Evidence for an Altered Lipid Metabolic State in Circulating Blood Monocytes Under Conditions of Hyperlipemia in Swine and Its Implications in Arterial Lipid Metabolism

Frank P. Bell and Ross G. Gerrity

Circulating blood monocytes were isolated from normal and hypercholesterolemic swine, and the monocyte lipid compositions and lipid biosynthesis profiles were assessed. The data indicate that monocytes freshly isolated from hyperlipemic swine have increased phospholipid and cholesterol contents and have increased biosynthetic capability for synthesizing phospholipids, triglycerides, and cholesteryl esters, but not cholesterol. The profile of the stimulated lipid synthesis capability is similar to that of the swine aortic intima undergoing atherogenic change. These studies indicate that circulating blood monocytes in hyperlipemic swine, which are known to give rise to intimal foam cells in the early fatty streak lesion, can contribute to altered vessel lipid metabolism without a requirement for in situ modification by wall factors. (Arteriosclerosis and Thrombosis 1992;12:155–162)

One of the earliest detectable cellular events in the atherogenic process is the infiltration of monocytes/macrophages into the arterial wall. Additionally, the lipid-filled foam cells present in atherosclerotic tissue are considered to be derived, in part, from the monocyte/macrophage. For this reason, a number of laboratories have been investigating macrophage lipid metabolism and have been profiling the characteristics of their lipoprotein receptors. Although some studies have been performed with arterial (monocyte-derived macrophage) foam cells, many of the macrophage studies to date have used macrophages elicited from peritoneum and lung or a macrophage cell line. In our studies, we have focused on lipid metabolism in the freshly isolated blood monocyte, as this is the cellular entity that invades the vessel wall, and we previously reported that monocytes from hypercholesterolemic rabbits have a stimulated lipid synthesis profile that differs significantly from that of normal lipemic blood monocytes and that resembles the lipid synthesis profile of atherosclerotic vessels. In the present studies, we have successfully isolated monocytes from the blood of normal and hypercholesterolemic swine and have compared their lipid metabolism. Additionally, the lipid metabolism of aortic intimas from normal swine and from lesioned and nonlesioned areas of aortas from hypercholesterolemic swine was studied in vitro. The results indicate that hypercholesterolemic swine blood monocytes contain higher percentages of cholesterol and cholesteryl esters and have increased acyl-coenzyme A:cholerster O-acyltransferase (ACAT) activity when compared with monocytes from normal swine. Additionally, the former have a pattern of increased lipid biosynthesis from [14C]acetate and [14C]oleate, which resembles the lipid metabolic profile of cholesterol-enriched or lesioned aortic intima. The data suggest that monocytes invading the vessel wall from hypercholesterolemic plasma are capable of contributing to altered wall lipid metabolism without an obligatory requirement for in situ modification.

Methods

Animals and Diets

Pairs of male Yorkshire swine (6 weeks of age, 15–20 kg at initiation) were fed either normal hog chow or chow supplemented with 1.5% cholesterol and 19.5% lard for periods of 15–20 weeks. Serum cholesterol levels ranged from 70 to 110 mg/dl in normal swine and between 400 and 600 mg/dl in the hyperlipemic swine. Details of euthanasia and tissue collection have been previously described. In the present studies, abdominal aortic tissue samples were...
Arterial Tissue, Incubation, and Lipid Analysis

The aortas were removed after killing the swine containing medial tissue while being viewed under a dissecting microscope. The tissues were incubated at 37°C for 90 minutes in 9.0 ml of the medium 199/ balanced salt solution (with Ca²⁺ and Mg²⁺; Whittaker Products, Walkerville, Md.), and then extracted as above, 19 and the lipid extracts fractionated by high-performance liquid chromatography. 22 Statistical analysis was performed on logarithmically transformed data (log₁₀); comparisons were made between groups with Student’s t test for paired variates.

Lipid Analysis

The lipid composition of freshly isolated blood monocytes from normal and hyperlipemic swine is shown in Table 1. The data indicate that hyperlipemic swine monocytes had a twofold greater lipid content and were enriched in cholesterol, cholesteryl esters, and phospholipids relative to normal swine monocytes. The greatest proportionate increases were in the cholesteryl esters, which increased about 14-fold. Additionally, cholesterol content was increased about three times from 0.24 to 0.71 µg/10⁶ cells, and phospholipids increased about two times, from 1.77 to 3.24 µg/10⁶ cells.

The lipid synthesis profile, in which [¹⁴C]acetate and [¹⁴C]oleate were used as substrates, of monocytes from normal and hyperlipemic swine is shown in Table 2. Monocytes from both sources showed full capacity for de novo fatty acid biosynthesis ([¹⁴C]acetate) and for the incorporation of fatty acids into complex lipids (glycerolipids and steryl esters). There were, however, quantitative differences evident between the cells, in that monocytes from hyperlipemic swine demonstrated an increased incorporation of [¹⁴C]acetate into all lipid classes except the sterol fraction (digitonin-precipitable sterols). [¹⁴C]acetate incorporation into digitonin-precipitable sterols was reduced about 18%, whereas an increase of approximately 60% was observed in [¹⁴C]acetate incorporation from four matched pairs of swine, and blood monocytes from eight matched pairs were examined.

Isolation of Blood Monocytes, Incubation, and Lipid Analysis

Swine were bled either at the time they were killed via a jugular cannula, while under pentobarbital anesthesia, or via chronically implanted subcutaneous vascular ports accessing the jugular vein in conscious swine. Monocytes were isolated by countercflow centrifugation by a modification of the technique of Fogelman et al 18 as previously described. 17 Freshly isolated monocytes of >95% purity were incubated (1.5–2×10⁶ cells/ml) at 37°C for up to 90 minutes in 2.0 ml of a mixture of medium 199 (GIBCO, Grand Island, N.Y.) and normal swine serum (1:1, vol/vol), respectively; NEN Research Products, Boston, Mass.). After incubation, the cells were sedimented by centrifugation, rinsed with Hanks’ balanced salt solution (with Ca²⁺ and Mg²⁺; Whittaker Products, Walkerville, Md.), and then extracted with chloroform/methanol mixtures. 19 The lipid extracts were fractionated by thin-layer chromatography on silica gel G-coated glass plates by using a solvent system of n-hexane/diethyl ether/glacial acetic acid, 146:50:4 (vol/vol/vol). 20 Lipid bands were scraped into vials and assayed directly for radioactivity by liquid scintillation counting. 20

In the case of incubations with [¹⁴C]acetate, a portion of the lipid extracts was spiked with 100 µg carrier cholesterol and then saponified, and the total radioactivity in digitonin-precipitable sterols was determined. 21 Samples of freshly isolated monocytes were also directly extracted as above, 19 and the lipid extracts were fractionated by high-performance liquid chromatography for purposes of determining endogenous lipid mass of the cells.

Arterial Tissue, Incubation, and Lipid Analysis

The aortas were removed after killing the swine with an overdose of pentobarbital. Aortas were immediately rinsed in chilled phosphate-buffered saline (PBS) and opened longitudinally, and intima-media preparations were carefully stripped from the underlying medial tissue while being viewed under a dissecting microscope. The tissues were incubated at 37°C for 90 minutes in 9.0 ml of the medium 199/ normal swine serum medium described above, containing 1.5 µCi/ml [¹⁴C]oleic acid (specific activity, 57.0 Ci/mol; NEN Research Products). After incubation, the tissues were rinsed in PBS and extracted by homogenization in chloroform/methanol mixtures as previously described. 21, 22 One portion of the lipid extract was fractionated by thin-layer chromatography as described above, while a second portion was saponified and the total cholesterol content determined after precipitation of the sterols by digitonin. 21 Two-millimeter slices of aortic tissue from normal, grossly normal, and grossly lesioned abdominal aortas immediately adjacent to those used for biochemical analysis were prepared for light and electron microscopy. These samples were fixed in 2% glutaraldehyde in 0.13 M phosphate buffer, pH 7.4, at room temperature for 2 hours, postfixed in 1% OsO₄, dehydrated in ethanol, and embedded in Spurr’s resin as previously described. 1 One-micron plastic sections were mounted on glass slides, stained with methylene blue/azure II/basic fuchsin, and photographed with an Olympus BH-2 light microscope.

Results

The lipid composition of freshly isolated blood monocytes from normal and hyperlipemic swine is shown in Table 1. The data indicate that hyperlipemic swine monocytes had a twofold greater lipid content and were enriched in cholesterol, cholesteryl esters, and phospholipids relative to normal swine monocytes. The greatest proportionate increases were in the cholesteryl esters, which increased about 14-fold. Additionally, cholesterol content was increased about three times, from 0.24 to 0.71 µg/10⁶ cells, and phospholipids increased about two times, from 1.77 to 3.24 µg/10⁶ cells.

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was evident as early as 15 minutes and was 65% greater than in normal cells by 90 minutes.

ACAT activity to chemical inhibition, hyperlipemic swine monocytes were incubated in the presence of [14C]oleate ([14C]acetate 2 µCi/ml) and [14C]oleate (3 µCi/ml) in 2.0 ml Hanks' balanced salt solution/normal swine serum (1:1, vol/vol), which contained 3 pCi [1-14C]oleate and [14C]acetate formation (dpm/10^6 cells).

Values shown are in dpm/10^6 cells and are means of data obtained from the two swine per group; individual swine data are given in parentheses. PL, phospholipids; DG, diglycerides; TG, triglycerides; CE, cholesteryl esters; NEFA, nonesterified fatty acid; DPS, digitonin-precipitable sterols.

To determine the sensitivity of the monocytic ACAT activity to chemical inhibition, hyperlipemic swine monocytes were incubated in the presence of the ACAT inhibitor CL277-082,24 and ACAT was evaluated by following the incorporation of [14C]oleate into cholesteryl esters (Table 3). Inhibition of monocytic ACAT was achievable and dose related. At 4 and 16 µM, CL277-082 achieved ACAT inhibition of 13% and 29%, respectively.

In addition to studies of the swine monocytes, intima–media tissue from the abdominal aortas of swine was taken for measurement of cholesterol content and for in vitro incubation with [14C]oleate to evaluate intimal lipid metabolism. Because hyperlipemic swine had begun to develop atherosclerotic lesions, intimal tissue from areas of grossly visible lesions and adjacent grossly normal areas in the abdominal aorta were independently evaluated and compared with intima–media preparations taken from identical sites in normal swine aorta. Normal swine aorta showed typical intimal morphology at the light-microscopic level (Figure 2), with endothelium

![Figure 1. Comparison of cholesterol esterification activity over time in monocytes freshly isolated from a normal (●) and hyperlipemic (○) swine pair. Monocytes were incubated in vitro at 37°C in 5.0 ml Hanks' balanced salt solution/normal swine serum (1:1, vol/vol), which contained 3 µCi [1-14C]oleate and 2.5 x 10^6 cells/ml. One-milliliter aliquots were withdrawn from each incubation at the time intervals shown, and cells were collected, extracted, and analyzed for formation of cholesteryl [14C]oleate formation (dpm/10^6 cells).](image-url)

### Table 2. Incorporation of [14C]Oleate and [14C]Acetate Into Lipids of Blood Monocytes Isolated From Normal and Hyperlipemic Swine

<table>
<thead>
<tr>
<th></th>
<th>PL (dpm)</th>
<th>DG (dpm)</th>
<th>TG (dpm)</th>
<th>CE (dpm)</th>
<th>NEFA (dpm)</th>
<th>DPS (dpm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>1,567</td>
<td>667</td>
<td>369</td>
<td>241</td>
<td>758</td>
<td>3.4</td>
</tr>
<tr>
<td></td>
<td>(1,348, 1,786)</td>
<td>(480, 854)</td>
<td>(390, 348)</td>
<td>(140, 342)</td>
<td>(925, 591)</td>
<td>(4.0, 2.8)</td>
</tr>
<tr>
<td>Hyperlipemic</td>
<td>2,545</td>
<td>1,645</td>
<td>773</td>
<td>435</td>
<td>1,467</td>
<td>2.8</td>
</tr>
<tr>
<td></td>
<td>(2,075, 3,015)</td>
<td>(1,985, 1,305)</td>
<td>(670, 876)</td>
<td>(335, 530)</td>
<td>(1,350, 1,584)</td>
<td>(3.5, 2.1)</td>
</tr>
<tr>
<td>Percent of normal</td>
<td>162</td>
<td>247</td>
<td>209</td>
<td>180</td>
<td>194</td>
<td>82</td>
</tr>
<tr>
<td>[14C]Oleate</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>5,786</td>
<td>10,418</td>
<td>3,485</td>
<td>414</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td></td>
<td>(6,946, 4,626)</td>
<td>(7,891, 12,945)</td>
<td>(2,550, 4,420)</td>
<td>(443, 385)</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Hyperlipemic</td>
<td>12,509</td>
<td>15,067</td>
<td>15,083</td>
<td>727</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td></td>
<td>(8,230, 16,788)</td>
<td>(13,600, 16,534)</td>
<td>(12,330, 17,836)</td>
<td>(875, 579)</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Percent of normal</td>
<td>216</td>
<td>145</td>
<td>433</td>
<td>176</td>
<td>...</td>
<td>...</td>
</tr>
</tbody>
</table>
TABLE 3. Effect of Acyl-CoA:Cholesterol Acyltransferase Inhibitor CL277-082 on the Incorporation of \([\textbf{1}^{\textbf{4}}\textbf{C}]\text{Oleate} \) into Cholesterol Esters by Monocytes Isolated From Hyperlipemic Swine Blood

<table>
<thead>
<tr>
<th>CL277-082 concentration ((\mu\text{M}))</th>
<th>([\textbf{1}^{\textbf{4}}\textbf{C}]\text{cholesteryl ester} ) formation (dpm/4(\times)10^6 cells)</th>
<th>Inhibition (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 (control)</td>
<td>425</td>
<td>0</td>
</tr>
<tr>
<td>4</td>
<td>369</td>
<td>13</td>
</tr>
<tr>
<td>16</td>
<td>302</td>
<td>29</td>
</tr>
</tbody>
</table>

Monocytes (4\(\times\)10^6 cells) freshly isolated from blood of a hyperlipemic swine were incubated for 60 minutes at 37°C in vitro in 2.0 ml Hanks’ balanced salt solution/normal swine serum (1:1, vol/vol), which contained 3.0 \(\mu\text{Ci} \) [\(\textbf{1}^{\textbf{4}}\textbf{C}]\text{oleate}/ml. CL277-082 dissolved in 20 \(\mu\text{l} \) DMSO was added to the incubations; controls received DMSO alone. Data are means of duplicate incubations. ACAT, acyl-coenzyme A:cholesterol \(\text{O-acyltransferase}; \) DMSO, dimethyl sulfoxide.

separated from the internal elastic lamina by a thin intimal space occupied by ground substance, scattered elastica, and a few intimal cells. In contrast, grossly visible lesion areas (Figure 3) showed well-developed atheromatous lesions several millimeters in thickness, characterized by macrophage foam cells and some smooth muscle cell infiltration. At this stage, foam cell necrosis was not prevalent. Grossly normal areas from hyperlipemic swine (Figure 4) showed a histological appearance intermediate between normal vessels from control swine (Figure 2) and grossly lesioned areas of the same vessel (Figure 3). Such areas showed intimal thickening of various degrees, due to accumulation of ground substance and fragmented elastica (Figure 4). The internal elastic lamina was frequently reduplicated (Figure 4), a finding common in lesioned areas. Monocytes were frequently seen adherent to the endothelium and in the intima directly below the endothelium, while smooth muscle cells were typically (although not always) seen deeper in the lesion (Figure 4). Only a few foam cells were present in the intima of such areas.

The results of lipid metabolism studies from these areas are shown in Table 4. Intima–media cholesterol content in the normal swine was approximately 7 \(\mu\text{g}/\text{mg} \) dry wt and was increased dramatically in the hyperlipemic swine, to 24.8 \(\mu\text{g}/\text{mg} \) dry wt in the lesion-free intima and to 78.6 \(\mu\text{g}/\text{mg} \) dry wt in the lesioned intima. The enrichment of the grossly normal intima with cholesterol was associated with a dramatic significant increase in ACAT activity, as evidenced by the 16-fold increase in the incorporation of \([\textbf{1}^{\textbf{4}}\textbf{C}]\text{oleate} \) into cholesteryl esters \((p<0.05)\); incorporation into phospholipids was also increased (60%, \(p<0.05)\), but to a much lesser extent. In
times normal (14 versus 926 dpm/mg dry wt), whereas the increases in triglyceride and phospholipid synthesis were 2.5-fold to threefold greater than normal ($p<0.05$). As a further point of comparison, the cholesterol content and the incorporation of $[^{14}C]$oleate into the three lipid classes observed in the lesioned intima were significantly greater ($p<0.05$) than their counterparts in lesion-free intima.

**Discussion**

Monocyte infiltration of the arterial intima is regarded as an early event in the pathogenesis of atherosclerosis.$^1$-$^4$ In the lipid-fed swine model of atherogenesis, blood monocytes have been identified in the intima of lesion-prone areas before and during development of lesions$^5$-$^8$ and are considered to be the major source of foam cells in fatty streak lesions$^9$; in more complicated (advanced) lesions, foam cells of smooth muscle cell origin predominate.$^{10}$ Once inside the intima, the monocytes transform into phagocytic cells and accumulate lipid. Studies in vitro with monocyte-derived macrophages have demonstrated that they possess a variety of receptors for the uptake of lipoprotein materials$^7$-$^9$ and that they can actively synthesize lipid.$^{7,15,26}$ For the macrophage to be synthesizing lipid at a time when lipid from exogenous sources is accumulating suggests that the synthesis is involved with the processing of incoming substrates. Further to this, our present observations suggest that monocytes from hyperlipemic swine have acquired a stimulated lipid synthesis potential while in the circulation (Table 2), that is, they undergo alterations in their lipid metabolism activity before their differentiation into macrophages in the arterial wall. The differences between "normal" and "hyperlipemic" monocytes cannot be explained as artifacts of their isolation or of the experimental conditions because the same procedures were common to all cells and cells from matched pairs of normal and hyperlipemic swine were prepared and studied on the same day. Further evidence of their differences is also indicated by the greater total lipid content of the hyperlipemic mono-

![Figure 4. Light photomicrograph of intima and inner media of grossly normal abdominal aorta immediately adjacent to lesion shown in Figure 3. Compare thickness of intima (I) with that in Figures 2 and 3. Thicken intima is relatively acellular, with scattered foam cells (FC), subendothelial monocytes (M), and a few smooth muscle cells (S) in the deep intima often associated with reduplication (arrow) of internal elastic lamina (IEL). Methylene blue/azure II/basic fuchsin stain, $\times178$.](image)

| Table 4. $[^{14}C]$Oleate Incorporation Into Swine Abdominal Aortic Intima and Intimal Cholesterol Content |
|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| Group           | Intimal tissue  | Total cholesterol ($\mu$g/mg dry wt) | $[^{14}C]$oleate incorporation (dpm/mg dry wt) | Phospholipid | Triglyceride | Steryl ester |
| Normal          | Normal          | 6.6±0.9*        | 793±171*        | 34±18*        | 14±2*         |
| Hyperlipemic    | Lesion free     | 24.8±0.2†       | 1,262±138†      | 47±14*        | 218±60†       |
| Hyperlipemic    | Lesioned        | 78.6±8.2‡       | 2,365±207‡      | 84±3‡         | 926±222‡      |

Intima-media preparations from normal swine and hyperlipemic swine were incubated individually in vitro for 90 minutes at 37°C in 9.0 ml medium 199/normal swine serum (1:1, vol/vol), which contained 1.5 $\mu$Ci/ml $[^{14}C]$oleic acid (specific activity, 57.0 Ci/mol). After incubation, tissues were rinsed in phosphate-buffered saline and lipid-extracted by homogenization in chloroform/methanol mixtures, and portions of each lipid extract were fractionated by thin-layer chromatography as described in "Methods." Another portion of each lipid extract was used for determination of total cholesterol after digitonin precipitation.$^{21}$

Values are mean±SEM of data from three individual swine. Statistical analysis was performed on logarithmically transformed data (log$_{10}$) by analysis of variance; pairwise comparisons between means were made with Student's t test. Within each vertical column, values with the same superscript designation are not statistically significantly different ($p>0.05$).
cytes (Table 1). Virtually all of the increased lipid mass was accounted for as cholesterol and phospholipid. Although the cells were not subfractionated and analyzed, the increases in cellular cholesterol and phospholipid are likely indicative of changes in membrane composition, as the cells did not contain lipid droplets visible at either the light- or the electron-microscopic level. Enrichment of the cells with cholesterol may be similar to the enrichment seen in platelet and erythrocyte membranes under certain conditions of hyperlipemia. Sterol enrichment could have taken place in the plasma compartment via surface transfer or receptor mechanisms, or it could have been established during monocyte formation from the bone marrow promonocyte, a situation analogous to the proposed mechanism by which platelets become cholesterol enriched during hyperlipemia by alterations in megakaryocyte sterol metabolism. It seems unlikely that the increased sterol arose directly in synthesis in the circulating monocytes because the incorporation of [14C]acetate into digitonin-precipitable sterols by the hyperlipemic monocytes was somewhat less than that observed in normal monocytes (Table 2). On the other hand, increased phospholipid synthesis could account for the increased phospholipid mass (Table 2). Less easily explained, however, are the increased triglyceride and cholesterol-esterifying activities observed in the hyperlipemic monocytes. The compositional data indicate that triglycerides and steryl esters are a minor component in monocytes from both sources and are not reflective of the twofold to fourfold increases in the synthesis of these lipids seen in the hyperlipemic monocytes (Table 2). The data suggest two possibilities. One is that the enhanced capability for synthesis of cholesteryl esters and triglycerides is held in reserve in vivo in the circulating cells or, alternately, that these lipids are being synthesized by the circulating cells but are removed or hydrolyzed to limit their excessive accumulation. Irrespective of which situation prevails, monocytes from hyperlipemic swine are primed for lipid synthesis and seem likely to carry this primed condition with them on penetration into the arterial intima.

This may in fact account, in whole or in part, for the similar pattern of lipid synthesis observed in the intimal preparations obtained from the hyperlipemic swine aorta (Table 4), where synthesis of phospholipids, steryl esters, and triglycerides was also enhanced. Arterial tissue preparations were of two compositions. Lesioned areas were stripped at the level of the internal elastic lamina and were purely intimal in nature. Our previous studies have shown such lesions in the thoracic aorta to be composed of macrophage foam cells and a few undifferentiated intimal cells, with little or no smooth muscle involvement at this stage. In the present study, abdominal aortic lesions showed slightly more smooth muscle involvement but were still predominantly of a macrophage foam cell nature. In the case of normal aorta or lesion-free aortic segments from hyperlipemic swine, the intima–media preparations consisted of the intima and (approximately) the inner quarter of the media. Histological examination of areas that are grossly lesion free demonstrate the presence of a thickened, relatively acellular intima with variable, but small, numbers of intimal monocytes and macrophage foam cells. Presumably, these areas are at a prelesion stage because in this animal model, the abdominal aorta eventually develops 95–100% lesion coverage. This being the case, lesion-free-area intima–media preparations are comparable to intima–media preparations taken from the same sites in normal swine except for the presence of monocytes/macrophages. Lipid metabolism values observed (Table 4) in normal swine preparations can, therefore, be attributable to the endothelium and underlying medial smooth muscle. Differences from these values and those seen in lesion-free intima–media and lesioned intima–media from hyperlipemic swine are therefore most likely attributable to the additional contributions of intimal monocytes/macrophages and macrophage foam cells. Lesion-free intima–media, with its variable (but lesser than that of lesions) content of monocyte-derived cells, shows values intermediate between those of normal aorta and lesions.

We previously demonstrated and quantified the preferential recruitment of blood monocytes into lesion-susceptible areas of swine aorta and the apparent efflux of large numbers of lipid-laden monocyte-derived foam cells from fatty streak lesions. The mechanism controlling the site-specific influx of monocytes into lesion-susceptible areas is associated with the production of monocyte-specific chemotactic factor(s) in such areas. The numbers of adherent and intimal monocytes continue to increase with increased duration of hyperlipemia, as does the number of foam cells exiting the lesion. The process is facilitated by a monocyteosis in hyperlipemic animals resulting from enhanced proliferation of monocyte progenitor cells in the bone marrow. On the basis of these findings, we have postulated that the role of the monocyte/macrophage in early atherosclerosis is one of lipid removal from susceptible sites, which preferentially accumulate lipoproteins. However, while it has been proposed that these monocyte-derived phagocytic cells are part of the process by which cholesterol and altered (modified) lipoproteins can be removed from the arterial intima under hyperlipemic conditions, their propensity to synthesize lipid could be viewed as a factor contributing to the total lipid burden amassed by the foam cell. It is equally plausible, however, that the enhanced lipid synthesis capability of these monocytes/macrophages facilitates the retention of lipid entering these cells by converting highly mobile lipo-protein/lipid digestion (hydrolysis) products, for example, cholesterol and fatty acids, into storable species such as phospholipids, triglycerides, and steryl esters. If this is the case, blood monocytes in hyperlipemic plasma are in a metabolic state that preconditions them for a more effective function in the scavenging of plasma lipids.
deposited in the vessel wall and their subsequent removal by foam cell emigration.

We did not investigate the mechanism of the stimulated lipid synthesis in the present studies except to examine the response of cellular ACAT to the known ACAT inhibitor CL277-082 (Table 3).²⁷ Inhibition of swine monocyte/macrophage ACAT activity is consistent with the observations of others who have demonstrated that CL277-082 blocked cholesteryl ester accumulation, in vivo, in macrophage-foam cells in rabbit carotid atheroma granuloma tissue.²⁴

Acknowledgments

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Evidence for an altered lipid metabolic state in circulating blood monocytes under conditions of hyperlipemia in swine and its implications in arterial lipid metabolism.

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