</th>
<th>S</th>
<th>Regression slope of wall area, 100 (%/day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arch</td>
<td>27</td>
<td>27</td>
<td>26 ± 12 ( ^) 12 ± 12</td>
</tr>
<tr>
<td>Descending</td>
<td>147</td>
<td>165</td>
<td>35 ± 5 ( ^) 13 ± 5</td>
</tr>
<tr>
<td>Thoracic</td>
<td>56</td>
<td>63</td>
<td>17 ± 9 ( ^) 8 ± 7</td>
</tr>
<tr>
<td>Celiac</td>
<td>27</td>
<td>30</td>
<td>35 ± 11 ( ^) 17 ± 8</td>
</tr>
<tr>
<td>Renomesenteric</td>
<td>24</td>
<td>27</td>
<td>48 ± 13 ( ^) 12 ± 14</td>
</tr>
<tr>
<td>Suprailiac</td>
<td>40</td>
<td>45</td>
<td>52 ± 10 ( ^) 22 ± 9</td>
</tr>
</tbody>
</table>

\( n = \) total number of histologic sections obtained from seven control (C) or eight Separan-treated (S) animals.

\( ^p < .05. \)

### TABLE 2
Effect of Separan AP-30 on aortic atheromas in cholesterol-fed rabbits: luminal occlusion

<table>
<thead>
<tr>
<th>Aortic subdivisions</th>
<th>C</th>
<th>S</th>
<th>Regression slope of occlusion, 100 (%/day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arch</td>
<td>27</td>
<td>27</td>
<td>32 ± 6 ( ^) 8 ± 5</td>
</tr>
<tr>
<td>Descending</td>
<td>147</td>
<td>165</td>
<td>27 ± 2 ( ^) 3 ± 1</td>
</tr>
<tr>
<td>Thoracic</td>
<td>56</td>
<td>63</td>
<td>20 ± 5 ( ^) 1 ± 1</td>
</tr>
<tr>
<td>Celiac</td>
<td>27</td>
<td>30</td>
<td>18 ± 4 ( ^) 4 ± 2</td>
</tr>
<tr>
<td>Renomesenteric</td>
<td>24</td>
<td>27</td>
<td>41 ± 7 ( ^) 2 ± 3</td>
</tr>
<tr>
<td>Suprailiac</td>
<td>40</td>
<td>45</td>
<td>35 ± 5 ( ^) 5 ± 3</td>
</tr>
</tbody>
</table>

\( n = \) total number of histologic sections from control (C) or Separan-treated (S) group.

\( ^p < .05. \)
grams are an index of plaque thickness. In relative terms polymer treatment was most effective in the descending thoracic aorta, where the occlusion was only approximately one-tenth that in the control group, and least effective in the aortic arch, where the occlusion was about 43% of that in untreated animals. In all subdivisions of the aorta the extent as well as the thickness of the plaque was markedly less in the test group than it was in the control group.

Discussion

Mostardi et al,\textsuperscript{10} first proposed that drag-reducing polymers, known to laminarize flow both in vitro\textsuperscript{4, 17, 18} and in vivo,\textsuperscript{8} might inhibit atherosclerosis by dampening flow disturbances. Photographs of plaque formations in exposed aortic intimae from Separan-treated and untreated rabbits on a high-cholesterol diet showed dramatic differences, in support of Mostardi's hypothesis. The objective of our study was to test this hypothesis, quantifying the effects of Separan treatment by morphometric analysis. This analysis was specifically designed to determine not only the effect of Separan on the fraction of aortic intima covered by atheromas, but also to assess the fraction of lumen occluded with and without therapy. The latter assessment is infrequently attempted in the aorta by quantitative techniques. However, it is therapeutically the most relevant variable, because vascular blood flow is related exponentially to luminal cross-sectional area.

A problem with the experimental protocol concerned the difficulty of maintaining the control animals on a prolonged high-cholesterol diet. It would be preferable to compare the atheromas in Separan-treated and untreated rabbits that had all been on a 6 month high-cholesterol diet. However, given the morbidity of the control rabbits this would have required a much larger colony of animals than we had anticipated. Nevertheless, statistical analyses establish with high probability that Separan AP-30 is a powerful antiatherogenic agent under the conditions applied in the present experiments, predicting that Separan can inhibit plaque formation to half that expected in the aortic arch and to about one-fifth that expected in the descending aorta.

The impression that Separan-treated animals were distinctly healthier than untreated animals was a subje-
tive assessment. However, the fact that all eight cohorts had to be terminated because of the actual or the apparent impending demise of the control member of the cohort gave an objective dimension to the assessment. This was further supported by the greater gain of body weight observed in all but one Separan-treated animal relative to its cohort control partner. Parenthetically, although the amount of food ingested was not quantified, these findings all but exclude the possibility that the observed atherosclerotic differences between the two groups on atherogenic diets were related to differences in the amounts of cholesterol ingested. The finding that plasma cholesterol levels were not significantly different in the two groups is in accord with this suggestion and implies that the effect of Separan is not dependent on differences in gastrointestinal absorption of cholesterol.

Evidence continues to mount that atherosclerosis does not develop haphazardly, but tends to appear at specific geometric sites associated with various types of flow disturbance. The term “flow disturbance” is used here in a general sense, incorporating the many types of flows reported to occur at atherosclerotic sites that are distinguished by marked departures from Poiseuillean character, including turbulence, eddying, swirling, oscillation, vibration, separation, stagnation, and other nonlaminar or unstable flows. Studies of flow patterns in tubes simulating the vasculature have already established the instability of flows through nonlinear conduit systems, particularly when flows are pulsatile and the tubes are elastic. The variations observed in correlations of atherogenic site and vascular geometry are not surprising, given the relatively small alterations in conduit geometry that are capable of causing major changes in flow patterns.

The controversy surrounding the relationship between atherogenesis and high versus low shear stress seems to have subsided with growing evidence that low shears stimulate and moderately high shears protect against the formation of atheromas. Fry’s demonstration of acute endothelial injury in the presence of very high shear stress is likely to be of less clinical pertinence than his observation of endothelial changes in regions of low shear combined with strong turbulence. Caro also has refined his hypothesis of shear-dependent mass transport in recognition of the susceptibility of blood-wall transport to nonsteady shear stresses. These and similar findings are compatible with a correlation between flow disturbance and atherogenesis. In this connection it might be useful to consider the hypothesis that an increased heart rate might be a factor in atherogene-

sis, because oscillatory flow is a type of flow disturbance that has been repeatedly shown to worsen atherosclerosis.

The relationship between heart rate and atherogenesis might be difficult to elucidate without quantitative experimentation specifically designed to control the variability of vascular geometry, cholesterol intake and metabolism, blood pressure, and other complicating factors of atherogenesis. In monkeys on a high-cholesterol diet, some subject to surgical ablation of the sinoatrial node, the development of coronary arterial lesions and stenosis was significantly less in animals with heart rates below the preoperative mean than in those with rates above that mean. The retardation of atherosclerosis was unrelated to blood pressures or plasma cholesterol levels, which were not significantly different in the two groups. Of particular interest in this regard is the recent report of Blumlein et al., who quantitated the effect of several drugs on the area of aortic intima covered by plaque in cholesterol-fed rabbits. Although these investigators concluded that an antiatherogenic action of verapamil could not be explained by its “hemodynamic” actions, or more specifically its effect on blood pressure, in fact a linear plot of mean plaque areas versus heart rates from seven groups yields a regression line with a correlation coefficient of .84. An analysis of the original data would be required to assess the statistical significance of this correlation.

Since 1971, when Hoyt listed over 20 linear polymers of high molecular weight (>1·10⁶ daltons) demonstrating the Toms phenomenon, additional natural and synthetic macromolecules with the molecular attributes necessary for polymer drag reduction have become available. However, only four such polymers — Separan, Polyox, an okra polysaccharide extract, and a calf thymus deoxyribonucleic acid — have demonstrated drag-reduction in blood flow in vitro. Three of these polymers — Separan, Polyox, and an okra extract identified as a rhamnogalactogalacturonan — augment cardiac output in association with a marked reduction in peripheral resistance in experimental animals. These macromolecules are characterized by extraordinary linear dimensions, with molecular lengths much longer than those of drag-reducing polymers that have no effect on blood flow, and in all cases their lengths exceed the diameters of several erythrocytes. The hemodynamic effects of these substances are compatible with polymer drag reduction but not with inotropic or vasoactive mecha

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*Polimeni PI, Ottenbreit B: Unpublished observation.
nisms. Given the diversity of the chemical composition of these macromolecules and their physical similarities, it is difficult to avoid the conclusion that their hemodynamic effects reflect a physical rather than a conventional pharmacologic phenomenon. It remains to be seen whether Mostardi’s suggestion that the antiatherogenic action of Separan is based on a physical mechanism is reinforced or weakened after one or more of the other hemodynamically active macromolecules are tested for therapeutic effect. However, given the ample evidence that intravascular flow disturbance is a significant factor in atherogenesis and that Separan dampens flow disturbances, such a mechanism is compatible with a large body of work in medicine and fluid dynamics.

If drag-reducing polymers other than Separan also demonstrate antiatherogenic effects in future studies, it would strongly support the view that hemodynamics play a primary role in causing atherosclerosis and that a novel therapeutic approach is possible against this disease. In principle this approach would have the advantage of ameliorating the pathologic condition in two distinct ways. The immediate effect would be to facilitate blood flow through partially occluded vessels and enhance cardiac output without commensurate stress on the heart. The long-term effect would be to inhibit atherogenesis, or perhaps, given the dynamic nature of atherosclerosis, cause a regression of the atheromas. Recent findings in monkeys indicate that although diet or drug therapies correcting hyperlipidemia cause much of the stainable lipid to disappear from atherosclerotic lesions and reduce the size of necrotic centers, the vascular lumens do not enlarge, presumably because of scarring and concentric contraction. If this occurs in humans as well, then drag-reducing polymers might be unique among antiatherogenic agents in facilitating blood flow through such vascular constrictions, as they do in constricted pipes, after atherogenesis has been suppressed or atherosclerosis reversed.

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