ARMACOLOGICAL REVIEWS

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Cationic Amphiphilic Drugs and Phospholipid Storage **Disorder***

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I. Introduction

A. *What Is Drug-induced Phospholipidosis?*
Phospholipidosis (phospholipid storage disorder) re-I. Introduction

What Is Drug-induced Phospholipidosis?

Phospholipidosis (phospholipid storage disorder) re-

rs to an excessive accumulation of phospholipids in the fers to an excessive accumulation of phospholipidesis?

A. What Is Drug-induced Phospholipidosis?

Phospholipidosis (phospholipid storage disorder) refers to an excessive accumulation of phospholipids in the

tissues. Phos A. What Is Drug-induced Phospholipidosis?
Phospholipidosis (phospholipid storage disorder)
fers to an excessive accumulation of phospholipids in t
tissues. Phospholipids are essential structural comports of animal cell mem nents of animal cell membranes and cytoskeletons
fers to an excessive accumulation of phospholipids in the
tissues. Phospholipids are essential structural compo-
nents of animal cell membranes and cytoskeletons
(Stryer, 19 Phospholipidosis (phospholipid storage disorder) refers to an excessive accumulation of phospholipids in the tissues. Phospholipids are essential structural components of animal cell membranes and cytoskeletone (Stryer, 19 fers to an excessive accumulation of phospholipids in the
tissues. Phospholipids are essential structural compo-
nents of animal cell membranes and cytoskeletons
(Stryer, 1988). Consequently, their synthesis, utilization,
 tissues. Phospholipids are essential structural compo-
nents of animal cell membranes and cytoskeletons
(Stryer, 1988). Consequently, their synthesis, utilization,
and turnover are regulated in the cell. Drugs, chemicals,
 tryer, 1988). Consequently, their synthesis, utilization, get turnover are regulated in the cell. Drugs, chemicals, care dogenous substances such as hormones, cofactors, and H_i This work was supported and the review was

other agents may perturb this regulation resulting in

phospholipidosis. Direct interactions of drugs and other phospholipidosis. Direct interactions of drugs and other agents may perturb this regulation resulting in phospholipidosis. Direct interactions of drugs and other xenobiotics with phospholipids, or indirect effects other agents may perturb this regulation resulting in
phospholipidosis. Direct interactions of drugs and other
xenobiotics with phospholipids, or indirect effects
brought about through changes in the synthesis and other agents may perturb this regulation resulting in
phospholipidosis. Direct interactions of drugs and other
xenobiotics with phospholipids, or indirect effects
brought about through changes in the synthesis and
metaboli other agents may perturb this regulation resulting
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venobiotics with phospholipids, or indirect effector
brought about through changes in the synthesis a
metabolism o phospholipidosis. Direct interactions of drugs and other
xenobiotics with phospholipids, or indirect effects
brought about through changes in the synthesis and
metabolism of phospholipids, can lead to several signifi-
cant xenobiotics with phospholipids, or indirect effects brought about through changes in the synthesis and metabolism of phospholipids, can lead to several significant alterations in cellular structure and function. The partic brought about through changes in the synthesis and
metabolism of phospholipids, can lead to several signifi-
cant alterations in cellular structure and function. The
participation of various lipids in the regulation of cel metabolism of phospholipids, can lead to several significant alterations in cellular structure and function. The participation of various lipids in the regulation of cellular functions through inositol phosphatide second m cant alterations in cellular structure and function. The participation of various lipids in the regulation of cellular functions through inositol phosphatide second messengers and through hormones of the arachidonic acid c participation of various lipids in the regulation of cellular functions through inositol phosphatide second messengers and through hormones of the arachidonic acid cascade is being increasingly recognized (Champe and Harve functions through inositol phosphatide second messengers and through hormones of the arachidonic acid cascade is being increasingly recognized (Champe and Harvey, 1988; Farese, 1988). Phospholipidosis may occur as the resu gers and through hormones of the arachidonic acid cas-
cade is being increasingly recognized (Champe and
Harvey, 1988; Farese, 1988). Phospholipidosis may occur
as the result of metabolic dysfunction and genetic dis-
order cade is being increasingly recognized (Champe and Harvey, 1988; Farese, 1988). Phospholipidosis may occur as the result of metabolic dysfunction and genetic disorders such as Niemann-Pick and Tay-Sachs disease (Terry and W Harvey, 1988; Farese, 1988). Phospholipidosis may occur as the result of metabolic dysfunction and genetic disorders such as Niemann-Pick and Tay-Sachs disease (Terry and Weiss, 1963; Lazarus et al., 1967) or may occur due ders such as Niemann-Pick and Tay-Sachs disear
'erry and Weiss, 1963; Lazarus et al., 1967) or ma
cur due to long-term treatment with CADs‡ (Lullman
‡Abbreviations: CAD, cationic amphiphilic drug; ATPase, aden
e triphospha

occur due to long-term treatment with CADs‡ (Lullmann
‡Abbreviations: CAD, cationic amphiphilic drug; ATPase, adeno-
sine triphosphatase.

and turnover are regulated in the cent. Drugs, chemicals,
endogenous substances such as hormones, cofactors, and
Fris work was supported and the review was made possible through
a grant from National Institute of Heart, Lu

et al., 1978; Hostetler and Matsuzawa, 1981; Camus, 1978; Hostetler and Matsuzawa, 1981; Camendale, 1978; Hostetler and Matsuzawa, 1981; Camendale, 1989). Drug-induced exces-
1989; Joshi and Mehendale, 1989). Drug-induced exces-
1989; Sive storage of phospholipids can occur sive storage of phospholipids can occur in lung, liver, brain, kidney, cornea, adipose and several other tissues brain, kidney, cornea, adipose and several other tissues et al., 1978; Hostetler and Matsuzawa, 1981; Camus, 1989; Joshi and Mehendale, 1989). Drug-induced excessive storage of phospholipids can occur in lung, liver, brain, kidney, cornea, adipose and several other tissues (De l et al., 1978; Hostetler and Matsuzawa, 1981; Camus, 1989; Joshi and Mehendale, 1989). Drug-induced excessive storage of phospholipids can occur in lung, liver, brain, kidney, cornea, adipose and several other tissues (De l 1989; Joshi and Mehendale, 1989). Drug-induced excessive storage of phospholipids can occur in lung, liver, brain, kidney, cornea, adipose and several other tissues (De la Iglesia et al., 1974; Leech et al., 1984; Hostetle sive storage of phospholipids can occur in lung, liver,
brain, kidney, cornea, adipose and several other tissues
(De la Iglesia et al., 1974; Leech et al., 1984; Hostetler
et al., 1985; Kacew, 1985; Martin and Standing, 19 et al., 1985; Kacew, 1985; Martin and Standing, 1988;
Pirovino et al., 1988). Excessive phospholipid storage has
been shown to occur in a variety of animal species and
in humans. Considerable species variation exists with
 et al., 1985; Kacew, 1985; Martin and Standing, 1988; ver
Pirovino et al., 1988). Excessive phospholipid storage has
been shown to occur in a variety of animal species and
in humans. Considerable species variation exists w Pirovino et al., 1988). Excessive phospholipid storage has
been shown to occur in a variety of animal species and
in humans. Considerable species variation exists with
regard to the degree of phospholipidosis that occurs a in humans. Considerable species variation exists with
regard to the degree of phospholipidosis that occurs and
the target organ being affected (Schmien et al., 1974;
Sakuragawa et al., 1977; Lullmann-Rauch, 1979; Reasor,
1 in humans. Considerable species variation exists w
regard to the degree of phospholipidosis that occurs a
the target organ being affected (Schmien et al., 19
Sakuragawa et al., 1977; Lullmann-Rauch, 1979; Reas
1981; Miles regard to the degree of phospholipidosis that the target organ being affected (Schmien et Sakuragawa et al., 1977; Lullmann-Rauch, 1971
1981; Miles et al., 1986; Kacew, 1987; Martin s
ing, 1988; Kodavanti and Mehendale, 19 e target organ being affected (Schmien et al., 1974
kuragawa et al., 1977; Lullmann-Rauch, 1979; Reasor
81; Miles et al., 1986; Kacew, 1987; Martin and Stand
g, 1988; Kodavanti and Mehendale, 1991).
The time required for d

Sakuragawa et al., 1977; Lullmann-Rauch, 1979; Reasor, 1981; Miles et al., 1986; Kacew, 1987; Martin and Standing, 1988; Kodavanti and Mehendale, 1991).
The time required for development of phospholipidosis varies dependin 1981; Miles et al., 1986; Kacew, 1987; Martin and Standing, 1988; Kodavanti and Mehendale, 1991).
The time required for development of phospholipidosis
varies depending on the dose, type of drug, animal species, or the nat ing, 1988; Kodavanti and Mehendale, 1991).
The time required for development of phospholipidosis
varies depending on the dose, type of drug, animal spe-
cies, or the nature and origin of the cells used in the cell
culture The time required for development of phospholipido
varies depending on the dose, type of drug, animal sp
cies, or the nature and origin of the cells used in the c
culture system. The use of cultured isolated macrophag
and varies depending on the dose, type of drug, animal species, or the nature and origin of the cells used in the cell
culture system. The use of cultured isolated macrophages
and bovine pulmonary artery endothelial cells in cies, or the nature and origin of the cells used in the cell
culture system. The use of cultured isolated macrophages
and bovine pulmonary artery endothelial cells in study-
ing the mechanism of phospholipidosis and other culture system. The use of cultured isolated macrophages
and bovine pulmonary artery endothelial cells in study-
ing the mechanism of phospholipidosis and other effects
of CADs has become increasingly popular (Ruben et al. ing the mechanism of phospholipidosis and other effects of CADs has become increasingly popular (Ruben et al., 1985; Martin et al., 1989). This approach has the special advantages of avoiding extensive metabolism of CADs a of CADs has become increasingly popular (Ruben et al., inan
1985; Martin et al., 1989). This approach has the special hydradvantages of avoiding extensive metabolism of CADs phili
and having a relatively short time require 1985; Martin et al., 1989). This approach has the special advantages of avoiding extensive metabolism of CAD and having a relatively short time required for the development of changes in phospholipid metabolism (Ruben et a and having a relatively short time required for the development of changes in phospholipid metabolism (Ruben et al., 1985). Several morphological, biochemical, and functional changes accompany phospholipidosis. and having a relatively short time required for the development of changes in phospholipid metabolism in (Ruben et al., 1985). Several morphological, biochemical, and functional changes accompany phospholipidosis. chere i velopment of changes in phospholipid metabolism
(Ruben et al., 1985). Several morphological, biochemical
and functional changes accompany phospholipidosis
These include an increase in cellular phospholipids, the
appearance (Ruben et al., 1985). Several morphological, biochemical,
and functional changes accompany phospholipidosis.
These include an increase in cellular phospholipids, the
appearance of lamellated inclusion bodies (lamellar bodand functional changes accompany phospholipidos
These include an increase in cellular phospholipids, t
appearance of lamellated inclusion bodies (lamellar bo
ies) in the cells, and macrophage infiltration, particular
in th appearance of lamellated inclusion bodies (lamellar bodies) in the cells, and macrophage infiltration, particularly in the lung (Reasor, 1981; Fernandez et al., 1986; Kodavanti and Mehendale, 1991). Excellent reviews of ma ies) in the cells, and macrophage infiltration, particularly
in the lung (Reasor, 1981; Fernandez et al., 1986; Koda
vanti and Mehendale, 1991). Excellent reviews of many
of these aspects have appeared in the literature (S in the lung (Reasor, 1981; Fernandez et al., 1986; Ko
vanti and Mehendale, 1991). Excellent reviews of mo
of these aspects have appeared in the literature (Shik
et al., 1972; Lullmann-Rauch and Scheid, 1975; Lu
mann et al. vanti and Mehendale, 1991). Excellent reviews of many
of these aspects have appeared in the literature (Shikata
et al., 1972; Lullmann-Rauch and Scheid, 1975; Lull-
mann et al., 1975; Michell et al., 1976; Lullmann-Rauch,
 of these aspects have appeared in the literature (Shikata
et al., 1972; Lullmann-Rauch and Scheid, 1975; Lull-
mann et al., 1975; Michell et al., 1976; Lullmann-Rauch,
1979; Reasor, 1981, 1989; Hruban, 1984; Kacew, 1984;
K et al., 1972; Lullmann-Rauch and Scheid, 1975; Lull-

mann et al., 1975; Michell et al., 1976; Lullmann-Rauch, and

1979; Reasor, 1981, 1989; Hruban, 1984; Kacew, 1984; [

Kacew and Reasor, 1985; Martin and Rosenow, 1988a, mann et al., 1975; Michell et al., 1976; Lullmann-Rauch
1979; Reasor, 1981, 1989; Hruban, 1984; Kacew, 1984
Kacew and Reasor, 1985; Martin and Rosenow, 1988a,b)
Some of the reviews were published many years ago and
in some 1979; Reasor, 1981, 1989; Hruban, 1984; Kacew, 198
Kacew and Reasor, 1985; Martin and Rosenow, 1988a, Some of the reviews were published many years ago an
in some relatively narrow aspects of phospholipidos
were examined. Kacew and Reasor, 1985; Martin and Rosenow, 1988a,b).
Some of the reviews were published many years ago and by
in some relatively narrow aspects of phospholipidosis
Rivere examined. Furthermore, more rapid and new devel-
o Some of the reviews were published many years ago and
in some relatively narrow aspects of phospholipidosis Ri
were examined. Furthermore, more rapid and new devel-
Mopments in this area make the availability of a more
de in some relat
were examine
opments in tl
detailed and u
and desirable.
We have at examined. Furthermore, more rapid and new develments in this area make the availability of a more tailed and up-to-date review of phospholipidosis timely desirable.
We have attempted to cover as many diverse aspects drug-i % opments in this area make the availability of a more
detailed and up-to-date review of phospholipidosis timely
and desirable. (
We have attempted to cover as many diverse aspects the
of drug-induced phospholipidosis as

and desirable.
We have attempted to cover as many diverse aspects
of drug-induced phospholipidosis as possible including
characteristics, consequences, influence of drugs, relation
to metabolism and disposition of drugs, s We have attempted to cover as many diverse aspects the of drug-induced phospholipidosis as possible including characteristics, consequences, influence of drugs, relation ten to metabolism and disposition of drugs, species of drug-induced phospholipidosis as possible including characteristics, consequences, influence of drugs, relation to metabolism and disposition of drugs, species variation, rand tissue specificity, which may shed some lig characteristics, consequences, influence of drugs, relat
to metabolism and disposition of drugs, species variati
and tissue specificity, which may shed some light on
mechanism of drug-induced phospholipidosis. Beca
one of to metabolism and disposition of drugs, species variation,
and tissue specificity, which may shed some light on the
mechanism of drug-induced phospholipidosis. Because
one of the remarkable features of drug-induced phospho mechanism of drug-induced phospholipidosis. Because blocker and its action is receptor mediated (Levy and
one of the remarkable features of drug-induced phospho-
light dividosis is infiltration of alveolar macrophages, an one of the remarkable features of drug-induced phosphoone of the remarkable features of drug-induced phospho-
lipidosis is infiltration of alveolar macrophages, an ac-
count of how macrophages play an important role in the
and etiology of pulmonary phospholipidosis also is de lipidosis is infiltration of alveolar macrophages,
count of how macrophages play an important role
etiology of pulmonary phospholipidosis also is d
in this review. The mechanism of action of CAD
relation to phospholipidosi etiology of pulmonary phospholipidosis also is detailed
in this review. The mechanism of action of CADs with
relation to phospholipidosis and the phospholipid-sig-
naling system is given special consideration.

B. *Pharmacology and Therapeutic Uses of Drugs Known HEHENDALE
<i>B. Pharmacology and Then*
to Induce Phospholipidosis
In this review we focus

sive storage or phospholipids can occur in lung, liver,
brain, kidney, cornea, adipose and several other tissues
induced by CADs, because this group of drugs is by far
(De la Iglesia et al., 1974; Leech et al., 1984; Hoste IEHENDALE

Pharmacology and Therapeutic Uses of Drugs Known

Induce Phospholipidosis

In this review we focus primarily on phospholipidosis

duced by CADs, because this group of drugs is by far B. Pharmacology and Therapeutic Uses of Drugs Known
to Induce Phospholipidosis
In this review we focus primarily on phospholipidosis
induced by CADs, because this group of drugs is by far
the most well studied in this rega B. Pharmacology and Therapeutic Uses of Drugs Known
to Induce Phospholipidosis
In this review we focus primarily on phospholipidosis
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the most well studied in this rega versum to induce Phospholiplosis

In this review we focus primarily on phospholipidosis

induced by CADs, because this group of drugs is by far

the most well studied in this regard. CADs, having di-

verse therapeutic use In this review we focus primarily on phospholipidosis
induced by CADs, because this group of drugs is by far
the most well studied in this regard. CADs, having di-
verse therapeutic uses (fig. 1), are known to induce
phosp induced by CADs, because this group of drugs is by far
the most well studied in this regard. CADs, having di-
verse therapeutic uses (fig. 1), are known to induce
phospholipidosis and alter phospholipid metabolism to a
var the most well studied in this regard. CADs, having diverse therapeutic uses (fig. 1), are known to induce phospholipidosis and alter phospholipid metabolism to a variable extent. Extensive use of these drugs and clinical e verse therapeutic uses (fig. 1), are known to induce
phospholipidosis and alter phospholipid metabolism to a
variable extent. Extensive use of these drugs and clinical
evidence of the side effects associated with their use phospholipidosis and alter phospholipid metabolism to
variable extent. Extensive use of these drugs and clinic
evidence of the side effects associated with their use ha
necessitated increased investigation of drug-induci
p variable extent. Extensive use of these drugs and clinical
evidence of the side effects associated with their use have
necessitated increased investigation of drug-induced
phospholipidosis. Drugs with phospholipidosis-indu evidence of the side effects associated with their use have necessitated increased investigation of drug-induce phospholipidosis. Drugs with phospholipidosis-inducing propensity include examples from almost every class of necessitated increased investigation of drug-ind
phospholipidosis. Drugs with phospholipidosis-indu
propensity include examples from almost every cla
pharmacological agents including antipsychotics,
depressants, antianrhyt phospholipidosis. Drugs with phospholipidosis-inducing
propensity include examples from almost every class of
pharmacological agents including antipsychotics, anti-
depressants, antiarrhythmics, antianginals, antibacteri-
 propensity include examples from almost every class of pharmacological agents including antipsychotics, anti-
depressants, antiarrhythmics, antianginals, antibacteri-
als, antimalarials, anorexic agents, cholesterol-reduci pharmacological agents including antipsychotics, anti-
depressants, antiarrhythmics, antianginals, antibacteri-
als, antimalarials, anorexic agents, cholesterol-reducing
agents, etc. (Lullmann-Rauch and Scheid, 1975; Joshi pressants, antiarrhythmics, antianginals, antibacteri-

I, antimalarials, anorexic agents, cholesterol-reducing

ents, etc. (Lullmann-Rauch and Scheid, 1975; Joshi

al., 1988; Joshi and Mehendale, 1989; Reasor, 1989).

In agents, etc. (Lullmann-Rauch and Scheid, 1975; Joshi
et al., 1988; Joshi and Mehendale, 1989; Reasor, 1989).
In contrast to their diverse pharmacological actions et al., 1988; Joshi and Mehendale, 1989; Reasor, 1989).

ing the mechanism of phospholipidosis and other effects
of CADs has become increasingly popular (Ruben et al.,
1985; Martin et al., 1989). This approach has the special
advantages of avoiding extensive metabolism of CADs
 These include an increase in cellular phospholipids, the
appearance of lamellated inclusion bodies (lamellar bod-
ies) in the cells, and macrophage infiltration, particularly
in the lung (Reasor, 1981; Fernandez et al., 19 et al., 1988; Joshi and Mehendale, 1989; Reasor, 1989).
In contrast to their diverse pharmacological actions
and therapeutic applications, these drugs share several
common physicochemical similarities. The most predom-
ina In contrast to their diverse pharmacological action
and therapeutic applications, these drugs share sever
common physicochemical similarities. The most predor
inant physicochemical properties shared by CADs are
hydrophobic and therapeutic applications, these drugs share several
common physicochemical similarities. The most predom-
inant physicochemical properties shared by CADs are a
hydrophobic ring structure on the molecule and a hydro-
ph common physicochemical similarities. The most predominant physicochemical properties shared by CADs are a hydrophobic ring structure on the molecule and a hydrophilic side chain with a charged cationic amine group (fig. 1) inant physicochemical properties shared by CADs are a
hydrophobic ring structure on the molecule and a hydro-
philic side chain with a charged cationic amine group
(fig. 1), which impart the characteristic amphiphilicity
i hydrophobic ring structure on the molecule and a hydro-
philic side chain with a charged cationic amine group
(fig. 1), which impart the characteristic amphiphilicity
inherent in these drugs. Therefore, these classes of dr philic side chain with a charged cationic amine group
(fig. 1), which impart the characteristic amphiphilicity
inherent in these drugs. Therefore, these classes of drugs
are termed cationic amphiphilic amines. Hydrophobic
 (fig. 1), which impart the characteristic amphiphilicity
inherent in these drugs. Therefore, these classes of drugs
are termed cationic amphiphilic amines. Hydrophobic
characteristics allow the molecules to permeate throug inherent in these drugs. Therefore, these classes of drugare termed cationic amphiphilic amines. Hydrophob characteristics allow the molecules to permeate through the plasma membrane when they are not ionized. This ionized are termed cationic amphiphilic amines. Hydrophobic
characteristics allow the molecules to permeate through
the plasma membrane when they are not ionized. The
ionized form usually remains associated with the mem-
brane and characteristics allow the molecules to permeate through
the plasma membrane when they are not ionized. The
ionized form usually remains associated with the mem-
brane and induces membrane structure perturbation
(Seydel and the plasma membrane when they are not ionized. The
ionized form usually remains associated with the mem-
brane and induces membrane structure perturbation
(Seydel and Wassermann, 1976; Lullmann et al., 1978).
CADs interact ionized form usually remains associated with the mobrane and induces membrane structure perturbat
(Seydel and Wassermann, 1976; Lullmann et al., 19
CADs interact with negatively charged and neutral po
lipids, such as phosp brane and induces membrane structure perturbation (Seydel and Wassermann, 1976; Lullmann et al., 1978).
CADs interact with negatively charged and neutral polar
lipids, such as phospholipids. The membrane phospho-
lipids an (Seydel and Wassermann,
CADs interact with negati
lipids, such as phospholip
lipids and their charged io
and binding in the cells.
Therapeutic actions of ADs interact with negatively charged and neutral polarids, such as phospholipids. The membrane phospholids and their charged ionic groups regulate CAD entry dolining in the cells.
Therapeutic actions of many anesthetics,

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detailed and up-to-date review of phospholipidosis timely to the cell and also modulates cellular Ca^{2+} homeostasis and desirable.

We have attempted to cover as many diverse aspects these actions of amiodarone are mani lipids, such as phospholipids. The membrane phospholipids and their charged ionic groups regulate CAD entry and binding in the cells.
Therapeutic actions of many anesthetics, β -blockers, antipsychotics, antiarrhythmics lipids and their charged ionic groups regulate CAD entry
and binding in the cells.
Therapeutic actions of many anesthetics, β -blockers,
antipsychotics, antiarrhythmics, etc. are mainly elicited
by their actions on ion and binding in the cells.
Therapeutic actions of many anesthetics, β -blockers,
antipsychotics, antiarrhythmics, etc. are mainly elicited
by their actions on ion channels and receptors (Levy and
Richards, 1966; Luxnatt Therapeutic actions of many anesthetics, β -blocke
antipsychotics, antiarrhythmics, etc. are mainly elicit
by their actions on ion channels and receptors (Levy a
Richards, 1966; Luxnatt and Galla, 1986; Zychlinski a
Mon antipsychotics, antiarrhythmics, etc. are mainly elicited
by their actions on ion channels and receptors (Levy and
Richards, 1966; Luxnatt and Galla, 1986; Zychlinski and
Montgomery, 1986; Nagai et al., 1987). The antiarby their actions on ion channels and receptors (Levy and
Richards, 1966; Luxnatt and Galla, 1986; Zychlinski and
Montgomery, 1986; Nagai et al., 1987). The antiar-
rhythmic drug, amiodarone, blocks the entry of Na⁺ in
to Richards, 1966; Luxnatt and Galla, 1986; Zychlinski and
Montgomery, 1986; Nagai et al., 1987). The antiar-
rhythmic drug, amiodarone, blocks the entry of Na⁺ in
to the cell and also modulates cellular Ca²⁺ homeostasis
 Montgomery, 1986; Nagai et al., 1987). The antiar-
rhythmic drug, amiodarone, blocks the entry of Na⁺ in
to the cell and also modulates cellular Ca^{2+} homeostasis
(Mason et al., 1984; Chatelain et al., 1985). Whether
 rhythmic drug, amiodarone, blocks the entry of Na⁺ in
to the cell and also modulates cellular Ca²⁺ homeostasis
(Mason et al., 1984; Chatelain et al., 1985). Whether
these actions of amiodarone are manifested through
ch to the cell and also modulates cellular Ca²⁺ homeostasis (Mason et al., 1984; Chatelain et al., 1985). Whether these actions of amiodarone are manifested through changes in membrane composition, decreased transition temp (Mason et al., 1984; Chatelain et al., 1985). Whet
these actions of amiodarone are manifested throu
changes in membrane composition, decreased transiti
temperature, or membrane fluidization or are recep
mediated remains t these actions of amiodarone are manifested through
changes in membrane composition, decreased transition
temperature, or membrane fluidization or are receptor
mediated remains to be investigated. Another antiar-
rhythmic changes in membrane composition, decreased transition
temperature, or membrane fluidization or are receptor
mediated remains to be investigated. Another antiar-
rhythmic drug, propranolol, is a potent β -adrenergic
bloc temperature, or memorane nuidization or are receptor mediated remains to be investigated. Another antiar-
rhythmic drug, propranolol, is a potent β -adrenergic
blocker and its action is receptor mediated (Levy and
Richa rhythmic drug, propranolol, is a potent β -adrenergic
blocker and its action is receptor mediated (Levy and
Richards, 1966; Patil, 1968). Antipsychotic drugs and
other neuroleptics, such as chlorpromazine, promazine,
an other neuroleptics, such as chlorpromazine, promazine, Richards, 1966; Patil, 1968). Antipsychotic drugs and
other neuroleptics, such as chlorpromazine, promazine,
and imipramine (fig. 1), are highly lipid soluble and
surface active. Very high octanol to water partition coef-
 surface active. Very high octanol to water partition coefficients of these drugs are indicative of a high solubility in biological membranes (Seeman, 1972; Seydel and Was-sermann, 1976; Lullmann and Wehling, 1979; Welti et and imipramine (fig. 1), are highly lipid soluble and
surface active. Very high octanol to water partition coef-
ficients of these drugs are indicative of a high solubility
in biological membranes (Seeman, 1972; Seydel and

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al., 1984). At higher concentrations **(mM range), these** EXECUTE THE MODA WANT WE SAID MI

al., 1984). At higher concentrations (mM range), these son

drugs interact with the membranes in a nonspecific way pha

and induce fluidization of all presynaptic and postsyn- lam KODAVANT
al., 1984). At higher concentrations (mM range), the
drugs interact with the membranes in a nonspecific v
and induce fluidization of all presynaptic and posts
aptic membranes. These actions lead to enhanced sp al., 1984). At higher concentrations (mM range), these drugs interact with the membranes in a nonspecific we and induce fluidization of all presynaptic and postsyr aptic membranes. These actions lead to enhanced spontaneou al., 1984). At higher concentrations (mM range), the
drugs interact with the membranes in a nonspecific we
and induce fluidization of all presynaptic and postsyr
aptic membranes. These actions lead to enhanced spor
taneous interact with the membranes in a honspectic way
and induce fluidization of all presynaptic and postsyn-
aptic membranes. These actions lead to enhanced spon-
taneous release of neurotransmitters and altered phys-
iological

aptic membranes. These actions lead to enhanced spon-
taneous release of neurotransmitters and altered phys-
iological responses (Seeman, 1977).
Membrane effects of CADs on phospholipids have
been extensively studied (Seyd taneous release of neurotransmitters and altered physiological responses (Seeman, 1977).
Membrane effects of CADs on phospholipids have
been extensively studied (Seydel and Wassermann, 1976).
Lullmann and Wehling, 1979; Ph iological responses (Seeman, 1977).
Membrane effects of CADs on phospholipids have
been extensively studied (Seydel and Wassermann, 1976;
Lullmann and Wehling, 1979; Phadke et al., 1981; Bras-
seur et al., 1985; Henry et a Membrane effects of CADs on phospholipids have
been extensively studied (Seydel and Wassermann, 1976;
Lullmann and Wehling, 1979; Phadke et al., 1981; Bras-
seur et al., 1985; Henry et al., 1985; Chatelain et al.,
1986; Jo been extensively studied (Seydel and Wassermann, 19
Lullmann and Wehling, 1979; Phadke et al., 1981; B.
seur et al., 1985; Henry et al., 1985; Chatelain et
1986; Joshi et al., 1989). There is a good correlat
between the in Lullmann and Wehling, 1979; Phadke et al., 1981; Bras-
seur et al., 1985; Henry et al., 1985; Chatelain et al., zym
1986; Joshi et al., 1989). There is a good correlation in la
between the interaction of these drugs with p seur et al., 1985; Henry et al., 1985; Chatelain et al., 1986; Joshi et al., 1989). There is a good correlation
between the interaction of these drugs with phospho-
lipids and their phospholipidosis-inducing capacity in
vi 1986; Joshi et al., 1989). There is a good correlatio
between the interaction of these drugs with phospholipids and their phospholipidosis-inducing capacity i
vivo (Joshi and Mehendale, 1989; Joshi et al., 1989
However, it between the interaction of these drugs with phospholipids and their phospholipidosis-inducing capacity in vivo (Joshi and Mehendale, 1989; Joshi et al., 1989).
However, it is not clear whether drug-phospholipid phys-icoche vivo (Joshi and Mehendale, 1989; Joshi et al., 1989). new
However, it is not clear whether drug-phospholipid phys-
linii
cochemical interactions make phospholipids unsuitable
recy
substrates for the action of phospholipase However, it is not clear whether drug-phospholipid phys-
icochemical interactions make phospholipids unsuitable
substrates for the action of phospholipases or whether
drugs directly inhibit the action of phospholipases by icochemical interactions make phospholipids unsuitable
substrates for the action of phospholipases or whether
drugs directly inhibit the action of phospholipases by substrates for the action of phospholipases or whether
drugs directly inhibit the action of phospholipases by G
binding to the active site. There is some evidence for di
both of these mechanisms, and it is not inconceivab drugs directly inhibit the action of phospholipases by
binding to the active site. There is some evidence for
both of these mechanisms, and it is not inconceivable
that a given drug may cause phospholipidosis through
both both of these mechanisms, and it is not inconceivable
that a given drug may cause phospholipidosis through
both of these mechanisms (Lullmann and Wehling, 1979;
Kubo and Hostetler, 1985; Joshi et al., 1988, 1989).
Detailed both of these mechanisms, and it is not inconceivable mation of precursors for new surfactant synthesis (Roothat a given drug may cause phospholipidosis through ney, 1984, 1985). Surfactant material is known to contain bot both of these mechanisms (Lullmann and Wehling, 1979;
Kubo and Hostetler, 1985; Joshi et al., 1988, 1989).
Detailed mechanistic considerations will be discussed
later in the appropriate sections.
C. Characteristics of Phos phospholipidosis usually appears after chronic intake

CADs. The latency for appearance of phospholipidosis characteristics of *Phospholipidosis*

CADs. The latency for appearance of phospholipidosis controlled a controll

Deter in the appropriate sections.

C. Characteristics of Phospholipidosis

Phospholipidosis usually appears after chronic intake

of CADs. The latency for appearance of phospholipidosis

varies from a few days to months, C. Characteristics of Phospholipidosis

Phospholipidosis usually appears after chronic intake

of CADs. The latency for appearance of phospholipidosis

varies from a few days to months, depending on animal

species (Yamamo C. Characteristics of Phosphoupidosis
Phospholipidosis usually appears after chronic inti
of CADs. The latency for appearance of phospholipido
varies from a few days to months, depending on anir
species (Yamamoto et al., 1 Phospholipidosis usually appears after chronic inta
of CADs. The latency for appearance of phospholipido
varies from a few days to months, depending on anin
species (Yamamoto et al., 1971a,b; Seiler and Wass-
mann, 1975; L of CADs. The latency for appearance of phospholipidosis varies from a few days to months, depending on animal
species (Yamamoto et al., 1971a,b; Seiler and Wassermann, 1975; Lullmann et al., 1978; Blohm, 1979; Hoste-
tler varies from a few days to months, depending on animal
species (Yamamoto et al., 1971a,b; Seiler and Wasser-
mann, 1975; Lullmann et al., 1978; Blohm, 1979; Hoste-
tler and Matsuzawa, 1981; Reasor, 1981). In isolated
cultur species (Yamamoto et al., 1971a,b; Seiler and Wassermann, 1975; Lullmann et al., 1978; Blohm, 1979; Hoste-
tler and Matsuzawa, 1981; Reasor, 1981). In isolated
cultured cells, lamellar bodies filled with phospholipids
can

tler and Matsuzawa, 1981; Reasor, 1981). In isolated
cultured cells, lamellar bodies filled with phospholipids
can appear within a few hours of exposure to CADs.
There are three major changes that occur in lung tissue
of a cultured cells, lamellar bodies filled with phospholip can appear within a few hours of exposure to CADs.
There are three major changes that occur in lung tis
of animals receiving CADs that are capable of induc
phospholipi can appear within a few hours of exposure to CADs.

There are three major changes that occur in lung tissue

of animals receiving CADs that are capable of inducing

phospholipidosis. One hallmark of pulmonary phospho-

lip There are three major changes that occur in lung tissue
of animals receiving CADs that are capable of inducing
phospholipidosis. One hallmark of pulmonary phospho-
lipidosis is the infiltration of alveolar macrophages and
 phospholipidosis. One hallmark of pulmonary phospholipidosis is the infiltration of alveolar macrophages and other lymphocytes in the alveolar spaces. In the other tissues such as liver and kidney, macrophage infiltration phospholipidosis. One hallmark of pulmonary phospho-
lipidosis is the infiltration of alveolar macrophages and
other lymphocytes in the alveolar spaces. In the other
tissues such as liver and kidney, macrophage infiltratio lipidosis is the infiltration of alveolar macrophages and
other lymphocytes in the alveolar spaces. In the other
tissues such as liver and kidney, macrophage infiltration
has not been characterized. A detailed account of other lymphocytes in the alveolar spaces. In the other tissues such as liver and kidney, macrophage infiltration has not been characterized. A detailed account of the role of alveolar macrophages in drug-induced pulmonary tissues such as liver and kidney, macrophage infiltra
has not been characterized. A detailed account of
role of alveolar macrophages in drug-induced pulmor
phospholipidosis is given in the following section. l
spective of has not been characterized. A detailed account of the role of alveolar macrophages in drug-induced pulmonary phospholipidosis is given in the following section. Irrespective of the type of tissue being affected, phospholip role of alveolar macrophages in drug-induced pulmonary
phospholipidosis is given in the following section. Irre-
spective of the type of tissue being affected, phospholi-
pidosis is usually evident in the form of membranou phospholipidosis is given in the following section. Irrespective of the type of tissue being affected, phospholipidosis is usually evident in the form of membranous lamellar bodies in the cells (Reasor, 1989). Normally, la spective of the type of tissue being affected, phospholipidosis is usually evident in the form of membranous lamellar bodies in the cells (Reasor, 1989). Normally, lamellar bodies are present in type II cells and surfactan pidosis is usually evident in the form of membranous oth lamellar bodies in the cells (Reasor, 1989). Normally, efferentiand in the alveolar macrophages (Fisher and Chander, the 1985), signifying their role in synthesis, s lamellar bodies in the cells (Reasor, 1989). Normally, effects are specific for a drug and not a general manifes-
lamellar bodies are present in type II cells and surfactant tation of all CADs. One example of uncertainty a lamellar bodies are present in type II cells and surfactant tation
and in the alveolar macrophages (Fisher and Chander, the re
1985), signifying their role in synthesis, secretion, and comes
turnover of alveolar surfactant and in the alveolar macrophages (Fisher and Chander, 1985), signifying their role in synthesis, secretion, and turnover of alveolar surfactant. These lamellar bodies increase in number and enlarge in size during CAD treatm 1985), signifying their role in synthesis, secretion, and conductor of alveolar surfactant. These lamellar bodies hip increase in number and enlarge in size during CAD efficient (Hruban et al., 1972; Drenckhahn et al., 197 turnover of alveolar surfactant. These lamellar bodies lip
increase in number and enlarge in size during CAD eff
treatment (Hruban et al., 1972; Drenckhahn et al., 1976; pn
Kannan et al., 1989). Although lamellar bodies ha increase in number and enlarge in size during CAD
treatment (Hruban et al., 1972; Drenckhahn et al., 1976;
Kannan et al., 1989). Although lamellar bodies have been
thought to originate from lysosomes (Reasor, 1989), the
or treatment (Hruban et al., 1972; Drenckhahn et al., 1976
Kannan et al., 1989). Although lamellar bodies have been
thought to originate from lysosomes (Reasor, 1989), the
origin and function of this lysosomal involvement re

somes take up newly synthesized surfactant by an auto-
phagic mechanism and process it to the characteristic
lamellar bodies before it is released from the cell by phagic mechanism and process it to the characteristic MEHENDALE
somes take up newly synthesized surfactant by an auto-
phagic mechanism and process it to the characteristic
lamellar bodies before it is released from the cell by
exocytosis (Heath and Jacobson, 1976, 1980a,b; N somes take up newly synthesized surfactant by an auto-
phagic mechanism and process it to the characteristic
lamellar bodies before it is released from the cell by
exocytosis (Heath and Jacobson, 1976, 1980a,b; Notter
and phagic mechanism and process it to the characteristic
lamellar bodies before it is released from the cell by
exocytosis (Heath and Jacobson, 1976, 1980a,b; Notter
and Finkelstein, 1984; Rooney, 1984, 1985; Fisher and
Chand lamellar bodies before it is released from the cell by
exocytosis (Heath and Jacobson, 1976, 1980a,b; Notter
and Finkelstein, 1984; Rooney, 1984, 1985; Fisher and
Chander, 1985; Dobbs, 1989; Tierney, 1989; Wright and
Hawgo exocytosis (Heath and Jacobson, 1976, 1980a,b; Notter
and Finkelstein, 1984; Rooney, 1984, 1985; Fisher and
Chander, 1985; Dobbs, 1989; Tierney, 1989; Wright and
Hawgood, 1989). Lung cells, particularly type II cells and
a and Finkelstein, 1984; Rooney, 1984, 1985; Fisher and Chander, 1985; Dobbs, 1989; Tierney, 1989; Wright and Hawgood, 1989). Lung cells, particularly type II cells and alveolar macrophages, are involved in the synthesis and Chander, 1985; Dobbs, 1989; Tierney, 1989; Wright and
Hawgood, 1989). Lung cells, particularly type II cells and
alveolar macrophages, are involved in the synthesis and
recycling of alveolar surfactant. Many hydrolytic en-Hawgood, 1989). Lung cells, particularly type II cells and
alveolar macrophages, are involved in the synthesis and
recycling of alveolar surfactant. Many hydrolytic en-
zymes, including phospholipases, also have been detec alveolar macrophages, are involved in the synthesis and
recycling of alveolar surfactant. Many hydrolytic en-
zymes, including phospholipases, also have been detected
in lamellar bodies of the lung (DiAugustine, 1974). The recycling of alveolar surfactant. Many hydrolytic en-
zymes, including phospholipases, also have been detected
in lamellar bodies of the lung (DiAugustine, 1974). The
contents of lamellar bodies are secreted into the alveo zymes, including phospholipases, also have been detected
in lamellar bodies of the lung (DiAugustine, 1974). The
contents of lamellar bodies are secreted into the alveolar
spaces by exocytosis. Secreted inclusion bodies ac in lamellar bodies of the lung (DiAugustine, 1974). The contents of lamellar bodies are secreted into the alveolar spaces by exocytosis. Secreted inclusion bodies act as newly synthesized surfactant material in intraalveol contents of lamellar bodies are secreted into the alveolar
spaces by exocytosis. Secreted inclusion bodies act as
newly synthesized surfactant material in intraalveolar
linings (Wright and Hawgood, 1989). This material is
 spaces by exocytosis. Secreted inclusion bodies act as
newly synthesized surfactant material in intraalveolar
linings (Wright and Hawgood, 1989). This material is
recycled by the pinocytic action of alveolar macrophages
an newly synthesized surfactant material in intraalveolar
linings (Wright and Hawgood, 1989). This material is
recycled by the pinocytic action of alveolar macrophages
and by reuptake into type II cells via endocytosis (Van
G linings (Wright and Hawgood, 1989). This material is
recycled by the pinocytic action of alveolar macrophages
and by reuptake into type II cells via endocytosis (Van
Golde, 1985; Stern et al., 1986). Recaptured surfactant recycled by the pinocytic action of alveolar macrophage
and by reuptake into type II cells via endocytosis (Va
Golde, 1985; Stern et al., 1986). Recaptured surfactant
digested by lysosomal phospholipases leading to the fo
 and by reuptake into type II cells via endocytosis (Van
Golde, 1985; Stern et al., 1986). Recaptured surfactant is
digested by lysosomal phospholipases leading to the for-
mation of precursors for new surfactant synthesis Golde, 1985; Stern et al., 1986). Recaptured surfactant is
digested by lysosomal phospholipases leading to the for-
mation of precursors for new surfactant synthesis (Roo-
ney, 1984, 1985). Surfactant material is known to digested by lysosomal phospholipases leading to the formation of precursors for new surfactant synthesis (Rooney, 1984, 1985). Surfactant material is known to contain higher numbers of lamellar inclusion bodies after CAD t mation of pree
ney, 1984, 198
higher numbe
treatment (Hi
et al., 1987).
Either one o y, 1984, 1985). Surfactant material is known to contain
gher numbers of lamellar inclusion bodies after CAD
eatment (Hruban, 1984; Miles et al., 1986; Israel-Biet
al., 1987).
Either one or more of phospholipid-recycling an

higher numbers of lamellar inclusion bodies after CAD
treatment (Hruban, 1984; Miles et al., 1986; Israel-Biet
et al., 1987).
Either one or more of phospholipid-recycling and me-
tabolism processes, which occur in lamellar treatment (Hruban, 1984; Miles et al., 1986; Israel-
et al., 1987).
Either one or more of phospholipid-recycling and
tabolism processes, which occur in lamellar bodies
lysosomes, are affected by CADs that induce phosph
pid et al., 1987).
Either one or more of phospholipid-recycling and me-
tabolism processes, which occur in lamellar bodies and
lysosomes, are affected by CADs that induce phospholi-
pidosis. A detailed account of how phospholi Either one or more of phospholipid-recycling and metabolism processes, which occur in lamellar bodies and lysosomes, are affected by CADs that induce phospholipidosis. A detailed account of how phospholipases and other enz tabolism processes, which occur in lamellar bodies a
lysosomes, are affected by CADs that induce phospho
pidosis. A detailed account of how phospholipases a
other enzyme systems are affected by CADs leading
the development lysosomes, are affected b
pidosis. A detailed accou
other enzyme systems are
the development of phos
anism of Phospholipidos
The understanding of o dosis. A detailed account of how phospholipases and
her enzyme systems are affected by CADs leading to
e development of phospholipidosis appears in "Mech-
ism of Phospholipidosis".
The understanding of drug accumulation in

Example 1975; Lullmann et al., 1978; Blohm, 1979; Hoste-

The understanding of drug accumulation in lamellated

The understanding of drug accumulation in lamellated

Itured cells, lamellar bodies filled with phospholipids
 other enzyme systems are affected by CADs leading to
the development of phospholipidosis appears in "Mech-
anism of Phospholipidosis".
The understanding of drug accumulation in lamellated
bodies, their interaction with pho the development of phospholipidosis appears in Wech-
anism of Phospholipidosis".
The understanding of drug accumulation in lamellated
bodies, their interaction with phospholipids as well as
phospholipases, changes in the i anism or Phosphonpidosis.

The understanding of drug accumulation in lamellated

bodies, their interaction with phospholipids as well as

phospholipases, changes in the intraorganelle pH, and

its relation to the pathobiol bodies, their interaction with phospholipids as well
phospholipases, changes in the intraorganelle pH, and
its relation to the pathobiology of these structures mig
help to further define the relationship of drug-induc
phos phospholipa
its relation
help to furt
phospholipi
lar bodies.
CADs ha relation to the pathobiology of these structures might
lp to further define the relationship of drug-induced
cospholipidosis and the increased appearance of lamel-
r bodies.
CADs have several other side effects in addition

lar bodies.
CADs have several other side effects in addition to
inducing phospholipidosis (Hobbs et al., 1959; Whisnant
et al., 1963; Lewis et al., 1983; Manolis et al., 1987; phospholipidosis and the increased appearance of lamellar bodies.

CADs have several other side effects in addition to

inducing phospholipidosis (Hobbs et al., 1959; Whisnant

et al., 1963; Lewis et al., 1983; Manolis et lar bodies.
CADs have several other side effects in addition to
inducing phospholipidosis (Hobbs et al., 1959; Whisnant
et al., 1963; Lewis et al., 1983; Manolis et al., 1987;
Mason, 1987; Stein et al., 1987; Dunn and Glas CADs have several other side effects in addition to
inducing phospholipidosis (Hobbs et al., 1959; Whisnant
et al., 1963; Lewis et al., 1983; Manolis et al., 1987;
Mason, 1987; Stein et al., 1987; Dunn and Glassroth,
1989; inducing phospholipidosis (Hobbs et al., 1959; Whisnant
et al., 1963; Lewis et al., 1983; Manolis et al., 1987;
Mason, 1987; Stein et al., 1987; Dunn and Glassroth,
1989; Vrobel et al., 1989; Young and Mehendale, 1989).
Th et al., 1963; Lewis et al., 1983; Manolis et al., 1987;
Mason, 1987; Stein et al., 1987; Dunn and Glassroth,
1989; Vrobel et al., 1989; Young and Mehendale, 1989).
The direct relationship between phospholipidosis and
other 1989; Vrobel et al., 1989; Young and Mehendale, 1989). 1989; Vrobel et al., 1989; Young and Mehendale, 1989).
The direct relationship between phospholipidosis and
other side effects is not established, because these side
effects are specific for a drug and not a general manife other side effects is not established, because these side other side effects is not established, because these side
effects are specific for a drug and not a general manifes-
tation of all CADs. One example of uncertainty about
the relation between side effects and phospholipidos effects are specific for a drug and not a general manifestation of all CADs. One example of uncertainty about
the relation between side effects and phospholipidosis
comes from studies using amiodarone. In addition to
lipid tation of all CADs. One example of uncertainty about
the relation between side effects and phospholipidosis
comes from studies using amiodarone. In addition to
lipid accumulation, this drug also has several other side
effe the relation between side effects and phospholipidosis
comes from studies using amiodarone. In addition to
lipid accumulation, this drug also has several other side
effects including bradycardia, congestive heart failure
p lipid accumulation, this drug also has several other side effects including bradycardia, congestive heart failure, pneumonitis, gastrointestinal intolerance, hepatitis, neurological effects, impaired vision, skin photosens lipid accumulation, this drug also has several other side
effects including bradycardia, congestive heart failure,
pneumonitis, gastrointestinal intolerance, hepatitis, neu-
rological effects, impaired vision, skin photose effects including bradycardia, congestive heart failure,
pneumonitis, gastrointestinal intolerance, hepatitis, neu-
rological effects, impaired vision, skin photosensitivity,
blue skin, hypothyroidism, and hyperthyroidism pneumonitis, gastrointestinal intolerance, hepatitis, neu-
rological effects, impaired vision, skin photosensitivity,
blue skin, hypothyroidism, and hyperthyroidism (Vrobel
et al., 1989). Such side effects may not be obser

PHARMACOLOGICAL REVIEWS

DRUG-INDUCED
retinopathy and myopathy (Hobbs et al., 1959; Whisnant
et al., 1963). Another example is chlorphentermine, the DRUG-INDUCED PHOS

retinopathy and myopathy (Hobbs et al., 1959; Whisnant ha

et al., 1963). Another example is chlorphentermine, the size

use of which was discontinued because of its severe ch BRUG-INDUCED PHOS

retinopathy and myopathy (Hobbs et al., 1959; Whisnant has

et al., 1963). Another example is chlorphentermine, the situse of which was discontinued because of its severe

pulmonary and other unacceptabl retinopathy and myopathy (Hobbs et al., 1959; Whisnant et al., 1963). Another example is chlorphentermine, the use of which was discontinued because of its severe pulmonary and other unacceptable side effects (Ciborska et retinopathy are
et al., 1963). *A*
use of which
pulmonary and
et al., 1969).
In conclusion al., 1963). Another example is chlorphentermine, the
e of which was discontinued because of its severe
lmonary and other unacceptable side effects (Ciborska
al., 1969).
In conclusion, the relationship between generalized

pulmonary and other unacceptable side effects (Ciborska expression of several regulatory factors have a definite
et al., 1969).
In conclusion, the relationship between generalized pholipidosis (Turner and Kuo, 1985).
drug-In conclusion, the relationship between generalized. et al., 1969).
In conclusion, the relationship between generalized
drug-induced phospholipidosis and the other specific side
effects produced by the drug has not been established.
However, it has been well-documented that In conclusion, the relationship between generalized photography of the drug has not been established. filt effects produced by the drug has not been established. filt However, it has been well-documented that drug-induced drug-induced phospholipidosis and the other specific side
effects produced by the drug has not been established. fi
However, it has been well-documented that drug-induced and
trastructural myeloid bodies are present in all effects produced by the drug has not been established.
However, it has been well-documented that drug-induced
ultrastructural myeloid bodies are present in all of the
organs that are affected (Abraham et al., 1968; Fedorko However, it has been well-documented that drug-
ultrastructural myeloid bodies are present in al
organs that are affected (Abraham et al., 1968; l
et al., 1968a,b; Hruban et al., 1973; Wibo and
1974; Reasor et al., 1978; K organs that are affected (Abraham et al., 1968; Fedorko et al., 1968a,b; Hruban et al., 1973; Wibo and Poole, 1974; Reasor et al., 1978; Kannan et al., 1989).

D. Pulmonary Macrophages Our understanding of the pulmonary ma

1974; Reasor et al., 1978; Kannan et al., 1989).

D. Pulmonary Macrophages

Our understanding of the pulmonary macrophage bi-

ology has been greatly facilitated by the relative ease

with which they can be isolated. Macr D. Pulmonary Macrophages

Our understanding of the pulmonary macrophage bired

ology has been greatly facilitated by the relative ease

with which they can be isolated. Macrophages can be

isolated by alveolar lavage and D. Putmonary Macrophages
Our understanding of the pulmonary macrophage bi-
ology has been greatly facilitated by the relative ease
with which they can be isolated. Macrophages can be
isolated by alveolar lavage and culture Our understanding of the pulmonary macrophage bi-

ology has been greatly facilitated by the relative ease Lull

with which they can be isolated. Macrophages can be mar

isolated by alveolar lavage and cultured in the lab ology has been greatly facilitated by the relative ease with which they can be isolated. Macrophages can bisolated by alveolar lavage and cultured in the laboratory and the responses can be studied relatively easily is lab with which they can be isolated. Macrophages can
isolated by alveolar lavage and cultured in the laborato
and the responses can be studied relatively easily
laboratory animal models (Myrvik et al., 1961). A co-
plete revie isolated by alveolar lavage and cultured in the laborato
and the responses can be studied relatively easily
laboratory animal models (Myrvik et al., 1961). A co
plete review by Reasor (1981) of all aspects of mac:
phage bi and the responses can be studied relatively easily in dosilaboratory animal models (Myrvik et al., 1961). A complete review by Reasor (1981) of all aspects of macro-
phage biology and CADs appeared a decade ago. Availabil laboratory animal models (Myrvik et al., 1961). A c
plete review by Reasor (1981) of all aspects of ma
phage biology and CADs appeared a decade ago. Ava
bility of human lung lavage samples also represent
excellent opportun plete review by Reasor (1981) of all aspects of macro-
phage biology and CADs appeared a decade ago. Availa-
bility of human lung lavage samples also represents an
excellent opportunity to study CAD-induced phospholi-
pido age biology and CADs appeared a decade ago. Availa
ity of human lung lavage samples also represents a
cellent opportunity to study CAD-induced phospholi
dosis (Martin et al., 1985; Martin and Standing, 1988)
Alveolar macro bility of human lung lavage samples also represents an excellent opportunity to study CAD-induced phospholi-
pidosis (Martin et al., 1985; Martin and Standing, 1988).
Alveolar macrophages have several functions in addi-
ti

excellent opportunity to study CAD-induced phospholipidosis (Martin et al., 1985; Martin and Standing, 1988).
Alveolar macrophages have several functions in addition to scavenging extraneous toxicants and endogenous waste pidosis (Martin et al., 1985; Martin and Standing, 1988).
Alveolar macrophages have several functions in addi-
tion to scavenging extraneous toxicants and endogenous
waste such as surfactant material (Naimark, 1973; Geiger Alveolar macrophages have several functions in addition to scavenging extraneous toxicants and endogenous provaste such as surfactant material (Naimark, 1973; Geiger et al., 1975; Nichols, 1976; Fisher and Chander, 1985; tion to scavenging extraneous toxicants and endogenes
waste such as surfactant material (Naimark, 1973; Gei
et al., 1975; Nichols, 1976; Fisher and Chander, 19
Stern et al., 1986). They are involved in interactions w
other waste such as surfactant material (Naimark, 1973; Geiget al., 1975; Nichols, 1976; Fisher and Chander, 198 Stern et al., 1986). They are involved in interactions wither cells of the immune system, principally lymph cytes, et al., 1975; Nichols, 1976; Fisher and Chander, 1985;
Stern et al., 1986). They are involved in interactions with
other cells of the immune system, principally lympho-
cytes, in the elicitation of cell-mediated immunity Stern et al., 1986). They are involved in interactions with
other cells of the immune system, principally lympho-
cytes, in the elicitation of cell-mediated immunity (John-
son et al., 1975; Moore and Myrvik, 1977; Hocking other cells of the immune system, principally lympho-
cytes, in the elicitation of cell-mediated immunity (John-
son et al., 1975; Moore and Myrvik, 1977; Hocking and
Golde, 1979). Alveolar macrophages have an important
ro cytes, in the elicitation of cell-mediated immunity (Johnson et al., 1975; Moore and Myrvik, 1977; Hocking a Golde, 1979). Alveolar macrophages have an importation of granulocytes and mono-
role in the release of factors a son et al., 1975; Moore and Myrvik, 1977; Hocking a Golde, 1979). Alveolar macrophages have an import role in the release of factors and chemical mediators to may modulate the migration of granulocytes and mocytes to the l Golde, 1979). Alveolar macrophages have an important
role in the release of factors and chemical mediators that
may modulate the migration of granulocytes and mono-
cytes to the lung (Kazmierowski et al., 1977; Hunnin-
gha role in the release of factors and chemical mediato
may modulate the migration of granulocytes and
cytes to the lung (Kazmierowski et al., 1977; H_i
ghake et al., 1978; Hocking and Golde, 1979; Me
al., 1980), the inductio may modulate the migration of granulocytes and monocytes to the lung (Kazmierowski et al., 1977; Hunninghake et al., 1978; Hocking and Golde, 1979; Merrill et al., 1980), the induction of fibrogenesis, bronchoconstriction, cytes to the lung (Kazmierowski et al., 1977; Hunnighake et al., 1978; Hocking and Golde, 1979; Merrill al., 1980), the induction of fibrogenesis, bronchoconstriction, vasoconstriction, and perhaps several other university ghake et al., 1978; Hocking and Golde, 1979; Merrial., 1980), the induction of fibrogenesis, bronchocons
tion, vasoconstriction, and perhaps several other
known functions. Several aspects of the alveolar ma
phage biology i al., 1980), the induction of fibrogenesis, bronchoconstric-
tion, vasoconstriction, and perhaps several other un-
known functions. Several aspects of the alveolar macro-
phetaphage biology including their origin and fate, tion, vasoconstriction, and perhaps several other un-

known functions. Several aspects of the alveolar macro-

phage biology including their origin and fate, ultrastruc-

phage biology including their origin and fate, ult known functions. Several aspects of the alveolar macro-
phage biology including their origin and fate, ultrastruc-
tural features, physiology, and metabolism, their role in
defensive mechanisms, and their adaptive respons Fural features, physiology, and metabolism, their role in defensive mechanisms, and their adaptive responses have been well characterized (Cohen and Gold, 1975; Greenet al., 1977). Changes in macrophage function may predis defensive mechanisms, and their adaptive responses have
been well characterized (Cohen and Gold, 1975; Greene
et al., 1977). Changes in macrophage function may pre-
dispose the host organism to increased disease suscepti-
 been well characterized (Cohen and Gold, 1975; Green
et al., 1977). Changes in macrophage function may predispose the host organism to increased disease suscept
bility or tissue damage. A suspected cause of interstitiis
pn et al., 1977). Changes in macrophage function may pre-
dispose the host organism to increased disease suscepti-
bility or tissue damage. A suspected cause of interstitial
pneumonitis in amiodarone-treated patients is an al dispose the host organism to increased disease suscepti-
bility or tissue damage. A suspected cause of interstitial seems to be enhanced in vitro (McNulty and Reasor,
pneumonitis in amiodarone-treated patients is an alterbility or tissue damage. A suspected cause of interstit pneumonitis in amiodarone-treated patients is an altation of the host immune system (Suarez et al., 1986), Akoun et al., 1984; Venet et al., 1985; Sandron et al., 198 pneumonitis in amiodarone-treated patients is an alter-
ation of the host immune system (Suarez et al., 1983;
Akoun et al., 1984; Venet et al., 1985; Sandron et al., of
1986), perhaps involving infiltration of alveolar mac ation of the host immune system (Suarez et al., 1983)
Akoun et al., 1984; Venet et al., 1985; Sandron et al.
1986), perhaps involving infiltration of alveolar macro
phages and lymphocytes. The relationship among the
molecu Akoun et al., 1984; Venet et al., 1985; Sandron et al., 1986), perhaps involving infiltration of alveolar macro-
phages and lymphocytes. The relationship among the
molecular alteration in phospholipid metabolism,
changes i 1986), perhaps involving infiltration of alveolar macro-
phages and lymphocytes. The relationship among the independencular alteration in phospholipid metabolism, invest
changes in membrane constitution by CADs, and signal

)
have not been established. However, it should be empl
sized that any alteration in phospholipid metabolis SCOSPHOLIPIDOSIS
have not been established. However, it should be empha
sized that any alteration in phospholipid metabolism
change in membrane phospholipid composition, an COMET 331

compose in membrane phospholipid composized that any alteration in phospholipid metabolism,

change in membrane phospholipid composition, and

expression of several regulatory factors have a definite have not been established. However, it should be emphasized that any alteration in phospholipid metabolism, change in membrane phospholipid composition, and expression of several regulatory factors have a definite mechanis have not been established. However, it should be emphabized that any alteration in phospholipid metabolish
change in membrane phospholipid composition, an
expression of several regulatory factors have a definit
mechanistic sized that any alteration in phospholchange in membrane phospholipid expression of several regulatory factor mechanistic link with the etiology of C4 pholipidosis (Turner and Kuo, 1985).
Pulmonary phospholipidosis is assoc ange in membrane phospholipid composition, and
pression of several regulatory factors have a definite
echanistic link with the etiology of CAD-induced phos-
olipidosis (Turner and Kuo, 1985).
Pulmonary phospholipidosis is

expression of several regulatory factors have a definimechanistic link with the etiology of CAD-induced phopholipidosis (Turner and Kuo, 1985).
Pulmonary phospholipidosis is associated with the inflitration of foamy macrop mechanistic link with the etiology of CAD-induced phos-
pholipidosis (Turner and Kuo, 1985).
Pulmonary phospholipidosis is associated with the in-
filtration of foamy macrophages and lymphocytes (Vijey-
aratnam and Corrin, pholipidosis (Turner and Kuo, 1985).

Pulmonary phospholipidosis is associated with the infiltration of foamy macrophages and lymphocytes (Vijey-

aratnam and Corrin, 1972; Lullmann-Rauch and Scheid,

1975; Reasor, 1981; H Pulmonary phospholipidosis is associated with the infiltration of foamy macrophages and lymphocytes (Vijey-
aratnam and Corrin, 1972; Lullmann-Rauch and Scheid,
1975; Reasor, 1981; Heyneman and Reasor, 1986a; Ogle
and Reas aratnam and Corrin, 1972; Lullmann-Rauch and Scheid, 1975; Reasor, 1981; Heyneman and Reasor, 1986a; Ogle and Reasor, 1990). Extensive infiltration of macrophages was seen in chlorphentermine-treated rat lungs. Macro-phage aratnam and Corrin, 1972; Lullmann-Rauch and Scheid, 1975; Reasor, 1981; Heyneman and Reasor, 1986a; Ogle and Reasor, 1990). Extensive infiltration of macrophages was seen in chlorphentermine-treated rat lungs. Macrophages 1975; Reasor, 1981; Heyneman and Reasor, 1986a; Ogle
and Reasor, 1990). Extensive infiltration of macrophages
was seen in chlorphentermine-treated rat lungs. Macro-
phages play a key role in the etiology of pulmonary
phosp and Reasor, 1990). Extensive infiltration of macrophages
was seen in chlorphentermine-treated rat lungs. Macro-
phages play a key role in the etiology of pulmonary
phospholipidosis and have been extensively studied with
re was seen in chlorphentermine-treated rat lungs. Macro-
phages play a key role in the etiology of pulmonary
phospholipidosis and have been extensively studied with
regard to phospholipidosis (Vijeyaratnam and Corrin,
1972; phages play a key role in the etiology of pulmona
phospholipidosis and have been extensively studied w
regard to phospholipidosis (Vijeyaratnam and Corr
1972; Hruban et al., 1973; Karabelnik and Zbinden, 19
Lullmann-Rauch phospholipidosis and have l
regard to phospholipidosis
1972; Hruban et al., 1973; K
Lullmann-Rauch and Schei
man and Reasor, 1986a,b).
Infiltration of alveolar 1 gard to phospholipidosis (Vijeyaratnam and Co
72; Hruban et al., 1973; Karabelnik and Zbinden, i
illmann-Rauch and Scheid, 1975; Reasor, 1981; He
an and Reasor, 1986a,b).
Infiltration of alveolar macrophages in phospho
sis

1972; Hruban et al., 1973; Karabelnik and Zbinden, 19
Lullmann-Rauch and Scheid, 1975; Reasor, 1981; Hey
man and Reasor, 1986a,b).
Infiltration of alveolar macrophages in phosphol
dosis, in general, is associated with incr Lullmann-Rauch and Scheid, 1975; Reasor, 1981; He
man and Reasor, 1986a,b).
Infiltration of alveolar macrophages in phospho
dosis, in general, is associated with increased phos
lipid levels. Reasor et al. (1979) reported t man and Reasor, 1986a,b).

Infiltration of alveolar macrophages in phospholipi-

dosis, in general, is associated with increased phospho-

lipid levels. Reasor et al. (1979) reported that chlorphen-

termine (30 mg/kg, ip) Infiltration of alveolar macrophages in phospholipi-
dosis, in general, is associated with increased phospho-
lipid levels. Reasor et al. (1979) reported that chlorphen-
termine (30 mg/kg, ip) for 4 weeks resulted in an 18 dosis, in general, is associated with increased phospholipid levels. Reasor et al. (1979) reported that chlorphen-
termine (30 mg/kg, ip) for 4 weeks resulted in an 18-fold
increase in total phospholipids in macrophages. M lipid levels. Reasor et al. (1979) reported that chlorphen-
termine (30 mg/kg, ip) for 4 weeks resulted in an 18-fold
increase in total phospholipids in macrophages. McNulty
and Reasor (1981b) reported a 24.5-fold increas termine (30 mg/kg, ip) for 4 weeks resulted in an 18-fold
increase in total phospholipids in macrophages. McNulty
and Reasor (1981b) reported a 24.5-fold increase in total
phospholipids in macrophages treated with iprindo increase in total phospholipids in macrophages. McNulty
and Reasor (1981b) reported a 24.5-fold increase in total
phospholipids in macrophages treated with iprindole
(100 mg/kg, po) for 4 weeks. The cell size increases in
 and Reasor (1981b) reported a 24.5-fold increase in total phospholipids in macrophages treated with iprindole (100 mg/kg, po) for 4 weeks. The cell size increases in proportion to the phospholipid accumulation for at least phospholipids
(100 mg/kg, p
proportion to
4 weeks. The
of the cases.
Alveolar ma 00 mg/kg, po) for 4 weeks. The cell size increases
oportion to the phospholipid accumulation for at laweeks. The dose and response are proportional in m
the cases.
Alveolar macrophages treated with chlorphenterm
MI 10,393

proportion to the phospholipid accumulation for at least
4 weeks. The dose and response are proportional in most
of the cases.
Alveolar macrophages treated with chlorphentermine,
RMI 10,393, or chloramitryptyline contained 4 weeks. The dose and response are proportional in mos
of the cases.
Alveolar macrophages treated with chlorphentermine
RMI 10,393, or chloramitryptyline contained larg
amounts of phosphoglycerides, sphingomyelin, and plas of the cases.

Alveolar macrophages treated with chlorphentermine,

RMI 10,393, or chloramitryptyline contained large

amounts of phosphoglycerides, sphingomyelin, and plas-

malogens and small amounts of free fatty acids RMI 10,393, or chloramitryptyline contained large
amounts of phosphoglycerides, sphingomyelin, and plas-
malogens and small amounts of free fatty acids and
cholesterol; no sulfides, triglycerides, or gangliosides
were dete amounts of phosphoglycerides, sphingomyelin, and plas-
malogens and small amounts of free fatty acids and
cholesterol; no sulfides, triglycerides, or gangliosides
were detected (Karabelnik and Zbinden, 1976). The com-
posi regard to phospholynidosus (Vieyaratham and Corrin, por particular and Chinam-Rauch and Scheid, 1975; Reasor, 1981; Heyneman and Reasor, 1986a,b).

Lullmann-Rauch and Scheid, 1975; Reasor, 1981; Heyneman and Reasor, 1986a, malogens and small amounts of free fatty acids are
cholesterol; no sulfides, triglycerides, or gangliosid
were detected (Karabelnik and Zbinden, 1976). The con
positional increase in various classes of phospholipids
import cholesterol; no sulfides, triglycerides, or gangliosides
were detected (Karabelnik and Zbinden, 1976). The com-
positional increase in various classes of phospholipids is
important in understanding the structure-activity r were detected (Karabelnik and Zbinden, 1976). The compositional increase in various classes of phospholipids is
important in understanding the structure-activity rela-
tionships between types of phospholipid being affected positional increase in various classes of phospholipids
important in understanding the structure-activity rel
tionships between types of phospholipid being affect
and various drugs. Reasor et al. (1979) also report
several important in understanding the structure-activity relationships between types of phospholipid being affecte and various drugs. Reasor et al. (1979) also reporte several other changes in alveolar macrophages in chlor phente tionships between types of phospholipid being affected
and various drugs. Reasor et al. (1979) also reported
several other changes in alveolar macrophages in chlor-
phentermine-treated rats. In the case of amiodarone,
phos and various drugs. Reasor et al. (1979) also reported
several other changes in alveolar macrophages in chlor-
phentermine-treated rats. In the case of amiodarone,
phospholipidosis in macrophages has been associated
with dr several other changes in alveolar macrophages in
phentermine-treated rats. In the case of amio
phospholipidosis in macrophages has been ass
with drug accumulation and distribution (Kirk
1988, 1990). Alveolar macrophages of phentermine-treated rats. In the case of amiodarone,
phospholipidosis in macrophages has been associated
with drug accumulation and distribution (Kirk et al.,
1988, 1990). Alveolar macrophages of chlorphentermine-
treated with drug accumulation and distribution (Kirk et al., 1988, 1990). Alveolar macrophages of chlorphentermine-
treated rats are susceptible to lipid peroxidation, and
reduced glutathione plays a protective role (Reasor and
K 1988, 1990). Alveolar macrophages of chlorphentermine-
treated rats are susceptible to lipid peroxidation, and
reduced glutathione plays a protective role (Reasor and 1981a,b). duced glutathione plays a protective role (Reasor and oshut, 1980). Phagocytic activity of cells, however, ems to be enhanced in vitro (McNulty and Reasor, 81a,b).
Generally, it has been understood that the infiltration ma

Koshut, 1980). Phagocytic activity of cells, howeve
seems to be enhanced in vitro (McNulty and Reaso
1981a,b).
Generally, it has been understood that the infiltratio
of macrophages is a characteristic of CAD-induced phos-
 Generally, it has been understood that the infiltration 1981a,b).
Generally, it has been understood that the infiltration
of macrophages is a characteristic of CAD-induced phos-
pholipidosis. However, some exceptions do exist. Two
independent studies were conducted in our labor Generally, it has been understood that the infiltration
of macrophages is a characteristic of CAD-induced phos-
pholipidosis. However, some exceptions do exist. Two
independent studies were conducted in our laboratory to
i of macrophages is a characteristic of CAD-induced phos-
pholipidosis. However, some exceptions do exist. Two
independent studies were conducted in our laboratory to
investigate the potency of chlorpromazine in inducing
pho pholipidosis. However, some exceptions do exist. Two
independent studies were conducted in our laboratory to
investigate the potency of chlorpromazine in inducing
phospholipidosis in the lung and in macrophages of male
Spr

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Example 232
et al., 1991a,b). Consistently, we observed that ehlorp
mazine treatment decreased the number of alveolar m EXTERN MODAVANTI
et al., 1991a,b). Consistently, we observed that chlorpro
mazine treatment decreased the number of alveolar mac
rophages despite its limited ability to increase macro KODAVANT
et al., 1991a,b). Consistently, we observed that chlorp
mazine treatment decreased the number of alveolar ma
rophages despite its limited ability to increase macro-
phage phospholipid levels. Chlorpromazine may re et al., 1991a,b). Consistently, we observed that chlorpr
mazine treatment decreased the number of alveolar ma
rophages despite its limited ability to increase macr
phage phospholipid levels. Chlorpromazine may repr
sent an et al., 1991a,b). Consistently, we observed that chlorpromazine treatment decreased the number of alveolar mac-
rophages despite its limited ability to increase macro-
phage phospholipid levels. Chlorpromazine may repre-
s mazine treatment decreased the number of alveolar mac-
rophages despite its limited ability to increase macro-
phage phospholipid levels. Chlorpromazine may repre-
sent another unique class of drugs exhibiting rather
speci rophages despite its limited ability to increase macro-
phage phospholipid levels. Chlorpromazine may repre-
sent another unique class of drugs exhibiting rather (
specific effects on alveolar macrophages. Amiodarone
may r sent another unique class of drugs exhibiting rat specific effects on alveolar macrophages. Amiodarmay represent another class of drugs in this regard has been reported that, in patients receiving long-tamiodarone therapy, specific effects on alveolar macrophages. Amiodarone
may represent another class of drugs in this regard. It
has been reported that, in patients receiving long-term
amiodarone therapy, there is an infiltration of polymor-
 may represent another class of drugs in this regard. It has been reported that, in patients receiving long-term amiodarone therapy, there is an infiltration of polymorphonuclear lymphocytes and other phagocytic cells but n not macrophages (Martin et al., 1985; Myers et al., 1987). phonuclear lymphocytes and other phagocytic cells but
not macrophages (Martin et al., 1985; Myers et al., 1987).
In addition to any specific effects on macrophages, effects
et an lymphocytes and other phagocytic cells in r not macrophages (Martin et al., 1985; Myers et al., 1987).
In addition to any specific effects on macrophages, effects
on lymphocytes and other phagocytic cells in relation to
phospholipidosis, as well as other cellular ch In addition to any specific effects on macrophages, effects et a
on lymphocytes and other phagocytic cells in relation to has
phospholipidosis, as well as other cellular changes, need vac
to be investigated. Work on alveo on lymphocytes and other phagocytic cells in relation to
phospholipidosis, as well as other cellular changes, need
to be investigated. Work on alveolar macrophages might
be of special significance, because these cells can phospholipidosis, as well as other cellular changes, need
to be investigated. Work on alveolar macrophages might
be of special significance, because these cells can be
obtained from patients. Hence, any relationships be-
t be of special significance, because these cells can be obtained from patients. Hence, any relationships between drug-induced phospholipidosis and effects on pulmonary macrophages might be of predictive and diagnostic value be of special significance, because these cells can be obtained from patients. Hence, any relationships between drug-induced phospholipidosis and effects on pulmonary macrophages might be of predictive and diagnostic value *Tissue, Species, and Age Specificity*
Tissue, Species, and Age Specificity
The distribution pattern of all phononical

stic value.

Phospholipids, Various Phospholipid Classes, and data

issue, Species, and Age Specificity

The distribution pattern of all phospholipids in the nat

sues depends on the structure and function of that E. Phospholipids, Various Phospholipid Classes, and
Tissue, Species, and Age Specificity
The distribution pattern of all phospholipids in the
tissues depends on the structure and function of that
particular tissue or organ E. Phospholipids, Various Phospholipid Classes, and

Tissue, Species, and Age Specificity

The distribution pattern of all phospholipids in the

tissues depends on the structure and function of that

particular tissue or Tissue, Species, and Age Specificity

The distribution pattern of all phospholipids in the

tissues depends on the structure and function of that

particular tissue or organ. Likewise, the effects of CADs

on a particular tissues depends on the structure and function of that
particular tissue or organ. Likewise, the effects of CADs
on a particular phospholipid are dependent on the tissue
specificity for CAD accumulation. For example, the su tissues depends on the structure and function of that
particular tissue or organ. Likewise, the effects of CADs
on a particular phospholipid are dependent on the tissue
specificity for CAD accumulation. For example, the su particular tissue or organ. Likewise, the effects of CADs
on a particular phospholipid are dependent on the tissue
specificity for CAD accumulation. For example, the sur-
factant component of the lung is rich in disaturate on a particular phospholipid are dependent on the tissue
specificity for CAD accumulation. For example, the sur-
factant component of the lung is rich in disaturated
phosphatidylcholine. It is known that drug-induced pulspecificity for CAD accumulation. For example, the sfactant component of the lung is rich in disaturat phosphatidylcholine. It is known that drug-induced p monary phospholipidosis primarily results in elevation of this pho mactant component of the lung is rich in disaturated
phosphatidylcholine. It is known that drug-induced pul-
monary phospholipidosis primarily results in elevation
of this phospholipid (Ma et al., 1988; Reasor and Heyne-
m monary phospholipidosis primarily results in elevation of this phospholipid (Ma et al., 1988; Reasor and Heyneman, 1983; Camus et al., 1989). Additionally, the severity of the effect on a particular class of phospholipid of this phospholipid (Ma et al., 1988; Reasor and Heyneman, 1983; Camus et al., 1989). Additionally, the severity of the effect on a particular class of phospholipid seems to depend on the type of CAD as well as on the tis man, 1983; Camus et al., 1989). Additionally, the severity
of the effect on a particular class of phospholipid seems
to depend on the type of CAD as well as on the tissue
that is being affected (Lullmann et al., 1978; Mats of the effect on a particular class of phospholipid see
to depend on the type of CAD as well as on the tis
that is being affected (Lullmann et al., 1978; Matsuzz
and Hostetler, 1980d; Kacew, 1985; Pirovino et al., 198
For to depend on the type of CAD as well as on the tissue
that is being affected (Lullmann et al., 1978; Matsuzawa
and Hostetler, 1980d; Kacew, 1985; Pirovino et al., 1988).
For example, a marked accumulation of neutral disatu that is being affected (Lullmann et al., 1978; Matsuzawa
and Hostetler, 1980d; Kacew, 1985; Pirovino et al., 1988).
For example, a marked accumulation of neutral disatur-
ated phosphatidylcholine, including cholesterol, ch and Hostetler, 1980d; Kacew, 1985; Pirovino et al., 1985
For example, a marked accumulation of neutral disatt
ated phosphatidylcholine, including cholesterol, chole
terol esters, and free fatty acids, occurs in macrophag
i belnik and Zbinden, 1975).
In the case of chlorphentermine and amiodarone-ined phosphatidylcholine, including cholesterol, c
rol esters, and free fatty acids, occurs in macrop
blated from 1-chloramitryptyline-treated rats (
lnik and Zbinden, 1975).
In the case of chlorphentermine and amiodaro:
ced

terol esters, and free fatty acids, occurs in macrophages
isolated from 1-chloramitryptyline-treated rats (Kara-
belnik and Zbinden, 1975).
In the case of chlorphentermine and amiodarone-in-
duced phospholipidosis, the spe isolated from 1-chloramitryptyline-treated rats (Karabelnik and Zbinden, 1975).

In the case of chlorphentermine and amiodarone-in-

duced phospholipidosis, the specific type of phospholipid

and the specific tissue in whi belnik and Zbinden, 1975).
In the case of chlorphentermine and amiodarone-induced phospholipidosis, the specific type of phospholipi
and the specific tissue in which such increases occur an
of interest. Chlorphentermine-in In the case of chlorphentermine and amiodarone-in-
duced phospholipidosis, the specific type of phospholipid
and the specific tissue in which such increases occur are
of interest. Chlorphentermine-induced pulmonary phos-
a duced phospholipidosis, the specific type of phospholipid
and the specific tissue in which such increases occur are
of interest. Chlorphentermine-induced pulmonary phos-
pholipidosis is associated with a maximum increase i and the specific tissue in which such increases occur a
of interest. Chlorphentermine-induced pulmonary pho
pholipidosis is associated with a maximum increase is
disaturated phosphatidylcholine in the lung (Schmien
al., 19 of interest. Chlorphentermine-induced pulmonary phos-
pholipidosis is associated with a maximum increase in
disaturated phosphatidylcholine in the lung (Schmien et
al., 1974; Gloster et al., 1976; Kacew, 1988). Also, fluox pholipidosis is associated with a maximum increase in divergistaturated phosphatidylcholine in the lung (Schmien et prop
al., 1974; Gloster et al., 1976; Kacew, 1988). Also, fluox- une
etine, an inhibitor of serotonin upta disaturated phosphatidylcholine in the lung (Schmien et productional, 1974; Gloster et al., 1976; Kacew, 1988). Also, fluox-
etine, an inhibitor of serotonin uptake (Wong et al., lip
1975), induces accumulation of phosphat al., 1974; Gloster et al., 1976; Kacew, 1988). Also, fluox
etine, an inhibitor of serotonin uptake (Wong et al
1975), induces accumulation of phosphatidylcholine is
the lung, a property shared by chlorphentermine (Woler al etine, an inhibitor of serotonin uptake (Wong et a
1975), induces accumulation of phosphatidylcholine
the lung, a property shared by chlorphentermine (We
et al., 1976). A marked elevation of phosphatidylcholi
occurs partic 1975), induces accumulation of phosphatidylcholine in encounted the lung, a property shared by chlorphentermine (Wold ghe et al., 1976). A marked elevation of phosphatidylcholine acy occurs particularly in type II cells a the lung, a property shared by chlorphentermine (We
et al., 1976). A marked elevation of phosphatidylcholi
occurs particularly in type II cells and alveolar mac
phages and in the lung surfactant due to amiodarone a
chlorph occurs particularly in type II cells and alveolar macro-
phages and in the lung surfactant due to amiodarone and
chlorphentermine treatment (Smith et al., 1973; March-
linski et al., 1982; Reasor and Heyneman, 1983; Chate-

sent another unique class of drugs exhibiting rather Chatelain and Brotelle, 1985; Reasor et al., 1988; Koda-
specific effects on alveolar macrophages. Amiodarone vanti and Mehendale, 1991). Other tissues also are af-
may amiodarone therapy, there is an infiltration of polymoric included, 1988). Amiodarone-induced phospholipidosis
phonuclear lymphocytes and other phagocytic cells but
not macrophages (Martin et al., 1985; Myers et al., 1987) MEHENDALE
lain and Brotelle, 1985; Reasor et al., 1988). Amiodarone
chlorphentermine, and chlorcyclizine induce phospholi MEHENDALE
lain and Brotelle, 1985; Reasor et al., 1988). Amiodar
chlorphentermine, and chlorcyclizine induce phosph
pidosis in the lung, particularly in macrophages (Glo MEHENDALE
lain and Brotelle, 1985; Reasor et al., 1988). Amiodarone,
chlorphentermine, and chlorcyclizine induce phospholi-
pidosis in the lung, particularly in macrophages (Gloster
et al., 1976; Gaton and Wolman, 1979; Ku lain and Brotelle, 1985; Reasor et al., 1988). Amiodarone,
chlorphentermine, and chlorcyclizine induce phospholi-
pidosis in the lung, particularly in macrophages (Gloster
et al., 1976; Gaton and Wolman, 1979; Kudenchuk, 1 lain and Brotelle, 1985; Reasor et al., 1988). Amiodaror
chlorphentermine, and chlorcyclizine induce phospho
pidosis in the lung, particularly in macrophages (Glost
et al., 1976; Gaton and Wolman, 1979; Kudenchuk, 198
Chat chlorphentermine, and chlorcyclizine induce phospholipidosis in the lung, particularly in macrophages (Gloster
et al., 1976; Gaton and Wolman, 1979; Kudenchuk, 1984;
Chatelain and Brotelle, 1985; Reasor et al., 1988; Kodaet al., 1976; Gaton and Wolman, 1979; Kudenchuk, 1984; et al., 1976; Gaton and Wolman, 1979; Kudenchuk, 198
Chatelain and Brotelle, 1985; Reasor et al., 1988; Kod
vanti and Mehendale, 1991). Other tissues also are afected but to a considerably lesser extent (Lullmann
al., 1978 Chatelain and Brotelle, 1985; Reasor et al., 1988; Kodavanti and Mehendale, 1991). Other tissues also are affected but to a considerably lesser extent (Lullmann et al., 1978; Kannan et al., 1982; Mazue et al., 1984; Pirovi vanti and Mehendale, 1991). Other tissues also are af-
fected but to a considerably lesser extent (Lullmann et
al., 1978; Kannan et al., 1982; Mazue et al., 1984; Pirov-
ino et al., 1988). Amiodarone-induced phospholipidos fected but to a considerably lesser extent (Lullmann et al., 1978; Kannan et al., 1982; Mazue et al., 1984; Pirovino et al., 1988). Amiodarone-induced phospholipidosis in the liver is associated with a maximum increase in al., 1978; Kannan et al., 1982; Mazue et al., 1984; Pirovino et al., 1988). Amiodarone-induced phospholipidosis
in the liver is associated with a maximum increase in
phosphatidylserine and phosphatidylethanolamine (Yap
et ino et al., 1988). Amiodarone-induced phospholipidosis
in the liver is associated with a maximum increase in
phosphatidylserine and phosphatidylethanolamine (Yap
et al., 1987; Pirovino et al., 1988, 1990). Furthermore, it
 in the liver is associated with a maximum increase in
phosphatidylserine and phosphatidylethanolamine (Yap
et al., 1987; Pirovino et al., 1988, 1990). Furthermore, it
has been shown that amiodarone does induce cytoplasmic
 et al., 1987; Pirovino et al., 1988, 1990). Furthermore, it has been shown that amiodarone does induce cytoplasmic vacuoles, but not lamellar bodies, in the liver (Lambert et al., 1989; Pirovino et al., 1990). Certainly, a et al., 1987; Pirovino et al., 1988, 1990). Furth
has been shown that amiodarone does induce cy
vacuoles, but not lamellar bodies, in the liver
et al., 1989; Pirovino et al., 1990). Certainly,
evidence is necessary to conf is been shown that amiodarone does induce cytoplasmic
cuoles, but not lamellar bodies, in the liver (Lambert
al., 1989; Pirovino et al., 1990). Certainly, additional
idence is necessary to confirm this finding.
Because ami

vacuoles, but not lamellar bodies, in the liver (Lambert
et al., 1989; Pirovino et al., 1990). Certainly, additional
evidence is necessary to confirm this finding.
Because amiodarone binds only to the hydrophobic
moiety of evidence is necessary to confirm this finding.
evidence is necessary to confirm this finding.
Because amiodarone binds only to the hydrophobic
moiety of the phospholipids (Joshi et al., 1988, 1989) and
the ionic interactio evidence is necessary to confirm this finding.
Because amiodarone binds only to the hydrophob
moiety of the phospholipids (Joshi et al., 1988, 1989) an
the ionic interactions of the polar moiety of the drug an
a phospholip Because amiodarone binds only to the hydrophobic
moiety of the phospholipids (Joshi et al., 1988, 1989) and
the ionic interactions of the polar moiety of the drug and
a phospholipid are minimal, one can speculate that amio moiety of the phospholipids (Joshi et al., 1988, 1989) and
the ionic interactions of the polar moiety of the drug and
a phospholipid are minimal, one can speculate that amio-
darone is able to induce an accumulation of man the ionic interactions of the polar moiety of the drug and
a phospholipid are minimal, one can speculate that amio-
darone is able to induce an accumulation of many kinds
of phospholipids irrespective of ionic charges and/ a phospholipid are minimal, one can speculate that amio-
darone is able to induce an accumulation of many kinds
of phospholipids irrespective of ionic charges and/or the
nature of the polar group of the phospholipids. On t darone is able to induce an accumulation of many kind
of phospholipids irrespective of ionic charges and/or th
nature of the polar group of the phospholipids. On th
other hand, chlorphentermine-phospholipid interaction
occ of phospholipids irrespective of ionic charges and/or the nature of the polar group of the phospholipids. On the other hand, chlorphentermine-phospholipid interaction occur mainly through polar, ionic moieties. Surprisingl other hand, chlorphentermine-phospholipid interactions
occur mainly through polar, ionic moieties. Surprisingly,
hydrophobic interactions are minimal and, predictably,
chlorphentermine affects mainly phosphatidylcholine other hand, chlorphentermine-phospholipid interactions
occur mainly through polar, ionic moieties. Surprisingly,
hydrophobic interactions are minimal and, predictably,
chlorphentermine affects mainly phosphatidylcholine
an occur mainly through polar, ionic moieties. Surprisingly, hydrophobic interactions are minimal and, predictably, chlorphentermine affects mainly phosphatidylcholine and the charged anionic polar lipids with which ionic int hydrophobic interactions are minimal and, predictate chlorphentermine affects mainly phosphatidylchol and the charged anionic polar lipids with which io interactions occur in the lung tissue (Joshi et al., 198 Thus, unders chlorphentermine affects mainly phosphatidylcholine
and the charged anionic polar lipids with which ionic
interactions occur in the lung tissue (Joshi et al., 1989).
Thus, understanding the ionic and hydropholic interac-
t interactions occur in the lung tissue (Joshi et al., 1989).
Thus, understanding the ionic and hydrophobic interac-
tions of CADs with phospholipids is important in ex-
plaining the tissue specificity of phospholipidosis.
P teractions occur in the lung tissue (Joshi et al., 1989).
hus, understanding the ionic and hydrophobic interac-
ons of CADs with phospholipids is important in ex-
aining the tissue specificity of phospholipidosis.
Phosphol

Thus, understanding the ionic and hydrophobic interactions of CADs with phospholipids is important in explaining the tissue specificity of phospholipidosis.
Phospholipid fatty liver observed after chloroquine treatment has tions of CADs with phospholipids is important in explaining the tissue specificity of phospholipidosis.

Phospholipid fatty liver observed after chloroquine

treatment has been extensively studied by Hostetler and

his coi plaining the tissue specificity of phospholipidosis.

Phospholipid fatty liver observed after chloroque

treatment has been extensively studied by Hostetler et

his coinvestigators (Matsuzawa and Hostetler, 198

Hostetler Phospholipid fatty liver observed after chloroque treatment has been extensively studied by Hostetler his coinvestigators (Matsuzawa and Hostetler, 19 Hostetler et al., 1985). Chloroquine induces an acculation of phosphati treatment has been extensively studied by Hostetler and
his coinvestigators (Matsuzawa and Hostetler, 1980c
Hostetler et al., 1985). Chloroquine induces an accumu
lation of phosphatidylglycerol and phosphatidylinosito
in v his coinvestigators (Matsuzawa and Hostetler, 1980c;
Hostetler et al., 1985). Chloroquine induces an accumu-
lation of phosphatidylglycerol and phosphatidylinositol
in various fractions of rat livers (Matsuzawa and Hos-
te Hostetler et al., 1985). Chloroquine induces an accumulation of phosphatidylglycerol and phosphatidylinositol
in various fractions of rat livers (Matsuzawa and Hostetler, 1980a,d). Chloroquine-induced phospholipidosis is
l lation of phosphatidylglycerol and phosphatidylinositol
in various fractions of rat livers (Matsuzawa and Hos-
tetler, 1980a,d). Chloroquine-induced phospholipidosis is
less common and less prominent in the lung tissue.
Ch in various fractions of rat livers (Matsuzawa and Hostetler, 1980a,d). Chloroquine-induced phospholipidosis is
less common and less prominent in the lung tissue
Chloroquine has a divalent cationic group in contrast to
ther tetler, 1980a,d). Chloroquine-induced phospholipidosis is
less common and less prominent in the lung tissue.
Chloroquine has a divalent cationic group in contrast to
other CADs such as chlorphentermine and amiodarone.
Lull less common and less prominent in the lung tissue.
Chloroquine has a divalent cationic group in contrast to
other CADs such as chlorphentermine and amiodarone.
Lullmann and Wehling (1979) postulated that the tissue
specifi Chloroquine has a divalent cationic group in contrast to
other CADs such as chlorphentermine and amiodarone.
Lullmann and Wehling (1979) postulated that the tissue
specificity and the specific class of phospholipid being
a other CADs such as chlorphentermine and amiodarone.
Lullmann and Wehling (1979) postulated that the tissue
specificity and the specific class of phospholipid being
affected by chloroquine is related to the presence of the
 Lullmann and Wehling (1979) postulated that the tissue
specificity and the specific class of phospholipid being
affected by chloroquine is related to the presence of the
divalent cationic moiety on this drug molecule. They specificity and the specific class of phospholipid being
affected by chloroquine is related to the presence of the
divalent cationic moiety on this drug molecule. They
proposed that the divalent cationic moiety possesses a affected by chloroquine is related to the presence of th
divalent cationic moiety on this drug molecule. The
proposed that the divalent cationic moiety possesses a
unexpectedly high affinity for negatively charged pola
lip divalent cationic moiety on this drug molecule. The proposed that the divalent cationic moiety possesses innexpectedly high affinity for negatively charged pollipids and, therefore, chloroquine has a remarkable ten ency to proposed that the divalent cationic moiety possesses
unexpectedly high affinity for negatively charged p
lipids and, therefore, chloroquine has a remarkable te
ency to induce an accumulation of gangliosides (K
ghardt, 1976 unexpectedly high affinity for negatively charged polar
lipids and, therefore, chloroquine has a remarkable tend-
ency to induce an accumulation of gangliosides (Klin-
ghardt, 1976), the anionic lipids such as bis(mono-
ac lipids and, therefore, chloroquine has a remarkable tend-
ency to induce an accumulation of gangliosides (Klin-
ghardt, 1976), the anionic lipids such as bis(mono-
acylglycero)-phosphate, and phosphatidylinositol, all of
w ency to induce an accumulation of gangliosides (Klinghardt, 1976), the anionic lipids such as bis(mono-
acylglycero)-phosphate, and phosphatidylinositol, all of
which are present in relatively higher concentrations in
the ghardt, 1976), the anionic lipids such as bis(mono-
acylglycero)-phosphate, and phosphatidylinositol, all of
which are present in relatively higher concentrations in
the liver in comparison to the lung (Yamamoto et al.,
19 acylglycero)-phosphate, and phosphatidylinositol, all of which are present in relatively higher concentrations in the liver in comparison to the lung (Yamamoto et al., 1976; Tjiong et al., 1978). Similarly, gentamicin was

by increasing phosphatidylinositol in adult rats (Felman et al., 1982; Wilmotte et al., 1983). D
by increasing phosphatidylinositol in ad
man et al., 1982; Wilmotte et al., 1983).
Gentamicin-induced lamellar bodies ir

BRUG-INDUCED PHOS
an et al., 1982; Wilmotte et al., 1983).
Gentamicin-induced lamellar bodies in humans have ca
en associated with kidney toxicity (Kosek et al., 1974; by increasing phosphatidylinositol in adult rats (Feldman et al., 1982; Wilmotte et al., 1983).
Gentamicin-induced lamellar bodies in humans have
been associated with kidney toxicity (Kosek et al., 1974;
Houghton et al., 1 by increasing phosphatidylinositol in adult rats (Feldman et al., 1982; Wilmotte et al., 1983).
Gentamicin-induced lamellar bodies in humans have
been associated with kidney toxicity (Kosek et al., 1974;
Houghton et al., 1 man et al., 1982; Wilmotte et al., 1983).
Gentamicin-induced lamellar bodies in humans have
been associated with kidney toxicity (Kosek et al., 1974;
Houghton et al., 1978; Smith et al., 1980). Gentamicin
and amantadine in Gentamicin-induced lamellar bodies in humans have
been associated with kidney toxicity (Kosek et al., 1974;
Houghton et al., 1978; Smith et al., 1980). Gentamicin
and amantadine induce phospholipidosis predominantly
in the been associated with kidney toxicity (Kosek et al., Houghton et al., 1978; Smith et al., 1980). Gentamical amantadine induce phospholipidosis predominin the kidney (Feldman et al., 1982; Wilmotte et al., Kacew, 1985, 1987; Houghton et al., 1978; Smith et al., 1980). Gentamicin tailed
and amantadine induce phospholipidosis predominantly lipid
in the kidney (Feldman et al., 1982; Wilmotte et al., 1983; speci
Kacew, 1985, 1987; Burmester et al. and amantadine induce phospholipidosis predomina
in the kidney (Feldman et al., 1982; Wilmotte et al., 1
Kacew, 1985, 1987; Burmester et al., 1987). Gentaminduced phospholipidosis is associated with a maxim
elevation of ph in the kidney (Feldman et al., 1982; Wilmotte et al., 1983;
Kacew, 1985, 1987; Burmester et al., 1987). Gentamicin-
induced phospholipidosis is associated with a maximum
elevation of phosphatidylserine, phosphatidylcholine induced phospholipidosis is associated with a maximum
elevation of phosphatidylserine, phosphatidylcholine,
and phosphatidylinositol detectable in kidney lysosomes
as well as in rat whole kidney homogenates (Kacew,
1987). elevation of phosphatidylserine, phosphatidylcholine, in
and phosphatidylinositol detectable in kidney lysosomes CA
as well as in rat whole kidney homogenates (Kacew,
1987). Chlorphentermine also exerted a maximum in-
crea and phosphatidylinositol detectable in kidney lysosomes CA
as well as in rat whole kidney homogenates (Kacew, In
1987). Chlorphentermine also exerted a maximum in-
crease in phosphatidylinositol in the kidney, whereas the as well as in rat whole kidney homogenates (Kacew, 1987). Chlorphentermine also exerted a maximum crease in phosphatidylinositol in the kidney, whereas maximum increase in phosphatidylcholine occurredung tissue (Kacew, 198 1987). Chlorphentermine also exerted a maximum increase in phosphatidylinositol in the kidney, whereas the maximum increase in phosphatidylcholine occurred in lung tissue (Kacew, 1985). Because phosphatidylinositol can be crease in phosphatidylinositol in the kidney, whereas
maximum increase in phosphatidylcholine occurred
lung tissue (Kacew, 1985). Because phosphatidylinos
can be affected the most (Feldman et al., 1982; Wilmo
et al., 1983) maximum increase in phosphatidylcholine occurred in taking tissue (Kacew, 1985). Because phosphatidylinositol change can be affected the most (Feldman et al., 1982; Wilmotte net al., 1983), the deleterious long-term effec lung tissue (Kacew, 1985). Because phosphatidylinositol can be affected the most (Feldman et al., 1982; Wilmotte net al., 1983), the deleterious long-term effects, particularly on regulation of signal transduction and prot can be affected the most (Feldman et al., 1982; Wilmotte et al., 1983), the deleterious long-term effects, particularly on regulation of signal transduction and protein phosphorylation, cannot be ignored. The relationship et al., 1983), the deleterious long-term efferting in the phosphorylation, cannot be ignored. The rephospholipidosis and other cellular changes cussed in "Mechanism of Phospholipidosis." Brain is the other phospholipid-ric rly on regulation of signal transduction and prote
cosphorylation, cannot be ignored. The relationship
cospholipidosis and other cellular changes will be dissed in "Mechanism of Phospholipidosis."
Brain is the other phosph

phospholipidosis and other cellular changes will be
cussed in "Mechanism of Phospholipidosis."
Brain is the other phospholipid-rich organ. The di
bution of phospholipids in the white and gray matt
brain is variable. In gen cussed in "Mechanism of Phospholipidosis."
Brain is the other phospholipid-rich organ. The distribution of phospholipids in the white and gray matter c
brain is variable. In general, brain is rich in phosphatidy
dylethanol Brain is the other phospholipid-rich organ. The distribution of phospholipids in the white and gray matter obtain is variable. In general, brain is rich in phosphatidylethanolamine and lecithin (phosphatidylcholine), folow bution of phospholipids in the white and gray matter of
brain is variable. In general, brain is rich in phosphati-
dylethanolamine and lecithin (phosphatidylcholine), fol-
lowed by sphingomyelin, phosphatidylserine, and ph brain is variable. In general, brain is rich in phosphatidy
dylethanolamine and lecithin (phosphatidylcholine), fol
lowed by sphingomyelin, phosphatidylserine, and phos
phatidylinositol (Suzuki, 1976). It is well known tha lowed by sphingomyelin, phosphatidylserine, and phos-

phatidylinositol (Suzuki, 1976). It is well known that

called effects in the drug-induced phospholipidosis may

called the call.

CADs interact with phospholipid memb lowed by sphingomyelin, phosphatidylserine, and phosphatidylinositol (Suzuki, 1976). It is well known the CADs interact with phospholipid membranes and regulate ion transport across membranes in the nervous system elicitin phatidylinositol (Suzuki, 1976). It is well known that CADs interact with phospholipid membranes and regulate ion transport across membranes in the nervous system eliciting physiological responses (Levy and Richards, 1966; CADs interact with phospholipid membranes and regulate ion transport across membranes in the nervous
system eliciting physiological responses (Levy and Richards, 1966; Patil, 1968; Seeman, 1977; Mason et al., 1984;
Zychlin late ion transport across membranes in the ner
system eliciting physiological responses (Levy and I
ards, 1966; Patil, 1968; Seeman, 1977; Mason et al., 1
Zychlinski and Montgomery, 1986; Nagai et al., 1
Chatelain et al., system eliciting physiological responses (Levy and Riards, 1966; Patil, 1968; Seeman, 1977; Mason et al., 19
Zychlinski and Montgomery, 1986; Nagai et al., 19
Chatelain et al., 1989). Chloroquine- and amiodarc
induced neur ards, 1966; Patil, 1968; Seeman, 1977; Mason et al., 1984;
Zychlinski and Montgomery, 1986; Nagai et al., 1987;
Chatelain et al., 1989). Chloroquine- and amiodarone-
induced neurotoxicity has been associated with phospho-
 Zychlinski and Montgomery, 1986; Nagai et al., 1987;
Chatelain et al., 1989). Chloroquine- and amiodarone-
induced neurotoxicity has been associated with phospho-
lipidosis in the brain (Meier et al., 1979; Estes et al., Chatelain et al., 1989). Chloroquine- and amiodarone-
induced neurotoxicity has been associated with phospho-
induced neurotoxicity has been associated with phospho-
lipidosis in the brain (Meier et al., 1979; Estes et al induced neurotoxicity has been associated with phospho-
lipidosis in the brain (Meier et al., 1979; Estes et al., D
1987). There is very little evidence that a small degree of
phospholipidosis could result in the brain fo lipidosis in the brain (Meier et al., 1979; Estes et al., D 1987). There is very little evidence that a small degree of phospholipidosis could result in the brain following chronic CAD treatment (Klinghardt et al., 1981 1987). There is very little evidence that a small degree c
phospholipidosis could result in the brain followin
chronic CAD treatment (Klinghardt et al., 1981; Nilsso
et al., 1981; Lemaire et al., 1982). However, lack c
det phospholipidosis could result in the brain following
chronic CAD treatment (Klinghardt et al., 1981; Nilsson
et al., 1981; Lemaire et al., 1982). However, lack of
detailed information concerning phospholipidosis in-
duced et al., 1981; Lemaire et al., 1982). However, lack of detailed information concerning phospholipidosis induced by CADs in the brain and its significance limits any interpretation of a relationship among tissue specificity, et al., 1981; Lemaire et al., 1982). However, lacketailed information concerning phospholipidosis duced by CADs in the brain and its significance lineary interpretation of a relationship among tissue specity, membrane acti detailed information concerning phospholipidosis in-
duced by CADs in the brain and its significance limits
any interpretation of a relationship among tissue speci-
ficity, membrane action, and the mechanism of phospho-
li duced by CADs in the brain and its significance limits
any interpretation of a relationship among tissue speci-
ficity, membrane action, and the mechanism of phospho-
lipidosis in this organ. As far as other tissues are co any interpretation of a relationship among tissue speciety, membrane action, and the mechanism of phosphipidosis in this organ. As far as other tissues are cocerned, Wong and Hruban (1972) reported that testicul degenerati ficity, membrane action, and the mechanis
lipidosis in this organ. As far as other tis
cerned, Wong and Hruban (1972) reported
degeneration in chlorcyclizine-treated rat
ated with phospholipidosis-like alterations
It shoul idosis in this organ. As far as other tissues are corned, Wong and Hruban (1972) reported that testics generation in chlorcyclizine-treated rats was assed with phospholipidosis-like alterations.
It should be noted that bot cerned, Wong and Hruban (1972) reported that testicu degeneration in chlorcyclizine-treated rats was associed with phospholipidosis-like alterations.
It should be noted that both the intensity of phospholipidosis-like ultr

degeneration in chlorcyclizine-treated rats was associ-
ated with phospholipidosis-like alterations.
It should be noted that both the intensity of phospho-
ipidosis-like ultrastructural alterations and the magni-
197
tude ated with phospholipidosis-like alterations.
It should be noted that both the intensity of phospho-
lipidosis-like ultrastructural alterations and the magni-
tude of chlorphentermine-induced phospholipidosis in
the lung an It should be noted that both the intensity of phospholipidosis-like ultrastructural alterations and the magnitude of chlorphentermine-induced phospholipidosis is the lung and adrenal gland were reported to be species speci lipidosis-like ultrastructural alterations and the magnitude of chlorphentermine-induced phospholipidosis in the lung and adrenal gland were reported to be species specific (Lullmann-Rauch and Reil, 1974). Species specific tude of chlorphentermine-induced phospholipidosis in L
the lung and adrenal gland were reported to be species
specific (Lullmann-Rauch and Reil, 1974). Species spec-
ificity in the intensity of CAD-induced phospholipidosis the lung and adrenal gland were reported to be species
specific (Lullmann-Rauch and Reil, 1974). Species spec-
ificity in the intensity of CAD-induced phospholipidosis
may be due predominantly to the differences in capacit

ospholaribosis and the nontarget tissues. Metabolism of several CADs
by the lung and liver has been shown to differ signifios

by the lung and liver has been shown to differ signicantly

by the lung and liver has been shown to differ signicantly

between rats and rabbits (Ohmiya and Mehends 333

or in the nontarget tissues. Metabolism of several CAD

by the lung and liver has been shown to differ signifi

cantly between rats and rabbits (Ohmiya and Mehendale

1980b, 1981, 1982; Young and Mehendale, 1986). De or in the nontarget tissues. Metabolism of several CADs
by the lung and liver has been shown to differ signifi-
cantly between rats and rabbits (Ohmiya and Mehendale,
1980b, 1981, 1982; Young and Mehendale, 1986). De-
tail by the lung and liver has been shown to differ significantly between rats and rabbits (Ohmiya and Mehendale, 1986). Detailed studies have not been conducted on the phosphoby the lung and liver has been shown to differ significantly between rats and rabbits (Ohmiya and Mehendale, 1986). Detailed studies have not been conducted on the phospholipidosis-inducing potency of several CADs in vario cantly between rats and rabbits (Ohmiya and Mehendale, 1986). Detailed studies have not been conducted on the phospholipidosis-inducing potency of several CADs in various species, types of phospholipids being affected, or 1980b, 1981, 1982; Young and Mehendale, 1986). Detailed studies have not been conducted on the phospholipidosis-inducing potency of several CADs in various species, types of phospholipids being affected, or the tissue spec tailed studies have not been conducted on the phospholipidosis-inducing potency of several CADs in various species, types of phospholipids being affected, or the tissue specificity. A major factor that could play a role in species, types of phospholipids being affected, or the tissue specificity. A major factor that could play a role in species differences is the status of metabolic enzymes in target or nontarget tissues and the overall turn species, types of phospholipids being affec
tissue specificity. A major factor that could
in species differences is the status of metabol
in target or nontarget tissues and the overall
CADs by tissues in different animal s In an attempt to investigate the settlempt species differences is the status of metabolic er target or nontarget tissues and the overall turn
ADs by tissues in different animal species.
In an attempt to investigate the pho

phosphorylation, cannot be ignored. The relationship of in phosphatidylinositol as compared to other classes of
phospholipidosis and other cellular changes will be dis-
cussed in "Mechanism of Phospholipidosis."
Brain is t in species differences is the status of metabolic enzymes
in target or nontarget tissues and the overall turnover of
CADs by tissues in different animal species.
In an attempt to investigate the phospholipidosis-
inducing in target or nontarget tissues and the overall turnover of CADs by tissues in different animal species.
In an attempt to investigate the phospholipidosis-
inducing properties of chlorphentermine and gentamicin
in newborn r CADs by tissues in different animal species.
In an attempt to investigate the phospholipidosis-
inducing properties of chlorphentermine and gentamicin
in newborn rats, Kacew (1984) demonstrated that gen-
tamicin induces ph In an attempt to investigate the phospholipidosis-
inducing properties of chlorphentermine and gentamicin
in newborn rats, Kacew (1984) demonstrated that gen-
tamicin induces phospholipidosis in kidneys, whereas
chlorphent inducing properties of chlorphentermine and gentamicin
in newborn rats, Kacew (1984) demonstrated that gen-
tamicin induces phospholipidosis in kidneys, whereas
chlorphentermine is effective in both the lung and kid-
ney. in newborn rats, Kacew (1984) demonstrated that gentamicin induces phospholipidosis in kidneys, whereas chlorphentermine is effective in both the lung and kidney. Chlorphentermine or gentamicin, on the other hand, did not tamicin induces phospholipidosis in kidneys, whereas
chlorphentermine is effective in both the lung and kid-
ney. Chlorphentermine or gentamicin, on the other hand,
did not induce phospholipidosis in the lung or liver of
c chlorphentermine is effective in both the lung and kid-
ney. Chlorphentermine or gentamicin, on the other hand,
did not induce phospholipidosis in the lung or liver of
chick embryos. Gentamicin exerted the greatest increas ney. Chlorphentermine or gentamicin, on the other hand, did not induce phospholipidosis in the lung or liver of chick embryos. Gentamicin exerted the greatest increase in phosphatidylinositol as compared to other classes o did not induce phospholipidosis in the lung or liver
chick embryos. Gentamicin exerted the greatest increasin
phosphotipid in newborn rats, unlike in adults (Kacev
1987; Kacew and Reasor, 1985). In comparing the CAI
induce chick embryos. Gentamicin exerted the greatest increase
in phosphatidylinositol as compared to other classes of
phospholipid in newborn rats, unlike in adults (Kacew,
1987; Kacew and Reasor, 1985). In comparing the CAD-
in in phosphatidylinositol as compared to other classes of phospholipid in newborn rats, unlike in adults (Kacew, 1987; Kacew and Reasor, 1985). In comparing the CAD-induced phospholipidosis in newborn rats and in chick embry phospholipid in newborn rats, unlike in adults (Kacew,
1987; Kacew and Reasor, 1985). In comparing the CAD-
induced phospholipidosis in newborn rats and in chick
embryos, Kacew (1985) did not consider the possibility
of th 1987; Kacew and Reasor, 1985). In comparing the CA induced phospholipidosis in newborn rats and in chiembryos, Kacew (1985) did not consider the possibil of the influence of an enzyme development pattern newborns at differ channel nucles busepholipidosis in states in the driver of the drug-streament in the drug-induced phospholipidosis in the lung or liver of did not induce phospholipidosis in the lung or liver of did not induced phospholip embryos, Kacew (1985) did not consider the possibility
of the influence of an enzyme development pattern in
newborns at different stages. Furthermore, the age-re-
lated effects in the drug-induced phospholipidosis may
be d of the influence of an enzyme devertieved in the cell.

Internal component stages. Furthermore, the cell.

The celle to differences in the enzy

structural components of the cell.

It is important to study the devel wborns at different stages. Furthermore, the age-re-
ted effects in the drug-induced phospholipidosis may
due to differences in the enzyme profile and the
ructural components of the cell.
It is important to study the devel

lated effects in the drug-induced phospholipidosis may
be due to differences in the enzyme profile and the
structural components of the cell.
It is important to study the developmental aspects of
phospholipid synthesis and be due to differences in the enzyme profile and the structural components of the cell.
It is important to study the developmental aspects of
phospholipid synthesis and catabolism pathways in the
lung and other tissues with structural components of the cell.

It is important to study the developmental aspects of

phospholipid synthesis and catabolism pathways in the

lung and other tissues with respect to different classes

of phospholipids It is important to study the developmental aspects of phospholipid synthesis and catabolism pathways in the lung and other tissues with respect to different classe of phospholipidosis and several other effects of CADs.
F. *F. Affinity of Drugs for Various for Phospholipids to understand the precise mechanis* of phospholipidosis and several other effects of CADs.
F. Affinity of Drugs for Various Tissues, Intracellular Distribution, Pharmaco

phospholipidosis and several other effects of CADs.
Affinity of Drugs for Various Tissues, Intracellular
istribution, Pharmacokinetics, and Metabolism
The diversity in the pharmacological actions of the
ugs known to induce F. Affinity of Drugs for Various Tissues, Intracellular
Distribution, Pharmacokinetics, and Metabolism
The diversity in the pharmacological actions of the
drugs known to induce phospholipidosis is also reflected
in the div F. Affinity of Drugs for Various Tissues, Intracellular
Distribution, Pharmacokinetics, and Metabolism
The diversity in the pharmacological actions of the
drugs known to induce phospholipidosis is also reflected
in the div Distribution, Pharmacokinetics, and Metabolism
The diversity in the pharmacological actions of the
drugs known to induce phospholipidosis is also reflected
in the diversity in uptake, distribution, metabolism, and
excretio The diversity in the pharmacological actions of the
drugs known to induce phospholipidosis is also reflected
in the diversity in uptake, distribution, metabolism, and
excretion of these drugs. There is considerable evidenc drugs known to induce phospholipidosis is also reflecte
in the diversity in uptake, distribution, metabolism, an
excretion of these drugs. There is considerable evidenc
to indicate that pharmacokinetics and metabolism of
d in the diversity in uptake, distribution, metabolism, and
excretion of these drugs. There is considerable evidence
to indicate that pharmacokinetics and metabolism of
drugs play an important role in the etiology of drug-
i excretion of these drugs. There is considerable evidence
to indicate that pharmacokinetics and metabolism of
drugs play an important role in the etiology of drug
induced phospholipidosis. For example, drugs that are
rapidl to indicate that pharmacokinetics and metabolism
drugs play an important role in the etiology of di
induced phospholipidosis. For example, drugs that
rapidly metabolized fail to induce phospholipid
(Joshi and Mehendale, 19 drugs play an important role in the etiology of α induced phospholipidosis. For example, drugs that rapidly metabolized fail to induce phospholipii (Joshi and Mehendale, 1989; Joshi et al., 1989). Fur more, drugs known induced phospholipidosis. For example, drugs that are
rapidly metabolized fail to induce phospholipidosis
(Joshi and Mehendale, 1989; Joshi et al., 1989). Further-
more, drugs known to induce pulmonary phospholipi-
dosis m rapidly metabolized fail to induce phospholipidosis
(Joshi and Mehendale, 1989; Joshi et al., 1989). Further-
more, drugs known to induce pulmonary phospholipi-
dosis may no longer induce phospholipidosis upon en-
hancemen (Joshi and Mehendale, 1989; Joshi et al., 1989). Furthermore, drugs known to induce pulmonary phospholipidosis may no longer induce phospholipidosis upon enhancement of their metabolism by prior administration of agents kn more, drugs known to induce pulmonary phospholipi-
dosis may no longer induce phospholipidosis upon en-
hancement of their metabolism by prior administration
of agents known to induce drug metabolism (Svendsen,
1977; Kacew dosis may no longer induce phospholipidosis upon enhancement of their metabolism by prior administration
of agents known to induce drug metabolism (Svendsen,
1977; Kacew et al., 1981; Kacew and Reasor, 1983).
Likewise, inh hancement of their metabolism by prior administration
of agents known to induce drug metabolism (Svendse
1977; Kacew et al., 1981; Kacew and Reasor, 1983
Likewise, inhibition of metabolism of some drugs ma
result in an inc pholipidosis. 77; Kacew et al., 1981; Kacew and Reasor, 198
kewise, inhibition of metabolism of some drugs n
sult in an increased potential for drug-induced ph
olipidosis.
Various classes of CADs, such as adrenergics, antih
mines, antip Likewise, inhibition of metabolism of some drugs may
result in an increased potential for drug-induced phos-
pholipidosis. Various classes of CADs, such as adrenergics, antihis-
tamines, antipsychotics, antimalarials, morp

result in an increased potential for drug-induced phos-
pholipidosis.
Various classes of CADs, such as adrenergics, antihis-
tamines, antipsychotics, antimalarials, morphine-like
analgesics, synthetic analgesics, anorectic

External of the Magnetian of the Magnetic State
antidepressants, antiarrhythmics, adrenergic blocking shagents, etc. (fig. 1), have been shown to accumulate di EXTERN MODAVANTI AND MODAVANTI AND MODAVANTI AND Antidepressants, antiarrhythmics, adrenergic blocking
agents, etc. (fig. 1), have been shown to accumulate
selectively in the lung with lower concentrations found selectively in the lung with lower concentrations and a
selectively in the lung with lower concentrations found
in the brain, liver, adipose, and other tissues (Brodie et main
the brain, liver, adipose, and other tissues (antidepressants, antiarrhythmics, adrenergic blocking sagents, etc. (fig. 1), have been shown to accumulate oselectively in the lung with lower concentrations found lin the brain, liver, adipose, and other tissues (Brodie antidepressants, antiarrhythmics, adrenergic blocking
agents, etc. (fig. 1), have been shown to accumulate
selectively in the lung with lower concentrations found
in the brain, liver, adipose, and other tissues (Brodie et
 agents, etc. (fig. 1), have been shown to accumulate diselectively in the lung with lower concentrations found H
in the brain, liver, adipose, and other tissues (Brodie et m
al., 1950; Brown, 1974; Philpot et al., 1977; Be selectively in the lung with lower concentrations found
in the brain, liver, adipose, and other tissues (Brodie et
al., 1950; Brown, 1974; Philpot et al., 1977; Bend et al.,
1985). Preferential retention of CADs in the lun al., 1950; Brown, 1974; Philpot et al., 1977; Bend et al., 1985). Preferential retention of CADs in the lung tissue has been attributed to a lower pH of the extravascular space in the lung tissue (Effros and Chinard, 1969; al., 1950; Brown, 1974; Philpot et al., 1977; Bend et 1985). Preferential retention of CADs in the lung tis has been attributed to a lower pH of the extravascuspace in the lung tissue (Effros and Chinard, 1969; Nison et al 1985). Preferential retention of CADs in the lung tissue present that been attributed to a lower pH of the extravascular et space in the lung tissue (Effros and Chinard, 1969; Niel-
son et al., 1981). In recent years, it h has been attributed to a lower pH of the extravascula
space in the lung tissue (Effros and Chinard, 1969; Niel
son et al., 1981). In recent years, it has become increas
ingly evident that CADs have a special affinity for t son et al., 1981). In recent years, it has become increasingly evident that CADs have a special affinity for the neutral and acidic phospholipids which are predominant components of the surfactant in the lung tissue (Notte son et al., 1981). In recent years, it has become increase ingly evident that CADs have a special affinity for the neutral and acidic phospholipids which are predominan components of the surfactant in the lung tissue (Nott ingly evident that CADs have a special affinity for the
neutral and acidic phospholipids which are predominant
components of the surfactant in the lung tissue (Notter
and Finkelstein, 1984; Fisher and Chander, 1985; Roo-
n neutral and acidic phospholipids which are predominant in
components of the surfactant in the lung tissue (Notter or
and Finkelstein, 1984; Fisher and Chander, 1985; Roo-
eney, 1985; Dobbs, 1989; Tierney, 1989; Ruben et al components of the surfactant in the lung tissue (Notter or
and Finkelstein, 1984; Fisher and Chander, 1985; Roo-
ney, 1985; Dobbs, 1989; Tierney, 1989; Ruben et al., cl
1989). This affinity may be associated with the capac and Finkelstein, 1984; Fisher and Chander, 1985; Roomey, 1985; Dobbs, 1989; Tierney, 1989; Ruben et a 1989). This affinity may be associated with the capacitof CADs to bind to phospholipids of the lung. The degree of phosp ney, 1985; Dobbs, 1989; Tierney, 1989; Ruben et
1989). This affinity may be associated with the capac
of CADs to bind to phospholipids of the lung. The deg
of phospholipid binding and the types of binding int
actions have 1989). This affinity may be associated with the capacity
of CADs to bind to phospholipids of the lung. The degree
of phospholipid binding and the types of binding inter-
actions have been studied recently using pure dipalm of CADs to bind to phospholipids of the lung. The degree rol
of phospholipid binding and the types of binding inter-
actions have been studied recently using pure dipalmi-
bitoylphosphatidylcholine vesicles and concentric of phospholipid binding and the types of binding inter-
actions have been studied recently using pure dipalmi-
toylphosphatidylcholine vesicles and concentric lamellar
bodies (Joshi et al., 1988, 1989). A strong correlatio actions have been studied recently using pure dipalm
toylphosphatidylcholine vesicles and concentric lamella
bodies (Joshi et al., 1988, 1989). A strong correlation
possible between the affinity of CADs for the lung tissu
 toylphosphatidylcholine vesicles and conce
bodies (Joshi et al., 1988, 1989). A strong
possible between the affinity of CADs for t
and their binding ability to a major cons
pholipid component of alveolar surfactant
Biotran dies (Joshi et al., 1988, 1989). A strong correlation
ssible between the affinity of CADs for the lung tiss
d their binding ability to a major constitutive ph
olipid component of alveolar surfactant.
Biotransformation of d

possible between the affinity of CADs for the lung tissue aniand their binding ability to a major constitutive phos-
the pholipid component of alveolar surfactant. For Biotransformation of drugs has important implica-
tion and their binding ability to a major constitutive phos-
pholipid component of alveolar surfactant.
Biotransformation of drugs has important implica-
tions for the induction of phospholipidosis. Drugs may
be metabolized to pholipid component of alveolar surfactant.
Biotransformation of drugs has important implications for the induction of phospholipidosis. Drugs ma
be metabolized to products that have a higher propensit
for accumulation in t Biotransformation of drugs has important impl
tions for the induction of phospholipidosis. Drugs i
be metabolized to products that have a higher propen
for accumulation in tissues or, conversely, their a
mulation may be va tions for the induction of phospholipidosis. Drugs may i.e
be metabolized to products that have a higher propensity da
for accumulation in tissues or, conversely, their accu-
mulation may be vastly decreased by biotransfor be metabolized to products that have a higher propensity
for accumulation in tissues or, conversely, their accu-
mulation may be vastly decreased by biotransformation.
The uptake and metabolism of some classic CADs known
t for accumulation in tissues or, conversely, their accumulation may be vastly decreased by biotransformation.
The uptake and metabolism of some classic CADs known
to induce phospholipidosis have been investigated in our
lab mulation may be vastly decreased by biotransformation.
The uptake and metabolism of some classic CADs known
to induce phospholipidosis have been investigated in our
laboratory (Angevine and Mehendale, 1980a,b; Camus
and Me The uptake and metabolism of some classic CADs known
to induce phospholipidosis have been investigated in our
laboratory (Angevine and Mehendale, 1980a,b; Camus la
and Mehendale, 1986; Ohmiya and Mehendale, 1979, ci
1980a, to induce phospholipidosis have been investigated in our dic
laboratory (Angevine and Mehendale, 1980a,b; Camus larged
and Mehendale, 1986; Ohmiya and Mehendale, 1979, cia
1980a,b, 1981, 1982; Young and Mehendale, 1986). I laboratory (Angevine and Mehendale, 1980a,b; Camus
and Mehendale, 1986; Ohmiya and Mehendale, 1979,
1980a,b, 1981, 1982; Young and Mehendale, 1986). It has
been reported that the lung possesses a surprisingly high
capacity and Mehendale, 1986; Ohmiya and Mehendale, 1979, 1980a,b, 1981, 1982; Young and Mehendale, 1986). It has been reported that the lung possesses a surprisingly high capacity for the metabolism of some of the CADs (Brown, 197 1980a,b, 1981, 1982; Young and Mehendale, 1986). It has 1981). Remarkable species variation has been observed
been reported that the lung possesses a surprisingly high in the pulmonary metabolism of imipramine and chlor-
c been reported that the lung possesses a surprisingly high capacity for the metabolism of some of the CADs (Brown 1974; Ohmiya and Mehendale, 1980a,b, 1981, 1982). Iso lated, perfused, and ventilated lung preparations have capacity for the metabolism of some of the CADs (Brown, proved 1974; Ohmiya and Mehendale, 1980a,b, 1981, 1982). Iso-
lated, perfused, and ventilated lung preparations have an been extensively used to study the uptake, met 1974; Ohmiya and Mehendale, 1980a,b, 1981, 1982). Iso-
lated, perfused, and ventilated lung preparations have
been extensively used to study the uptake, metabolism, the
and affinity of CADs for this organ. Chlorpromazine lated, perfused, and ventilated lung preparations have
been extensively used to study the uptake, metabolism,
and affinity of CADs for this organ. Chlorpromazine is
rapidly taken up by the isolated perfused lung with a
sub been extensively used to study the uptake, metabolism, these and affinity of CADs for this organ. Chlorpromazine is end rapidly taken up by the isolated perfused lung with a and subsequent elimination of the nitrogen oxide and affinity of CADs for this organ. Chlorpromazine is encorrapidly taken up by the isolated perfused lung with a and subsequent elimination of the nitrogen oxide metabolite N-cin the perfusate, indicating that the lung is rapidly taken up by the isolated perfused lung with a subsequent elimination of the nitrogen oxide metabolite
in the perfusate, indicating that the lung is able to
metabolize and rid itself of chlorpromazine (Ohmiya and
Me subsequent elimination of the nitrogen oxide metabolite N
in the perfusate, indicating that the lung is able to m
metabolize and rid itself of chlorpromazine (Ohmiya and fi
Mehendale, 1982). These observations are consiste in the perfusate, indicating that the lung is able to metabolize and rid itself of chlorpromazine (Ohmiya and Mehendale, 1982). These observations are consistent with the lack of phospholipidosis-inducing potency of chlorp 1984). ehendale, 1982). These observations are consisth the lack of phospholipidosis-inducing potence lorpromazine in vivo (Lullmann et al., 1978; Hru 84).
Although in vivo acute administration of ³⁵S-chlor azine indicates that with the lack of phospholipidosis-inducing potency
chlorpromazine in vivo (Lullmann et al., 1978; Hrub
1984).
Although in vivo acute administration of ³⁵S-chlorp
mazine indicates that the drug is preferentially accun
lat

chlorpromazine in vivo (Lullmann et al., 1978; Hruban, 1984).

Although in vivo acute administration of ³⁵S-chlorpro-

mazine indicates that the drug is preferentially accumu-

lated in the lung tissue of rats (Hackman e 1984).

Although in vivo acute administration of ^{36}S -chlorpro-

mazine indicates that the drug is preferentially accumu-

lated in the lung tissue of rats (Hackman et al., 1970;

Bickel et al., 1983), in vivo phosphol mazine indicates that the drug is preferentially accumu-
lated in the lung tissue of rats (Hackman et al., 1970; (Drenckhahn et al., 1976; Lullmann et al., 1978; Hruban,
Bickel et al., 1983), in vivo phospholipidosis is mi mazine indicates that the drug is preferentially accumu-
lated in the lung tissue of rats (Hackman et al., 1970; (D
Bickel et al., 1983), in vivo phospholipidosis is minimal 19
because of extensive nitrogen oxidation of th lated in the lung tissue of rats (Hackman et al., 1970
Bickel et al., 1983), in vivo phospholipidosis is minima
because of extensive nitrogen oxidation of this compound
by the lung and because of the loss of affinity of th Bickel et al., 1983), in vivo phospholipidosis is minimal
because of extensive nitrogen oxidation of this compound
by the lung and because of the loss of affinity of the
metabolite for the lung tissue (Ohmiya and Mehendale because of extensive nitrogen oxidation of this compound
by the lung and because of the loss of affinity of the duc
metabolite for the lung tissue (Ohmiya and Mehendale, Kao
1980a, 1982; Beckett et al., 1988). Consistently

show phospholipidosis-like alterations when exposed to MEHENDALE
show phospholipidosis-like alterations when exposed to
drugs (Drenckhahn et al., 1976; Lullmann et al., 1978;
Hruban, 1984). In humans receiving chlorpromazine, two MEHENDALE
show phospholipidosis-like alterations when exposed to
drugs (Drenckhahn et al., 1976; Lullmann et al., 1978;
Hruban, 1984). In humans receiving chlorpromazine, two
major metabolites have been detected, one is de show phospholipidosis-like alterations when expose
drugs (Drenckhahn et al., 1976; Lullmann et al., 1
Hruban, 1984). In humans receiving chlorpromazine,
major metabolites have been detected, one is dehalog
ated and the oth show phospholipidosis-like alterations when exposed to
drugs (Drenckhahn et al., 1976; Lullmann et al., 1978;
Hruban, 1984). In humans receiving chlorpromazine, two
major metabolites have been detected, one is dehalogen-
a drugs (Drenckhahn et al., 1976; Lullmann et al., 1978; Hruban, 1984). In humans receiving chlorpromazine, two major metabolites have been detected, one is dehalogenated and the other is the nitrogen oxide form, in which pr Hruban, 1984). In humans receiving chlorpromazine, two
major metabolites have been detected, one is dehalogen-
ated and the other is the nitrogen oxide form, in which
promazine is a major metabolite in the plasma (Sgaragli major metabolites have been detected, one is dehalogen-
ated and the other is the nitrogen oxide form, in which
promazine is a major metabolite in the plasma (Sgaragli
et al., 1986). Thus, a lack of pulmonary retention due promazine is a major metabolite in the plasma (Sgaragli et al., 1986). Thus, a lack of pulmonary retention due to nitrogen oxidation and dehalogenation appears to explain the lack of significant pulmonary toxicity seen aft nitrogen oxidation and dehalogenation appears to explain the lack of significant pulmonary toxicity seen after
long-term chlorpromazine treatment. Reductive dechlor-
ination of chloramphenicol by rat liver microsomes also et al., 1986). Thus, a lack of pulmonary retention due to
nitrogen oxidation and dehalogenation appears to ex-
plain the lack of significant pulmonary toxicity seen after
long-term chlorpromazine treatment. Reductive dechl nitrogen oxidation and dehalogenation appears to explain the lack of significant pulmonary toxicity seen after long-term chlorpromazine treatment. Reductive dechlorination of chloramphenicol by rat liver microsomes also oc plain the lack of significant pulmonary toxicity seen after
long-term chlorpromazine treatment. Reductive dechlor-
ination of chloramphenicol by rat liver microsomes also
occurs (Morris et al., 1983). Experiments in which long-term chlorpromazine treatment. Reductive dechlor-
ination of chloramphenicol by rat liver microsomes also
occurs (Morris et al., 1983). Experiments in which the
effects of inhibitors of metabolism on the ability of
ch ination of chloramphenicol by rat liver microsomes also
occurs (Morris et al., 1983). Experiments in which the
effects of inhibitors of metabolism on the ability of
chlorpromazine to induce phospholipidosis are evaluated
w occurs (Morris et al., 1983). Experiments in which the effects of inhibitors of metabolism on the ability of chlorpromazine to induce phospholipidosis are evaluated will be of considerable importance in understanding the r effects of inhibitors of metabolism on the ability
chlorpromazine to induce phospholipidosis are evalue
will be of considerable importance in understanding
role of drug metabolism in phospholipidosis. This
proach has not b chlorpromazine to induce phospholipidosis are evaluated
will be of considerable importance in understanding the
role of drug metabolism in phospholipidosis. This ap-
proach has not been attempted because of the unavaila-
b will be of considerable importance in understanding the role of drug metabolism in phospholipidosis. This approach has not been attempted because of the unavailability of a specific inhibitor of nitrogen oxidation in the l role of drug metabolism in phospholipidosis. This approach has not been attempted because of the unavaila-
bility of a specific inhibitor of nitrogen oxidation in the
lung tissue. Even when such an inhibitor becomes availproach has not been attempted because of the unavaila-
bility of a specific inhibitor of nitrogen oxidation in the
lung tissue. Even when such an inhibitor becomes avail-
able, it should be devoid of toxic effects in the t bility of a specific inhibito
lung tissue. Even when suce
able, it should be devoid
animals as well as any und
the drug and the inhibitor.
Extensive nitrogen oxids ng tissue. Even when such an inhibitor becomes avail-
le, it should be devoid of toxic effects in the test
imals as well as any undesirable interactions between
e drug and the inhibitor.
Extensive nitrogen oxidation of imi

able, it should be devoid of toxic effects in the tanimals as well as any undesirable interactions betwe the drug and the inhibitor.
Extensive nitrogen oxidation of imipramine by the r
lung is catalyzed by a flavin-contain i.e., the same well as any undesirable interactions between
the drug and the inhibitor.
Extensive nitrogen oxidation of imipramine by the rat
lung is catalyzed by a flavin-containing monooxygenase,
i.e., the same enzyme re the drug and the inhibitor.

Extensive nitrogen oxidation of imipramine by the ra

lung is catalyzed by a flavin-containing monooxygenase

i.e., the same enzyme responsible for the nitrogen oxid

dation of chlorpromazine (Extensive nitrogen oxidation of imipramine by the lung is catalyzed by a flavin-containing monooxygena
i.e., the same enzyme responsible for the nitrogen of
dation of chlorpromazine (Ohmiya and Mehenda
1980b, 1981). The fo lung is catalyzed by a flavin-containing monooxygenase,
i.e., the same enzyme responsible for the nitrogen oxi-
dation of chlorpromazine (Ohmiya and Mehendale,
1980b, 1981). The formation of a nitrogen oxide metab-
olite w i.e., the same enzyme responsible for the nitrogen oxidation of chlorpromazine (Ohmiya and Mehendale, 1980b, 1981). The formation of a nitrogen oxide metabolite was not inhibited by classic cytochrome P-450 inhibitors such dation of chlorpromazine (Ohmiya and Mehendale,
1980b, 1981). The formation of a nitrogen oxide metab-
olite was not inhibited by classic cytochrome P-450 in-
hibitors such as SKF-525A and piperonyl butoxide, in-
dicating 1980b, 1981). The formation of a nitrogen oxide metabolite was not inhibited by classic cytochrome P-450 in hibitors such as SKF-525A and piperonyl butoxide, in dicating that there is a flavin monooxygenase present is larg hibitors such as SKF-525A and piperonyl butoxide, in-
dicating that there is a flavin monooxygenase present in
large quantity in the lung microsomes that is not asso-
ciated with cytochrome P-450 (Ohmiya and Mehendale, **1981). Remarkable species variation has been observed** dicating that there is a flavin monooxygenase present large quantity in the lung microsomes that is not associated with cytochrome P-450 (Ohmiya and Mehendal 1981). Remarkable species variation has been observe in the pulm large quantity in the lung microsomes that is not associated with cytochrome P-450 (Ohmiya and Mehendale, 1981). Remarkable species variation has been observed in the pulmonary metabolism of imipramine and chlor-promazine ciated with cytochrome P-450 (Ohmiya and Mehendale,
1981). Remarkable species variation has been observed
in the pulmonary metabolism of imipramine and chlor-
promazine (Drew et al., 1981). Rabbit lungs have minimal
capaci 1981). Remarkable species variation has been observed
in the pulmonary metabolism of imipramine and chlor-
promazine (Drew et al., 1981). Rabbit lungs have minimal
capacity to form the nitrogen oxide from imipramine
and ch in the pulmonary metabolism of imipramine and chloupromazine (Drew et al., 1981). Rabbit lungs have minima capacity to form the nitrogen oxide from imipramine and chlorpromazine, whereas rat lungs can metabolize these drug promazine (Drew et al., 1981). Rabbit lungs have minimal capacity to form the nitrogen oxide from imipramine and chlorpromazine, whereas rat lungs can metabolize these drugs to their nitrogen oxide (Ohmiya and Mehendale, 1 capacity to form the nitrogen oxide from imipramine
and chlorpromazine, whereas rat lungs can metabolize
these drugs to their nitrogen oxide (Ohmiya and Meh-
endale, 1980b, 1981). On the other hand, both rabbit
and rat lun endale, 1980b, 1981). On the other hand, both rabbit
and rat lungs possess the capacity to oxidize nitrogen,
N-dimethylaniline, a reaction that is mediated by a flavin
monooxygenase (Ohmiya and Mehendale, 1980b). These these drugs to their nitrogen oxide (Ohmiya and Mehendale, 1980b, 1981). On the other hand, both rabbit
and rat lungs possess the capacity to oxidize nitrogen,
N-dimethylaniline, a reaction that is mediated by a flavin
mon endale, 1980b, 1981). On the other hand, both rabbit
and rat lungs possess the capacity to oxidize nitrogen,
N-dimethylaniline, a reaction that is mediated by a flavin
monooxygenase (Ohmiya and Mehendale, 1980b). These
fin and rat lungs possess the capacity to oxidize nitrogen,

N-dimethylaniline, a reaction that is mediated by a flavin

monooxygenase (Ohmiya and Mehendale, 1980b). These

findings suggest the presence of more than one form o N-dimethylaniline, a reaction that is mediated by a flavin
monooxygenase (Ohmiya and Mehendale, 1980b). These
findings suggest the presence of more than one form of
flavin monooxygenase in the rat lung and only one in
the monooxygenase (Ohmiya and Mehendale, 1980b). These
findings suggest the presence of more than one form of
flavin monooxygenase in the rat lung and only one in
the rabbit lung. Nitrogen oxides lack an affinity for lung
or o findings suggest the presence of more than one form of
flavin monooxygenase in the rat lung and only one in
the rabbit lung. Nitrogen oxides lack an affinity for lung
or other tissues and are ultimately eliminated from the flavin monooxygenase in the rat lung and only or
the rabbit lung. Nitrogen oxides lack an affinity for
or other tissues and are ultimately eliminated from
body. The explanation for the inability of imiprai
and chlorpromazi the rabbit lung. Nitrogen oxides lack an affinity for lung
or other tissues and are ultimately eliminated from the
body. The explanation for the inability of imipramine
and chlorpromazine to produce extensive phospholipi-
 or other tissues and are ultimately eliminated from the body. The explanation for the inability of imipramine and chlorpromazine to produce extensive phospholipidosis in vivo is their extensive metabolic elimination (Drenc body. The explanation for the inaband chlorpromazine to produce ext
dosis in vivo is their extensive me
(Drenckhahn et al., 1976; Lullmann
1984; Joshi and Mehendale, 1989).
The importance of metabolism c d chlorpromazine to produce extensive phospholisis in vivo is their extensive metabolic eliminat
brenckhahn et al., 1976; Lullmann et al., 1978; Hrub
84; Joshi and Mehendale, 1989).
The importance of metabolism of drugs in

dosis in vivo is their extensive metabolic elimination
(Drenckhahn et al., 1976; Lullmann et al., 1978; Hruban,
1984; Joshi and Mehendale, 1989).
The importance of metabolism of drugs in drug-in-
duced phospholipidosis als (Drenckhahn et al., 1976; Lullmann et al., 1978; Hruban, 1984; Joshi and Mehendale, 1989).
The importance of metabolism of drugs in drug-in-
duced phospholipidosis also has been demonstrated by
Kacew, Reasor, and other inv 1984; Joshi and Mehendale, 1989).
The importance of metabolism of drugs in drug-in-
duced phospholipidosis also has been demonstrated by
Kacew, Reasor, and other investigators (Svendsen, 1977;
Kacew et al., 1981; Kacew and The importance of metabolism of drugs in drug-in-
duced phospholipidosis also has been demonstrated by
Kacew, Reasor, and other investigators (Svendsen, 1977;
Kacew et al., 1981; Kacew and Reasor, 1983). They
demonstrated

PHARMACOLOGICAL REVIEWS

aspet

DRUG-INDUCI
lipidosis can be controlled or decreased by the simul
neous treatment with phenobarbital, a well-known DRUG-INDUCED P
lipidosis can be controlled or decreased by the simulta-
neous treatment with phenobarbital, a well-known in-
ducer of drug-metabolizing enzymes. The significantly DRUG-INDUCED PH
lipidosis can be controlled or decreased by the simulta-
neous treatment with phenobarbital, a well-known in-
ducer of drug-metabolizing enzymes. The significantly
decreased phospholipidosis was associated lipidosis can be controlled or decreased by the simulta-
neous treatment with phenobarbital, a well-known in-
ducer of drug-metabolizing enzymes. The significantly de
decreased phospholipidosis was associated with a marked lipidosis can be controlled or decreased by the simulta-
neous treatment with phenobarbital, a well-known in-
ducer of drug-metabolizing enzymes. The significantly
decreased phospholipidosis was associated with a marked
in neous treatment with phenobarbital, a well-known in-lation
ducer of drug-metabolizing enzymes. The significantly dosidecreased phospholipidosis was associated with a marked N
increase in drug-metabolizing capacity (Kacew e ducer of drug-metabolizing enzymes. The significantly decreased phospholipidosis was associated with a marked increase in drug-metabolizing capacity (Kacew et al., 1963). Chlorphentermine has been demonstrated to undergo m decreased phospholipidosis was associated with a marked
increase in drug-metabolizing capacity (Kacew et al., p
1981). Chlorphentermine has been demonstrated to m
undergo minimal metabolism (Dubnick et al., 1963, 1968; p
L increase in drug-metabolizing capacity (Kacew et al. 1981). Chlorphentermine has been demonstrated tundergo minimal metabolism (Dubnick et al., 1963, 1963). Lullmann et al., 1973). Presumably, the enhancement of the metabo 1981). Chlorphentermine has been demonstrated to rundergo minimal metabolism (Dubnick et al., 1963, 1968; ILullmann et al., 1973). Presumably, the enhancement of (the metabolism of chlorphentermine and, consequently, It i undergo minimal metabolism (Dubnick et al., 1963, 1968;
Lullmann et al., 1973). Presumably, the enhancement of
the metabolism of chlorphentermine and, consequently,
its accelerated elimination from the body are implicated
 Illmann et al., 1973). Presumably, the enhancement of (G

e metabolism of chlorphentermine and, consequently, pr

accelerated elimination from the body are implicated

the mechanisms in this respect (Kacew et al., 1981).

the metabolism of chlorphentermine and, consequently, profits accelerated elimination from the body are implicated tigally as the mechanisms in this respect (Kacew et al., 1981). Is a Some CADs produce lipophilic metabolit as the mechanisms in this respect (Kacew et al., 1981). is a Some CADs produce lipophilic metabolites that have Prothe same affinity for the tissue as the parent drugs and wit also produce phospholipidosis (Holt et al., 19 Some CADs produce lipophilic metabolites that have
the same affinity for the tissue as the parent drugs and
also produce phospholipidosis (Holt et al., 1983; Adams
et al., 1985; Camus and Mehendale, 1986; Young and
Mehenda the same affinity for the tissue as the parent drugs and
also produce phospholipidosis (Holt et al., 1983; Adams
et al., 1985; Camus and Mehendale, 1986; Young and
Mehendale, 1986, 1987). Two such drugs have been ex-
tensi also produce phospholipidosis (Holt et al., 1983; Adams is
et al., 1985; Camus and Mehendale, 1986; Young and ⁸⁴
Mehendale, 1986, 1987). Two such drugs have been ex-
tensively studied. Nor-chlorcyclizine is a nonpolar me et al., 1985; Camus and Mehendale, 1986; Young and server high Mehendale, 1986, 1987). Two such drugs have been ex-
tensively studied. Nor-chlorcyclizine is a nonpolar me-
tabolite of chlorcyclizine that has a similar affi Mehendale, 1986, 1987). Two such drugs have been ex-
tensively studied. Nor-chlorcyclizine is a nonpolar me-
tabolite of chlorcyclizine that has a similar affinity for
the lung tissue and induces phospholipidosis similar t tensively studied. Nor-chlorcyclizine is a nonpolar metabolite of chlorcyclizine that has a similar affinity for the lung tissue and induces phospholipidosis similar to light that produced by chlorcyclizine (Kuntzman et al tabolite of chlorcyclizine that has a similar affinity for
the lung tissue and induces phospholipidosis similar to
that produced by chlorcyclizine (Kuntzman et al., 1965;
Hruban et al., 1973; Blohm, 1979; Reasor, 1989). T the lung tissue and induces phospholipidosis similar to
that produced by chlorcyclizine (Kuntzman et al., 1965;
Hruban et al., 1973; Blohm, 1979; Reasor, 1989). The
other drug that is of current clinical concern regarding
 Hruban et al., 1973; Blohm, 1979; Reasor, 1989). The other drug that is of current clinical concern regarding its pulmonary toxicity is amiodarone (Mason, 1987; Myers et al., 1987; Martin and Rosenow, 1988a,b; Vrobel et al Hruban et al., 1973; Blohm, 1979; Reasor, 1989)
other drug that is of current clinical concern regits
pulmonary toxicity is amiodarone (Mason,
Myers et al., 1987; Martin and Rosenow, 1988a,b;
et al., 1989). The principal m other drug that is of current clinical concern regarding
its pulmonary toxicity is amiodarone (Mason, 1987
Myers et al., 1987; Martin and Rosenow, 1988a,b; Vrobe
et al., 1989). The principal metabolite, desethylamioda
rone its pulmonary toxicity is amiodarone (Mason, 1987; Myers et al., 1987; Martin and Rosenow, 1988a,b; Vrobel et al., 1989). The principal metabolite, desethylamioda-
rone, formed mainly in the liver (Young and Mehendale, 198 Myers et al., 1987; Martin and Rosenow, 1988a,b; Vrobel
et al., 1989). The principal metabolite, desethylamioda-
rone, formed mainly in the liver (Young and Mehendale,
1986), possesses greater affinity for the lung tissue et al., 1989). The principal metabolite, desethylamioda-
rone, formed mainly in the liver (Young and Mehendale,
1986), possesses greater affinity for the lung tissue (Ca-A.
mus and Mehendale, 1986) and is capable of greate rone, formed mainly in the liver (Young and Mehendale, 1986), possesses greater affinity for the lung tissue (Camus and Mehendale, 1986) and is capable of greater *toxicity* (Kodavanti and Mehendale, 1991); it also is a st 1986), possesses greater affinity for the lung tissue (Camus and Mehendale, 1986) and is capable of greater toxicity (Kodavanti and Mehendale, 1991); it also is a stronger inducer of pulmonary phospholipidosis (Camus and M us and Mehendale, 1986) and is capable of greater
xicity (Kodavanti and Mehendale, 1991); it also is a
conger inducer of pulmonary phospholipidosis (Camus
d Mehendale, 1986; Kodavanti and Mehendale, 1991).
Typically, it is

toxicity (Kodavanti and Mehendale, 1991); it also is a
stronger inducer of pulmonary phospholipidosis (Camu
and Mehendale, 1986; Kodavanti and Mehendale, 1991)
Typically, it is believed that chlorinated drugs posses
a high stronger inducer of pulmonary phospholipidosis (Camus
and Mehendale, 1986; Kodavanti and Mehendale, 1991).
Typically, it is believed that chlorinated drugs possess
a high capacity for accumulation in the lung when com-
par and Mehendale, 1986; Kodavanti and Mehendale, 1991).
Typically, it is believed that chlorinated drugs possess
a high capacity for accumulation in the lung when com-
pared to nonchlorinated congeners (Kuntzman et al.,
1965; Typically, it is believed that chlorinated drugs possess
a high capacity for accumulation in the lung when com-
pared to nonchlorinated congeners (Kuntzman et al.,
1965; Brown, 1974; Morita and Mehendale, 1983b). Also,
ar pared to nonchlorinated congeners (Kuntzman et al., 1965; Brown, 1974; Morita and Mehendale, 1983b). Also, aromatic p-chlorination of some CADs blocks the much favored p-hydroxylation (Brown, 1974). p-Chlorination pared to nonchlorinated congeners (Kuntzman et al., 1965; Brown, 1974; Morita and Mehendale, 1983b). Also, aromatic *p*-chlorination of some CADs blocks the much favored *p*-hydroxylation (Brown, 1974). *p*-Chlorination ma 1965; Brown, 1974; Morita and Mehendale, 1983b). Also,
aromatic p-chlorination of some CADs blocks the much
favored p-hydroxylation (Brown, 1974). p-Chlorination
may also affect other pathways of metabolism. For ex-
ample, aromatic p-chlorination of some CADs blocks the much
favored p-hydroxylation (Brown, 1974). p-Chlorination
may also affect other pathways of metabolism. For ex-
ample, Kruger et al. (1986) reported that hydroxylation
and d favored p-hydroxylation (Brown, 1974). p-Chlorinationay also affect other pathways of metabolism. For eample, Kruger et al. (1986) reported that hydroxylation and demethylation of imipramine by rat liver microsom were grea ample, Kruger et al. (1986) reported that hydroxylation and demethylation of imipramine by rat liver microsomes were greater than observed for chlorimipramine. Nitrogen oxidation, on the other hand, was more prominent ample, Kruger et al. (1986) reported that hydroxylation the and demethylation of imipramine by rat liver microsomes inture greater than observed for chlorimipramine. Nitrogen oxidation, on the other hand, was more prominen and demethylation of imipramine by rat liver microsomes
were greater than observed for chlorimipramine. Nitro-
gen oxidation, on the other hand, was more prominent
with imipramine than chlorimipramine (Ohmiya and
Mehendale were greater than observed for chlorimipramine. Nitro-
gen oxidation, on the other hand, was more prominent
with imipramine than chlorimipramine (Ohmiya and
Mehendale, 1980b, 1981, 1984; Beckett et al., 1988).
Decreased me gen oxidation, on the other hand, was more prominent
with imipramine than chlorimipramine (Ohmiya and
Mehendale, 1980b, 1981, 1984; Beckett et al., 1988).
Decreased metabolic elimination of chlorimipramine ow-
ing to *p*-c with imipramine than chlorimipramine (Ohmiya and m
Mehendale, 1980b, 1981, 1984; Beckett et al., 1988).
Decreased metabolic elimination of chlorimipramine ow-
ing to p-chlorination might have been expected to in-
crease t Mehendale, 1980b, 1981, 1984; Beckett et al., 1988). 1
Decreased metabolic elimination of chlorimipramine ow-
ing to p-chlorination might have been expected to in-
crease the metabolism of this compound via nitrogen
oxida Decreased metabolic elimination of chlorimipramine owing to p-chlorination might have been expected to increase the metabolism of this compound via nitrogen oxidation. Also, it is important to note that nitrogen oxidation ing to p-chlorination might have been expected to increase the metabolism of this compound via nitrogen (oxidation. Also, it is important to note that nitrogen chloridation may represent the main process of elimination the crease the metabolism of this compound via nitroger oxidation. Also, it is important to note that nitroger oxidation may represent the main process of elimination mot only in the lung but also in the liver (Ohmiya and Mehe oxidation. Also, it is important to note that nitrogen choidation may represent the main process of elimination the not only in the lung but also in the liver (Ohmiya and take Mehendale, 1980b, 1981). As far as chlorinate between may represent the main process of elimination
not only in the lung but also in the liver (Ohmiya and
Mehendale, 1980b, 1981). As far as chlorinated and non-
chlorinated analogs are concerned, little progress has
be not only in the lung but also in the liver (Ohmiya and take Mehendale, 1980b, 1981). As far as chlorinated and non-
chlorinated analogs are concerned, little progress has ied
been made in understanding the structure-activi Mehendale, 1980b, 1981). As far as chlorinated and non-
chlorinated analogs are concerned, little progress has
been made in understanding the structure-activity rela-
tionship of various metabolic processes. More work in
t chlorinated analogs are concerned, little progress has ied
been made in understanding the structure-activity rela-
tionship of various metabolic processes. More work in
the area of metabolism of CADs and an understanding
o

OSPHOLIPIDOSIS 335
the phospholipidosis will help in understanding the re-
lationship between drug metabolism and phospholipi-OSPHOLIPIDOSIS
the phospholipidosis will help in understanding th
lationship between drug metabolism and phospho
dosis. dosis. e phospholipidosis will help in understanding the re-
ionship between drug metabolism and phospholipi-
sis.
Not all drugs known to be taken up in the lung induce
ospholipidosis, although the lung does seem to be a

its accelerated elimination from the body are implicated tigations have revealed that a major portion of this drug
as the mechanisms in this respect (Kacew et al., 1981). is accumulated in human lungs (Geddes et al., 1979) the phospholipidosis will help in understanding the re-
lationship between drug metabolism and phospholipi-
dosis.
Not all drugs known to be taken up in the lung induce
phospholipidosis, although the lung does seem to be a lationship between drug metabolism and phospholipidosis.

Not all drugs known to be taken up in the lung induce

phospholipidosis, although the lung does seem to be a

major organ for uptake and accumulation of CADs. Pro-
 dosis.
Not all drugs known to be taken up in the lung induce
phospholipidosis, although the lung does seem to be a
major organ for uptake and accumulation of CADs. Pro-
pranolol possesses a high affinity for the lung tissu Not all drugs known to be taken up in the lung induphospholipidosis, although the lung does seem to be major organ for uptake and accumulation of CADs. Propranolol possesses a high affinity for the lung tiss (Geddes et al. phospholipidosis, although the lung does seem to be
major organ for uptake and accumulation of CADs. Pr
pranolol possesses a high affinity for the lung tiss
(Geddes et al., 1979), but its phospholipidosis-inducin
property major organ for uptake and accumulation of CADs. Pro-
pranolol possesses a high affinity for the lung tissue
(Geddes et al., 1979), but its phospholipidosis-inducing
property has not been well characterized. Clinical inves pranolol possesses a high affinity for the lung tissue
(Geddes et al., 1979), but its phospholipidosis-inducing
property has not been well characterized. Clinical inves-
tigations have revealed that a major portion of this (Geddes et al., 1979), but its phospholipidosis-inducing
property has not been well characterized. Clinical inves-
tigations have revealed that a major portion of this drug
is accumulated in human lungs (Geddes et al., 197 property has not been well characterized. Clinical investigations have revealed that a major portion of this drug
is accumulated in human lungs (Geddes et al., 1979).
Propranolol uptake by the lung in vitro is competitive
 is accumulated in human lungs (Geddes et al., 1979). is accumulated in human lungs (Geddes et al., 1979).
Propranolol uptake by the lung in vitro is competitive
with other CADs (Dollery and Junod, 1976), and there
is some evidence for an active uptake process (Kornhau-
ser e Propranolol uptake by the lung in vitro is competitive
with other CADs (Dollery and Junod, 1976), and there
is some evidence for an active uptake process (Kornhau-
ser et al., 1980). Alveolar macrophages possess a specific with other CADs (Dollery and Junod, 1976), and there is some evidence for an active uptake process (Kornhauser et al., 1980). Alveolar macrophages possess a specific high affinity for propranolol accumulation and the uptak is some evidence for an active uptake process (Kornh
ser et al., 1980). Alveolar macrophages possess a spec
high affinity for propranolol accumulation and the
take has been noted to be active (Vestal et al., 19:
One may sp ser et al., 1980). Alveolar macrophages possess a specific
high affinity for propranolol accumulation and the up-
take has been noted to be active (Vestal et al., 1980).
One may speculate that propranolol is a weak phospho high affinity for propranolol accumulation and the uptake has been noted to be active (Vestal et al., 1980).
One may speculate that propranolol is a weak phospholipidosis-inducing agent, because this drug has only a weak a take has been noted to be active (Vestal et al., 1980).

One may speculate that propranolol is a weak phosphololipidosis-inducing agent, because this drug has only a

weak affinity for phospholipids (Joshi et al., 1988, 1 One may speculate that propranolol is a weak phospholipidosis-inducing agent, because this drug has only a weak affinity for phospholipids (Joshi et al., 1988, 1989).
Alternatively, propranolol may also undergo metabolism
 lipidosis-inducing agent, because this drug has only a
weak affinity for phospholipids (Joshi et al., 1988, 1989).
Alternatively, propranolol may also undergo metabolism
to produce hydrophilic metabolites, thereby making i weak affinity fo
Alternatively, p
to produce hyd
less effective in
Shetty, 1986). Internal producing phospholipidosis (Nuclear 1986).

II. Consequences of Phospholipidosis

II. Consequences of Phospholipidos

II. Consequences of Phospholipidos

Internal Photophism of Biogenic and F

A. Effects on the Metabolism of Biogenic and Exogenous
A. Effects on the Metabolism of Biogenic and Exogenous
*Amines by Lung A. Effects on the Meta
<i>A. Effects on the Meta
<i>Amines by Lung*
CADs and biogenia

II. Consequences of Phospholipidosis
A. Effects on the Metabolism of Biogenic and Exogenous
Amines by Lung
CADs and biogenic amines share common transport
mechanisms across the cell membrane, and thus, CADs
may interfere w A. Effects on the Metabolism of Biogenic and Exogenous
Amines by Lung
CADs and biogenic amines share common transport
mechanisms across the cell membrane, and thus, CADs
may interfere with the uptake of biogenic amines (Mo may interfere with the uptake of biogenic and Exogenous
Amines by Lung
CADs and biogenic amines share common transport
mechanisms across the cell membrane, and thus, CADs
may interfere with the uptake of biogenic amines (M Antines by Lang

CADs and biogenic amines share common transport

mechanisms across the cell membrane, and thus, CADs

may interfere with the uptake of biogenic amines (Morita

and Mehendale, 1983a,b; Mehendale, 1984; Hart CADs and biogenic amines share common transport
mechanisms across the cell membrane, and thus, CADs
may interfere with the uptake of biogenic amines (Morita
and Mehendale, 1983a,b; Mehendale, 1984; Hart and
Block, 1989). C mechanisms across the cell membrane, and thus, CADs
may interfere with the uptake of biogenic amines (Morita
and Mehendale, 1983a,b; Mehendale, 1984; Hart and
Block, 1989). Clearance of exogenous and endogenous
amines is a may interfere with the uptake of biogenic amines (Morita
and Mehendale, 1983a,b; Mehendale, 1984; Hart and
Block, 1989). Clearance of exogenous and endogenous
amines is a prominent non-respiratory function of the
lung (Gil and Mehendale, 1983a,b; Mehendale, 1984; Hart and
Block, 1989). Clearance of exogenous and endogenous
amines is a prominent non-respiratory function of the
lung (Gillis, 1973; Bakhle and Vane, 1974; Smith et al.,
1974; Gil Block, 1989). Clearance of exogenous and endogenous
amines is a prominent non-respiratory function of the
lung (Gillis, 1973; Bakhle and Vane, 1974; Smith et al.,
1974; Gillis and Roth, 1977; Gillis et al., 1979; Angevine
 amines is a prominent non-respiratory function of the
lung (Gillis, 1973; Bakhle and Vane, 1974; Smith et al.,
1974; Gillis and Roth, 1977; Gillis et al., 1979; Angevine
et al., 1982; Prasada Rao and Mehendale, 1987). The
 lung (Gillis, 1973; Bakhle and Vane, 1974; Smith et al., 1974; Gillis and Roth, 1977; Gillis et al., 1979; Angevine
et al., 1982; Prasada Rao and Mehendale, 1987). The
presence of 5-hydroxytryptamine in the endothelium of
 1974; Gillis and Roth, 1977; Gillis et al., 1979; Angevine
et al., 1982; Prasada Rao and Mehendale, 1987). The
presence of 5-hydroxytryptamine in the endothelium of
the lung may indicate its role in lung physiology. CADs
 et al., 1982; Prasada Rao and Mehendale, 1987). The
presence of 5-hydroxytryptamine in the endothelium of
the lung may indicate its role in lung physiology. CADs
interfere not only with the pulmonary uptake of 5-hy-
droxyt presence of 5-hydroxytryptamine in the endothelium of
the lung may indicate its role in lung physiology. CADs
interfere not only with the pulmonary uptake of 5-hy-
droxytryptamine but also with its metabolism to a non-
rea the lung may indicate its role in lung physiology. CAD:
interfere not only with the pulmonary uptake of 5-hy
droxytryptamine but also with its metabolism to a non
reactive metabolite, 5-hydroxyindole acetic acid, by the
mo interfere not only with the pulmonary uptake of 5-hydroxytryptamine but also with its metabolism to a nor
reactive metabolite, 5-hydroxyindole acetic acid, by th
monoamine oxidase system (Angevine and Mehendale
1980a,b, 19 droxytryptamine but also with its metabolism to a no
reactive metabolite, 5-hydroxyindole acetic acid, by t
monoamine oxidase system (Angevine and Mehenda
1980a,b, 1982; Mehendale et al., 1983; Morita and Me
endale, 1983a, reactive metaboli
monoamine oxid
1980a,b, 1982; M
endale, 1983a,b; l
gomery, 1985b).
Chlorphenterm onoamine oxidase system (Angevine and Mehendale 80a,b, 1982; Mehendale et al., 1983; Morita and Meh
dale, 1983a,b; Mehendale, 1984; Zychlinski and Mont
mery, 1985b).
Chlorphentermine, chlorimipramine, and their non-
lorina 1980a,b, 1982; Mehendale et al., 1983; Morita and Mehendale, 1983a,b; Mehendale, 1984; Zychlinski and Mont-gomery, 1985b).
Chlorphentermine, chlorimipramine, and their non-chlorinated analogs have been systematically studi

endale, 1983a,b; Mehendale, 1984; Zychlinski and Mont-gomery, 1985b).
Chlorphentermine, chlorimipramine, and their non-chlorinated analogs have been systematically studied for
their effect on 5-hydroxytryptamine metabolism gomery, 1985b).
Chlorphentermine, chlorimipramine, and their non-
chlorinated analogs have been systematically studied for
their effect on 5-hydroxytryptamine metabolism and up-
take by lung in vivo and in vitro. The inhib Chlorphentermine, chlorimipramine, and their non
chlorinated analogs have been systematically studied fo
their effect on 5-hydroxytryptamine metabolism and up
take by lung in vivo and in vitro. The inhibition of 5
hydroxyt chlorinated analogs have been systematically studied for
their effect on 5-hydroxytryptamine metabolism and up-
take by lung in vivo and in vitro. The inhibition of 5-
hydroxytryptamine uptake by these drugs has been studtheir effect on 5-hydroxytryptamine metabolism and up-
take by lung in vivo and in vitro. The inhibition of 5-
hydroxytryptamine uptake by these drugs has been stud-
ied using isolated rat and rabbit lungs (Angevine and
Me take by lung in vivo
hydroxytryptamine up
ied using isolated rat
Mehendale, 1983a,b).
Mehendale, 1983a,b).
The presence of chl droxytryptamine uptake by these drugs has been stud-
d using isolated rat and rabbit lungs (Angevine and
ehendale, 1982; Mehendale et al., 1983; Morita and
ehendale, 1983a,b).
The presence of chlorphentermine in the lung, ied using isolated rat and rabbit lungs (Angevine and Mehendale, 1982; Mehendale et al., 1983; Morita and Mehendale, 1983a,b).
The presence of chlorphentermine in the lung, in addition to inducing phospholipidosis, interfe

Example of the Universal of the S386
hydroxytryptamine uptake by the lung (Angevine and upt
Mehendale, 1982; Mehendale et al., 1983). Chlorinated pho Example of the lung (Angevine and hydroxytryptamine uptake by the lung (Angevine and Mehendale, 1982; Mehendale et al., 1983). Chlorinated analogs which are taken up more effectively by the lung EXECUTE AND MI
hydroxytryptamine uptake by the lung (Angevine and upt
Mehendale, 1982; Mehendale et al., 1983). Chlorinated pho
analogs which are taken up more effectively by the lung Me
seem to affect 5-hydroxytryptamine hydroxytryptamine uptake by the lung (Angevine a
Mehendale, 1982; Mehendale et al., 1983). Chlorinat
analogs which are taken up more effectively by the lu
seem to affect 5-hydroxytryptamine transport and mon
amine oxidases hydroxytryptamine uptake by the lung (Angevine and upta
Mehendale, 1982; Mehendale et al., 1983). Chlorinated pho
analogs which are taken up more effectively by the lung Mel
seem to affect 5-hydroxytryptamine transport and Mehendale, 1982; Mehendale et al., 1983). Chlorinated
analogs which are taken up more effectively by the lung
seem to affect 5-hydroxytryptamine transport and mono-
amine oxidases to a greater extent when compared to
nonch analogs which are taken up more effectively by the lu
seem to affect 5-hydroxytryptamine transport and mon
amine oxidases to a greater extent when compared
nonchlorinated drugs (Morita and Mehendale, 1983
Interference of 5 seem to affect 5-hydroxytryptamine transport and mono
amine oxidases to a greater extent when compared t
nonchlorinated drugs (Morita and Mehendale, 1983a)
Interference of 5-hydroxytryptamine uptake and metab
olism by chlo amine oxidases to a greater extent when compared to Theorem incomplomented drugs (Morita and Mehendale, 1983a). leverther interference of 5-hydroxytryptamine uptake and metab-
Chism by chlorphentermine has been shown to be nonchlorinated drugs (Morita and Mehendale, 1983a).
Interference of 5-hydroxytryptamine uptake and metab-
olism by chlorphentermine has been shown to be asso-
ciated with the occurrence of pulmonary hypertension in
patient Interference of 5-hydroxytryptamine uptake and metolism by chlorphentermine has been shown to be assciated with the occurrence of pulmonary hypertension patients receiving this anorexic drug (Lullmann et 1972; Harris and H olism by chlorphentermine has been shown to be asso-
ciated with the occurrence of pulmonary hypertension in
patients receiving this anorexic drug (Lullmann et al., fes
1972; Harris and Heath, 1977). However, there is cont ciated with the occurrence of pulmonary hypertension
patients receiving this anorexic drug (Lullmann et a
1972; Harris and Heath, 1977). However, there is containing the assumption. Also, not all CADs a
known to affect 5-h patients receiving this anorexic drug (Lullmann et a
1972; Harris and Heath, 1977). However, there is contr
versy regarding this assumption. Also, not all CADs a
known to affect 5-hydroxytryptamine uptake and metal
olism i 1972; Harris and Heath, 1977). However, there is controrsy regarding this assumption. Also, not all CADs at known to affect 5-hydroxytryptamine uptake and metallism in the lung. For example, propranolol and chlopromazine w versy regarding this assumption. Also, not all CADs
known to affect 5-hydroxytryptamine uptake and met
olism in the lung. For example, propranolol and chl
promazine were shown to have no effect on the puln
nary clearance o known to affect 5-hydroxytryptamine uptake and metabolism in the lung. For example, propranolol and chlor
promazine were shown to have no effect on the pulmo
nary clearance of 5-hydroxytryptamine and its metabolism (Morita olism in the lung. For example, propranolol and clear
promazine were shown to have no effect on the pul
nary clearance of 5-hydroxytryptamine and its met
lism (Morita and Mehendale, 1983a). Propran
however, has been report promazine were shown to have no effect on the pulmonary clearance of 5-hydroxytryptamine and its metabolism (Morita and Mehendale, 1983a). Propranolol, however, has been reported to interfere with noradrenamary clearance of 5-hydroxytryptamine and its metabo-

lism (Morita and Mehendale, 1983a). Propranolol, al.

however, has been reported to interfere with noradrena-

line uptake by the heart (Foo et al., 1968). Chlorimipra lism (Morita and Mehendale, 1983a). Propranolol, al., however, has been reported to interfere with noradrena-
line uptake by the heart (Foo et al., 1968). Chlorimipra-
mine and chlorgyline affect the regional level of brai however, has been reported to interfere with noradrena-
line uptake by the heart (Foo et al., 1968). Chlorimipra-
mine and chlorgyline affect the regional level of brain
amines and their metabolism after chronic treatment mine and chlorgyline affect the regional level of brain
amines and their metabolism after chronic treatment in
rats (Mousseau and Greenshaw, 1989). Effects of CADs
on serotonin metabolism may influence serotonergic or
adre amines and their metabolism after chronic treatment in
rats (Mousseau and Greenshaw, 1989). Effects of CADs quen
on serotonin metabolism may influence serotonergic or ation
adrenergic control of cellular responses. The eff rats (Mousseau and Greenshaw, 1989). Effects of CADs
on serotonin metabolism may influence serotonergic or
adrenergic control of cellular responses. The effects of
amiodarone and other CADs on serotonergic metabolism
in th studied. amiodarone and other CADs on serotonergic metabolism
in the lung and other organ systems have not been well
studied.
CADs interfere with the uptake of other exogenously
CADs interfere with the uptake of other exogenously
amiodarone and other CADs on serotonergic metabolis
in the lung and other organ systems have not been w
studied.
CADs interfere with the uptake of other exogenous
added amine drugs that are structurally related (Ange
ine e

in the lung and other organ systems have not been well
studied.
CADs interfere with the uptake of other exogenously
added amine drugs that are structurally related (Angev-
ine et al., 1982, 1984; Ohmiya et al., 1983; Koda studied. B.
CADs interfere with the uptake of other exogenously
added amine drugs that are structurally related (Angev-
ine et al., 1982, 1984; Ohmiya et al., 1983; Kodavanti and
Mehendale, 1991). Imipramine and chlorproma CADs interfere with the uptake of other exogenously
added amine drugs that are structurally related (Angev-
ine et al., 1982, 1984; Ohmiya et al., 1983; Kodavanti and
Mehendale, 1991). Imipramine and chlorpromazine have
be added amine drugs that are structurally related (Angevine et al., 1982, 1984; Ohmiya et al., 1983; Kodavanti and
Mehendale, 1991). Imipramine and chlorpromazine have
been demonstrated to displace propranolol from the iso-
 ine et al., 1982, 1984; Ohmiya et al., 1983; Kodavanti and
Mehendale, 1991). Imipramine and chlorpromazine have
been demonstrated to displace propranolol from the iso-
lated perfused rabbit lung (Ohmiya and Mehendale, 1979 Mehendale, 1991). Imipramine and chlorpromazine have
been demonstrated to displace propranolol from the iso-
lated perfused rabbit lung (Ohmiya and Mehendale, 1979;
chlorimipramine and kinetics in the lung were affected by been demonstrated to displace propranolol from the isolated perfused rabbit lung (Ohmiya and Mehendale, 1979;
Ohmiya et al., 1983). Amiodarone displacement and kinetics in the lung were affected by chlorimipramine and
prom lated perfused rabbit lung (Ohmiya and Mehendale, 1979;
Ohmiya et al., 1983). Amiodarone displacement and ki-
netics in the lung were affected by chlorimipramine and
promazine; however, propranolol did not have any effect
 The binding competities and interesting the binding capacities

induced by chlorphentermine affected lung respiratory

Camus et al., 1983). Amiodarone displacement and ki-

promazine; however, propranolol did not have any netics in the lung were affected by chlorimipramine and
promazine; however, propranolol did not have any effect
(Camus et al., 1990). There are several such examples.
Structurally related CADs presumably compete for the
up promazine; however, propranolol did not have any effect (Camus et al., 1990). There are several such examples.
Structurally related CADs presumably compete for the uptake of other drugs by the lung. The binding capacities
 (Camus et al., 1990). There are several such examples.
Structurally related CADs presumably compete for the
uptake of other drugs by the lung. The binding capacities
to phospholipids vary considerably with the individual
 uptake of other drugs by the lung. The binding capacities
to phospholipids vary considerably with the individual
that alveolar filling with macrophages caused this effect
drug (Joshi et al., 1988). The drugs with greater b to phospholipids vary considerably with the individual
drug (Joshi et al., 1988). The drugs with greater binding
and uptake are retained or are able to displace less tightly
bound drugs and vice versa.
Drug-induced phospho phospholipids vary considerably with the individual
ug (Joshi et al., 1988). The drugs with greater binding
d uptake are retained or are able to displace less tightly
und drugs and vice versa.
Drug-induced phospholipidosis

drug (Joshi et al., 1988). The drugs with greater binding
and uptake are retained or are able to displace less tightly
bound drugs and vice versa.
Drug-induced phospholipidosis, on the other hand,
increases the uptake and and uptake are retained or are able to displace less tight
bound drugs and vice versa.
Drug-induced phospholipidosis, on the other han
increases the uptake and affinity of the same or oth
CADs. For example, chlorphentermin bound drugs and vice versa.

Drug-induced phospholipidosis, on the other han

increases the uptake and affinity of the same or oth

CADs. For example, chlorphentermine-induced pho

pholipidosis results in increased uptake Drug-induced phospholipidosis, on the other hand,
increases the uptake and affinity of the same or other
CADs. For example, chlorphentermine-induced phos-
pholipidosis results in increased uptake of other pneu-
mophilic dr increases the uptake and affinity of the same or other and CADs. For example, chlorphentermine-induced phos-
pholipidosis results in increased uptake of other pneu-
mophilic drugs (Angevine et al., 1982; Ohmiya et al., Dan CADs. For example, chlorphentermine-induced phos-
pholipidosis results in increased uptake of other pneu-
mophilic drugs (Angevine et al., 1982; Ohmiya et al.,
1983). Recent observations of amiodarone uptake in
amiodaronepholipidosis results in increased uptake of other prophilic drugs (Angevine et al., 1982; Ohmiya et 1983). Recent observations of amiodarone uptake amiodarone-induced phospholipidosis also indicate hanced accumulation of a mophilic drugs (Angevine et al., 1982; Ohmiya et a
1983). Recent observations of amiodarone uptake is
amiodarone-induced phospholipidosis also indicate en
hanced accumulation of amiodarone during phosphol
pidosis (Kodavant 1983). Recent observations of amiodarone uptake in
amiodarone-induced phospholipidosis also indicate en-
hanced accumulation of amiodarone during phospholi-
pidosis (Kodavanti and Mehendale, 1991). When amio-
darone-induce amiodarone-induced phospholipidosis also indicate en-
hanced accumulation of amiodarone during phospholi-
pidosis (Kodavanti and Mehendale, 1991). When amio-
darone-induced phospholipidosis was not prominently
manifested a hanced accumulation of amiodarone during phospholi-
pidosis (Kodavanti and Mehendale, 1991). When amio-
darone-induced phospholipidosis was not prominently re
manifested after 2 days of treatment, there was no in-
ficreas pidosis (Kodavanti and Mehendale, 1991). When amio-
darone-induced phospholipidosis was not prominently
manifested after 2 days of treatment, there was no in-
crease in [¹⁴C]amiodarone sequestration by the perfused
lung

MEHENDALE
uptake was increased in the isolated perfused lung when
phospholipidosis became prominent (Kodavanti and MEHENDALE
uptake was increased in the isolated perfused lung when
phospholipidosis became prominent (Kodavanti and
Mehendale, 1991) upon continuation of amiodarone MEHENDALE
uptake was increased in the isolated perfused lung when
phospholipidosis became prominent (Kodavanti and
Mehendale, 1991) upon continuation of amiodarone
treatment. treatment. take was increased in the isolated perfused lung when
nospholipidosis became prominent (Kodavanti and
ehendale, 1991) upon continuation of amiodarone
atment.
These studies indicate that increased phospholipid
vels increase

phospholipidosis became prominent (Kodavanti and Mehendale, 1991) upon continuation of amiodarone treatment.
These studies indicate that increased phospholipid
levels increase the affinity of drugs for the lung tissue.
Two Mehendale, 1991) upon continuation of amiodar
treatment.
These studies indicate that increased phospholi
levels increase the affinity of drugs for the lung tiss
Two possibilities can be suggested. First, the phosp
lipid-dr treatment.

These studies indicate that increased phospholipid

levels increase the affinity of drugs for the lung tissue.

Two possibilities can be suggested. First, the phospho-

lipid-drug binding during phospholipidosi These studies indicate that increased phospholip
levels increase the affinity of drugs for the lung tissu
Two possibilities can be suggested. First, the phosph
lipid-drug binding during phospholipidosis induction
need not Two possibilities can be suggested. First, the phospholipid-drug binding during phospholipidosis induction need not be saturated for phospholipidosis to be manifested. Second, the increase in phospholipids of the mem-brane Two possibilities can be suggested. First, the phospholipid-drug binding during phospholipidosis induction need not be saturated for phospholipidosis to be manifested. Second, the increase in phospholipids of the membranes fested. Second, the increase in phospholipids of the membranes may result in sufficient membrane alterations to open up additional binding sites for the drug. Chlorphentermine-induced pulmonary phospholipidosis not only need not be saturated for phospholipidosis to be manifested. Second, the increase in phospholipids of the membranes may result in sufficient membrane alterations to open up additional binding sites for the drug. Chlorphent fested. Second, the increase in phospholipids of the membranes may result in sufficient membrane alterations to open up additional binding sites for the drug. Chlorphentermine-induced pulmonary phospholipidosis not only in branes may result in sufficient membrane alteration
open up additional binding sites for the drug. Chlorp
termine-induced pulmonary phospholipidosis not
increased the uptake of chlorphentermine but also
creased the uptake open up additional binding sites for the drug. Chlorphentermine-induced pulmonary phospholipidosis not only increased the uptake of chlorphentermine but also increased the uptake of other CADs such as chlorpromazine and im increased the uptake of chlorphentermine but also increased the uptake of other CADs such as chlorpromazine and imipramine (Ohmiya et al., 1983; Angevine et al., 1984).
These observations have important clinical implicacreased the uptake of chlorphentermine but also
beased the uptake of other CADs such as chlorpron
ne and imipramine (Ohmiya et al., 1983; Angevine
, 1984).
These observations have important clinical impli
ons because drug-

mine and chlorgyline affect the regional level of brain can be predicted to result in an enhanced pulmonary
amines and their metabolism after chronic treatment in
rats (Mousseau and Greenshaw, 1989). Effects of CADs quenc creased the uptake of other CADs such as chlorproma-
zine and imipramine (Ohmiya et al., 1983; Angevine et
al., 1984).
These observations have important clinical implica-
tions because drug-induced pulmonary phospholipidos zine and imipramine (Ohmiya et al., 1983; Angevine et al., 1984).

These observations have important clinical implica-

tions because drug-induced pulmonary phospholipidosis

can be predicted to result in an enhanced pulmo al., 1984).
These observations have important clinical implica-
tions because drug-induced pulmonary phospholipidosis
can be predicted to result in an enhanced pulmonary
sequestration of other pneumophilic drugs. Such a se These observations have important clinical implitions because drug-induced pulmonary phospholipido
can be predicted to result in an enhanced pulmons
sequestration of other pneumophilic drugs. Such a
quence of events would tions because drug-induced pulmonary phospholipidosis
can be predicted to result in an enhanced pulmonary
sequestration of other pneumophilic drugs. Such a se-
quence of events would potentially result in an acceler-
ation can be predicted to result in an enhanced pulmonary
sequestration of other pneumophilic drugs. Such a sequence of events would potentially result in an acceler-
ation of compromised non-respiratory and, possibly, res-
pira quence of events would potentially result in an accelerquence of events w
ation of compromis
piratory functions.
be carried out to une
pholipids in vivo.
B. Effects on Besnit Action of compromised non-respiratory and, possibly,
piratory functions. Clearly, many investigations need
be carried out to understand drug interactions with pl
pholipids in vivo.
B. Effects on Respiratory Functions of th

Pulmonary affinity for CADs and induction of phospholipids in vivo.

B. Effects on Respiratory Functions of the Lung

Pulmonary affinity for CADs and induction of phos-

pholipidosis have been well studied in the lung. However,

the extent to which respiratory function i B. Effects on Respiratory Functions of the Lung
Pulmonary affinity for CADs and induction of phos-
pholipidosis have been well studied in the lung. However,
the extent to which respiratory function is compromised
has not b B. Effects on Respiratory Functions of the Lung
Pulmonary affinity for CADs and induction of phos-
pholipidosis have been well studied in the lung. However,
the extent to which respiratory function is compromised
has not b pholipidosis have been well studied in the lung. However,
the extent to which respiratory function is compromised
has not been extensively examined. A systematic study
was carried out to investigate whether phospholipidosi pholipidosis have been well studied in the lung. However,
the extent to which respiratory function is compromised
has not been extensively examined. A systematic study
was carried out to investigate whether phospholipidosi the extent to which respiratory function is compromis
has not been extensively examined. A systematic stu
was carried out to investigate whether phospholipidor
induced by chlorphentermine affected lung respirato
functions has not been extensively examined. A systematic study was carried out to investigate whether phospholipidosis induced by chlorphentermine affected lung respiratory functions (Camus et al., 1989). Despite a massive inductio was carried out to investigate whether phospholipidosis
induced by chlorphentermine affected lung respiratory
functions (Camus et al., 1989). Despite a massive induc-
tion of phospholipidosis by chlorphentermine, only mi-
 induced by chlorphentermine affected lung respiratory
functions (Camus et al., 1989). Despite a massive induc-
tion of phospholipidosis by chlorphentermine, only mi-
nor effects were observed on lung mechanics. The only
ma tion of phospholipidosis by chlorphentermine, only minor effects were observed on lung mechanics. The only marginal effect evident was a slightly compromised recoil pressure in the lung. However, the effect on recoil press nor effects were observed on lung mechanics. The only marginal effect evident was a slightly compromised recoil pressure in the lung. However, the effect on recoil pressure was abolished in histeresis experiments, indicati marginal effect evident was a slightly compromised recoil

Amiodarone-induced pulmonary dysfunction with resure was abolished in histeresis experiments, indicating
that alveolar filling with macrophages caused this effec
(Camus et al., 1989).
Amiodarone-induced pulmonary dysfunction with re
strictive type changes has been assoc that alveolar filling with macrophages caused this effect
(Camus et al., 1989).
Amiodarone-induced pulmonary dysfunction with re-
strictive type changes has been associated with a mod-
erate decrease in the percentage of p (Camus et al., 1989).
Amiodarone-induced pulmonary dysfunction with restrictive type changes has been associated with a moderate decrease in the percentage of predicted forced vital
and total lung capacities (Marchlinski e Amiodarone-induced pulmonary dysfunction with restrictive type changes has been associated with a moderate decrease in the percentage of predicted forced vital and total lung capacities (Marchlinski et al., 1982; Veltri an strictive type changes has been associated with a moderate decrease in the percentage of predicted forced vital
and total lung capacities (Marchlinski et al., 1982; Veltri
and Reid, 1985). Amiodarone treatment predisposes
 erate decrease in the percentage of predicted forced vital
and total lung capacities (Marchlinski et al., 1982; Veltri
and Reid, 1985). Amiodarone treatment predisposes
hamsters to pulmonary fibrosis (Cantor et al., 1984;
 and total lung capacities (Marchlinski et al., 1982; Veltri
and Reid, 1985). Amiodarone treatment predisposes
hamsters to pulmonary fibrosis (Cantor et al., 1984;
Daniels et al., 1989). The pulmonary fibrogenic action of
a and Reid, 1985). Amiodarone treatment predisposes
hamsters to pulmonary fibrosis (Cantor et al., 1984;
Daniels et al., 1989). The pulmonary fibrogenic action of
amiodarone after intratracheal instillation was studied
by pa hamsters to pulmonary fibrosis (Cantor et al., 1984;
Daniels et al., 1989). The pulmonary fibrogenic action of
amiodarone after intratracheal instillation was studied
by pathological examination, presence of hyperplastic
t Daniels et al., 1989). The pulmonary fibrogenic action of amiodarone after intratracheal instillation was studied by pathological examination, presence of hyperplastic type II cells, and synthesis and content of lung elast amiodarone after intratracheal instillation was studied
by pathological examination, presence of hyperplastic
type II cells, and synthesis and content of lung elastin
(Cantor et al., 1987). Clinical experience with amiodaby pathological examination, presence of hyperplastic type II cells, and synthesis and content of lung elastin (Cantor et al., 1987). Clinical experience with amiodarone also indicates significant evidence of pulmonary fib type II cells, and synthesis and content of lung elasti
(Cantor et al., 1987). Clinical experience with amiods
rone also indicates significant evidence of pulmonary
fibrosis (Marchlinski et al., 1982; Gefter et al., 1983
T (Cantor et al., 1987). Clinical experience with amioda-
rone also indicates significant evidence of pulmonary
fibrosis (Marchlinski et al., 1982; Gefter et al., 1983).
The relationship between CAD accumulation and amio-
da

PHARMACOLOGICAL REVIEWS

DRUG-INDUCED I
tension, and phospholipidosis need to be examined fur-
ther in detail. tension, and p is the indetail. ENCE

III. Mechanism of Phospholipidos

III. Mechanism of Phospholipidos

III. Mechanism of Phospholipidos

Internace Effects of Cationic Amphiphilic *A. Membrane Effects of Cationic Amphiphilic Drugs*

III. Mechanism of Phospholipidosis
A. Membrane Effects of Cationic Amphiphilic Drugs
Biological activities of drug molecules are most oft
dependent on their interactions with biomembrane
Even though the ultimate pharmacolo A. Membrane Effects of Cationic Amphiphilic Drugs

Biological activities of drug molecules are most often

dependent on their interactions with biomembranes.

Even though the ultimate pharmacological effects may

depend on dependent on their interactions with biomembranes.
Biological activities of drug molecules are most often
dependent on their interactions with biomembranes.
Even though the ultimate pharmacological effects may
depend on dr Biological activities of drug molecules are most often
dependent on their interactions with biomembranes.
Even though the ultimate pharmacological effects may
depend on drug-protein interactions, drug molecules
must cross dependent on their interactions with biomembranes.
Even though the ultimate pharmacological effects may
depend on drug-protein interactions, drug molecules
must cross lipid membrane barriers before reaching the
target site Even though the ultimate pharmacological effects may
depend on drug-protein interactions, drug molecules
must cross lipid membrane barriers before reaching the
target site. Therefore, the interactions of drugs with
phospho depend on drug-protein interactions, drug molecules
must cross lipid membrane barriers before reaching the
target site. Therefore, the interactions of drugs with
phospholipids and phospholipid-containing membranes
play cri must cross lipid membrane barriers before reaching the target site. Therefore, the interactions of drugs with phospholipids and phospholipid-containing membranes play critical roles in drug disposition and drug action. Bec target site. Therefore, the interactions of drugs with
phospholipids and phospholipid-containing membranes
play critical roles in drug disposition and drug action.
Because CADs contain lipophilic as well as hydrophilic
moi play critical roles in drug disposition and drug action.
Because CADs contain lipophilic as well as hydrophilic
moieties, their interactions with lipid membranes tend
to be more complex.
1. Partition coefficients, transiti Because CADs contain lipophilic as well as hydrophilic moieties, their interactions with lipid membranes tend
to be more complex.
1. Partition coefficients, transition temperatures, and
defective structures in membranes.

moieties, their interactions with lipid membranes ten
to be more complex.
1. Partition coefficients, transition temperatures, an
defective structures in membranes. The mechanism
pharmacological actions of drugs resides in to be more complex.

1. Partition coefficients, transition temperatures, and

defective structures in membranes. The mechanism of

pharmacological actions of drugs resides in their mem-

brane-binding properties. Because m 1. Partition coefficients, transition temperatures, and defective structures in membranes. The mechanism of pharmacological actions of drugs resides in their membrane-binding properties. Because most CADs interact with pho pharmacological actions of drugs resides in their membrane-binding properties. Because most CADs interact with phospholipids and phospholipid-containing membranes, it is important to consider the relationship between this brane-binding properties. Because most CADs interact
with phospholipids and phospholipid-containing mem-
branes, it is important to consider the relationship be-
tween this interaction and phospholipidosis. Reactions
of se with phospholipids and phospholipid-containing membranes, it is important to consider the relationship be-
tween this interaction and phospholipidosis. Reactions
of several neuroleptic CADs including phenothiazines
and ane branes, it is important tween this interaction and anesthetics on bid known for a long time.
In an artificial bilayer Freen this interaction and phospholipidosis. React
several neuroleptic CADs including phenothiaz
d anesthetics on biological membranes have town for a long time.
In an artificial bilayer of dioleoylphosphatidylcho
in a bi

and anesthetics on biological membranes have been

known for a long time.

In an artificial bilayer of dioleoylphosphatidylcholine

or in a biological membrane, the cationic group of CADs

is normally placed between the p known for a long time.

In an artificial bilayer of dioleoylphosphatidylcholine

or in a biological membrane, the cationic group of CADs

is normally placed between the polar head groups of

phospholipids, and the hydroph In an artificial bilayer of dioleoylphosphatidylcholine
or in a biological membrane, the cationic group of CADs
is normally placed between the polar head groups of
phospholipids, and the hydrophobic portion is directed
tow or in a biological membrane, the cationic group of CADs
is normally placed between the polar head groups of
phospholipids, and the hydrophobic portion is directed
toward the hydrophobic interior of the membrane; thus,
the is normally placed between the polar head groups of phospholipids, and the hydrophobic portion is directed toward the hydrophobic interior of the membrane; thus, the drug molecule intercalates between lipid molecules in (phospholipids, and the hydrophobic por
toward the hydrophobic interior of the m
the drug molecule intercalates between
(Seeman, 1972; Conrad and Singer, 1973
et al., 1983; Harder and Debuch, 1986).
The incorporation of dru ward the hydrophobic interior of the membrane; thue drug molecule intercalates between lipid molecule
eeman, 1972; Conrad and Singer, 1979, 1981; Kursc
al., 1983; Harder and Debuch, 1986).
The incorporation of drug molecul the drug molecule intercalates between lipid molecules

(Seeman, 1972; Conrad and Singer, 1979, 1981; Kursch

et al., 1983; Harder and Debuch, 1986).

The incorporation of drug molecules affects the phys-

icochemical prop

(Seeman, 1972; Conrad and Singer, 1979, 1981; Kurst al., 1983; Harder and Debuch, 1986).
The incorporation of drug molecules affects the phicochemical properties of the lipid bilayer such that the phase transition temperat et al., 1983; Harder and Debuch, 1986).
The incorporation of drug molecules affects the
icochemical properties of the lipid bilayer such the
phase transition temperature from gel to liquid cr
line state may be altered (See The incorporation of drug molecules affects the physicochemical properties of the lipid bilayer such that the phase transition temperature from gel to liquid crystal-
line state may be altered (Seeman, 1972; Papahadjopouicochemical properties of the lipid bilayer such that the
phase transition temperature from gel to liquid crystal-
line state may be altered (Seeman, 1972; Papahadjopou-
los et al., 1975). CADs are known to decrease phase
 phase transition temperature from gel to liquid crystal-
line state may be altered (Seeman, 1972; Papahadjopou-
los et al., 1975). CADs are known to decrease phase
transition temperature (Seeman, 1972; Lee, 1978). The
met line state may be altered (Seeman, 1972; Papahadjopou-
los et al., 1975). CADs are known to decrease phase
transition temperature (Seeman, 1972; Lee, 1978). The
molecular configuration, pK_a of the phospholipid, and in t transition temperature (Seeman, 1972; Lee, 1978). The
phase transition temperatures of phospholipids vary with
molecular configuration, pK_a of the phospholipid, and
pH of the surrounding medium. For example, the tran-
s transition temperature (Seeman, 1972; Lee, 1978). The metapologies transition temperatures of phospholipids vary with metapological metapological metapological in the phospholipid, and in the surrounding medium. For examp phase transition temperatures of phospholipids vary with
molecular configuration, pK_a of the phospholipid, and
pH of the surrounding medium. For example, the tran-
sition for dioleoylphosphatidylcholine occurs at 41°C;
 molecular configuration, pK_a of the phospholipid, an pH of the surrounding medium. For example, the transition for dioleoylphosphatidylcholine occurs at 41° C however, it is 44° C for phosphatidylglycerol (Kur pH of the surrounding medium. For example, the tran-
sition for dioleoylphosphatidylcholine occurs at 41°C; (Seemathowever, it is 44°C for phosphatidylglycerol (Kursch et has been
al., 1983). For phosphatidylglycerol, the sition for dioleoylphosphatidylcholine occurs at 41 however, it is 44°C for phosphatidylglycerol (Kursclal., 1983). For phosphatidylglycerol, the increase in tration temperature occurs at a lower pH, ranging fi $41^{\circ}C$ a however, it is 44°C for phosphatidylglycerol (Kursch et had, 1983). For phosphatidylglycerol, the increase in transition temperature occurs at a lower pH, ranging from ity 41°C at pH 7 to 61°C at pH 2. The transition tempe sition temperature occurs at a lower pH, ranging from ity is obtained. Also, if carbon 2 on the side chain is 41°C at pH 7 to 61°C at pH 2. The transition tempera-
ture, the pK_a values, and the membrane changes are (Gor 41° C at pH 7 to 61°C at pH 2. The transition temperature, the pK_a values, and the membrane changes are measures indicative of the integrity of the membran (Kursch et al., 1983). The intensity of drug effects of transition temperature is concentration dependent an varies w measures indicative of the integrity of the membrane (Kursch et al., 1983). The intensity of drug effects on transition temperature is concentration dependent and varies with the individual drugs. A decrease in the transit (Kursch et al., 1983). The intensity of drug effects of transition temperature is concentration dependent and varies with the individual drugs. A decrease in the transition temperature induces fluidization of membrane (Cul transition temperature is concentration dependent and
varies with the individual drugs. A decrease in the tran-
sition temperature induces fluidization of membranes
(Cullis et al., 1978). Decreased transition temperature,

ther in detail.

III. Mechanism of Phospholipidosis

III. Mechanism of Phospholipidosis

A. Membrane Effects of Cationic Amphiphilic Drugs

Biological activities of drug molecules are most often

Biological activities of d DRUG-INDUCED PHOSPHOLIPIDOSIS
De examined fur- receptor configuration, and, ultimately, leads to a therospholaribosis 337

receptor configuration, and, ultimately, leads to a ther-

apeutic or pharmacological response (Kanaho et al.,

1981; Verkleij et al., 1982; Rooney and Lee, 1983; Welti 337

1987 receptor configuration, and, ultimately, leads to a ther-

1981; Verkleij et al., 1982; Rooney and Lee, 1983; Welti

1981; Verkleij et al., 1982; Rooney and Lee, 1983; Welti

1984; Luxnatt and Galla, 1986; Muller receptor configuration, and, ultimately, leads to a ther-
apeutic or pharmacological response (Kanaho et al., 1981; Verkleij et al., 1982; Rooney and Lee, 1983; Welti
et al., 1984; Luxnatt and Galla, 1986; Muller et al., 1 receptor configuration, and, ultimately, leads to a ther-
apeutic or pharmacological response (Kanaho et al.,
1981; Verkleij et al., 1982; Rooney and Lee, 1983; Welti
et al., 1984; Luxnatt and Galla, 1986; Muller et al., 1 apeutic or pharmacological response (Kanaho et al., 1981; Verkleij et al., 1982; Rooney and Lee, 1983; Welti et al., 1984; Luxnatt and Galla, 1986; Muller et al., 1986).
Relatively higher drug concentrations are required t 1981; Verkleij et al., 1982; Rooney and Lee, 1983; Welti
et al., 1984; Luxnatt and Galla, 1986; Muller et al., 1986).
Relatively higher drug concentrations are required to
exert fluidizing effects on membranes. The presenc et al., 1984; Luxnatt and Galla, 1986; Muller et al., 1986)
Relatively higher drug concentrations are required to
exert fluidizing effects on membranes. The presence of α
halogen group on the hydrophobic domain of the d Relatively higher drug concentrations are requestert fluidizing effects on membranes. The prese halogen group on the hydrophobic domain of t molecule increases the fluidizing effect, the physicand pharmacological potency, exert fluidizing effects on membranes. The presence of *a* halogen group on the hydrophobic domain of the drum molecule increases the fluidizing effect, the physiologica and pharmacological potency, and phospholipidosis-in halogen group on the hydrophobic domain of the ϵ molecule increases the fluidizing effect, the physiolog and pharmacological potency, and phospholipidosis ducing capacity of CADs (Seydel et al., 1981). The incombine be molecule increases the fluidizing effect, then and pharmacological potency, and phosp ducing capacity of CADs (Seydel et al., 19, tionship between the membrane effects a pidosis has not been studied systematicall As may b d pharmacological potency, and phospholipidosis-in-
cing capacity of CADs (Seydel et al., 1981). The rela-
onship between the membrane effects and phospholi-
dosis has not been studied systematically.
As may be anticipated

phosphonphas and phosphonpha-containing membranes

play critical roles in drug disposition and drug action.

Because CADs contain lipophilic as well as hydrophilic

moieties, their interactions with lipid membranes tend

t and anesthetics on biological membranes have been

known for a long time.

In an artificial bilayer of dioleoylphosphatidylcholine

or in a biological membrane, the cationic group of CADs

is normally placed between the po ducing capacity of CADs (Seydel et al., 1981). The rela-
tionship between the membrane effects and phospholi-
pidosis has not been studied systematically.
As may be anticipated from the diversity of their
chemical structur tionship between the membrane effects and phospholi-
pidosis has not been studied systematically.
As may be anticipated from the diversity of their
chemical structures, drugs vary in their lipid to water
partition coeffici pidosis has not been studied systematically.
As may be anticipated from the diversity of their
chemical structures, drugs vary in their lipid to water
partition coefficients. High lipid solubility allows drugs
to partition As may be anticipated from the diversity of their
chemical structures, drugs vary in their lipid to water
partition coefficients. High lipid solubility allows drugs
to partition into the bilayer more effectively. Amiodaron chemical structures, drugs vary in their lipid to water
partition coefficients. High lipid solubility allows drugs
to partition into the bilayer more effectively. Amiodarone
has low water solubility, the lipid to water par partition coefficients. High lipid solubility allows drugs
to partition into the bilayer more effectively. Amiodarone
has low water solubility, the lipid to water partition
coefficient is 5.95 (the log value of the neutral to partition into the bilayer more effectively. Amiodarone
has low water solubility, the lipid to water partition
coefficient is 5.95 (the log value of the neutral form of
the drug) and displays significant hydrophobic beh has low water solubility, the lipid to water partit coefficient is 5.95 (the log value of the neutral form
the drug) and displays significant hydrophobic behave.
(Warren et al., 1970). The drug alters lipid dynamics at
the coefficient is 5.95 (the log value of the neutral form of
the drug) and displays significant hydrophobic behavior
(Warren et al., 1970). The drug alters lipid dynamics and
the physiological state of normal membranes at mic the drug) and displays significant hydrophobic beh.
(Warren et al., 1970). The drug alters lipid dynamic:
the physiological state of normal membranes at mic
olar concentrations (Chatelain et al., 1986) and fluoresce
polari (Warren et al., 1970). The drug alters lipid dynamics and
the physiological state of normal membranes at microm-
olar concentrations (Chatelain et al., 1985). Fluorescence
polarization (Chatelain et al., 1986) and fluoresc the physiological state of normal membranes at microm-
olar concentrations (Chatelain et al., 1985). Fluorescence
polarization (Chatelain et al., 1986) and fluorescence-
binding studies of amiodarone with lipids have indic olar concentrations (Chatelain et al., 1985). Fluorescence
polarization (Chatelain et al., 1986) and fluorescence-
binding studies of amiodarone with lipids have indicated
that amiodarone partitions into the hydrophobic co polarization (Chatelain et al., 1986) and fluorescence-
binding studies of amiodarone with lipids have indicated
that amiodarone partitions into the hydrophobic core of
the lipid bilayer (Joshi et al., 1988, 1989). A stron that amiodarone partitions into the hydrophobic core of that amiodarone partitions into the hydrophobic core of the lipid bilayer (Joshi et al., 1988, 1989). A stron correlation exists between binding of amiodarone, in vive phospholipidosis-inducing potency of the drug, and it the lipid bilay
correlation exist
phospholipidosi
phospholipase-i
endale, 1991).
The issue of t rrelation exists between binding of amiodarone, in vivo
nospholipidosis-inducing potency of the drug, and it
nospholipase-inhibiting capacity (Kodavanti and Meh
dale, 1991).
The issue of the relationship between phospholip

phospholipase-inhibiting capacity (Kodavanti and Mehendale, 1991).
The issue of the relationship between phospholipidosis
induction and phospholipase inhibition or drug binding
to phospholipids and their relative role in d phospholipase-inhibiting capacity (Kodavanti and Mehendale, 1991).

The issue of the relationship between phospholipidosis

induction and phospholipase inhibition or drug-induced

to phospholipidosis is mechanistically puz endale, 1991).
The issue of the relationship between phospholipidosis
induction and phospholipase inhibition or drug binding
to phospholipids and their relative role in drug-induced
phospholipidosis is mechanistically puzz The issue of the relationship between phospholipidos
induction and phospholipase inhibition or drug bindit
to phospholipids and their relative role in drug-induce
phospholipidosis is mechanistically puzzling and will consi induction and phospholipase inhibition or drug binding
to phospholipids and their relative role in drug-induced
phospholipidosis is mechanistically puzzling and will be
considered in some detail. The antipsychotic drug, ch to phospholipids and their relative role in drug-indephospholipidosis is mechanistically puzzling and wiconsidered in some detail. The antipsychotic drug, clear promazine, is extremely fat soluble and surface as (Seeman, 1 phospholipidosis is mechanistically puzzling and will be considered in some detail. The antipsychotic drug, chlor-
promazine, is extremely fat soluble and surface active
(Seeman, 1977). At higher than therapeutic concentra considered in some detail. The antipsychotic drug, chlor-
promazine, is extremely fat soluble and surface active
(Seeman, 1977). At higher than therapeutic concentra-
tions, chlorpromazine and other neuroleptics interact
w promazine, is extremely fat soluble and surface active (Seeman, 1977). At higher than therapeutic concentrations, chlorpromazine and other neuroleptics interact with membranes in a nonspecific way and fluidize all membrane (Seeman, 1977). At higher than therapeutic concentra-
tions, chlorpromazine and other neuroleptics interact
with membranes in a nonspecific way and fluidize all
membranes, leading to enhanced spontaneous release of
neurotr tions, chlorpromazine and other neuroleptics interact
with membranes in a nonspecific way and fluidize all
membranes, leading to enhanced spontaneous release of
neurotransmitters (Seeman, 1977). The activity, at least
in t with membranes in a nonspecific way and fluidize all
membranes, leading to enhanced spontaneous release of
neurotransmitters (Seeman, 1977). The activity, at least
in the case of neuroleptics, depends on the nature of the
 membranes, leading to enhanced spontaneous release of
neurotransmitters (Seeman, 1977). The activity, at least
in the case of neuroleptics, depends on the nature of the
polar side chain as well as the hydrophobic ring stru neurotransmitters (Seeman, 1977). The activity, at least
in the case of neuroleptics, depends on the nature of the
polar side chain as well as the hydrophobic ring structure
(Seeman et al., 1974; Schwendener and Weder, 197 in the case of neuroleptics, depends on the nature of the polar side chain as well as the hydrophobic ring structu
(Seeman et al., 1974; Schwendener and Weder, 1978).
has been postulated that, if carbon 2 is attached to th polar side chain as well as the hydrophobic ring structure (Seeman et al., 1974; Schwendener and Weder, 1978). It has been postulated that, if carbon 2 is attached to the methyl group on the polar side chain moieties, less (Seeman et al., 1974; Schwendener and Weder, 1978). It
has been postulated that, if carbon 2 is attached to the
methyl group on the polar side chain moieties, less activ-
ity is obtained. Also, if carbon 2 on the side chai has been postulated that, if carbon 2 is attached to the methyl group on the polar side chain moieties, less activity is obtained. Also, if carbon 2 on the side chain is bound in a ring form, a decrease in activity is obta methyl group on the polar side chain moieties, less activity is obtained. Also, if carbon 2 on the side chain is bound in a ring form, a decrease in activity is obtained (Gordon et al., 1963). A halogen substitution on the ity is obtained. Also, if carbon 2 on the side chair bound in a ring form, a decrease in activity is obta (Gordon et al., 1963). A halogen substitution on carbon-2 position on the hydrophobic ring, on the of hand, increase bound in a ring form, a decrease in activity is obtained (Gordon et al., 1963). A halogen substitution on the carbon-2 position on the hydrophobic ring, on the other hand, increases the physiological activity of phenothiaz (Gordon et al., 1963). A halogen substitution on the carbon-2 position on the hydrophobic ring, on the other hand, increases the physiological activity of phenothiazines (Gordon et al., 1963; Zirkle and Kaiser, 1980) and t carbon-2 position on the hydrophobic ring, on the other hand, increases the physiological activity of phenothiazines (Gordon et al., 1963; Zirkle and Kaiser, 1980) and the hydrophilic interaction of drugs with phospholipid hand, increases the physiological activity of phenoth
zines (Gordon et al., 1963; Zirkle and Kaiser, 1980) a
the hydrophilic interaction of drugs with phospholip
(Joshi et al., 1989). Thus, structure-activity relationshi
e the hydrophilic interaction of drugs with phospholipids (Joshi et al., 1989). Thus, structure-activity relationships exist in CAD-membrane interactions. Further understanding of their actions on the phospholipids of mem338 KODAVANTI
branes and subsequent static or dynamic cellular inter-
actions are important in examining the mechanism actions are important in examining the mechanism of by-
drug-induced phospholipidosis.
drug-induced phospholipidosis. 338
branes and subsequent stati
actions are important in ex
drug-induced phospholipido
In general, it has been INTERTENTIFICATE

In general, it has been concluded that halogenated

ugs are more lipophilic (Leo et al., 1971; Cerbon, 1972);

In general, it has been concluded that halogenated

ugs are more lipophilic (Leo et al., 1971

branes and subsequent static or dynamic cellular inter-
actions are important in examining the mechanism of
drug-induced phospholipidosis.
In general, it has been concluded that halogenated
drugs are more lipophilic (Leo e actions are important in examining the mechanism of drug-induced phospholipidosis.
In general, it has been concluded that halogenated drugs are more lipophilic (Leo et al., 1971; Cerbon, 1972)
however, partition coefficien drug-induced phospholipidosis.
In general, it has been concluded that halogenat
drugs are more lipophilic (Leo et al., 1971; Cerbon, 1973
however, partition coefficients of chlorinated and no
chlorinated drugs are not comp In general, it has been concluded that halogenated drugs are more lipophilic (Leo et al., 1971; Cerbon, 1972); two
however, partition coefficients of chlorinated and non-
chlorinated drugs are not comparable in terms of di drugs are more lipophilic (Leo et al., 1971; Cerbon, 19 however, partition coefficients of chlorinated and n
chlorinated drugs are not comparable in terms of dif
ences in their lipophilicity. Definitive conclusions v
regar however, partition coefficients of chlorinated and no
chlorinated drugs are not comparable in terms of diffe
ences in their lipophilicity. Definitive conclusions wi
regard to the effects of halogenation and other substit
t chlorinated drugs are not comparable in terms of differences in their lipophilicity. Definitive conclusions with regard to the effects of halogenation and other substitutions affecting lipophilicity of CADs and the consequ regard to the effects of halogenation and other substitu-
tions affecting lipophilicity of CADs and the conse-
quences on phospholipidosis are difficult because of lim-
ited information. Nevertheless, it can be stated that tions affecting lipophilicity of CADs and the consetions affecting lipophilicity of CADs and the conse-
quences on phospholipidosis are difficult because of lim-
ited information. Nevertheless, it can be stated that is
hydrophobic interactions of chlorinated and nonchloriquences on phospholipidosis are difficult because of limited information. Nevertheless, it can be stated that
hydrophobic interactions of chlorinated and nonchlori-
nated drugs, which do not differ significantly between
th ited information. Nevertheless, it can be stated that
hydrophobic interactions of chlorinated and nonchlori-
nated drugs, which do not differ significantly between
the two analogs (Joshi et al., 1989), may relate to their
 hydrophobic interaction
nated drugs, which do
the two analogs (Joshi
lipid to water partition
hydrophilic interactions.
2. Hydrophobic and *2. Hydrophobic and hydrophilic interactions of drugs*, which do not differ significantly between α is two analogs (Joshi et al., 1989), may relate to their pid to water partition coefficients rather than to their Edrop

the two analogs (Joshi et al., 1989), may relate to their photomathelipid to water partition coefficients rather than to their Binding hydrophilic interactions. The binding of cationic drugs to lipid individues to lipid in lipid to water partition coefficients rather than to their
hydrophilic interactions.
2. Hydrophobic and hydrophilic interactions of drugs
with phospholipids. The binding of cationic drugs to lipid
bilayers (fig. 2) and the hydrophilic interactions.

2. Hydrophobic and hydrophilic interactions of drugs

with phospholipids. The binding of cationic drugs to lipid

bilayers (fig. 2) and the relationship between this binding

and phospholipidosis 2. Hydrophobic and hydrophilic interactions of drugs
with phospholipids. The binding of cationic drugs to lipid
bilayers (fig. 2) and the relationship between this binding
and phospholipidosis has become an issue of contro with phospholipids. The binding of cationic drugs to lipid
bilayers (fig. 2) and the relationship between this binding
and phospholipidosis has become an issue of controversy
knowing because of the diversity of in vitro te bilayers (fig. 2) and the relationship between this binding and
and phospholipidosis has become an issue of controversy know
mainly because of the diversity of in vitro test systems ver
and techniques used in such studies. and phospholipidosis has become an issue of controversy
mainly because of the diversity of in vitro test systems
and techniques used in such studies. As discussed in the
previous section, it is apparent that CADs partition mainly because of the diversity of in vitro test systems
and techniques used in such studies. As discussed in the
previous section, it is apparent that CADs partition into
artificial and biological membranes and induce def and techniques used in such studies. As discussed in the previous section, it is apparent that CADs partition into artificial and biological membranes and induce defects in the membrane structure accompanied by alterations previous section, it is apparent that CADs partition in
artificial and biological membranes and induce defec
in the membrane structure accompanied by alteration
in membrane fluidity (Seydel and Wassermann, 197
Lullmann and artificial and biological membranes and induce defects
in the membrane structure accompanied by alterations
in membrane fluidity (Seydel and Wassermann, 1976;
Lullmann and Wehling, 1979; Phadke et al., 1981; Verk-
leij et in membrane fluidity (Seydel and Wassermann, 1976;
Lullmann and Wehling, 1979; Phadke et al., 1981; Verk-
leij et al., 1982; Kursch et al., 1983; Chatelain et al., 1986,
1989; Harder and Debuch, 1986; Kubo et al., 1986).
B in membrane fluidity (Seydel and Wassermann, 1976; c
Lullmann and Wehling, 1979; Phadke et al., 1981; Verk-
leij et al., 1982; Kursch et al., 1983; Chatelain et al., 1986,
1989; Harder and Debuch, 1986; Kubo et al., 1986). Lullmann and Wehling, 1979; Phadke et al., 1981; Verk-heijet al., 1982; Kursch et al., 1983; Chatelain et al., 1986, 1989; Harder and Debuch, 1986; Kubo et al., 1986).
Binding of drugs with membranes is reversible dependin leij et al., 1982; Kursch et al., 1983; Chatelain et al., 1986, 1989; Harder and Debuch, 1986; Kubo et al., 1986).
Binding of drugs with membranes is reversible depending
on the ionic charge of the drug and hydrophobicity 1989; Harder and Debuch, 1986; Kubo et al., 1986).
Binding of drugs with membranes is reversible depending
on the ionic charge of the drug and hydrophobicity of
the bilayer, partition coefficient, pH, and pK_a of the
amp Binding of drugs with membranes is reversible depending
on the ionic charge of the drug and hydrophobicity of
the bilayer, partition coefficient, pH, and pK_a of the
amphiphilic molecules. Any change in the drug molecule
 on the ionic charge of the drug and hydrophobicity of
the bilayer, partition coefficient, pH, and pK_a of the
amphiphilic molecules. Any change in the drug molecule
structure alters the drug-phospholipid-binding profile.

KODAVANTI AND MEHENDALE
cellular inter- using fluorescent probe techniques, originally described
mechanism of by Ma et al. (1985). The hydrophobic fluoroprobe, 1,6-MEHENDALE
using fluorescent probe techniques, originally described
by Ma et al. (1985). The hydrophobic fluoroprobe, 1,6-
diphenyl-1,3,5-hexatriene, is very useful in studying MEHENDALE
using fluorescent probe techniques, originally described
by Ma et al. (1985). The hydrophobic fluoroprobe, 1,6-
diphenyl-1,3,5-hexatriene, is very useful in studying
drug-phospholipid interactions because it posi drug-matterial university using fluorescent probe techniques, originally described
by Ma et al. (1985). The hydrophobic fluoroprobe, 1,6-
diphenyl-1,3,5-hexatriene, is very useful in studying
drug-phospholipid interactions using fluorescent probe techniques, originally described
by Ma et al. (1985). The hydrophobic fluoroprobe, 1,6-
diphenyl-1,3,5-hexatriene, is very useful in studying
drug-phospholipid interactions because it positions be-
 by Ma et al. (1985). The hydrophobic fluoroprobe, 1,6-
diphenyl-1,3,5-hexatriene, is very useful in studying
drug-phospholipid interactions because it positions be-
tween fatty acyl chains of phospholipids, changing the
em diphenyl-1,3,5-hexatriene, is very useful in studying
drug-phospholipid interactions because it positions be-
tween fatty acyl chains of phospholipids, changing the
emission spectra (London and Feigenson, 1978; Ma et
al., drug-phospholipid interactions because it positions b
tween fatty acyl chains of phospholipids, changing the
mission spectra (London and Feigenson, 1978; Ma e
al., 1985). The competition between the probe and the
drug mole tween fatty acyl chains of phospholipids, changing
emission spectra (London and Feigenson, 1978; M
al., 1985). The competition between the probe and
drug molecule for the hydrophobic moiety on the p
pholipid will depend on emission spectra (Lone)
al., 1985). The compet
drug molecule for the l
pholipid will depend on
ity in a drug (fig. 3).
Fifteen structurally, al., 1985). The competition between the probe and the drug molecule for the hydrophobic moiety on the phos-
pholipid will depend on the strength of the hydrophobic-
ity in a drug (fig. 3).
Fifteen structurally, pharmacolog

drug molecule for the hydrophobic moiety on the phos-
pholipid will depend on the strength of the hydrophobic-
ity in a drug (fig. 3).
Fifteen structurally, pharmacologically, and mechan-
istically dissimilar CADs have bee pholipid will depend on the strength of the hydrophobic-
ity in a drug (fig. 3).
Fifteen structurally, pharmacologically, and mechan-
istically dissimilar CADs have been studied for their
interaction with dipalmitoylphosph ity in a drug (fig. 3).
Fifteen structurally, pharmacologically, and mechanistically dissimilar CADs have been studied for their
interaction with dipalmitoylphosphatidylcholine vesicles
(Joshi et al., 1988; Joshi and Mehen Fifteen structurally, pharmacologically, and mechanistically dissimilar CADs have been studied for their interaction with dipalmitoylphosphatidylcholine vesicles (Joshi et al., 1988; Joshi and Mehendale, 1989). Their phosp istically dissimilar CADs have been studied for their
interaction with dipalmitoylphosphatidylcholine vesicles
(Joshi et al., 1988; Joshi and Mehendale, 1989). Their
phospholipid-binding potencies are also quite variable.
 interaction with dipalmitoylphosphatidylcholine ve
(Joshi et al., 1988; Joshi and Mehendale, 1989).
phospholipid-binding potencies are also quite van
Binding capacities and affinities of the drugs for ise
rat lung lamellar (Joshi et al., 1988; Joshi and Mehendale, 1989). Their
phospholipid-binding potencies are also quite variable.
Binding capacities and affinities of the drugs for isolated
rat lung lamellar bodies showed similar concentrati phospholipid-binding potencies are also quite variable.
Binding capacities and affinities of the drugs for isolated
rat lung lamellar bodies showed similar concentration-
response patterns in binding at the hydrophobic moi Binding capacities and affinities of the drugs for isolate
rat lung lamellar bodies showed similar concentration
response patterns in binding at the hydrophobic moiety
indicating that such binding to phospholipid membrane
 rat lung lamellar bodies showed similar concentration-
response patterns in binding at the hydrophobic moiety,
indicating that such binding to phospholipid membranes
and organelles may occur in vivo. Some of the well-
know response patterns in binding at the hydrophobic moindicating that such binding to phospholipid membra
and organelles may occur in vivo. Some of the w
known phospholipidosis-inducing drugs did partit
very effectively in the indicating that such binding to phospholipid membranes
and organelles may occur in vivo. Some of the well-
known phospholipidosis-inducing drugs did partition
very effectively in the hydrophobic region of phospho-
lipids, and organelles may occur in vivo. Some of the well-
known phospholipidosis-inducing drugs did partition
very effectively in the hydrophobic region of phospho-
lipids, whereas others did not. For example, amiodarone
partiti known phospholipidosis-inducing drugs did partitioury effectively in the hydrophobic region of phospholipids, whereas others did not. For example, amiodaror partitioning with the hydrophobic region was very remarkable and very effectively in the hydrophobic region of phospho-
lipids, whereas others did not. For example, amiodarone
partitioning with the hydrophobic region was very re-
markable and was characterized by an equally high affin-
 lipids, whereas others did not. For example, amiodarone
partitioning with the hydrophobic region was very re-
markable and was characterized by an equally high affin-
ity. However, other phospholipidotic agents, such as
ch partitioning with the hydrophobic region was very re-
markable and was characterized by an equally high affin-
ity. However, other phospholipidotic agents, such as
chlorphentermine and chloroquine, did not partition into
h

CHLORPROMAZINE

 $R_{\rm g}C = 0 - P = 0 - C R_{\rm g} - C R_{\rm g} - M (C R_{\rm g})_{\rm g}$
 \vdots
 L - α -PHOSPHATIDYLCHOLDE (DPALMITOYL)

FIG. 3. Hydrophobic and hydrophilic interactions between fluores-

cent probes, an amphiphilic drug, and dipalmitoylphosph $L-d$ **-PHOSPHATEDYLCHOLERE/DPALMITOYL)**
FIG. 3. Hydrophobic and hydrophilic interactions between fluorescent probes, an amphiphilic drug, and dipalmitoylphosphatidylcholine.
Structure of chlorpromazine is given as an examp From Solid Andreas and Mehendale drag and dipalmitory
hybric drag and dipalmitory
hybric Structure of chlorpromazine is given as an example
react with both sites on dipalmitoylphosphatidylc
with permission from Joshi and M

ARMACOLOGI

DRUG-INDUCED PHOSP
findings suggest that any generalization based simply on bine
lipophilicity and anticipated impact of structural modi- bine DRUG-INDUCEI

findings suggest that any generalization based simply c

lipophilicity and anticipated impact of structural modifications on lipophilicity will not permit an accura DRUG-INDUCED PHO
findings suggest that any generalization based simply on
lipophilicity and anticipated impact of structural modi-
fications on lipophilicity will not permit an accurate
prediction of the relationship betwe findings suggest that any generalization based simply of lipophilicity and anticipated impact of structural modifications on lipophilicity will not permit an accurat prediction of the relationship between hydrophobic drugfindings suggest that any generalization based simply
lipophilicity and anticipated impact of structural mo
fications on lipophilicity will not permit an accur
prediction of the relationship between hydropholoic dr
phospho ophilicity and anticipated impact of structural modi-
ations on lipophilicity will not permit an accurate 1
ediction of the relationship between hydrophobic drug-
cospholipid-binding phenomena and phospholipidosis.
Hydroph

fications on lipophilicity will not permit an accurate
prediction of the relationship between hydrophobic drug-
phospholipid-binding phenomena and phospholipidosis.
Hydrophobic and hydrophilic interactions of drugs
with ph prediction of the relationship between hydrophobic drug-
phospholipid-binding phenomena and phospholipidosis. ac
Hydrophobic and hydrophilic interactions of drugs
in
with phospholipids investigated using several other ap-
 phospholipid-binding phenomena and phospholipidosis. act
Hydrophobic and hydrophilic interactions of drugs ind
with phospholipids investigated using several other ap-
interpreaches (Frenzel et al., 1978; Ahmed et al., 1980 Hydrophobic and hydrophilic interactions of drugs in
with phospholipids investigated using several other ap-
proaches (Frenzel et al., 1978; Ahmed et al., 1980) have
phospholipids will almost entirely determine the
and pho with phospholipids investigated using several other approaches (Frenzel et al., 1978; Ahmed et al., 1980) have also led to a conclusion that hydrophobic forces of drug and phospholipids will almost entirely determine the d proaches (Frenzel et al., 1978; Ahmed et al., 1980) have
also led to a conclusion that hydrophobic forces of drug
and phospholipids will almost entirely determine the
degree of binding for neutral lipids. This is in contra also led to a conclusion that hydrophobic forces of drand phospholipids will almost entirely determine t
degree of binding for neutral lipids. This is in contra
with the negatively charged phosphatidylserine and ga
gliosid and phospholipids will almost entirely determine the degree of binding for neutral lipids. This is in contrast with the negatively charged phosphatidylserine and gangliosides (Lullmann and Wehling, 1979), in which hydrophi degree of binding for neutral lipids. This is in contrast cause with the negatively charged phosphatidylserine and gan-lipid gliosides (Lullmann and Wehling, 1979), in which hydro-term philic forces become important in bin with the negatively charged phosphatidylserine and gan-
gliosides (Lullmann and Wehling, 1979), in which hydro-
terphilic forces become important in binding to drugs. Al-
though Lullmann and Wehling (1979) were not able to gliosides (Lullmann and Wehling, 1979), in which hydroter
philic forces become important in binding to drugs. Altathough Lullmann and Wehling (1979) were not able to phi
distinguish precisely between the role of electrosta philic forces become important in binding to drugs. Al-
though Lullmann and Wehling (1979) were not able to
phil
distinguish precisely between the role of electrostatic and
in dhydrophobic forces in drug-phospholipid bindi though Lullmann and Wehling (1979) were not
distinguish precisely between the role of electrosta
hydrophobic forces in drug-phospholipid bindin
did speculate that both kinds of forces were invo
the binding of drugs to the stinguish precisely between the role of electrostatic and
drophobic forces in drug-phospholipid binding, they
d speculate that both kinds of forces were involved in
hydrophilic interactions of several drugs with the
Joutra

hydrophobic forces in drug-phospholipid bindid
did speculate that both kinds of forces were inv
the binding of drugs to the phospholipid bilayer
The hydrophilic interactions of several drugs
neutral phospholipid, dipalmito did speculate that both kinds of forces were involved in
the binding of drugs to the phospholipid bilayer.
The hydrophilic interactions of several drugs with the
neutral phospholipid, dipalmitoylphosphatidylcholine,
also v the binding of drugs to the phospholipid bilay
The hydrophilic interactions of several drug
neutral phospholipid, dipalmitoylphosphatialso vary with the drug used. Our studies of l
interactions of drugs with dipalmitoylpho The hydrophilic interactions of several drugs with the Jonetral phospholipid, dipalmitoylphosphatidylcholine, halso vary with the drug used. Our studies of hydrophilic hinteractions of drugs with dipalmitoylphosphatidylcho neutral phospholipid, dipalmitoylphosphatidylcholine,
also vary with the drug used. Our studies of hydrophilic
interactions of drugs with dipalmitoylphosphatidylcho-
line were facilitated by the use of a fluorescent probe, also vary with the drug used. Our studies of hydrophilic
interactions of drugs with dipalmitoylphosphatidylcho-
line were facilitated by the use of a fluorescent probe, 1-
anilino-8-naphthalene sulfonic acid. This fluoresc interactions of drugs with dipalmitoylphosphatidylcho
line were facilitated by the use of a fluorescent probe, 1
anilino-8-naphthalene sulfonic acid. This fluorescen
probe has been extensively used to demonstrate severa
ki line were facilitated by the use of a fluorescent probe, 1-
anilino-8-naphthalene sulfonic acid. This fluorescent
probe has been extensively used to demonstrate several
kinds of membrane interactions (Vanderkooi and Mar-
t anilino-8-naphthalene sulfonic acid. This fluorescent of
probe has been extensively used to demonstrate several ch
kinds of membrane interactions (Vanderkooi and Mar-
liptonosi, 1971; Flanagan and Hesketh, 1973; Ma et al., probe has been extensively used to demonstrate severals of membrane interactions (Vanderkooi and Monosi, 1971; Flanagan and Hesketh, 1973; Ma et 1985). 1-Anilino-8-naphthalene sulfonate does not a fluorescence signals with kinds of membrane interactions (Vanderkooi and Martonosi, 1971; Flanagan and Hesketh, 1973; Ma et al., 1985). 1-Anilino-8-naphthalene sulfonate does not give fluorescence signals with negatively charged phospholipids such tonosi, 1971; Flanagan and Hesketh, 1973; Ma et al., I
1985). 1-Anilino-8-naphthalene sulfonate does not give
fluorescence signals with negatively charged phospho-
lipids such as phosphatidylserine (Ma et al., 1985), but I 1985). 1-Anilino-8-naphthalene sulfonate does not give
fluorescence signals with negatively charged phospho-
lipids such as phosphatidylserine (Ma et al., 1985), but
fluoresces intensely upon binding to the positively inte fluorescence signals with negatively charged phospho-
lipids such as phosphatidylserine (Ma et al., 1985), but
fluoresces intensely upon binding to the positively in
charged amino group in the hydrophilic region of the cl lipids such as phosphatidylserine (Ma et al., 1985), but Influoresces intensely upon binding to the positively intendence been charged amino group in the hydrophilic region of the clephospholipid (Ma et al., 1985). Cation fluoresces intensely upon binding to the positively intendence of the clephospholipid (Ma et al., 1985). Cationic species such as the Ca²⁺ and several monovalent cationic drugs have been the shown to bind with the negat charged amino group in the hydrophilic region of the cles
phospholipid (Ma et al., 1985). Cationic species such as the
 Ca^{2+} and several monovalent cationic drugs have been the
shown to bind with the negative phosphate phospholipid (Ma et al., 1985). Cationic species such as the Ca²⁺ and several monovalent cationic drugs have been the shown to bind with the negative phosphate head group dy (Rojas and Tobias, 1965; Verkleij et al., 1982 Ca^{2+} and several monovalent cationic drugs have been
shown to bind with the negative phosphate head group
(Rojas and Tobias, 1965; Verkleij et al., 1982). Based or
this, Ma et al. (1985) suggested that the binding of 1 shown to bind with the negative phosphate head group dy

(Rojas and Tobias, 1965; Verkleij et al., 1982). Based on Jo

this, Ma et al. (1985) suggested that the binding of 1-

anilino-8-naphthalene sulfonate with phospholi (Rojas and Tobias, 1965; Verkleij et al., 1982). Based c
this, Ma et al. (1985) suggested that the binding of
anilino-8-naphthalene sulfonate with phospholipid ves
cles should be augmented in the presence of CADs if the
d this, Ma et al. (1985) suggested that the binding of 1-
anilino-8-naphthalene sulfonate with phospholipid vesi-
cles should be augmented in the presence of CADs if the
drug interacts with the net negative charge on the dip anilino-8-naphthalene sulfonate with phospholipid vesicles should be augmented in the presence of CADs if the subsety drag interacts with the net negative charge on the dipalmitoylphosphatidylcholine vesicles. They observe drug interacts with the net negative charge on the dipalmitoylphosphatidylcholine vesicles. They observed that fluorescence signals of the probe-phospholipid complex were intensified in the presence of calcium and chlor-ph itoylphosphatidylcholine vesicles. They observed that
iorescence signals of the probe-phospholipid complex
pre intensified in the presence of calcium and chlor-
entermine, a phospholipidotic drug (Ma et al., 1985).
The stu

fluorescence signals of the probe-phospholipid complement were intensified in the presence of calcium and chlophentermine, a phospholipidotic drug (Ma et al., 1985
The studies conducted with 15 drugs serve to illustrat
tha were intensified in the presence of calcium and chlor-
phentermine, a phospholipidotic drug (Ma et al., 1985).
The studies conducted with 15 drugs serve to illustrate
that these drugs vary in their interaction with the hyd phentermine, a phospholipidotic drug (Ma et al., 1985).
The studies conducted with 15 drugs serve to illustrate
that these drugs vary in their interaction with the hydro-
philic moiety of phospholipids. A potent phospholip The studies conducted with 15 drugs serve to illustrate
that these drugs vary in their interaction with the hydro-
philic moiety of phospholipids. A potent phospholipidotic
drug, amiodarone, which shows intense hydrophobic that these drugs vary in their interaction with the hydrophilic moiety of phospholipids. A potent phospholipidotidrug, amiodarone, which shows intense hydrophobic interaction did not bind to the hydrophilic moiety (Joshet philic moiety of phospholipids. A potent phospholipidot
drug, amiodarone, which shows intense hydrophobic in
teraction did not bind to the hydrophilic moiety (Jos)
et al., 1988; 1989). Consistent with our observation
Chate drug, amiodarone, which shows intense hydrophobic in-
teraction did not bind to the hydrophilic moiety (Joshi
et al., 1988; 1989). Consistent with our observations, gh
Chatelain et al. (1986, 1989) also concluded that amio et al., 1988; 1989). Consistent with our observations, Chatelain et al. (1986, 1989) also concluded that amiodarone buries deeply in the hydrophobic core and is able to alter the physical characteristics of biological membranes.

OSPHOLIPIDOSIS
bind to the hydrophobic moiety but instead exhibits
binding with hydrophilic sites (Joshi and Mehendale, 339
bind to the hydrophobic moiety but instead exhibit
binding with hydrophilic sites (Joshi and Mehendale
1989; Joshi et al., 1988, 1989). Others have reported tha 1989; 339

1989; Joshi et al., 1988, 1989). Others have reported that

1989; Joshi et al., 1988, 1989). Others have reported that

1989; Joshi et al., 1988, 1989). Others have reported that

chlorphentermine does participa bind to the hydrophobic moiety but instead exhibit
binding with hydrophilic sites (Joshi and Mehendal
1989; Joshi et al., 1988, 1989). Others have reported the
chlorphentermine does participate in hydrophobic inter-
action bind to the hydrophobic moiety but instead exhibits
binding with hydrophilic sites (Joshi and Mehendale,
1989; Joshi et al., 1988, 1989). Others have reported that
chlorphentermine does participate in hydrophobic inter-
ac binding with hydrophilic sites (Joshi and Mehendale, 1989; Joshi et al., 1988, 1989). Others have reported that chlorphentermine does participate in hydrophobic interactions to some extent (Ma et al., 1985). Gentamicin, an 1989; Joshi et al., 1988, 1989). Others have reported that
chlorphentermine does participate in hydrophobic inter-
actions to some extent (Ma et al., 1985). Gentamicin, an
inducer of phospholipidosis in the kidney (Kacew, chlorphentermine does participate in hydrophobic inter-
actions to some extent (Ma et al., 1985). Gentamicin, an
inducer of phospholipidosis in the kidney (Kacew, 1987),
interacted mainly with the hydrophilic moiety of aci actions to some extent (Ma et al., 1985). Gentamicin, an
inducer of phospholipidosis in the kidney (Kacew, 1987),
interacted mainly with the hydrophilic moiety of acidic
phospholipid vesicles (Kubo et al., 1986). Interacti inducer of phospholipidosis in the kidney (Kacew, 1987),
interacted mainly with the hydrophilic moiety of acidic
phospholipid vesicles (Kubo et al., 1986). Interaction of
acidic phospholipid substrates with gentamicin and interacted mainly with the hydrophilic moiety of acceptosynbolipid vesicles (Kubo et al., 1986). Interaction acidic phospholipid substrates with gentamicin and ot aminogly
coside antibiotics has been implicated as cause of acidic phospholipid substrates with gentamicin and other
aminoglycoside antibiotics has been implicated as the
cause of phospholipase inhibition and perhaps phospho-
lipidosis (Mingeot-Leclercq et al., 1990a,b). Chlorphentermine, amiodarone, and gentamicin are examples of aminoglycoside antibiotics has been implicated as t
cause of phospholipase inhibition and perhaps phosph
lipidosis (Mingeot-Leclercq et al., 1990a,b). Chlorphe
termine, amiodarone, and gentamicin are examples
drugs that in cause of phospholipase inhibition and perhaps phospholipidosis (Mingeot-Leclercq et al., 1990a,b). Chlorphentermine, amiodarone, and gentamicin are examples of drugs that interact with either hydropholic or hydrophilic moi lipidosis (Mingeot-Leclercq et
termine, amiodarone, and gen
drugs that interact with eithe
philic moieties of phospholipido
in drug-induced phospholipido
Chloroquine does not inter rmine, amiodarone, and gentamicin are examples of
ugs that interact with either hydrophobic or hydro-
ilic moieties of phospholipidos that might be implicated
drug-induced phospholipidosis.
Chloroquine does not interact wi

drugs that interact with either hydrophobic or h
philic moieties of phospholipids that might be impli
in drug-induced phospholipidosis.
Chloroquine does not interact with hydrophot
hydrophilic moieties of dipalmitoylphosph philic moieties of phospholipids that might be implicated
in drug-induced phospholipidosis.
Chloroquine does not interact with hydrophobic or
hydrophilic moieties of dipalmitoylphosphatidylcholine
(Lullmann and Wehling, 19 in drug-induced phospholipidosis.
Chloroquine does not interact with hydrophobic or
hydrophilic moieties of dipalmitoylphosphatidylcholine
(Lullmann and Wehling, 1979; Kubo and Hostetler, 1985;
Joshi et al., 1988, 1989). I Chloroquine does not interact with hydrophobic or hydrophilic moieties of dipalmitoylphosphatidylcholine (Lullmann and Wehling, 1979; Kubo and Hostetler, 1985; Joshi et al., 1988, 1989). It possesses a well-defined hydroph hydrophilic moieties of dipalmitoylphosphatidylcholine

(Lullmann and Wehling, 1979; Kubo and Hostetler, 1985;

Joshi et al., 1988, 1989). It possesses a well-defined

hydrophobic moiety akin to that of chlorphentermine. I (Lullmann and Wehling, 1979; Kubo and Hostetler, 1985;
Joshi et al., 1988, 1989). It possesses a well-defined
hydrophobic moiety akin to that of chlorphentermine. If
hydrophobic interactions are of primary importance in
th Joshi et al., 1988, 1989). It possesses a well-defined
hydrophobic moiety akin to that of chlorphentermine. If
hydrophobic interactions are of primary importance in
the binding of drugs with phospholipids, one would ex-
pe hydrophobic moiety akin to that of chlorphentermine. If
hydrophobic interactions are of primary importance in
the binding of drugs with phospholipids, one would ex-
pect that, regardless of the hydrophilic moiety on both
o hydrophobic interactions are of primary importance in
the binding of drugs with phospholipids, one would ex-
pect that, regardless of the hydrophilic moiety on both
of these drugs, they should partition into fatty acyl
cha the binding of drugs with phospholipids, one would expect that, regardless of the hydrophilic moiety on both of these drugs, they should partition into fatty acyl chains, because both of these molecules have fairly high li pect that, regardless of the hydrophilic moiety on both
of these drugs, they should partition into fatty acyl
chains, because both of these molecules have fairly high
lipid to water partition coefficients (Leo et al., 1971 of these drugs, they should partition into fatty acyl
chains, because both of these molecules have fairly high
lipid to water partition coefficients (Leo et al., 1971).
However, ionic charges on polar side chains of drugs, chains, because both of these molecules have fairly highlipid to water partition coefficients (Leo et al., 1971
However, ionic charges on polar side chains of drugs, a
well as on the polar phospholipid molecules, seem to b lipid to water partition coefficients (Leo et al., 1971).
However, ionic charges on polar side chains of drugs, as
well as on the polar phospholipid molecules, seem to be
of primary importance in drug-phospholipid interact However, ionic charges on polar side chains of drugs, well as on the polar phospholipid molecules, seem to be of primary importance in drug-phospholipid interaction In the case of chloroquine, the absence of hydrophil inte well as on the polar phospholipid molecules, seem to be
of primary importance in drug-phospholipid interactions.
In the case of chloroquine, the absence of hydrophilic
interactions with dipalmitoylphosphatidylcholine vesiof primary importance in drug-phospholipid interactions.
In the case of chloroquine, the absence of hydrophilic
interactions with dipalmitoylphosphatidylcholine vesi-
cles was explained in terms of electrostatic repulsions In the case of chloroquine, the absence of hydenteractions with dipalmitoylphosphatidylcholicles was explained in terms of electrostatic reputhe two cationic amine groups on the polar side the cationic amine of the neutral interactions with dipalmitoylphosphatidylcholine vesi-
cles was explained in terms of electrostatic repulsions of
the two cationic amine groups on the polar side chain to
the cationic amine of the neutral dipalmitoylphosph cles was explained in terms of
the two cationic amine groups
the cationic amine of the neut
dylcholine molecules (Lullma
Joshi and Mehendale, 1989).
Chloroquine interactions wi e two cationic amine groups on the polar side chain to
e cationic amine of the neutral dipalmitoylphosphati-
lcholine molecules (Lullmann and Wehling, 1979;
shi and Mehendale, 1989).
Chloroquine interactions with the polar

Chatelain et al. (1986, 1989) also concluded that amio-
darone buries deeply in the hydrophobic core and is able
to accumulation of gangliosides (Klinghardt, 1977) and
to alter the physical characteristics of biological me the cationic amine of the neutral dipalmitoylphosphati-
dylcholine molecules (Lullmann and Wehling, 1979;
Joshi and Mehendale, 1989).
Chloroquine interactions with the polar side chain of
negatively charged phosphatidylser dylcholine molecules (Lullmann and Wehling, 1979;
Joshi and Mehendale, 1989).
Chloroquine interactions with the polar side chain of
negatively charged phosphatidylserine and gangliosides
suggest that an excessive overall p Joshi and Mehendale, 1989).
Chloroquine interactions with the polar side chengatively charged phosphatidylserine and gangli
suggest that an excessive overall positive charge
result in electrostatic repulsions with dipalmit Chloroquine interactions with the polar side chain of
negatively charged phosphatidylserine and gangliosides
suggest that an excessive overall positive charge might
result in electrostatic repulsions with dipalmitoylphos-
 negatively charged phosphatidylserine and gangliosides
suggest that an excessive overall positive charge might
result in electrostatic repulsions with dipalmitoylphos-
phatidylcholine (Klinghardt, 1977; Drenckhahn and
Lull suggest that an excessive overall positive charge might
result in electrostatic repulsions with dipalmitoylphos-
phatidylcholine (Klinghardt, 1977; Drenckhahn and
Lullmann-Rauch, 1978; Lullmann and Wehling, 1979).
In an at result in electrostatic repulsions with dipalmitoylph
phatidylcholine (Klinghardt, 1977; Drenckhahn
Lullmann-Rauch, 1978; Lullmann and Wehling, 19
In an attempt to correlate the affinity of chloroque
with negatively charge phatidylcholine (Klinghardt, 1977; Drenckhahn and
Lullmann-Rauch, 1978; Lullmann and Wehling, 1979).
In an attempt to correlate the affinity of chloroquine
with negatively charged phospholipids and its phospho-
lipidosis i Lullmann-Rauch, 1978; Lullmann and Wehling, 1979).
In an attempt to correlate the affinity of chloroquine
with negatively charged phospholipids and its phospho-
lipidosis inducing potency, some investigators have pos-
tula In an attempt to correlate the affinity of chloroquine with negatively charged phospholipids and its phospholipidosis inducing potency, some investigators have positilated that chloroquine differs to some extent from the m with negatively charged phospholipids and its phospholipidosis inducing potency, some investigators have producted that chloroquine differs to some extent from monovalent CADs with respect to its effect on the ult structur lipidosis inducing potency, some investigators have pos-
tulated that chloroquine differs to some extent from the
monovalent CADs with respect to its effect on the ultra-
structure of cytoplasmic inclusion bodies and distr structure of cytoplasmic inclusion bodies and distribumonovalent CADs with respect to its effect on the ultra-
structure of cytoplasmic inclusion bodies and distribu-
tion pattern of phospholipidosis (Gray et al., 1971; Klin-
ghardt, 1977; Lullmann and Wehling, 1979). Further structure of cytoplasmic inclusion bodies and distribu-
tion pattern of phospholipidosis (Gray et al., 1971; Klin-
ghardt, 1977; Lullmann and Wehling, 1979). Further-
more, chloroquine has a particular tendency to induce
t tion pattern of phospholipidosis (Gray et al., 1971; Klinghardt, 1977; Lullmann and Wehling, 1979). Furthemore, chloroquine has a particular tendency to induction accumulation of gangliosides (Klinghardt, 1977) and anionic ghardt, 1977; Lullmann and Wehling, 1979). Further
more, chloroquine has a particular tendency to induc
the accumulation of gangliosides (Klinghardt, 1977) and
anionic lipids, bis(monoacylglycero)phosphate and phos
phatidy more, chloroquine has a particular tendency to induce
the accumulation of gangliosides (Klinghardt, 1977) and
anionic lipids, bis(monoacylglycero)phosphate and phos-
phatidylinositol (Tjiong et al., 1978; Frisch and Lull-

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Example 340
chloroquine for anionic lipids, and its tendency to induce haccumulation of such lipids in the tissues, may be due to ex EXTERN AND ME

accumulation of such lipids, and its tendency to induce hyde

accumulation of such lipids in the tissues, may be due to end

the specificity of chloroquine binding. The lower efficacy met KODAVANTI AND A
chloroquine for anionic lipids, and its tendency to induce
accumulation of such lipids in the tissues, may be due to
the specificity of chloroquine binding. The lower efficacy
of chloroquine to induce pulmo chloroquine for anionic lipids, and its tendency to induce
accumulation of such lipids in the tissues, may be due to
the specificity of chloroquine binding. The lower efficacy
of chloroquine to induce pulmonary phospholipi chloroquine for anionic lipids, and its tendency to inducted accumulation of such lipids in the tissues, may be due
the specificity of chloroquine binding. The lower efficity
of chloroquine to induce pulmonary phospholipid the specificity of chloroquine binding. The lower efficacy metabolism (Kuntzman et al., 1965; Dubnick et al., 1968; of chloroquine to induce pulmonary phospholipidosis Brown, 1974; Young and Mehendale, 1986). This concept of chloroquine to induce pulmonary phospholipidosis of chloroquine to induce pulmonary phospholipidosis
may be explained on the basis of relatively lower concen-
trations of anionic lipids in the lung (Lullmann and
Wehling, 1979). The liver, which is relatively richer in
an may be explained on the basis of relatively lower concentrations of anionic lipids in the lung (Lullmann and C
Wehling, 1979). The liver, which is relatively richer in is anionic lipid composition, exhibits chloroquine-ind trations of anionic lipids in the lung (Lullmann and
Wehling, 1979). The liver, which is relatively richer in is
anionic lipid composition, exhibits chloroquine-induced drephospholipidosis (Lullmann and Wehling, 1979). It nature of the aromatic structure. ospholipidosis (Lullmann and Wehling, 1979). It als
likely that, after the primary ionic interactions and
tablished, the hydrophobic interactions depend on the
ture of the aromatic structure.
The affinity of various CADs f

is likely that, after the primary ionic interactions are polaestablished, the hydrophobic interactions depend on the hydronture of the aromatic structure. The affinity of various CADs for amphiphilic phos- compholipids app established, the hydrophobic interactions depend on the hy
nature of the aromatic structure. In
The affinity of various CADs for amphiphilic phos-
co
pholipids appears to involve many factors in addition to ha
charge neutr nature of the aromatic structure. In interaction in the affinity of various CADs for amphiphilic phos-
pholipids appears to involve many factors in addition to hadrage neutralization. It may depend on overall ionic chinera The affinity of various CADs for amphiphilic phos-
pholipids appears to involve many factors in addition to
charge neutralization. It may depend on overall ionic
interaction in hydrophilic and hydrophobic regions, the
cond pholipids appears to involve many factors in addition to have charge neutralization. It may depend on overall ionic chiredinteraction in hydrophilic and hydrophobic regions, the miconditions of the medium, ionic charges of charge neutralization. It may depend on overall ioniteraction in hydrophilic and hydrophobic regions, to conditions of the medium, ionic charges of the mediu
presence of cations or anions, and the nature of t
buffers used. interaction in hydrophilic and hydrophobic regions, the miniconditions of the medium, ionic charges of the medium, (e.g presence of cations or anions, and the nature of the hall buffers used. Although charge neutralization conditions of the medium, ionic charges of the mediu
presence of cations or anions, and the nature of t
buffers used. Although charge neutralization is impo
tant, the in vitro models used for the model studies m
or may not esence of cations or anions, and the nature of t
ffers used. Although charge neutralization is import,
the in vitro models used for the model studies m
may not be representative of the in vivo conditions
Chlorpromazine exh

buffers used. Although charge neutralization is im
tant, the in vitro models used for the model studies
or may not be representative of the in vivo conditio
Chlorpromazine exhibits a strong binding to hy
phobic as well as tant, the in vitro models used for the model studies may cor may not be representative of the in vivo conditions.
Chlorpromazine exhibits a strong binding to hydro-ofphobic as well as hydrophilic moieties of dipalmitoyl-si or may not be representative of the in vivo conditions.
Chlorpromazine exhibits a strong binding to hydro-
phobic as well as hydrophilic moieties of dipalmitoyl-
phosphatidylcholine as evidenced by fluorescence probe
studi Chlorpromazine exhibits a strong binding to hydrophobic as well as hydrophilic moieties of dipalmitoy
phosphatidylcholine as evidenced by fluorescence prob
studies, nuclear magnetic resonance, or equilibrium dir
tribution phobic as well as hydrophilic moieties of dipalmitoyl-
phosphatidylcholine as evidenced by fluorescence probe
studies, nuclear magnetic resonance, or equilibrium dis-
tribution of radiolabeled drug (Seydel and Wassermann,
 phosphatidylcholine as evidenced by fluorescence probe
studies, nuclear magnetic resonance, or equilibrium dis-
tribution of radiolabeled drug (Seydel and Wassermann,
1976; Lullmann et al., 1978; Lullmann and Wehling,
1979 studies, nuclear magnetic resonance, or equilibrium distribution of radiolabeled drug (Seydel and Wassermann
1976; Lullmann et al., 1978; Lullmann and Wehlin
1979; Joshi and Mehendale, 1989; Joshi et al., 1989
Chlorpromazi tribution of radiolabeled drug (Seydel and Wassermann, to 1976; Lullmann et al., 1978; Lullmann and Wehling, w
1979; Joshi and Mehendale, 1989; Joshi et al., 1989). tichlorpromazine increases 1-anilino-8-naphthalene sul-
f 1976; Lullmann et al., 1978; Lullmann and Wehling,
1979; Joshi and Mehendale, 1989; Joshi et al., 1989).
Chlorpromazine increases 1-anilino-8-naphthalene sul-
fonate fluorescence more than 50-fold in a suspension of
isolat 1979; Joshi and Mehendale, 1989; Joshi et al., 1989). t
Chlorpromazine increases 1-anilino-8-naphthalene sulfonate fluorescence more than 50-fold in a suspension of c
isolated lamellar bodies, indicating strong hydrophilic Chlorpromazine increases 1-anilino-8-naphthalene sulfonate fluorescence more than 50-fold in a suspension of cisolated lamellar bodies, indicating strong hydrophilic cinteractions (Joshi et al., 1989). In contrast, Di Fran fonate fluorescence more than 50-fold in a suspension
isolated lamellar bodies, indicating strong hydroph
interactions (Joshi et al., 1989). In contrast, Di France
and Bickel (1977) reported that chlorpromazine bi
only to isolated lamellar bodies, indicating strong hydrophilic dues interactions (Joshi et al., 1989). In contrast, Di Francesco ate and Bickel (1977) reported that chlorpromazine binds moonly to the hydrophobic moiety on membran interactions (Joshi et al., 1989). In contrast, Di Francesco atec
and Bickel (1977) reported that chlorpromazine binds moi
only to the hydrophobic moiety on membrane phospho-
proi
lipids. The approach used by them might no and Bickel (1977) reported that chlorpromazine binds
only to the hydrophobic moiety on membrane phospho-
lipids. The approach used by them might not have been
sufficient to conclude that chlorpromazine does bind to
polar p

lipids. The approach used by them might not have been ing
sufficient to conclude that chlorpromazine does bind to inc
polar phospholipids with hydrophilic interactions. for
Similarly, imipramine also exhibits strong hydrop sufficient to conclude that chlorpromazine does bind to
polar phospholipids with hydrophilic interactions.
Similarly, imipramine also exhibits strong hydrophilic
and relatively weak hydrophobic interactions (Joshi and
Mehe polar phospholipids with hydrophilic interactions.
Similarly, imipramine also exhibits strong hydrophi
and relatively weak hydrophobic interactions (Joshi a
Mehendale, 1989; Joshi et al., 1989). Both imiprami
and chlorprom Similarly, imipramine also exhibits strong hydrophilic inventional elatively weak hydrophobic interactions (Joshi and bra
Mehendale, 1989; Joshi et al., 1989). Both imipramine tion
and chlorpromazine induce phospholipidosi and relatively weak hydrophobic interactions (Joshi and Mehendale, 1989; Joshi et al., 1989). Both imipramine
and chlorpromazine induce phospholipidosis-like alterations in vitro but fail to do so in the lung in vivo
(Lull Mehendale, 1989; Joshi et al., 1989). Both imipraminend chlorpromazine induce phospholipidosis-like altertions in vitro but fail to do so in the lung in vitro (Lullmann et al., 1978; Hruban, 1984). The explanatiof or this and chlorpromazine induce phospholipidosis-like alterations in vitro but fail to do so in the lung in vivo
(Lullmann et al., 1978; Hruban, 1984). The explanation if
or this difference may lie in the metabolism and elimi-
n tions in vitro but fail to do so in the lung in vivo we (Lullmann et al., 1978; Hruban, 1984). The explanation in for this difference may lie in the metabolism and elimi-
nation of these drugs. Both of these drugs are exte (Lullmann et al., 1978; Hruban, 1984). The explanation
for this difference may lie in the metabolism and elimi-
nation of these drugs. Both of these drugs are extensively
metabolized to polar metabolites, with loss of affi for this difference may lie in the metabolism and elimi-
nation of these drugs. Both of these drugs are extensively a
metabolized to polar metabolites, with loss of affinity for
the membrane (Ohmiya and Mehendale, 1979, 19 nation of these drugs. Both of these drugs are extensi
metabolized to polar metabolites, with loss of affinity
the membrane (Ohmiya and Mehendale, 1979, 1980
1981, 1982, 1984). It could be speculated from our bind
studies metabolized to polar metabolites, with loss of affinity for
the membrane (Ohmiya and Mehendale, 1979, 1980a,b, rir
1981, 1982, 1984). It could be speculated from our binding att
studies that, if a drug displays binding to the membrane (Ohmiya and Mehendale, 1979, 1980a, 1981, 1982, 1984). It could be speculated from our bindistudies that, if a drug displays binding to both hydropholic and hydrophilic moieties of the phospholipid, the metabo 1981, 1982, 1984). It could be speculated from our binding at studies that, if a drug displays binding to both hydrophololololol and hydrophilic moieties of the phospholipid, the operation is relatively higher. Thus, chlo studies that, if a drug displays binding to both hydrophobic and hydrophilic moieties of the phospholipid, the metabolic elimination is relatively higher. Thus, chlor-promazine, imipramine, and propranolol are examples of bic and hydrophilic moieties of the phospholipid, the ogeneratebolic elimination is relatively higher. Thus, chlor-
chapromazine, imipramine, and propranolol are examples of int
drugs that bind to both hydrophobic and hydr metabolic elimination is relatively higher. Thus, chlo
promazine, imipramine, and propranolol are examples
drugs that bind to both hydrophobic and hydrophil
sites of phospholipids. These drugs are also known to lextensivel promazine, imipramine, and propranolol are examples of intervals drugs that bind to both hydrophobic and hydrophilic ansites of phospholipids. These drugs are also known to be Poettensively metabolized. Amiodarone, cyclizi

MEHENDALE
hydrophobic or the hydrophilic moiety (Joshi and Meh-
endale, 1989; Joshi et al., 1989) and exhibit minima endale, 1989; Muslim and Mehendale, 1989; Joshi et al., 1989) and exhibit minimal metabolism (Kuntzman et al., 1965; Dubnick et al., 1968; MEHENDALE
hydrophobic or the hydrophilic moiety (Joshi and Mehendale, 1989; Joshi et al., 1989) and exhibit minimal
metabolism (Kuntzman et al., 1965; Dubnick et al., 1968;
Brown, 1974; Young and Mehendale, 1986). This con hydrophobic or the hydrophilic moiety (Joshi and Mehendale, 1989; Joshi et al., 1989) and exhibit minimal metabolism (Kuntzman et al., 1965; Dubnick et al., 1968; Brown, 1974; Young and Mehendale, 1986). This concept needs hydrophobic or the hydrophilic moiety (Joshi and Mehendale, 1989; Joshi et al., 1989) and exhibit minimal metabolism (Kuntzman et al., 1965; Dubnick et al., 1968; Brown, 1974; Young and Mehendale, 1986). This concept needs

anionic lipid composition, exhibits chloroquine-induced drugs to phospholipids. It has long been believed that
phospholipidosis (Lullmann and Wehling, 1979). It also halogen substitution at a critical carbon atom on a nonmetabolism (Kuntzman et al., 1965; Dubnick et al., 1968;
Brown, 1974; Young and Mehendale, 1986). This concept
needs further verification.
One additional issue needing attention in this section
is the binding of halo-subst Brown, 1974; Young and Mehendale, 1986). This concept
needs further verification.
One additional issue needing attention in this section
is the binding of halo-substituted or nonhalogenated
drugs to phospholipids. It has l is the binding of halo-substituted or nonhalogenated One additional issue needing attention in this section
is the binding of halo-substituted or nonhalogenated
drugs to phospholipids. It has long been believed that
halogen substitution at a critical carbon atom on a non-
po is the binding of halo-substituted or nonhalogenated
drugs to phospholipids. It has long been believed that
halogen substitution at a critical carbon atom on a non-
polar ring structure makes an amphiphilic drug more
hydro drugs to phospholipids. It has long been believed that
halogen substitution at a critical carbon atom on a non-
polar ring structure makes an amphiphilic drug more
hydrophobic (Leo et al., 1971). This may be true in some
i halogen substitution at a critical carbon atom on a non-
polar ring structure makes an amphiphilic drug more
hydrophobic (Leo et al., 1971). This may be true in some
instances. However, this does not seem to be true if we
 polar ring structure makes an amphiphilic drug more hydrophobic (Leo et al., 1971). This may be true in som instances. However, this does not seem to be true if w compare octanol to water partition coefficients of the halo hydrophobic (Leo et al., 1971). This may be true in so
instances. However, this does not seem to be true if
compare octanol to water partition coefficients of
halogenated and nonhalogenated drugs (imipram
chlorimipramine; halogenated and nonhalogenated drugs (imipramine, chlorimipramine; promazine, chlorpromazine; phentermine and chlorphentermine). In fact, some of the drugs (e.g., chlorimipramine versus imipramine) containing a compare octanol to water partition coefficients of the
halogenated and nonhalogenated drugs (imipramine,
chlorimipramine; promazine, chlorpromazine; phenter-
mine and chlorphentermine). In fact, some of the drugs
(e.g., ch halogenated and nonhalogenated drugs (imipramine,
chlorimipramine; promazine, chlorpromazine; phenter-
mine and chlorphentermine). In fact, some of the drugs
(e.g., chlorimipramine versus imipramine) containing a
halogenat chlorimipramine; promazine, chlorpromazine; phenter-
mine and chlorphentermine). In fact, some of the drugs
(e.g., chlorimipramine versus imipramine) containing a
halogenated group actually have smaller octanol to water
pa mine and chlorphentermine). I
(e.g., chlorimipramine versus is
halogenated group actually have
partition coefficients than do the
compounds (Leo et al., 1971).
If a high lipid to water partiti g., chlorimipramine versus imipramine) containing a logenated group actually have smaller octanol to water rition coefficients than do the nonhalogenated parent mpounds (Leo et al., 1971).
If a high lipid to water partitio

bids. The approach used by them might not have been ingly, the report from Kanaho et al. (1981) indicated that
ifficient to conclude that chlorpromazine does bind to increased affinity of the drugs (cationic phenothiazines halogenated group actually have smaller octanol to water
partition coefficients than do the nonhalogenated parent
compounds (Leo et al., 1971).
If a high lipid to water partition coefficient is an index
of hydrophobicity, partition coefficients than do the nonhalogenated parent
compounds (Leo et al., 1971).
If a high lipid to water partition coefficient is an index
of hydrophobicity, chlorinated analogs should have con-
siderably higher lip compounds (Leo et al., 1971).
If a high lipid to water partition coefficient is an index
of hydrophobicity, chlorinated analogs should have con-
siderably higher lipid to water partition coefficients than
their parent comp If a high lipid to water partition coefficient is an index
of hydrophobicity, chlorinated analogs should have con-
siderably higher lipid to water partition coefficients than
their parent compounds. Although the chlorinate of hydrophobicity, chlorinated analogs should have considerably higher lipid to water partition coefficients than
their parent compounds. Although the chlorinated drugs
interact with phospholipids more intensely, in contra their parent compounds. Although the chlorinated drugs
interact with phospholipids more intensely, in contrast
to the anticipated augmentation of hydrophobic binding,
we have observed highly intensified hydrophilic interac their parent compounds. Although the chlorinated drugs
interact with phospholipids more intensely, in contrast
to the anticipated augmentation of hydrophobic binding,
we have observed highly intensified hydrophilic interac interact with phospholipids more intensely, in contrast to the anticipated augmentation of hydrophobic binding
we have observed highly intensified hydrophilic interactions (Joshi and Mehendale, 1989; Joshi et al., 1989)
Th to the anticipated augmentation of hydrophobic binding,
we have observed highly intensified hydrophilic interac-
tions (Joshi and Mehendale, 1989; Joshi et al., 1989).
Therefore, the difference between chlorinated and nonwe have observed highly intensified hydrophilic inter
tions (Joshi and Mehendale, 1989; Joshi et al., 198
Therefore, the difference between chlorinated and ne
chlorinated drugs in interacting with phospholipids
due to an a Therefore, the difference between chlorinated and non-
chlorinated drugs in interacting with phospholipids is
due to an augmentation of hydrophilic binding. Chlorin-
ated and nonchlorinated drugs react with hydrophobic Therefore, the difference between chlorinated and noichlorinated drugs in interacting with phospholipids
due to an augmentation of hydrophilic binding. Chlorinated and nonchlorinated drugs react with hydrophob
moieties wit chlorinated drugs in interacting with phospholipid
due to an augmentation of hydrophilic binding. Chlo
ated and nonchlorinated drugs react with hydrophe
moieties with similar intensity, as illustrated by ch
promazine and p due to an augmentation of hydrophilic binding. Chlorinated and nonchlorinated drugs react with hydrophobic moieties with similar intensity, as illustrated by chlor-promazine and promazine (Joshi et al., 1989). Interestingl ated and nonchlorinated drugs react with hydrophobi
moieties with similar intensity, as illustrated by chlor
promazine and promazine (Joshi et al., 1989). Interest
ingly, the report from Kanaho et al. (1981) indicated the
 moieties with similar intensity, as illustrated by chlor-
promazine and promazine (Joshi et al., 1989). Interest-
ingly, the report from Kanaho et al. (1981) indicated that
increased affinity of the drugs (cationic phenoth promazine and promazine (Joshi et al., 1989). Interes
ingly, the report from Kanaho et al. (1981) indicated the
increased affinity of the drugs (cationic phenothiazine
for the plasma membrane by halogen substitution ma
inv ingly, the report from Kanaho et al. (1981) indicated that increased affinity of the drugs (cationic phenothiazines for the plasma membrane by halogen substitution mativolve the polar head group of the phospholipid membran increased affinity of the drugs (cationic phenothip
for the plasma membrane by halogen substitution
involve the polar head group of the phospholipic
brane. The halogen atom, which is incorporated ation 2 on a hydrophobic r for the plasma membrane by halogen substitution may
involve the polar head group of the phospholipid mem-
brane. The halogen atom, which is incorporated at posi-
tion 2 on a hydrophobic ring, has an electron-withdraw-
ing involve the polar head group of the phospholipid mem-
brane. The halogen atom, which is incorporated at posi-
tion 2 on a hydrophobic ring, has an electron-withdraw-
ing property. This property of the halogen may tend to
w brane. The halogen atom, which is incorporated at position 2 on a hydrophobic ring, has an electron-withdrawing property. This property of the halogen may tend to withdraw electrons from the adjacent carbon ring and make t tion 2 on a hydrophobic ring, has an electron-withdraw-
ing property. This property of the halogen may tend to
withdraw electrons from the adjacent carbon ring and
make the ring more electropositive (Bloom and Laubach,
196 ing property. This property of the halogen may tend to withdraw electrons from the adjacent carbon ring and make the ring more electropositive (Bloom and Laubach, 1962; Gordon et al., 1963; Zirkle and Kaiser, 1980). Such a withdraw electrons from the adjacent carbon ring and
make the ring more electropositive (Bloom and Laubach,
1962; Gordon et al., 1963; Zirkle and Kaiser, 1980). Such
a molecular change on a drug can alter the electronic
co make the ring more electropositive (Bloom and Laubach, 1962; Gordon et al., 1963; Zirkle and Kaiser, 1980). Such a molecular change on a drug can alter the electronic configuration of a drug molecule. Electropositivity of 1962; Gordon et al., 1963; Zirkle and Kaiser, 1980). Such
a molecular change on a drug can alter the electronic
configuration of a drug molecule. Electropositivity of a
ring moiety of a drug might be involved in increased
 a molecular change on a drug can alter the electronic configuration of a drug molecule. Electropositivity of a ring moiety of a drug might be involved in increased attraction to the negatively charged oxygen head group on configuration of a drug molecule. Electropositivity of a
ring moiety of a drug might be involved in increased
attraction to the negatively charged oxygen head group
on dipalmitoylphosphatidylcholine. Interactions of hal-
o ring moiety of a drug might be involved in increased
attraction to the negatively charged oxygen head group
on dipalmitoylphosphatidylcholine. Interactions of hal-
ogenated and nonhalogenated drugs with negatively
charged attraction to the negatively charged oxygen head group
on dipalmitoylphosphatidylcholine. Interactions of hal-
ogenated and nonhalogenated drugs with negatively
charged phospholipids, therefore, might be of greater
interes on dipalmitoylphosphatidylcholine. Interactions of halogenated and nonhalogenated drugs with negatively charged phospholipids, therefore, might be of greater interest in understanding the role of the polar head group and c ogenated and nonhalogenated drugs with negatively charged phospholipids, therefore, might be of greater interest in understanding the role of the polar head group and changes in the nonpolar moiety of a drug molecule. Poss charged phospholipids, therefore interest in understanding the roland changes in the nonpolar more possible interactions of CADs bilayer are depicted in fig. 2.
3. Structure-activity relations and changes in the nonpolar moiety of a drug molecule.
Possible interactions of CADs with the phospholipid
bilayer are depicted in fig. 2.
3. Structure-activity relationship for cationic amphi-

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philic drug-induced vacuoles and lamellar body formation. DRUG-INDUCED
p*hilic drug-induced vacuoles and lamellar body formation*
The appearance of clear cytoplasmic vacuoles (drug stor-
age site) has been reported for some CADs (Ruben et al. DRUG-INDUCED PH
philic drug-induced vacuoles and lamellar body formation.
The appearance of clear cytoplasmic vacuoles (drug stor-
age site) has been reported for some CADs (Ruben et al.,
1985, 1989; Rorig et al., 1987; Ru philic drug-induced vacuoles and lamellar body formation. con
The appearance of clear cytoplasmic vacuoles (drug stor-
son age site) has been reported for some CADs (Ruben et al., Ta,
1985, 1989; Rorig et al., 1987; Ruben, philic drug-induced vacuoles and lamellar body formatio.
The appearance of clear cytoplasmic vacuoles (drug sto
age site) has been reported for some CADs (Ruben et a
1985, 1989; Rorig et al., 1987; Ruben, 1987). Ruben an
h The appearance of clear cytoplasmic vacuoles (drug stons)
age site) has been reported for some CADs (Ruben et al
1985, 1989; Rorig et al., 1987; Ruben, 1987). Ruben an
his coinvestigators established a structure-activity r age site) has been reported for some CADs (Ruben et al., T₁
1985, 1989; Rorig et al., 1987; Ruben, 1987). Ruben and T₁
his coinvestigators established a structure-activity rela-
intionship for the development of clear 1985, 1989; Rorig et al., 1987; Ruben, 1987). Ruben and
his coinvestigators established a structure-activity rela-
tionship for the development of clear cytoplasmic vacu-
oles, based on their studies on disobutamide and it his coinvestigators established a structure-activity rela-
tionship for the development of clear cytoplasmic vacu-
oles, based on their studies on disobutamide and its
structural analogs. It is obvious from their work that tionship for the development of clear cytoplasmic vacu-
oles, based on their studies on disobutamide and its
structural analogs. It is obvious from their work that
action clear cytoplasmic vacuoles and lamellar bodies are oles, based on their studies on disobutamide and its structural analogs. It is obvious from their work that a clear cytoplasmic vacuoles and lamellar bodies are two in different manifestations of CAD action. Although the structural analogs. It is obvious from their work that clear cytoplasmic vacuoles and lamellar bodies are two different manifestations of CAD action. Although the cationic amine group and its basicity are essential for the clear cytoplasmic vacuoles and lamellar bodies are two
different manifestations of CAD action. Although the
cationic amine group and its basicity are essential for
the development of cytoplasmic vacuoles, the lipophilic-
i different manifestations of CAD action. Although the cationic amine group and its basicity are essential for the development of cytoplasmic vacuoles, the lipophilicity of molecules does not appear to play a significant rol cationic amine group and its basicity are essential for
the development of cytoplasmic vacuoles, the lipophilic-
ity of molecules does not appear to play a significant
role. Furthermore, two basic amines on the hydrophilic ity of molecules does not appear to play a significant role. Furthermore, two basic amines on the hydrophilic side chain are necessary. This seems true for chloroquine, libecause this drug also has two basic amines and is role. Furthermore, two basic amines on the hydrophilic side chain are necessary. This seems true for chloroquine, because this drug also has two basic amines and is and capable of producing clear cytoplasmic vacuoles. Unli side chain are necessary. This seems true for chloroquine,
because this drug also has two basic amines and is
capable of producing clear cytoplasmic vacuoles. Unlike
clear cytoplasmic vacuoles, lamellar bodies appear with
 because this drug also has two basic amines and is
capable of producing clear cytoplasmic vacuoles. Unlike
clear cytoplasmic vacuoles, lamellar bodies appear with
CADs having one or two basic amines on the hydrophilic
side capable of producing clear cytoplasmic vacuoles. Unlike
clear cytoplasmic vacuoles, lamellar bodies appear with
CADs having one or two basic amines on the hydrophilic
side chain. Moreover, the lipophilic nature of CADs is
 clear cytoplasmic vacuoles, lamellar bodies appear with
CADs having one or two basic amines on the hydrophilic
side chain. Moreover, the lipophilic nature of CADs is
very essential for the development of lamellar bodies.
T CADs having one or two basic amines on the hydrophiliside chain. Moreover, the lipophilic nature of CADs is very essential for the development of lamellar bodies The drugs with two basic amines and a well-define-lipophilic side chain. Moreover, the lipophilic nature of CADs is
very essential for the development of lamellar bodies.
The drugs with two basic amines and a well-defined
lipophilic region, such as disobutamide and chloroquine,
are very essential for the development of lamellar bodies.
The drugs with two basic amines and a well-defined
lipophilic region, such as disobutamide and chloroquine,
are capable of inducing a mixed type of structures with
la The drugs with two basic amines and a well-defined
lipophilic region, such as disobutamide and chloroquine,
are capable of inducing a mixed type of structures with
lamellar bodies and clear cytoplasmic vacuoles. The
drugs lipophilic region, such as disobutamide and chloroquine,
are capable of inducing a mixed type of structures with
lamellar bodies and clear cytoplasmic vacuoles. The
drugs with a well-defined lipophilic region and only one
 are capable of inducing a mixed type of structures with
lamellar bodies and clear cytoplasmic vacuoles. The
drugs with a well-defined lipophilic region and only one
basic amine on the side chain, such as imipramine and
ami lamellar bodies and clear cytoplasmic vacuoles. The $\frac{a}{b}$ m
drugs with a well-defined lipophilic region and only one have
basic amine on the side chain, such as imipramine and the
amiodarone, are capable of developing drugs with a well-defined lipophilic region and only one basic amine on the side chain, such as imipramine and amiodarone, are capable of developing only lamellar bodies. Unlike disobutamide, the halogen substitution on CA basic amine on the side chain, such as imipramine and amiodarone, are capable of developing only lamellar bodies. Unlike disobutamide, the halogen substitution on CADs with one basic amine makes the drug more potent in ind amiodarone, are capable of developing only lamellar bodies. Unlike disobutamide, the halogen substitution on CADs with one basic amine makes the drug more potent in inducing lamellar bodies. Also, we have noted that haloge ies. Unlike disobutamide, the halogen substitution on CADs with one basic amine makes the drug more potent in inducing lamellar bodies. Also, we have noted that halogen substitution on a lipophilic ring structure increases CADs with one basic amine makes the drug more potent
in inducing lamellar bodies. Also, we have noted that
halogen substitution on a lipophilic ring structure in-
creases the affinity of the drug for polar phospholipids
an in inducing lamella
halogen substitutio:
creases the affinity
and lamellar bodies
et al., 1988, 1989).
It is believed that logen substitution on a lipophilic ring structure in-

eases the affinity of the drug for polar phospholipids

Hd lamellar bodies (Joshi and Mehendale, 1989; Joshi te

al., 1988, 1989).

It is believed that clear cytoplasm creases the affinity of the drug for polar phospholipids Holler
and lamellar bodies (Joshi and Mehendale, 1989; Joshi tetler
et al., 1988, 1989). Ivsoso
It is believed that clear cytoplasmic vacuoles are drug oresce
storag

and lamellar bodies (Joshi and Mehendale, 1989; Josef al., 1988, 1989).
It is believed that clear cytoplasmic vacuoles are d
storage sites and the tissues with vacuoles do sleevation of phospholipids. The presence of phosp et al., 1988, 1989). It is believed that clear cytoplasmic vacuoles are drug ores
storage sites and the tissues with vacuoles do show chic
elevation of phospholipids. The presence of phospho-
insi-
lipids also has been not It is believed that clear cytoplasmic vacuoles are detorage sites and the tissues with vacuoles do sleevation of phospholipids. The presence of phospholipids also has been noted in these vacuoles. However what extent the v storage sites and the tissues with vacuoles do shelevation of phospholipids. The presence of phosphipids also has been noted in these vacuoles. However, what extent the vacuoles contribute in overall phosphipidosis is far storage sites and the tissues with vacuoles do show chlorpromazine, rapid accumulation was shown to occur
elevation of phospholipids. The presence of phospho-
inside the negatively charged membrane vesicles and a
lipids al lipids also has been noted in these vacuoles. However, t
what extent the vacuoles contribute in overall phospho
lipidosis is far from clear. Usually, vacuolation is accom
panied by the appearance of lamellar bodies. Althou what extent the vacuoles contribute in overall phospholipidosis is far from clear. Usually, vacuolation is accompanied by the appearance of lamellar bodies. Although storage, these contentions of CAD-induced phospholipid s lipidosis is far from clear. Usually, vacuolation is acc
panied by the appearance of lamellar bodies. Altho
the cytoplasmic vacuoles and lamellar bodies are cl
acteristics of CAD-induced phospholipid storage, tl
are strict panied by the appearance of lamellar bodies. Although
the cytoplasmic vacuoles and lamellar bodies are char-
acteristics of CAD-induced phospholipid storage, these
are strictly different in nature and obey strong structure the cytoplasmic vacuoles and lamellar bodies are characteristics of CAD-induced phospholipid storage, these are strictly different in nature and obey strong structure-activity relationships. Thus, these studies do shed som acteristics of CAD-induced phospholipid storage, these
are strictly different in nature and obey strong structure-
activity relationships. Thus, these studies do shed some
light on the mechanism of the development of cellu are strictly different in nature and obey strong structure-
activity relationships. Thus, these studies do shed some
light on the mechanism of the development of cellular
structures. However, several questions remain to be activity relationships. Thus, these studies do shed some light on the mechanism of the development of cellular charactructures. However, several questions remain to be advessed: (a) why these structures do not seem to alte light on the mechanism of the development of cellula
structures. However, several questions remain to be ad
dressed: (*a*) why these structures do not seem to alt
cell function, (*b*) at what degree of these changes is the structures. However, several questions remain to be addressed: (a) why these structures do not seem to alter cell function, (b) at what degree of these changes is the cell function affected, (c) what is their pathobiologic dressed: (a) why these structures do not cell function, (b) at what degree of these cell function affected, (c) what is their significance, and (d) what is the threshomal physiological range and toxicity? *B. Lysosomes, and (d)* what is their pathobiological significance, and (d) what is the threshold between normal physiological range and toxicity?
 B. Lysosomes, Phospholipid Metabolism, and Cationic Amphiphilic Drugs mal physiological range and toxicity?

Lysosomes, Phospholipid Metabolism, and Cationian
Dysosomes, Phospholipid Metabolism, and Cationian
phiphilic Drugs
Lysosomes are important in the etiology of phospidosis because it is now established that some CA

B. Lysosomes, Phospholipid Metabolism, and Cationic
Amphiphilic Drugs
Lysosomes are important in the etiology of phospho-
lipidosis because it is now established that some CADs (

OSPHOLIPIDOSIS
concentrate in the lysosomes and inhibit the intraly
somal breakdown of phospholipids (Reijngoud ospholipidosis and inhibit the intralyso-
concentrate in the lysosomes and inhibit the intralyso-
somal breakdown of phospholipids (Reijngoud and
Tager, 1976; Ohkuma and Poole, 1978; Tulkens and 341

concentrate in the lysosomes and inhibit the intralyso-

somal breakdown of phospholipids (Reijngoud and

Tager, 1976; Ohkuma and Poole, 1978; Tulkens and

Trouet, 1978; Hostetler et al., 1985). Whether CADconcentrate in the lysosomes and inhibit the intralys
somal breakdown of phospholipids (Reijngoud ar
Tager, 1976; Ohkuma and Poole, 1978; Tulkens ar
Trouet, 1978; Hostetler et al., 1985). Whether CAI
induced clear cytoplas concentrate in the lysosomes and inhibit the intralyso-
somal breakdown of phospholipids (Reijngoud and
Tager, 1976; Ohkuma and Poole, 1978; Tulkens and
Trouet, 1978; Hostetler et al., 1985). Whether CAD-
induced clear cyt somal breakdown of phospholipids (Reijngoud and Tager, 1976; Ohkuma and Poole, 1978; Tulkens and Trouet, 1978; Hostetler et al., 1985). Whether CAD-
induced clear cytoplasmic vacuoles and the hydrolytic activity inside vac Tager, 1976; Ohkuma and Poole, 1978; Tulkens and
Trouet, 1978; Hostetler et al., 1985). Whether CAD-
induced clear cytoplasmic vacuoles and the hydrolytic
activity inside vacuoles interfere with phospholipid me-
tabolism i Trouet, 1978; Hostetler et al., 1985). Whether CA induced clear cytoplasmic vacuoles and the hydroly activity inside vacuoles interfere with phospholipid is tabolism is not known. It has been understood that acid milieu of induced clear cytoplasmic vacuoles and the hydrolytic
activity inside vacuoles interfere with phospholipid me-
tabolism is not known. It has been understood that the
acid milieu of the lysosomes is conducive to the predomactivity inside vacuoles interfere with phospholipid me-
tabolism is not known. It has been understood that the
acid milieu of the lysosomes is conducive to the predom-
inant ionization of pneumophilic drug molecules. Majo tabolism is not known. It has been understood that t
acid milieu of the lysosomes is conducive to the predo-
inant ionization of pneumophilic drug molecules. Ma
effects of CADs on both phospholipid metabolism a
the accumul inant ionization of pneumophilic drug molecules. Major
effects of CADs on both phospholipid metabolism and
the accumulation of lamellated bodies have been attrib-
uted to an altered lysosomal metabolism.
There has been con effects of CADs on both phospholipid metabolism and

lipid catabolism in the lysosomes. De Duve et al. (1974) the accumulation of lamellated bodies have been attributed to an altered lysosomal metabolism.
There has been considerable interest and debate concerning the subject of how CADs interfere with phospholipid catabolism in th uted to an altered lysosomal metabolism.
There has been considerable interest and debate concerning the subject of how CADs interfere with phospholipid catabolism in the lysosomes. De Duve et al. (1974) and others (Wibo an There has been considerable interest and debate concerning the subject of how CADs interfere with phospholipid catabolism in the lysosomes. De Duve et al. (1974) and others (Wibo and Poole, 1974) have shown that weak bases cerning the subject of how CADs interfere with phospholipid catabolism in the lysosomes. De Duve et al. (1974) and others (Wibo and Poole, 1974) have shown that weak bases, including certain drugs and dyes, accumulate in t lipid catabolism in the lysosomes. De Duve et al. (1974)
and others (Wibo and Poole, 1974) have shown the
weak bases, including certain drugs and dyes, accumula
in the lysosomes. Weak organic bases of an amphiphil
nature c and others (Wibo and Poole, 1974) have shown the weak bases, including certain drugs and dyes, accumulin the lysosomes. Weak organic bases of an amphiphic nature cannot pass through the lipid phase of the me brane when the weak bases, including certain drugs and dyes, accumulate
in the lysosomes. Weak organic bases of an amphiphilic
nature cannot pass through the lipid phase of the mem-
brane when the compound is in its ionized form. Ioniza in the lysosomes. Weak organic bases of an amphiphilic nature cannot pass through the lipid phase of the membrane when the compound is in its ionized form. Ionization of a drug depends on the hydrogen ion concentration an nature cannot pass through the lipid phase of the mem-
brane when the compound is in its ionized form. Ioniza-
tion of a drug depends on the hydrogen ion concentration
and the pK_a of the base. For most basic dyes, the brane when the compound is in its ionized form. Ionization of a drug depends on the hydrogen ion concentration and the pK_a of the base. For most basic dyes, the pK_a falls in the range of 8 or greater. Because lysosome tion of a drug depends on the hydrogen ion concentration

and the pK_a of the base. For most basic dyes, the pK_a

falls in the range of 8 or greater. Because lysosomes have

a markedly lower interior pH, CADs that are and the pK_a of the base. For most basic dyes, the pK_a falls in the range of 8 or greater. Because lysosomes have a markedly lower interior pH , CADs that are basic, i.e., have a pK_a in excess of 7 or 8, maximally c falls in the range of 8 or greater. Because lysosomes have
a markedly lower interior pH, CADs that are basic, i.e.
have a p K_a in excess of 7 or 8, maximally concentrate in
the lysosomes (Lullmann et al., 1978). Thus, CA a markedly lower interi
have a pK_a in excess of
the lysosomes (Lullman
their most favorable en
taining anionic lipids.
Lysosomal accumula Example 2018 apply concentrate in expresses of 7 or 8, maximally concentrate in elysosomes (Lullmann et al., 1978). Thus, CADs find
eir most favorable environment within lysosomes con-
ining anionic lipids.
Lysosomal accu

the lysosomes (Lullmann et al., 1978). Thus, CADs find
their most favorable environment within lysosomes con-
taining anionic lipids.
Lysosomal accumulation of chloroquine in very high
concentrations (mM) has been noted in their most favorable environment within lysosomes containing anionic lipids.
Lysosomal accumulation of chloroquine in very high
concentrations (mM) has been noted in vivo and in vitro
(Allison and Young, 1964; Ohkuma and P taining anionic lipids.
Lysosomal accumulation of chloroquine in very high
concentrations (mM) has been noted in vivo and in vitre
(Allison and Young, 1964; Ohkuma and Poole, 1978
Hollemans et al., 1981; Poole and Ohkuma, Lysosomal accumulation of chloroquine in very high
concentrations (mM) has been noted in vivo and in vitro
(Allison and Young, 1964; Ohkuma and Poole, 1978;
Hollemans et al., 1981; Poole and Ohkuma, 1981; Hos-
tetler et al concentrations (mM) has been noted in vivo and in vitro (Allison and Young, 1964; Ohkuma and Poole, 1978; Hollemans et al., 1981; Poole and Ohkuma, 1981; Hostetler et al., 1985). Accumulation of chloroquine in the lysosome (Allison and Young, 1964; Ohkuma and Poole, 1978;
Hollemans et al., 1981; Poole and Ohkuma, 1981; Hos-
tetler et al., 1985). Accumulation of chloroquine in the
lysosomes also has been studied using pH-sensitive flu-
oresce Hollemans et al., 1981; Poole and Ohkuma, 1981; Hostetler et al., 1985). Accumulation of chloroquine in the lysosomes also has been studied using pH-sensitive flu-
orescent dyes (Ohkuma and Poole, 1978). In the case of chl tetler et al., 1985). Accumulation of chloroquine in the lysosomes also has been studied using pH-sensitive flu-
orescent dyes (Ohkuma and Poole, 1978). In the case of
chlorpromazine, rapid accumulation was shown to occur
 lysosomes also has been studied using pH-sensitive flu-
orescent dyes (Ohkuma and Poole, 1978). In the case of
chlorpromazine, rapid accumulation was shown to occur
inside the negatively charged membrane vesicles and a
con orescent dyes (Ohkuma and Poole, 1978). In the case of chlorpromazine, rapid accumulation was shown to occur inside the negatively charged membrane vesicles and a concentration of more than two orders of magnitude greater chlorpromazine, rapid accumulation was shown to occur
inside the negatively charged membrane vesicles and a
concentration of more than two orders of magnitude
greater than its exterior concentration was observed
(Bally et inside the negatively charged membrane vesicles and a concentration of more than two orders of magnitude greater than its exterior concentration was observed (Bally et al., 1985). In contrast, amiodarone does not seem to b concentration of more than two orders of magnitude
greater than its exterior concentration was observed
(Bally et al., 1985). In contrast, amiodarone does not
seem to be lysosomotropic (Heath et al., 1985), raising
the que greater than its exterior concentration was observed
(Bally et al., 1985). In contrast, amiodarone does not
seem to be lysosomotropic (Heath et al., 1985), raising
the question of why some CADs are lysosomotropic and
other (Bally et al., 1985). In contrast, amiodarone does no
seem to be lysosomotropic (Heath et al., 1985), raising
the question of why some CADs are lysosomotropic and
others are not? A partial explanation may come from the
stu seem to be lysosomotropic (Heath et al., 1985), raisin
the question of why some CADs are lysosomotropic an
others are not? A partial explanation may come from th
studies of disobutamide-induced clear cytoplasmic vesi
cles. others are not? A partial explanation may come from the studies of disobutamide-induced clear cytoplasmic vesi-
cles. Amiodarone, unlike disobutamide and chloroquine,
has only one basic amine, and the hydrophilic portion
d others are not? A partial explanation may come from the
studies of disobutamide-induced clear cytoplasmic vesi-
cles. Amiodarone, unlike disobutamide and chloroquine,
has only one basic amine, and the hydrophilic portion
d studies of disobutamide-induced clear cytoplasmic ves
cles. Amiodarone, unlike disobutamide and chloroquin
has only one basic amine, and the hydrophilic portic
does not react with polar phospholipids. On the othe
hand, lip cles. Amiodarone, unlike disobutamide and chloroquine
has only one basic amine, and the hydrophilic portion
does not react with polar phospholipids. On the othe
hand, lipophilic interactions of amiodarone and phos
pholipid has only one basic amine, and the hydrophilic portion
does not react with polar phospholipids. On the other
hand, lipophilic interactions of amiodarone and phos-
pholipids as well as lamellar bodies are prominent.
Therefor does not react with polar phospholipids. On the other hand, lipophilic interactions of amiodarone and phospholipids as well as lamellar bodies are prominent. Therefore, amiodarone does not meet the structural requirement t cell. pholipids as well as lamellar bodies are prominent.
Therefore, amiodarone does not meet the structural requirement to be stored in the acid compartment of the cell.
Drugs exert several effects on the lysosomes and ly-

Therefore, amiodarone does not meet the structural r
quirement to be stored in the acid compartment of the
cell.
Drugs exert several effects on the lysosomes and l
sosomal enzymes. Lysosomal stabilizing effects of chlor
ph quirement to be stored in the acid compartment of the
cell.
Drugs exert several effects on the lysosomes and ly-
sosomal enzymes. Lysosomal stabilizing effects of chlor-
phentermine have some functional implications in ede cell.
Drugs exert several effects on the lysosomes and ly-
sosomal enzymes. Lysosomal stabilizing effects of chlor-
phentermine have some functional implications in edema
(Merkow et al., 1971; Lullmann et al., 1975; Reasor

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Walker, 1979; Townsley et al., 1985; Wohns et al., 1985; KODAVANTI
Fazekas and Szekeres, 1988; Wohns et al., 1988
Fazekas and Szekeres, 1988; White et al., 1988). Lull-
mann et al. (1975) found that the formation of paw edem KODAVANTI AND I
Walker, 1979; Townsley et al., 1985; Wohns et al., 1985; m
Fazekas and Szekeres, 1988; White et al., 1988). Lull-
mann et al. (1975) found that the formation of paw edema
induced by dextran in rats was inhi induced by dextran in 1985; Wohns et al., 1985; nearly Walker, 1979; Townsley et al., 1985; Wohns et al., 1988). Lull-
Fazekas and Szekeres, 1988; White et al., 1988). Lull-
mann et al. (1975) found that the formation of p Walker, 1979; Townsley et al., 1985; Wohns et al., 1985; m
Fazekas and Szekeres, 1988; White et al., 1988). Lull-
mann et al. (1975) found that the formation of paw edema
induced by dextran in rats was inhibited by chronic Fazekas and Szekeres, 1988; White et al., 1988). Lull
mann et al. (1975) found that the formation of paw edem
induced by dextran in rats was inhibited by chronic
pretreatment with amphiphilic drugs. These effects were
attr mann et al. (1975) found that the formation of paw edema
induced by dextran in rats was inhibited by chronic dire
pretreatment with amphiphilic drugs. These effects were con
attributed to the stabilizing effects of drugs pretreatment with amphiphilic drugs. These effects were complexes are unsuitable substrates for phospholipases.
attributed to the stabilizing effects of drugs on the lyso-
somes resulting in reduced drug availability to pr pretreatment with amphiphilic drugs. These effects were
attributed to the stabilizing effects of drugs on the lyso-
somes resulting in reduced drug availability to produce a
response (Reasor and Walker, 1979). Chloroquine, attributed to the stabilizing effects of drugs on the lysosomes resulting in reduced drug availability to produce a response (Reasor and Walker, 1979). Chloroquine, a phospholipidotic drug (Abraham et al., 1968; Lullmann e somes resulting in reduced drug availability to produce a
response (Reasor and Walker, 1979). Chloroquine, a
phospholipidotic drug (Abraham et al., 1968; Lullmann
et al., 1975), also has been shown to stabilize lysosomal
m response (Reasor an
phospholipidotic druget al., 1975), also has
membranes (Weissman
in vivo and in vitro.
CAD-induced accur ospholipidotic drug (Abraham et al., 1968; Lullmann
al., 1975), also has been shown to stabilize lysosomal
embranes (Weissmann, 1966; Wibo and Poole, 1974)
vivo and in vitro.
CAD-induced accumulation of lamellar bodies in et al., 1975), also has been shown to stabilize lysosomal
membranes (Weissmann, 1966; Wibo and Poole, 1974)
in vivo and in vitro.
CAD-induced accumulation of lamellar bodies in var-
ious cell types also has been attributed

membranes (Weissmann, 1966; Wibo and Poole, 1974)
in vivo and in vitro.
CAD-induced accumulation of lamellar bodies in var-
ious cell types also has been attributed to metabolic
changes in the lysosomes. Lamellar bodies po in vivo and in vitro.
CAD-induced accumulation of lamellar bodies in var-
ious cell types also has been attributed to metabolic
changes in the lysosomes. Lamellar bodies possess sev-
eral similarities to lysosomes. Lullman CAD-induced accumulation of lamellar bodies in various cell types also has been attributed to metabolic changes in the lysosomes. Lamellar bodies possess several similarities to lysosomes. Lullmann-Rauch and Watermann (198 ious cell types also has been attributed to metabolic in changes in the lysosomes. Lamellar bodies possess several similarities to lysosomes. Lullmann-Rauch and Watermann (1987) reported that lipid storage lysosomes ly (la autophagosomes/autolysosomes.

C. Inhibition of Phospholipases autophagosomes/autolysosomes.

C. Inhibition of Phospholipases

Depletion of major membrane phospholipids in situ

can occur by the action of phospholipases $(A_1 \text{ and } A_2)$,

lysophospholipases, and diesterases and/or by d C. Inhibition of Phospholipases
Depletion of major membrane phospholipids in situ
can occur by the action of phospholipases $(A_1 \text{ and } A_2)$,
lysophospholipases, and diesterases and/or by direct hy-
drolysis mediated throug C. Inhibition of Phospholipases
Depletion of major membrane phospholipids in situ
can occur by the action of phospholipases $(A_1 \text{ and } A_2)$,
lysophospholipases, and diesterases and/or by direct hy-
drolysis mediated throug Depletion of major membrane phospholipids in situ
can occur by the action of phospholipases $(A_1 \text{ and } A_2)$,
lysophospholipases, and diesterases and/or by direct hy-
drolysis mediated through phospholipase C (Stryer,
1988) can occur by the action of phospholipases $(A_1 \text{ and } B_2)$
lysophospholipases, and diesterases and/or by direct
drolysis mediated through phospholipase C (Str.
1988). Lysosomal phospholipase C type activity agai
sphingomyel lysophospholipases, and diesterases and/or by direct hydrolysis mediated through phospholipase C (Stryer, 1988). Lysosomal phospholipase C type activity against sphingomyelin, phosphoinositol, and other phospholipids is we 1988). Lysosomal phospholipase C type activity agaisphingomyelin, phosphoinositol, and other phosplipids is well documented (Matsuzawa and Hostetl 1979, 1980a). CADs accumulate in the lysosomes a inhibit phospholipases (Br sphingomyelin, phosphoinositol, and other phospho-
lipids is well documented (Matsuzawa and Hostetler, are
1979, 1980a). CADs accumulate in the lysosomes and (1
inhibit phospholipases (Brindley et al., 1975; Defrise-
Quert lipids is well documented (Matsuzawa and Hostetler, 1979, 1980a). CADs accumulate in the lysosomes and inhibit phospholipases (Brindley et al., 1975; Defrise-Quertain et al., 1978; Gaton and Wolman, 1979; Heath and Jacobso 1979, 1980a). CADs accumulate in the lysosomes and
inhibit phospholipases (Brindley et al., 1975; Defrise-
Quertain et al., 1978; Gaton and Wolman, 1979; Heath
and Jacobson, 1980b; Matsuzawa and Hostetler, 1980b;
Hostetler inhibit phospholipases (Brindley et al., 1975; Defrise-Quertain et al., 1978; Gaton and Wolman, 1979; Heath and Jacobson, 1980b; Matsuzawa and Hostetler, 1980b; Hostetler and Matsuzawa, 1981; Beckman et al., 1982; Kunze et Quertain et al., 1978; Gaton and Wolman, 1979; Heath and Jacobson, 1980b; Matsuzawa and Hostetler, 1980b; Hostetler and Matsuzawa, 1981; Beckman et al., 1982; Kunze et al., 1982; Zborowski and Brindley, 1983; Hostetler, 19 and Jacobson, 1980b; Matsuzawa and Hostetler, 1980b; Hostetler and Matsuzawa, 1981; Beckman et al., 1982; Kunze et al., 1982; Zborowski and Brindley, 1983; Hostetler, 1984; Kubo and Hostetler, 1985; Heath et al., 1985; Fre Hostetler and Matsuzawa, 1981; Beckman et al., 1982; Kunze et al., 1982; Zborowski and Brindley, 1983; Hostetler, 1984; Kubo and Hostetler, 1985; Heath et al., 1985; Fredman et al., 1986; Grabner, 1987; Baumann et al., 198 Kunze et al., 1982; Zborowski and Brindley, 1983; Hostetler, 1984; Kubo and Hostetler, 1985; Heath et al., 1985; Fredman et al., 1986; Grabner, 1987; Baumann et al., 1987; Shaikh et al., 1987; Hostetler et al., 1988; Kacew tler, 1984; Kubo and Hostetler, 1985; Heath et al., ^{tiv}

85; Fredman et al., 1986; Grabner, 1987; Baumann et

0., 1987; Shaikh et al., 1987; Hostetler et al., 1988; of

acew, 1988; Martin et al., 1989).

Two different pr

mechanism of phospholipidosis. One of these basically al., 1987; Shaikh et al., 1987; Hostetler et al., 1988; $\frac{60 \text{ V}}{\text{atio}}$
Kacew, 1988; Martin et al., 1989). Two different proposals were made regarding the $\frac{\text{int}}{\text{time}}$ mechanism of phospholipidosis. One of these basic Kacew, 1988; Martin et al., 1989).
Two different proposals were made regarding the
mechanism of phospholipidosis. One of these basically
comes from Lullmann and his coinvestigators' work on
the binding of CADs to phospholi Two different proposals were made regarding the
mechanism of phospholipidosis. One of these basically
comes from Lullmann and his coinvestigators' work on
the binding of CADs to phospholipids (Lullmann et al.,
1978). In o mechanism of phospholipidosis. One of these basically surfaces from Lullmann and his coinvestigators' work on which the binding of CADs to phospholipids (Lullmann et al., the 1978). In our study, we also have determined th comes from Lullmann and his coinvestigators' work on
the binding of CADs to phospholipids (Lullmann et al.,
1978). In our study, we also have determined that CADs
bind to phospholipids and isolated lamellar bodies of the
l the binding of CADs to phospholipids (Lullmann et al., 1978). In our study, we also have determined that CADs bind to phospholipids and isolated lamellar bodies of the lung with hydrophobic and hydrophilic moieties (Joshi 1978). In our study, we also have determined that C bind to phospholipids and isolated lamellar bodies of lung with hydrophobic and hydrophilic moieties (J α det al., 1988, 1989). Lullmann and his coinvestigat hypothe bind to phospholipids and isolated lamellar bodies of the
lung with hydrophobic and hydrophilic moieties (Joshington
et al., 1988, 1989). Lullmann and his coinvestigators stare
hypothesized that, after the binding of drugs lung with hydrophobic and hydrophilic moieties (Joshinstein, 1988, 1989). Lullmann and his coinvestigators step hypothesized that, after the binding of drugs to phosphological initial, drug-phospholipid complexes are forme et al., 1988, 1989). Lullmann and his coinvestigators
hypothesized that, after the binding of drugs to phospho-
lipids, drug-phospholipid complexes are formed that are
resistant to phospholipase action, resulting in a buil hypothesized that, after the binding of drugs to phospholipids, drug-phospholipid complexes are formed that are which resistant to phospholipase action, resulting in a buildup line of phospholipids in the lysosomes (Lullma lipids, drug-phospholipid complexes are formed that are wild resistant to phospholipase action, resulting in a buildup lim of phospholipids in the lysosomes (Lullmann et al., 1978). Holomore is several binding studies, inc resistant to phospholipase action, resulting in a buildup

of phospholipase A and C (Matsuzawa and

of phospholipids in the lysosomes (Lullmann et al., 1978). Hostetler, 1980b; Hostetler and Matsuzawa, 1981; Kubo

Several of phospholipids in the lysosomes (Lullmann et al., 19
Several binding studies, including our approach w
involved 15 different CADs and phospholipids as we
lamellar bodies, are in good correlation with the ab
of various dr Several binding studies, including our approach which and
involved 15 different CADs and phospholipids as well as
demellar bodies, are in good correlation with the ability cho
of various drugs to induce phospholipidosis. D involved 15 different CADs and phospholipids as well a lamellar bodies, are in good correlation with the ability of various drugs to induce phospholipidosis. Drug-phopholipid complexes are unstable. Hence, the binding and

MEHENDALE
ment or removal of the drug from the incubation medium.
This is not an insignificant consideration, because this MEHENDALE
ment or removal of the drug from the incubation medium.
This is not an insignificant consideration, because this
aspect of the interaction makes it difficult to obtain MEHENDALE
ment or removal of the drug from the incubation medium.
This is not an insignificant consideration, because this
aspect of the interaction makes it difficult to obtain
direct evidence for the proposal that drug-p ment or removal of the drug from the incubation medium.
This is not an insignificant consideration, because this
aspect of the interaction makes it difficult to obtain
direct evidence for the proposal that drug-phospholipi ment or removal of the drug from the incubation mediu
This is not an insignificant consideration, because the
aspect of the interaction makes it difficult to obte
direct evidence for the proposal that drug-phospholipase
co his is not an insignificant consideration, because there of the interaction makes it difficult to obtained the rect evidence for the proposal that drug-phospholipid mplexes are unsuitable substrates for phospholipase.
Alth

eral similarities to lysosomes. Lullmann-Rauch and Wa-
termann (1987) reported that lipid storage lysosomes
(lamellar bodies) in renal duct cells and hepatocytes of al., 1985; Hostetler et al., 1986, 1988; Shaikh et al., 1 rats, induced by CADs, retain the ability to fuse with Martin et al., 1989; Kodavanti and Mehendale, 1991).

autophagosomes/autolysosomes.

C. Inhibition of Phospholipases was attributed to hypothyroidism associated with aspect of the interaction makes it difficult to obtain
direct evidence for the proposal that drug-phospholipic
complexes are unsuitable substrates for phospholipases.
Although drug binding to phospholipids and its phos
pho direct evidence for the proposal that drug-phospholipid
complexes are unsuitable substrates for phospholipases.
Although drug binding to phospholipids and its phos-
pholipidosis-inducing potency are in good correlation,
th complexes are unsuitable substrates for phospholipases.
Although drug binding to phospholipids and its phos-
pholipidosis-inducing potency are in good correlation.
the inhibition of phospholipases in vitro also correlates
 Although drug binding to phospholipids and its phos-
pholipidosis-inducing potency are in good correlation,
the inhibition of phospholipases in vitro also correlates
well with a drug's ability to induce phospholipidosis
(H pholipidosis-inducing potency are in good correlation,
the inhibition of phospholipases in vitro also correlates
well with a drug's ability to induce phospholipidosis
(Hostetler, 1984; Kubo and Hostetler, 1985; Martin et
a the inhibition of phospholipases in vitro also correlates
well with a drug's ability to induce phospholipidosis
(Hostetler, 1984; Kubo and Hostetler, 1985; Martin et
al., 1989). Inhibition of phospholipases as the cause of (Hostetler, 1984; Kubo and Hostetler, 1985; Martin et al., 1989). Inhibition of phospholipases as the cause of drug-induced phospholipid accumulation has been suggested as an alternative hypothesis for the mechanism involv (Hostetler, 1984; Kubo and Hostetler, 1985; Martin et al., 1989). Inhibition of phospholipases as the cause of drug-induced phospholipid accumulation has been suggested as an alternative hypothesis for the mechanism involv al., 1989). Inhibition of phospholipases as the cause of drug-induced phospholipid accumulation has been suggested as an alternative hypothesis for the mechanism involved in phospholipidosis. Consistent with this hypothesi drug-induced phospholipid accumulation has been suggested as an alternative hypothesis for the mechanism
involved in phospholipidosis. Consistent with this hypothesis, amiodarone, a strong phospholipidotic drug in
humans a gested as an alternative hypothesis for the mechanism
involved in phospholipidosis. Consistent with this hy-
pothesis, amiodarone, a strong phospholipidotic drug in
humans and in animal models, is a potent inhibitor of
lys involved in phospholipidosis. Consistent with this hypothesis, amiodarone, a strong phospholipidotic drug in humans and in animal models, is a potent inhibitor of lysosomal phospholipases in vivo and in vitro (Heath et al. pothesis, amiodarone, a strong phospholipidotic drug in
humans and in animal models, is a potent inhibitor of
lysosomal phospholipases in vivo and in vitro (Heath et
al., 1985; Hostetler et al., 1986, 1988; Shaikh et al., humans and in animal models, is a potent inhibitor of lysosomal phospholipases in vivo and in vitro (Heath et al., 1985; Hostetler et al., 1986, 1988; Shaikh et al., 1987; Martin et al., 1989; Kodavanti and Mehendale, 1991 lysosomal phospholipases in vivo and in vitro (Heath al., 1985; Hostetler et al., 1986, 1988; Shaikh et al., 198
Martin et al., 1989; Kodavanti and Mehendale, 1991
Inhibition of hepatic triglyceride lipase activity in ra
w al., 1985; Hostetler et al., 1986, 1988; Shaikh et al., 1
Martin et al., 1989; Kodavanti and Mehendale, 19
Inhibition of hepatic triglyceride lipase activity in
was attributed to hypothyroidism associated with a
darone the Inhibition of hepatic triglyceride lipase activity in rats hibition of hepatic triglyceride lipase activity in rats
as attributed to hypothyroidism associated with amio-
rone therapy (Kasim et al., 1987) because supplemen-
tion with thyroxine abrogated this effect.
Purified rat l

drolysis mediated through phospholipase C (Stryer, and chloroquine in vitro (Hostetler, 1984; Kubo and sphingomyelin, phosphoinositol, and other phosphoinositel, 1985; Grabner, 1987). To evaluate the mech-
lipids is well d was attributed to hypothyroidism associated with amid darone therapy (Kasim et al., 1987) because supplementation with thyroxine abrogated this effect.
Purified rat liver lysosomal phospholipase A_1 has been reported to darone therapy (Kasim et al., 1987) because supplementation with thyroxine abrogated this effect.

Purified rat liver lysosomal phospholipase A_1 has been

reported to be inhibited by chlorpromazine, propranolol,

and c tation with thyroxine abrogated this effect.

Purified rat liver lysosomal phospholipase A_1 has be

reported to be inhibited by chlorpromazine, propranol

and chloroquine in vitro (Hostetler, 1984; Kubo an

Hostetler, Purified rat liver lysosomal phospholipase A_1 has been
reported to be inhibited by chlorpromazine, propranolol,
and chloroquine in vitro (Hostetler, 1984; Kubo and
Hostetler, 1985; Grabner, 1987). To evaluate the mechreported to be inhibited by chlorpromazine, propranolol,
and chloroquine in vitro (Hostetler, 1984; Kubo and
Hostetler, 1985; Grabner, 1987). To evaluate the mech-
anism of phospholipase inhibition, Kubo and Hostetler
(198 and chloroquine in vitro (Hostetler, 1984; Kubo
Hostetler, 1985; Grabner, 1987). To evaluate the m
anism of phospholipase inhibition, Kubo and Host
(1985) conducted substrate and drug saturation ki
experiments in vitro usi Hostetler, 1985; Grabner, 1987). To evaluate the mechanism of phospholipase inhibition, Kubo and Hostetler (1985) conducted substrate and drug saturation kinetic experiments in vitro using chloroquine and chlorpromazine. T (1985) conducted substrate and drug saturation kinetic experiments in vitro using chloroquine and chlorpromazine. The purpose was to evaluate whether the drug is bound to the enzyme, thereby making an enzyme non-reactive t experiments in vitro using chloroquine and chlorpron
zine. The purpose was to evaluate whether the drug
bound to the enzyme, thereby making an enzyme n
reactive to the substrate, or whether the drug is bou
to the substrate zine. The purpose was to evaluate whether the drug is
bound to the enzyme, thereby making an enzyme non-
reactive to the substrate, or whether the drug is bound
to the substrate, thereby making the substrate nonreac-
tive bound to the enzyme, thereby making an enzyme non-
reactive to the substrate, or whether the drug is bound
to the substrate, thereby making the substrate nonreac-
tive to the enzyme. Either may be the case and the result
w reactive to the substrate, or whether the drug is bound to the substrate, thereby making the substrate nonreactive to the enzyme. Either may be the case and the result would be a decreased breakdown of phospholipids. Most to the substrate, thereby making the substrate nonreactive to the enzyme. Either may be the case and the result would be a decreased breakdown of phospholipids. Most of the inhibition studies are carried out in in vitro si tive to the enzyme. Either may be the case and the result
would be a decreased breakdown of phospholipids. Most
of the inhibition studies are carried out in in vitro situ-
ations, which involve addition of bolus amounts of would be a decreased breakdown of phospholipids. Most
of the inhibition studies are carried out in in vitro situ-
ations, which involve addition of bolus amounts of drug
into the incubation medium containing enzyme and the of the inhibition studies are carried out in in vitro situations, which involve addition of bolus amounts of drug into the incubation medium containing enzyme and the substrate. If the purpose of the study is to determine ations, which involve addition of bolus amounts of drug
into the incubation medium containing enzyme and the
substrate. If the purpose of the study is to determine
whether phospholipase inhibition was due to binding of
the into the incubation medium containing enzyme and the substrate. If the purpose of the study is to determine whether phospholipase inhibition was due to binding of the drug to the enzyme or due to the binding of the drug to substrate. If the purpose of the study is to determine
whether phospholipase inhibition was due to binding of
the drug to the enzyme or due to the binding of the drug
to the substrate phospholipid, in vitro incubations may whether phospholipase inhibition was due to binding of the drug to the enzyme or due to the binding of the drug to the substrate phospholipid, in vitro incubations may not be the appropriate way unless special kinds of sub the drug to the enzyme or due to the binding of the drug
to the substrate phospholipid, in vitro incubations may
not be the appropriate way unless special kinds of sub-
strate saturation kinetics are employed in some in-
s to the substrate phospholipid, in vitro incubations may
not be the appropriate way unless special kinds of sub-
strate saturation kinetics are employed in some in-
stances. Perhaps, saturation kinetics may be the only
vali not be the appropriate way unless special kinds of substrate saturation kinetics are employed in some instances. Perhaps, saturation kinetics may be the only valid in vitro approach, as demonstrated for chloroquine which, strate saturation kinetics are employed in some in-
stances. Perhaps, saturation kinetics may be the only
valid in vitro approach, as demonstrated for chloroquine
which, despite not binding to dioleoylphosphatidylcho-
line stances. Perhaps, saturation kinetics may be the only valid in vitro approach, as demonstrated for chloroquine which, despite not binding to dioleoylphosphatidylcholine, inhibits phospholipase A and C (Matsuzawa and Hostet Hostetler, 1980b; Hostetler and Matsuzawa, 1981; Kubo line, inhibits phospholipase A and C (Matsuzawa and line, inhibits phospholipase A and C (Matsuzawa and Hostetler, 1980b; Hostetler and Matsuzawa, 1981; Kubo and Hostetler, 1985). However, although chloroquine does not bind to dioleoyl- and dipalmitoylphosphatidyl-choline (Hostetler, 1980b; Hostetler and Matsuzawa, 1981; Kubo
and Hostetler, 1985). However, although chloroquine
does not bind to dioleoyl- and dipalmitoylphosphatidyl-
choline (neutral phospholipids) (Kubo and Hostetler,
1985; J and Hostetler, 1985). However, although chloro
does not bind to dioleoyl- and dipalmitoylphospha
choline (neutral phospholipids) (Kubo and Host
1985; Joshi et al., 1988, 1989), it is known to bi
negatively charged phosphol does not bind to dioleoyl- and dipalmitoylphosphatidyl-
choline (neutral phospholipids) (Kubo and Hostetler,
1985; Joshi et al., 1988, 1989), it is known to bind to
negatively charged phospholipids such as phosphatidyl-
se

prug-INDUCED
and Lullmann-Rauch, 1978; Lullmann and Wehling,
1979). Therefore, in vivo, chloroquine may yield an out-BRUG-INDUCED
1979). Therefore, in vivo, chloroquine may yield an out-
1979). Therefore, in vivo, chloroquine may yield an out-
1979 come not predicted by the in vitro studies. DRU
and Lullmann-Rauch, 1978; Lullmann a
1979). Therefore, in vivo, chloroquine may
come not predicted by the in vitro studies.
Association of chlorphentermine with d Lullmann-Rauch, 1978; Lullmann and Wehling, 1
79). Therefore, in vivo, chloroquine may yield an out-
me not predicted by the in vitro studies.
Association of chlorphentermine with pulmonary
lospholipids, but not phospho

and Lullmann-Rauch, 1978; Lullmann and Wehling, browned in the sum of the series of the in vitro studies.

he come not predicted by the in vitro studies. Show the come not predicted by the in vitro studies. Association of 1979). Therefore, in vivo, chloroquine may yield an come not predicted by the in vitro studies.
Association of chlorphentermine with pulmo
phospholipids, but not phospholipases, in vivo has
believed to be the mechanism inv come not predicted by the in vitro studies.
Association of chlorphentermine with pulmona
phospholipids, but not phospholipases, in vivo has be
believed to be the mechanism involved in phospholip
dosis (Ma et al., 1988). In Association of chlorphentermine with pulmonar
phospholipids, but not phospholipases, in vivo has been
believed to be the mechanism involved in phospholipi
dosis (Ma et al., 1988). In this investigation, the association
of phospholipids, but not phospholipases, in vivo has been it believed to be the mechanism involved in phospholipi-
dosis (Ma et al., 1988). In this investigation, the associ-
fation of chlorphentermine with phospholipids was believed to be the mechanism involved in phospholipi-1983
dosis (Ma et al., 1988). In this investigation, the associ-file
ation of chlorphentermine with phospholipids was stud-
drol by quantitating radioactive drug in the dosis (Ma et al., 1988). In this investigation, the associ-
filement of chlorphentermine with phospholipids was stud-
ied by quantitating radioactive drug in the lipid fraction
particle bound to the phospholipids or the dr of the lung tissue. There may be a technical problem in a interpreting these results because the drug is not covalently bound to the phospholipids or the drug may be soluted with lipids causing an artifact. This was of is interpreting these results because the drug is not covalently bound to the phospholipids or the drug may be coeluted with lipids causing an artifact. This was of particular concern in our studies of amiodarone uptake exper lently bound to the phospholipids or the drug may be serceluted with lipids causing an artifact. This was of is particular concern in our studies of amiodarone uptake broexperiments (Kodavanti and Mehendale, 1991). We obs particular concern in our studies of amiodarone uptake
experiments (Kodavanti and Mehendale, 1991). We ob-
served that the 2:1 mixture of chloroform:methanol used
for the extraction of lipids also extracted free (unbound)
 particular concern in our studies of amiodarone uptake browsperiments (Kodavanti and Mehendale, 1991). We observed that the 2:1 mixture of chloroform:methanol used photofor the extraction of lipids also extracted free (unb experiments (Kodavanti and Mehendale, 1991). We observed that the 2:1 mixture of chloroform:methanol used por the extraction of lipids also extracted free (unbound) examiodarone from the aqueous solution (Kodavanti and pMe served that the 2:1 mixture of chloroform:methanol used
for the extraction of lipids also extracted free (unbound) et
amiodarone from the aqueous solution (Kodavanti and ph
Mehendale, 1991). If such a likely situation prev for the extraction of lipids also extracted free (unbound) et amiodarone from the aqueous solution (Kodavanti and photometremine, 1991). If such a likely situation prevails for duchlorphentermine, no conclusion can be draw amiodarone from the aqueous solution (Kodavanti a
Mehendale, 1991). If such a likely situation prevails
chlorphentermine, no conclusion can be drawn from t
above study of the association of chlorphentermine w.
the lipid fr Mehendale, 1991). If such a likely situation prevails
chlorphentermine, no conclusion can be drawn from a
hove study of the association of chlorphentermine w
the lipid fraction. In our studies, not only chlo
form:methanol chlorphentermine, no conclusion can be drawn from the nabove study of the association of chlorphentermine with p
the lipid fraction. In our studies, not only chloro-
form:methanol extracted 100% of the unbound amioda-
rone above study of the association of chlorphentermine with photo-
the lipid fraction. In our studies, not only chloro-
form:methanol extracted 100% of the unbound amioda-
rone from the aqueous phase, the free drug also migrat the lipid fraction. In our studies, not only chlomather form: methanol extracted 100% of the unbound amic rone from the aqueous phase, the free drug also migration of various phosphotic separation of various phosphoids (Ko form:methanol extracted 100% of the unbound amioda-
rone from the aqueous phase, the free drug also migrated talong with dipalmitoylphosphatidylcholine in the thin
layer chromatographic separation of various phospho-
lipid rone from the aqueous phase, the free drug also migrated
along with dipalmitoylphosphatidylcholine in the thin
layer chromatographic separation of various phospho-
lipids (Kodavanti and Mehendale, 1991). Because of this
ki along with dipalmitoylphosphatidylcholine in the this layer chromatographic separation of various phospholipids (Kodavanti and Mehendale, 1991). Because of this hind of inherent technical problem and the characteristic rev layer chromatographic separation of various phospho-
lipids (Kodavanti and Mehendale, 1991). Because of this
kind of inherent technical problem and the characteristic
at reversibility in drug binding to phospholipids, it i lipids (Kodavanti and Mehendale, 1991). Because of this be
kind of inherent technical problem and the characteristic afferent
reversibility in drug binding to phospholipids, it is diffi-
cult to rule out the possibility th reversibility in drug binding to phospholipids, it is difficant cult to rule out the possibility that the association of where drugs with phospholipids in vivo could be involved as a chermechanism rendering the phospholipi cult to rule out the possibility that the association of which
drugs with phospholipids in vivo could be involved as a chomechanism rendering the phospholipid-drug complex an was
unsuitable substrate for phospholipases. Al drugs with phospholipids in vivo could be involved
mechanism rendering the phospholipid-drug comple:
unsuitable substrate for phospholipases. Although
should consider that drug binding to phospholipid
vitro is strongly cor mechanism rendering the phospholipid-drug complex
unsuitable substrate for phospholipases. Although of
should consider that drug binding to phospholipids
vitro is strongly correlated with their in vivo phospho
pidosis-indu unsuitable substrate for phospholipas
should consider that drug binding to
vitro is strongly correlated with their i
pidosis-inducing potency, the obtaining
ing direct evidence would be desirable.
Hostetler and his coinves ould consider that drug binding to phospholipids
tro is strongly correlated with their in vivo phospho
dosis-inducing potency, the obtaining of more conving
direct evidence would be desirable.
Hostetler and his coinvestiga

vitro is strongly correlated with their in vivo phospholipidosis-inducing potency, the obtaining of more convincing direct evidence would be desirable.
Hostetler and his coinvestigators studied the inhibitory effects of se pidosis-inducing potency, the obtaining of more convincing direct evidence would be desirable.
Hostetler and his coinvestigators studied the inhibitory effects of several CADs on lysosomal phospholipases
A and C isolated f ing direct evidence would be desirable.
Hostetler and his coinvestigators studied the inhitory effects of several CADs on lysosomal phospholipa
A and C isolated from the rat liver and lung (Hostet
and Matsuzawa, 1981; Host Hostetler and his coinvestigators studied the inhibitory effects of several CADs on lysosomal phospholipases not and C isolated from the rat liver and lung (Hostetler nand Matsuzawa, 1981; Hostetler et al., 1986). Amiodato tory effects of several CADs on lysosomal phospholipases
A and C isolated from the rat liver and lung (Hostetler
and Matsuzawa, 1981; Hostetler et al., 1986). Amioda-
rone was shown to be the most potent inhibitor of (
pho A and C isolated from the rat liver and lung (Hostetler nat
and Matsuzawa, 1981; Hostetler et al., 1986). Amioda-
rone was shown to be the most potent inhibitor of C c
phospholipases in vitro (Hostetler et al., 1986; Marti and Matsuzawa, 1981; Hostetler et al., 1986). Amioda-
rone was shown to be the most potent inhibitor of C
phospholipases in vitro (Hostetler et al., 1986; Martin et ly
al., 1989). Except for the drug amiodarone, there is a rone was shown to be the most potent inhibitor of phospholipases in vitro (Hostetler et al., 1986; Martin et al., 1989). Except for the drug amiodarone, there is a correlation between drug concentration and inhibition of p phospholipases in vitro (Hostetler et al., 1986; Martin et lal., 1989). Except for the drug amiodarone, there is a correlation between drug concentration and inhibition of phospholipases in the lysosome. Although amiodaron al., 1989). Except for the drug amiodarone, there is a cercorrelation between drug concentration and inhibition of garehospholipases in the lysosome. Although amiodarone vividoes not seem to be highly lysosomotropic, Hoste correlation between drug concentration and inhibition ophospholipases in the lysosome. Although amiodaror
does not seem to be highly lysosomotropic, Hostetler of
al. (1986) suggested that the effect still can be see
becaus phospholipases in the lysosome. Although amiodarone
does not seem to be highly lysosomotropic, Hostetler et
al. (1986) suggested that the effect still can be seen
because of the high potency of this drug to inhibit phos-
p does not seem to be highly lysosomotropic, Hostetler et li
al. (1986) suggested that the effect still can be seen si
because of the high potency of this drug to inhibit phos-
pholipases at very low concentrations. Addition al. (1986) suggested that the effect still can be seen
because of the high potency of this drug to inhibit phos-
pholipases at very low concentrations. Additional studies
are needed to evaluate the intracellular distributi because of the high potency of this drug to inhibit phos-
pholipases at very low concentrations. Additional studies
are needed to evaluate the intracellular distribution of
amiodarone. Autoradiographic analysis of intracel pholipases at very low concentrations. Additional studies
are needed to evaluate the intracellular distribution of
amiodarone. Autoradiographic analysis of intracellular
distribution and other approaches such as fluorescen are needed to evalu
amiodarone. Autors
distribution and ot.
probe measurement
vide likely answers.
Grabner (1987) p niodarone. Autoradiographic analysis of intracellular
stribution and other approaches such as fluorescent
obe measurements of drug concentrations might pro-
de likely answers.
Grabner (1987) postulated that imipramine and

of the lung tissue. There may be a technical problem in al., 1981), bee venom (Upreti and Jain, 1980), and plate-
interpreting these results because the drug is not cova-
lets (Kannagi and Koizumi, 1979). Grabner (1987) o ${\small \begin{array}{l} \textbf{ospholipase A}_2 \textbf{ activity by decreasing} \\ \textbf{the transition temperature of the phospholipid substrate,} \end{array}}$ ospholiphosis

the transition temperature of the phospholipid substrate,

the transition temperature of the phospholipid substrate,

because the effect of imipramine on the temperature ospHOLIPIDOSIS 343
broxol influence phospholipase A_2 activity by decreasing
the transition temperature of the phospholipid substrate,
because the effect of imipramine on the temperature
profile of the phospholipase $A_$ broxol influence phospholipase A_2 activity by decreasing
the transition temperature of the phospholipid substrate,
because the effect of imipramine on the temperature
profile of the phospholipase A_2 activity is very the transition temperature of the phospholipid substrate,
because the effect of imipramine on the temperature
profile of the phospholipase A_2 activity is very similar to
its action on the phase transition profile (Kurs because the effect of imipramine on the temperature because the effect of imipramine on the temperature
profile of the phospholipase A_2 activity is very similar to
its action on the phase transition profile (Kursch et al.,
1983). A correspondence of the temperature acti profile of the phospholipase A_2 activity is very similar to
its action on the phase transition profile (Kursch et al.,
1983). A correspondence of the temperature activity pro-
file of phospholipase A_2 in relation to its action on the phase transition profile (Kursch et al., 1983). A correspondence of the temperature activity profile of phospholipase A_2 in relation to phospholipid hydrolysis was shown for phospholipase A_2 from p 1983). A correspondence of the temperature activity pr
file of phospholipase A_2 in relation to phospholipid h
drolysis was shown for phospholipase A_2 from porcin
pancreas (Op den Kamp et al., 1975; Goormaghtigh
al., file of phospholipase A_2 in relation to phospholipid hydrolysis was shown for phospholipase A_2 from porcine pancreas (Op den Kamp et al., 1975; Goormaghtigh et al., 1981), bee venom (Upreti and Jain, 1980), and plat pancreas (Op den Kamp et al., 1975; Goormaghtigh et pancreas (Op den Kamp et al., 1975; Goormaghtigh et al., 1981), bee venom (Upreti and Jain, 1980), and plate-
lets (Kannagi and Koizumi, 1979). Grabner (1987) observed that the hydrolytic potency of phospholipase A_2 is al., 1981), bee venom (Upreti and Jain, 1980), and plate-
lets (Kannagi and Koizumi, 1979). Grabner (1987) ob-
served that the hydrolytic potency of phospholipase A₂
is not substantially influenced by imipramine and am-
 lets (Kannagi and Koizumi, 1979). Grabner (1987) observed that the hydrolytic potency of phospholipase A_2 is not substantially influenced by imipramine and ambroxol. These studies suggest that CADs interfere with the m served that the hydrolytic potency of phospholipase A_2
is not substantially influenced by imipramine and am-
broxol. These studies suggest that CADs interfere with
the membrane bilayer structure and may not alter the
p is not substantially influenced by imipramine and am-
broxol. These studies suggest that CADs interfere with
the membrane bilayer structure and may not alter the
phospholipase properties by binding to the enzyme. Ma
et al the membrane bilayer structure and may not alter the phospholipase properties by binding to the enzyme. Ma
et al. (1985) also favor this idea that the inhibition of phospholipase A_2 in the presence of chlorphentermine phospholipase properties by binding to the enzyme. Met al. (1985) also favor this idea that the inhibition ophospholipase A_2 in the presence of chlorphentermine due to the formation of a drug-phospholipid complemaking pholipases. hosterlar and his coinvestigators (Matsuzawa and observation of a drug-phospholipid complex, aking the complex an unsuitable substrate for phostolipases.
Hostetler and his coinvestigators (Matsuzawa and ostetler, 1980b; H

reversibility in drug binding to phospholipids, it is diffi-
cult to rule out the possibility that the association of which amiodarone binding to dipalmitoylphosphatidyl-
drugs with phospholipids in vivo could be involved the membrane bilayer structure and may not alter the phospholipase expertises by binding to the enzyme. Ma

et al. (1985) also favor this idea that the inhibition of

phospholipase A₃ in the presence of chlorphentermine due to the formation of a drug-phospholipid complex
making the complex an unsuitable substrate for phos
pholipases.
Hostetler and his coinvestigators (Matsuzawa and
Hostetler, 1980b; Hostetler and Matsuzawa, 1981; Hos
tetl making the complex an unsuitable substrate for phos-
pholipases.
Hostetler and his coinvestigators (Matsuzawa and
Hostetler, 1980b; Hostetler and Matsuzawa, 1981; Hos-
tetler, 1984; Kubo and Hostetler, 1985, 1987; Hostetle pholipases.

Hostetler and his coinvestigators (Matsuzawa and

Hostetler, 1980b; Hostetler and Matsuzawa, 1981; Hos-

tetler, 1984; Kubo and Hostetler, 1985, 1987; Hostetler

et al., 1986, 1988) suggested that drugs comple Hostetler and his coinvestigators (Matsuzawa and Hostetler, 1980b; Hostetler and Matsuzawa, 1981; Hostetler, 1984; Kubo and Hostetler, 1985, 1987; Hostetler et al., 1986, 1988) suggested that drugs complex with enzymes and Hostetler, 1980b; Hostetler and Matsuzawa, 1981; Hostetler, 1984; Kubo and Hostetler, 1985, 1987; Hostetler et al., 1986, 1988) suggested that drugs complex with enzymes and inhibit phospholipases. Kinetically, it will be et al., 1986, 1988) suggested that drugs complex with enzymes and inhibit phospholipases. Kinetically, it will be difficult to prove that the enzyme was or was not et al., 1986, 1988) suggested that drugs complex with
enzymes and inhibit phospholipases. Kinetically, it will
be difficult to prove that the enzyme was or was not
affected simply by measuring the activity. We have ob-
se enzymes and inhibit phospholipases. Kinetica
be difficult to prove that the enzyme was or
affected simply by measuring the activity. We
served this phenomenon in our drug-binding
which amiodarone binding to dipalmitoylphos be difficult to prove that the enzyme was or was not
affected simply by measuring the activity. We have ob-
served this phenomenon in our drug-binding studies in
which amiodarone binding to dipalmitoylphosphatidyl-
choline served this phenomenon in our drug-binding studies in served this phenomenon in ou
which amiodarone binding to
choline at a hydrophobic site
was still half the quantity of
free drug (Joshi et al., 1988).
There are only a few repor hich amiodarone binding to dipalmitoylphosphatidyl-
oline at a hydrophobic site was saturated when there
as still half the quantity of amiodarone remaining as
se drug (Joshi et al., 1988).
There are only a few reports conc

choline at a hydrophobic site was saturated when there was still half the quantity of amiodarone remaining as free drug (Joshi et al., 1988).
There are only a few reports concerning the in vivo inhibition of phospholipases was still half the quantity of amiodarone remaining as
free drug (Joshi et al., 1988).
There are only a few reports concerning the in vivo
inhibition of phospholipases. Inhibition of phospholipase
A by gentamicin and phos free drug (Joshi et al., 1988).
There are only a few reports concerning the in vivo
inhibition of phospholipases. Inhibition of phospholipase
A by gentamicin and phospholipase C inhibition by
chlorphentermine were studied There are only a few reports concerning the in vivo
inhibition of phospholipases. Inhibition of phospholipase
A by gentamicin and phospholipase C inhibition by
chlorphentermine were studied (Kacew, 1987, 1988).
However, th inhibition of phospholipases. Inhibition of phospholip
A by gentamicin and phospholipase C inhibition
chlorphentermine were studied (Kacew, 1987, 198
However, the effects of a large number of other drugs
not known and thes A by gentamicin and phospholipase C inhibition
chlorphentermine were studied (Kacew, 1987, 19
However, the effects of a large number of other drug
not known and these investigators used crude hom
nates for the estimation o chlorphentermine were studied (Kacew, 1987, 1988).
However, the effects of a large number of other drugs are
not known and these investigators used crude homoge-
nates for the estimation of phospholipases. Chlorphen-
termi However, the effects of a large number of other drugs are
not known and these investigators used crude homoge-
nates for the estimation of phospholipases. Chlorphen-
termine in vivo was able to inhibit phospholipase A and
 not known and these investigators used crude homogenates for the estimation of phospholipases. Chlorphentermine in vivo was able to inhibit phospholipase A and C of alveolar macrophages without any effect on lung lysosomal nates for the estimation of phospholipases. Chlorphen-
termine in vivo was able to inhibit phospholipase A and
C of alveolar macrophages without any effect on lung
lysosomal phospholipase (Kodavanti et al., 1991b). Re-
cen termine in vivo was able to inhibit phospholipase A and
C of alveolar macrophages without any effect on lung
lysosomal phospholipase (Kodavanti et al., 1991b). Re-
cent studies have revealed substantial information re-
gar C of alveolar macrophages without any effect on l
lysosomal phospholipase (Kodavanti et al., 1991b).
cent studies have revealed substantial information
garding amiodarone- and desethylamiodarone-induce
vivo inhibition of p lysosomal phospholipase (Kodavanti et al., 1991b). Recent studies have revealed substantial information regarding amiodarone- and desethylamiodarone-induced in vivo inhibition of phospholipases in the lung. Phospholipases cent studies have revealed substantial information regarding amiodarone- and desethylamiodarone-induced in
vivo inhibition of phospholipases in the lung. Phospho-
lipases of the lung lysosomes were inhibited with tran-
sie garding amiodarone- and desethylamiodarone-induced i
vivo inhibition of phospholipases in the lung. Phospho
lipases of the lung lysosomes were inhibited with tran
sient recovery during the treatment (Kodavanti an
Mehendale vivo inhibition of phospholipases in the lung. Phospholipases of the lung lysosomes were inhibited with transient recovery during the treatment (Kodavanti and Mehendale, 1991). The inhibition of macrophage phospholipases w lipases of the lung ly
sient recovery durir
Mehendale, 1991). T
pholipases was subst
during the treatment
Although our stu ehendale, 1991). The inhibition of macrophage phos-
olipases was substantial with no recovery in activity
ring the treatment.
Although our studies with amiodarone indicate a
rong correlation between phospholipase inhibitio

Mehendale, 1991). The inhibition of macrophage phos-
pholipases was substantial with no recovery in activity
during the treatment.
Although our studies with amiodarone indicate a
strong correlation between phospholipase in pholipases was substantial with no recovery in activity
during the treatment.
Although our studies with amiodarone indicate a
strong correlation between phospholipase inhibition and
phospholipidosis, it is difficult to exp during the treatment.

Although our studies with amiodarone indicate

strong correlation between phospholipase inhibition an

phospholipidosis, it is difficult to explain the actions c

all CADs based only on this mechanis Although our studies with amiodarone indicate a
strong correlation between phospholipase inhibition and
phospholipidosis, it is difficult to explain the actions of
all CADs based only on this mechanism. Also, the spec-
ifi

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lipid substrate being affected, proportion of substrates

present in tissue, and the role in metabolism of phospho-Example 1944

present in tissue, and the role in metabolism of substrate

present in tissue, and the role in metabolism of phosp

lipids should be considered with care (Heath and Jac KODAVANT

lipid substrate being affected, proportion of substrate

present in tissue, and the role in metabolism of phosph

lipids should be considered with care (Heath and Jaco

son, 1980a,b). The de novo pathways of phos something affected, proportion of substressent in tissue, and the role in metabolism of photolipids should be considered with care (Heath and J son, 1980a,b). The de novo pathways of phosphatholine synthesis in the lung pr lipid substrate being affected, proportion of substrate present in tissue, and the role in metabolism of phosph
lipids should be considered with care (Heath and Jaccson, 1980a,b). The de novo pathways of phosphatid
choline present in tissue, and the role in metabolism of phospho-
lipids should be considered with care (Heath and Jacob-
sigs on, 1980a,b). The de novo pathways of phosphatidyl-
int
choline synthesis in the lung produce principal lipids should be considered with care (Heath and Jacobson, 1980a,b). The de novo pathways of phosphatidyl-choline synthesis in the lung produce principally unsaturated molecules (Possmayer et al., 1977; Rooney and Wai-Lee, son, 1980a,b). The de novo pathways of phosphatidyl-
choline synthesis in the lung produce principally unsat-
urated molecules (Possmayer et al., 1977; Rooney and
Wai-Lee, 1977) that must be converted to dipalmitoyl
speci choline synthesis in the lung produce principally unsat-
urated molecules (Possmayer et al., 1977; Rooney and chlo
Wai-Lee, 1977) that must be converted to dipalmitoyl dosi
species (saturated) by a remodeling process (Bru urated molecules (Possmayer et al., 1977; Roone
Wai-Lee, 1977) that must be converted to dipal
species (saturated) by a remodeling process (Br
and van den Bosch, 1977) involving phospholip-
action. Under normal conditions, Wai-Lee, 1977) that must be converted to dipalmitoyl dospecies (saturated) by a remodeling process (Brumley R and van den Bosch, 1977) involving phospholipase A_2 the action. Under normal conditions, the dipalmitoylphos species (saturated) by a remodeling process (Brumley R
and van den Bosch, 1977) involving phospholipase A_2 th
action. Under normal conditions, the dipalmitoylphos-
phatidylcholine is not degraded by these enzymes (Heat and van den Bosch, 1977) involving phospholipase A_2
action. Under normal conditions, the dipalmitoylphos-
phatidylcholine is not degraded by these enzymes (Heath
and Jacobson, 1980a). Therefore, it is difficult to envi action. Under normal conditions, the dipalmitoylphos-
phatidylcholine is not degraded by these enzymes (Heath
and Jacobson, 1980a). Therefore, it is difficult to envision
a mechanistic role for CAD inhibition of phospholi phatidylcholine is not degraded by these enzymes (Heath phand Jacobson, 1980a). Therefore, it is difficult to envision a mechanistic role for CAD inhibition of phospholipase spectrally because A_2 in CAD-induced phospho and Jacobson, 1980a). Therefore, it is difficult to envise a mechanistic role for CAD inhibition of phospholip A_2 in CAD-induced phospholipidosis, especially becan increase in unsaturated phospholipids has not beyorted a mechanistic role for CAD inhibition of phospholipas A_2 in CAD-induced phospholipidosis, especially becaus an increase in unsaturated phospholipids has not beerported. The substrate specificity and types of phospholipi A_2 in CAD-induced phospholipidosis, especially because an increase in unsaturated phospholipids has not been reported. The substrate specificity and types of phospholipids being affected by CADs should be considered th an increase in unsaturated phospholipids has not been
reported. The substrate specificity and types of phospho-
lipids being affected by CADs should be considered thor-
oughly before invoking inhibition of any particular p phospholipidosis. oughly before invoking inhibition of any particular phos-
pholipase as a generalized mechanism of drug-induced
phospholipidosis.
D. Effects of Cationic Amphiphilic Drugs on
Phospholipid Synthesis

D. Effects of Cationic Amphiphilic Drugs on

One can postulate that the mechanism of CAD-in-
duced phospholipidosis should either involve decreased
degradation or increased synthesis of phospholipid(s). D. Effects of Cationic Amphiphilic Drugs on
Phospholipid Synthesis
One can postulate that the mechanism of CAD-i
duced phospholipidosis should either involve decreas
degradation or increased synthesis of phospholipid
Some Phospholipid Synthesis

One can postulate that the mechanism of CAD-in-

duced phospholipidosis should either involve decreased

degradation or increased synthesis of phospholipid(s).

Some critical examples from in vitro One can postulate that the mechanism of CAD-in-
duced phospholipidosis should either involve decreased Inter-
degradation or increased synthesis of phospholipid(s). Phosp
Some critical examples from in vitro and in vivo st duced phospholipidosis should either involve decrease
degradation or increased synthesis of phospholipid(s)
Some critical examples from in vitro and in vivo studie
are available to suggest that CADs do have effects of
phos degradation or increased synthesis of phospholipid(s).
Some critical examples from in vitro and in vivo studies
are available to suggest that CADs do have effects on
phospholipid synthesis. In human skin fibroblasts, chlo-Some critical examples from in vitro and in vivo studies
are available to suggest that CADs do have effects on
phospholipid synthesis. In human skin fibroblasts, chlo-
roquine in vitro stimulates incorporation of precursor are available to suggest that CADs do have effects on the phospholipid synthesis. In human skin fibroblasts, chlolector is roquine in vitro stimulates incorporation of precursor mecomponents into fatty acid, phospholipid, phospholipid synthesis. In human skin fibroblasts, chlo-
roquine in vitro stimulates incorporation of precursor
rechanistic aspects of drug-induced phospholipidosis is
components into fatty acid, phospholipid, and choleste roquine in vitro stimulates incorporation of precursor
components into fatty acid, phospholipid, and cholesterol
and stimulates their synthesis (Chen et al., 1986). In the
rat liver, chloroquine in vitro has been shown to components into fatty acid, phospholipid, and cholesterol
and stimulates their synthesis (Chen et al., 1986). In the
rat liver, chloroquine in vitro has been shown to increase
glycerol incorporation into phospholipids with and stimulates their synthesis (Chen et al., 1986). In the rat liver, chloroquine in vitro has been shown to increasubly
glycerol incorporation into phospholipids within the mechosomes as well as glycerol transport to the rat liver, chloroquine in vitro has been shown to increase
glycerol incorporation into phospholipids within the mi-
crosomes as well as glycerol transport to the lysosomes
(Matsuzawa and Hostetler, 1980a). However, the mec glycerol incorporation into phospholipids within the microsomes as well as glycerol transport to the lysosomes (Matsuzawa and Hostetler, 1980a). However, the mechanism by which chloroquine stimulates phospholipid synthesis crosomes as well as glycerol transport to the lysose (Matsuzawa and Hostetler, 1980a). However, the m
anism by which chloroquine-stimulates phospho
synthesis and transport is not clear. Although tents
these observations pe (Matsuzawa and Hostetler, 1980a). However, the mechanism by which chloroquine stimulates phospholipiesynthesis and transport is not clear. Although tentative these observations permit us to infer that chloroquine induced p anism by which chloroquine stimulates phospholip synthesis and transport is not clear. Although tentative these observations permit us to infer that chloroquine induced phospholipidosis may be due to increased phospholipid synthesis and transport is not clear. Although these observations permit us to infer that chlo induced phospholipidosis may be due to increase pholipid synthesis (Reasor and Hostetler, 1984 promazine, which has minimal pho these observations permit us to infer that chloroquine-
induced phospholipidosis may be due to increased phos-
pholipid synthesis (Reasor and Hostetler, 1984). Chlor-
promazine, which has minimal phospholipidosis-induc-
in induced phospholipidosis may be due to increased pholipid synthesis (Reasor and Hostetler, 1984). Chipromazine, which has minimal phospholipidosis-ind
ing potency, affects the intermediary metabolism
phospholipids by inhib pholipid synthesis (Reasor and Hostetler, 1984). Chlor-
promazine, which has minimal phospholipidosis-induc-
ing potency, affects the intermediary metabolism of lipids. Metabolically inert drugs, which bind with phos-
phos promazine, which has minimal phospholipidosis-induc-
ing potency, affects the intermediary metabolism of
phospholipids by inhibiting 1-acylglycerol-3-phosphate
acyltransferase (Yada et al., 1986). Chlorpromazine also
affec ing potency, affects the intermediary metabol
phospholipids by inhibiting 1-acylglycerol-3-pho
acyltransferase (Yada et al., 1986). Chlorpromazine
affects phospholipid synthesis in vitro. Leli and l
(1987) reported that ch phospholipids by inhibiting 1-acylglycerol-3-phosph
acyltransferase (Yada et al., 1986). Chlorpromazine affects phospholipid synthesis in vitro. Leli and Hau
(1987) reported that chlorpromazine, desmethylimin
mine, propran acyltransferase (Yada et al., 1986). Chlorpromazine
affects phospholipid synthesis in vitro. Leli and H
(1987) reported that chlorpromazine, desmethylin
mine, propranolol, and other CADs may affect pho
lipid metabolism by affects phospholipid synthesis in vitro. Leli and Hauser (1987) reported that chlorpromazine, desmethylimipramine, propranolol, and other CADs may affect phospholipid metabolism by inhibiting cystosine triphosphate-phospho (1987) reported that chlorpromazine, desmethylimipra-
mine, propranolol, and other CADs may affect phospho-
drugs. The information on comparative effects of chlo-
lipid metabolism by inhibiting cystosine triphosphate-
inat mine, propranolol, and other CADs may affect phospho-
lipid metabolism by inhibiting cystosine triphosphate-
phosphocholine cytidyltransferase, thus decreasing in-
corporation of precursors into phosphatidylcholine and
pho lipid metabolism by inhibiting cystosine triphosphate-
phosphocholine cytidyltransferase, thus decreasing in-
corporation of precursors into phosphatidylcholine and
phosphatidylethanolamine or inhibiting phosphatidic m
aci phosphocholine cytidyltransferase, thus decreasing in corporation of precursors into phosphatidylcholine and phosphatidylethanolamine or inhibiting phosphatidiacid phosphohydrolase and thus stimulating synthesis o acidic p corporation of precursors into phosphatidylcholine and
phosphatidylethanolamine or inhibiting phosphatidic m
acid phosphohydrolase and thus stimulating synthesis of
diciphospholipids by inositol exchange reactions. Kar-
ab phosphatidylethanolamine or inhibiting phosphatid
acid phospholydrolase and thus stimulating synthesis
acidic phospholipids by inositol exchange reactions. Ka
abelnik and Zbinden (1976) observed an inhibition
phospholipid

KODAVANTI AND MEHENDALE
of substrates ured by incorporation of $[^{14}C]$ palmitic acid into phospho-
n of phospho- lipids, by chlorphentermine and RMI 10.393. However. significant stimulation of 14 C loalmitate incorporation MEHENDALE
ured by incorporation of $[^{14}C]$ palmitic acid into phospho-
lipids, by chlorphentermine and RMI 10,393. However,
significant stimulation of $[^{14}C]$ palmitate incorporation
into phospholipids was seen with ano ured by incorporation of $[{}^{14}C]$ palmitic acid into phos
lipids, by chlorphentermine and RMI 10,393. How
significant stimulation of $[{}^{14}C]$ palmitate incorpora
into phospholipids was seen with another phospho
dotic ag ured by incorporation of $[^{14}C]$ palmitic acid into phospholipids, by chlorphentermine and RMI 10,393. However, significant stimulation of $[^{14}C]$ palmitate incorporation into phospholipids was seen with another phospho lipids, by chlorphentermine and RMI 10,393. How
significant stimulation of $[^{14}C]$ palmitate incorporation
into phospholipids was seen with another phospho
dotic agent (RO 4–4318). The authors suggested
chlorphentermine significant stimulation of $[^{14}C]$ palmitate incorporation
into phospholipids was seen with another phospholipi-
dotic agent (RO 4-4318). The authors suggested that
chlorphentermine and RMI 10,393 induce phospholipi-
dos dotic agent (RO 4-4318). The authors suggested that chlorphentermine and RMI 10,393 induce phospholipidosis by decreasing phospholipid degradation, whereas RO 4-4318 induces phospholipidosis by increasing syndotic agent (RO 4–4318). The authors suggested that
chlorphentermine and RMI 10,393 induce phospholipi-
dosis by decreasing phospholipid degradation, whereas
RO 4–4318 induces phospholipidosis by increasing syn-
thesis. In chlorphentermine and RMI 10,393 induce phospholip dosis by decreasing phospholipid degradation, where RO 4-4318 induces phospholipidosis by increasing synthesis. In accord with these observations, it was also reported that dosis by decreasing phospholipid degradation, whereas RO 4-4318 induces phospholipidosis by increasing synthesis. In accord with these observations, it was also reported that chlorphentermine does not increase phospholipid O 4–4318 induces phospholipidosis by increasing synesis. In accord with these observations, it was also ported that chlorphentermine does not increase phosolipid synthesis in the rat lung (Gonmori et al., 1986). Results of

reported that chlorphentermine does not increase phospholipid synthesis in the rat lung (Gonmori et al., 1986).
Results of the above reports suggest that CADs have
specific effects on various enzyme systems involved in
pho reported that chlorphentermine does not increase p
pholipid synthesis in the rat lung (Gonmori et al., 19
Results of the above reports suggest that CADs l
specific effects on various enzyme systems involve
phospholipid syn pholipid synthesis in the rat lung (Gonmori et al., 1986).
Results of the above reports suggest that CADs have
specific effects on various enzyme systems involved in
phospholipid synthesis and catabolism. No generaliza-
ti Results of the above reports suggest that CADs have specific effects on various enzyme systems involved phospholipid synthesis and catabolism. No generalize tion among all CADs can be made relative to their effects on the specific effects on various enzyme systems involved in
phospholipid synthesis and catabolism. No generaliza-
tion among all CADs can be made relative to their effects
on the enzymes involved in synthesis of phospholipids.
 phospholipid synthesis and catabolism. No generalization among all CADs can be made relative to their effects on the enzymes involved in synthesis of phospholipids. The effects may vary with the type of cell system or tiss tion among all CADs can be made relative to their effects
on the enzymes involved in synthesis of phospholipids.
The effects may vary with the type of cell system or
tissue, species, duration of drug exposure, and the dose on the enzymes involved in synthesis of phospholipids.
The effects may vary with the type of cell system or
tissue, species, duration of drug exposure, and the dose
level used in the study. Additional evidence is needed to The effects may vary with the type of cell system or
tissue, species, duration of drug exposure, and the dose
level used in the study. Additional evidence is needed to
establish whether there is a structure-activity relati tissue, species, duration
level used in the study.
establish whether there
ship among various CA
phospholipid synthesis.
F. Correlations: Partitic From about means of the collapse in the correlation of the establish whether there is a structure-activity relation
ship among various CADs in relation to their effects
phospholipid synthesis.
E. Correlations: Partition C

D. Effects of Cationic Amphiphilic Drugs on

Phospholipid synthesis.

Phospholipidosis should either involve decreased

duced phospholipidosis should either involve decreased Interactions, Pharmacokinetics, Inhibition of
 France Schooling Cation in Francisch phospholipid synthesis.
 Tissues, Cationic Amphiphilic Drugs-Phospholipidite Drugs-Phospholipid
 Tissues, Cationic Amphiphilic Drugs-Phospholipidite
 Interactions, Pharmacokinetics phospholipid synthesis.
 E. Correlations: Partition Coefficients, Affinity f
 *Tissues, Cationic Amphiphilic Drugs-Phospholip

Interactions, Pharmacokinetics, Inhibition of*
 Phospholipases, and Phospholipidosis

Drug-

Drug-induced phospholipidosis is a manifestation of the interaction of CADs at the tissue, cellular, and mo-Tissues, Cationic Amphiphilic Drugs-Phospholipid
Interactions, Pharmacokinetics, Inhibition of
Phospholipases, and Phospholipidosis
Drug-induced phospholipidosis is a manifestation of
the interaction of CADs at the tissue, Interactions, Pharmacokinetics, Inhibition of
Phospholipases, and Phospholipidosis
Drug-induced phospholipidosis is a manifestation of
the interaction of CADs at the tissue, cellular, and mo-
lecular level. In table 1 a gr Phospholipases, and Phospholipidosis
Drug-induced phospholipidosis is a manifestation of
the interaction of CADs at the tissue, cellular, and mo-
lecular level. In table 1 a graded evaluation of various
mechanistic aspects Drug-induced phospholipidosis is a manifestation of
the interaction of CADs at the tissue, cellular, and mo-
lecular level. In table 1 a graded evaluation of various
mechanistic aspects of drug-induced phospholipidosis is
 the interaction of CADs at the tissue, cellular, and m
lecular level. In table 1 a graded evaluation of vario
mechanistic aspects of drug-induced phospholipidosis
presented. Based on the selected criteria listed in t
table lecular level. In table 1 a graded evaluation of various mechanistic aspects of drug-induced phospholipidosis is presented. Based on the selected criteria listed in the table, an outline describing phospholipidosis-inducin mechanistic aspects of drug-induced phospholipidosis is
presented. Based on the selected criteria listed in the
table, an outline describing phospholipidosis-inducing
capacity of drugs is given in fig. 4. Because most of t presented. Based on the selected criteria listed in table, an outline describing phospholipidosis-inducapacity of drugs is given in fig. 4. Because most of details have been presented in previous sections, on few major poi table, an outline describing ph
capacity of drugs is given in fig.
details have been presented in p
few major points important in u
lipidosis are reconsidered here.
It is clear from table 1 that pacity of drugs is given in fig. 4. Because most of the tails have been presented in previous sections, only a
w major points important in understanding phospho-
idosis are reconsidered here.
It is clear from table 1 that

details have been presented in previous sections, only a
few major points important in understanding phospho-
lipidosis are reconsidered here.
It is clear from table 1 that binding of CADs with
phospholipids and inhibition few major points important in understanding phospholipidosis are reconsidered here.
It is clear from table 1 that binding of CADs with phospholipids and inhibition of phospholipases are correlated with their ability to ind lipidosis are reconsidered here.
It is clear from table 1 that binding of CADs with
phospholipids and inhibition of phospholipases are cor-
related with their ability to induce phospholipidosis. The
octanol to water partit It is clear from table 1 that binding of CADs with
phospholipids and inhibition of phospholipases are cor-
related with their ability to induce phospholipidosis. The
octanol to water partition coefficient does not correlat phospholipids and inhibition of phospholipases are explaned with their ability to induce phospholipidosis.

cotanol to water partition coefficient does not corre

with phospholipidosis, nor does drug binding corre

with hy related with their ability to induce phospholipidosis. The octanol to water partition coefficient does not correlat with phospholipidosis, nor does drug binding correlat with hydrophobic and hydrophilic moieties of phospho octanol to water partition coefficient does not correlate with phospholipidosis, nor does drug binding correlate with hydrophobic and hydrophilic moieties of phospholipids. Metabolically inert drugs, which bind with phosph with phospholipidosis, nor does drug binding correlate with hydrophobic and hydrophilic moieties of phospho-
lipids. Metabolically inert drugs, which bind with phos-
pholipid on either the hydrophobic or hydrophilic moiety,
seem to be effective (fig. 4). Furthermore, specifici lipids. Metabolically inert drugs, which bind with phos-
pholipid on either the hydrophobic or hydrophilic moiety,
seem to be effective (fig. 4). Furthermore, specificity of
the phospholipid affected by drugs depends on th the phospholipid affected by drugs depends on the nature seem to be effective (fig. 4). Furthermore, specificity of
the phospholipid affected by drugs depends on the nature
of the cationic side chain and hydrophobic moiety of
drugs. The information on comparative effects of chlo the phospholipid affected by drugs depends on the nature
of the cationic side chain and hydrophobic moiety of
drugs. The information on comparative effects of chlo-
rinated and nonchlorinated drugs is not available for
pho of the cationic side chain and hydrophobic moiety of
drugs. The information on comparative effects of chlo-
rinated and nonchlorinated drugs is not available for
phospholipase inhibition. Such a comparative study
would be drugs. The information on comparative effects of chlominated and nonchlorinated drugs is not available for phospholipase inhibition. Such a comparative study would be beneficial in further defining the role and mechanism o rinated and nonchlorinated drugs is not available for phospholipase inhibition. Such a comparative study would be beneficial in further defining the role and mechanism of CAD-induced phospholipidosis. Based on the availabl phospholipase inhibition. Such a comparative study
would be beneficial in further defining the role and
mechanism of CAD-induced phospholipidosis. Based on
the available information regarding the two hypotheses,
one cannot would be beneficial in further defining the role and
mechanism of CAD-induced phospholipidosis. Based on
the available information regarding the two hypotheses,
one cannot suggest either mechanism as a generalization
for a mechanism of CAD-induced phospholipidosis. Based on
the available information regarding the two hypotheses,
one cannot suggest either mechanism as a generalization
for all CADs. The formation of a drug-phospholipid
complex

PHARMACOLOGICAL REVIEWS

EXECUSE PROSPHOLIPIDOSIS
TABLE 1
Comparison of toxicological and metabolic properties of several amphiphilic drugs^{*}
Inhibition

Propranolol <u>2</u>
 t The tabulation for phospholipidotic potency, binding capacities, affinities for the lung tissue, and metabolic elimination are given in the r of increasing effectiveness. 0, no effect; 1, mild effect; Trippianology and the tabulation for phospholipidotic potency, binding capacities, affinities for the lung tissue, and metabolic elimination are given in the ler of increasing effectiveness. 0, no effect; 1, mild effect; 2 Reasor, 1986b. **er of increasing effectiveness**. 0, no effect; 1, mild effect; 2, moderate effect; 3, maximum effect.
† References: Lullmann et al., 1978; Hostetler and Matsuzawa, 1981; Ohmiya et al., 1983; Hrubs
‡ References: Dubnick et † References: Lullmann et al., 1978; Hostetler and Matsuzawa, 1981; Ohmiya et al., 1983; Hruban, 19
‡ References: Dubnick et al., 1968; Brown, 1974; Ohmiya and Mehendale, 1980b, 1982, 1984; Camu
asor, 1986b.
§ References

FIGSPIDIIPIQUOSIS every correlation of drug-induced phospholipidosis in ethics.

Fig. 4. Proposed mechanism of drug-induced phospholipidosis in ethics.

ii iii)

because of the strong correlation that exists between fundin vivo. Reproduced with permission from Joshi and Mehendale (1989).
because of the strong correlation that exists between
binding to phospholipids and phospholipidosis.
The general picture of the mechanism seems to be that

o. Reproduced with permission from Joshi and Mehendale (1989).

cause of the strong correlation that exists between

nding to phospholipids and phospholipidosis.

The general picture of the mechanism seems to be that

ADs lipies
because of the strong correlation that exists between fur-
binding to phospholipids and phospholipidosis.
The general picture of the mechanism seems to be that
CADs interact with phospholipids and interfere with chi because of the strong correlation that exists between funding to phospholipids and phospholipidosis. The general picture of the mechanism seems to be that this CADs interact with phospholipids and interfere with chief meta binding to phospholipids and phospholipidosis.
The general picture of the mechanism seems to be that
CADs interact with phospholipids and interfere with
their metabolism at similar concentrations and with ϵ
similar pot The general picture of the mechanism seems to be that this CADs interact with phospholipids and interfere with chicken their metabolism at similar concentrations and with a and similar potency. At least with aminogly cosid CADs interact with phospholipids and interfere with chain their metabolism at similar concentrations and with a an similar potency. At least with aminogly coside antibiotics, 19 it was reported recently that changes in the their metabolism at similar concentrations and with a
similar potency. At least with aminoglycoside antibiotics,
it was reported recently that changes in the charge on
the polar side chain of the phospholipid by a drug is
 similar potency. At least with aminoglycoside antibiotics, it was reported recently that changes in the charge on the polar side chain of the phospholipid by a drug is involved in the inactivation of phospholipase and perh it was reported recently that changes in the charge on Destel oplar side chain of the phospholipid by a drug is the involved in the inactivation of phospholipase and periodicity mechanistic link haps phospholipidosis (Ming the polar side chain of the phospholipid by a drug
involved in the inactivation of phospholipase and po
haps phospholipidosis (Mingeot-Leclercq et al., 1990a,
Although there seems to be a definitive mechanistic lifetween t involved in the inactivation of phospholipase and per-
haps phospholipidosis (Mingeot-Leclercq et al., 1990a,b).
Although there seems to be a definitive mechanistic link is
between these two major effects of CADs, a finer

both and Shetty, 1986.
F, 1984; Hostetler et al., 1988.
both mechanisms, for any particular phospholip
inducing CAD needs additional experimental scru It, 1984; Hostetler et al., 1988.
both mechanisms, for any particular phospholipidosis
inducing CAD needs additional experimental scrutiny. Iv. The mechanisms, for any particular phospholipidosis-
ducing CAD needs additional experimental scrutiny.
IV. Cationic Amphiphilic Drugs, Phospholipid
Metabolism, and Regulation of Cell Function In mechanisms, for any particular phospholipidosis-

incing CAD needs additional experimental scrutiny.

N. Cationic Amphiphilic Drugs, Phospholipid

Metabolism, and Regulation of Cell Function

Cationic Amphiphilic Drugs,

Inducing CAD needs additional experimental so
 IV. Cationic Amphiphilic Drugs, Phospholipid
 A. Cationic Amphiphilic Drugs, Phospholipid
 Metabolism, and Generation of Second Messeng **IV. Cationic Amphiphilic Drugs, Phospholip Metabolism, and Regulation of Cell Function A. Cationic Amphiphilic Drugs, Phospholipid Metabolism, and Generation of Second Messengers** Understanding signal transduction pathway

Metabolism, and Regulation of Cell Function
Cationic Amphiphilic Drugs, Phospholipid
etabolism, and Generation of Second Messengers
Understanding signal transduction pathways is imported
because several phospholipidosis-in A. Cationic Amphiphilic Drugs, Phospholipid
Metabolism, and Generation of Second Messengers
Understanding signal transduction pathways is impor-
tant because several phospholipidosis-inducing CADs are
inhibitors of phospho From the Ample phase. The phospholipas

Metabolism, and Generation of Second Messengers

Understanding signal transduction pathways is impor-

tant because several phospholipidosis-inducing CADs are

inhibitors of phosphol metabolism, and deneration of Second messengers
Understanding signal transduction pathways is impor-
tant because several phospholipidosis-inducing CADs are
inhibitors of phospholipases (Couturier et al., 1984; Jeng
and Bl Understanding signal transduction pathways is important because several phospholipidosis-inducing CADs are inhibitors of phospholipases (Couturier et al., 1984; Jeng and Blumberg, 1989). Furthermore, CAD-membrane interacti tant because several phospholipidosis-inducing CADs are
inhibitors of phospholipases (Couturier et al., 1984; Jeng
and Blumberg, 1989). Furthermore, CAD-membrane in-
teractions may bring about changes in receptor-mediated
 inhibitors of phospholipases (Couturier et al., 1984; Jeng
and Blumberg, 1989). Furthermore, CAD-membrane in-
teractions may bring about changes in receptor-mediated
events (Kanaho et al., 1981; Ondrias et al., 1983; Kubo
 and Blumberg, 1989). Furthermore, CAD-membrane in-
teractions may bring about changes in receptor-mediated
events (Kanaho et al., 1981; Ondrias et al., 1983; Kubo
et al., 1986) either directly or indirectly through altered teractions may bring about changes in receptor-mediated
events (Kanaho et al., 1981; Ondrias et al., 1983; Kubo
et al., 1986) either directly or indirectly through altered
lipid metabolism. The importance of various kinds events (Kanaho et al., 1981; Ondrias et al., 1983; Kubo
et al., 1986) either directly or indirectly through altered
lipid metabolism. The importance of various kinds of
lipids and lipid by-products in the regulation of cel et al., 1986) either directly or indirectly through altered
lipid metabolism. The importance of various kinds of
lipids and lipid by-products in the regulation of cell
function and growth has been increasingly recognized
d lipid metabolism. The importance of various kinds of lipids and lipid by-products in the regulation of cell function and growth has been increasingly recognized during the last two decades. Of particular importance in this lipids and lipid by-products in the regulation of cell function and growth has been increasingly recognized during the last two decades. Of particular importance in this regard are phosphatidylinositol, diacylglycerol, ara function and growth has been increasingly recognized
during the last two decades. Of particular importance in
this regard are phosphatidylinositol, diacylglycerol, ara-
chidonic acid, prostaglandins, platelet-activating fa during the last two decades. Of particular importance in
this regard are phosphatidylinositol, diacylglycerol, ara-
chidonic acid, prostaglandins, platelet-activating factors,
and leukotrienes (Famulski and Carafoli, 1984; this regard are phosphatidylinositol, diacylglycerol, ara-
chidonic acid, prostaglandins, platelet-activating factors,
and leukotrienes (Famulski and Carafoli, 1984; Farese,
1988; Kaczmarek, 1988; Stacey, 1988; McManus and chidonic acid, prostaglandins, platelet-activating factors,
and leukotrienes (Famulski and Carafoli, 1984; Farese,
1988; Kaczmarek, 1988; Stacey, 1988; McManus and
Deavers, 1989; Tada and Kadoma, 1989). Any change in
the m and leukotrienes (Famulski and Carafoli, 1984; Farese
1988; Kaczmarek, 1988; Stacey, 1988; McManus an
Deavers, 1989; Tada and Kadoma, 1989). Any change is
the metabolism of membrane phospholipids directly of
indirectly inf 1988; Kaczmarek, 1988; Stacey, 1988; McManus a Deavers, 1989; Tada and Kadoma, 1989). Any change the metabolism of membrane phospholipids directly indirectly influences one or more of the important coponents of the phospho Deavers, 1989; Tada and Kadoma, 1989). Any change in
the metabolism of membrane phospholipids directly or
indirectly influences one or more of the important com-
ponents of the phospholipid-signaling pathway (Surew-
icz an the metabolism of membrane phospholipids directly or
indirectly influences one or more of the important com-
ponents of the phospholipid-signaling pathway (Surew-
icz and Epand, 1986; Farese, 1988). A few examples may
be c indirectly influences one or more of the important components of the phospholipid-signaling pathway (Surewicz and Epand, 1986; Farese, 1988). A few examples may be considered in this connection. Perturbation of these pathw

different ways (Blackmore, 1988; Stull et al., 1988; Col-346
different ways (Blackmore, 1988;
bran et al., 1989; Taylor, 1989).
The family of enzymes catalyzi

different ways (Blackmore, 1988; Stull et al., 1988; Colbran et al., 1989; Taylor, 1989).
The family of enzymes catalyzing phosphorylation are
the protein kinases. These enzymes are a structurally
diverse group of proteins different ways (Blackmore, 1988; Stull et al., 1988; Co
bran et al., 1989; Taylor, 1989).
The family of enzymes catalyzing phosphorylation a
the protein kinases. These enzymes are a structural
diverse group of proteins dif bran et al., 1989; Taylor, 1989).
The family of enzymes catalyzing phosphorylation are
the protein kinases. These enzymes are a structurally
diverse group of proteins differing in size, subunit struc-
ture, localization, m The family of enzymes catalyzing phosphorylation are
the protein kinases. These enzymes are a structurally
diverse group of proteins differing in size, subunit struc-
ture, localization, mechanism of action, and substrate
 the protein kinases. These enzymes are a structurally ediverse group of proteins differing in size, subunit structure, localization, mechanism of action, and substrate specificity (Nishizuka, 1984; Blackshear, 1988; Taylor diverse group of proteins differing in size, subunit structure, localization, mechanism of action, and substrate
specificity (Nishizuka, 1984; Blackshear, 1988; Taylor
1989; Colbran et al., 1989). Protein kinases are regul ture, localization, mechanism of action, and substrate specificity (Nishizuka, 1984; Blackshear, 1988; Taylor, 1989; Colbran et al., 1989). Protein kinases are regulated p
by endogenous regulatory substances. For example, specificity (Nishizuka, 1984; Blackshear, 1988; Tay
1989; Colbran et al., 1989). Protein kinases are regula
by endogenous regulatory substances. For example, p
tein kinase C is activated with diacylglycerol libera
by break 1989; Colbran et al., 1989). Protein kinases are regulate
by endogenous regulatory substances. For example, pro
tein kinase C is activated with diacylglycerol liberate
by breakdown of phospholipase (Farese, 1988). Generati by endogenous regulatory substances. For example, protein kinase C is activated with diacylglycerol liberated
by breakdown of phospholipids (Farese, 1988). Genera-
tion of diacylglycerol by phospholipase C activation stimtein kinase C is activated with diacylglycerol liberated red
by breakdown of phospholipids (Farese, 1988). Genera-
tion of diacylglycerol by phospholipase C activation stim-
ulates protein kinase C and protein phosphorylat by breakdown of phospholipids (Farese, 1988). Generation of diacylglycerol by phospholipase C activation stimulates protein kinase C and protein phosphorylation directly (Nishizuka, 1984; Housey et al., 1988; Jeng and Blum tion of diacylglycerol by phospholipase C activation stimulates protein kinase C and protein phosphorylation
directly (Nishizuka, 1984; Housey et al., 1988; Jeng and
Blumberg, 1989; Kikkawa et al., 1989; Ogita et al., 1989 ulates protein kinase C and protein phosphorylation
directly (Nishizuka, 1984; Housey et al., 1988; Jeng and
Blumberg, 1989; Kikkawa et al., 1989; Ogita et al., 1989).
Short- and long-term functional and structural changes directly (Nishizuka, 1984; Housey et al., 1988; Jeng and Blumberg, 1989; Kikkawa et al., 1989; Ogita et al., 1989).
Short- and long-term functional and structural changes are elicited in the cell (Nishizuka, 1984; Blackmor Blumberg, 1989; Kikkawa et al., 1989; Ogita et al., 19
Short- and long-term functional and structural chare elicited in the cell (Nishizuka, 1984; Blackmore, 1
Kaczmarek, 1988; Stacey, 1988; Tada and Kadoma, 1
by protein k ylation. e elicited in the cell (Nishizuka, 1984; Blackmore, 1988; eaczmarek, 1988; Stacey, 1988; Tada and Kadoma, 1989)

protein kinase C and consequent protein phosphor-

phospholipases participate in an enzymatic cascade

at gen

by protein kinase C and consequent protein phosphor-
ylation.
Phospholipases participate in an enzymatic cascade
that generates highly active lipids or transduction signals
(Champe and Harvey, 1988; Farese, 1988). For exam ylation.

Phospholipases participate in an enzymatic cascade sites that generates highly active lipids or transduction signals new (Champe and Harvey, 1988; Farese, 1988). For example, a phospholipase A_2 releases arach Phospholipases participate in an enzymatic cascade signal that generates highly active lipids or transduction signals nii.
(Champe and Harvey, 1988; Farese, 1988). For example, are phospholipase A_2 releases arachidonat that generates highly active lipids or transduction sign (Champe and Harvey, 1988; Farese, 1988). For examples phospholipase A_2 releases arachidonate, a precursor prostaglandins, and phospholipase C participates in pho (Champe and Harvey, 1988; Farese, 1988). For exam phospholipase A_2 releases arachidonate, a precurso prostaglandins, and phospholipase C participates in phosphoinositide cascade (Stryer, 1988). Second mess gers generat phospholipase A_2 releases arachidonate, a precursor prostaglandins, and phospholipase C participates in the phosphoinositide cascade (Stryer, 1988). Second messe gers generated by the breakdown of phosphatidylinosit ph prostaglandins, and phospholipase C participates in the phosphoinositide cascade (Stryer, 1988). Second messengers generated by the breakdown of phosphatidylinositol phosphates are diacylglycerol and inositol trisphosphate phosphoinositide cascade (Stryer, 1988). Second messengers generated by the breakdown of phosphatidylinositol
phosphates are diacylglycerol and inositol trisphosphate.
Most of the effects of diacylglycerol and inositol tri gers generated by the breakdown of phosphatidylinositol
phosphates are diacylglycerol and inositol trisphosphate.
Most of the effects of diacylglycerol and inositol tris-
phosphate are synergistic (Nishizuka, 1984; Stacey, Kikkawa et al., 1989; Tada and Kadoma, 1989). Whether, and to what extent, CADs influence this cascade of events has not been investigated in detail. Chlorproma-zine is one example of a CAD known to be a potent inhibitor o phosphate are synergistic (Nishizuka, 1984; Stacey, 1988; Kikkawa et al., 1989; Tada and Kadoma, 1989). Whether, and to what extent, CADs influence this cascade of events has not been investigated in detail. Chlorpromazine events has not been investigated in detail. Chlorpromazine is one example of a CAD known to be a potent inhibitor of phospholipases (Hostetler and Matsuzawa, 1981; Beckman et al., 1982; Hostetler, 1984; Kubo and and to what extent, CADs influence this cascade of bevents has not been investigated in detail. Chlorpromazine is one example of a CAD known to be a potent est inhibitor of phospholipases (Hostetler and Matsuzawa, ing 1981 events has not been investigated in detail. Chlorprom
zine is one example of a CAD known to be a pote
inhibitor of phospholipases (Hostetler and Matsuzaw
1981; Beckman et al., 1982; Hostetler, 1984; Kubo an
Hostetler, 1985 zine is one example of a CAD known to be a potent
inhibitor of phospholipases (Hostetler and Matsuzawa, ing in
1981; Beckman et al., 1982; Hostetler, 1984; Kubo and
Hostetler, 1985; Shaikh et al., 1987). Additionally, chlo inhibitor of phospholipases (Hostetler and Matsuzawa, $\frac{1981}{1881}$; Beckman et al., 1982; Hostetler, 1984; Kubo and Hostetler, 1985; Shaikh et al., 1987). Additionally, chlor-promazine is a powerful inhibitor of protein 1981; Beckman et al., 1982; Hostetler, 1984; Kubo and
Hostetler, 1985; Shaikh et al., 1987). Additionally, chlor-
promazine is a powerful inhibitor of protein kinase C
(Giedroc et al., 1985; Opstvedt et al., 1986; Jeng and Hostetler, 1985; Shaikh et al., 1987). Additionally, ch
promazine is a powerful inhibitor of protein kinas
(Giedroc et al., 1985; Opstvedt et al., 1986; Jeng
Blumberg, 1989). The question is whether CADs ac
inhibiting phos (Giedroc et al., 1985; Opstvedt et al., 1986; Jeng and Blumberg, 1989). The question is whether CADs act by inhibiting phospholipase C, and thus affect diacylglycerol-mediated protein kinase C activation, or act by inosito (Giedroc et al., 1985; Opstvedt et al., 1986; Jeng
Blumberg, 1989). The question is whether CADs act
inhibiting phospholipase C, and thus affect diacylg
erol-mediated protein kinase C activation, or act
inositol trisphosph lumberg, 1989). The question is whether CADs act by
hibiting phospholipase C, and thus affect diacylglyc-
ol-mediated protein kinase C activation, or act by
ositol trisphosphate-mediated calcium mobilization.
It is known

erol-mediated protein kinase C activation, or act by inositol trisphosphate-mediated calcium mobilization.
It is known that serotonin binds to its receptor and thereby mediates the activation of phospholipase C (Cor-
bet e erol-mediated protein kinase C activation, or act by
inositol trisphosphate-mediated calcium mobilization.
It is known that serotonin binds to its receptor and
thereby mediates the activation of phospholipase C (Cor-
bet inositol trisphosphate-mediated calcium mobilization.
It is known that serotonin binds to its receptor and
thereby mediates the activation of phospholipase C (Cor-
bet et al., 1985; Li et al., 1988; Reinhardt, 1989). In th It is known that serotonin binds to its receptor and
thereby mediates the activation of phospholipase C (Cor-
bet et al., 1985; Li et al., 1988; Reinhardt, 1989). In this
case, do CADs affect serotonin metabolism by their thereby mediates the activation of phospholipase C (Corbet et al., 1985; Li et al., 1988; Reinhardt, 1989). In this case, do CADs affect serotonin metabolism by their effect on phospholipase C, receptor binding, monoamine bet et al., 1985; Li et al., 1988; Reinhardt, 1989). In this case, do CADs affect serotonin metabolism by their effect on phospholipase C, receptor binding, monoamine oxidase inhibition, or simply by inhibiting serotonin u case, do CADs affect serotonin metabolism by their effect
on phospholipase C, receptor binding, monoamine oxi-
dase inhibition, or simply by inhibiting serotonin uptake
(Mehendale, 1984; Zychlinski and Montgomery, 1985a,b; on phospholipase C, receptor bind
dase inhibition, or simply by inhibit
(Mehendale, 1984; Zychlinski and N
Trouve and Nahas, 1987; Li et a
myriad of effects can be envisioned
Much work is needed before prec (Mehendale, 1984; Zychlinski and Montgomery, 1985a,b;
Trouve and Nahas, 1987; Li et al., 1988)? Clearly, a
myriad of effects can be envisioned.
Much work is needed before predominant and critical

(Mehendale, 1984; Zychlinski and Montgomery, 1985a,b; Trouve and Nahas, 1987; Li et al., 1988)? Clearly, a myriad of effects can be envisioned.
Much work is needed before predominant and critical interactions can be identi Trouve and Nahas, 1987; Li et al., 1988)? Clearly, a
myriad of effects can be envisioned.
Much work is needed before predominant and critical
interactions can be identified. One must consider mu-
tually antagonizing effect myriad of effects can be envisioned.
Much work is needed before predominant and critic
interactions can be identified. One must consider m
tually antagonizing effects as well as potentiating effec
before the predominant an

KODAVANTI AND MEHENDALE
different ways (Blackmore, 1988; Stull et al., 1988; Col-
bran et al., 1989; Taylor, 1989).
The family of enzymes catalyzing phosphorylation are
the protein kinases. These enzymes are a structurally MEHENDALE
itized. Hypothetical relationships, such as effects of
CADs on membrane lipids and inhibition of phospholi-MEHENDALE
itized. Hypothetical relationships, such as effect
CADs on membrane lipids and inhibition of phospholiases
pases occurring at higher than therapeutic levels, can parameter in a seffects of
itized. Hypothetical relationships, such as effects of
CADs on membrane lipids and inhibition of phospholi-
pases occurring at higher than therapeutic levels, can be
envisioned as well. Proposed ending as a seffects increased in the involvement in the CADs on membrane lipids and inhibition of phosphopases occurring at higher than therapeutic levels, can envisioned as well. Proposed pathways of the involve-
ment of itized. Hypothetical relationships, such as effec
CADs on membrane lipids and inhibition of phosp
pases occurring at higher than therapeutic levels, c
envisioned as well. Proposed pathways of the inv
ment of CADs at variou CADs on membrane lipids and inhibition pases occurring at higher than therapeutic
envisioned as well. Proposed pathways of
ment of CADs at various stages of the p
signaling system are illustrated in fig. 5.
The stimulus th uses occurring at higher than therapeutic levels, can be
wisioned as well. Proposed pathways of the involve-
ent of CADs at various stages of the phospholipid-
grading system are illustrated in fig. 5.
The stimulus that ac

ment of CADs at various stages of the phospholipid-
signaling system are illustrated in fig. 5.
The stimulus that activates protein kinase C, and thus
protein phosphorylation, also leads to enhanced cell pro-
liferation. S ment of CADs at various stages of the phospholipid-
signaling system are illustrated in fig. 5.
The stimulus that activates protein kinase C, and thus
protein phosphorylation, also leads to enhanced cell pro-
liferation. S signaling system are illustrated in fig. 5.
The stimulus that activates protein kinase C, and thus
protein phosphorylation, also leads to enhanced cell pro-
liferation. Suppression of such events may be helpful in
reducing protein phosphorylation, also leads to enhanced cell pro-
liferation. Suppression of such events may be helpful in
reducing the incidence of normal cell growth and perhaps
cancer. Chlorpromazine has been postulated to be a protein phosphorylation, also leads to enhanced cell pro-
liferation. Suppression of such events may be helpful in
reducing the incidence of normal cell growth and perhaps
cancer. Chlorpromazine has been postulated to be a liferation. Suppression of such events may be helpful in reducing the incidence of normal cell growth and perhaps cancer. Chlorpromazine has been postulated to be anticarcinogenic because it is a potent inhibitor of protei reducing the incidence of normal cell growth and perhaps cancer. Chlorpromazine has been postulated to be anti-
carcinogenic because it is a potent inhibitor of protein
kinase C, is a calmodulin antagonist, and also can in cancer. Chlorpromazine has been postulated to be anti-
carcinogenic because it is a potent inhibitor of protein
kinase C, is a calmodulin antagonist, and also can inhibit
phospholipases (Beckman et al., 1982; Hostetler, 19 carcinogenic because it is a potent inhibitor of protein
kinase C, is a calmodulin antagonist, and also can inhibit
phospholipases (Beckman et al., 1982; Hostetler, 1984;
Nishizuka, 1984; Kubo and Hostetler, 1985; Giedroc kinase C, is a calmodulin antagonist, and also can inhibit
phospholipases (Beckman et al., 1982; Hostetler, 1984;
Nishizuka, 1984; Kubo and Hostetler, 1985; Giedroc et
al., 1985; Price et al., 1985; Opstvedt et al., 1986; phospholipases (Beckman et al., 1982; Hostetler, 1984;
Nishizuka, 1984; Kubo and Hostetler, 1985; Giedroc et
al., 1985; Price et al., 1985; Opstvedt et al., 1986; Shaikh
et al., 1987). Inhibition of protein phosphorylation Nishizuka, 1984; K
al., 1985; Price et al
et al., 1987). Inhib
these second messer
of tumor promotion
Thus, the import al., 1985; Price et al., 1985; Opstvedt et al., 1986; Shaikh et al., 1987). Inhibition of protein phosphorylation by these second messenger pathways brings about inhibition of tumor promotion.
Thus, the importance of CADs et al., 1987). Inhibition of protein phosphorylation is
these second messenger pathways brings about inhibition
of tumor promotion.
Thus, the importance of CADs as modifiers of the
signal transduction pathways is beginning

Kaczmarek, 1988; Stacey, 1988; Tada and Kadoma, 1989) these second messenger pathways brings about inhibition
by protein kinase C and consequent protein phosphor-
flus, the importance of CADs as modifiers of these
Phosphol these second messenger pathways brings about inhibition
of tumor promotion.
Thus, the importance of CADs as modifiers of these
signal transduction pathways is beginning to be recog-
nized. It may not be surprising that som of tumor promotion.
Thus, the importance of CADs as modifiers of these
signal transduction pathways is beginning to be recog-
nized. It may not be surprising that some of the CADs
are proposed for use in cell growth regula Thus, the importance of CADs as modifiers of the signal transduction pathways is beginning to be reco nized. It may not be surprising that some of the CAI are proposed for use in cell growth regulation in son diseases. Chl signal transduction pathways is beginning to be reconized. It may not be surprising that some of the CAI are proposed for use in cell growth regulation in son diseases. Chloroquine has been proposed for the treament of AID nized. It may not be surprising that some of the CAD are proposed for use in cell growth regulation in some diseases. Chloroquine has been proposed for the treat ment of AIDS because it prevents the pH-dependen entry of th phocytes (Kagan, 1987).
Do CADs affect cellular function and growth by inhibseases. Chloroquine has been proposed for the treacher of AIDS because it prevents the pH-dependentry of the human immunodeficiency virus into lynocytes (Kagan, 1987).
Do CADs affect cellular function and growth by inhing entry of the human immunodeficiency virus into lym-

Most of the effects of diacylglycerol and inositol tris-

phospholipases and by reacting with phospholipid-

phosphate are synergistic (Nishizuka, 1984; Stacey, 1988;

Kikkawa et al., 1989; Tada and Kadoma, 1989). Whether, entry of the human immunodeficiency virus into lym-
phocytes (Kagan, 1987).
Do CADs affect cellular function and growth by inhib-
iting phospholipases and by reacting with phospholipid-
derived second messengers? If so, th phocytes (Kagan, 1987).

Do CADs affect cellular function and growth by inhibiting phospholipases and by reacting with phospholipid-

derived second messengers? If so, the mechanistic link

between these changes and phosph derived second messengers? If so, the mechanistic link iting phospholipases and by reacting with phospholical derived second messengers? If so, the mechanistic between these changes and phospholipidosis remaint be investigated. It has been postulated that chloroquinduced inhi derived second messengers? If so, the mechanistic li
between these changes and phospholipidosis remains
be investigated. It has been postulated that chloroquin
induced inhibition of calmodulin-stimulated phospho
esterase between these changes and phospholipidosis remains to
be investigated. It has been postulated that chloroquine-
induced inhibition of calmodulin-stimulated phosphodi-
esterase as well as Ca^{2+}, Mg^{2+} -ATPase activities, re

REVIEW

PHARMACOLOGICAL

DRUG-INDUCED PHOS
inhibition of phospholipases (Nagai et al., 1987). With ful
the use of several cell culture systems, investigators have Ge DRUG-INDUCED PHOS
inhibition of phospholipases (Nagai et al., 1987). With fu
the use of several cell culture systems, investigators have
reported that chloroquine, chlorphentermine, and pro-BRUG-INDUCED
inhibition of phospholipases (Nagai et al., 1987). With
the use of several cell culture systems, investigators have
reported that chloroquine, chlorphentermine, and pro-
methazine affect signal transduction sy inhibition of phospholipases (Nagai et al., 1987). With
the use of several cell culture systems, investigators have
reported that chloroquine, chlorphentermine, and pro-
methazine affect signal transduction systems (Zamora inhibition of phospholipases (Nagai et al., 1987). With
the use of several cell culture systems, investigators have
reported that chloroquine, chlorphentermine, and pro-
methazine affect signal transduction systems (Zamora the use of several cell culture systems, investigators have
reported that chloroquine, chlorphentermine, and pro-
methazine affect signal transduction systems (Zamora
and Beck, 1986; Sauers et al., 1986; Kalisz et al., 198 reported that chloroquine, chlorphentermine, and pro-
methazine affect signal transduction systems (Zamora
and Beck, 1986; Sauers et al., 1986; Kalisz et al., 1987;
Sharp et al., 1987; Bottger et al., 1988). However, to wh methazine affect signal transduction systems (Zamora nize
and Beck, 1986; Sauers et al., 1986; Kalisz et al., 1987;
Sharp et al., 1987; Bottger et al., 1988). However, to what
extent drug effects on phospholipid metabolism and Beck, 198
Sharp et al., 198
Extent drug established
be established
Although n Although et al., 1987; Bottger et al., 1988). However, to when
tent drug effects on phospholipid metabolism are inved in the alteration of signal transduction needs
established.
Although not much has been understood of the

extent drug effects on phospholipid metabolism are in-
volved in the alteration of signal transduction needs to
be established.
Although not much has been understood of the mech-
anism by which some CADs affect immune func volved in the alteration of signal transduction needs to
be established.
Although not much has been understood of the mech-
anism by which some CADs affect immune functions,
there are good reasons to suggest that these eff be established.

Although not much has been understood of the meclenism by which some CADs affect immune function

there are good reasons to suggest that these effects migloccur

(Catena, 1989). Some reports concerning CAI Although not much has been understood of the mechanism by which some CADs affect immune functions,
there are good reasons to suggest that these effects might
and occur (Catena, 1989). Some reports concerning CAD-
mediated anism by which some CADs affect immune functions,
there are good reasons to suggest that these effects might
occur (Catena, 1989). Some reports concerning CAD-
mediated immune abnormalities have appeared in the
literature there are good reasons to suggest that these effects might
occur (Catena, 1989). Some reports concerning CAD-
mediated immune abnormalities have appeared in the
iterature (Jackson and Longmore, 1988; Sauers et al.,
1988). occur (Catena, 1989). Some reports concerning CAD-
mediated immune abnormalities have appeared in the
literature (Jackson and Longmore, 1988; Sauers et al.,
1988). Many inflammatory pulmonary disorders are
thought to be in mediated immune abnormalities have appeared in the $\frac{p}{q}$
literature (Jackson and Longmore, 1988; Sauers et al.,
1988). Many inflammatory pulmonary disorders are chought to be initiated by deposition of immunoglobulins pulmonary toxicity (Suarez et al., 1983; Joelson et al., 1988). Many inflammatory pulmonary disorders are
thought to be initiated by deposition of immunoglobulins
in alveolar capillaries. Such deposition has been reported
in biopsy specimens of patients with amiodarone-induced
p thought to be initiated by deposition of immunoglobulins
in alveolar capillaries. Such deposition has been reported
in biopsy specimens of patients with amiodarone-induced
pulmonary toxicity (Suarez et al., 1983; Joelson e in alveolar capillaries. Such deposition has been reported
in biopsy specimens of patients with amiodarone-induced
pulmonary toxicity (Suarez et al., 1983; Joelson et al.,
1984; Akoun et al., 1988). Recent reports indicate in biopsy specimens of patients with amiodarone-induced
pulmonary toxicity (Suarez et al., 1983; Joelson et al., st
1984; Akoun et al., 1988). Recent reports indicate that with
amiodarone increases leukotriene levels a pulmonary toxicity (Suarez et al., 1983; Joelson et a
1984; Akoun et al., 1988). Recent reports indicate the
amiodarone increases leukotriene levels and affects are
chidonic acid metabolism in the lung and that the
effects 1984; Akoun et al., 1988). Recent reports indicate that
amiodarone increases leukotriene levels and affects ara-
chidonic acid metabolism in the lung and that these
effects have been abolished by several antioxidants (Kenamiodarone increases leukotriene levels and affects
chidonic acid metabolism in the lung and that t
effects have been abolished by several antioxidants (1
nedy et al., 1988). One hypothesis relating to amioda
pulmonary tox effects have been abolished by several antioxidants (Kennedy et al., 1988). One hypothesis relating to amiodarone pulmonary toxicity concerns the potential immunomodulating effects of amiodarone. However, the relation-ship effects have been abolished by several antioxidants (Kennedy et al., 1988). One hypothesis relating to amiodarone pulmonary toxicity concerns the potential immunomodulating effects of amiodarone. However, the relationship medy et al., 1988). One hypothesis relating to amioda
pulmonary toxicity concerns the potential immund
dulating effects of amiodarone. However, the relat
ship among pulmonary toxicity, pneumonitis, and
munodysfunction has pulmonary toxicity concerns the potential immunomo-
dulating effects of amiodarone. However, the relation-
ship among pulmonary toxicity, pneumonitis, and im-
munodysfunction has not been elucidated. Chlorphen-
termine-ind dulating effects of amiodarone. However, the relation-
ship among pulmonary toxicity, pneumonitis, and im-
munodysfunction has not been elucidated. Chlorphen-
termine-induced inhibition of immune responses are
presumably d ship among pulmonary toxicity, pneumonitis, and im-

munodysfunction has not been elucidated. Chlorphen-

termine-induced inhibition of immune responses are

presumably due to an inhibition of phospholipases

(Sauers et a munodysfunction has not been elucidated. Chlorphen-
termine-induced inhibition of immune responses are
presumably due to an inhibition of phospholipases
(Sauers et al., 1986; Kacew, 1987, 1988), leading to a
decreased prod termine-induced inhibition of immune responses are
presumably due to an inhibition of phospholipases (Sauers et al., 1986; Kacew, 1987, 1988), leading to a
decreased production of inositol trisphosphate and di-
acylglycer presumably due to an inhibition of phospholipases (Sauers et al., 1986; Kacew, 1987, 1988), leading to a decreased production of inositol trisphosphate and di-
acylglycerol from phosphoinositides. Promethazine also
possess (Sauers et al., 1986; Kacew, 1987, 1988), leading to a
decreased production of inositol trisphosphate and di-
acylglycerol from phosphoinositides. Promethazine also
possesses immunosuppressive activity (Orlowski et al., 1 decreased production of inositol trisphosphate and
acylglycerol from phosphoinositides. Promethazine a
possesses immunosuppressive activity (Orlowski et a
1983; Rychlik et al., 1988). However, the mechanism
its action is u acylglycerol from phosphoinositides. Promethazine also
possesses immunosuppressive activity (Orlowski et al., 1
1983; Rychlik et al., 1988). However, the mechanism of
its action is unknown. In our drug-phospholipid-binding possesses immunosuppressive activity (Orlowski et al., 1983; Rychlik et al., 1988). However, the mechanism of its action is unknown. In our drug-phospholipid-binding studies, we observed that promethazine binds extensively 1983; Rychlik et al., 1988). However, the mechanism
its action is unknown. In our drug-phospholipid-bindi
studies, we observed that promethazine binds extensive
to isolated lamellar bodies and phospholipid vesic
(Joshi et its action is unknown. In our drug-phospholipid-binding
studies, we observed that promethazine binds extensively
to isolated lamellar bodies and phospholipid vesicles
(Joshi et al., 1988, 1989). The phospholipidosis-induci to isolated lamellar bodies and phospholipid vesicles
(Joshi et al., 1988, 1989). The phospholipidosis-inducing
potency and phospholipase-inhibiting property of pro-
methazine have not been investigated. Chlorpromazine
and (Joshi et al., 1988, 1989). The phospholipidosis-inducing potency and phospholipase-inhibiting property of pro-
methazine have not been investigated. Chlorpromazine induced release and verapamil accumulate in the lung (Ba potency and phospholipase-inhibiting property of pro-
methazine have not been investigated. Chlorpromazine in
and verapamil accumulate in the lung (Bakhle and Vane, she
1974) and are known to inhibit antigen-induced releas methazine have not been investigated. Chlorpromazine
and verapamil accumulate in the lung (Bakhle and Vane,
1974) and are known to inhibit antigen-induced release
of slow reacting substance of anaphylaxis in the cat lung
(and verapamil accumulate in the lung (Bakhle and Vane, shaped 1974) and are known to inhibit antigen-induced release $\frac{\text{Al}t}{\text{Al}t}$ of slow reacting substance of anaphylaxis in the cat lung choof. (Dell'Osa and Temple 1974) and are known to inhibit antigen-induced
of slow reacting substance of anaphylaxis in the
(Dell'Osa and Temple, 1986). It might be sugges
the immunosuppressive effect of promethazine is
its effect on the phospholipid slow reacting substance of anaphylaxis in the cat lung
hell'Osa and Temple, 1986). It might be suggested that
fole immunosuppressive effect of promethazine is due to
an
effect on the phospholipid-signaling system.
From the (Dell'Osa and Temple, 1986). It might be suggested that
the immunosuppressive effect of promethazine is due to
its effect on the phospholipid-signaling system.
From these few examples of CADs known to affect the
immune re

the immunosuppressive effect of promethazine is due to
its effect on the phospholipid-signaling system.
From these few examples of CADs known to affect the
immune responses, it could be suggested that the effects
of CADs o its effect on the phospholipid-signaling system.

From these few examples of CADs known to affect the

immune responses, it could be suggested that the effects

of CADs on the immune system may represent a general

phenom From these few examples of CADs known to affect the
immune responses, it could be suggested that the effects
of CADs on the immune system may represent a general of Ca^2
phenomenon rather than a drug-specific effect. Bec immune responses, it could be suggested that the effects tonic of CADs on the immune system may represent a general of C
phenomenon rather than a drug-specific effect. Because pho
CADs interfere with the phospholipid-signa of CADs on the immune system may represent a general
phenomenon rather than a drug-specific effect. Because
CADs interfere with the phospholipid-signaling system
in a more general way, it is likely that their effects on
th CADs interfere with the phospholipid-signaling system
in a more general way, it is likely that their effects on
the immune system are through signal transduction
pathways. However, this generalization needs to be care-

fully evaluated using various experimental approaches. Generalization will only be possible after carefully se-SCONFIDUPIDOSIS

fully evaluated using various experimental approach

Generalization will only be possible after carefully

lected representative CADs are experimentally scrutized for these effects. Generalization will only be possible after carefully selected representative CADs are experimentally scruti-
nized for these effects.
B. Ion Transport Across Cell Membranes
As discussed earlier, CADs alter lipid dynamics o ted representative CADs are experimentally scruti-
zed for these effects.
Ion Transport Across Cell Membranes
As discussed earlier, CADs alter lipid dynamics of
embranes, affect receptor function, and inhibit phos-

mized for these effects.

B. Ion Transport Across Cell Membranes

As discussed earlier, CADs alter lipid dynamics

membranes, affect receptor function, and inhibit phos-

pholipases. Thus, it is not surprising that they al B. Ion Transport Across Cell Membranes
As discussed earlier, CADs alter lipid dynamics of
membranes, affect receptor function, and inhibit phos-
pholipases. Thus, it is not surprising that they alter ion
transport mechanis B. Ion Transport Across Cell Membranes

As discussed earlier, CADs alter lipid dynamics of

membranes, affect receptor function, and inhibit phos-

pholipases. Thus, it is not surprising that they alter ion

transport mech As discussed earlier, CADs alter lipid dynamics of
membranes, affect receptor function, and inhibit phos-
pholipases. Thus, it is not surprising that they alter ion
transport mechanisms in the cell and phosphorylation
pat pholipases. Thus, it is not surprising that they alter ion
transport mechanisms in the cell and phosphorylation
pathways such as oxidative phosphorylation (Zychlinski
and Montgomery, 1985a). Cytosolic free Ca^{2+} modulat pholipases. Thus, it is not surprising that they alter ion
transport mechanisms in the cell and phosphorylation
pathways such as oxidative phosphorylation (Zychlinski
and Montgomery, 1985a). Cytosolic free Ca²⁺ modulates transport mechanisms in the cell and phosphorylation
pathways such as oxidative phosphorylation (Zychlinski
and Montgomery, 1985a). Cytosolic free Ca^{2+} modulates
several calmodulin-dependent protein phosphorylation
pro pathways such as oxidative phosphorylation (Zychlinski
and Montgomery, 1985a). Cytosolic free Ca²⁺ modulates
several calmodulin-dependent protein phosphorylation
processes and, similarly, free Ca²⁺ levels are modulated and Montgomery, 1985a). Cytosolic free Ca^{2+} modulates
several calmodulin-dependent protein phosphorylation
processes and, similarly, free Ca^{2+} levels are modulated
by hormones, receptors, protein kinases, and feedba several calmodulin-dependent processes and, similarly, free Ca²⁻
by hormones, receptors, protein
control by protein phosphorylati
Farese, 1988; Kaczmarek, 1988).
Amiodarone inhibits Na^{+} , K^{+} . ocesses and, similarly, free Ca²⁺ levels are modulated

thermones, receptors, protein kinases, and feedback

ntrol by protein phosphorylation (Blackmore, 1988;

rese, 1988; Kaczmarek, 1988).

Amiodarone inhibits $Na^+, K^-.$

by hormones, receptors, protein kinases, and feedback
control by protein phosphorylation (Blackmore, 1988;
Farese, 1988; Kaczmarek, 1988).
Amiodarone inhibits Na⁺,K⁺-ATPase and Mg²⁺-
ATPase activities in the rat lung control by protein phosphorylation (Blackmore, 1988; Farese, 1988; Kaczmarek, 1988).

Amiodarone inhibits $Na^+, K^-.ATP$ ase and $Mg^{2+}.$

ATPase activities in the rat lung where phospholipid

storage also occurs maximally (Re Farese, 1988; Kaczmarek, 1988).

Amiodarone inhibits Na^{+} , K⁺-ATPase and Mg²⁺-

ATPase activities in the rat lung where phospholipid

storage also occurs maximally (Reasor et al., 1989) as

well as in other tissues, Amiodarone inhibits $Na^+, K^-.ATPase$ and Mg^{2+} -
ATPase activities in the rat lung where phospholipid
storage also occurs maximally (Reasor et al., 1989) as
well as in other tissues, thus affecting active ion transport
pheno storage also occurs maximally (Reasor et al., 1989) as
well as in other tissues, thus affecting active ion transport
phenomena and oxidative phosphorylation (Prasada Rao
et al., 1986; Chatelain et al., 1989). These effects sy nontrollar protein, photon annihilar same of the same of the proposed to the same of t creasing cytosolic free Ca^{2+} in bovine pulmonary artery phenomena and oxidative phosphorylation (Prasada Rao
et al., 1986; Chatelain et al., 1989). These effects of
amiodarone have been proposed to be due to its effect on
lipid dynamics. Amiodarone induces cytotoxicity by in-
c et al., 1986; Chatelain et al., 1989). These effects of amiodarone have been proposed to be due to its effect on lipid dynamics. Amiodarone induces cytotoxicity by increasing cytosolic free Ca^{2+} in bovine pulmonary art amiodarone have been proposed to be due to its effect on lipid dynamics. Amiodarone induces cytotoxicity by increasing cytosolic free Ca^{2+} in bovine pulmonary artery endothelial cells (Powis et al., 1990). The therapeu lipid dynamics. Amiodarone induces cytotoxicity by increasing cytosolic free Ca^{2+} in bovine pulmonary artery endothelial cells (Powis et al., 1990). The therapeutic action of amiodarone also relates to its effect on th creasing cytosolic free Ca^{2+} in bovine pulmonary artery
endothelial cells (Powis et al., 1990). The therapeutic
action of amiodarone also relates to its effect on the Ca^{2+}
transport system in the heart. If amiodaron endothelial cells (Powis et al., 1990). The therapeutic
action of amiodarone also relates to its effect on the Ca²⁺
transport system in the heart. If amiodarone inhibits
phospholipases, it should inhibit activation of p action of amiodarone also relates to its effect on the Ca²⁺
transport system in the heart. If amiodarone inhibits
phospholipases, it should inhibit activation of protein
kinase C by diacylglycerol and at the same time i transport system in the heart. If amiodarone inhibits
phospholipases, it should inhibit activation of protein
kinase C by diacylglycerol and at the same time inhibit
synthesis of inositol trisphosphate which mediates Ca^{2 phospholipases, it should inhibit activation of prot
kinase C by diacylglycerol and at the same time inhi
synthesis of inositol trisphosphate which mediates C
release from intracellular storage. Thus, one would
pect an act kinase C by diacylglycerol and at the same time inhilaynthesis of inositol trisphosphate which mediates Carelease from intracellular storage. Thus, one would epect an actual decrease in Ca^{2+} levels following amiod rone synthesis of inositol trisphosphate which mediates C
release from intracellular storage. Thus, one would
pect an actual decrease in Ca^{2+} levels following amio
rone administration, unless there is a very high stitution release from intracellular storage. Thus, one would ex-
pect an actual decrease in Ca^{2+} levels following amioda-
rone administration, unless there is a very high stimu-
lation of influx of Ca^{2+} from the extracellula pect an actual decrease in Ca^{2+} levels following amioda-
rone administration, unless there is a very high stimu-
lation of influx of Ca^{2+} from the extracellular environ-
ment or Ca^{2+} -pumping mechanisms are impair rone administration, unless there is a
lation of influx of Ca^{2+} from the exti-
ment or Ca^{2+} -pumping mechanisms
exact mechanism by which amiodarc
calcium-signaling system is unknown.
Chloroquine, another lysosomotrop ment or Ca^{2+} -pumping mechanisms are impaired. The exact mechanism by which amiodarone modulates the calcium-signaling system is unknown.
Chloroquine, another lysosomotrophic and phospholi-pidotic drug, inhibits calmodu

ment or Ca^{2+} -pumping mechanisms are impaired. The exact mechanism by which amiodarone modulates the calcium-signaling system is unknown.
Chloroquine, another lysosomotrophic and phospholi-pidotic drug, inhibits calmodu exact mechanism by which amiodarone modulates the calcium-signaling system is unknown.
Chloroquine, another lysosomotrophic and phospholi-
pidotic drug, inhibits calmodulin-mediated stimulation
of phosphodiesterase and Ca calcium-signaling system is unknown.
Chloroquine, another lysosomotrophic and phospholi-
pidotic drug, inhibits calmodulin-mediated stimulation
of phosphodiesterase and Ca^{2+} , Mg²⁺-ATPase activities
in red blood cells. Chloroquine, another lysosomotrophic and phospholi-
pidotic drug, inhibits calmodulin-mediated stimulation
of phosphodiesterase and $Ca^{2+}, Mg^{2+}-ATP$ ase activities
in red blood cells. These changes are associated with
shape pidotic drug, inhibits calmodulin-mediated stimulation of phosphodiesterase and Ca^{2+} , Mg^{2+} -ATPase activities in red blood cells. These changes are associated with shape change in erythrocyte ghosts (Nagai et al., 19 of phosphodiesterase and Ca^{2+} , Mg^{2+} -ATPase activities
in red blood cells. These changes are associated with
shape change in erythrocyte ghosts (Nagai et al., 1987).
Alteration of oxidative phosphorylation involving in red blood cells. These changes are associated with shape change in erythrocyte ghosts (Nagai et al., 1987). Alteration of oxidative phosphorylation involving mito-chondrial membranes also has been reported in vivo follo shape change in erythrocyte ghosts (Nagai et al., 198
Alteration of oxidative phosphorylation involving mi
chondrial membranes also has been reported in v
following chlorphentermine administration (Zychlin
and Montgomery, Alteration of oxidative phosphorylation involving mito-
chondrial membranes also has been reported in vivo
following chlorphentermine administration (Zychlinski
and Montgomery, 1985a,b, 1986). Increases in imipra-
mine tox chondrial membranes also has been reported in vivo
following chlorphentermine administration (Zychlinsk
and Montgomery, 1985a,b, 1986). Increases in imipra
mine toxicity in rats by Ca²⁺ modulators which exer
antagonistic following chlorphentermine administration (Zychlinsl
and Montgomery, 1985a,b, 1986). Increases in imipre
mine toxicity in rats by Ca^{2+} modulators which exercent
antagonistic effects against catecholamines and serc
toni and Montgomery, 1985a,b, 1986). Increases in imipramine toxicity in rats by Ca^{2+} modulators which exertaing and sertain suggest a neurotransmitter-mediated enhancement of Ca^{2+} release by imipramine. Effects on oxida mine toxicity in rats by Ca^{2+} modulators which exert
antagonistic effects against catecholamines and sero-
tonin suggest a neurotransmitter-mediated enhancement
of Ca^{2+} release by imipramine. Effects on oxidative ph antagonistic effects against catecholamines and servenin suggest a neurotransmitter-mediated enhancement of Ca²⁺ release by imipramine. Effects on oxidative photophorylation by prolonged imipramine treatment have been pr tonin suggest a neurotransmitter-mediated enhancement of Ca²⁺ release by imipramine. Effects on oxidative ph
phorylation by prolonged imipramine treatment have been proposed to be due to an alteration in the mi
chondrial of Ca²⁺ release by imipramine. Effects on oxidative phos-
phorylation by prolonged imipramine treatment have
been proposed to be due to an alteration in the mito-
chondrial membrane lipid milieu and membrane stabili-
zat From such a proposed impromine treatment have
the proposed to be due to an alteration in the mito-
ondrial membrane lipid milieu and membrane stabili-
tion after drug treatment (Katyare and Rajan, 1988).
From such examples

EXTERN MARK CODA WATTLY AND MARK CODAVANT AND MARK THAT AND MARK THE PRESENT OF THE UPS AND THE UPS AN By two different pathways. One is
the pay react principally by two different pathways. One is vit
the second one is by altering the lipid dynamics of membranes and be
the second one lipid dynamics of membranes and be KODAVANTI AND MI

may react principally by two different pathways. One is vitt

by altering receptor-mediated events and the second one lipit

is by altering the lipid dynamics of membranes and be

phospholipases. Many mor may react principally by two different pathways. One is view altering receptor-mediated events and the second one list by altering the lipid dynamics of membranes and by phospholipases. Many more studies of the effects of may react principally by two different pathways. One is
by altering receptor-mediated events and the second one
is by altering the lipid dynamics of membranes and
phospholipases. Many more studies of the effects of
CADs on by altering receptor-mediated events and the second one
is by altering the lipid dynamics of membranes and
phospholipases. Many more studies of the effects of
CADs on ion transport are needed to understand their
role in cy

V. Conclusions

role in cytotoxicity mediated by calcium and other ions.
V. Conclusions
CADs share sufficient similarities in their structure
even though they come from diverse pharmacological
classes. One of the many general effects of C V. Conclusions
CADs share sufficient similarities in their structure
even though they come from diverse pharmacological
classes. One of the many general effects of CADs is that
they induce a phospholipid storage disorder i v. Conclusions
CADs share sufficient similarities in their structure
even though they come from diverse pharmacological
classes. One of the many general effects of CADs is that
they induce a phospholipid storage disorder i CADs share sufficient similarities in their structure
even though they come from diverse pharmacological de
classes. One of the many general effects of CADs is that
they induce a phospholipid storage disorder in various
t even though they come from diverse pharmacological declasses. One of the many general effects of CADs is that lip they induce a phospholipid storage disorder in various tissues and species of animals as well as in humans. classes. One of the many general effects of CADs is they induce a phospholipid storage disorder in various
tissues and species of animals as well as in humans. T
presence of lamellated inclusion bodies, and, as far
the lun they induce a phospholipid storage disorder in various
tissues and species of animals as well as in humans. The
presence of lamellated inclusion bodies, and, as far as
the lung is concerned, massive infiltration of macro-
 tissues and species of animals as well as in humans. The presence of lamellated inclusion bodies, and, as far as the lung is concerned, massive infiltration of macrophages, is one of the primary characteristics of their ac presence of lamellated inclusion bodies, and, as far as the lung is concerned, massive infiltration of macro-
phages, is one of the primary characteristics of their
action. Phospholipidosis-inducing potency largely de-
pen the lung is concerned, massive infiltration of macro-
phages, is one of the primary characteristics of their
action. Phospholipidosis-inducing potency largely de-
pends on the affinity of CADs for the particular tissue,
th phages, is one of the primary characteristics of the action. Phospholipidosis-inducing potency largely depends on the affinity of CADs for the particular tissue their ability to bind to phospholipids, their inhibitor poten pends on the affinity of CADs for the particular tissue, their ability to bind to phospholipids, their inhibitory potential toward various phospholipases, and their pharmacokinetic properties. The nature of phospholipidosi pends on the affinity of CADs for the particular tissue,

their ability to bind to phospholipids, their inhibitory

potential toward various phospholipases, and their phar-

potential toward various phospholipases, and the macokinetic properties. The nature of phospholipidosis potential toward various phospholipases, and their pharmacokinetic properties. The nature of phospholipidosis and the tissue being affected are largely influenced by the structure of the drug molecule, the nature of its hy macokinetic properties. The nature of phospholipidosis and the tissue being affected are largely influenced by the structure of the drug molecule, the nature of its hydrophilic side chain, the substitution of a halogen at and the tissue being affected are largely influenced by
the structure of the drug molecule, the nature of its
hydrophilic side chain, the substitution of a halogen
atom, the hydropholoicity of the ring structure, the ionic the structure of the drug molecule, the nature of its
hydrophilic side chain, the substitution of a halogen
atom, the hydrophobicity of the ring structure, the ionic
environment in the cell, and the type of phospholipids
 hydrophilic side chain, the substitution of a halogen A_K^{AK} atom, the hydrophobicity of the ring structure, the ionic
environment in the cell, and the type of phospholipids A_K^{AK}
present. Generally, CADs are lys atom, the hydrophobicity of the ring structure, the ionic
environment in the cell, and the type of phospholipids
present. Generally, CADs are lysosomotrophic with few
exceptions. The acidic pH of lysosomes results in the
i environment in the cell, and the type of phospholipids

present. Generally, CADs are lysosomotrophic with few

exceptions. The acidic pH of lysosomes results in the

ionization of these relatively basic drugs, and the dru present. Generally
exceptions. The according to the membranes.
to the membranes.
CAD-induced p ceptions. The acidic pH of lysosomes results in the inization of these relatively basic drugs, and the druge either trapped in the lysosomal milieu or are bour the membranes.
CAD-induced phospholipidosis, at least with chl

ionization of these relatively basic drugs, and the drug
are either trapped in the lysosomal milieu or are boun
to the membranes.
CAD-induced phospholipidosis, at least with chlop
phentermine, influences respiratory functi are either trapped in the lysosomal milieu or are bound
to the membranes.
CAD-induced phospholipidosis, at least with chlor-
phentermine, influences respiratory function to a mini-
mal extent. Non-respiratory or biochemica to the membranes.
CAD-induced phospholipidosis, at least with chlor-
phentermine, influences respiratory function to a mini-
mal extent. Non-respiratory or biochemical functions of
the lung are perturbed to a much greater CAD-induced phospholipidosis, at least with chlor-
phentermine, influences respiratory function to a mini-
mal extent. Non-respiratory or biochemical functions of
the lung are perturbed to a much greater extent by CADs.
Pu phentermine, influences respiratory function to a m
mal extent. Non-respiratory or biochemical function
the lung are perturbed to a much greater extent by CA
Pulmonary clearance of circulating vasoactive s
stances is impai mal extent. Non-respiratory or biochemical function
the lung are perturbed to a much greater extent by CA
Pulmonary clearance of circulating vasoactive s
stances is impaired by CADs and CAD-induced phosp
lipidosis. Althoug the lung are perturbed to a much greater extent by CADs.

Pulmonary clearance of circulating vasoactive sub-

stances is impaired by CADs and CAD-induced phospho-

lipidosis. Although these compounds react with phospho-
 Pulmonary clearance of circulating vasoactive substances is impaired by CADs and CAD-induced phospholipidosis. Although these compounds react with phospholipids and inhibit phospholipases, the precise mechanism involved in stances is impaired by CADs and CAD-induced phospho-

lipidosis. Although these compounds react with phospho-

lipids and inhibit phospholipases, the precise mechanism

involved in phospholipid accumulation is not clear. lipidosis. Although these compounds react with phospholipids and inhibit phospholipases, the precise mechanism
involved in phospholipid accumulation is not clear. Evidence that CAD administration renders phospholipid an
un lipids and inhibit phospholipases, the precise mechanism
involved in phospholipid accumulation is not clear. Evi-
dence that CAD administration renders phospholipid an
unsuitable substrate for phospholipases needs to be c involved in phospholipid accumulation is not clear. Evidence that CAD administration renders phospholipid an unsuitable substrate for phospholipases needs to be considered further as does CAD-associated inhibition of phosp dence that CAD administration renders phospholipid an
unsuitable substrate for phospholipases needs to be con-
sidered further as does CAD-associated inhibition of
phospholipases in vivo and alteration of intracellular pH. unsuitable substrate for phospholipases needs to be considered further as does CAD-associated inhibition of hospholipases in vivo and alteration of intracellular pH.
Certainly, CAD-induced phospholipid storage disorder
of sidered further as does CAD-associated inhibition of
phospholipases in vivo and alteration of intracellular pH.
Certainly, CAD-induced phospholipid storage disorder
offers an important experimental model to study the
rela phospholipases in vivo and alteration
Certainly, CAD-induced phospholip
offers an important experimental
relative importance of these factors
turnover of pulmonary phospholipid
One should be critical when inter Certainly, CAD-induced phospholipid storage disorder

Offers an important experimental model to study the

offers an importance of these factors in the synthesis and

relative importance of these factors in the synthesis a offers an important experimental model to study the

relative importance of these factors in the synthesis and

turnover of pulmonary phospholipids.

One should be critical when interpreting the cause of

phospholipidosis

relative importance of these factors in the synthesis and
turnover of pulmonary phospholipids.
One should be critical when interpreting the cause of
phospholipidosis in vivo, especially with regard to its
relationship to p turnover of pulmonary phospholipids.

One should be critical when interpreting the cause of

phospholipidosis in vivo, especially with regard to its

relationship to phospholipid binding and phospholipase

inhibition becau One should be critical when interpreting the cause of
phospholipidosis in vivo, especially with regard to its
relationship to phospholipid binding and phospholipase
inhibition because the pharmacokinetic handling of in-
di phospholipidosis in vivo, especially with regard to its
relationship to phospholipid binding and phospholipase
inhibition because the pharmacokinetic handling of in-
dividual CADs can be an important determinant in in-
flu relationship to phospholipid binding and phospholipase
inhibition because the pharmacokinetic handling of in-
dividual CADs can be an important determinant in in-
fluencing the ability of CADs to bind to phospholipids
and inhibition because the pharmacokinetic handling of in-
dividual CADs can be an important determinant in in-
fluencing the ability of CADs to bind to phospholipids
and cause phospholipase inhibition. Thus, examples of
drug dividual CADs can be an important determinant in in-
fluencing the ability of CADs to bind to phospholipids
and cause phospholipase inhibition. Thus, examples of
drugs known to be bound to phospholipids and having
affinity

KODAVANTI AND MEHENDALE
hways. One is vitro experiments, may not induce pulmonary phospho-
he second one lipidosis because in in vivo such drug accumulation may
embranes and be obviated by pulmonary metabolism and eliminat MEHENDALE
vitro experiments, may not induce pulmonary phospho-
lipidosis because in in vivo such drug accumulation may
be obviated by pulmonary metabolism and elimination.
CADs affect ion transport, immune function, tumor Example 11 and the pulmonary phospho-

idosis because in in vivo such drug accumulation may

obviated by pulmonary metabolism and elimination.

CADs affect ion transport, immune function, tumor

owth, serotonin metabolism,

CADs on ion transport are needed to understand their growth, serotonin metabolism, and several other func-
role in cytotoxicity mediated by calcium and other ions.
V. Conclusions
CADs share sufficient similarities in thei vitro experiments, may not induce pulmonary phospholipidosis because in in vivo such drug accumulation ma
be obviated by pulmonary metabolism and elimination.
CADs affect ion transport, immune function, tumo
growth, seroto lipidosis because in in vivo such drug accumulation m.
be obviated by pulmonary metabolism and elimination
CADs affect ion transport, immune function, tum
growth, serotonin metabolism, and several other fun
tions in the bo be obviated by pulmonary metabolism and elimination. CADs affect ion transport, immune function, ture growth, serotonin metabolism, and several other futions in the body. Some of these effects could be collated with the ab associated side effects of CADs have generated a great growth, serotonin metabolism, and several other func-
tions in the body. Some of these effects could be corre-
lated with the ability of CADs to interact with phospho-
lipids and phospholipases. Extensive therapeutic use a tions in the body. Some of these effects could be correlated with the ability of CADs to interact with phospholipids and phospholipases. Extensive therapeutic use and associated side effects of CADs have generated a great lipidosis. **Acknowledgments.** We thank Dr. Arthur Hume for important sug-
Acknowledgments. We thank Dr. Arthur Hume for important sug-
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stions and Dr. Prasada Rao S. Kod

Acknowledgments. We thank Dr. Arthur Hume for important suggestions and Dr. Prasada Rao S. Kodavanti for his help in preparing this manuscript. gestions and Dr. Prasada Rao S. Kodavanti for his help in preparing

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