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 COICAL REVIEWS
 Effects of Oxidized Low-Density Lipoprotein on
 ASCULAR Contraction and Relaxation: Clinical and Vascular Contraction and Relaxation: Clinical and DESERVIEWS CONSIDERTIES IN The American Society for Pharmacology and Experimental Therapeutics **Properties**
 Pharmacological Low-Density Lipoprotein of
 Pharmacological Implications in Atheroscleros

DAVID A COX AND MA **al Implications in**
DAVID A. COX AND MARLENE L. COHEN*
rch Laboratories, Eli Lilly and Co. Indianance *Lilly Research Laboratories, Eli Lilly and Co., Indianapolis, Indiana*

I. Introduction

I. Introduction

Elevated plasma levels of low-density lipoprotein

(LDL) have been associated with the development of

atherosclerosis for more than 20 years (Kannel et al., **Elevated plasma levels of low-density lipoprotein**
(LDL) have been associated with the development of
atherosclerosis for more than 20 years (Kannel et al.,
1971), and lipid-lowering therapy is a beneficial ap-1. Introduction

1971), have been associated with the development of

1971), and lipid-lowering therapy is a beneficial ap-

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1971), and lipid-lowering therapy is a ben Elevated plasma levels of low-density lipoprotein (LDL) have been associated with the development of atherosclerosis for more than 20 years (Kannel et al., 1971), and lipid-lowering therapy is a beneficial approach to slow (LDL) have been associated with the development c
atherosclerosis for more than 20 years (Kannel et al
1971), and lipid-lowering therapy is a beneficial ap
proach to slowing the progression of this disease (Ty
roler, 1987) atherosclerosis for more than 20 years (Kannel et al., 1971), and lipid-lowering therapy is a beneficial approach to slowing the progression of this disease (Tyroler, 1987). More recently, modification of LDL, especially bach to slowing the progression of this disease (1y-
ler, 1987). More recently, modification of LDL, espe-
ally oxidation of this lipoprotein, has become
* Address correspondences and reprint requests to: Dr. Marlene L.
he

recognized as important to many of the atherogenic ac-
recognized as important to many of the atherogenic ac-
tions ascribed to LDL (Steinberg et al., 1989; Young and
Parasarathy, 1994). Indeed, oxidized LDL exerts many Precognized as important to many of the atherogenic actions ascribed to LDL (Steinberg et al., 1989; Young and Parasarathy, 1994). Indeed, oxidized LDL exerts many effects in vitro that could contribute to the progression atherosclerosis if they occur in vivo. Thus, the "oxidation

effects in vitro that could contribute to the progression of atherosclerosis if they occur in vivo. Thus, the "oxidation Abbreviations: LDL, low-density lipoprotein; EDRF, endothelium-derived relaxing factor; NO, nitric ox Abbreviations: LDL, low-density lipoprotein; EDRF, endothelium-
derived relaxing factor; NO, nitric oxide; EDR, endothelium-depen-
dent relaxation; 5-HT, 5-hydroxytryptamine (serotonin); mRNA,
messenger ribonucleic acid; N ducible NOS; lyso PC, lysophosphatidylcholine; PLA₂, phospholipase Abbreviations: LDL, low-density lipoprotein; EDRF, endothelium-
derived relaxing factor; NO, nitric oxide; EDR, endothelium-depen-
dent relaxation; 5-HT, 5-hydroxytryptamine (serotonin); mRNA,
messenger ribonucleic acid; N derived relaxing factor; NO, nitric oxide; EDR, endothelium-dependent relaxation; 5-HT, 5-hydroxytryptamine (serotonin); mRNA, messenger ribonucleic acid; NOS, nitric oxide synthase; iNOS, inducible NOS; lyso PC, lysophosp dismutase.

Collumerate Conducts Conducts Cohen, Cardiovascular Research (0522), Lilly Research Laboration, Cardiovascular Research (0522), Lilly Research Laboration, Eli Lilly and Company, Indianapolis, IN 46285.

4
hypothesis" of atherosclerosis proposes that oxidative
modification of LDL (and possibly other lipoproteins) is COX AND CO
hypothesis" of atherosclerosis proposes that oxidative termodification of LDL (and possibly other lipoproteins) is ca
a pivotal event in the initiation and progression of ath-COX A
 hypothesis" of atherosclerosis proposes that oxidative

modification of LDL (and possibly other lipoproteins) is

a pivotal event in the initiation and progression of ath-

erosclerosis. eroscierosis. odification of LDL (and possibly other lipoproteins) is
pivotal event in the initiation and progression of ath
osclerosis.
Oxidized LDL also has direct effects on the vasomoto
operties of blood vessels and may play an impo

modification of LDL (and possibly other lipoproteins) is
a pivotal event in the initiation and progression of ath-
erosclerosis.
Oxidized LDL also has direct effects on the vasomotor
properties of blood vessels and may pla a pivotal event in the initiation and progression of ather
erosclerosis. prosclerosis. p
Cxidized LDL also has direct effects on the vasomotor last
properties of blood vessels and may play an important strole in the altera erosclerosis.

Oxidized LDL also has direct effects on the vasomotor

properties of blood vessels and may play an important

role in the alterations in vascular contractility observed

in hypercholesterolemia and atheroscl Oxidized LDL also has direct effects on the vasomoto
properties of blood vessels and may play an importance in the alterations in vascular contractility observe
in hypercholesterolemia and atherosclerosis. Vascula
dysfunct properties of blood vessels and may play an important
role in the alterations in vascular contractility observed
in hypercholesterolemia and atherosclerosis. Vascular
dysfunction, especially inappropriate or enhanced vasorole in the alterations in vascular contractility observed
in hypercholesterolemia and atherosclerosis. Vascular
dysfunction, especially inappropriate or enhanced vaso-
constriction, may be involved in the genesis of sever In hypercholesterolemia and atheroscierosis. vascula
dysfunction, especially inappropriate or enhanced vaso
constriction, may be involved in the genesis of severa
clinical manifestations of atherosclerosis, including sta
b dysiunction, especially inappropriate or emianced vasconstriction, may be involved in the genesis of sever
clinical manifestations of atherosclerosis, including st
ble and unstable angina, acute myocardial infarctio
and su **1994; Kalsner, 1995). To the extent that oxidized LDL** is

1994; Kalsner, 1995). To the extent that oxidized LDL is

1994; Kalsner, 1995). To the extent that oxidized LDL is

1994; Kalsner, 1995). To the extent that oxidi ble and unstable angina, acute myocardial infarction,
and sudden cardiac death (Zeiher and Schachinger,
1994; Kalsner, 1995). To the extent that oxidized LDL is
involved in enhanced vasoconstriction, pharmacological
interv and sudden cardiac death (Zeiher and Schachinger, and 1994; Kalsner, 1995). To the extent that oxidized LDL is sequinvolved in enhanced vasoconstriction, pharmacological modifiervention that inhibits either the formation o 1994; Kalsner, 1995). To the extent that oxidized LDL is securely involved in enhanced vasoconstriction, pharmacological monoterrelation in the formation or actions identify of oxidized LDL may normalize vascular function intervention that inhibits either the formation or actions of oxidized LDL may normalize vascular function in hypercholesterolemia and atherosclerosis and could be beneficial in the therapeutic management of these patholog intervention that inhibits either the formation or action of oxidized LDL may normalize vascular function hypercholesterolemia and atherosclerosis and could beneficial in the therapeutic management of these thologies. Addi of oxidized LDL may normalize vascular function in the precholest erolenia and atherosclerosis and could beneficial in the therapeutic management of these pathologies. Additionally, such pharmacological intervertion at a v hypercholesterolemia and atherosclerosis and could be
beneficial in the therapeutic management of these pa-
thologies. Additionally, such pharmacological interven-
tion at a vascular level may greatly augment the bene-
fic **of atherosclerosis,** including the pharmacological intervetion at a vascular level may greatly augment the ber
ficial effects of therapies currently used in the treatme
of atherosclerosis, including the pharmacological lo In at a vascular level may greatly augment the bene-
ial effects of therapies currently used in the treatment
atherosclerosis, including the pharmacological lower-
g of serum lipid levels.
This review focuses on the vasomo

ficial effects of therapies currently used in the treatment
of atherosclerosis, including the pharmacological lower-
ing of serum lipid levels.
This review focuses on the vasomotor actions of oxi-
dized LDL, their potentia of atherosclerosis, including the pharmacological lowe
ing of serum lipid levels.
This review focuses on the vasomotor actions of or
dized LDL, their potential contribution to the clinic
manifestations of atherosclerosis, ing of serum lipid levels.
This review focuses on the vasomotor actions of oxidized LDL, their potential contribution to the clinical
manifestations of atherosclerosis, and pharmacological
strategies that may inhibit these This review focuses on the vasomotor actions of oxidized LDL, their potential contribution to the clinica
manifestations of atherosclerosis, and pharmacologica
strategies that may inhibit these actions. For a broader
discu dized EDL, their potential contribution to the chincal
manifestations of atherosclerosis, and pharmacological ch
strategies that may inhibit these actions. For a broader the
discussion of the formation, physiochemical prop mannestations of atheroscierosis, and pharmacological
strategies that may inhibit these actions. For a broader
discussion of the formation, physiochemical properties,
and atherogenic actions of oxidatively modified LDL, th 1994). **II. Discovery and Characteristics of Oxidized**
II. Discovery and Chisolm, 1994; Holvoet and Collen,
II. Discovery and Characteristics of Oxidized
Low-Density Lipoprotein al., 1989; Penn and Chisolm, 1994; Holvoet and Collen, 1994).
 II. Discovery and Characteristics of Oxidized Low-Density Lipoprotein

II. Discovery and Characteristics of Oxidized in the **Low-Density Lipoprotein** ω_{m}
Realization of the importance of LDL modification to the ints oxidized form in atherosclerosis was primarily the presult of sever **1. Discovery and Characteristics of Oxidized**
 Low-Density Lipoprotein

Realization of the importance of LDL modification to

its oxidized form in atherosclerosis was primarily the

result of several apparently incongr Low-Density Lipoprotein

Realization of the importance of LDL modification

its oxidized form in atherosclerosis was primarily

result of several apparently incongruent observatio

(Steinberg et al., 1989): (a) increased s **the formation of the importance of LDL incontration to**
its oxidized form in atherosclerosis was primarily the
result of several apparently incongruent observations
(Steinberg et al., 1989): (*a*) increased serum LDL chol its oxidized form in atherosclerosis was primarily the p
result of several apparently incongruent observations the
(Steinberg et al., 1989): (*a*) increased serum LDL choles-
terol led to the formation of early atheroscle result of several apparently incongruent observations the (Steinberg et al., 1989): (*a*) increased serum LDL choles-
terol led to the formation of early atherosclerotic lesions incorriched in lipid-laden, macrophage-deriv (Steinberg et al., 1989): (a) increased serum LDL chol
terol led to the formation of early atherosclerotic lesic
enriched in lipid-laden, macrophage-derived foam co
(Fowler et al., 1979); (b) isolated macrophages have
v terol led to the formation of early atherosclerotic lesions incremiched in lipid-laden, macrophage-derived foam cells frag (Fowler et al., 1979); (*b*) isolated macrophages have a very limited ability to take up native LD (Fowler et al., 1979); (*b*) isolated macrophages have a very limited ability to take up native LDL, and incubation of macrophages with native LDL did not lead to foam cell formation (Goldstein et al., 1979); and (*c*) hyp very limited ability to take up native LDL, and incubation of macrophages with native LDL did not lead to foam cell formation (Goldstein et al., 1979); and (c) hypercholesterolemia led to atherosclerotic lesion formation, very limited ability to take up native LDL, and incubation of macrophages with native LDL did not lead to foam cell formation (Goldstein et al., 1979); and (c) hypercholesterolemia led to atherosclerotic lesion formation, LDL receptors (Goldstein et al., 1979); and (c) hypercholesterolemia led to atherosclerotic lesion formation, even in animals and humans with deficiencies in LDL receptors (Brown and Goldstein, 1986). From these observatio percholesterolemia led to atherosclerotic lesion formation, even in animals and humans with deficiencies in LDL receptors (Brown and Goldstein, 1986). From these observations, it was suggested that LDL must undergo some ty LDL receptors (Brown and Goldstein, 1986). Fro
bbservations, it was suggested that LDL must a
some type of modification to be recognized and the
by macrophages and induce foam cell formation
In 1979, Goldstein and coworker INDE receptors (Brown and Coldstein, 1980). From these

observations, it was suggested that LDL must undergo

some type of modification to be recognized and taken up

by macrophages and induce foam cell formation.

In 1979

some type or modification to be recognized and taken up
by macrophages and induce foam cell formation.
In 1979, Goldstein and coworkers discovered that
modification of LDL by acetylation resulted in a greatly
enhanced capa by macrophages and mauce foam cell formation.

In 1979, Goldstein and coworkers discovered that

modification of LDL by acetylation resulted in a greatly

enhanced capacity for it to be taken up and degraded by

macrophage

COHEN
termed acetyl-LDL, lost the ability to bind to the clas
cal LDL receptor, but gained the ability to bind to COHEN
termed acetyl-LDL, lost the ability to bind to the classi-
cal LDL receptor, but gained the ability to bind to a
novel receptor that mediated the uptake into macro-COHEN
termed acetyl-LDL, lost the ability to bind to the clas
cal LDL receptor, but gained the ability to bind to
novel receptor that mediated the uptake into mac
phages, termed the scavenger receptor. Although ace termed acetyl-LDL, lost the ability to bind to the class
cal LDL receptor, but gained the ability to bind to
novel receptor that mediated the uptake into macr
phages, termed the scavenger receptor. Although acet
lation of termed acetyl-LDL, lost the ability to bind to the classical LDL receptor, but gained the ability to bind to a novel receptor that mediated the uptake into macrophages, termed the scavenger receptor. Although acetylation o cal LDL receptor, but gained the ability to bind to a
novel receptor that mediated the uptake into macro-
phages, termed the scavenger receptor. Although acety-
lation of LDL was not likely to occur in vivo, these
studies Inver receptor that methated the uptake into macro-
phages, termed the scavenger receptor. Although acety-
lation of LDL was not likely to occur in vivo, these
studies were soon followed with the demonstration that
LDL cou lation of LDL was not likely to occur in vivo, these
studies were soon followed with the demonstration that
LDL could also be modified by cultured endothelial cells,
resulting in LDL that competed with acetyl LDL for
bindi studies were soon followed with the demonstration that
LDL could also be modified by cultured endothelial cells,
resulting in LDL that competed with acetyl LDL for
binding to the scavenger receptor and was avidly taken
up LDL could also be modified by cultured endothelial cells,
resulting in LDL that competed with acetyl LDL for
binding to the scavenger receptor and was avidly taken
up by macrophages (Henrickson et al., 1981). These data
pr resulting in LDL that competed with acetyl LDL for
binding to the scavenger receptor and was avidly taken
up by macrophages (Henrickson et al., 1981). These data
provided a potential mechanism by which LDL may be
modified binding to the scavenger receptor and was avidly taker
up by macrophages (Henrickson et al., 1981). These data
provided a potential mechanism by which LDL may be
modified in vivo to acquire the ability to form foam cells
a up by macrophages (Henrickson et al., 1981). These data
provided a potential mechanism by which LDL may be
modified in vivo to acquire the ability to form foam cells
and contribute to atherosclerotic lesion formation. Subprovided a potential mechanism by which LDL may be
modified in vivo to acquire the ability to form foam cells
and contribute to atherosclerotic lesion formation. Sub-
sequent studies demonstrated that the nature of the
mod modified in vivo to acquire the ability to form foam cells
and contribute to atherosclerotic lesion formation. Sub-
sequent studies demonstrated that the nature of the
modification mediated by cultured cells involved an ox and contribute to atherosclerotic lesion formation.
sequent studies demonstrated that the nature of
modification mediated by cultured cells involved a
idative process (Steinbrecher et al., 1984; Morel ϵ
1984): hence, t quent studies demonstrated that the hattire of the
odification mediated by cultured cells involved an ox-
ative process (Steinbrecher et al., 1984; Morel et al.,
084): hence, the term "oxidized LDL" was born.
LDL is compri

OXIDIZED LDL
 OXIDIZED LDL
 OXIDIZED LDL
 OXIDIZED LDL
 OXIDIZED LDL
 OXIDIZED LDL 1994).

I. Discovery and Characteristics of Oxidized with low levels of oxidized Low-Density Lipoprotein

Realization of the importance of LDL modification to the process is allowed to continue and oxidized lipid

its oxid modification mediated by cultured cells involved an oidative process (Steinbrecher et al., 1984; Morel et a
1984): hence, the term "oxidized LDL" was born.
LDL is comprised of a cholesterol ester core su
rounded by phosph idative process (Steinbrecher et al., 1984; Morel et al., 1984): hence, the term "oxidized LDL" was born.
LDL is comprised of a cholesterol ester core surrounded by phospholipids and lipophilic antioxidants, including α 1984): hence, the term "oxidized LDL" was born.

LDL is comprised of a cholesterol ester core sur-

rounded by phospholipids and lipophilic antioxidants,

including α -tocopherol and β -carotene. Embedded

within the LDL is comprised of a cholesterol ester core sur-
rounded by phospholipids and lipophilic antioxidants,
including α -tocopherol and β -carotene. Embedded
within the phospholipid coat is one molecule of the apo-
B100 p rounded by phospholipids and lipophilic antioxidants,
including α -tocopherol and β -carotene. Embedded
within the phospholipid coat is one molecule of the apo-
B100 protein, a portion of which serves as the ligand fo within the phospholipid coat is one molecule of the apo-
B100 protein, a portion of which serves as the ligand for
the LDL receptor (fig. 1). LDL can be oxidized in vitro by
exposure to either cultured cells as described a within the phospholipid coat is one molecule of the apo-
B100 protein, a portion of which serves as the ligand for
the LDL receptor (fig. 1). LDL can be oxidized in vitro by
exposure to either cultured cells as described a **1989), resulting in profound changes in the physio-**
the LDL receptor (fig. 1). LDL can be oxidized in vitro by
exposure to either cultured cells as described above, or
by incubation with copper ion (Parthasarathy et al., exposure to either cultured cells as described above, or
by incubation with copper ion (Parthasarathy et al.,
1989), resulting in profound changes in the physio-
chemical properties of the LDL particle (fig. 1). Initially, by included with copper foli (Farthasarathy et 1989), resulting in profound changes in the physichemical properties of the LDL particle (fig. 1). Initia the lipophilic antioxidants ward off modification of LDL particle. Ho chemical properties of the LDL particle (fig. 1). Initially,
the lipophilic antioxidants ward off modification of the
LDL particle. However, after depletion of the antioxi-
dants, polyunsaturated fatty acids of the phospho chemical properties of the LDL particle (fig. 1). Initially,
the lipophilic antioxidants ward off modification of the
LDL particle. However, after depletion of the antioxi-
dants, polyunsaturated fatty acids of the phospho the lipophilic antioxidants ward off modification of the LDL particle. However, after depletion of the antioxidants, polyunsaturated fatty acids of the phospholipids undergo oxidation, resulting in their depletion and the dants, polyunsaturated fatty acids of the phospholipids dants, polyunsaturated fatty acids of the phospholipids
undergo oxidation, resulting in their depletion and the
creation of reactive hydroxy fatty acids (Steinbrecher et
al., 1984; Morel et al., 1984). At this stage of oxi undergo oxidation, resulting in their depletion and the creation of reactive hydroxy fatty acids (Steinbrecher et al., 1984; Morel et al., 1984). At this stage of oxidation, with low levels of oxidized lipid products and a creation of reactive hydroxy fatty acids (Steinbrecher et al., 1984; Morel et al., 1984). At this stage of oxidation, with low levels of oxidized lipid products and a relatively intact apo B100 protein, the LDL particle is al., 1984; Morel et al., 1984). At this stage of oxidation,
with low levels of oxidized lipid products and a relatively
intact apo B100 protein, the LDL particle is considered
"minimally modified" (Berliner et al., 1990). with low levels of oxidized lipid products and a relatively
intact apo B100 protein, the LDL particle is considered
"minimally modified" (Berliner et al., 1990). However, if
the process is allowed to continue and oxidized intact apo B100 protein, the LDL particle is considered "minimally modified" (Berliner et al., 1990). However, if the process is allowed to continue and oxidized lipid products accumulate to higher levels in the particle, "minimally modified" (Berliner et al., 1990). However, if
the process is allowed to continue and oxidized lipid
products accumulate to higher levels in the particle,
they begin to react with and covalently modify amino
aci the process is allowed to continue and oxidized lipid
products accumulate to higher levels in the particle,
they begin to react with and covalently modify amino
acid residues on the apo B-100 protein, resulting in an
incre they begin to react with and covalently modify amino
acid residues on the apo B-100 protein, resulting in an
increase in negative charge of the LDL particle and a

OXIDIZED LOW-DENSITY LIPOPROTEIN
et al., 1992; Steinbrecher, 1987). These oxidative modi- muscle and med
fications of the apo-B100 protein lead to the loss of the tivity of soluble EXECTED LOW-DENSIT CONSIDERT ON A 1992; Steinbrecher, 1987). These oxidative modi-
fications of the apo-B100 protein lead to the loss of the tive
LDL receptor binding ligand, explaining the inability of level OXIDIZED LOW-DENS

et al., 1992; Steinbrecher, 1987). These oxidative modi-

fications of the apo-B100 protein lead to the loss of the

LDL receptor binding ligand, explaining the inability of

oxidized LDL to bind to the et al., 1992; Steinbrecher, 1987). These oxidative modifications of the apo-B100 protein lead to the loss of the LDL receptor binding ligand, explaining the inability of oxidized LDL to bind to the classical LDL receptor, meations of the apo-B100 protein lead to the loss of the

LDL receptor binding ligand, explaining the inability of

oxidized LDL to bind to the classical LDL receptor, but

opensult in new binding epitopes that allow inter LDL receptor binding ligand, explaining the inab oxidized LDL to bind to the classical LDL recept
result in new binding epitopes that allow inter
with the scavenger acetyl-LDL receptor. Oxidatic
results in an extensive con oxidized LDL to bind to the classical LDL receptor, but
result in new binding epitopes that allow interaction
with the scavenger acetyl-LDL receptor. Oxidation also
results in an extensive conversion of phosphatidylcho-
li result in new binding epitopes that allow interaction
with the scavenger acetyl-LDL receptor. Oxidation also
results in an extensive conversion of phosphatidylcho-
line to lysophosphatidylcholine (lyso PC) (Parthasarathy
e with the scavenger acetyl-LDL receptor. Oxidation als
results in an extensive conversion of phosphatidylch
line to lysophosphatidylcholine (lyso PC) (Parthasarath
et al., 1985), as well as to the production of oxystero
fro results in an extensive c
line to lysophosphatidylch
et al., 1985), as well as t
from the cholesterol ester
cle (Zhang et al., 1990).
Thus, oxidative modifics ie to lysophosphatidylcholine (lyso PC) (Parthasarathy al., 1985), as well as to the production of oxysterols om the cholesterol esters in the lipid core of the parti-

(Zhang et al., 1990).

Thus, oxidative modification o et al., 1985), as well as to the production of oxysterols
from the cholesterol esters in the lipid core of the parti-
cle (Zhang et al., 1990).
Thus, oxidative modification of LDL leads to alterations
(in both the lipid an

from the cholesterol esters in the lipid core of the particle. (Zhang et al., 1990).

Thus, oxidative modification of LDL leads to alterations (in both the lipid and protein components of the lipoprotein the particle. The cle (Zhang et al., 1990).
Thus, oxidative modification of LDL leads to alterations
in both the lipid and protein components of the lipoprotein
particle. The modified lipoprotein was studied extensively
to determine its eff Thus, oxidative modification of LDL leads to alterations
in both the lipid and protein components of the lipoprotein
particle. The modified lipoprotein was studied extensively
to determine its effects on macrophages and ot in both the lipid and protein components of the lipoprotein transmuticle. The modified lipoprotein was studied extensively et to determine its effects on macrophages and other cell ton types thought to be involved in athe particle. The modified lipoprotein was studied extensively et
to determine its effects on macrophages and other cell
types thought to be involved in atherosclerosis. Indeed, tre
oxidized LDL exerted a myriad of effects tha to determine its effects on macrophages and other cell to types thought to be involved in atherosclerosis. Indeed, to oxidized LDL exerted a myriad of effects that would be eatherogenic if they occurred in vivo, the majori types thought to be involved in atherosclerosis. Indee
oxidized LDL exerted a myriad of effects that would l
atherogenic if they occurred in vivo, the majority of whic
were not duplicated by native, unoxidized LDL, includi oxidized LDL exerted a myriad of effects that would b
atherogenic if they occurred in vivo, the majority of whic
were not duplicated by native, unoxidized LDL, includin
chemotaxis of monocytes, inhibition of macrophage mot atherogenic if they occurred in vivo, the majority of whi
were not duplicated by native, unoxidized LDL, includi
chemotaxis of monocytes, inhibition of macrophage mot
ity, foam cell formation, up-regulation of endothelial were not duplicated by native, unoxidized LDL, including L
chemotaxis of monocytes, inhibition of macrophage motil-
ity, foam cell formation, up-regulation of endothelial adhe-
losion molecules, stimulation of growth facto ity, foam cell formation, up-regulation of endothelial adhesion molecules, stimulation of growth factor and chemokine expression, and proliferative effects on smooth muscle and monocytes (Holvoet and Collen, 1994). In conc ity, foam cell formation, up-regulation of endothelial adhesion molecules, stimulation of growth factor and cheme
kine expression, and proliferative effects on smooth muscle and monocytes (Holvoet and Collen, 1994). In con sion molecules, stimulation of growth factor and chemo-
kine expression, and proliferative effects on smooth muscle
and monocytes (Holvoet and Collen, 1994). In concert,
these effects of oxidized LDL may contribute to the kine expression, and proliferative effects on smooth musc
and monocytes (Holvoet and Collen, 1994). In concer
these effects of oxidized LDL may contribute to the alte
ations in blood vessel morphology, characterized mo
pro and monocytes (Holvoet and Collen, 1994). In concert, diverse effects of oxidized LDL may contribute to the alter-
ations in blood vessel morphology, characterized most in
prominently by fatty streak formation and intimal these effects of oxidized LDL may contribute to the alter-
ations in blood vessel morphology, characterized most in
prominently by fatty streak formation and intimal thick-
ening, that occur during the initiation and progr ations in blood vessel morphology, characterized merominently by fatty streak formation and intimal thiering, that occur during the initiation and progression atherosclerosis. However, more recent work has reveal that oxid prominently by fatty streak formation and intimal thick-
ening, that occur during the initiation and progression of
atherosclerosis. However, more recent work has revealed
that oxidized LDL also exerts acute effects on the ening, that occur during the initiation and progression of or reach atherosclerosis. However, more recent work has revealed al., that oxidized LDL also exerts acute effects on the vasomo-oxid tor properties of blood vessel that oxidized LDL also exerts acute effects on the vasomo-
tor properties of blood vessels. These findings suggest that
effections in values in variable in the morpholog-
the well-known alterations in vasoactivity that occ oxidized LDL may be involved not only in the morphological alterations associated with atherosclerosis, but also in the well-known alterations in vasoactivity that occur in this disease. Equivalent and the main expectations in variables with a control of the well-known alterations in vasoactivity that occur in this disease.
 III. Effects of Oxidized Low-Density Lipoprotein
 III. Effects of Oxidized Low-

**anterations in vasoactivity
Oxidized Low-Density I
on Vascular Motility**
Endothelium-Dependent Re **A. I. Effects of Oxidized Low-Density Lipoprotein

on Vascular Motility
** *A. Inhibition of Endothelium-Dependent Relaxation***

The endothelium is involved in vasodilation by releas**

I. Effects of Oxidized Low-Density Lipoprotei

on Vascular Motility

Inhibition of Endothelium-Dependent Relaxation

The endothelium is involved in vasodilation by releas-

g multiple factors that diffuse to the underlyin on Vascular Motility

A. Inhibition of Endothelium-Dependent Relaxation

The endothelium is involved in vasodilation by releas-

ing multiple factors that diffuse to the underlying

smooth muscle and cause relaxation, incl A. Innibition of Endothelium-Dependent Relaxation
The endothelium is involved in vasodilation by releas-
ing multiple factors that diffuse to the underlying
smooth muscle and cause relaxation, including endothe-
lium-deriv The endotherium is involved in vasounation by releas-
ing multiple factors that diffuse to the underlying
smooth muscle and cause relaxation, including endothe-
lium-derived relaxing factor (EDRF), believed to be ni-
tric ing multiple factors that diffuse to the underlying est al., 1980 smooth muscle and cause relaxation, including endothe-
lium-derived relaxing factor (EDRF), believed to be ni-
tric oxide (NO) or an NO-containing compound smooth muscle and cause relaxation, including endoth
lium-derived relaxing factor (EDRF), believed to be
tric oxide (NO) or an NO-containing compound (Palm
et al., 1987; Feelisch et al., 1994), prostacyclin (Siegel
al., 19 lium-derived relaxing factor (EDRF), believed to be n
tric oxide (NO) or an NO-containing compound (Palme
et al., 1987; Feelisch et al., 1994), prostacyclin (Siegel e
al., 1989), and possibly an endothelium-derived hyper
p tric oxide (NO) or an NO-containing compound (Palmer
et al., 1987; Feelisch et al., 1994), prostacyclin (Siegel et
al., 1989), and possibly an endothelium-derived hyper-
polarization factor (Hecker et al., 1994). Of these et al., 1987; Feelisch et al., 1994), prostacyclin (Siegel et oxidely), and possibly an endothelium-derived hyper-
polarization factor (Hecker et al., 1994). Of these endo-
the lium-derived mediators, however, NO has been al., 1989), and possibly an endothelium-derived hyper-
polarization factor (Hecker et al., 1994). Of these endo-
thelium-derived mediators, however, NO has been sug-
legested to be most important in the regulation of both polarization factor (Hecker et al., 1994). Of these endo-
thelium-derived mediators, however, NO has been sug-
gested to be most important in the regulation of both Van
basal tone and vasodilation produced by stimuli such thelium-derived mediators, however, NO has been suggested to be most important in the regulation of both basal tone and vasodilation produced by stimuli such as acetylcholine and shear stress in humans in vivor (Haynes et gested to be most important in the regulation of both basal tone and vasodilation produced by stimuli such as acetylcholine and shear stress in humans in vivo (Haynes et al., 1993; Quyyumi et al., 1995). NO is generated in basal tone and vasodilation produced by stimuli such as 1995), acetylcholine and shear stress in humans in vivo NO rel
(Haynes et al., 1993; Quyyumi et al., 1995). NO is gen- tive m
erated in endothelial cells by the oxida acetylcholine and shear stress in humans in vivo NO
(Haynes et al., 1993; Quyyumi et al., 1995). NO is gen-
tive erated in endothelial cells by the oxidation of L-arginine (Kil
to l-citrulline in a reaction catalyzed by en (Haynes et al., 1993; Quyyumi et al., 1995). NO is gen-

erated in endothelial cells by the oxidation of L-arginine (K

to l-citrulline in a reaction catalyzed by endothelial NO

esynthase (eNOS) (Palmer et al., 1988). NO

5
muscle and mediates relaxation by stimulating the ac-
tivity of soluble guanylate cyclase and increasing the tivity LIPOPROTEIN
tivity of soluble guanylate cyclase and increasing the
divity of soluble guanylate cyclase and increasing the
level of cyclic $\texttt{GMP}\xspace$ within the smooth muscle cells (Raplevel and mediates relaxation by stimulating the a
tivity of soluble guanylate cyclase and increasing the
level of cyclic GMP within the smooth muscle cells (Ra
oport and Murad, 1983). NO generated by the endoth muscle and mediates relaxation by stimulating the activity of soluble guanylate cyclase and increasing the level of cyclic CMP within the smooth muscle cells (Rapoport and Murad, 1983). NO generated by the endothe-
hi hevel of cyclic CMP within the smooth muscle cells (Rapproport and Murad, 1983). NO generated by the endothelium also inhibits platelet aggregation and platelet adhesion to the blood vessel wall (Radomski et al., 1987). Th level of cyclic GMP within the smooth muscle cells (Rap
oport and Murad, 1983). NO generated by the endothe
lium also inhibits platelet aggregation and platelet ad
hesion to the blood vessel wall (Radomski et al., 1987)
Th oport and Murad, 1983). NO generated by the endothelium also inhibits platelet aggregation and platelet adhesion to the blood vessel wall (Radomski et al., 1987). Thus, NO plays an important role in the cardiovascular syst im also inhibits platelet aggregation and platelet ad-
sion to the blood vessel wall (Radomski et al., 1987).
nus, NO plays an important role in the cardiovascular
stem by regulating both vasomotion and hemostasis.
Exposur hesion to the blood vessel wall (Radomski et al., 1987).
Thus, NO plays an important role in the cardiovascular
system by regulating both vasomotion and hemostasis.
Exposure of isolated blood vessels to LDL oxidized by
inc

Thus, NO plays an important role in the cardiovascular
system by regulating both vasomotion and hemostasis.
Exposure of isolated blood vessels to LDL oxidized by
incubation with either copper ion or cultured endothelial
ce System by regulating both vasomotion and hemostasis.

Exposure of isolated blood vessels to LDL oxidized by

incubation with either copper ion or cultured endothelial

cells inhibited endothelium-dependent relaxation

(EDR incubation with either copper ion or cultured endothelia
cells inhibited endothelium-dependent relaxatio
(EDR), including relaxation to acetylcholine in precor
tracted rabbit aorta (Kugiyama et al., 1990; Yokoham
et al., 1 cells inhibited endothelium-dependent relaxation (EDR), including relaxation to acetylcholine in precontracted rabbit aorta (Kugiyama et al., 1990; Yokohainet al., 1990), and to 5-hydroxytryptamine (5-HT) (se tonin), throm (EDR), including relaxation to acetylcholine in precontracted rabbit aorta (Kugiyama et al., 1990; Yokohama et al., 1990), and to 5-hydroxytryptamine (5-HT) (serotonin), thrombin, and aggregating platelets in precontracted tracted rabbit aorta (Kugiyama et al., 1990; Yokohama
et al., 1990), and to 5-hydroxytryptamine (5-HT) (sero-
tonin), thrombin, and aggregating platelets in precon-
tracted pig coronary artery (Tanner et al., 1991; Simon
e et al., 1990), and to 5-hydroxytryptamine (5-HT) (serotonin), thrombin, and aggregating platelets in precontracted pig coronary artery (Tanner et al., 1991; Simon et al., 1990; Ohgushi et al., 1993; Murohara et al., 1994). tracted pig coronary artery (Tanner et al., 1991; Simon
et al., 1990; Ohgushi et al., 1993; Murohara et al., 1994).
This effect was selective for oxidized versus unoxidized
LDL and was mediated by concentrations of oxidize Let al., 1990; Ohgushi et al., 1993; Murohara et al., 1994).
This effect was selective for oxidized versus unoxidized
LDL and was mediated by concentrations of oxidized
LDL (10-100 μ g/ml) that are physiologically and p LDL and was mediated by concentrations of oxidized
LDL (10-100 μ g/ml) that are physiologically and patho-
logically relevant (see section IV.D). Although oxidized
LDL can be toxic to cultured endothelial cells with pro logically relevant (see section IV.D). Although oxidized LDL can be toxic to cultured endothelial cells with prolonged incubation (Hessler et al., 1979), oxidized LDL did not inhibit EDR to all relaxant agonists. Oxidized IDL can be toxic to cultured endothelial cells with pro-

IDL can be toxic to cultured endothelial cells with pro-

longed incubation (Hessler et al., 1979), oxidized LDL

IDL had little effect on bradykinin-induced relaxa longed incubation (Hessler et al., 1979), oxidized LDL
did not inhibit EDR to all relaxant agonists. Oxidized
LDL had little effect on bradykinin-induced relaxation
in porcine coronary arteries (Tanner et al., 1991), al-
t did not inhibit EDR to all relaxant agonists. Oxidized LDL had little effect on bradykinin-induced relaxation
in porcine coronary arteries (Tanner et al., 1991), al-
though this response was dependent upon the presence
of LDL had little effect on bradykinin-induced relaxation
in porcine coronary arteries (Tanner et al., 1991), al-
though this response was dependent upon the presence
of functional endothelium (Tanner et al., 1991; Cox et
al. though this response was dependent upon the presence
of functional endothelium (Tanner et al., 1991; Cox et
al., 1995). Thus, acute incubation of blood vessels with
oxidized LDL does not produce a generalized cytotoxic though this response was dependent upon the presence
of functional endothelium (Tanner et al., 1991; Cox et
al., 1995). Thus, acute incubation of blood vessels with
oxidized LDL does not produce a generalized cytotoxic
ef of functional endothelium (Tanner et al., 1991; Cozal., 1995). Thus, acute incubation of blood vessels woxidized LDL does not produce a generalized cytote effect on the endothelium. Furthermore, oxidized L does not inhibit al., 1995). Thus, acute incubation of blood vessels with oxidized LDL does not produce a generalized cytotox effect on the endothelium. Furthermore, oxidized LD does not inhibit smooth muscle relaxation nonsele tively, bec oxidized LDL does not produce a generalized cytotoxic
effect on the endothelium. Furthermore, oxidized LDL
does not inhibit smooth muscle relaxation nonselec-
tively, because relaxation to NO donors such as nitro-
glycerin does not inhibit smooth muscle relaxation nonselectively, because relaxation to NO donors such as nitro-
glycerin and 3-morpholinosydnonimine was unaffected
(Kugiyama et al., 1990; Tanner et al., 1991; Plane et al.,
1992). Taken together, these observations indicate that
 tonin), thrombin, and aggregating platelets in precontant at the selective picomary artery (Tanner et al., 1993), Simon et al., 1993) This effect was selective for oxidized versus unoxidized LDL and was mediated by concen (Kugiyama et al., 1990; Tanner et al., 1991; Plane et al., 1992). Taken together, these observations indicate that oxidized LDL has a selective effect on the endothelium to inhibit vascular relaxation to some agonists. Oxi 1992). Taken together, these observations indicate that oxidized LDL has a selective effect on the endothelium to inhibit vascular relaxation to some agonists.
Oxidized LDL inhibited most effectively vascular relaxation m 1992). Taken together, these observations indicate that oxidized LDL has a selective effect on the endothelium to inhibit vascular relaxation to some agonists.
Cxidized LDL inhibited most effectively vascular relaxation me

oxidized LDL has a selective effect on the endothelium
inhibit vascular relaxation to some agonists.
Oxidized LDL inhibited most effectively vascular r
laxation mediated by agonists that release EDRF(N
from the endothelium inhibit vascular relaxation to some agonists.

Oxidized LDL inhibited most effectively vascular re-

laxation mediated by agonists that release EDRF(NO)

from the endothelium. For example, oxidized LDL mark-

edly inhibite Oxidized LDL inhibited most effectively vascular re-
laxation mediated by agonists that release EDRF(NO)
from the endothelium. For example, oxidized LDL mark-
edly inhibited coronary arterial relaxation to 5-HT and
thrombi laxation mediated by agonists that release EDRF(NO)
from the endothelium. For example, oxidized LDL mark-
edly inhibited coronary arterial relaxation to 5-HT and
thrombin (Tanner et al., 1991; Ohgushi et al., 1993), two
ag edly inhibited coronary arterial relaxation to 5-HT and
thrombin (Tanner et al., 1991; Ohgushi et al., 1993), two
agents whose relaxation is highly sensitive to NO syn-
thase inhibitors (Nagao and Vanhoutte, 1992), whereas early innibited coronary arterial relaxation to 5-ri1 and
thrombin (Tanner et al., 1991; Ohgushi et al., 1993), two
agents whose relaxation is highly sensitive to NO syn-
thase inhibitors (Nagao and Vanhoutte, 1992), where agents whose relaxation is highly sensitive to NO syn-
thase inhibitors (Nagao and Vanhoutte, 1992), whereas
oxidized LDL was less effective in inhibiting relaxation
to bradykinin and the calcium ionophore A23187 (Tan-
ner thase inhibitors (Nagao and Vanhoutte, 1992), whereas
oxidized LDL was less effective in inhibiting relaxation
to bradykinin and the calcium ionophore A23187 (Tan-
ner et al., 1991). EDR to the latter two agonists was also oxidized LDL was less enective in inhibiting relaxation
to bradykinin and the calcium ionophore A23187 (Tan-
ner et al., 1991). EDR to the latter two agonists was also
less sensitive to NO synthase inhibitors (Nagao and
Va ner et al., 1991). EDR to the latter two agonists was also
less sensitive to NO synthase inhibitors (Nagao and
Vanhoutte, 1992; Holzmann et al., 1994; Cox et al.,
1995), suggesting that these mediators do not depend on
NO less sensitive to NO synthase inhibitors (Nagao and Vanhoutte, 1992; Holzmann et al., 1994; Cox et al., 1995), suggesting that these mediators do not depend on NO release to cause relaxation, or can activate alternative me vannoutte, 1992; Holzmann et al., 1994; Cox et al., 1995), suggesting that these mediators do not depend on NO release to cause relaxation, or can activate alternative mechanisms when the NO pathway is inhibited (Kilpatric NO release to cause relaxation, or can activate alternative mechanisms when the NO pathway is inhibited (Kilpatrick and Cocks, 1994). These observations may be explained by an effect of oxidized LDL to either inhibit the p tive mechanisms when the (Kilpatrick and Cocks, 1994)
explained by an effect of outher production and/or biose
the rate of NO degradation

PHARMACOLOGICAL REVIEWS

6
COX AND COHEN
The inhibitory effect of oxidized LDL on endothelium-
dependent, NO-mediated relaxation in blood vessels has on response G

COX AND COX

dependent, NO-mediated relaxation in blood vessels has

prompted intense study of the effect of oxidized LDL on li COX AND COH
The inhibitory effect of oxidized LDL on endothelium-
dependent, NO-mediated relaxation in blood vessels has
on r
prompted intense study of the effect of oxidized LDL on lial
the EDRF(NO) pathway in various sys The inhibitory effect of oxidized LDL on endothelium
dependent, NO-mediated relaxation in blood vessels ha
prompted intense study of the effect of oxidized LDL of
the EDRF(NO) pathway in various systems. These stud
ies hav The inhibitory effect of oxidized LDL on endothelium-
dependent, NO-mediated relaxation in blood vessels has
prompted intense study of the effect of oxidized LDL on
the EDRF(NO) pathway in various systems. These stud-
ies dependent, NO-mediated relaxation in blood vessels has
prompted intense study of the effect of oxidized LDL on
the EDRF(NO) pathway in various systems. These stud-
ies have suggested multiple mechanisms by which oxi-
dized prompted intense study of the effect of oxidized LDL on lia
the EDRF(NO) pathway in various systems. These stud-
relies have suggested multiple mechanisms by which oxi-
midized LDL may inhibit NO-mediated vasorelaxation, i the EDRF(NO) pathway in various systems. These studies have suggested multiple mechanisms by which oxidized LDL may inhibit NO-mediated vasorelaxation, including: (*a*) direct inactivation of NO after its release via direc dized LDL may inhibit NO-mediated vasorelaxation, including: (a) direct inactivation of NO after its release via
a direct interaction with oxidized LDL without an alter-
ation in the amount of NO produced (Galle et al., dized LDL may inhibit NO-mediated vasorelaxation, in-
cluding: (a) direct inactivation of NO after its release via
a direct interaction with oxidized LDL without an alter-
in the absence of added tone, but contracts blood cluding: (a) direct inactivation of NO after its release via
a direct interaction with oxidized LDL without an alter-
ation in the amount of NO produced (Galle et al., 1991;
Chin et al., 1992), (b) alteration in the bioact a direct interaction with oxidized LDL without an alter-
ation in the amount of NO produced (Galle et al., 1991; that
Chin et al., 1992), (b) alteration in the bioactivity of the cont
NO that is released (Myers et al., 199 ation in the amount of NO produced (Galle et al., 1991; that a Chin et al., 1992), (b) alteration in the bioactivity of the contra NO that is released (Myers et al., 1994) or (c) a decrease rabbit in endothelial NO synthas Chin et al., 1992), (b) alteration in the bioactivity of the NO that is released (Myers et al., 1994) or (c) a decrease in endothelial NO synthase mRNA levels, leading to decreased NO synthase protein and to decreased N NO that is released (Myers et al., 1994) or (c) a decrease rabio in endothelial NO synthase mRNA levels, leading to production (Liao et al., 1995). However, more recent dependuction (Liao et al., 1995). However, more rec in endothelial NO synthase mRNA levels, leading to
decreased NO synthase protein and to decreased NO
production (Liao et al., 1995). However, more recent
studies suggest a more complex effect of oxidized LDL on
NO synthas decreased NO synthase protein and to decreased NO a man
production (Liao et al., 1995). However, more recent depend
studies suggest a more complex effect of oxidized LDL on oxidize
NO synthase levels. For example, lower c production (Liao et al., 1995). However, more recent
studies suggest a more complex effect of oxidized LDL on
NO synthase levels. For example, lower concentrations
of oxidized LDL $(1-10 \ \mu g/ml)$ actually increased NO
synth studies suggest a more complex effect of oxidized LDL on
NO synthase levels. For example, lower concentrations
of oxidized LDL $(1-10 \mu g/ml)$ actually increased NO
synthase messenger ribonucleic acid (mRNA) and pro-
tein le NO synthase levels. For example, lower concentrations
of oxidized LDL $(1-10 \mu\text{g/ml})$ actually increased NC
synthase messenger ribonucleic acid (mRNA) and pro
tein levels, whereas higher concentrations $(100 \mu\text{g/ml})$
decr of oxidized LDL $(1-10 \mu g/ml)$ actually increased NO
synthase messenger ribonucleic acid (mRNA) and pro-
tein levels, whereas higher concentrations $(100 \mu g/ml)$
decreased these parameters in bovine aortic endothelial
cells (synthase messenger ribonucleic acid (mRNA) and protein levels, whereas higher concentrations $(100 \mu g/ml)$ the decreased these parameters in bovine aortic endothelial vells (Hirata et al., 1995b), although data demonstratin tein levels, whereas higher concentrations $(100 \mu g/ml)$ tic decreased these parameters in bovine aortic endothelial vecells (Hirata et al., 1995b), although data demonstrating sefunctional consequences of these changes in decreased these parameters in bovine aortic endothelial
cells (Hirata et al., 1995b), although data demonstrating
functional consequences of these changes in NOS levels
were not presented in this study. Nevertheless, the
m cells (Hirata et al., 1995b), although data demonstrating
functional consequences of these changes in NOS level-
were not presented in this study. Nevertheless, the
mechanism by which oxidized LDL interferes with NO
mediat functional consequences of these changes in NOS level
were not presented in this study. Nevertheless, the
mechanism by which oxidized LDL interferes with NO
mediated EDR is not yet clear, and may involve a com
bination of were not presented in this study. Nevertheless, the may mechanism by which oxidized LDL interferes with NO-
mediated EDR is not yet clear, and may involve a com-
bination of acute and chronic effects. In any case, inhi-
bi mechanism by which oxidized LDL interferes with NO-
mediated EDR is not yet clear, and may involve a com-
bination of acute and chronic effects. In any case, inhi-
bition of EDRF(NO)-mediated vasorelaxation is likely to
be LDL. nation of acute and chronic effects. In any case, inhition of EDRF(NO)-mediated vasorelaxation is likely to a major mechanism for the vascular effects of oxidized DL.
It should also be noted that NO is produced in other ll

bition of EDRF(NO)-mediated vasorelaxation is likely to other s
be a major mechanism for the vascular effects of oxidized nephri
LDL.
Lt should also be noted that NO is produced in other oxidize
cell types and tissues by i the a major mechanism for the vascular effects of oxidized nephrincal
LDL. hanced
It should also be noted that NO is produced in other oxidize
cell types and tissues by isoforms of NOS distinct from Contract
that found in has left that NO is produced in other oxidel types and tissues by isoforms of NOS distinct from Conduct that found in endothelial cells (Hattori et al., 1994). A also neuronal NOS has been characterized in the brain and 2A It should also be noted that NO is produced in
cell types and tissues by isoforms of NOS distinc
that found in endothelial cells (Hattori et al., 19
neuronal NOS has been characterized in the brai
peripheral nerves that pr cell types and tissues by isoforms of NOS distinct from
that found in endothelial cells (Hattori et al., 1994). A
neuronal NOS has been characterized in the brain and
peripheral nerves that produces NO as a neurotransmit-
 that found in endothelial cells (Hattori et al., 1994). A
neuronal NOS has been characterized in the brain and
peripheral nerves that produces NO as a neurotransmit-
ter (Schmidt et al., 1992). Furthermore, an inducible
NO neuronal NOS has been characterized in the brain and
peripheral nerves that produces NO as a neurotransmit-
ter (Schmidt et al., 1992). Furthermore, an inducible
NOS is expressed in macrophages (Yui et al., 1991a),
leukocy peripheral nerves that produces NO as a neurotransmit-
ter (Schmidt et al., 1992). Furthermore, an inducible
prone to vasospasm in response to contractile stimuli,
NOS is expressed in macrophages (Yui et al., 1991a), effec ter (Schmidt et al., 1992). Furthermore, an inducible
NOS is expressed in macrophages (Yui et al., 1991a)
leukocytes (Yui et al., 1991b), and vascular smooth mus-
cle cells (Busse and Mulsch, 1990) upon stimulation by
cyto NOS is expressed in macrophages (Yui et al., 1991a), effectively expressed in macrophages (Yui et al., 1991a), effectively expressed by the cytokines or bacterial endotoxin. Unlike the endothelial Network and neuronal NOS leukocytes (Yui et al., 1991b), and vascular smooth m
cle cells (Busse and Mulsch, 1990) upon stimulation
cytokines or bacterial endotoxin. Unlike the endothe
and neuronal NOS isoforms, which are regulated by
concentration cle cells (Busse and Mulsch, 1990) upon stimulation by related cytokines or bacterial endotoxin. Unlike the endothelial NO fro and neuronal NOS isoforms, which are regulated by the thase sconcentration of intracellular fr cytokines or bacterial endotoxin. Unlike the endothelial N
and neuronal NOS isoforms, which are regulated by the
concentration of intracellular free calcium via calmodu-
lin, the inducible NOS is produced in a fully active and neuronal NOS isoforms, which are regulated by the
concentration of intracellular free calcium via calmodu-
lin, the inducible NOS is produced in a fully active form
not regulated by calcium and capable of generating la concentration of intracellular free calcium via calmodu-

lin, the inducible NOS is produced in a fully active form

not regulated by calcium and capable of generating large

in amounts of NO. NO produced by iNOS is though lin, the inducible NOS is produced in a fully active form
not regulated by calcium and capable of generating large
amounts of NO. NO produced by iNOS is thought to play
an important role in host defense mechanisms by actin not regulated by calcium and capable of generating large tiles
amounts of NO. NO produced by iNOS is thought to play the
an important role in host defense mechanisms by acting do
as a cytotoxic agent released by neutrophil amounts of NO. NO produced by iNOS is thought to play
an important role in host defense mechanisms by acting
as a cytotoxic agent released by neutrophils and macro-
phages (Hibbs et al., 1987). Thus, in addition to its rol an important role in host defense mechanisms by acting cases a cytotoxic agent released by neutrophils and macrophages (Hibbs et al., 1987). Thus, in addition to its role 1 in regulating vascular tone, NO has also a regul phages (Hibbs et al., 1987). Thus, in addition to its role in regulating vascular tone, NO has also a regulatory role in the nervous and immune systems. The possibility exists that oxidized LDL may also affect NO-mediated phages (Hibbs et al., 1987). Thus, in a
in regulating vascular tone, NO has
role in the nervous and immune system
exists that oxidized LDL may also af
responses in these systems, as well.
P. Enhanced Artarial Contraction *B. Enhanced Arterial Contraction*
B. Enhanced Arterial Contraction
B. Enhanced Arterial Contraction
The fact that oxidized LDL can Exists that oxidized LDL may also affect NO-mediated
responses in these systems, as well.
B. Enhanced Arterial Contraction
The fact that oxidized LDL can alter relaxant re-

sponses by an effect on endothelial NO-related mecha-B. Enhanced Arterial Contraction of the fact that oxidized LDL can alter relaxant responses by an effect on endothelial NO-related mechanisms may translate into effects of oxidized LDL on the by contractile responses of bl B. Ennanced Arterial Contraction
The fact that oxidized LDL can alter relaxant re-
sponses by an effect on endothelial NO-related mecha-
nisms may translate into effects of oxidized LDL on the
contractile responses of bloo

Although oxidized LDL exerts its most prominent effects COHEN
Although oxidized LDL exerts its most prominent effe
on responses to relaxant agonists that activate endot
lial NO release, oxidized LDL may also affect basal COHEN
Although oxidized LDL exerts its most prominent effects
on responses to relaxant agonists that activate endothe-
lial NO release, oxidized LDL may also affect basal NO
release and produce direct effects on vascular s Although oxidized LDL exerts its most prominent effects
on responses to relaxant agonists that activate endothe-
lial NO release, oxidized LDL may also affect basal NO
release and produce direct effects on vascular smooth
 Although oxidized LDL exerts its most prominent effects
on responses to relaxant agonists that activate endothe-
lial NO release, oxidized LDL may also affect basal NO
release and produce direct effects on vascular smooth
 on responses to relaxant agonists that activate endoted in NO release, oxidized LDL may also affect basal release and produce direct effects on vascular smot muscle. All of these actions of oxidized LDL may of tribute to i l NO release, oxidized LDL may also affect basal NO
lease and produce direct effects on vascular smooth
uscle. All of these actions of oxidized LDL may con-
bute to its diverse effects on vascular contractility.
Oxidized L

release and produce direct effects on vascular smooth
muscle. All of these actions of oxidized LDL may con-
tribute to its diverse effects on vascular contractility.
Oxidized LDL has little effect on isolated blood vessels muscle. All of these actions of oxidized LDL may contribute to its diverse effects on vascular contractility.
Oxidized LDL has little effect on isolated blood vessels
in the absence of added tone, but contracts blood vesse tribute to its diverse effects on vascular contractility.
Oxidized LDL has little effect on isolated blood vessels
in the absence of added tone, but contracts blood vessels
that are pretreated with a threshold concentratio Oxidized LDL has little effect on isolated blood vessels
in the absence of added tone, but contracts blood vessels
that are pretreated with a threshold concentration of
contractile agonist. For example, perfused segments o in the absence of added tone, but contracts blood vessels
that are pretreated with a threshold concentration of
contractile agonist. For example, perfused segments of
rabbit femoral artery, pretreated with norepinephrine t that are pretreated with a threshold concentration of
contractile agonist. For example, perfused segments of
rabbit femoral artery, pretreated with norepinephrine to
provide tone, contracted in response to oxidized LDL in
 rabbit femoral artery, pretreated with norepinephrine to
provide tone, contracted in response to oxidized LDL in
a manner that was both concentration-dependent and
dependent on the extent to which the lipoprotein was
oxidi provide tone, contracted in response to oxidized LDL in
a manner that was both concentration-dependent and
dependent on the extent to which the lipoprotein was
oxidized (Galle et al., 1990). Oxidized LDL also con-
tracted provide tone, contracted in response to oxidized LDL in
a manner that was both concentration-dependent and
dependent on the extent to which the lipoprotein was
oxidized (Galle et al., 1990). Oxidized LDL also con-
tracted a manner that was both concentration-dependent and
dependent on the extent to which the lipoprotein was
oxidized (Galle et al., 1990). Oxidized LDL also con-
tracted porcine coronary arterial rings precontracted
with the t dependent on the extent to which the lipoprotein
oxidized (Galle et al., 1990). Oxidized LDL also
tracted porcine coronary arterial rings precontra
with the thromboxane mimetic U46619 (Simon et
1990; Murohara et al., 1994) oxidized (Galle et al., 1990). Oxidized LDL also contracted porcine coronary arterial rings precontracted with the thromboxane mimetic U46619 (Simon et al., 1990; Murohara et al., 1994). Comparable concentrations of unoxid tracted porcine coronary arterial rings precontracted
with the thromboxane mimetic U46619 (Simon et al.,
1990; Murohara et al., 1994). Comparable concentra-
tions of unoxidized LDL were without effect on blood
vessel tone with the thromboxane mimetic U46619 (Simon et a
1990; Murohara et al., 1994). Comparable concentr
tions of unoxidized LDL were without effect on blo
vessel tone in both tissues. Because arterial blood ve
sels possess basal 1990; Murohara et al., 1994). Comparable concentra-
tions of unoxidized LDL were without effect on blood
vessel tone in both tissues. Because arterial blood ves-
sels possess basal tone in vivo due to sympathetic inner-
v tions of unoxidized LDL were without effect on blood
vessel tone in both tissues. Because arterial blood ves-
sels possess basal tone in vivo due to sympathetic inner-
vation, these in vitro data suggest that oxidized LDL
 vessel tone in both ti
sels possess basal ton
vation, these in vitro
may contract blood ve
the intact vasculature.
In addition to direc Is possess basal tone in vivo due to sympathetic innertion, these in vitro data suggest that oxidized LDL
ay contract blood vessels and increase vascular tone in
e intact vasculature.
In addition to direct contractile act

vation, these in vitro data suggest that oxidized LDL
may contract blood vessels and increase vascular tone in
the intact vasculature.
In addition to direct contractile actions, oxidized LDL
potentiated the contractile res may contract blood vessels and increase vascular tone
the intact vasculature.
In addition to direct contractile actions, oxidized L
potentiated the contractile response of blood vessels
other stimuli. For example, contract the intact vasculature.
In addition to direct contractile actions, oxidized LDL
potentiated the contractile response of blood vessels to
other stimuli. For example, contractile effects of norepi-
nephrine, 5-HT, and potass In addition to direct contractile actions, oxidized LDL
potentiated the contractile response of blood vessels to
other stimuli. For example, contractile effects of norepi-
nephrine, 5-HT, and potassium chloride were all en potentiated the contractile response of blood vessels to
other stimuli. For example, contractile effects of norepi-
nephrine, 5-HT, and potassium chloride were all en-
hanced in perfused rabbit femoral arteries treated wit nephrine, 5-HT, and potassium chloride were all enhanced in perfused rabbit femoral arteries treated with oxidized but not unoxidized LDL (Galle et al., 1990).
Contraction of porcine coronary arteries by 5-HT was also enha nephrine, 5-HT, and potassium chloride were all enhanced in perfused rabbit femoral arteries treated with oxidized but not unoxidized LDL (Galle et al., 1990).
Contraction of porcine coronary arteries by 5-HT was also enha nanced in pertused rabolt lemoral arteries treated with
oxidized but not unoxidized LDL (Galle et al., 1990).
Contraction of porcine coronary arteries by 5-HT was
also enhanced after treatment with oxidized LDL (fig.
2A). Contraction of porcine coronary arteries by 5-HT was
also enhanced after treatment with oxidized LDL (fig.
2A). Thus, oxidized LDL may not only inhibit the ability
of blood vessels to relax, but may also make vessels more
 also enhanced after treatment
24). Thus, oxidized LDL may n
of blood vessels to relax, but ma
prone to vasospasm in respon
effects that may be interrelate
The procontractile actions of (a). Thus, oxidized LDL may not only inhibit the ability
blood vessels to relax, but may also make vessels more
one to vasospasm in response to contractile stimuli,
fects that may be interrelated.
The procontractile action

of blood vessels to relax, but may also make vessels more
prone to vasospasm in response to contractile stimuli,
effects that may be interrelated.
The procontractile actions of oxidized LDL may be
related to its ability to prone to vasospasm in response to contractile stimuligeffects that may be interrelated.
The procontractile actions of oxidized LDL may be related to its ability to inhibit the release or activity of NO from the endotheliu effects that may be interrelated.
The procontractile actions of oxidized LDL m
related to its ability to inhibit the release or active
NO from the endothelium. Indeed, inhibitors of N
thase such as L-N^G-nitro-L-arginine The procontractile actions of oxidized LDL may be related to its ability to inhibit the release or activity of NO from the endothelium. Indeed, inhibitors of NO synthase such as L-N^G-nitro-L-arginine and N^G-monometh-
 related to its ability to inhibit the release or activity NO from the endothelium. Indeed, inhibitors of NO s
thase such as L-N^G-nitro-L-arginine and N^G-monome
yl-L-arginine contracted isolated blood vessels (Palr
et NO from the endothelium. Indeed, inhibitors of NO synthase such as LN^G -nitro-L-arginine and N^G -monometh-
yl-L-arginine contracted isolated blood vessels (Palmer
et al., 1988; Rees et al., 1990) and enhanced the cont thase such as L-N^G-nitro-L-arginine and N^G-monometh-
yl-L-arginine contracted isolated blood vessels (Palmer
et al., 1988; Rees et al., 1990) and enhanced the contrac-
tile response to other agonists (Moncada et al., yl-L-arginine contracted isolated blood vessels (Palm
et al., 1988; Rees et al., 1990) and enhanced the contra
tile response to other agonists (Moncada et al., 1991) v
this mechanism. In fact, blockade of NO release by e
d et al., 1988; Rees et al., 1990) and enhanced the contractile response to other agonists (Moncada et al., 1991) via
this mechanism. In fact, blockade of NO release by endothelial removal or pretreatment with N^G-monomethtile response to other agonists (Moncada et al., 1991) via
this mechanism. In fact, blockade of NO release by en-
dothelial removal or pretreatment with N^G-monometh-
yl-L-arginine prevented the contractile action of oxid this mechanism. In fact, blockade of NO release by e
dothelial removal or pretreatment with N^G -monomet
yl-L-arginine prevented the contractile action of oxidize
LDL (Simon et al., 1990; Murohara et al., 1994), an
a dothelial removal or pretreatment with N^G -monometh-
yl-L-arginine prevented the contractile action of oxidized
LDL (Simon et al., 1990; Murohara et al., 1994), and
attenuated the ability of oxidized LDL to enhance yl-L-arginine prevented the contractile action of oxidized LDL (Simon et al., 1990; Murohara et al., 1994), and attenuated the ability of oxidized LDL to enhance 5-HT-
induced contraction in porcine coronary arteries (fig. LDL (Simon et al., 1990; Murohara et al., 1994), and
attenuated the ability of oxidized LDL to enhance 5-HT-
induced contraction in porcine coronary arteries (fig.
2B). These data are consistent with the hypothesis that
th attenuated the ability of oxidized LDL to enhance 5-HT-
induced contraction in porcine coronary arteries (fig.
2B). These data are consistent with the hypothesis that
the procontractile effects of oxidized LDL are a conseinduced contraction in porcine coronary arteries (fig. 2B). These data are consistent with the hypothesis that the procontractile effects of oxidized LDL are a consequence of its inhibitory effects on the release or activi muscle. quence of its inhibitory effects on the release or activity
of NO rather than a direct effect on vascular smooth
muscle.
Oxidized LDL may also enhance arterial contraction
by stimulating the release of contractile factors

of NO rather than a direct effect on vascular smooth
muscle.
Oxidized LDL may also enhance arterial contraction
by stimulating the release of contractile factors from the
endothelium. Indeed, oxidized LDL stimulated an inof NO rather than a direct effect on vascular smooth
muscle.
Oxidized LDL may also enhance arterial contraction
by stimulating the release of contractile factors from the
endothelium. Indeed, oxidized LDL stimulated an inREVIEW

EXECUTE: CONTROL CONTROL OXLDL CONTROL OXLDL TOO μ **g/ml** and the state of oxidized LDL on maximal 5-HT-induced contraction in porcine coronary artery. *(A)* Porcine coronary arterial rings were incubated 45 min with FIG. 2. Effect of oxidized LDL on maximal 5-HT-induced contration in porcine coronary artery. (A) Porcine coronary arterial rin were incubated 45 min with indicated concentrations of copportidized LDL, followed by cumulat oxidized LDL, followed by cumulative addition of increasing concentrations of 5-HT. (B) Endothelium was removed from porcine coro-FIG. 2. Effect of oxidized LDL on maximal 5-HT-induced contraction in porcine coronary artery. (A) Porcine coronary arterial ring were incubated 45 min with indicated concentrations of copper oxidized LDL, followed by cumu tion in porcine coronary artery. (A) Porcine coronary arterial rings
were incubated 45 min with indicated concentrations of copper-
oxidized LDL, followed by cumulative addition of increasing concen-
trations of 5-HT. (B) were incubated 45 min with indicated concentrations of copper-
oxidized LDL, followed by cumulative addition of increasing concentrations of 5-HT. (*B*) Endothelium was removed from porcine coro-
nary arterial rings by ge Extractions of 5-HT. (B) Endothelium was removed from porcine corronary arterial rings by gentle rubbing. NO synthase was inhibited by pretreating rings 30 min with N^G -monomethyl-L-arginine (100 μ M). Rings were then pretreating rings 30 min with N^G -monomethyl-L-arginine (100 μ M).
Rings were then incubated with oxidized LDL (100 μ g/ml) and challenged with 5-HT as described above.
crease in mRNA expression and release of the po

varies were then included with oxidized LDL (100µg/mi) and challenged with 5-HT as described above.
Crease in mRNA expression and release of the potent
vasoconstrictor peptide endothelin-1 from endothelial
cells isolated f crease in mRNA expression and release of the potent
vasoconstrictor peptide endothelin-1 from endothelial
cells isolated from porcine and human aortae (Boulanger
et al., 1992). Because low concentrations of endothelin-1 erease in mRNA expression and release of the potent
vasoconstrictor peptide endothelin-1 from endothelial
cells isolated from porcine and human aortae (Boulanger
et al., 1992). Because low concentrations of endothelin-1
po crease in mRNA expression and release of the potent Avasoconstrictor peptide endothelin-1 from endothelial role
cells isolated from porcine and human aortae (Boulanger other al., 1992). Because low concentrations of endoth vasoconstrictor peptide endothelin-1 from endothelial
cells isolated from porcine and human aortae (Boulanger
et al., 1992). Because low concentrations of endothelin-1
potentiated contractile responses of human arteries to cells isolated from porcine and human aortae (Boulanger other fiet al., 1992). Because low concentrations of endothelin-1 have no
potentiated contractile responses of human arteries to oxidize
norepinephrine and 5-HT (Yang et al., 1992). Because low concentrations of endothelin-1 have potentiated contractile responses of human arteries to oxide norepine phrine and 5-HT (Yang et al., 1990), the effect (Plase from al. (the endothelium may act potentiated contractile responses of human arteries to
norepinephrine and 5-HT (Yang et al., 1990), the effector
of oxidized LDL to enhance endothelin-1 release from
the endothelium may act in concert with a decrease if
ED spasm. oxidized LDL to enhance endothelin-1 release from al.
e endothelium may act in concert with a decrease in the
DRF(NO)-mediated vasodilation to promote vaso-
asm.
It is possible that in some tissues, oxidized LDL may lys
we

the endothelium may act in concert with a decrease in
EDRF(NO)-mediated vasodilation to promote vaso-
spasm.
It is possible that in some tissues, oxidized LDL may
have additional direct effects on smooth muscle to en-
hanc EDRF(NO)-mediated vasodilation to promote vaso-
spasm. (8
It is possible that in some tissues, oxidized LDL may ly
have additional direct effects on smooth muscle to en-
hance contractile actions of some agonists. The abil spasm.
It is possible that in some tissues, oxidized LDL may
have additional direct effects on smooth muscle to en-
hance contractile actions of some agonists. The ability of
oxidized LDL to contract rabbit femoral artery It is possible that in some tissues, oxidized LDL may lyso
have additional direct effects on smooth muscle to en-
isolitionare contractile actions of some agonists. The ability of icz oxidized LDL to contract rabbit femora have additional direct effects on smooth muscle to enhance contractile actions of some agonists. The ability of oxidized LDL to contract rabbit femoral artery was not dependent on the presence of a functional endothelium (hance contractile actions of some agonists. The ability of oxidized LDL to contract rabbit femoral artery was not dependent on the presence of a functional endothelium (Galle et al., 1990). Furthermore, contractile respons

FITY LIPOPROTEIN
were enhanced by oxidized LDL in an endothelium
dependent manner (Galle et al., 1990; Niu et al., TTY LIPOPROTEIN
were enhanced by oxidized LDL in an endothelium-in-
dependent manner (Galle et al., 1990; Niu et al., 1995).
These data suggest that oxidized LDL enhanced agonist-THE STRIFT STRIFT SITE OF STRIFT SUPPROTEIN
Were enhanced by oxidized LDL in an endothelium-dependent manner (Galle et al., 1990; Niu et al., 199
These data suggest that oxidized LDL enhanced agonis
induced vasoconstrictio were enhanced by oxidized LDL in an endothelium-in-
dependent manner (Galle et al., 1990; Niu et al., 1995).
These data suggest that oxidized LDL enhanced agonist-
induced vasoconstriction in rabbit peripheral arteries
via were enhanced by oxidized LDL in an endothelium-independent manner (Galle et al., 1990; Niu et al., 1995
These data suggest that oxidized LDL enhanced agonist
induced vasoconstriction in rabbit peripheral arterie
via a dir *C. Role of Lysophosphatidylcholine in the Vasomotoria* a direct interaction with vascular smooth muscle.
C. Role of Lysophosphatidylcholine in the Vasomotor
Effects of Oxidized Low-Density Lipoprotein

maticed vasoconstriction in rabort peripheral
via a direct interaction with vascular smooth if
C. Role of Lysophosphatidylcholine in the Vasc
Effects of Oxidized Low-Density Lipoprotein
Several studies suggested that t

Role of Lysophosphatidylcholine in the Vasomotor
Several studies suggested that the active component
ediating many of the in vitro effects of oxidized LDL C. Role of Lysophosphatidylcholine in the Vasomotor
Effects of Oxidized Low-Density Lipoprotein
Several studies suggested that the active component
mediating many of the in vitro effects of oxidized LDL
resides in the lipi C. Role of Lysophosphatalychothe in the vasomotor
Effects of Oxidized Low-Density Lipoprotein
Several studies suggested that the active component
mediating many of the in vitro effects of oxidized LDL
resides in the lipid Effects of Oxidized Low-Density Lipoprotein
Several studies suggested that the active component
mediating many of the in vitro effects of oxidized LDL
resides in the lipid rather than the protein component of
the lipoprote Several studies suggested that the active component
mediating many of the in vitro effects of oxidized LDL
resides in the lipid rather than the protein component of
the lipoprotein and is not present in the lipid fraction mediating many of the in vitro effects of oxidized LE
resides in the lipid rather than the protein component
the lipoprotein and is not present in the lipid fraction
native, unoxidized LDL. One of the lipid componen
unique resides in the lipid rather than the protein component of
the lipoprotein and is not present in the lipid fraction of
native, unoxidized LDL. One of the lipid components
unique to oxidized LDL, lysophosphatidylcholine, mim the lipoprotein and is not present in the lipid fraction of
native, unoxidized LDL. One of the lipid components
unique to oxidized LDL, lysophosphatidylcholine, mim-
icked many of the potentially proatherogenic effects of
 native, unoxidized LDL. One of the lipid components
unique to oxidized LDL, lysophosphatidylcholine, mim-
icked many of the potentially proatherogenic effects of
oxidized LDL, including increased monocyte motility
(Quinn e unique to oxidized LDL, lysophosphatidylcholine, minicked many of the potentially proatherogenic effects oxidized LDL, including increased monocyte motilition of al., 1987), decreased macrophage motilition (Quinn et al., 1 icked many of the potentially proatherogenic effects of oxidized LDL, including increased monocyte motility (Quinn et al., 1987), decreased macrophage motility (Quinn et al., 1985), and increased expression of adhesion mol oxidized LDL, including increased monocyte motility

(Quinn et al., 1987), decreased macrophage motility

(Quinn et al., 1985), and increased expression of adhesion molecules on endothelial cells (Sugiyama et al., 1994). (Quinn et al., 1987), decreased macrophage motility
(Quinn et al., 1985), and increased expression of adhesion molecules on endothelial cells (Sugiyama et al.,
1994). Several lines of evidence suggest that lyso PC
may als (Quinn et al., 1985), and increased expression of adhesion molecules on endothelial cells (Sugiyama et al.
1994). Several lines of evidence suggest that lyso P⁽may also be involved in the vasomotor effects of oxidize
LDL sion molecules on endothelial cells (Sugiyama et al., 1994). Several lines of evidence suggest that lyso PC may also be involved in the vasomotor effects of oxidized LDL, including the following: (a) authentic lyso PC mi 1994). Several lines of evidence suggest that lyso PC may also be involved in the vasomotor effects of oxidized LDL, including the following: (a) authentic lyso PC mimicked the vascular effects of oxidized LDL, including i may also be involved in the vasomotor effects of oxidized LDL, including the following: (a) authentic lyso PC mimicked the vascular effects of oxidized LDL, including inhibition of EDR in the rabbit aorta (Kugiyama et al LDL, including the following: (a) authentic lyso PC mimicked the vascular effects of oxidized LDL, including
inhibition of EDR in the rabbit aorta (Kugiyama et al.,
1990; Yokohama et al., 1990) and pig coronary artery
(O icked the vascular effects of oxidized LDL, including
inhibition of EDR in the rabbit aorta (Kugiyama et al.,
1990; Yokohama et al., 1990) and pig coronary artery
(Ohgushi et al., 1993; Murohara et al., 1994), and con-
tra inhibition of EDR in the rabbit aorta (Kugiyama et al., 1990; Yokohama et al., 1990) and pig coronary artery (Ohgushi et al., 1993; Murohara et al., 1994), and contraction of pig coronary artery (Murohara et al., 1994); (1990; Yokohama et al., 1990) and pig coronary artery
(Ohgushi et al., 1993; Murohara et al., 1994), and contraction of pig coronary artery (Murohara et al., 1994);
(b) oxidized LDL depleted of lyso PC by incubation with
d (Ohgushi et al., 1993; Murohara et al., 1994), and contraction of pig coronary artery (Murohara et al., 1994);

(b) oxidized LDL depleted of lyso PC by incubation with

defatted albumin or phospholipase B lost the ability unique to oxidzed LDL, lysphosphatdycholine, mim-
cicked many of the potentially protablencegence effects of
oxidized LDL, including increased macrophage motility
(Quinn et al., 1987), decreased macrophage motility
(Quinn (b) oxidized LDL depleted of lyso PC by incubation with
defatted albumin or phospholipase B lost the ability to
inhibit EDR and cause contraction (Ohgushi et al., 1993;
Murohara et al., 1994); (c) native LDL incubated wit defatted albumin or phospholipase B lost the ability to
inhibit EDR and cause contraction (Ohgushi et al., 1993;
Murohara et al., 1994); (c) native LDL incubated with
exogenous phospholipase A_2 (PLA₂) to generate lys inhibit EDR and cause contraction (Ohgushi et al., 1993;
Murohara et al., 1994); (c) native LDL incubated with
exogenous phospholipase A_2 (PLA₂) to generate lyso PC
in the lipoprotein imparted upon unoxidized LDL the Murohara et al., 1994); (c) native LDL incubated with exogenous phospholipase A_2 (PL A_2) to generate lyso PC in the lipoprotein imparted upon unoxidized LDL the ability to inhibit EDR (Yokohama et al., 1990); and (d) exogenous phospholipase A_2 (PL A_2) to generate lyso PC
in the lipoprotein imparted upon unoxidized LDL the
ability to inhibit EDR (Yokohama et al., 1990); and (d)
lyso PC inhibited phosphoinositide hydrolysis and ca in the lipoprotein imparted upon unoxidized LDL the
ability to inhibit EDR (Yokohama et al., 1990); and (d)
lyso PC inhibited phosphoinositide hydrolysis and cal-
cium mobilization, mechanisms that are both involved
in a ability to inhibit EDR (Yokohama et al., 1990); and (d. lyso PC inhibited phosphoinositide hydrolysis and calcium mobilization, mechanisms that are both involved
in agonist-stimulated NO release, in human (Inoue et al., 19 cells. Im mobilization, mechanisms that are both involved
agonist-stimulated NO release, in human (Inoue et
1, 1992) and bovine (Kugiyama et al., 1992) endothelial
Ills.
Although the bulk of the data support an important
le for l in agonist-stimulated NO release, in human (Inoue et al., 1992) and bovine (Kugiyama et al., 1992) endothelial
cells.
Although the bulk of the data support an important
role for lyso PC in the vascular effects of oxidized

al., 1992) and bovine (Kugiyama et al., 1992) endothelial
cells.
Although the bulk of the data support an important
role for lyso PC in the vascular effects of oxidized LDL,
other factors may also be involved. In fact, som cells.

Although the bulk of the data support an important

role for lyso PC in the vascular effects of oxidized LDL,

other factors may also be involved. In fact, some studies

have not shown a close association between t Although the bulk of the data support an important
role for lyso PC in the vascular effects of oxidized LDL,
other factors may also be involved. In fact, some studies
have not shown a close association between the ability role for lyso PC in the vascular effects of oxidized LDL,
other factors may also be involved. In fact, some studies
have not shown a close association between the ability of
oxidized LDL to inhibit EDR and its content of other factors may also be involved. In fact, some studies
have not shown a close association between the ability of
oxidized LDL to inhibit EDR and its content of lyso PC
(Plane et al., 1992; Hayashi et al., 1994), and Ta have not shown a close association between the ability of oxidized LDL to inhibit EDR and its content of lyso PC (Plane et al., 1992; Hayashi et al., 1994), and Tanner et al. (1991) reported that lyso PC (10 μ M) did no oxidized LDL to inhibit EDR and its content of lyso PC
(Plane et al., 1992; Hayashi et al., 1994), and Tanner et
al. (1991) reported that lyso PC (10 μ M) did not mimic
the effect of oxidized LDL to inhibit 5-HT-induced (Plane et al., 1992; Hayashi et al., 1994), and Tanner et al. (1991) reported that lyso PC (10 μ M) did not mimic the effect of oxidized LDL to inhibit 5-HT-induced EDR in porcine coronary arteries. Furthermore, chronic al. (1991) reported that lyso PC (10 μ M) did not mimic
the effect of oxidized LDL to inhibit 5-HT-induced EDR
in porcine coronary arteries. Furthermore, chronic
(8–12 hours) exposure of isolated endothelial cells to
ly the effect of oxidized LDL to inhibit 5-HT-induced E
in porcine coronary arteries. Furthermore, chro
(8–12 hours) exposure of isolated endothelial cells
lyso PC up-regulated NOS mRNA and protein levels
isolated endothelial $(8-12 \text{ hours})$ exposure of isolated endothelial cells to lyso PC up-regulated NOS mRNA and protein levels in isolated endothelial cells (Hirata et al., 1995b; Zembowicz et al., 1995), in contrast to its acute effect to inhi lyso PC up-regulated NOS mRNA and protein levels in lyso PC up-regulated NOS mRNA and protein levels in isolated endothelial cells (Hirata et al., 1995b; Zembow-
icz et al., 1995), in contrast to its acute effect to inhibit
EDR. These data suggest that other components of o isolated endothelial cells (Hirata et al., 1995b; Zembow-
icz et al., 1995), in contrast to its acute effect to inhibit
EDR. These data suggest that other components of oxi-
dized LDL may also contribute to its vascular ef icz et al., 1995), in contrast to its acute effect to inhibit EDR. These data suggest that other components of oxidized LDL may also contribute to its vascular effects. For example, oleic acid, a major fatty acid constitue

PHARMACOLOGI

8
line-induced EDR in rabbit aorta, mimicking the effect
of oxidized LDL (Niu et al., 1995). 8
line-induced EDR in rabbit aorta, n
of oxidized LDL (Niu et al., 1995).
In summary, it is clear that oxidiz

COX AND COH

in summary, it is clear that oxidized LDL, perhaps in the summary, it is clear that oxidized LDL, perhaps in

in summary, it is clear that oxidized LDL, perhaps in 199.

In via lyso PC, sensitizes isolated blo line-induced EDR in rabbit aorta, mimicking the effect inhitiant of oxidized LDL (Niu et al., 1995). The summary, it is clear that oxidized LDL, perhaps in 1998 part via lyso PC, sensitizes isolated blood vessels to lation line-induced EDR in rabbit aorta, mimicking the effect in
of oxidized LDL (Niu et al., 1995). en
In summary, it is clear that oxidized LDL, perhaps in
19 part via lyso PC, sensitizes isolated blood vessels to la
contractil of oxidized LDL (Niu et al., 1995). encompose in summary, it is clear that oxidized LDL, perhaps in 199
part via lyso PC, sensitizes isolated blood vessels to lation
tractile stimuli, although multiple cellular sites of ce In summary, it is clear that oxidized LDL, perhaps in
part via lyso PC, sensitizes isolated blood vessels to
contractile stimuli, although multiple cellular sites of
action may be involved, depending upon vascular bed
and part via lyso PC, sensitizes isolated blood vessels to contractile stimuli, although multiple cellular sites of action may be involved, depending upon vascular bed and species. The cellular mechanisms of the vascular effec contractile stimuli, although multiple cellular sites of action may be involved, depending upon vascular bed and species. The cellular mechanisms of the vascular effects of oxidized LDL remain ill-defined, but several poss and species. The cellular mechanisms of the vascular feature of exercises. The cellular mechanisms of the vascular feature of the possibilities are currently under investigation (fig. 3). P
 IV. Cellular Mechanisms for V

effects of oxidized LDL remain ill-defined, but several possibilities are currently under investigation (fig. 3).
 IV. Cellular Mechanisms for Vasomotor Effects of Oxidized Low-Density Lipoprotein

A. Activation of Prote *IV.* Cellular Mechanisms for Vasomotor Effects of

calcium mobilization by oxidized LDL or lyso PC were all A. Activation of Protein Kinase C

Inhibition of EDR, phosphoinositide hydrolysis, and

calcium mobilization by oxidized LDL or lyso PC were all

blocked by protein kinase C (PKC) inhibitors (Ohgushi

et al., 1993; Kugiyam et al., Activation of Frotein Kinase C

Inhibition of EDR, phosphoinositide hydrolysis, and

calcium mobilization by oxidized LDL or lyso PC were all

blocked by protein kinase C (PKC) inhibitors (Ohgushi

et al., 1993; Ku minotion of EDR, phosphomositiae hydrotysis, and
calcium mobilization by oxidized LDL or lyso PC were all $\frac{9}{10}$
blocked by protein kinase C (PKC) inhibitors (Ohgushi
et al., 1993; Kugiyama et al., 1992). Furthermore, blocked by protein kinase C (PKC) inhibitors (Ohgushi et al., 1993; Kugiyama et al., 1992). Furthermore, lyso PC activated PKC in human endothelial cells (Kugiyama et al., 1992) and PKC purified from porcine brain (Oishi e PC activated PKC in human endothelial cells ated with down- and up-regulation, respectively, of NO
(Kugiyama et al., 1992) and PKC purified from porcine synthase mRNA and protein levels of this enzyme in
brain (Oishi et al although activation of PKC by oxidized LDL has not yet (Kugiyama et al., 1992) and PKC purified from porcine
brain (Oishi et al., 1990). These data suggested that
activation of PKC by lyso PC in oxidized LDL may play
a role in the impaired EDR induced by these agents,
although brain (Oishi et al., 1990). These data suggested that
activation of PKC by lyso PC in oxidized LDL may play
a role in the impaired EDR induced by these agents,
although activation of PKC by oxidized LDL has not yet
been r activation of PKC by lyso PC in oxidized LDL may play
a role in the impaired EDR induced by these agents, $\frac{0}{10}$
although activation of PKC by oxidized LDL has not yet
been reported. Nevertheless, phorbol esters inhib a role in the impaired EDR induced by these agents,
although activation of PKC by oxidized LDL has not yet
been reported. Nevertheless, phorbol esters inhibited
EDR in blood vessels isolated from several vascular beds
the

PHOSE CONTRACTION
Phospholipase C; lyso PC, lysophosphatidylcholine; O₂, superoxide

phospholipase C; lyso PC, lysophosphatidylcholine; O₂, superoxide

anion; NOS, nitric oxide synthase; NO, nitric oxide; cGMP, cyc FIG. 3. Potential acute and chronic mechanisms of endothelial dysfunction produced by oxidized LDL. PKC, protein kinase C; PLC, phospholipase C; lyso PC, lysophosphatidylcholine; O_2^- , superoxide anion; NOS, nitric oxid

inhibited NO release from porcine and bovine aortic COHEN
inhibited NO release from porcine and bovine aortic
endothelial cells (Smith and Lang, 1990; Hirata et al.,
1995a). These data support a role for PKC in the regu-COHEN
inhibited NO release from porcine and bovine aorti
endothelial cells (Smith and Lang, 1990; Hirata et al
1995a). These data support a role for PKC in the regu
lation of agonist-stimulated NO release from endothelia inhibited NO release from porcine and bovine aorticendothelial cells (Smith and Lang, 1990; Hirata et al. 1995a). These data support a role for PKC in the regulation of agonist-stimulated NO release from endothelial cells. cells. dothelial cells (Smith and Lang, 1990; Hirata et al., 955a). These data support a role for PKC in the regution of agonist-stimulated NO release from endothelial lls.
Although the mechanism of these PKC-mediated ef-
tts on

V. Cellular Mechanisms for Vasomotor Effects of
 $\begin{array}{c}\n\text{For example, activation of PKC with phorbol esters in-} \\
\text{Dividing Dexidiized Low-Density Lipoprotein} \\
\text{activation of Protein Kinase C} \\
\text{Inhibition of EDR, phosphoinositide hydrolysis, and} \\
\text{Inhibition of EDR, phosphoinositide hydrolysis, and} \\
\text{In addition, PKC phosphor-} \\
\text{In addition, PKC$ 1995a). These data support a role for PKC in the regulation of agonist-stimulated NO release from endothelial
cells.
Although the mechanism of these PKC-mediated ef-
fects on EDR and NO release is unclear, activation of
PK PRIMIT CHERC WAS SERVICED WAS SCHOCKED FOR SHOWN CONSULTER:
PECT SOME DR and NO release is unclear, activation of PKC was shown to modulate both receptor-effector cou-
pling and effector activity in the EDRF(NO) pathway.
F Although the mechanism of these PKC-mediated effects on EDR and NO release is unclear, activation of PKC was shown to modulate both receptor-effector coupling and effector activity in the EDRF(NO) pathway.
For example, act fects on EDR and NO release is unclear, activation of PKC was shown to modulate both receptor-effector coupling and effector activity in the EDRF(NO) pathway.
For example, activation of PKC with phorbol esters in-
hibited PKC was shown to modulate both receptor-effector coupling and effector activity in the EDRF(NO) pathway
For example, activation of PKC with phorbol esters in-
hibited receptor-mediated phosphoinositol hydrolysis
and intrac pling and effector activity in the EDRF(NO) pathway.
For example, activation of PKC with phorbol esters in hibited receptor-mediated phosphoinositol hydrolysies and intracellular calcium mobilization in endotheliancells (B For example, activation of PKC with phorbol esterabilited receptor-mediated phosphoinositol hydrol and intracellular calcium mobilization in endoth cells (Brock et al., 1988; Kugiyama et al., 1992), n icking the effects of hibited receptor-mediated phosphoinositol hydrolysis
and intracellular calcium mobilization in endothelial
cells (Brock et al., 1988; Kugiyama et al., 1992), mim-
icking the effects of lyso PC. In addition, PKC phosphor-
y and intracellular calcium mobilization in endothelial
cells (Brock et al., 1988; Kugiyama et al., 1992), mim-
icking the effects of lyso PC. In addition, PKC phosphor-
ylated purified NO synthase, resulting in a rapid de-
 cells (Brock et al., 1988; Kugiyama et al., 1992), minicking the effects of lyso PC. In addition, PKC phospher ylated purified NO synthase, resulting in a rapid crease in enzyme activity (Bredt et al., 1992). Morecently, a icking the effects of lyso PC. In addition, PKC phosphor-
ylated purified NO synthase, resulting in a rapid de-
crease in enzyme activity (Bredt et al., 1992). More
recently, activation and inhibition of PKC were associ-
 ylated purified NO synthase, resulting in a rapid de-
crease in enzyme activity (Bredt et al., 1992). More
recently, activation and inhibition of PKC were associ-
ated with down- and up-regulation, respectively, of NO
synt recently, activation and inhibition of PKC were associrecently, activation and inhibition of PKC were associated with down- and up-regulation, respectively, of NO synthase mRNA and protein levels of this enzyme in bovine aortic endothelial cells (Ohara et al., 1995a). Thus, P ated with down- and up-regulation, respectively, of NO
synthase mRNA and protein levels of this enzyme in
bovine aortic endothelial cells (Ohara et al., 1995a).
Thus, PKC may regulate NO synthesis by affecting not
only the synthase mRNA and protein levels of this enzyme in
bovine aortic endothelial cells (Ohara et al., 1995a).
Thus, PKC may regulate NO synthesis by affecting not
only the mechanisms of receptor-coupling to NO syn-
thase, but bovine aortic endothelial cells (Ohara et al., 1995a).
Thus, PKC may regulate NO synthesis by affecting not
only the mechanisms of receptor-coupling to NO syn-
thase, but also by affecting the amount and activity of
NO syn Thus, PKC may regulate NO synthesis by affecting not
only the mechanisms of receptor-coupling to NO syn-
thase, but also by affecting the amount and activity of
NO synthase itself. Taken together, these data suggest
that l only the mechanisms of receptor-coupling to NO synthase, but also by affecting the amount and activity of NO synthase itself. Taken together, these data suggest that lyso PC in oxidized LDL may activate PKC in endothelial thase, but also by affecting the amount and activity of NO synthase itself. Taken together, these data suggest
that lyso PC in oxidized LDL may activate PKC in endothelial cells, leading to an inhibition of NO synthase
and NO synthase itself. Taken together, these data suggest
that lyso PC in oxidized LDL may activate PKC in en-
dothelial cells, leading to an inhibition of NO synthase
and a decrease in agonist-stimulated NO release. This
sce that lyso PC in oxidized LDL may activate PKC in endothelial cells, leading to an inhibition of NO synthase and a decrease in agonist-stimulated NO release. This scenario may be one of the mechanisms by which oxidized LDL and a decrease in agonist-stimus
cenario may be one of the mec
dized LDL impairs EDR and esponses in isolated blood vessels *B.* **ID. ID. ID.**

Oxidized LDL-induced inhibition of EDR was selective
for agonists coupled to a pertussis toxin (PTX)-sensitive
G-protein. In the porcine coronary artery, EDR evoked sponses in isolated blood vessels.

B. Inhibition of G-Protein Function

Oxidized LDL-induced inhibition of EDR was selective

for agonists coupled to a pertussis toxin (PTX)-sensitive

G-protein. In the porcine coronary a B. Inhibition of G-Protein Function
Oxidized LDL-induced inhibition of EDR was selective
for agonists coupled to a pertussis toxin (PTX)-sensitive
G-protein. In the porcine coronary artery, EDR evoked
by 5-HT, platelets, a B. Inhibition of G-Protein Function

Oxidized LDL-induced inhibition of EDR was selective

for agonists coupled to a pertussis toxin (PTX)-sensitive

G-protein. In the porcine coronary artery, EDR evoked

by 5-HT, platelet Oxidized LDL-induced inhibition of EDR was selective
for agonists coupled to a pertussis toxin (PTX)-sensitive
G-protein. In the porcine coronary artery, EDR evoked
by 5-HT, platelets, and thrombin was inhibited by PTX,
wh for agonists coupled to a pertussis toxin (PTX)-sensitive G-protein. In the porcine coronary artery, EDR evoked by 5-HT, platelets, and thrombin was inhibited by PTX, whereas EDR evoked by bradykinin and A23187 was PTX-ins G-protein. In the porcine coronary artery, EDR evoked
by 5-HT, platelets, and thrombin was inhibited by PTX,
whereas EDR evoked by bradykinin and A23187 was
PTX-insensitive (Flavahan et al., 1989), a pattern that
parallele by 5-HT, platelets, and thrombin was inhibited by PTX,
whereas EDR evoked by bradykinin and A23187 was
PTX-insensitive (Flavahan et al., 1989), a pattern that
paralleled the effects of oxidized LDL (Tanner et al.,
1991; Co whereas EDR evoked by bradykinin and A23187 was
PTX-insensitive (Flavahan et al., 1989), a pattern that
paralleled the effects of oxidized LDL (Tanner et al.,
1991; Cox and Cohen, unpublished observations) and
lyso PC (Fla PTX-insensitive (Flavahan et al., 1989), a pattern that
paralleled the effects of oxidized LDL (Tanner et al.,
1991; Cox and Cohen, unpublished observations) and
lyso PC (Flavahan, 1993). These data have prompted the
hypot paralleled the effects of oxidized LDL (Tanner et al., 1991; Cox and Cohen, unpublished observations) and lyso PC (Flavahan, 1993). These data have prompted the hypothesis that oxidized LDL may affect the function of a PT 1991; Cox and Cohen, unpublished observations) and
lyso PC (Flavahan, 1993). These data have prompted the
hypothesis that oxidized LDL may affect the function of
a PTX-sensitive G₁-protein in endothelial cells. Indeed,
 lyso PC (Flavahan, 1993). These data have prompted
hypothesis that oxidized LDL may affect the function
a PTX-sensitive G_i -protein in endothelial cells. Inde
oxidized LDL down-regulated the level of $G_{i\alpha}$ subunit
bov hypothesis that oxidized LDL may affect the function
a PTX-sensitive G_i -protein in endothelial cells. Indee
oxidized LDL down-regulated the level of $G_{i\alpha}$ subunit
bovine aortic endothelial cells and inhibited agonis
 a PTX-sensitive G_i -protein in endothelial cells. Indeed, oxidized LDL down-regulated the level of $G_{i\alpha}$ subunit in bovine aortic endothelial cells and inhibited agonistinduced GTPase activity in concentrations that i oxidized LDL down-regulated the level of $G_{i\alpha}$ subunit in
bovine aortic endothelial cells and inhibited agonist-
induced GTPase activity in concentrations that inhib-
ited EDR in intact blood vessels (Liao and Clark, 1 bovine about endothenal cents and immoted agonist-
induced GTPase activity in concentrations that inhib-
ited EDR in intact blood vessels (Liao and Clark, 1995).
Thus, by inhibiting activity of the G_i-protein, oxidized
 ited EDR in intact blood vessels (Liao and Clark, 1995).
Thus, by inhibiting activity of the G_i -protein, oxidized
LDL may selectively uncouple certain receptors from
mediating EDRF(NO) release and, thus, selectively in-Thus, by inhibiting activity of the G_i -protein, oxidized LDL may selectively uncouple certain receptors from mediating EDRF(NO) release and, thus, selectively inhibit EDR. The mechanism by which oxidized LDL inhibits G LDL may selectively uncouple certain receptors from
mediating EDRF(NO) release and, thus, selectively in-
hibit EDR. The mechanism by which oxidized LDL in-
hibits G_i -protein function could be related to changes in
the mediating EDRF(NO) release and, thus, selectively in-
hibit EDR. The mechanism by which oxidized LDL in-
hibits G_i -protein function could be related to changes in
the fluidity or lipid composition of the cell membrane
(hibit EDR. The mechanism by which oxidized LDL in-
hibits G_i -protein function could be related to changes in
the fluidity or lipid composition of the cell membrane
(Flavahan, 1992). Alternatively, this action may be remous G_i -protein function could be related to changes
the fluidity or lipid composition of the cell membra
(Flavahan, 1992). Alternatively, this action may be
lated to PKC activation by oxidized LDL, which m
phosphorylat

ARMACOLOGICAL REVIEW

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OXIDIZED LOW-DENSITY LIPOPROTEIN
C. Stimulation of Superoxide Production
Lyso PC increased superoxide anion production from expression of enc OXIDIZED LOW-DENSITY LIP

Stimulation of Superoxide Production Becaus

Lyso PC increased superoxide anion production from express

lated rabbit aorta in a PKC-dependent manner 1993; lated OXIDIZED LOW-DEN
C. Stimulation of Superoxide Production
Lyso PC increased superoxide anion production from
isolated rabbit aorta in a PKC-dependent manner
(Ohara et al., 1994). Superoxide anion is generated as a C. Stimulation of Superoxide Production

Lyso PC increased superoxide anion production from

isolated rabbit aorta in a PKC-dependent manner

(Ohara et al., 1994). Superoxide anion is generated as a

by-product of many ce Example 19 Supervalue Production

Lyso PC increased supervalue anion production from

isolated rabbit aorta in a PKC-dependent manner

(Ohara et al., 1994). Supervalue anion is generated as a

by-product of many cellular Lyso PC increased superoxide anion production from
isolated rabbit aorta in a PKC-dependent manner
(Ohara et al., 1994). Superoxide anion is generated as a
by-product of many cellular reactions and is normally
maintained a isolated rabbit aorta in a PKC-dependent manner
(Ohara et al., 1994). Superoxide anion is generated as a
by-product of many cellular reactions and is normally
maintained at a very low level by the activity of a radical
sc (Ohara et al., 1994). Superoxide anion is generated as a
by-product of many cellular reactions and is normally
maintained at a very low level by the activity of a radical
scavenging system of enzymes consisting primarily o by-product of many cellular reactions and is normal
maintained at a very low level by the activity of a radiscavenging system of enzymes consisting primarily
superoxide dismutase (SOD) and catalase (Rubar
1988). Superoxide maintained at a very low level by the activity of a radica
scavenging system of enzymes consisting primarily o
superoxide dismutase (SOD) and catalase (Rubanyi
1988). Superoxide inactivated NO via a direct interac
tion (Gr scavenging system of enzymes consisting primarily
superoxide dismutase (SOD) and catalase (Ruban
1988). Superoxide inactivated NO via a direct interation
(Gryglewski et al., 1986; Rubanyi and Vanhout
1986a), suggesting tha superoxide dismutase (SOD) and catalase (Rubanyi
1988). Superoxide inactivated NO via a direct interaction (Gryglewski et al., 1986; Rubanyi and Vanhoutte
1986a), suggesting that an increase in vascular super
oxide product tion (Gryglewski et al., 1986; Rubanyi and Vanhoutte, 1986a), suggesting that an increase in vascular super-
oxide production could inhibit NO-mediated relaxation.
Consistent with this hypothesis, increasing endogenous tion (Gryglewski et al., 1986; Rubanyi and Vanhoutte, 1986a), suggesting that an increase in vascular super-
oxide production could inhibit NO-mediated relaxation.
Consistent with this hypothesis, increasing endogenous
sup 1986a), suggesting that an increase in vascular super-

oxide production could inhibit NO-mediated relaxation. P

Consistent with this hypothesis, increasing endogenous

superoxide by inhibition of vascular SOD activity (oxide production could inhibit NO-mediated relaxation
Consistent with this hypothesis, increasing endogenous
superoxide by inhibition of vascular SOD activity (Oma
et al., 1991) or exogenous generation of superoxide via
xa Consistent with this hypothesis, increasing endogenous
superoxide by inhibition of vascular SOD activity (Omar
et al., 1991) or exogenous generation of superoxide via
may
xanthine and xanthine oxidase (Rubanyi and Van-
ef et al., 1991) or exogenous generation of superoxide via
xanthine and xanthine oxidase (Rubanyi and Vanet al., 1991) or exogenous generation of superoxide via
xanthine and xanthine oxidase (Rubanyi and Vanhoutte, 1986b; Seccombe et al., 1994) inhibited EDR in
isolated blood vessels. Interestingly, the pattern of inhi-
bitio houtte, 1986b; Seccombe et al., 1994) inhibited EDR in
isolated blood vessels. Interestingly, the pattern of inhi-
bition of EDR produced by superoxide anions in canine
coronarary artery was similar to that reported for ox houtte, 1986b; Seccombe et al., 1994) inhibited EDR in

isolated blood vessels. Interestingly, the pattern of inhi-

bition of EDR produced by superoxide anions in canine

coronarary artery was similar to that reported for bition of EDR produced by superoxide anions in canine coronarary artery was similar to that reported for oxidized LDL and lyso PC in other blood vessels; relaxation evoked by acetylcholine was inhibited, whereas brady-kini coronarary artery was similar to that reported for o
dized LDL and lyso PC in other blood vessels; relaxati
evoked by acetylcholine was inhibited, whereas brac
kinin-induced relaxation was unaffected (Seccombe
al., 1994). dized LDL and lyso PC in other blood vessels; relaxation
evoked by acetylcholine was inhibited, whereas brady-
kinin-induced relaxation was unaffected (Seccombe et
al., 1994). Thus, increased vascular superoxide produc-
ti evoked by acetylchome was immoted, whereas brady-
kinin-induced relaxation was unaffected (Seccombe et
al., 1994). Thus, increased vascular superoxide produc-
tion is another potential mechanism by which oxidized
LDL and l *D. Induction of Adhesion Molecules and Inflammatory*
D. Induction of Adhesion Molecules and Inflammatory

Cytokines

19

Although the effects of oxidized LDL described above

although the effects of oxidized LDL described above

ay be involved in some of the acute and direct vaso-D. Induction of Adhesion Molecules and Inflammatory
Cytokines
Although the effects of oxidized LDL described abov
may be involved in some of the acute and direct vaso-
motor effects observed in isolated blood vessels, chro D . Induction of Adnesion Motecutes and Inflammatory
Cytokines

Although the effects of oxidized LDL described above

may be involved in some of the acute and direct vaso-

motor effects observed in isolated blood vessel cytokines

Although the effects of oxidized LDL described above

may be involved in some of the acute and direct vaso-

motor effects observed in isolated blood vessels, chronic

incubation of cultured cells with oxidized Although the effects of oxidized LDL described above promay be involved in some of the acute and direct vasometer motor effects observed in isolated blood vessels, chronic this incubation of cultured cells with oxidized LD may be involved in some of the acute and direct va
motor effects observed in isolated blood vessels, chro
incubation of cultured cells with oxidized LDL has be
shown to induce inflammatory gene products in vi
that may exer motor effects observed in isolated blood vessels, chronic the incubation of cultured cells with oxidized LDL has been Lishown to induce inflammatory gene products in vitro his that may exert indirect but profound effects o Included in the expression of cultured centers with oxidized LDL has
shown to induce inflammatory gene products in
that may exert indirect but profound effects on va
tion if these effects also occur in vivo. Minimally ox
L shown to induce inflammatory gene products in vitro
that may exert indirect but profound effects on vasomo-
tion if these effects also occur in vivo. Minimally oxidized
LDL induced the expression of monocyte chemoattrac-
t that may exert indirect but profound effects on vasomotion if these effects also occur in vivo. Minimally oxidized
LDL induced the expression of monocyte chemoattraction
tant peptide-1 and macrophage colony stimulating fac tion if these effects also occur in vivo. Minimally oxidized two UDL induced the expression of monocyte chemoattrachistant peptide-1 and macrophage colony stimulating faction in endothelial cells (Berliner et al., 1990; Cu LDL induced the expression of monocyte chemoattra
tant peptide-1 and macrophage colony stimulating fa
tor in endothelial cells (Berliner et al., 1990; Cushing e
al., 1990; Rajavashisth et al., 1990), and oxidized LD
and ly tant peptide-1 and macrophage colony stimulating fac-
tor in endothelial cells (Berliner et al., 1990; Cushing et iya
al., 1990; Rajavashisth et al., 1990), and oxidized LDL to i
and lyso PC stimulated expression of adhesi tor in endothelial cells (Berliner et al., 1990; Cushing et al., 1990; Rajavashisth et al., 1990), and oxidized LDI and lyso PC stimulated expression of adhesion mole cules that play a role in the binding of monocytes and al., 1990; Rajavashisth et al., 1990), and oxidized LDL to and lyso PC stimulated expression of adhesion mole-
cules that play a role in the binding of monocytes and The
leukocytes to endothelial cells (Kume et al., 1993; and lyso PC stimulated expression of adhesion mole-
cules that play a role in the binding of monocytes and
leukocytes to endothelial cells (Kume et al., 1993; Sug-
iyama et al., 1994). In concert, these effects may be
impo cules that play a role in the binding of monocytes and Theukocytes to endothelial cells (Kume et al., 1993; Sug-
iyama et al., 1994). In concert, these effects may be site
important in the recruitment of monocytes and the leukocytes to endothelial cells (Kume et al., 1993; Sug-
iyama et al., 1994). In concert, these effects may be
important in the recruitment of monocytes and the con-
version of these monocytes to macrophages during early iyama et al., 1994). In concert, these effects may be site
important in the recruitment of monocytes and the con-
version of these monocytes to macrophages during early I
lesion formation in atherosclerosis. In addition, a important in the recruitment of monocytes and the conversion of these monocytes to macrophages during early lesion formation in atherosclerosis. In addition, adherence of inflammatory leukocytes to the endothelium also inh version of these monocytes to macrophages during early Irlesion formation in atherosclerosis. In addition, adhermolence of inflammatory leukocytes to the endothelium also oxidinhibited EDR (Sugiyama et al., 1994), suggesti ence of inflammatory leukocytes to the endothelium also inhibited EDR (Sugiyama et al., 1994), suggesting that enhanced recruitment and retention of monocytes by oxidized LDL may also affect vasomotion. Furthermore, minim ence of inflammatory leukocytes to the endothelium also oxidized LDL may exert vascular effects. However, claribilitied EDR (Sugiyama et al., 1994), suggesting that ification of these mechanisms may provide opportunities e inhibited EDR (Sugiyama et al., 1994), suggesting tha
enhanced recruitment and retention of monocytes b
oxidized LDL may also affect vasomotion. Furthermore
minimally oxidized LDL was also shown to activat
NF- κ B (Parha enhanced recruitment and retention of monocytes
oxidized LDL may also affect vasomotion. Furtherm
minimally oxidized LDL was also shown to activ
NF-kB (Parhami et al., 1993; Peng et al., 1995), a t
scription factor involve oxidized LDL may also affect vasomotion. Furthermore,
minimally oxidized LDL was also shown to activate
NF- κ B (Parhami et al., 1993; Peng et al., 1995), a tran-
scription factor involved in the induction of inflamma-
t

9
Because certain cytokines potently down-regulated the
expression of endothelial NO synthase (Yoshizumi et al., 9
Because certain cytokines potently down-regulated the
expression of endothelial NO synthase (Yoshizumi et al.,
1993; Rosenkranz-Weiss et al., 1994), chronic effects of 9
1993; Rosenkranz-Weiss potently down-regulated the
1993; Rosenkranz-Weiss et al., 1994), chronic effects of
1993; Rosenkranz-Weiss et al., 1994), chronic effects of
1993; Rosenkranz-Weiss et al., 1994), chronic effects o Because certain cytokines potently down-regulated the
expression of endothelial NO synthase (Yoshizumi et al.,
1993; Rosenkranz-Weiss et al., 1994), chronic effects of
oxidized LDL on the transcription of inflammatory gene Because certain cytokines potently down-regulated the
expression of endothelial NO synthase (Yoshizumi et al.,
1993; Rosenkranz-Weiss et al., 1994), chronic effects of
oxidized LDL on the transcription of inflammatory gene expression of endothelial NO synth
1993; Rosenkranz-Weiss et al., 19
oxidized LDL on the transcription
products could produce vasomotor
inhibition of NO-mediated EDR. oxidized LDL on the transcription of inflammatory gene
products could produce vasomotor effects related to an
inhibition of NO-mediated EDR.
E. Activation of an Oxidized Low-Density Lipoprotein

Receptor

hibition of NO-mediated EDR.

Activation of an Oxidized Low-Density Lipoprotein

cceptor

The vasoactive effects of oxidized LDL may be inde-

ndent of receptor interaction. Indeed, lyso PC wa E. Activation of an Oxidized Low-Density Lipoprotein
Receptor
The vasoactive effects of oxidized LDL may be inde-
pendent of receptor interaction. Indeed, lyso PC was
passively transfered from oxidized LDL to the cell memexplores.

Receptor

The vasoactive effects of oxidized LDL may be independent of receptor interaction. Indeed, lyso PC was

passively transfered from oxidized LDL to the cell mem-

brane and into the cytosol via a recepto The vasoactive effects of oxidized LDL may be i
pendent of receptor interaction. Indeed, lyso PC
passively transfered from oxidized LDL to the cell m
brane and into the cytosol via a receptor-indepen
mechanism (Ohgushi et The vasoactive effects of oxidized LDL may be inde-
pendent of receptor interaction. Indeed, lyso PC was
passively transfered from oxidized LDL to the cell mem-
brane and into the cytosol via a receptor-independent
mechan pendent of receptor interaction. Indeed, lyso PC was
passively transfered from oxidized LDL to the cell mem-
brane and into the cytosol via a receptor-independent
mechanism (Ohgushi et al., 1993). Although lyso PC
may not passively transfered from oxidized LDL to the cell membrane and into the cytosol via a receptor-independent mechanism (Ohgushi et al., 1993). Although lyso PC may not be the sole mediator responsible for vasoactive effects brane and into the cytosol via a receptor-independent
mechanism (Ohgushi et al., 1993). Although lyso PC
may not be the sole mediator responsible for vasoactive
effects of oxidized LDL, other active components in oxi-
dize mechanism (Ohgushi et al., 1993). Although lyso PC
may not be the sole mediator responsible for vasoactive
effects of oxidized LDL, other active components in oxi-
dized LDL may be similarly transfered to target cell
memb may not be the sole mediator responsible for vasoactive effects of oxidized LDL, other active components in oxidized LDL may be similarly transfered to target cellular membranes. Alternatively, the binding of oxidized LD t effects of oxidized LDL, other active compoidized LDL may be similarly transfered to membranes. Alternatively, the binding of o
to a cell-surface receptor may also modify c
tion and contribute to its vascular actions.
Oxid is a LDL may be similarly transfered to target cell embranes. Alternatively, the binding of oxidized LDL a cell-surface receptor may also modify cellular function and contribute to its vascular actions. Oxidized LDL binds

dized LDL and lyso PC in other blood vessels; relaxation
evoked by acetylcholine was inhibited, whereas brady-
kinin-induced relaxation was unaffected (Seccombe et al., 1981), the glycoprotein CD36 (Endemann et al.,
al., Oxidized LDL binds to a variety of cell surface proteins, including the acetyl-LDL receptor (Henrikson et to a cell-surface receptor may also modify cellular function and contribute to its vascular actions.

Oxidized LDL binds to a variety of cell surface proteins, including the acetyl-LDL receptor (Henrikson et al., 1981), th tion and contribute to its vascular actions.

Oxidized LDL binds to a variety of cell surface pr

teins, including the acetyl-LDL receptor (Henrikson

al., 1981), the glycoprotein CD36 (Endemann et a

1993; Nicholson et al Oxidized LDL binds to a variety of cell surface p
teins, including the acetyl-LDL receptor (Henrikson
al., 1981), the glycoprotein CD36 (Endemann et a
1993; Nicholson et al., 1995), the immunoglobulin rec
tor FcyRII (Stant teins, including the acetyl-LDL receptor (Henrikson et al., 1981), the glycoprotein CD36 (Endemann et al., 1993; Nicholson et al., 1995), the immunoglobulin receptor FcyRII (Stanton et al., 1992), and a recently characteri al., 1981), the glycoprotein CD36 (Endemann et al.
1993; Nicholson et al., 1995), the immunoglobulin receptor FcyRII (Stanton et al., 1992), and a recently characterized 94-97 kDa macrophage plasma membrane protein (Ottnad 1993; Nicholson et al., 1995), the immunoglobulin receptor $Fc\gamma RII$ (Stanton et al., 1992), and a recently characterized 94-97 kDa macrophage plasma membrane protein (Ottnad et al., 1995; Sambrano and Steinberg, 1995). Of tor Fc γ RII (Stanton et al., 1992), and a recently characterized 94-97 kDa macrophage plasma membrane protein (Ottnad et al., 1995; Sambrano and Steinberg, 1995). Of these, the acetyl-LDL receptor (Stein and Stein, 1980 terized 94–97 kDa macrophage plasma membrane pro-
tein (Ottnad et al., 1995; Sambrano and Steinberg
1995). Of these, the acetyl-LDL receptor (Stein and
Stein, 1980; Voyta et al., 1984) and CD36 (Swerlick et
al., 1992) have tein (Ottnad et al., 1995; Sambrano and Steinberg, 1995). Of these, the acetyl-LDL receptor (Stein and Stein, 1980; Voyta et al., 1984) and CD36 (Swerlick et al., 1992) have already been identified on endothelial cells, su 1995). Of these, the acetyl-LDL receptor (Stein and Stein, 1980; Voyta et al., 1984) and CD36 (Swerlick et al., 1992) have already been identified on endothelial cells, suggesting that receptors for oxidized LDL are presen Stein, 1980; Voyta et al., 1984) and CD36 (Swerlick et al., 1992) have already been identified on endothelial cells, suggesting that receptors for oxidized LDL are present on endothelial cells that may play a role in the v al., 1992) have already been identified on endothel
cells, suggesting that receptors for oxidized LDL a
present on endothelial cells that may play a role in t
vascular motility effects of this lipoprotein. In support
this cells, suggesting that receptors for oxidized LDL are
present on endothelial cells that may play a role in the
vascular motility effects of this lipoprotein. In support of
this possibility, dextran sulfate, a blocker of th present on endothelial cells that may play a role in the vascular motility effects of this lipoprotein. In support of this possibility, dextran sulfate, a blocker of the acetyl-LDL receptor, blocked the effect of oxidized this possibility, dextran sulfate, a blocker of the acetyl-
LDL receptor, blocked the effect of oxidized LDL to in-
hibit 5-HT relaxation of porcine coronary artery (Tanner
et al., 1991). However, fucoidon and polyinosinic this possibility, dextran sulfate, a blocker of the acetyl-
LDL receptor, blocked the effect of oxidized LDL to in-
hibit 5-HT relaxation of porcine coronary artery (Tanner
et al., 1991). However, fucoidon and polyinosinic LDL receptor, blocked the effect of oxidized LDL to
hibit 5-HT relaxation of porcine coronary artery (Tar
et al., 1991). However, fucoidon and polyinosinic ϵ
two other blockers of the acetyl-LDL receptor, faile
block th hibit 5-HT relaxation of porcine coronary artery (Tanne
et al., 1991). However, fucoidon and polyinosinic acid
two other blockers of the acetyl-LDL receptor, failed t
block the effect of oxidized LDL to inhibit thrombir
me et al., 1991). However, fucoidon and polyinosinic acid,
two other blockers of the acetyl-LDL receptor, failed to
block the effect of oxidized LDL to inhibit thrombin-
mediated relaxation of porcine coronary artery (Sug-
iy block the effect of oxidized LDL to inhibit thrombin-
mediated relaxation of porcine coronary artery (Sug-
iyama et al., 1994). Additionally, acetylated LDL failed
to mimic the effect of oxidized LDL on thrombin-medi-
ated block the effect of oxidized LDL to inhibit thrombin-
mediated relaxation of porcine coronary artery (Sug-
iyama et al., 1994). Additionally, acetylated LDL failed
to mimic the effect of oxidized LDL on thrombin-medi-
ated mediated relaxation of porcine coronary artery (Sug-
iyama et al., 1994). Additionally, acetylated LDL failed
to mimic the effect of oxidized LDL on thrombin-medi-
ated relaxation in this tissue (Sugiyama et al., 1994).
Th iyama et al., 1994). Additionally, acetylated LDL failed
to mimic the effect of oxidized LDL on thrombin-medi-
ated relaxation in this tissue (Sugiyama et al., 1994).
Thus, further study is required before a role for the
a ated relaxation in this tissue (Sugiyama et al., 1994).
Thus, further study is required before a role for the
acetyl LDL receptor and other oxidized LDL binding
sites in the vasomotor effects of this lipoprotein can be
est established. In summary, there is required before a role for the etyl LDL receptor and other oxidized LDL binding
leas in the vasomotor effects of this lipoprotein can be
tablished.
In summary, there is clearly much to learn about the

acetyl LDL receptor and other oxidized LDL binding
sites in the vasomotor effects of this lipoprotein can be
established.
In summary, there is clearly much to learn about the
multiple cellular and molecular mechanisms by w sites in the vasomotor effects of this lipoprotein can be
established.
In summary, there is clearly much to learn about the
multiple cellular and molecular mechanisms by which
oxidized LDL may exert vascular effects. Howev established.
In summary, there is clearly much to learn about the
multiple cellular and molecular mechanisms by which
oxidized LDL may exert vascular effects. However, clar-
ification of these mechanisms may provide opport In summary, there is clearly much to learn about the
multiple cellular and molecular mechanisms by which
oxidized LDL may exert vascular effects. However, clar-
ification of these mechanisms may provide opportunities
to ph multiple cellular and molecular mechanisms by which
oxidized LDL may exert vascular effects. However, clar-
ification of these mechanisms may provide opportunities
to pharmacologically inhibit or reverse these vascular
act oxidized LDL may exert vascular effects. However
ification of these mechanisms may provide opportu
to pharmacologically inhibit or reverse these va
actions. If oxidized LDL is intimately involved
development of vascular dy ification of these mechanisms may provide opportunit
to pharmacologically inhibit or reverse these vascu
actions. If oxidized LDL is intimately involved in t
development of vascular dysfunction in hypercholest
olemia and a to pharmacologically inhibit or reverse these vascular actions. If oxidized LDL is intimately involved in the development of vascular dysfunction in hypercholester-
olemia and atherosclerosis, then inhibiting the vasomo-
t actions. If oxidized LDL is intimately involved in the development of vascular dysfunction in hypercholester-
olemia and atherosclerosis, then inhibiting the vasomo-
tor actions of oxidized LDL in vivo may normalize vas-
c

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letting to the control of t involved in atherosclerosis-induced disturbances in va-
somotion.
involved in atherosclerosis-induced disturbances in va-
somotion. somotion. Examples of evidence to suggest that oxidized LDL is, indeed only in a the rosclerosis-induced disturbances in variantion.
 V. Vascular Effects of Oxidized Low-Density
 Lipoprotein Associated with

Lipoprotein Associated Michael School
Lipoprotein Associated With
Lipoprotein Associated with
holesterolemia and Atheroscleros Hypercholesterolemia and **Atherosclerosis** V. Vascular Effects of Oxidized Low-Density
Lipoprotein Associated with
Hypercholesterolemia and Atherosclerosis
It is now well-accepted that human atherosclerosis
d hypercholesterolemia are associated with alter-

Lipoprotein Associated with
Hypercholesterolemia and Atherosclerosis
It is now well-accepted that human atherosclerosis
and hypercholesterolemia are associated with alter-
ations in vascular reactivity in vivo related to a ment in endothelium-mediated vasodilator function mypercholesterolemia and Atheroscierosis
It is now well-accepted that human atherosclerosis dand
hypercholesterolemia are associated with alter-
ations in vascular reactivity in vivo related to an impair-
ment in endotheli It is now well-accepted that human atherosclerosis development and hypercholesterolemia are associated with alter-
ations in vascular reactivity in vivo related to an impair-
ment in endothelium-mediated vasodilator functi and hypercholesterolemia are associated with alter-
ations in vascular reactivity in vivo related to an impair-
ment in endothelium-mediated vasodilator function ar
(Verbeuren, 1991; Harrison, 1994). An important role of ations in vascular reactivity in vivo related to an impair-
ment in endothelium-mediated vasodilator function a
(Verbeuren, 1991; Harrison, 1994). An important role of ti
oxidized LDL in these alterations in vascular funct ment in endothelium-mediated vasodilator functi
(Verbeuren, 1991; Harrison, 1994). An important role
oxidized LDL in these alterations in vascular function
suggested by four major lines of evidence (table 1):
the striking (Verbeuren, 1991; Harrison, 1994). An important role of tive oxidized LDL in these alterations in vascular function is whouggested by four major lines of evidence (table 1): (*a*) P ather striking similarity between the n oxidized LDL in these alterations in vascular function is wedgested by four major lines of evidence (table 1): (a) P the striking similarity between the nature of the vascu-
lar impairment produced by atherosclerosis in suggested by four major lines of evidence (table 1): (a)
the striking similarity between the nature of the vascu-
lar impairment produced by atherosclerosis in vivo and
that produced by oxidized LDL in vitro, (b) the ab the striking similarity between the nature of the valar impairment produced by atherosclerosis in vivo
that produced by oxidized LDL in vitro, (b) the abili-
elevated serum cholesterol to produce altered vasc
function in lar impairment produced by atherosclerosis in vivo and 1
that produced by oxidized LDL in vitro, (b) the ability of
elevated serum cholesterol to produce altered vascular
function independent of the presence of gross ath that produced by oxidized LDL in vitro, (b) the abilit
elevated serum cholesterol to produce altered vasco
function independent of the presence of gross atheros
rotic lesions, (c) the ability of antioxidants to revers
i elevated serum cholesterol to produce altered vascular point function independent of the presence of gross atherosclerotic lesions, *(c)* the ability of antioxidants to reverse or inhibit impairment of endothelial function transfer of the presence of gross attenuate-
trotic lesions, (c) the ability of antioxidants to reverse or
inhibit impairment of endothelial function in hypercho-
lesterolemia and atherosclerosis, and (d) confirmation of
 rotic lesions, (c) the ability of antioxidants to reverse or inhibit impairment of endothelial function in hypercholesterolemia and atherosclerosis, and (d) confirmation of the presence of oxidized LDL in vivo in human *A. Vascular Effects of Oxidized LDL* in vivo in hundlengtherman and atherosclerosis, and (d) confinition presence of oxidized Low-Density Lipoprotein Mimic the Vascular Dysfunction of

Lipoprotein Mimic the presence of oxidized LDL in vivo in human vessels with atherosclerosis.
 A. Vascular Effects of Oxidized Low-Density
 Lipoprotein Mimic the Vascular Dysfunction of Atherosclerosis and Hypercholes *A. Vascular Effects of Oxidized Low-Density*
Lipoprotein Mimic the Vascular Dysfunction
Atherosclerosis and Hypercholesterolemia

A. Vascular Effects of Oxidized Low-Density

Lipoprotein Mimic the Vascular Dysfunction of

Atherosclerosis and Hypercholesterolemia

Isolated segments of blood vessels from animals and

humans with hypercholesterolemia or exported variable variable to the the Atherosclerosis and Hypercholesterolemia

Isolated segments of blood vessels from animals and spontaneons with hypercholesterolemia or atherosclerosis den

exhibit altered vasomotor pr Huneroscierosis and Hypercholesterolemia
Isolated segments of blood vessels from animals and
humans with hypercholesterolemia or atherosclerosis
exhibit altered vasomotor properties very similar to
those produced by oxidiz Isolated segments of blood vessels from animals and
humans with hypercholesterolemia or atherosclerosis
exhibit altered vasomotor properties very similar to
those produced by oxidized LDL in vitro. For example,
aortic ring humans with hypercholesterolemia or atheroscle
exhibit altered vasomotor properties very similiathose produced by oxidized LDL in vitro. For exametic rings obtained from cholesterol-fed rashowed impaired ability to relax t exhibit altered vasomotor properties very similar to
those produced by oxidized LDL in vitro. For example,
aortic rings obtained from cholesterol-fed rabbits
showed impaired ability to relax to the endothelium-
dependent v those produced by oxidized LDL in vitro. For exametic rings obtained from cholesterol-fed rashowed impaired ability to relax to the endothelic
dependent vasodilators acetylcholine and adendiphosphate, whereas relaxation to diphosphate, whereas relaxation to the endothelium-
TABLE 1

Summary of evidence for the role of oxidized LDL in the vascular

independent vasodilator nitroglycerin was unaffected COHEN
independent vasodilator nitroglycerin was unaffected
except in the most severely lesioned arteries (Habib et
al., 1986; Verbeuren et al., 1986). Similar data were
reported for isolated coronary arterial segments from independent vasodilator nitroglycerin was unaffected
except in the most severely lesioned arteries (Habib et
al., 1986; Verbeuren et al., 1986). Similar data were
reported for isolated coronary arterial segments from
hyper independent vasodilator nitroglycerin was unaffected
except in the most severely lesioned arteries (Habib et
al., 1986; Verbeuren et al., 1986). Similar data were
reported for isolated coronary arterial segments from
hyper except in the most severely lesioned arteries (Habib et al., 1986; Verbeuren et al., 1986). Similar data were
reported for isolated coronary arterial segments from
hypercholesterolemic and atherosclerotic pigs, where
EDR t al., 1986; Verbeuren et al., 1986). Similar data were
reported for isolated coronary arterial segments from
hypercholesterolemic and atherosclerotic pigs, where
EDR to 5-HT and aggregating platelets was impaired,
whereas E reported for isolated coronary arterial segments in
hypercholesterolemic and atherosclerotic pigs, w
EDR to 5-HT and aggregating platelets was impair
whereas EDR to the calcium ionophore A23187 and
dothelium-independent re hypercholesterolemic and atherosclerotic pigs, where
EDR to 5-HT and aggregating platelets was impaired,
whereas EDR to the calcium ionophore A23187 and en-
dothelium-independent relaxation to sodium nitroprus-
side were b whereas EDR to the calcium ionophore A23187 and en-
dothelium-independent relaxation to sodium nitroprus-
side were both preserved (Cohen et al., 1988; Shi-
mokawa and Vanhoutte, 1989). Human coronary
arterial segments wit whereas EDR to the calcium ionophore A23187 and endothelium-independent relaxation to sodium nitropruside were both preserved (Cohen et al., 1988; Sh mokawa and Vanhoutte, 1989). Human coronan arterial segments with athero dothelium-independent relaxation to sodium nitropruside were both preserved (Cohen et al., 1988; Sh
mokawa and Vanhoutte, 1989). Human coronan
arterial segments with atherosclerosis were also sele
tively impaired in the ab side were both preserved (Cohen et al., 1988; Shi-
mokawa and Vanhoutte, 1989). Human coronary
arterial segments with atherosclerosis were also selec-
tively impaired in the ability to relax to acetylcholine,
whereas endot mokawa and Vanhoutte, 1989). Human coronary
arterial segments with atherosclerosis were also selec-
tively impaired in the ability to relax to acetylcholine,
whereas endothelial-dependent relaxation to substance
P and hist arterial segments with atherosclerosis were also selectively impaired in the ability to relax to acetylcholine, whereas endothelial-dependent relaxation to substance P and histamine were only partially affected, and that t tively impaired in the ability to relax to acetylcholine,
whereas endothelial-dependent relaxation to substance
P and histamine were only partially affected, and that to
A23187 was completely preserved (Bossaller et al.,
1 whereas endothelial-dependent relaxation to substance
P and histamine were only partially affected, and that to
A23187 was completely preserved (Bossaller et al.,
1987). Thus, blood vessels from animals and humans
with hyp P and histamine were only partially affected, and that to A23187 was completely preserved (Bossaller et al., 1987). Thus, blood vessels from animals and humans with hypercholesterolemia or atherosclerosis exhibited a patte A23187 was completely pr
1987). Thus, blood vessels f
with hypercholesterolemia or
pattern of impaired EDR th
produced by oxidized LDL.
Atherosclerotic blood vess with hypercholesterolemia or atherosclerosis exhibited a
pattern of impaired EDR that closely resembled that
produced by oxidized LDL.
Atherosclerotic blood vessels were also more sensi-
tive to certain contractile stimuli

with hypercholesterolemia or atherosclerosis exhibited a
pattern of impaired EDR that closely resembled that
produced by oxidized LDL.
Atherosclerotic blood vessels were also more sensi-
tive to certain contractile stimuli pattern of impaired EDR that closely resembled that
produced by oxidized LDL.
Atherosclerotic blood vessels were also more sensi-
tive to certain contractile stimuli (Verbeuren et al.,
1986; Shimokawa and Vanhoutte, 1989; produced by oxidized LDL.

Atherosclerotic blood vessels were also more sens

tive to certain contractile stimuli (Verbeuren et a

1986; Shimokawa and Vanhoutte, 1989; Cohen et a

1988; Lamping et al., 1994; Miwa et al., 1 Atherosclerotic blood vessels were also more sensitive to certain contractile stimuli (Verbeuren et al., 1986; Shimokawa and Vanhoutte, 1989; Cohen et al., 1988; Lamping et al., 1994; Miwa et al., 1994). Interestingly, the tive to certain contractile stimuli (Verbeuren et al., 1986; Shimokawa and Vanhoutte, 1989; Cohen et al., 1988; Lamping et al., 1994; Miwa et al., 1994). Interestingly, the mechanism of the enhanced contractile response in 1986; Shimokawa and Vanhoutte, 1989; Cohen et al.,
1988; Lamping et al., 1994; Miwa et al., 1994). Inter-
estingly, the mechanism of the enhanced contractile
response in atherosclerotic blood vessels differs
among species 1988; Lamping et al., 1994; Miwa et al., 1994). Inter-
estingly, the mechanism of the enhanced contractile
response in atherosclerotic blood vessels differs
among species and parallels the species differences in
the mechan estingly, the mechanism of the enhanced contractile
response in atherosclerotic blood vessels differs
among species and parallels the species differences in
the mechanism of oxidized LDL's in vitro vasomotor
effects. For e response in atherosclerotic blood vessels dif
among species and parallels the species difference
the mechanism of oxidized LDL's in vitro vasome
effects. For example, the enhanced contractile
sponse in atherosclerotic rabb among species and parallels the species differences in
the mechanism of oxidized LDL's in vitro vasomotor
effects. For example, the enhanced contractile re-
sponse in atherosclerotic rabbit arteries was indepen-
dent of th effects. For example, the enhanced contractile response in atherosclerotic rabbit arteries was independent of the endothelium and caused by direct effects on calcium handling in the vascular smooth muscle effects. For example, the enhanced contractile response in atherosclerotic rabbit arteries was independent of the endothelium and caused by direct effects on calcium handling in the vascular smooth muscle (Miwa et al., 199 sponse in atherosclerotic rabbit arteries was independent of the endothelium and caused by direct effects
on calcium handling in the vascular smooth muscle
(Miwa et al., 1994; Stepp and Tulenko, 1994; Cox and
Tulenko, 1995 dent of the endothelium and caused by direct effects
on calcium handling in the vascular smooth muscle
(Miwa et al., 1994; Stepp and Tulenko, 1994; Cox and
Tulenko, 1995). In contrast, enhanced contraction of
coronary arte on calcium handling in the vascular smooth mus
(Miwa et al., 1994; Stepp and Tulenko, 1994; Cox a
Tulenko, 1995). In contrast, enhanced contraction
coronary arteries produced by atherosclerosis in p
(Shimokawa and Vanhoutt (Miwa et al., 1994; Stepp and Tulenko, 1994; Cox and
Tulenko, 1995). In contrast, enhanced contraction of
coronary arteries produced by atherosclerosis in pigs
(Shimokawa and Vanhoutte, 1989), monkeys (Lamp-
ing et al., 19 Tulenko, 1995). In contrast, enhanced contraction of
coronary arteries produced by atherosclerosis in pigs
(Shimokawa and Vanhoutte, 1989), monkeys (Lamp-
ing et al., 1994), and humans (Golino et al., 1991) was
primarily d coronary arteries produced by atherosclerosis in pigs
(Shimokawa and Vanhoutte, 1989), monkeys (Lamp-
ing et al., 1994), and humans (Golino et al., 1991) was
primarily due to the inhibition of EDRF(NO) release
from the end (Shimokawa and Vanhoutte, 1989), monkeys (Lamping et al., 1994), and humans (Golino et al., 1991) was primarily due to the inhibition of $EDRF(NO)$ release from the endothelium and not related to direct effects on the vascul Impet al., 1994), and numans (Golino et al., 1991) was
primarily due to the inhibition of EDRF(NO) release
from the endothelium and not related to direct effects
on the vascular smooth muscle. The fact that oxidized
LDL ex from the endothelium and not related to direct effects
on the vascular smooth muscle. The fact that oxidized
LDL exhibited very similar species-dependent mech-
anistic differences in its effect on contractile re-
sponses (on the vascular smooth muscle. The fact that oxidized LDL exhibited very similar species-dependent mechanistic differences in its effect on contractile responses (see section II.B.) strongly supports the hypothesis that ox LDL exhibited very similar species-dependent
anistic differences in its effect on contracti
sponses (see section II.B.) strongly supports t
pothesis that oxidized LDL is involved directly
vasomotor disturbances produced by anistic differences in its effect on contract
sponses (see section II.B.) strongly supports
pothesis that oxidized LDL is involved directly
vasomotor disturbances produced by hyperche
olemia and atherosclerosis in various onses (see section II.B.) strongly supports the hy-
thesis that oxidized LDL is involved directly in the
somotor disturbances produced by hypercholester-
emia and atherosclerosis in various species.
The alterations in vasc

pothesis that oxidized LDL is involved directly in the vasomotor disturbances produced by hypercholester-
olemia and atherosclerosis in various species.
The alterations in vascular reactivity observed in vitro
in isolated vasomotor disturbances produced by hypercholester-
olemia and atherosclerosis in various species.
The alterations in vascular reactivity observed in vitro
in isolated blood vessels from atherosclerotic animals
and humans a olemia and atherosclerosis in various species.
The alterations in vascular reactivity observed in vitro
in isolated blood vessels from atherosclerotic animals
and humans appears to be present in vivo, as well.
Quantitative The alterations in vascular reactivity observed in vitro
in isolated blood vessels from atherosclerotic animals
and humans appears to be present in vivo, as well.
Quantitative angiography has been utilized to measure
chang in isolated blood vessels from atherosclerotic animals
and humans appears to be present in vivo, as well
Quantitative angiography has been utilized to measure
changes in human coronary blood flow in vivo after
intracoronar and humans appears to be present in vivo, as well.
Quantitative angiography has been utilized to measure
changes in human coronary blood flow in vivo after
intracoronary infusion of various vasoactive mediators.
Whereas in Quantitative angiography has been utilized to measure
changes in human coronary blood flow in vivo after
intracoronary infusion of various vasoactive mediators.
Whereas infusion of acetylcholine resulted in modest
vasodila changes in human coronary blood flow in vivo after intracoronary infusion of various vasoactive mediators.
Whereas infusion of acetylcholine resulted in modest vasodilation in patients without atherosclerosis, this treatme intracoronary infusion of various vasoactive mediators.
Whereas infusion of acetylcholine resulted in modest
vasodilation in patients without atherosclerosis, this
treatment caused vasoconstriction in patients with cor-
on Whereas infusion of acetylcholine resulted in modest
vasodilation in patients without atherosclerosis, this
treatment caused vasoconstriction in patients with cor-
onary artery disease (Ludmer et al., 1986). Coronary
vasod treatment caused vasoconstriction in patients with coronary artery disease (Ludmer et al., 1986). Coronary vasodilation in response to nitroglycerin was normal in patients with atherosclerosis (Ludmer et al., 1986), con-

PHARMACOLOGICAL REVIEW!

OXIDIZED LOW-DENSITY LIPOPROTEIN 11

oxidized Low-Disistent with the in vitro studies on atherosclerotic blood
vessels described above. More recently, a similar phe-
nomenon was demonstrated with 5-HT, which caused OXIDIZED LOW-DENSIT
sistent with the in vitro studies on atherosclerotic blood
rivessels described above. More recently, a similar phe-
tenomenon was demonstrated with 5-HT, which caused ro
coronary vasodilation and increa sistent with the in vitro studies on atherosclerotic blood risk
vessels described above. More recently, a similar phe-
nomenon was demonstrated with 5-HT, which caused rotic
coronary vasodilation and increased coronary flo sustent with the in vitro studies on atheroscierotic blood
vessels described above. More recently, a similar phe-
nomenon was demonstrated with 5-HT, which caused
coronary vasodilation and increased coronary flow in
patien vessels described dove: More recently, a similar photomore commenon was demonstrated with 5-HT, which caused ro
coronary vasodilation and increased coronary flow in 19
patients with angiographically normal arteries, but in momenon was demonstrated with 5-HT, which caused row coronary vasodilation and increased coronary flow in 19 patients with angiographically normal arteries, but intervalsed vasospasm and decreased flow in patients with ima coronary vasodilation and increased coronary flow in 1
patients with angiographically normal arteries, but in-
duced vasospasm and decreased flow in patients with in
angiographic evidence of coronary artery disease (Golino patients with angiographically normal arteries, but interduced vasospasm and decreased flow in patients with impangiographic evidence of coronary artery disease (Golino bloot al., 1991) or symptoms of variant or stable ang duced vasospasm and decreased flow in patients with
angiographic evidence of coronary artery disease (Golino
et al., 1991) or symptoms of variant or stable angina
(McFadden et al., 1991). Impaired vasodilation was also
dem angiographic evidence of coronary artery disease (Georgian et al., 1991) or symptoms of variant or stable an (McFadden et al., 1991). Impaired vasodilation was demonstrated in several regions of the peripheral culature in et al., 1991) or symptoms of variant or stable angina
(McFadden et al., 1991). Impaired vasodilation was also
demonstrated in several regions of the peripheral vas-
culature in patients with atherosclerosis or hypercholes-(McFadden et al., 1991). Impaired vasodilation was also et demonstrated in several regions of the peripheral vas-
culature in patients with atherosclerosis or hypercholes-
terolemia (Gilligan et al., 1994b; Casino et al., demonstrated in several regions of the peripheral vas-
culature in patients with atherosclerosis or hypercholes-
terolemia (Gilligan et al., 1994b; Casino et al., 1995;
Arcaro et al., 1995). Therefore, in vitro and in vivo terolemia (Gilligan et al., 1994b; Casino et al., 1995; r
Arcaro et al., 1995). Therefore, in vitro and in vivo data circum both animal and human studies suggest that hy-
percholesterolemia and atherosclerosis are associat Arcaro et al., 1995). Therefore, in vitro and in vivo data develop visible signs of atherosclerosis (Anderson et al., from both animal and human studies suggest that hy-1995b). Thus, vascular dysfunction in atherosclerosis percholesterolemia and atherosclerosis are associated
with vascular dysfunction characterized by a selective
inhibition of EDR and enhanced contraction to certain
agonists, similar to the in vitro vascular effects of oxi-
 percholesterc
with vascula
inhibition of
agonists, sim
dized LDL.
There are a th vascular dysfunction characterized by a selective lest hibition of EDR and enhanced contraction to certain blomists, similar to the in vitro vascular effects of oxical LDL.

contraction of the second LDL.

There are als

miniorition of EDR and emfanced contraction to certa
agonists, similar to the in vitro vascular effects of o
dized LDL.
There are also striking similarities between some of t
mechanisms that are thought to be involved in t agonists, similar to the in vitro vascular effects of
dized LDL.
There are also striking similarities between some of
mechanisms that are thought to be involved in the in
tion of EDR induced by atherosclerosis and hyperche dized LDL.
There are also striking similarities between some of t
mechanisms that are thought to be involved in the inhi
tion of EDR induced by atherosclerosis and hyperchol
terolemia and the mechanisms of oxidized LDL's v There are also striking similarities between some of the scler
mechanisms that are thought to be involved in the inhibialter
tion of EDR induced by atherosclerosis and hypercholes- modi
terolemia and the mechanisms of oxid mechanisms that are thought to be involved in the inhibition of EDR induced by atherosclerosis and hypercholes-
terolemia and the mechanisms of oxidized LDL's vasomo-
tor effects. Isolated blood vessels exposed to oxidized tion of EDR induced by atherosclerosis and hypercholes-
terolemia and the mechanisms of oxidized LDL's vasomo-
functor effects. Isolated blood vessels exposed to oxidized LDL with
(Tanner et al., 1991; Flavahan, 1993) and terolemia and the mechanisms of oxidized LDL's vasomotor effects. Isolated blood vessels exposed to oxidized LDL
(Tanner et al., 1991; Flavahan, 1993) and coronary arteries
from atherosclerotic pigs were both selectively d tor effects. Isolated blood vessels exposed to oxidized LDL (Tanner et al., 1991; Flavahan, 1993) and coronary arteries from atherosclerotic pigs were both selectively deficient in (EDR mediated by G_i -protein-coupled ag (Tanner et al., 1991; Flavahan, 1993) and coronary arteries
from atherosclerotic pigs were both selectively deficient in
EDR mediated by G_i -protein-coupled agonists (Shimokawa
et al., 1991). Similarities are also eviden from atherosclerotic pigs were both selectively deficient in (Harris EDR mediated by G_i -protein-coupled agonists (Shimokawa also no net al., 1991). Similarities are also evident in rabbit models responsion for atheroscl EDR mediated by G_i -protein-coupled agonists (Shimokawa alet al., 1991). Similarities are also evident in rabbit models reprosed of atherosclerosis where, similar to the effect of lyso PC, see superoxide anion production et al., 1991). Similarities are also evident in rabbit models of atherosclerosis where, similar to the effect of lyso PC, superoxide anion production was increased in aortae from hypercholesterolemic rabbits (Ohara et al., of atherosclerosis where, similar to the effect of lyso PC,
superoxide anion production was increased in aortae from
hypercholesterolemic rabbits (Ohara et al., 1993; Keaney
et al., 1995). In fact, the increased production superoxide anion production was increased in aortae from
hypercholesterolemic rabbits (Ohara et al., 1993; Keaney era
et al., 1995). In fact, the increased production of vascular als
superoxide anion induced by hypercholes hypercholesterolemic rabbits (Ohara et al., 1993; Keaney
et al., 1995). In fact, the increased production of vascular
superoxide anion induced by hypercholesterolemia posi-
tively correlated with increased tissue levels of et al., 1995). In fact, the increased production of vascular superoxide anion induced by hypercholesterolemia positively correlated with increased tissue levels of both lyso PC and indices of oxidized lipids (Keaney et al. superoxide anion induced by hypercholesterolemia p
tively correlated with increased tissue levels of both l
PC and indices of oxidized lipids (Keaney et al., 19:
suggesting that oxidized LDL was involved in the incre
in su tively correlated with increased tissue levels of both lyso hy
PC and indices of oxidized lipids (Keaney et al., 1995), sic
suggesting that oxidized LDL was involved in the increase vai
in superoxide production in vivo. Fu PC and indices of oxidized lipids (Keaney et al., 1995), si
suggesting that oxidized LDL was involved in the increase va
in superoxide production in vivo. Furthermore, hypercho-
lesterolemia-induced enhancement of superoxi suggesting that oxidized LDL was involved in the increase
in superoxide production in vivo. Furthermore, hypercho-
lesterolemia-induced enhancement of superoxide anion
production was reversed by either dietary normalizatio in superoxide production in vivo. Furthermore, hypercholesterolemia-induced enhancement of superoxide anion production was reversed by either dietary normalization of serum cholesterol levels (Ohara et al., 1995b) or conco desteroienna-induced ennancement of superoxide anion
production was reversed by either dietary normalization of
serum cholesterol levels (Ohara et al., 1995b) or concomi-
tant treatment with the antioxidant cholesterol-low production was reversed by either dietary normalization of
serum cholesterol levels (Ohara et al., 1995b) or concomi-
tant treatment with the antioxidant cholesterol-lowering
drug probucol (Keaney et al., 1995). Taken toge for the value of the value of the value of the variant treatment with the antioxidant cholesterol-loved drug probucol (Keaney et al., 1995). Taken together, data suggest that the underlying mechanisms respo
for the vascula tant treatment with the antioxidant cholesterol-lowering sendrug probucol (Keaney et al., 1995). Taken together, these studies are consistent during mechanisms responsible ize for the vascular dysfunction observed in hyper drug probucol (Keaney et al., 1995). Taken together, these st
data suggest that the underlying mechanisms responsible iz
for the vascular dysfunction observed in hypercholesterol-
pemia and atherosclerosis are consistent w data suggest that the underlying mechanisms responsible ized
for the vascular dysfunction observed in hypercholesterol-
percemia and atherosclerosis are consistent with some of the sion
effects of oxidized LDL on isolated for the vascular dysfunction observed in hypercholesterol-
emia and atherosclerosis are consistent with some of the
effects of oxidized LDL on isolated blood vessels, providing
further evidence for a role of this modified *B. Atherosclerosis-Induced B. Atherosclerosis-Induced DDL* on isolated blood vessels, providing further evidence for a role of this modified lipoprotein in pathological vasomotor disturbances.
B. Atherosclerosis-Induc First Primarily 1972 on Board Choice Server, primarily further evidence for a role of this modified lipopropathological vasomotor disturbances.
 R. Atherosclerosis-Induced Vascular Dysfunction
 Related Primarily to Elev

thological vasomotor disturbances.

Atherosclerosis-Induced Vascular Dysfunction Is

lated Primarily to Elevated Serum Cholesterol

Several lines of evidence suggest that the vascular

sfunction associated with atheroscler B. Atherosclerosis-Induced Vascular Dysfunction Is

Related Primarily to Elevated Serum Cholesterol crea

Several lines of evidence suggest that the vascular ather

dysfunction associated with atherosclerosis is due to

i B. Atherosclerosis-Induced Vascular Dysfunction Is
Related Primarily to Elevated Serum Cholesterol
Several lines of evidence suggest that the vascular
dysfunction associated with atherosclerosis is due to
increased serum c creased *Frimarity to Elevated Serum Cholesterot*
Several lines of evidence suggest that the vasculdysfunction associated with atherosclerosis is due
increased serum cholesterol levels (and presumedly is
creased levels of Several lines of evidence suggest that the vascular
dysfunction associated with atherosclerosis is due to
increased serum cholesterol levels (and presumedly in-
creased levels of oxidized LDL) rather than the forma-
tion a dysfunction associated with atherosclerosis is due to
increased serum cholesterol levels (and presumedly in-
creased levels of oxidized LDL) rather than the forma-
tion and progression of vascular atherosclerotic lesions.

OXIDIZED LOW-DENSITY LIPOPROTEIN
sistent with the in vitro studies on atherosclerotic blood risk factors for atherosclerosis, including hypercholes-
vessels described above. More recently, a similar phe- terolemia, before FITY LIPOPROTEIN
Fisk factors for atherosclerosis, including hypercholes-
terolemia, before the development of visible athero TTY LIPOPROTEIN
risk factors for atherosclerosis, including hyperch
terolemia, before the development of visible athero
rotic lesions (Celermajer et al., 1992; Zeiher et risk factors for atherosclerosis, including hypercholes-
terolemia, before the development of visible atheroscle-
rotic lesions (Celermajer et al., 1992; Zeiher et al.,
1991a; Creager et al., 1990). Furthermore, hyperchole risk factors for atheroscierosis, including hypercholesterolemia, before the development of visible atheroscle-
rotic lesions (Celermajer et al., 1992; Zeiher et al.,
1991a; Creager et al., 1990). Furthermore, hypercholesrotic lesions (Celermajer et al., 1992; Zeiher et al., 1991a; Creager et al., 1990). Furthermore, hypercholes-
terolemia in several species including human produced
impairment of endothelium-dependent responses in
blood ve rotic lesions (Celermajer et al., 1992; Zeiher et al., 1991
1991a; Creager et al., 1990). Furthermore, hypercholes-
terolemia in several species including human produced
impairment of endothelium-dependent responses in
blo 1991a; Creager et al., 1990). Furthermore, hypercholesterolemia in several species including human produced
impairment of endothelium-dependent responses in
blood vessels of the microcirculation, vascular beds that
do not derbiend in several species including numari produced
impairment of endothelium-dependent responses in
blood vessels of the microcirculation, vascular beds that
do not develop overt atherosclerotic lesions (Yamamoto
et al. blood vessels of the microcirculation, vascular beds that
do not develop overt atherosclerotic lesions (Yamamoto
et al., 1988; Sellke et al., 1990; Zeiher et al., 1991b). In
fact, impaired endothelial function in atheroscl do not develop overt atherosclerotic lesions (Yamamoto et al., 1988; Sellke et al., 1990; Zeiher et al., 1991b). In fact, impaired endothelial function in atherosclerosis was suggested to be systemic in nature, affecting m et al., 1988; Sellke et al., 1990; Zeiher et al., 1991b). In fact, impaired endothelial function in atherosclerosis was suggested to be systemic in nature, affecting many regions of the vasculature rather than only those t was suggested to be systemic in nature, affecting many regions of the vasculature rather than only those that was suggested to be systemic in nature, affecting many
regions of the vasculature rather than only those that
develop visible signs of atherosclerosis (Anderson et al.,
1995b). Thus, vascular dysfunction in atherosclerosis regions of the vasculature rather than only those that develop visible signs of atherosclerosis (Anderson et al., 1995b). Thus, vascular dysfunction in atherosclerosis was associated more closely with increased serum chole develop visible
1995b). Thus
was associate
lesterol rath
blood vessel.
The effecti was associated more closely with increased serum clesterol rather than morphological alterations of thood vessel.
The effectiveness of lowering serum lipid levels correcting the vascular dysfunction induced by athe
scleros

as associated more closely with increased serum choord vessel) rather than morphological alterations of the order of The effectiveness of lowering serum lipid levels in recting the vascular dysfunction induced by atherolo lesterol rather than morphological alterations of the
blood vessel.
The effectiveness of lowering serum lipid levels in
correcting the vascular dysfunction induced by athero-
sclerosis also supports a role for oxidized LDL blood vessel.
The effectiveness of lowering serum lipid levels in
correcting the vascular dysfunction induced by athero-
sclerosis also supports a role for oxidized LDL in these
alterations. Reduction of serum cholesterol The effectiveness of lowering serum lipid levels in
correcting the vascular dysfunction induced by athero
sclerosis also supports a role for oxidized LDL in these
alterations. Reduction of serum cholesterol via dietary
mod correcting the vascular dysfunction induced by athero-
sclerosis also supports a role for oxidized LDL in these
alterations. Reduction of serum cholesterol via dietary
modification completely restored impaired endothelial
 scierosis also supports a role for oxidazed EDE in these
alterations. Reduction of serum cholesterol via dietary
modification completely restored impaired endothelial
function in iliac arteries from Cynomolgus monkeys
with modification completely restored impaired endothelial
function in iliac arteries from Cynomolgus monkeys
with diet-induced atherosclerosis, whereas only a mod-
est regression of atherosclerotic plaque was observed
(Harriso function in iliac arteries from Cynomolgus monkeys
with diet-induced atherosclerosis, whereas only a mod-
est regression of atherosclerotic plaque was observed
(Harrison et al., 1987). Reduction of serum cholesterol
also n with diet-induced atherosclerosis, whereas only a modest regression of atherosclerotic plaque was observed (Harrison et al., 1987). Reduction of serum cholesterol also normalized the enhanced coronary vasoconstrictive resp est regression of atherosclerotic plaque was observed
(Harrison et al., 1987). Reduction of serum cholesterol
also normalized the enhanced coronary vasoconstrictive
response of intracoronary infusion of 5-HT in the ab-
sen (Harrison et al., 1987). Reduction of serum cholesterol
also normalized the enhanced coronary vasoconstrictive
response of intracoronary infusion of 5-HT in the ab-
sence of any regression of morphological evidence of
athe also normalized the enhanced coronary vasoconstrictive
response of intracoronary infusion of 5-HT in the ab-
sence of any regression of morphological evidence of
atherosclerosis in monkeys (Lamping et al., 1994). Sev-
eral response of intracoronary infusion of 5-HT in the absence of any regression of morphological evidence of atherosclerosis in monkeys (Lamping et al., 1994). Several clinical studies suggest that lipid-lowering therapy also atherosclerosis in monkeys (Lamping et al., 1994). Several clinical studies suggest that lipid-lowering therapy also normalized vascular function in humans with hypercholesterolemia and atherosclerosis. In patients with hy atherosclerosis in monkeys (Lamping et al., 1994). Several clinical studies suggest that lipid-lowering therapy
also normalized vascular function in humans with hy-
percholesterolemia and atherosclerosis. In patients with
 eral clinical studies suggest that lipid-lowering therapy
also normalized vascular function in humans with hy-
percholesterolemia and atherosclerosis. In patients with
hypercholesterolemia but free of significant coronary also normalized vascular function in humans with hypercholesterolemia and atherosclerosis. In patients with
hypercholesterolemia but free of significant coronary le-
sions as assessed by angiography, abnormal coronary
vaso percholesterolemia and atherosclerosis. In patients with
hypercholesterolemia but free of significant coronary le-
sions as assessed by angiography, abnormal coronary
vasoconstriction in response to intracoronary infusion my percholesterolemia but free of significant coronary iesions as assessed by angiography, abnormal coronary
vasoconstriction in response to intracoronary infusion of
acetylcholine was reversed after 6 months of treatment
 sions as assessed by anglography, abhormal coronary
vasoconstriction in response to intracoronary infusion of
acetylcholine was reversed after 6 months of treatment
with either a combination of diet modification and cho-
l acetylcholine was reversed after 6 months of treatment
with either a combination of diet modification and cho-
lestyramine (Leung et al., 1993) or pravastatin
(Egashira et al., 1994), regimens that decreased total
serum ch with either a combination of diet modification and clestyramine (Leung et al., 1993) or pravasta
(Egashira et al., 1994), regimens that decreased to
serum cholesterol levels by approximately 30% in b
studies. More recently (Egashira et al., 1994), regimens that decreased total serum cholesterol levels by approximately 30% in both studies. More recently, lipid-lowering therapy normalized coronary vasomotor function in patients with hyperchole serum cholesterol levels by approximately 30% in both serum cholesterol levels by approximately 30% in both
studies. More recently, lipid-lowering therapy normal-
ized coronary vasomotor function in patients with hy-
percholesterolemia and established coronary arterial le-
si studies. More recently, lipid-lowering therapy normal-
ized coronary vasomotor function in patients with hy-
percholesterolemia and established coronary arterial le-
sions (Treasure et al., 1995; Anderson et al., 1995a).
M ized coronary vasomotor function in patients with hypercholesterolemia and established coronary arterial lesions (Treasure et al., 1995; Anderson et al., 1995a).
Most importantly, normalization of endothelial function
by l sions (Treasure et al., 1995; Anderson et al., 1995a).
Most importantly, normalization of endothelial function
by lipid-lowering therapy occurred in the absence of any
significant regression in lesion size or extent of int Most importantly, normalization of endothelial function
by lipid-lowering therapy occurred in the absence of any
significant regression in lesion size or extent of intimal
thickening. Taken together, these data suggest tha by lipid-lowering therapy occurred in the absence of any
significant regression in lesion size or extent of intimal
thickening. Taken together, these data suggest that vas-
cular endothelial dysfunction is related more to significant regression in
thickening. Taken toget
cular endothelial dysficreased serum choleste
atherosclerotic lesions. *C. Antioxidants Improve Endothelial dysfunction* is related reveased serum cholesterol rather than the atherosclerotic lesions.
C. Antioxidants Improve Endothelium-Dependential Vasodilation in Atherosclerosis *Value and Serum cholesterol ratherosclerotic lesions.***
** *C. Antioxidants Improve Endot***
** *Vasodilation in Atherosclerosis***

The role of increased choleste**

herosclerotic lesions.

Antioxidants Improve Endothelium-Dependent

usodilation in Atherosclerosis

The role of increased cholesterol levels in the vascular

sfunction produced by hypercholesterolemia and ath-C. Antioxidants Improve Endothelium-Dependent
Vasodilation in Atherosclerosis
The role of increased cholesterol levels in the vascular
dysfunction produced by hypercholesterolemia and athDownloaded from pharmrev.aspetjournals.org at Thammasart University on December 3, 2012

aspet

erosclerosis has also been linked to an important role of $\begin{array}{ll}\n 12 & \text{COX A} \\
 \text{eroscleros} & \text{has also been linked to an important role of}\n or \text{indative processes. Treatment of rabbits with the anti-oscident compound } \alpha\text{-tocopherol (vitamin E) preventee\n }\n \end{array}$ COX AND

erosclerosis has also been linked to an important role of

oxidant compound α -tocopherol (vitamin E) prevented

the endothelial dysfunction produced by cholesterol

feeding (Stewart-Lee et al., 1994; Keaney et erosclerosis has also been linked to an important role of oxidative processes. Treatment of rabbits with the anti-
oxidant compound α -tocopherol (vitamin E) prevented
the endothelial dysfunction produced by cholesterol oxidative processes. Treatment of rabbits with the antioxidant compound α -tocopherol (vitamin E) prevented
the endothelial dysfunction produced by cholestero
feeding (Stewart-Lee et al., 1994; Keaney et al., 1994)
Buty oxidant compound α -tocopherol (vitamin E) prevented
the endothelial dysfunction produced by cholesterol
feeding (Stewart-Lee et al., 1994; Keaney et al., 1994).
Butylated hydroxytoluene, another antioxidant com-
pound, the endothelial dysfunction produced by cholesterol circulation (Stewart-Lee et al., 1994; Keaney et al., 1994). by Butylated hydroxytoluene, another antioxidant complyound, also prevented alterations in microcirculatory L feeding (Stewart-Lee et al., 1994; Keaney et al., 1994
Butylated hydroxytoluene, another antioxidant conpound, also prevented alterations in microcirculator
function produced by cholesterol feeding in rabbits (Xi
et al., 1 Butylated hydroxytoluene, another antioxidant compound, also prevented alterations in microcirculatory Lifunction produced by cholesterol feeding in rabbits (Xiu alet al., 1994). Antioxidant use may require a long dura-
ti pound, also prevented alterations in microcirculatory
function produced by cholesterol feeding in rabbits (Xiu
et al., 1994). Antioxidant use may require a long dura-
tion of treatment to show clinical benefit, inasmuch as function produced by cholesterol feeding in rabbits (Xi
et al., 1994). Antioxidant use may require a long durre
tion of treatment to show clinical benefit, inasmuch a
short-term (4 weeks) antioxidant therapy did not reflex et al., 1994). Antioxidant use may require a long dura-
tion of treatment to show clinical benefit, inasmuch as
ist short-term (4 weeks) antioxidant therapy did not re-
atterse endothelial dysfunction in hypercholesterolem tion of treatment to show clinical benefit, inasmuch as istishort-term (4 weeks) antioxidant therapy did not re-
verse endothelial dysfunction in hypercholesterolemic phorotients (Gilligan et al., 1994a). Indeed, patients short-term (4 weeks) antioxidant therapy did not
verse endothelial dysfunction in hypercholesteroler
patients (Gilligan et al., 1994a). Indeed, patients w
coronary artery disease treated for 6 months with
combination of lo verse endothelial dysfunction in hypercholesterolemic
patients (Gilligan et al., 1994a). Indeed, patients with
coronary artery disease treated for 6 months with a
combination of lovastatin and the antioxidant lipid-low-
er patients (Gilligan et al., 1994a). Indeed, patients with coronary artery disease treated for 6 months with a combination of lovastatin and the antioxidant lipid-low-
ering drug probucol showed significantly greater im-
pro coronary artery disease treated for 6 months with
combination of lovastatin and the antioxidant lipid-lovering drug probucol showed significantly greater in
provement in vasomotor function compared with p
tients treated wi combination of lovastatin and the antioxidant lipid-low
ering drug probucol showed significantly greater in
provement in vasomotor function compared with pe
tients treated with either the nonantioxidan
combination of lovas provement in vasomotor function compared with pa-
teal., 1994). However, assuming a plasma LDL concen-
tients treated with either the nonantioxidant tration of $1-2$ mg/ml (Creagor et al., 1990; Gilligan et al.,
combinati provement in vasomotor function compared with pa-
tients treated with either the nonantioxidant
combination of lovastatin and cholestyramine or lipid-
lowering diet alone (Anderson et al., 1995a). These data
suggest that o tients treated with either the nonantioxid
combination of lovastatin and cholestyramine or lip
lowering diet alone (Anderson et al., 1995a). These d
suggest that oxidation is an important contributing
tor in the vasomotor combination of lovastatin and cholestyramine or lipidlowering diet alone (Anderson et al., 1995a). These dasuggest that oxidation is an important contributing factor in the vasomotor disturbances produced in hyperchesterol lowering diet alone (Anderson et al., 1995a). These data cent
suggest that oxidation is an important contributing fac-
tor in the vasomotor disturbances produced in hypercho-
motelesterolemia and atherosclerosis, and inhib tor in the vasomotor disturbances produced in hypercho-
lesterolemia and atherosclerosis, and inhibiting oxida-
lesterolemia and atherosclerosis, and inhibiting oxida-
lesterosclerosis. One aspect of the oxidation process lesterolemia and atherosclerosis, and inhibiting oxidaatherosclerosis. One aspect of the oxidation process may cholesterolemia and atherosclerosis.

D. Oxidized Low-Density Lipoprotein Exists In Vivo *D. Oxidized Low-Density Lipoprotein Exists In Vivo* lved in vascular motility changes produced by hyper-
olesterolemia and atherosclerosis.
Oxidized Low-Density Lipoprotein Exists In Vivo
Whether LDL becomes oxidized in vivo and the extent
this oxidation relative to that pr

cholesterolemia and atherosclerosis. The this oxidized Low-Density Lipoprotein Exists In Vivo

Whether LDL becomes oxidized in vivo and the extent

of this oxidation relative to that produced in vitro via

incubation with D. Oxidized Low-Density Lipoprotein Exists In Vivo
Whether LDL becomes oxidized in vivo and the extent
of this oxidation relative to that produced in vitro via
tincubation with copper ion or cultured endothelial cells
have D . Oxidized Low-Density Lipoprotein Exists D . Vivo
Whether LDL becomes oxidized in vivo and the extent
of this oxidation relative to that produced in vitro via
incubation with copper ion or cultured endothelial cells
 Whether LDL becomes oxidized in vivo and the extent
of this oxidation relative to that produced in vitro via
incubation with copper ion or cultured endothelial cells
have been difficult to establish. However, recent studie of this oxidation relative to that produced in vitro
incubation with copper ion or cultured endothelial co
have been difficult to establish. However, recent stud
have suggested that oxidized LDL is present in rab
and human incubation with copper ion or cultured endothelial cells
have been difficult to establish. However, recent studies
have suggested that oxidized LDL is present in rabbit
and human blood vessels and is associated with athero have been unificult to establish. However, recent studies
have suggested that oxidized LDL is present in rabbit c
and human blood vessels and is associated with athero-
sclerotic lesions. Modified lipoproteins have been ex have suggested that oxidized LDL is present in rabolic oxidered and human blood vessels and is associated with athero-reposelerotic lesions. Modified lipoproteins have been ex-
tracted from atherosclerotic lesions of rabbi sclerotic lesions. Modified lipoproteins have been ex-
tracted from atherosclerotic lesions of rabbit and human
blood vessels. These lipoproteins possess the physio-
chemical properties of LDL that has been oxidized in
out tracted from atherosclerotic lesions of rabbit and human
blood vessels. These lipoproteins possess the physio-
les
chemical properties of LDL that has been oxidized in
oxitro, including an increased electrophoretic mobilit blood vessels. These lipoproteins possess the physio-
chemical properties of LDL that has been oxidized in
vitro, including an increased electrophoretic mobility
relative to native LDL, extensive fragmentation of the
pho B chemical properties of LDL that has been oxidized in
vitro, including an increased electrophoretic mobility
relative to native LDL, extensive fragmentation of the
Apo B protein, and an increase in peroxidized lipids
(Daugh vitro, including an increased electrophoretic movellative to native LDL, extensive fragmentation composition of the providing different (Daugherty et al., 1988; Hoff and O'Neil, 1991; Herttuala et al., 1989). Furthermore, relative to native LDL, extensive fragmentation of the positive Apo B protein, and an increase in peroxidized lipids m
(Daugherty et al., 1988; Hoff and O'Neil, 1991; Yla-stiturala et al., 1989). Furthermore, immunohisto-p Apo B protein, and an increase in peroxidized lipids measured by formation of thiobarbaturic reactive sub-
(Daugherty et al., 1988; Hoff and O'Neil, 1991; Yla-
stances (Daugherty et al., 1988), (b) increased electro-
Hertt (Daugherty et al., 1988; Hoff and O'Neil, 1991; Yla-
Herttuala et al., 1989). Furthermore, immunohisto-
chemistry using antibodies raised against epitopes of O'I
the modified protein component of oxidized LDL has cre
recog Herttuala et al., 1989). Furthermore, immunohisto-
chemistry using antibodies raised against epitopes of O'N
the modified protein component of oxidized LDL has
creeognized modified lipoprotein in atherosclerotic blood leng chemistry using antibodies raised against epiopes of C
the modified protein component of oxidized LDL has c:
recognized modified lipoprotein in atherosclerotic blood levessels (Palinski et al., 1989; Haberland et al., 1988 recognized modified lipoprotein in atherosclerotic bluessels (Palinski et al., 1989; Haberland et al., 1988).
fact, autoantibodies that recognized oxidized LDL widentified in serum of patients with carotid artery a
eroscle fact, autoantibodies that recognized oxidized LDL were oxidized in vitro, including the vasoactive effects of this identified in serum of patients with carotid artery ath-
erosclerosis and were predictive of the rate of pr the arterial wall, and the endogenous oxidized form of these locales, oxidized LDL may exert effects analogous
LDL is similar to the oxidized form of LDL that is to those demonstrated in isolated blood vessels in vitro, identified in serum of patients with carotid artery ath-
erosclerosis and were predictive of the rate of progres-
sion of this disease (Salonen et al., 1992). These data
manggest that LDL oxidation does indeed occur in viv erosclerosis and were predictive of the rate of progression of this disease (Salonen et al., 1992). These data masuppest that LDL oxidation does indeed occur in vivo in mathe arterial wall, and the endogenous oxidized form sion of this disease (Salonen et
suggest that LDL oxidation does
the arterial wall, and the endog
LDL is similar to the oxidized
generated and studied in vitro.

HEN
In addition to oxidatively modified LDL in atheros
tic lesions, subfractionation of human plasma has rotic lesions, subfractively modified LDL in atheroscle-
rotic lesions, subfractionation of human plasma has re-
cently suggested that oxidized LDL may also exist in the COHEN
In addition to oxidatively modified LDL in atheroscle-
rotic lesions, subfractionation of human plasma has re-
cently suggested that oxidized LDL may also exist in the
circulation. Analysis of total LDL from human pl In addition to oxidatively modified LDL in atheroscle-
rotic lesions, subfractionation of human plasma has re-
cently suggested that oxidized LDL may also exist in the
circulation. Analysis of total LDL from human plasma
b In addition to oxidatively modified LDL in ather
rotic lesions, subfractionation of human plasma high-performance liquid chromatographic circulation. Analysis of total LDL from human pl
by ion exchange high-performance liq rotic lesions, subfractionation of human plasma has recently suggested that oxidized LDL may also exist in the circulation. Analysis of total LDL from human plasma
by ion exchange high-performance liquid chromatography rev Lentry suggested that oxidized LDL may also exist in the
circulation. Analysis of total LDL from human plasma
by ion exchange high-performance liquid chromatogra-
phy revealed two major subfractions: unmodified, native
LDL circulation. Analysis of total LDL from human plasma
by ion exchange high-performance liquid chromatogra-
phy revealed two major subfractions: unmodified, native
LDL and a more negatively charged LDL (Cazzolato et
al., 199 by ion exchange high-performance liquid chromato
phy revealed two major subfractions: unmodified, na
LDL and a more negatively charged LDL (Cazzolat
al., 1991; Hodis et al., 1994). The more negati
charged LDL (LDL-) posses LDL and a more negatively charged LDL (Cazzolato et al., 1991; Hodis et al., 1994). The more negatively charged LDL (LDL-) possessed many of the characteristics of LDL that was oxidized in vitro or extracted from al., 1991; Hodis et al., 1994). The more negatively al., 1991; Hodis et al., 1994). The more negatively
charged LDL (LDL-) possessed many of the character-
istics of LDL that was oxidized in vitro or extracted from
atherosclerotic lesions, including increased electro-
phore charged LDL (LDL-) possessed many of the characteristics of LDL that was oxidized in vitro or extracted from a
therosclerotic lesions, including increased electro-
phoretic mobility, an increased content of conjugated
dien istics of LDL that was oxidized in vitro or extracted from
atherosclerotic lesions, including increased electro-
phoretic mobility, an increased content of conjugated
dienes, oxycholesterols, and peroxidized lipids, and a
 phoretic mobility, an increased content of conjugated dienes, oxycholesterols, and peroxidized lipids, and a decreased content of vitamin E. The fraction of total plasma LDL present in this modified form was relatively dienes, oxycholesterols, and peroxidized lipids, and a decreased content of vitamin E. The fraction of total decreased content of vitamin E. The fraction of total plasma LDL present in this modified form was relatively small, approximately 5% (Cazzolato et al., 1991; Hodis et al., 1994). However, assuming a plasma LDL concentrati plasma LDL present in this modified form was relatively
small, approximately 5% (Cazzolato et al., 1991; Hodis
et al., 1994). However, assuming a plasma LDL concen-
tration of 1–2 mg/ml (Creagor et al., 1990; Gilligan et et al., 1994). However, assuming a plasma LDL concenet al., 1994). However, assuming a plasma LDL concentration of 1–2 mg/ml (Creagor et al., 1990; Gilligan et al. 1994b), this fraction would translate to a plasma correntration of modified LDL of 50–100 μ g/ml, consisten tration of 1–2 mg/ml (Creagor et al., 1990; Gilligan et al., 1994b), this fraction would translate to a plasma concentration of modified LDL of 50–100 μ g/ml, consistent with concentrations of oxidized LDL that mediate 1994b), this fraction would translate to a plasma concentration of modified LDL of $50-100 \mu\text{g/ml}$, consistent with concentrations of oxidized LDL that mediate vasomotor effects in vitro (Kugiyama et al., 1990; Simon et centration of modified LDL of 50–100 μ g/ml, consistent
with concentrations of oxidized LDL that mediate vaso-
motor effects in vitro (Kugiyama et al., 1990; Simon et
al., 1990; Tanner et al., 1991; Murohara et al., 199 with concentrations of oxidized LDL that mediate vaso-
motor effects in vitro (Kugiyama et al., 1990; Simon et
al., 1990; Tanner et al., 1991; Murohara et al., 1994).
Although these studies did not clarify whether the cirmotor effects in vitro (Kugiyama et al., 1990; Simon et al., 1990; Tanner et al., 1991; Murohara et al., 1994).
Although these studies did not clarify whether the circulating LDL – originated from the oxidation of LDL in p al., 1990; Tanner et al., 1991; Murohara et al., 1994).
Although these studies did not clarify whether the circulating LDL – originated from the oxidation of LDL in
plasma or within the arterial wall, they suggest that
vas Although these studies did not clarify whether the circulating LDL – originated from the oxidation of LDL in plasma or within the arterial wall, they suggest that vasoactive concentrations of oxidized LDL may exist in the culating LDL – originated from the oxidation of LD
plasma or within the arterial wall, they suggest
vasoactive concentrations of oxidized LDL may exit
the circulation of humans, and would presumedl
elevated in hypercholest next assume or within the arterial wall, they suggest that
soactive concentrations of oxidized LDL may exist in
e circulation of humans, and would presumedly be
vated in hypercholesterolemia and atherosclerosis.
The extent the circulation of humans, and would presumedly be
elevated in hypercholesterolemia and atherosclerosis.
The extent to which LDL is oxidized in vivo relative to
the levels of oxidation produced in vitro remains uncer-

the circulation of humans, and would presumedly be
elevated in hypercholesterolemia and atherosclerosis.
The extent to which LDL is oxidized in vivo relative to
the levels of oxidation produced in vitro remains uncer-
tain elevated in hypercholesterolemia and atheroscieros.
The extent to which LDL is oxidized in vivo relative
the levels of oxidation produced in vitro remains un
tain. However, the fact that modified LDL extra
from rabbit and The extent to which LDL is oxidized in vivo relative to
the levels of oxidation produced in vitro remains uncer-
tain. However, the fact that modified LDL extracted
from rabbit and human lesions had extensive fragmen-
tati the levels of oxidation produced in vitro remains uncertain. However, the fact that modified LDL extracted from rabbit and human lesions had extensive fragmentation of the apo-B protein suggests a substantial level of oxid tain. However, the fact that modified LDL extracted
from rabbit and human lesions had extensive fragmen-
tation of the apo-B protein suggests a substantial level of
oxidation, as opposed to the lower levels of oxidation
re from rabbit and human lesions had extensive fragmentation of the apo-B protein suggests a substantial level of oxidation, as opposed to the lower levels of oxidation reported for minimally modified LDL, where apo-B remains tation of the apo-B protein suggests a substantial levoxidation, as opposed to the lower levels of oxida
reported for minimally modified LDL, where apo-B
mains intact (Berliner et al., 1990). Quantitative n
sures of LDL mo oxidation, as opposed to the lower levels of oxidation
reported for minimally modified LDL, where apo-B re-
mains intact (Berliner et al., 1990). Quantitative mea-
sures of LDL modification in vivo are limited. Neverthe-
 reported for minimally modified LDL, where apo-B remains intact (Berliner et al., 1990). Quantitative measures of LDL modification in vivo are limited. Nevertheless, the properties of LDL modified in vivo and LDL oxidized mains intact (Berliner et al., 1990). Quantitative measures of LDL modification in vivo are limited. Nevertheless, the properties of LDL modified in vivo and LDL oxidized in vitro are qualitatively and quantitatively compa less, the properties of LDL modified in vivo and LDL oxidized in vitro are qualitatively and quantitatively comparable as measured by several independent approaches, including: (a) extent of lipid peroxidation as less, the properties of LDL modified in vivo and LDL oxidized in vitro are qualitatively and quantitatively comparable as measured by several independent approaches, including: (*a*) extent of lipid peroxidation as measure oxidized in vitro are qualitatively and quantitative comparable as measured by several independent is proaches, including: (*a*) extent of lipid peroxidation measured by formation of thiobarbaturic reactive stances (Daughe comparable as measured by several independent approaches, including: (a) extent of lipid peroxidation as measured by formation of thiobarbaturic reactive substances (Daugherty et al., 1988), (b) increased electrophoreti proaches, including: (*a*) extent of lipid peroxidation as
measured by formation of thiobarbaturic reactive sub-
stances (Daugherty et al., 1988), (*b*) increased electro-
phoretic mobility (Daugherty et al., 1988; Hoff an measured by formation of thiobarbaturic reactive su
stances (Daugherty et al., 1988), (b) increased electr
phoretic mobility (Daugherty et al., 1988; Hoff ar
O'Neil, 1991; Yla-Herttuala et al., 1989), and (c) i
creased flu stances (Daugherty et al., 1988), (b) increased electro-
phoretic mobility (Daugherty et al., 1988; Hoff and
O'Neil, 1991; Yla-Herttuala et al., 1989), and (c) in-
creased fluorescence measured at an excitation wave-
lengt phoretic mobility (Daugherty et al., 1988; Hoff and
O'Neil, 1991; Yla-Herttuala et al., 1989), and (c) in-
creased fluorescence measured at an excitation wave-
length of 360 nm (Hoff and O'Neil, 1991). Thus, the
functional O'Neil, 1991; Yla-Herttuala et al., 1989), and (c) increased fluorescence measured at an excitation wavelength of 360 nm (Hoff and O'Neil, 1991). Thus, the functional effects demonstrated with LDL that has been oxidized in creased fluorescence measured at an excitation w
length of 360 nm (Hoff and O'Neil, 1991). Thus,
functional effects demonstrated with LDL that has
oxidized in vitro, including the vasoactive effects of
lipoprotein, have re In summary, there is strong evidence that LDL is
inctional effects demonstrated with LDL that has been
idized in vitro, including the vasoactive effects of this
oprotein, have relevance to the in vivo situation.
In summary

functional effects demonstrated with LDL that has been
oxidized in vitro, including the vasoactive effects of this
lipoprotein, have relevance to the in vivo situation.
In summary, there is strong evidence that LDL is
modi oxidized in vitro, including the vasoactive effects of this
lipoprotein, have relevance to the in vivo situation.
In summary, there is strong evidence that LDL is
modified by an oxidative mechanism in humans and
may exist lipoprotein, have relevance to the in vivo situation.
In summary, there is strong evidence that LDL is
modified by an oxidative mechanism in humans and
may exist in both the circulation and the arterial wall. In
these loca In summary, there is strong evidence that LDL is
modified by an oxidative mechanism in humans and
may exist in both the circulation and the arterial wall. In
these locales, oxidized LDL may exert effects analogous
to those these locales, oxidized LDL may exert effects analogous
to those demonstrated in isolated blood vessels in vitro,
and thus produce the vasomotor disturbances associated

OXIDIZED LOW-DENSITY LIPOPROTEIN
with hypercholesterolemia and atherosclerosis. There-
fore, inhibition of the in vivo actions of oxidized LDL with atheroscler OXIDIZED LOW-DENSITY I
with hypercholesterolemia and atherosclerosis. There-
fore, inhibition of the in vivo actions of oxidized LDL with
would likely improve or normalize vascular functioning prom OXIDIZED LOW-DENS
with hypercholesterolemia and atherosclerosis. There-
fore, inhibition of the in vivo actions of oxidized LDL
would likely improve or normalize vascular functioning
in atherosclerosis. However, would such with hypercholesterolemia and atherosclerosis. Therefore, inhibition of the in vivo actions of oxidized LDL would likely improve or normalize vascular functioning in atherosclerosis. However, would such intervention have a with hypercholesterolemia and atherosclerosis. Therefore, inhibition of the in vivo actions of oxidized LDI would likely improve or normalize vascular functioning in atherosclerosis. However, would such intervention have a fore, inhibition of the in vivo actions of oxidized LDL would likely improve or normalize vascular functioning
in atherosclerosis. However, would such intervention
have any benefit in reducing the clinical manifestations
o would likely improve or normalize vascular functioning
in atherosclerosis. However, would such intervention
have any benefit in reducing the clinical manifestations
of this disease? Recent studies suggest that the direct
r in atherosclerosis. However, would such intervention
have any benefit in reducing the clinical manifestations
of this disease? Recent studies suggest that the direct
role of increased plasma cholesterol levels and the re-
 have any benefit in reducing the clinical manifestat
of this disease? Recent studies suggest that the di
role of increased plasma cholesterol levels and the
sulting vascular dysfunctioning in acute clinical
dromes of ather mated. role of increased plasma cholesterol levels and the resulting vascular dysfunctioning in acute clinical syn-
dromes of atherosclerosis may have been underesti-
mated.
VI. Role of the Vasomotor Actions of Oxidized
Low-Densi

Low-Density Constants and School
 Low-Density Lipoprotein in the Clinical
 Low-Density Lipoprotein in the Clinical
 Manifestations of Atherosclerosis Manufestations may have seen
 **le of the Vasomotor Actions of C

w-Density Lipoprotein in the Cli**
 Manifestations of Atheroscleros

sclerosis is clearly a chronic, multifa VI. Role of the Vasomotor Actions of Oxidized
Low-Density Lipoprotein in the Clinical
Manifestations of Atherosclerosis
Atherosclerosis is clearly a chronic, multifactorial dis-
se process with several regulatory pathways

Atherosclerosis is clearly a chronic, multifactorial disease process with several regulatory pathways influencing its development and progression. Thus, arguments Low-Density Lipoprotein in the Chincan
Manifestations of Atherosclerosis
Atherosclerosis is clearly a chronic, multifactorial dis-
ease process with several regulatory pathways influenc-
ing its development and progression mannestations of Atheroscierosis

presented here to support an important role for

the support and progression. Thus, arguments for

the presented here to support an important role for

boxidized LDL and its vasomotor acti Atheroscierosis is clearly a chronic, inditiated and the ease process with several regulatory pathways influencing its development and progression. Thus, arguments for the oxidized LDL and its vasomotor actions in some of ing its development and progression. Thus, arguments for the presented here to support an important role for boxidized LDL and its vasomotor actions in some of the racute clinical syndromes associated with this disease, of are presented here to support an important role for bear original constituted LDL and its vasomotor actions in some of the racute clinical syndromes associated with this disease, of while recognizing that this mediator may while recognizing that this mediator may be only one of several important mechanisms involved in these processes.
Contrary to conventional wisdom, the abundance of data suggests that the incidence of clinical events asso-

cesses.
Contrary to conventional wisdom, the abundance of redata suggests that the incidence of clinical events associated with atherosclerosis is not related to the extent of decoronary artery stenosis due to plaque forma coronary to conventional wisdom, the abundance of red
data suggests that the incidence of clinical events asso-
ciated with atherosclerosis is not related to the extent of de
coronary artery stenosis due to plaque formatio data suggests that the incidence of clinical events associated with atherosclerosis is not related to the extent of coronary artery stenosis due to plaque formation and expansion into the arterial lumen. Several angiograph clated with atheroscierosis is not related to the extent of
coronary artery stenosis due to plaque formation and
expansion into the arterial lumen. Several angiographic
studies demonstrated that the majority of patients un expansion into the arterial lumen. Several angiographic
studies demonstrated that the majority of patients un-
dergoing examination following incidents of unstable
angina or myocardial infarction had lesions with steno-
si studies demonstrated that the majority of patients undergoing examination following incidents of unstable
angina or myocardial infarction had lesions with steno-
sis of less than 50% (Ambrose et al., 1986; Little et al.
19 dergoing examination following incidents of unstable angina or myocardial infarction had lesions with stends is of less than 50% (Ambrose et al., 1986; Little et al. 1988), too small to be hemodynamically significant. Furt angina or myocardial infarction had lesions with steno-
sis of less than 50% (Ambrose et al., 1986; Little et al.,
1988), too small to be hemodynamically significant. Fur-
thermore, clinical trials of lipid-lowering therap sis of less than 50% (Ambrose et al., 1986; Little et al., pl
1988), too small to be hemodynamically significant. Fur-
thermore, clinical trials of lipid-lowering therapies dem-
constrated that although lowering serum chol 1988), too small to be hemodynamically significant. Fur-
thermore, clinical trials of lipid-lowering therapies dem-
constrated that although lowering serum cholesterol was
liun
associated with little or no regression in th thermore, clinical trials of lipid-lowering therapies demonstrated that although lowering serum cholesterol was
associated with little or no regression in the extent of
stenosis, these treatments nevertheless resulted in a onstrated that although lowering serum cholesteror was
associated with little or no regression in the extent of
stenosis, these treatments nevertheless resulted in a
substantial decrease in the frequency of clinical events stenosis, these treatments nevertheless resulted in a my
substantial decrease in the frequency of clinical events of t
(Brown et al., 1990; Watts et al., 1992). Taken together, C
these studies suggest that the occurrence o (Brown et al., 1990; Watts et al., 1992). Taken together, these studies suggest that the occurrence of clinical events associated with atherosclerosis is not rooted in a decrease in lumen diameter due to plaque formation. (Brown et al., 1990; Watts et al., 1992). Taken together, Oxiduese studies suggest that the occurrence of clinical drome events associated with atherosclerosis is not rooted in a essari-
decrease in lumen diameter due to p these studies suggest that the occurrence of clinical devents associated with atherosclerosis is not rooted in a edecrease in lumen diameter due to plaque formation. contraction of plaque formation of plaque (i size or c events associated with atherosclerosis is
decrease in lumen diameter due to pla
Furthermore, the beneficial effects of l
cholesterol cannot be explained by a regr
size or change in the extent of stenosis.
To explain this l crease in lumen diameter due to plaque formation.

urthermore, the beneficial effects of lowering serum

olesterol cannot be explained by a regression of plaque

e or change in the extent of stenosis.

To explain this lack Furthermore, the beneficial effects of lowering serum
cholesterol cannot be explained by a regression of plaque
size or change in the extent of stenosis.
To explain this lack of correlation between clinical
events and exte

cholesterol cannot be explained by a regression of plaque
size or change in the extent of stenosis.
To explain this lack of correlation between clinical
events and extent of stenosis, current theory suggests
that progressi size or change in the extent of stenosis.
To explain this lack of correlation between clinical
events and extent of stenosis, current theory suggests
that progression of atherosclerosis from a chronic pro-
gressive disease To explain this lack of correlation between clinical
events and extent of stenosis, current theory suggests
that progression of atherosclerosis from a chronic pro-
gressive disease to an acute clinical event such as un-
st events and extent of stenosis, current theory suggests relative progression of atherosclerosis from a chronic progressive disease to an acute clinical event such as un-
stable angina or myocardial infarction involves the r that progression of atherosclerosis from a chronic progressive disease to an acute clinical event such as unstable angina or myocardial infarction involves the rupwature of smaller, hemodynamically insignificant plaque ca gressive disease to an acute clinical event such as ustable angina or myocardial infarction involves the rule of smaller, hemodynamically insignificant plaque (Fuster et al., 1990). Release of the contents of the plaque in stable angina or myocardial infarction involves the rup-
ture of smaller, hemodynamically insignificant plaque
(Fuster et al., 1990). Release of the contents of the
plaque into the bloodstream results in platelet activa-
t ture of smaller, hemodynamically insignificant plaque contents of the endependence into the bloodstream results in platelet activation, thrombus formation, and eventual arterial occlupion. The vasomotor disturbances produc (Fuster et al., 1990). Release of the contents of the plaque into the bloodstream results in platelet activation, thrombus formation, and eventual arterial occlusion. The vasomotor disturbances produced by elevated serum c plaque into the bloodstream results in platelet activation, thrombus formation, and eventual arterial occlusion. The vasomotor disturbances produced by elevated serum cholesterol, and possibly increased levels of oxidized

tribute to the generation of clinical events in patients with atherosclerosis via at least two mechanisms: *(a)* 13

primary LIPOPROTEIN 13

promoting conditions that are favorable for plaque rup-

promoting conditions that are favorable for plaque rup-

ture and (b) aggravating the arterial response to events tribute to the generation of clinical events in patients with atherosclerosis via at least two mechanisms: (a) promoting conditions that are favorable for plaque rupture and (b) aggravating the arterial response to even with atherosclerosis via at least two mechanisms: (a)
promoting conditions that are favorable for plaque rup-
ture and (b) aggravating the arterial response to events
subsequent to the rupture.
Oxidized LDL in atheroscl promoting conditions that are favorable for plaque rup-

promoting conditions that are favorable for plaque rupture and (b) aggravating the arterial response to events subsequent to the rupture.
Cxidized LDL in atherosclerosis may promote plaque rupture both directly and indir ture and (b) aggravating the arterial response to events
subsequent to the rupture.
Oxidized LDL in atherosclerosis may promote plaque
rupture both directly and indirectly. Although debated
(Kaski et al., 1992), intense subsequent to the rupture.

Oxidized LDL in atherosclerosis may promote plaque

rupture both directly and indirectly. Although debated

(Kaski et al., 1992), intense vasospasm at the locus of an

atherosclerotic plaque has rupture both directly and indirectly. Although debated (Kaski et al., 1992), intense vasospasm at the locus of an atherosclerotic plaque has the potential to induce plaque rupture via compression of the lesion against the rupture both directly and indirectly. Although debated (Kaski et al., 1992), intense vasospasm at the locus of an atherosclerotic plaque has the potential to induce plaque rupture via compression of the lesion against the (Kaski et al., 1992), intense vasospasm at the locus of an
atherosclerotic plaque has the potential to induce plaque
rupture via compression of the lesion against the arte-
rial wall (Leary, 1934; Lin et al., 1988; Ciampri atherosclerotic plaque has the potential to induce plaque
rupture via compression of the lesion against the arte-
rial wall (Leary, 1934; Lin et al., 1988; Ciampricotti et
al., 1990). The ability of oxidized LDL to increas rupture via compression of the lesion against the arte-
rial wall (Leary, 1934; Lin et al., 1988; Ciampricotti et
al., 1990). The ability of oxidized LDL to increase the
sensitivity of blood vessels to contractile stimuli rial wall (Leary, 1934; Lin et al., 1988; Ciampricotti et al., 1990). The ability of oxidized LDL to increase the sensitivity of blood vessels to contractile stimuli may promote this mechanism of plaque rupture. In additi al., 1990). The ability of oxidized LDL to increase the
sensitivity of blood vessels to contractile stimuli may
promote this mechanism of plaque rupture. In addition,
impaired endothelial function produced by oxidized LDL
 sensitivity of blood vessels to contractile stimuli may
promote this mechanism of plaque rupture. In addition,
impaired endothelial function produced by oxidized LDL
in atherosclerosis may increase hemodynamic shear
forces promote this mechanism of plaque rupture. In addition,
impaired endothelial function produced by oxidized LDL
in atherosclerosis may increase hemodynamic shear
forces in the coronary circulation, an effect that has also
be impaired endothelial function produced by oxidized LDL
in atherosclerosis may increase hemodynamic shear
forces in the coronary circulation, an effect that has also
been suggested to weaken plaque stability and promote
rup In adderesterosis may increase hemodynamic shear
forces in the coronary circulation, an effect that has also
been suggested to weaken plaque stability and promote
rupture (Loree et al., 1992). Thus, the vasomotor effects
o en suggested to weaken plaque stability and promote
pture (Loree et al., 1992). Thus, the vasomotor effects
oxidized LDL may contribute to an environment that
creases the likelihood of plaque rupture.
The presence of oxidi

studies demonstrated that the majority of patients unally and in normal arteries incubated with oxidized LDL
dergoing examination following incidents of unstable (Tanner et al., 1991). Oxidized LDL also impaired endo-
angi rupture (Lores et al., 1992). Thus, the vasomotor enects
of oxidized LDL may contribute to an environment that
increases the likelihood of plaque rupture.
The presence of oxidized LDL within atherosclerotic
coronary arteri of oxidized LDL may contribute to an environment that
increases the likelihood of plaque rupture.
The presence of oxidized LDL within atherosclerotic
coronary arteries may also exacerbate the contractile
response of these increases the likelihood of plaque rupture.
The presence of oxidized LDL within atherosclerotic
coronary arteries may also exacerbate the contractile
response of these vessels to mediators released from
aggregating platele The presence of oxidized LDL within atherosclerotic
coronary arteries may also exacerbate the contractile
response of these vessels to mediators released from
aggregating platelets subsequent to plaque rupture. In-
deed, e coronary arteries may also exacerbate the contractile
response of these vessels to mediators released from
aggregating platelets subsequent to plaque rupture. In-
deed, endothelium-dependent relaxation to aggregating
plate response of these vessels to mediators released from
aggregating platelets subsequent to plaque rupture. In-
deed, endothelium-dependent relaxation to aggregating
platelets was profoundly impaired in atherosclerotic pig
co aggregating platelets subsequent to plaque rupture. Indeed, endothelium-dependent relaxation to aggregating
platelets was profoundly impaired in atherosclerotic pig
coronary arteries (Shimokawa and Vanhoutte, 1989)
and in deed, endothelium-dependent relaxation to aggregatin
platelets was profoundly impaired in atherosclerotic picoronary arteries (Shimokawa and Vanhoutte, 1989
and in normal arteries incubated with oxidized LD
(Tanner et al., impaired endothelial function produced by oxidized LDL
in atheroselerosis may increase hemodynamic shear
forces in the coronary circulation, an effect that has also
been suggested to weaken plaque stability and promote
ru (Simon et al., 1990; Tanner et al., 1991). Thus, platelet and in normal arteries incubated with oxidized LDL
(Tanner et al., 1991). Oxidized LDL also impaired endo-
thelium-dependent relaxation of pig coronary arteries to
platelet-derived mediators such as 5-HT and thrombin
(Simo (Tanner et al., 1991). Oxidized LDL also impaired en
the lium-dependent relaxation of pig coronary arterie
platelet-derived mediators such as 5-HT and throm
(Simon et al., 1990; Tanner et al., 1991). Thus, plat
aggregation thelium-dependent relaxation of pig coronary arteries to
platelet-derived mediators such as 5-HT and thrombin
(Simon et al., 1990; Tanner et al., 1991). Thus, platelet
aggregation in the presence of a dysfunctional endothe platelet-derived mediators such as 5-HT and thrombin
(Simon et al., 1990; Tanner et al., 1991). Thus, platele
aggregation in the presence of a dysfunctional endothe
lium as occurs in atherosclerotic blood vessels may b
agg (Simon et al., 1990; Tamier et al., 1991). Thus, platelet
aggregation in the presence of a dysfunctional endothe-
lium as occurs in atherosclerotic blood vessels may be
aggravated by oxidized LDL, resulting in vasospasm,
m aggregation in the presence of a dysfunctional endothe-
lium as occurs in atherosclerotic blood vessels may be
aggravated by oxidized LDL, resulting in vasospasm,
myocardial ischemia and, depending upon the severity
of the Im as occurs in atherosclerotic blood vessels may be gravated by oxidized LDL, resulting in vasospasm, yocardial ischemia and, depending upon the severity the thrombus, acute myocardial infarction and death. Oxidized LDL a

aggravated by oxidized LDL, resulting in vasospasm,
myocardial ischemia and, depending upon the severity
of the thrombus, acute myocardial infarction and death.
Oxidized LDL also may be involved in clinical syn-
dromes ass myocardial ischemia and, depending upon the severity
of the thrombus, acute myocardial infarction and death.
Oxidized LDL also may be involved in clinical syn-
dromes associated with atherosclerosis that do not nec-
essari of the thrombus, acute myocardial infarction and death.

Oxidized LDL also may be involved in clinical syn-

dromes associated with atherosclerosis that do not nec-

essarily involve plaque rupture. Myocardial ischemia

ca Oxidized LDL also may be involved in clinical syn-
dromes associated with atherosclerosis that do not nec-
essarily involve plaque rupture. Myocardial ischemia
can be triggered in patients with stable angina via a
variety dromes associated with atherosclerosis that do not necessarily involve plaque rupture. Myocardial ischemia
can be triggered in patients with stable angina via a
variety of stimuli, including exercise and cold-exposure
(Zei essarily involve plaque rupture. Myocardial ischemia
can be triggered in patients with stable angina via a
variety of stimuli, including exercise and cold-exposure
(Zeiher and Schachinger, 1994). Whereas these stimuli
prod can be triggered in patients with stable angina v
variety of stimuli, including exercise and cold-export
(Zeiher and Schachinger, 1994). Whereas these stip
produced vasodilation in normal coronary arteries, a
caused constr variety of stimuli, including exercise and cold-exp (Zeiher and Schachinger, 1994). Whereas these st
produced vasodilation in normal coronary arteries,
caused constriction of coronary arteries with ather
rosis due to a los (Zeiher and Schachinger, 1994). Whereas these stimuli
produced vasodilation in normal coronary arteries, both
caused constriction of coronary arteries with atheroscle-
rosis due to a loss of normal endothelium-dependent
va produced vasodilation in normal coronary arteries, both caused constriction of coronary arteries with atherosclerosis due to a loss of normal endothelium-dependent vasodilator function (Gage et al., 1986; Nabel et al., 198 caused constriction of coronary arteries with atheroscle-
rosis due to a loss of normal endothelium-dependent
vasodilator function (Gage et al., 1986; Nabel et al.,
1988). Furthermore, atherosclerotic coronary arteries
wer rosis due to a loss of normal endothelium-dependent vasodilator function (Gage et al., 1986; Nabel et al., 1988). Furthermore, atherosclerotic coronary arteries were much more sensitive to constriction by infusion of catec vasounator function (Gage et al., 1980; Nabel et al., 1988). Furthermore, atherosclerotic coronary arteries were much more sensitive to constriction by infusion of catecholamines (Vita et al., 1992). Thus, loss of normal e 1966). Furthermore, atheroscierotic coronary arteries
were much more sensitive to constriction by infusion of
catecholamines (Vita et al., 1992). Thus, loss of normal
endothelium-dependent relaxation due, in part, to oxi-
 were much more sensitive to constriction by infusion
catecholamines (Vita et al., 1992). Thus, loss of norr
endothelium-dependent relaxation due, in part, to d
dized LDL in diseased coronary blood vessels may a
plify vasoc catecholamines (vita et al., 1992). Thus, loss of hormal
endothelium-dependent relaxation due, in part, to oxi-
dized LDL in diseased coronary blood vessels may am-
plify vasoconstriction in response to sympathetic activadized LDL in diseased coronary blood vessels may amplify vasoconstriction in response to sympathetic activation and lead to myocardial ischemia associated with stable angina without necessarily involving rupture of atheros

REVIEW

ARMACOLOGIO

²⁴ COX AND
 VII. Inhibiting the Vasoactive Effects of Oxidized
 Low-Density Lipoprotein: Potential Low-Density Lipoprotein: Potential COX
 Example 1. In all is propertier of Oxidiz
 **Pharmacological Strategies and Therapeutic

Implications Implications** The mechanism by which lowering serum cholesterol
The mechanism by which lowering serum cholesterol
creases the frequency of clinical manifestations of ath-

DECREASE TO ENGINEERT POSSET TO PRETTREASE THE METATRICAL METATRICAL THE mechanism by which lowering serum cholesterol
decreases the frequency of clinical manifestations of ath-
erosclerosis in the absence of any substanti FRATIFICATION IMPLICATION INTERPRETATION THE MECHANIST THE MECHANIST OF MECHANIST CHANGED INTERPRETATION (SPINGTORS) decreases the frequency of clinical manifestations of atherosclerosis in the absence of any substantial c Implications
decreases the frequency of clinical manifestations of atherosclerosis in the absence of any substantial change in
lesion size or stenosis is not clear (Levine et al., 1995).
Although many components of serum c The mechanism by which lowering serum cholesterol
decreases the frequency of clinical manifestations of atherosclerosis in the absence of any substantial change in
lesion size or stenosis is not clear (Levine et al., 1995 decreases the frequency of clinical manifestations of atherosclerosis in the absence of any substantial change in lesion size or stenosis is not clear (Levine et al., 1995).
Although many components of serum cholesterol m erosclerosis in the absence of any substantial change in
lesion size or stenosis is not clear (Levine et al., 1995).
Although many components of serum cholesterol may be
responsible for its detrimental effects, oxidized LD lesion size or stenosis is not clear (Levine et al., 199
Although many components of serum cholesterol may
responsible for its detrimental effects, oxidized LDI
likely to play an important role based on the argume
presente Although many components of serum cholesterol may be
responsible for its detrimental effects, oxidized LDL is
likely to play an important role based on the arguments
presented above. Lipid lowering may alter the charac-
s responsible for its detrimental effects, oxidized LDL is
likely to play an important role based on the arguments
presented above. Lipid lowering may alter the characteristics of atherosclerotic lesions such that they are
 likely to play an important role based on the arguments
presented above. Lipid lowering may alter the characteristics of atherosclerotic lesions such that they are
more resistant to rupture and may improve endothelium
func presented above. Lipid lowering may after the characteristics of atherosclerotic lesions such that they are more resistant to rupture and may improve endothelium function and normalize vasoactivity to account for the clini more resistant to rupture and may improve endothelium
function and normalize vasoactivity to account for the
clinical benefit. Because much evidence suggests that
oxidized LDL is a primary determinant in the vascular
dysf lunction and normanze vasoactivity to account for the
clinical benefit. Because much evidence suggests that
oxidized LDL is a primary determinant in the vascular
dysfunction of atherosclerosis and an important factor in
le dysfunction of atherosclerosis and an important factor in lesion formation and progression (Steinberg et al., 1989), it is reasonable to hypothesize that interventions that either decrease the formation of oxidized LDL, in dysfunction of atherosclerosis and an important factor in
lesion formation and progression (Steinberg et al., 1989),
it is reasonable to hypothesize that interventions that
either decrease the formation of oxidized LDL, i lesion formation and progression (Steinberg et al., 1989),
it is reasonable to hypothesize that interventions that
either decrease the formation of oxidized LDL, increase
its degradation, and/or inhibit its action on targ either decrease the formation of oxidized LDL, increase its degradation, and/or inhibit its action on target cell will be beneficial in the treatment of this disease (fig. 4)
A. Inhibiting the Formation of Oxidized Low-Den

Lipoprotein will be beneficial in the treatment of this disease (fig. 4).
A. Inhibiting the Formation of Oxidized Low-Density
Lipoprotein
Thus far, pharmacological efforts to decrease the for-
mation of oxidized LDL have been limited

A. Inhibiting the Formation of Oxidized Low-Density
Lipoprotein
Thus far, pharmacological efforts to decrease the for-
mation of oxidized LDL have been limited to the use of
antioxidant compounds. Although probucol is use Lipoprotein

Thus far, pharmacological efforts to decrease the for

mation of oxidized LDL have been limited to the use o

antioxidant compounds. Although probucol is used clin

ically to lower serum cholesterol (Buckley e Thus far, pharmacological efforts to decrease the for-

mation of oxidized LDL have been limited to the use of

intioxidant compounds. Although probucol is used clin-

ically to lower serum cholesterol (Buckley et al., 19 mation of oxidized LDL have been limited to the use of
antioxidant compounds. Although probucol is used clinically to lower serum cholesterol (Buckley et al., 1989),
this compound is also an antioxidant that inhibits the
 antioxidant compounds. Atthough probucol is used cini-
ically to lower serum cholesterol (Buckley et al., 1989), LD
this compound is also an antioxidant that inhibits the
oxidation of LDL in vitro and ex vivo (Parthasarat this compound is also an antioxidant that inhibits the poxidation of LDL in vitro and ex vivo (Parthasarathy et 1 al., 1986). The ability of probucol to slow the progression 1 of atherosclerosis in rabbits (Carew et a

FIG. 4. Potential targets for pharmacological intervention to inhibition of oxidized LDL formation, *(b)* inhibition of oxidized the LDL interaction with target cells, *(c)* inhibition of intracellular in actions of oxidiz FIG. 4. Potential targets for pharmacological intervention to inhibit or reverse oxidized LDL-induced vascular dysfunction: (a) inhibition of oxidized LDL formation, (b) inhibition of oxidized LDL interaction with target c hibit or reverse oxidized LDL-induced vascular dysfunction: (a) inhibition of oxidized LDL formation, (b) inhibition of oxidized LDL interaction with target cells, (c) inhibition of intracellular actions of oxidized LD inhibition of oxidized LDL formation, (b) inhibition of oxidized LDL interaction with target cells, (c) inhibition of intracellular actions of oxidized LDL, (d) correction of oxidized LDL-induced EDRF(NO) deficit via augme LDL interaction with target cells, (c) inhibition of intracellula
actions of oxidized LDL, (d) correction of oxidized LDL-induce
EDRF(NO) deficit via augmentation of endogenous synthesis or expension with NO donors. nLDL, actions of oxidized LDL, (
EDRF(NO) deficit via augnogenous supplementation v
LDL, oxidized LDL; PKC, p
PLA₂, phospholipase A₂.

COHEN
due to its antioxidant activity and independent of its
lipid-lowering effects. In fact, some antioxidant com-COHEN
due to its antioxidant activity and independent of its
lipid-lowering effects. In fact, some antioxidant com-
pounds slowed the progression of atherosclerosis in the
absence of a substantial change in serum lipid lev due to its antioxidant activity and independent of its lipid-lowering effects. In fact, some antioxidant compounds slowed the progression of atherosclerosis in the absence of a substantial change in serum lipid levels (Spa due to its antioxidant activity and independent of its
lipid-lowering effects. In fact, some antioxidant com-
pounds slowed the progression of atherosclerosis in the
absence of a substantial change in serum lipid levels
(S mplu-lowering enects. In fact, some antioxidant com
pounds slowed the progression of atherosclerosis in the
absence of a substantial change in serum lipid level
(Sparrow et al., 1992), consistent with the possibility
that absence of a substantian change in serum liptu levels
(Sparrow et al., 1992), consistent with the possibility
that decreased oxidized LDL was important in the ben-
eficial effects observed. Indeed, intake of the antioxidan (Sparrow et al., 1992), consistent with the possibility
that decreased oxidized LDL was important in the ben-
eficial effects observed. Indeed, intake of the antioxidant
vitamin α -tocopherol increased the resistance of that decreased oxidized LDL was important in the ben-
eficial effects observed. Indeed, intake of the antioxidant
vitamin α -tocopherol increased the resistance of LDL to
ex vivo oxidation in humans (Jialal et al., 1995 eficial effects observed. Indeed, intake of the antioxidavitamin α -tocopherol increased the resistance of LDI
ex vivo oxidation in humans (Jialal et al., 1995; Princet al., 1995). However, as discussed above, data on t
 vitamin *a*-tocopherol increased the resistance of LDL to
ex vivo oxidation in humans (Jialal et al., 1995; Princen
et al., 1995). However, as discussed above, data on the
effects of antioxidants on vascular functioning in ex vivo oxidation in humans (Jialal et al., 1995; Princen
et al., 1995). However, as discussed above, data on the
effects of antioxidants on vascular functioning in athero-
sclerosis are limited. Although the predicted ben et al., 1995). However, as discussed above, data on the effects of antioxidants on vascular functioning in atherosclerosis are limited. Although the predicted benefit of antioxidant vitamins in slowing the progression of a effects of antioxidants on vascular functioning in atherosclerosis are limited. Although the predicted benefit of antioxidant vitamins in slowing the progression of atherosclerosis has not yet been proven in humans, a sign sclerosis are limited. Although the predicted benefit of
antioxidant vitamins in slowing the progression of ath-
erosclerosis has not yet been proven in humans, a sig-
nificant inverse correlation between serum levels of n antioxidant vitamins in slowing the progression of atherosclerosis has not yet been proven in humans, a significant inverse correlation between serum levels of natural antioxidant vitamins and the frequency of occurrence o erosclerosis has not yet been proven in humans, a significant inverse correlation between serum levels of natural antioxidant vitamins and the frequency of occurrence of cardiovascular disease has been documented (Gey et a mificant inverse correlation between serum levels of nat
ural antioxidant vitamins and the frequency of
occurrence of cardiovascular disease has been docu
mented (Gey et al., 1991). Additionally, several limited
prospectiv ural antioxidant vitamins and the frequency of occurrence of cardiovascular disease has been documented (Gey et al., 1991). Additionally, several limited prospective trials have associated intake of antioxidant vitamins wi occurrence of cardiovascular disease has been documented (Gey et al., 1991). Additionally, several limited prospective trials have associated intake of antioxidant vitamins with a decrease in clinical events associated wit mented (Gey et al., 1991). Additionally, several limited
prospective trials have associated intake of antioxidant
vitamins with a decrease in clinical events associated
with atherosclerosis (Stampfer et al., 1993; Rimm et prospective trials have associated intake of antioxidant
vitamins with a decrease in clinical events associated
with atherosclerosis (Stampfer et al., 1993; Rimm et al.,
1993). Because of these preliminary encouraging resu 1993). Because of these preliminary encouraging results
with antioxidant vitamins, the search for more potent
and safe antioxidant compounds with oral activity is
currently underway (Breugnot et al., 1994).
Our current un

and safe antioxidant compounds with oral activity is currently underway (Breugnot et al., 1994).
Our current understanding of the mechanisms of LDL oxidation in vivo is limited. Elucidation of these mechaand safe antioxidant compounds with oral activity is
currently underway (Breugnot et al., 1994).
Our current understanding of the mechanisms of LDL
oxidation in vivo is limited. Elucidation of these mecha-
nisms may reveal currently underway (Breugnot et al., 1994).

Our current understanding of the mechanisms of LDL

oxidation in vivo is limited. Elucidation of these mecha-

misms may reveal novel and perhaps more effective

strategies for Our current understanding of the mechanisms of LDL
oxidation in vivo is limited. Elucidation of these mecha-
nisms may reveal novel and perhaps more effective
strategies for inhibiting the in vivo formation of oxidized
LDL nisms may reveal novel and perhaps more effective
strategies for inhibiting the in vivo formation of oxidized
LDL. For example, several recent studies suggested im-
portant roles for 15-lipoxygenase (Parthasarathy et al.,
 strategies for innibiting the in vivo formation of oxidated
LDL. For example, several recent studies suggested im-
portant roles for 15-lipoxygenase (Parthasarathy et al.
1989) and PKC (Li and Cathcart, 1994) in cell-media portant roles for 15-lipoxygenase (Parthasarathy et al., 1989) and PKC (Li and Cathcart, 1994) in cell-mediated LDL oxidation. In addition, LDL was suggested to possess an intrinsic PLA₂ activity responsible for the ext 1989) and PKC (Li and Cathcart, 1994) in cell-mediated

LDL oxidation. In addition, LDL was suggested to possess an intrinsic PLA₂ activity responsible for the extensive conversion of phosphatidylcholine to lyso PC upon sess an intrinsic PLA_2 activity responsible for the exten
sive conversion of phosphatidylcholine to lyso PC upor
oxidation and, indeed, PLA_2 inhibitors attenuated LDI
oxidation (Parthasarathy et al., 1985). If similar sess an intrinsic PLA₂ activity responsible for the extensive conversion of phosphatidylcholine to lyso PC upon oxidation and, indeed, PLA₂ inhibitors attenuated LDL oxidation (Parthasarathy et al., 1985). If similar sive conversion of phosphatidylcholine to lyso PC upon
oxidation and, indeed, PLA_2 inhibitors attenuated LDL
oxidation (Parthasarathy et al., 1985). If similar pro-
cesses participate in the oxidation of LDL in vivo, th oxidation and, indeed, PLA_2 inhibitors attenuated LDL oxidation (Parthasarathy et al., 1985). If similar processes participate in the oxidation of LDL in vivo, then selective inhibitors of these enzymes may inhibit the oxidation (Parthasarathy et al., 1985). If similar presses participate in the oxidation of LDL in vivo, the selective inhibitors of these enzymes may inhibit the vivo oxidation of LDL, and could be of potential ben in corr tion. Frequency of the Indian of LDL, and could be of potential beneficial correcting atherosclerosis-induced vascular dysfund
in correcting atherosclerosis-induced vascular dysfund
ion.
B. Inhibiting the Interaction of Oxidize Lipoprotein atherosclerosis-indu
Lipoprotein with Target Cells
In addition to inhibiting the in

ANO In addition to inhibiting the in vivo formation of oxidized LDL, blocking its interaction with vascular target VASCULAR cells may also be an effective strategy in reversing ath-

FFECTS erosclerosis-induced vascular dysfunction. If the vasoac-

FIG. 4. Potential targets for pharmacological intervention to in-

hibit or reverse oxid Inhibiting the Interaction of Oxidized Low-Density
poprotein with Target Cells
In addition to inhibiting the in vivo formation of oxi-
sed LDL, blocking its interaction with vascular target B. Inhibiting the Interaction of Oxidized Low-Density
Lipoprotein with Target Cells
In addition to inhibiting the in vivo formation of oxi-
dized LDL, blocking its interaction with vascular target
cells may also be an effe Example interaction of Oxidized Low-Density
Cipoprotein with Target Cells
In addition to inhibiting the in vivo formation of oxi-
dized LDL, blocking its interaction with vascular target
cells may also be an effective stra Lipoprotein with 1 arget Cetts
In addition to inhibiting the in vivo formation of o
dized LDL, blocking its interaction with vascular targells
may also be an effective strategy in reversing a
erosclerosis-induced vascular tive effects of oxidized LDL were confirmed to be a direct dized LDL, blocking its interaction with vascular target
cells may also be an effective strategy in reversing ath-
erosclerosis-induced vascular dysfunction. If the vasoac-
tive effects of oxidized LDL were confirmed to be cells may also be an effective strategy in reversing a
erosclerosis-induced vascular dysfunction. If the vaso
tive effects of oxidized LDL were confirmed to be a dir
consequence of its interaction with a specific recept
th erosclerosis-induced vascular dysfunction. If the vasoactive effects of oxidized LDL were confirmed to be a direct consequence of its interaction with a specific receptor, then this would provide the opportunity for the de tive effects of oxidized LDL were confirmed to be a direct
consequence of its interaction with a specific receptor,
then this would provide the opportunity for the develop-
ment of an oxidized LDL "antagonist" with which t consequence of its interaction with a specific receptor,
then this would provide the opportunity for the develop-
ment of an oxidized LDL "antagonist" with which to
block cellular effects of this lipoprotein. However, the
 then this would provide the opportunity for the development of an oxidized LDL "antagonist" with which though several. However, the nature of oxidized LDL's interaction with target cells is currently unclear. Although seve block cellular effects of this lipoprotein. However, the nature of oxidized LDL's interaction with target cells is currently unclear. Although several oxidized LDL binding proteins have been described (Endemann et al.,

OXIDIZED LOW-DENS
1993; Stanton et al., 1992; Ottnad et al., 1995), their
role, if any, in the vascular effects of oxidized LDL is oxider to oxiding the value of the vascular effects of oxidized LDL is
role, if any, in the vascular effects of oxidized LDL is
unknown. Thus, understanding the consequences of the cu oxider to understanding the consequences of the consequences o 1993; Stanton et al., 1992; Ottnad et al., 1995), their role, if any, in the vascular effects of oxidized LDL is unknown. Thus, understanding the consequences of the binding of oxidized LDL to these sites on cellular funct 1993; Stanton et al., 1992; Ottnad et al., 1995), their prole, if any, in the vascular effects of oxidized LDL is vunknown. Thus, understanding the consequences of the chinding of oxidized LDL to these sites on cellular f role, if any, in the vascular effects of oxidized l
unknown. Thus, understanding the consequences
binding of oxidized LDL to these sites on cellula
tion and biochemistry is clearly an important a:
future research and pharm binding of oxidized LDL to these sites on cellular
tion and biochemistry is clearly an important are
future research and pharmacological intervention
C. Inhibiting the Cellular Actions of Oxidized Lou
Density Lipoprotei France and biochemistry is clearly an important area for
 Density Lipoprotein
 Density Lipoprotein
 Density Lipoprotein

An alternative approach to blockade of oxidized LDL

ture research and pharmacological intervention.
 $\begin{array}{c}$ $\begin{array}{c}$ \end{array} $\begin{array}{c}$ \end{array} C. Inhibiting the Cellular Actions of Oxidized Low-
Density Lipoprotein
An alternative approach to blockade of oxidized LD
vascular receptors may be to target the cellular path-
ways by which oxidized LDL mediates its effe C. Inhibiting the Cellular Actions of Oxidized Low-
Density Lipoprotein
An alternative approach to blockade of oxidized LDL
wascular receptors may be to target the cellular path-
ways by which oxidized LDL mediates its ef example, and alternative approach to blockade of oxidized LDL
vascular receptors may be to target the cellular path-
since ways by which oxidized LDL mediates its effects. For to
example, lyso PC has been implicated as one An alternative approach to blockade of oxidized LDL strusscular receptors may be to target the cellular path-
since ways by which oxidized LDL mediates its effects. For to example, lyso PC has been implicated as one of the vascular receptors may be to target the cellular p
ways by which oxidized LDL mediates its effects.
example, lyso PC has been implicated as one of
components of oxidized LDL with vascular activity,
PKC has been suggested t ways by which oxidized LDL mediates its effects. For to the sumple, lyso PC has been implicated as one of the sum components of oxidized LDL with vascular activity, and cure PKC has been suggested to be an important intrac example, lyso PC has been implicated as one of the components of oxidized LDL with vascular activity, and PKC has been suggested to be an important intracellular target in the actions of both oxidized LDL and lyse PC. The components of oxidized LDL with vascular activity, and curse
PKC has been suggested to be an important intracellu-
lar target in the actions of both oxidized LDL and lyso et al
PC. The ability of PKC inhibitors to reverse PKC has been suggested to be an important intracellu-
lar target in the actions of both oxidized LDL and lyso
PC. The ability of PKC inhibitors to reverse impairment
of endothelium-dependent relaxation by oxidized LDL
(Oh lar target in the actions of both oxidized LDL and lyso PC. The ability of PKC inhibitors to reverse impairment of endothelium-dependent relaxation by oxidized LDL (Ohgushi et al., 1993) suggests that selective inhibition PC. The ability of PKC inhibitors to reverse impairm
of endothelium-dependent relaxation by oxidized L
(Ohgushi et al., 1993) suggests that selective inhibit
of this intracellular signaling pathway may be benefic
in correc of endothelium-dependent relaxation by oxidized LDL so
(Ohgushi et al., 1993) suggests that selective inhibition
of this intracellular signaling pathway may be beneficial tr
in correcting atherosclerosis-induced vascular d (Ohgushi et al., 1993) suggests that selective inhibition
of this intracellular signaling pathway may be beneficial
in correcting atherosclerosis-induced vascular dysfunc-
tion. However, to date, selective inhibitors of PK of this intracellular signaling pathway may be beneficial tree
in correcting atherosclerosis-induced vascular dysfunc-
tion. However, to date, selective inhibitors of PKC have side
not been examined for their ability to im in correcting atherosclerosis-induced vascular dysfunc-
tion. However, to date, selective inhibitors of PKC have
not been examined for their ability to improve vascular
function in hypercholesterolemia or atherosclerosis i tion. However, to date, selective inhibitors of PKC have
not been examined for their ability to improve vascular
function in hypercholesterolemia or atherosclerosis in
vivo. Furthermore, PKC is a heterogeneous family of
en not been examined for their ability to improve vascular
function in hypercholesterolemia or atherosclerosis in ED
vivo. Furthermore, PKC is a heterogeneous family of vat
enzymes that regulates a variety of cellular functio vivo. Furthermore, PKC is a heterogeneous family of enzymes that regulates a variety of cellular functions (Parker et al., 1989), and additional research will be required to understand which isoform(s) may potentially regu vivo. Furthermore, PKC is a heterogeneous family
enzymes that regulates a variety of cellular functic
(Parker et al., 1989), and additional research will
required to understand which isoform(s) may potentia
regulate the ED enzymes that regulates a variety of cellular functions (Parker et al., 1989), and additional research will be required to understand which isoform(s) may potentially regulate the EDRF(NO) pathway. Undesirable physiological (Parker et al., 1989), and additional research will be required to understand which isoform(s) may potentially regulate the EDRF(NO) pathway. Undesirable physiological effects due to the nonselective nature of currently av required to understand which isoform(s) may pote
regulate the EDRF(NO) pathway. Undesirable
logical effects due to the nonselective nature of cu
available PKC inhibitors has hindered the clini
ploration of this strategy to regulate the EDRF(NO) pathway. Undesirable physiological effects due to the nonselective nature of currently available PKC inhibitors has hindered the clinical exploration of this strategy to reverse atherosclerosis-induce logical effects due to the nonselective nature of currently
available PKC inhibitors has hindered the clinical ex-
ploration of this strategy to reverse atherosclerosis-in-
duced vascular dysfunction. Therefore, the develo available PKC inhibitors has hindered the clinical ex-
ploration of this strategy to reverse atherosclerosis-in-
duced vascular dysfunction. Therefore, the development sclere
and utilization of isoform-selective PKC inhibi ploration of this strategy to reverse atherosclerosis-in-
duced vascular dysfunction. Therefore, the development
and utilization of isoform-selective PKC inhibitors LD
would provide a deeper understanding of the role of PK duced vascular dysfunction. Therefore, the development
and utilization of isoform-selective PKC inhibitors L
would provide a deeper understanding of the role of PKC
in modulating vascular function in atherosclerosis and
al and utilization of isoform-selective PKC inhibitors L
would provide a deeper understanding of the role of PKC or
in modulating vascular function in atherosclerosis and or
allow a better evaluation of the clinical utility disease. modulating vascular function in atherosclerosis and
low a better evaluation of the clinical utility of these
hibitors in normalizing vascular functioning in this
sease.
Oxidized LDL has been shown to affect several other
c

inhibitors in normalizing vascular functioning in this disease.

Oxidized LDL has been shown to affect several other

second-messenger pathways in addition to PKC, includ-

ing phosphatidylinositol hydrolysis (Hamilton et 1994) and phospholipase D (Natarajan et al., 1993). De- ifestations of atherosclerosis. disease.

Oxidized LDL has been shown to affect several other

second-messenger pathways in addition to PKC, includ-

ing phospholipase D (Natarajan et al., 1993). De-

velopment of selective inhibitors of these pathways w Oxidized LDL has been shown to affect several other
second-messenger pathways in addition to PKC, includ-
ing phosphatidylinositol hydrolysis (Hamilton et al.,
1994) and phospholipase D (Natarajan et al., 1993). De-
velopm second-messenger pathways in addition to PKC, including phosphatidylinositol hydrolysis (Hamilton et 1994) and phospholipase D (Natarajan et al., 1993). I velopment of selective inhibitors of these pathways walso be import ing phosphatidylinositol hydrolysis (Hamilton et al., 1994) and phospholipase D (Natarajan et al., 1993). Development of selective inhibitors of these pathways will also be important in elucidating their role in the inhibi 94) and phospholipase D (Natarajan et al., 1993). De-
ifestiopment of selective inhibitors of these pathways will
so be important in elucidating their role in the inhibi-
on of endothelial function produced by oxidized LDL

velopment of selective inhibitors of these pathways will
also be important in elucidating their role in the inhibi-
tion of endothelial function produced by oxidized LDL.
A role for increased superoxide anion production in also be important in elucidating their role in the inhibition of endothelial function produced by oxidized LDL.
A role for increased superoxide anion production in the vasomotor actions of oxidized LDL may provide another tion of endothelial function produced by oxidized LDL.
A role for increased superoxide anion production in
the vasomotor actions of oxidized LDL may provide an-
other site of pharmacological intervention to improve
vascula A role for increased superoxide anion production in
the vasomotor actions of oxidized LDL may provide an-
other site of pharmacological intervention to improve
vascular function in atherosclerosis. Indeed, treatment
of rab the vasomotor actions of oxidized LDL may provide an-
other site of pharmacological intervention to improve with
vascular function in atherosclerosis. Indeed, treatment man
of rabbits in vivo with polyethylene-glycolated S other site of pharmacological intervention to improve wit
vascular function in atherosclerosis. Indeed, treatment ma
of rabbits in vivo with polyethylene-glycolated SOD par-
nor
tially prevented the impairment of EDR produ vascular function in atherosclerosis. Indeed, treatment
of rabbits in vivo with polyethylene-glycolated SOD par-
tially prevented the impairment of EDR produced by
atherosclerosis (Mugge et al., 1991). Furthermore, a
pharm of rabbits in vivo with polyethylene-glycolated SOD partially prevented the impairment of EDR produced by the atherosclerosis (Mugge et al., 1991). Furthermore, a sclude pharmacological SOD mimetic, SC52608, enhanced NO-al tially prevented the impairment of EDR produced by
atherosclerosis (Mugge et al., 1991). Furthermore, a
pharmacological SOD mimetic, SC52608, enhanced NO-
mediated vascular relaxation in vitro by increasing the
biological atherosclerosis (Mugge et al., 1991). Furthermore, a sclub pharmacological SOD mimetic, SC52608, enhanced NO-
mediated vascular relaxation in vitro by increasing the embiological half-life of NO (Kasten et al., 1995). Thus

potentiate the activity of endogenous NO, inhibit the valid in the extend of the detections of the potentiate the activity of endogenous NO, inhibit the vas-
variant variance of oxidized LDL, and normalize vas-
cular function in atherosclerosis. FITY LIPOPROTEIN
potentiate the activity of end
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cular function in atheroscleros potentiate the activity of endogenous NO, inhibit the vasomotor actions of oxidized LDL, and normalize vascular function in atherosclerosis.
D. Augmentation of Endogenous Nitric Oxide Release or *Exogenous Replacement of or Exogenous of oxidized LDL, and norm*

cular function in atherosclerosis.

D. Augmentation of Endogenous Nitric Oxide

or Exogenous Replacement of Nitric Oxide

Because the bulk of the data suggest that

cular function in atherosclerosis.

D. Augmentation of Endogenous Nitric Oxide Release

or Exogenous Replacement of Nitric Oxide

Because the bulk of the data suggest that oxidized

LDL and atherosclerosis cause vascular d

D. Augmentation of Endogenous Nitric Oxide Release
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LDL and atherosclerosis cause vascular dysfunction via
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LDL and atherosclerosis cause vascular dysfunction via
an effect on the EDRF(NO) pat or *Exogenous Replacement of Nuric Oxide*
Because the bulk of the data suggest that oxide
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strategy to normalize vascular fu Because the bulk of the data suggest that oxidized
LDL and atherosclerosis cause vascular dysfunction via
an effect on the EDRF(NO) pathway, another potential
strategy to normalize vascular function in atherosclero-
sis ma LDL and atherosclerosis cause vascular dysfunction via
an effect on the EDRF(NO) pathway, another potential
strategy to normalize vascular function in atherosclero-
sis may be either to augment endogenous NO release or
to an effect on the EDRF(NO) pathway, another potential
strategy to normalize vascular function in atherosclero-
sis may be either to augment endogenous NO release or
to deliver exogenous NO via orally active NO donors. In
su strategy to normalize vascular function in ath
sis may be either to augment endogenous NO
to deliver exogenous NO via orally active NO or
support of this concept, treatment with the
curser L-arginine normalized hypercholes sis may be either to augment endogenous NO release or
to deliver exogenous NO via orally active NO donors. In
support of this concept, treatment with the NO pre-
curser L-arginine normalized hypercholesterolemia-in-
duced to deliver exogenous NO via orally active NO donors
support of this concept, treatment with the NO p
curser L-arginine normalized hypercholesterolemia
duced endothelial dysfunction in both rabbits (Ross
et al., 1991) and h support of this concept, treatment with the NO p
curser L-arginine normalized hypercholesterolemia
duced endothelial dysfunction in both rabbits (Rossi
et al., 1991) and humans (Creager et al., 1992). Furth
more, pentaeryt curser L-arginine normalized hypercholesterolemia-
duced endothelial dysfunction in both rabbits (Rossit
et al., 1991) and humans (Creager et al., 1992). Furth
more, pentaerythrityl-tetranitrate, an organic nitrov
sodilato duced endothelial dysfunction in both rabbits (Rossitch et al., 1991) and humans (Creager et al., 1992). Furthermore, pentaerythrityl-tetranitrate, an organic nitrovasodilator, also prevented impairment of EDR in cholester more, pentaerythrityl-tetranitrate, an organic nitrova-
sodilator, also prevented impairment of EDR in choles-
terol-fed rabbits (Kojda et al., 1995). However, chronic
treatment of rabbits with organic nitrovasodilators
(K more, pentaerythrityl-tetranitrate, an organic nitrova
sodilator, also prevented impairment of EDR in choles
terol-fed rabbits (Kojda et al., 1995). However, chronic
treatment of rabbits with organic nitrovasodilators
(Koj sodilator, also prevented impairment of EDR in cholerol-fed rabbits (Kojda et al., 1995). However, chromotreatment of rabbits with organic nitrovasodilat (Kojda et al., 1995) and direct NO donors such as not sidomine (Bult terol-fed rabbits (Kojda et al., 1995). However, chronic
treatment of rabbits with organic nitrovasodilators
(Kojda et al., 1995) and direct NO donors such as mol-
sidomine (Bult et al., 1995), also resulted in a desensi-
 treatment of rabbits with organic nitrovasodilato (Kojda et al., 1995) and direct NO donors such as m sidomine (Bult et al., 1995), also resulted in a desentization of EDR due to down-regulation of the EDRF(NO) pathway, an (Kojda et al., 1995) and direct NO donors such as molsidomine (Bult et al., 1995), also resulted in a desensi-
tization of EDR due to down-regulation of the
EDRF(NO) pathway, an effect that could actually aggra-
vate rathe tization of EDR due to down-regulation of the
EDRF(NO) pathway, an effect that could actually aggra-
vate rather than alleviate atherosclerosis-induced vas-
cular dysfunction. Thus, the utility of NO donors in
normalizing EDRF(NO) pathway, an effect
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cular dysfunction. Thus, the
normalizing pathological vaso
LDL requires further study.
In summary, there are sev is the rather than alleviate atherosclerosis-induced vas-
lar dysfunction. Thus, the utility of NO donors in
rmalizing pathological vasomotion caused by oxidized
DL requires further study.
In summary, there are several con

related to drug development that may prevent or incommentating pathological vasomotion caused by oxidized LDL requires further study.
In summary, there are several conceptual strategies related to drug development that may normalizing pathological vasomotion caused by oxidized
LDL requires further study.
In summary, there are several conceptual strategies
related to drug development that may prevent or inhibit
oxidized LDL-induced endothelia LDL requires further study.
In summary, there are several conceptual strategerelated to drug development that may prevent or inhition in ather boxidized LDL-induced endothelial dysfunction and m
be beneficial in normalizin In summary, there are several conceptual strategies
related to drug development that may prevent or inhibit
oxidized LDL-induced endothelial dysfunction and may
be beneficial in normalizing vascular function in athero-
scl related to drug development that may prevent or inhibit
oxidized LDL-induced endothelial dysfunction and may
be beneficial in normalizing vascular function in athero-
sclerosis. Inhibiting the formation and action of oxidi oxidized LDL-induced endothelial dysfunction and may
be beneficial in normalizing vascular function in athero-
sclerosis. Inhibiting the formation and action of oxidized
LDL may have additional benefit beyond normalization be beneficial in normalizing vascular function in athero-
sclerosis. Inhibiting the formation and action of oxidized
LDL may have additional benefit beyond normalization
of vascular function, including slowing the progress sclerosis. Inhibiting the formation and action of oxidized LDL may have additional benefit beyond normalization
of vascular function, including slowing the progression
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chan of vascular function, including slowing the progression
of lesion formation and perhaps decreasing the lipid and
foam-cell content of the lesion, thereby decreasing
chances of plaque rupture. However, further research
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foam-cell content of the lesion, thereby decreasing
chances of plaque rupture. However, further research
into the basic mechanism of oxidized LDL's vasoactive
effect foam-cell content of the lesion, thereby decreasing
chances of plaque rupture. However, further research
into the basic mechanism of oxidized LDL's vasoactive
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valid chances of plaque rupture. However, further researce into the basic mechanism of oxidized LDL's vasoactive
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VIII. Summary and Conclusions
d LDL exerts profound effects on the of these interventions on the occurrence of clinical manifestations of atherosclerosis.
 VIII. Summary and Conclusions

Oxidized LDL exerts profound effects on the vasomo-

tor response of isolated blood vessels to vario

ifestations of atherosclerosis.

VIII. Summary and Conclusions

Oxidized LDL exerts profound effects on the vasomo-

tor response of isolated blood vessels to various stimuli

that closely mimic the vascular dysfunction as VIII. Summary and Conclusions
Oxidized LDL exerts profound effects on the vasomo-
tor response of isolated blood vessels to various stimuli
that closely mimic the vascular dysfunction associated
with hypercholesterolemia a VIII. Summary and Conclusions
Oxidized LDL exerts profound effects on the vasomo-
tor response of isolated blood vessels to various stimuli
that closely mimic the vascular dysfunction associated
with hypercholesterolemia a Oxidized LDL exerts profound effects on the vasomo-
tor response of isolated blood vessels to various stimuli
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with hypercholesterolemia and atherosclerosis in hu-
mans tor response of isolated blood vessels to various stimuli
that closely mimic the vascular dysfunction associated
with hypercholesterolemia and atherosclerosis in hu-
mans. The beneficial effect of lipid-lowering therapy in that closely mimic the vascular dysfunction association with hypercholesterolemia and atherosclerosis in 1 mans. The beneficial effect of lipid-lowering therapy normalizing vascular function and greatly decreasies the freq with hypercholesterolemia and atherosclerosis in humans. The beneficial effect of lipid-lowering therapy in normalizing vascular function and greatly decreasing the frequency of clinical events associated with atherosclero normalizing vascular function and greatly decreasing
the frequency of clinical events associated with athero-
sclerosis, combined with the ability of antioxidants to
alleviate vasomotor disturbances in hypercholesterol-
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sclerosis, combined with the ability of antioxidants
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stron sclerosis, combined with the ability of antioxidants to
alleviate vasomotor disturbances in hypercholesterol-
emia and slow the progression of atherosclerosis,
strongly support a causative role of oxidized LDL in
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to the clinical sequalae of coronary artery disease. Fur-
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veal novel strategies to inhibit these events, a to the clinical sequalae of coronary artery disease. Fur-
ther research to understand more fully the mechanisms
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veal novel strategies to inhibit these events, and may
 to the clinical sequalae of coronary artery disease. Further research to understand more fully the mechanisms of oxidized LDL formation and actions in vivo may reveal novel strategies to inhibit these events, and may prove ther research to und
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