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PETER J. BARNES, K. FAN CHUNG, and CLIVE P. PAGE
 Inflammatory Mediators and Asthma*

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This Paushaus State Large, SW2 6LV (P. L.R. K.E.C.) and Papertment of Pharmacolog

Inflammatory Mediators and Asthma*
PETER J. BARNES, K. FAN CHUNG, and CLIVE P. PAGE
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I. Introduction

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ASTHMA is characterized by variable and rev
airflow obstruction and by bronchial hyper-responses, an excessive airway narrowing in respons I. Introduction hum
ASTHMA is characterized by variable and reversible
airflow obstruction and by bronchial hyper-responsive-
ness, an excessive airway narrowing in response to a
variety of apparently unrelated stimuli. Al EXTERNA is characterized by variable and reversible
airflow obstruction and by bronchial hyper-responsive-
ness, an excessive airway narrowing in response to a
variety of apparently unrelated stimuli. Although con-
tractio ASTHMA is characterized by variable and reversible
airflow obstruction and by bronchial hyper-responsive-
ness, an excessive airway narrowing in response to a
variety of apparently unrelated stimuli. Although con-
traction airflow obstruction and by bronchial hyper-responsiness, an excessive airway narrowing in response to variety of apparently unrelated stimuli. Although contraction of airway smooth muscle has been emphasis as an important ness, an excessive airway narrowing in response to a
variety of apparently unrelated stimuli. Although con-
traction of airway smooth muscle has been emphasized
as an important mechanism of asthmatic airway obstruc-
tion, variety of apparently unrelated stimuli. Although contraction of airway smooth muscle has been emphasized as an important mechanism of asthmatic airway obstruction, it is now appreciated that edema of the airway wall resul traction of airway smooth muscle has been emphasized
as an important mechanism of asthmatic airway obstruc-
tion, it is now appreciated that edema of the airway wall
resulting from microvascular leakage and luminal ob-
str may also be contributory. Inflammation in the airway solution, it is now appreciated that edema of the airway wall
resulting from microvascular leakage and luminal obstruction with plasma exudation and airway secretions
ma tion, it is now appreciated that edema of the airway wall
resulting from microvascular leakage and luminal obstruction with plasma exudation and airway secretions
may also be contributory. Inflammation in the airway
wall resulting from microvascular leakage and luminal obstruction with plasma exudation and airway secretions
may also be contributory. Inflammation in the airway
wall has long been recognized as a prominent feature of
fatal as struction with plasma exudation and airway secretions
may also be contributory. Inflammation in the airway
wall has long been recognized as a prominent feature of
fatal asthma attacks (234, 186), and recently similar
chan may also be contributory. Inflammation in the airway wall has long been recognized as a prominent feature of fatal asthma attacks (234, 186), and recently similar changes have been found in bronchial biopsies of even mild wall has long been recognized as a prominent feature of
fatal asthma attacks (234, 186), and recently similar
changes have been found in bronchial biopsies of even
mild asthmatics (331). There is now abundant experi-
ment fatal asthma attacks $(234, 186)$, and recently similar A.
changes have been found in bronchial biopsies of even
mild asthmatics (331) . There is now abundant experi-
mental evidence that inflammation of the airways may
 changes have been found in bronchial biopsies of eve
mild asthmatics (331). There is now abundant exper
mental evidence that inflammation of the airways ma
lead to bronchial hyper-responsiveness (129), which
such a charact mild asthmatics (331). There is now abundant experimental evidence that inflammation of the airways may
lead to bronchial hyper-responsiveness (129), which is
such a characteristic feature of asthma (89). These path-
olog mental evidence that inflammation of the airways may
lead to bronchial hyper-responsiveness (129), which is
such a characteristic feature of asthma (89). These path-
ological changes are likely to be produced by the relea lead to bronchial hyper-responsiveness (129), which is
such a characteristic feature of asthma (89). These path-
ological changes are likely to be produced by the release
of various mediators from inflammatory cells in th such a characteristic feature of asthma (89). These patiological changes are likely to be produced by the release of various mediators from inflammatory cells in the inflammatory mediators which have been implicated. There ological changes are likely to be produced by the release
of various mediators from inflammatory cells in the
airways, and the purpose of this review is to discuss some
of the inflammatory mediators which have been impli-
 of various mediators from inflammatory cells in airways, and the purpose of this review is to discuss so of the inflammatory mediators which have been imported. There is a vast and rapidly increasing literation dealing wit airways, and the purpose of this review is to discuss some
of the inflammatory mediators which have been impli-
cated. There is a vast and rapidly increasing literature
dealing with these mediators, and knowledge is advan cated. There is a vast and rapidly increasing literature dealing with these mediators, and knowledge is advancing very rapidly, made possible by greatly improved assays for mediators, by synthetic chemistry which provides cated. There is a vast and rapidly increasing literature
dealing with these mediators, and knowledge is advanc-
ing very rapidly, made possible by greatly improved
assays for mediators, by synthetic chemistry which pro-
vi dealing with these mediators, and knowledge is advancing very rapidly, made possible by greatly improved cassays for mediators, by synthetic chemistry which provides pure forms of the mediators, and, perhaps most importan ing very rapidly, made possible by greatly improved
assays for mediators, by synthetic chemistry which pro-
vides pure forms of the mediators, and, perhaps most
importantly, by the development of potent and specific
antag assays for mediators, by synthetic chemistry which pro-
vides pure forms of the mediators, and, perhaps most
importantly, by the development of potent and specific
antagonists, so that the contribution of each mediator to vides pure forms of the mediators, and, perhaps most
importantly, by the development of potent and specific fog.
antagonists, so that the contribution of each mediator to
asthma can be evaluated. Because the literature is

ASTHMA is characterized by variable and reversible
airflow obstruction and by bronchial hyper-responsive-
apparent that inflammatory cells, the generation of mehuman airways, although we have used data from animal
studies when information about humans is not possible studies when information about humans is not possible
to obtain or is not yet available. It is now increasingly human airways, although we have used data from animal
studies when information about humans is not possible
to obtain or is not yet available. It is now increasingly
apparent that inflammatory cells, the generation of mehuman airways, although we have used data from animal
studies when information about humans is not possible
to obtain or is not yet available. It is now increasingly
apparent that inflammatory cells, the generation of me-
 human airways, although we have used data from animal
studies when information about humans is not possible
to obtain or is not yet available. It is now increasingly
apparent that inflammatory cells, the generation of me-
 studies when information about humans is not possible
to obtain or is not yet available. It is now increasingly
apparent that inflammatory cells, the generation of me-
diators, and airway responses are markedly different
 to obtain or is not yet available. It is now increasingly
apparent that inflammatory cells, the generation of me-
diators, and airway responses are markedly different
between species, and it is difficult to extrapolate fro apparent that inflammatory cells, the generation of me-
diators, and airway responses are markedly different
between species, and it is difficult to extrapolate from
animal experiments to human airway disease. Although
var between species, and it is difficult to extrapolate from animal experiments to human airway disease. Although various animal models share some of the features of asthma, there is no entirely satisfactory model. It is, between species, and it is difficult to extrapolate freminal experiments to human airway disease. Althouvarious animal models share some of the features asthma, there is no entirely satisfactory model. It therefore, import animal experiments to human airway disease. Although various animal models share some of the features of asthma, there is no entirely satisfactory model. It is, therefore, important that more research should concentrate on various animal
asthma, there is
therefore, importate on human
in such studies. *A. Cellular Origin of Mediators*
A. Cellular Origin of Mediators
A. Cellular Origin of Mediators
Many different inflammatory

it are on human asthma, despite the difficulties involv
such studies.
Cellular Origin of Mediators
Many different inflammatory cells may release med
rs, which interact in a complex way to produce inflat in such studies.

A. Cellular Origin of Mediators

Many different inflammatory cells may release med

tors, which interact in a complex way to produce infla

matory changes in airways (fig. 1). A. Cellular Origin of Mediators
Many different inflammatory cells
tors, which interact in a complex way
matory changes in airways (fig. 1).
1. Mast cells. For many years, ma Leautar Origin of Mediators

1. Many different inflammatory cells may release media-

1. *Mast cells.* For many years, mast cells have been

1. *Mast cells.* For many years, mast cells have been

1. Mast cells a central ro

extensive, we have chosen to concentrate on studies in extensive, we have chosen to concentrate on studies in extensive, we have chosen to concentrate on studies in \cdot Funding was from the Medical Research Council and As Many different inflammatory cells may release media-
tors, which interact in a complex way to produce inflam-
matory changes in airways (fig. 1).
1. Mast cells. For many years, mast cells have been
assumed to play a centra tors, which interact in a complex way to produce infla
matory changes in airways (fig. 1).
1. Mast cells. For many years, mast cells have be
assumed to play a central role in the pathogenesis
asthma; mast cell mediators, matory changes in airways (fig. 1).

1. Mast cells. For many years, mast cells have been

assumed to play a central role in the pathogenesis of

asthma; mast cell mediators, such as histamine, prosta-

glandin (PG) D_2 , 1. Mast cells. For many years, mast cells have been
assumed to play a central role in the pathogenesis of
asthma; mast cell mediators, such as histamine, prosta-
glandin (PG) D_2 , and sulfidopeptide leukotrienes, may
ex assumed to play a central role in the pathogen
asthma; mast cell mediators, such as histamine, $_{\rm g}$
glandin (PG) D_2 , and sulfidopeptide leukotriene
explain several of the features of asthma (599, 49
table 1 for abbr asthma; mast cell mediators, such as histamine, prosta-
glandin (PG) D_2 , and sulfidopeptide leukotrienes, may
explain several of the features of asthma (599, 496) (see
table 1 for abbreviations). It is likely that immu glandin $(PG) D_2$, and sulfidopeptide leukotrienes, may explain several of the features of asthma $(599, 496)$ (see table 1 for abbreviations). It is likely that immunoglobulin E (IgE)-dependent release of mediators from m explain several of the features of asthma (599, 496) (see
table 1 for abbreviations). It is likely that immunoglob-
ulin E (IgE)-dependent release of mediators from mast
cells may account for the immediate bronchial respon table 1 for abbreviations). It is likely that immunoglobulin E (IgE)-dependent release of mediators from mast cells may account for the immediate bronchial response to allergen, and mast cells may also be involved in the b ulin E (IgE)-dependent release of mediators from mast
cells may account for the immediate bronchial response
to allergen, and mast cells may also be involved in the
bronchoconstrictor response to exercise, cold air, and
fo cells may account for the immediate bronchial response
to allergen, and mast cells may also be involved in the
bronchoconstrictor response to exercise, cold air, and
fog. Recent evidence, however, questions their central
i to allergen, and mast cells may also be involved in the bronchoconstrictor response to exercise, cold air, and fog. Recent evidence, however, questions their central involvement in bronchial hyper-responsiveness and chroni bronchoconstrictor response to exercise, cold air, and
fog. Recent evidence, however, questions their central
involvement in bronchial hyper-responsiveness and
chronic inflammation, since drugs which "stabilize" mast
cells fog. Recent evidence, however, questions their central involvement in bronchial hyper-responsiveness and chronic inflammation, since drugs which "stabilize" mast cells, such as beta-2 adrenoceptor agonists, do not prevent involvement in bronchial hyper-responsiveness and
chronic inflammation, since drugs which "stabilize" mast
cells, such as beta-2 adrenoceptor agonists, do not pre-
vent the late-phase response to allergen, nor the subse-
q chronic inflammation, since drugs which "stabilize" mast
cells, such as beta-2 adrenoceptor agonists, do not pre-
vent the late-phase response to allergen, nor the subse-
quent bronchial hyper-responsiveness. On the other

TABLE 1 *ExpLanation of terms*

Abbreviation	Definition
A23187	Calcium ionophore
AA	Arachidonic acid
AA-361	2,3,5-Trimethyl-6-(12-hydroxy-5,10-dodeca-
	diynyl)-1,4-benzoquinone
ACE	Angiotensin converting enzyme
AGEPC	Acetyl glyceryl ether phosphorylcholine
AI	Anaphylatoxin inactivator
APRL BN 52021	Anti-hypertensive polar renomedullary lipid Ginkgolide B
BN 52063	Mixture of ginkgolides A, B, and C
CGRP	Calcitonin gene-related peptide
ECF-A	Eosinophilic chemotactic factor of anaphylaxis
ECP	Eosinophil cationic protein
EpDRF	Epithelium-derived relaxant factor
EPO FMLP	Eosinophil peroxidase
FPL	Formyl-methionyl-leucyl-phenylalanine 7-[3-(4-Acetyl-3-hydroxy-2-propylphenoxy)-
55712	2-hydroxypropoxy]-4-oxo-8-propyl-4H-1-
	benzopyran-2-carboxylic acid monosodium salt
Gi	Inhibitory guanine nucleotide protein
н,•	Second histamine receptor subtype
15-HETE	15-Hydroxy-5,8,11,13-eicosatetraenoic acid
HMWK	High-molecular-weight kininogen
HPETE	Hydroperoxyeicosatetraenoic acid 5-Hydroxytryptamine (serotonin)
5-HT IgE*	Immunoglobulin E
IP3	Inositol 1,4,5-trisphosphate
L-649,923	(±)-4-[3-(4-Acetyl-3-hydroxy-2-propylphen-
	oxy)propyl]thio-γ-hydroxy-β-methylben-
	zene butanoic acid
LT	Leukotriene
LTB.* LXA	Leukotriene B.
MBP	Lipoxin A Major basic protein
NAAGA	N-Acetyl-aspartyl-glutamic acid
NANC	Nonadrenergic, noncholinergic
NCA	Neutrophil chemotactic activity
NECA	N-Ethylcarboxamide adenosine
NKA* NPK	Neurokinin A
NSAID	Neuropeptide K Nonsteroidal antiinflammatory drug
OKY-046	Sodium (E)-3-[4-(1-imidazolymethyl)phenyl]-
	2-propanoate
PAF	Platelet-activating factor
PG	Prostaglandin
PGDH	15-Hydroxyprostaglandin dehydrogenase
PGI,	Prostacyclin
PI PIA	Phosphoinositides Phenylisopropyl adenosine
PLA,	Phospholipase A ₂
REV 5901	α -Pentyl-3-(2-quindinylmethoxy)benzene
	methanol
SP	Substance P
SRS-A	Slow-reacting substance of anaphylaxis
Tc-DTPA TxA,	⁵⁹ Tc-diethylene triamine pentaacetate Thromboxane A ₂
U46619	$9,11$ -Dideoxy-11 α , 9 α -epoxymethanoprostag-
	landin F ₂₋
$U-60,257$	6,9-Deepoxy-6,9-(phenylimino)-delta-6,8-
	prostaglandin I ₁
WEB 2086	3-[4-(2-Chlorophenyl)-9-methyl-6H-
	thieno)(3,2-f)(1,2,4)triazolo(4,3- α) diaze-
	pin-2-yl-1-(4-morpholinyl)-1-propanone)

Variations of root abbreviation defined similarly.

process in asthma, leading to the production of many inflammatory
process in asthma, leading to the production of many inflammatory
mediators which, in combination, lead to the pathophysiological features of asthma. FIG. 1. Several different cells may be involved in the inflammatory
process in asthma, leading to the production of many inflammatory
mediators which, in combination, lead to the pathophysiological fea-
tures of asthma.
ce

process in assumit, isating to the protection of many inflammatory
mediators which, in combination, lead to the pathophysiological fea-
tures of asthma.
cell mediator release are effective (139). This suggests
that other i tures of asthma.

cell mediator reles

that other inflamn

diators in asthma.

2. Macrophages. 2. *Macrophages* are effective (139). This suggest other inflammatory cells may be the source of a ators in asthma.
2. *Macrophages*. Macrophages are abundant throught the respiratory tract, and recent evidence that t

cell mediator release are effective (139). This suggests
that other inflammatory cells may be the source of me-
diators in asthma.
2. Macrophages. Macrophages are abundant through-
out the respiratory tract, and recent ev diators in asthma.

2. Macrophages. Macrophages are abundant through-

out the respiratory tract, and recent evidence that they

may be activated by IgE-dependent mechanisms has

suggested their involvement in allergic inf 2. Macrophages. Macrophages are abundant through-
out the respiratory tract, and recent evidence that they
may be activated by IgE-dependent mechanisms has
suggested their involvement in allergic inflammation
(308). Macrop out the respiratory tract, and recent evidence that the may be activated by IgE-dependent mechanisms have assumed as the such as thromboxanes of mediators, such as thromboxanes prostaglandins, and platelet-activating facto may be activated by IgE-dependent mechanisms has suggested their involvement in allergic inflammation (308). Macrophages from asthmatic patients release greater amounts of mediators, such as thromboxane, prostaglandins, an suggested their involvement in allergic inflammatio (308). Macrophages from asthmatic patients released greater amounts of mediators, such as thromboxan prostaglandins, and platelet-activating factor (PAF than those derive (308). Macrophages from asthmatic patients release
greater amounts of mediators, such as thromboxane,
prostaglandins, and platelet-activating factor (PAF),
than those derived from normal subjects. Interestingly,
human lung greater amounts of mediators, such as thromboxane,
prostaglandins, and platelet-activating factor (PAF),
than those derived from normal subjects. Interestingly,
human lung macrophages are potently inhibited by cor-
ticoste than those derived from normal subjects. Interestingly,

human lung macrophages are potently inhibited by cor-
 3. Eosinophils. Eosinophil infiltration is a prominent

feature of asthma (186) and differentiates asthma fr

that other inflammatory cells may be the source of me-

distorts in asthma.

2. Macrophages Macrophages are abundant through-

2. Macrophages Macrophages are abundant incolaries has

may be activated by IgE-dependent mech than those derived from normal subjects. Interestingly,
human lung macrophages are potently inhibited by cor-
ticosteriods (225).
3. Eosinophils. Eosinophil infiltration is a prominent
feature of asthma (186) and differen human lung macrophages are potently inhibited by corticosteriods (225).
3. Eosinophils. Eosinophil infiltration is a prominent
feature of asthma (186) and differentiates asthma from
other inflammatory conditions of the air ticosteriods (225).

3. Eosinophils. Eosinophil infiltration is a prominent

feature of asthma (186) and differentiates asthma from

other inflammatory conditions of the airway. Antigen

inhalation results in a marked inc 3. Eosinophils. Eosinophil infiltration is a prominent feature of asthma (186) and differentiates asthma from other inflammatory conditions of the airway. Antigen inhalation results in a marked increase in eosinophils in b feature of asthma (186) and differentiates asthma from
other inflammatory conditions of the airway. Antigen
inhalation results in a marked increase in eosinophils in
bronchoalveolar lavage at the time of the late reaction
 other inflammatory conditions of the airway. Antig
inhalation results in a marked increase in eosinophils
bronchoalveolar lavage at the time of the late reacti
(171), and there is a relationship between peripher
blood eosi inhalation results in a marked increase in eosinophils
bronchoalveolar lavage at the time of the late reacti
(171), and there is a relationship between periphe
blood eosinophilia and bronchial hyper-responsiven
(216, 567). (171), and there is a relationship between peripheral blood eosinophilia and bronchial hyper-responsiveness (216, 567). Eosinophils may release a variety of mediators, including leukotrienes (609) and PAF (344), and (171), and there is a relationship between peripheral
blood eosinophilia and bronchial hyper-responsiveness
(216, 567). Eosinophils may release a variety of media-
tors, including leukotrienes (609) and PAF (344), and
als blood eosinophilia and bronchial hyper-responsiveness (216, 567). Eosinophils may release a variety of mediators, including leukotrienes (609) and PAF (344), and also release basic proteins, such as major basic protein and epithelium. rs, including leukotrienes (609) and PAF (344), anso release basic proteins, such as major basic proteind eosinophil cationic protein, which are toxic to airway ithelium.
4. *Neutrophils*. Neutrophils are also found in ast

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also release basic proteins, such as major basic protein
and eosinophil cationic protein, which are toxic to airway
epithelium.
4. Neutrophils. Neutrophils are also found in asth-
matic airways and may release a number of and eosinophil cationic protein, which are toxic to airway
epithelium.
4. Neutrophils. Neutrophils are also found in asth-
matic airways and may release a number of mediators,
including leukotriene B_4 (182), prostaglan epithelium.
4. Neutrophils. Neutrophils are also found in asthmatic airways and may release a number of mediators,
including leukotriene B₄ (182), prostaglandins (245),
PAF (378), and adenosine (386). In animal models of 4. Neutrophils. Neutrophils are also found in asthmatic airways and may release a number of mediators, including leukotriene B_4 (182), prostaglandins (245), PAF (378), and adenosine (386). In animal models of bronchia matic airways and may release a number of mediators,
including leukotriene B_4 (182), prostaglandins (245),
PAF (378), and adenosine (386). In animal models of
bronchial hyperresponsiveness, neutrophils have been
implic including leukotriene B_4 (182), prostaglan PAF (378), and adenosine (386). In animal bronchial hyperresponsiveness, neutrophils implicated (418), but their role in asthma remains less defined than that of eosinophils 5 AF (378), and adenosine (386). In animal models of onchial hyperresponsiveness, neutrophils have been pplicated (418), but their role in asthmatic airway mains less defined than that of eosinophils.
5. Epithelial cells. Ai

bronchial hyperresponsiveness, neutrophils have been implicated (418), but their role in asthmatic airways remains less defined than that of eosinophils.
5. Epithelial cells. Airway epithelial damage is a common feature o remains less defined than that of eosinophils.
5. Epithelial cells. Airway epithelial damage is a com-
mon feature of even mild asthma (331), and this may
underlie bronchial hyper-responsiveness, since many of
the conditio mon feature of even mild asthma (331), and this may 5. Epithelial cells. Airway epithelial damage is a con
mon feature of even mild asthma (331), and this ma
underlie bronchial hyper-responsiveness, since many
the conditions known to increase bronchial responsiveness
(ozone mon feature of even mild asthma (331), and this may underlie bronchial hyper-responsiveness, since many of the conditions known to increase bronchial responsiveness (ozone exposure, upper respiratory tract viral infection, underlie bronchial hyper-responsiveness, since many
the conditions known to increase bronchial respons
ness (ozone exposure, upper respiratory tract viral in
tion, allergen exposure) are associated with epithe
damage. Loss the conditions known to increase bronchial responsiveness (ozone exposure, upper respiratory tract viral infection, allergen exposure) are associated with epithelial damage. Loss of epithelial cells increases the bronchoco ness (ozone exposure, upper respiratory tract viral infection, allergen exposure) are associated with epithelial damage. Loss of epithelial cells increases the broncho-constrictor actions of spassnogens in vitro, possibly tion, allergen exposure) are associated with epitheld
damage. Loss of epithelial cells increases the bronch
constrictor actions of spasmogens in vitro, possibly l
cause airway epithelial cells release a relaxant fact
(206, damage. Loss of epithelial cells increases the broncho-
constrictor actions of spasmogens in vitro, possibly be-
cause airway epithelial cells release a relaxant factor
(206, 55, 159) and will also expose sensory nerve end constrictor actions of spasmogens in vitro, possibly be-
cause airway epithelial cells release a relaxant factor
(206, 55, 159) and will also expose sensory nerve endings,
which may lead to local and cholinergic reflex br cause airway epithelial cells release a relaxant factor (206, 55, 159) and will also expose sensory nerve endings, which may lead to local and cholinergic reflex broncho-constriction (43). Epithelial cells may also themse (206, 55, 159) and will also expose sensory nerve endings,
which may lead to local and cholinergic reflex broncho-
constriction (43). Epithelial cells may also themselves
release inflammatory mediators, such as leukotrien

aspet

INFLAMMATORY
(15-HETE) (291), which are chemotactic for inflam
tory cells. (15-HETE)
tory cells.
6. *Platel*e

(15-HETE) (291), which are chemotactic for inflamma-
tory cells.
6. Platelets. Abnormalities in platelet function have
been found in asthma, and animal studies suggest that
platelets are involved in bronchial hyper-respons (15-HETE) (291), which are chemotactic for inflamm
tory cells.
6. Platelets. Abnormalities in platelet function ha
been found in asthma, and animal studies suggest th
platelets are involved in bronchial hyper-responsivene
 tory cells. abnormalities in platelet function have numbeen found in asthma, and animal studies suggest that breaktlests are involved in bronchial hyper-responsiveness the (416). Platelets may release a variety of mediator 6. Platelets. Abnormalities in platelet function have
been found in asthma, and animal studies suggest that
platelets are involved in bronchial hyper-responsiveness
(416). Platelets may release a variety of mediators such
 been found in asthma, and animal studies suggest that
platelets are involved in bronchial hyper-responsiveness the
(416). Platelets may release a variety of mediators such lea
as serotonin, thromboxane, 5- and 12-lipoxygen platelets are involved in bronchial hyper-respons
(416). Platelets may release a variety of mediato
as serotonin, thromboxane, 5- and 12-lipoxy
products, PAF, and oxygen-free radicals and
activated by IgE-dependent mechani (416). Platelets may release a variety of mediators such
as serotonin, thromboxane, 5- and 12-lipoxygenease
products, PAF, and oxygen-free radicals and may be
activated by IgE-dependent mechanisms (307).
B. Mediator Effec

asthma (fig. 2; table 2). They may lead to contraction of The role of each mediator itself is probably complex,
airway smooth muscle, either directly or indirectly, via but it seems likely that there is an even more comple B. Mediator Effects

Inflammatory mediators may have a variety of effects

on target cells in the airways, which may be relevant to

asthma (fig. 2; table 2). They may lead to contraction of

airway smooth muscle, either B. Mediator Effects

Inflammatory mediators may have a variety of effects

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asthma (fig. 2; table 2). They may lead to contraction c
airway smooth muscle, either directly or indirectly, vi
r on target cells in the airways, which may be relevant asthma (fig. 2; table 2). They may lead to contraction airway smooth muscle, either directly or indirectly, release of secondary mediators or via neural mechanism They asthma (fig. 2; table 2). They may lead to contraction of airway smooth muscle, either directly or indirectly, via burelease of secondary mediators or via neural mechanisms. in They may also lead to increased secretion fro release of secondary mediators or via neural mechanisms.
They may also lead to increased secretion from submu-
cosal glands, to increased fluid transport across airway
epithelium, and to increased microvascular leakage,
wh release of secondary mediators or via neural mechanisms. in
They may also lead to increased secretion from submu-
cosal glands, to increased fluid transport across airway
pepithelium, and to increased microvascular leakage They may also lead to increased secretion from submu-
cosal glands, to increased fluid transport across airway
protepithelium, and to increased microvascular leakage, resp
which results in edema of the airway and exudation cosal glands, to increased fluid transport across airway
epithelium, and to increased microvascular leakage,
which results in edema of the airway and exudation of
plasma into the airway lumen, which itself may result in
th epithelium, and to increased microvascular leakage, rewhich results in edema of the airway and exudation of the plasma into the airway lumen, which itself may result in let the formation of new mediators (461). Inflammator which results in edema of the airway and exudation of plasma into the airway lumen, which itself may result in the formation of new mediators (461). Inflammatory mediators may attract and activate inflammatory cells which the formation of new mediators (461). Inflammatory
mediators may attract and activate inflammatory cells
which themselves release a whole array of mediators
which serve to perpetuate and emphasize the inflammatory response.
C. Mediator Receptors which themselves release a whole array of mediators

known about receptors for mediators in lung and the certain cytokines leads to augmented release of mediators R_{J} response.
 α Mediator Receptors
 α Mediators produce their effects on target cells by the
 α activation of specific cell surface receptors. More is now
 α how about receptors for mediators in lung an C. Mediator Receptors

Mediators produce their effects on target cells by the

activation of specific cell surface receptors. More is now

known about receptors for mediators in lung and the

biochemical pathways involved Mediators produce their effects on target cells by the
activation of specific cell surface receptors. More is now
known about receptors for mediators in lung and the
diochemical pathways involved in receptor activation
(4 activation of specific cell surface receptors. More is now

known about receptors for mediators in lung and the

biochemical pathways involved in receptor activation

(47). Using radioligand binding methods, it has been

p known about receptors for mediators in lung and the biochemical pathways involved in receptor activation (47). Using radioligand binding methods, it has been lipossible to characterize and localize these receptors in lung biochemical pathways involved in receptor activation (47). Using radioligand binding methods, it has been possible to characterize and localize these receptors in lung. It is hoped that further understanding of these recep (47). Using radioligand binding methods, it has been possible to characterize and localize these receptors in lung. It is hoped that further understanding of these receptors may lead to the development of more selective possible to characterize and localize these receptors in lung. It is hoped that further understanding of these free preceptors may lead to the development of more selective E antagonists which will provide evidence for lung. It is hoped that further understanding of these
receptors may lead to the development of more selective
antagonists which will provide evidence for the role of a
mediator in such a complex inflammatory disease as
ast receptors may lead to the development of more selective E
antagonists which will provide evidence for the role of a
mediator in such a complex inflammatory disease as in
asthma. More is now understood about the biochemi

INFLAMMATORY MEDIATORS AND ASTHMA 51
(15-HETE) (291), which are chemotactic for inflamma-
tory cells.
6. *Platelets*. Abnormalities in platelet function have included protein (Gi), whereas for other receptors,
been found i as serotonin, thromboxane, 5- and 12-lipoxygenease may be operative and may be interdependent. For mus-
products, PAF, and oxygen-free radicals and may be carrinic receptors, there is a close relationship between
activate 51
smooth muscle. Activation of some receptors leads to
inhibition of adenvlate cyclase via an inhibitory guanine index and the same of some receptors leads to
inhibition of adenylate cyclase via an inhibitory guanine
individue protein (Gi), whereas for other receptors, 51
smooth muscle. Activation of some receptors leads to
inhibition of adenylate cyclase via an inhibitory guanine
nucleotide protein (Gi), whereas for other receptors,
breakdown of membrane phosphoinositides (PI) leads to smooth muscle. Activation of some receptors leads to
inhibition of adenylate cyclase via an inhibitory guanine
nucleotide protein (Gi), whereas for other receptors,
breakdown of membrane phosphoinositides (PI) leads to
the smooth muscle. Activation of some receptors leads to
inhibition of adenylate cyclase via an inhibitory guanine
nucleotide protein (Gi), whereas for other receptors,
breakdown of membrane phosphoinositides (PI) leads to
the inhibition of adenylate cyclase via an inhibitory guanine
nucleotide protein (Gi), whereas for other receptors,
breakdown of membrane phosphoinositides (PI) leads to
the generation of inositol trisphosphate (IP3) which remucleotide protein (Gi), whereas for other receptors
breakdown of membrane phosphoinositides (PI) leads t
the generation of inositol trisphosphate (IP3) which re
leases intracellular calcium ions (76). Both mechanism
may b breakdown of membrane phosphoinositides (PI) leads to
the generation of inositol trisphosphate (IP3) which re-
leases intracellular calcium ions (76). Both mechanisms
may be operative and may be interdependent. For mus-
ca the generation of inositol trisphosphate (IP3) which re-
leases intracellular calcium ions (76). Both mechanisms
may be operative and may be interdependent. For mus-
carinic receptors, there is a close relationship between leases intracellular calcium ions (76). Both mechanisms
may be operative and may be interdependent. For mus-
carinic receptors, there is a close relationship between
receptor occupancy and stimulation of PI turnover (249), may be operation
carinic recepto
receptor occupa
and the same a
diators (248).
D. Mediator In Frame *Deepbors*, there is
receptor occupancy and still
and the same applies to rediators (248).
D. Mediator Interactions
The role of each mediat The role of each mediator itself is probably complex,
The role of each mediator itself is probably complex,
it it seems likely that there is an even more complex

but it seems (248).

D. Mediator Interactions

The role of each mediator itself is probably complex,

but it seems likely that there is an even more complex

interaction between different mediators, and that this D. Mediator Interactions
The role of each mediator itself is probably complex,
but it seems likely that there is an even more complex
interaction between different mediators, and that this
may lead to hyper-responsiveness. D. Mediator Interactions
The role of each mediator itself is probably complex,
but it seems likely that there is an even more complex
interaction between different mediators, and that this
may lead to hyper-responsiveness The role of each mediator itself is probably complex,
but it seems likely that there is an even more complex
interaction between different mediators, and that this
may lead to hyper-responsiveness. Thus, inhalation of
pro but it seems likely that there is an even more complex
interaction between different mediators, and that this
may lead to hyper-responsiveness. Thus, inhalation of
prostaglandins E_2 , $F_{2\alpha}$, and D_2 may lead to inc interaction between different mediators, and that this
may lead to hyper-responsiveness. Thus, inhalation of
prostaglandins E_2 , $F_{2\alpha}$, and D_2 may lead to increased
responsiveness, to inhaled spasmogens (593, 224) may lead to hyper-responsiveness. Thus, inhalation
prostaglandins E_2 , F_{2a} , and D_2 may lead to increas
responsiveness, to inhaled spassmogens (593, 224),
though such an increase is only transient, whereas P
leads prostaglandins E_2 , $F_{2\alpha}$, and D_2 manufresponsiveness, to inhaled spasmothough such an increase is only transleads to a more sustained increase siveness (160), as discussed below.
Mediator interaction in the skin though such an increase is only transient, whereas PAF
leads to a more sustained increase in bronchial respon-
siveness (160), as discussed below.
Mediator interaction in the skin is well described (9), but it seems likely that there is an even more complex
metrodon between different mediators, and that this
may lead to hyper-responsiveness. Thus, inhalation of
prostaglandins E_2 , F_{2a} , and D_2 may lead to increas The mediators, and that this increased blood increased passingles in the set in the set of D_2 may lead to increased D_2 may lead to increased D_2 may lead to increased D_2 may lead to increase in bronchial respon

which themselves release a whole array of mediators and mediators which lead to increased blood flow (such
which serve to perpetuate and emphasize the inflamma-
tory response.
C. Mediator Receptors
C. Mediator Receptors
M leads to a more sustained increase in bronchial responsiveness (160), as discussed below.
Mediator interaction in the skin is well described (9), and mediators which lead to increased blood flow (such as PGE₂ and PGI₂) siveness (160), as discussed below.
Mediator interaction in the skin is well described (9),
and mediators which lead to increased blood flow (such
as PGE_2 and PGI_2) potentiate the plasma extravasation
caused by other Mediator interaction in the skin is well described (9) ,
and mediators which lead to increased blood flow (such
as PGE_2 and PGI_2) potentiate the plasma extravasation
caused by other mediators (such as bradykinin) (63 and mediators which
as PGE₂ and PGI₂
caused by other 1
Whether such inte
is not yet certain.
Mediator intera PGE_2 and PGI_2) potentiate the plasma extravasation
used by other mediators (such as bradykinin) (63).
hether such interactions occur in the asthmatic airway
not yet certain.
Mediator interaction may also occur by "pri

caused by other mediators (such as bradykinin) (63).

Whether such interactions occur in the asthmatic airway

is not yet certain.

Mediator interaction may also occur by "priming" of

inflammatory cells. Thus, exposure o Whether such interactions occur in the asthmatic airway
is not yet certain.
Mediator interaction may also occur by "priming" of
inflammatory cells. Thus, exposure of eosinophils to
certain cytokines leads to augmented rele is not yet certain.

Mediator interaction may also occur by "priming" of

inflammatory cells. Thus, exposure of eosinophils to

certain cytokines leads to augmented release of mediators

(532). The number of possible inter Mediator interaction may also occur by "priming" of
inflammatory cells. Thus, exposure of eosinophils to
certain cytokines leads to augmented release of mediators
(532). The number of possible interactions is almost
limitl fruitful. (532). The number of possible interactions is almost limitless, and further research in this area should prove fruitful.
E. Mediator Antagonists The most convincing way to elucidate the role of and
dividual mediator in a complex inflammatory process,

individual mediator in a complex inflammatory process,
individual mediator in a complex inflammatory process,
such as asthma, is to study the effect of a selective E. Mediator Antagonists

The most convincing way to elucidate the role of an

individual mediator in a complex inflammatory process,

such as asthma, is to study the effect of a selective

mediator antagonist or an inhibit E. Mediator Antagonists
The most convincing way to elucidate the role of an
individual mediator in a complex inflammatory process,
such as asthma, is to study the effect of a selective
mediator antagonist or an inhibitor o

ARMACOLOGICAL REVIEW

Oxygen radicals $\overline{}$

* Key: ++, pronounced effect; +, moderate effect; ±, uncertain effect; ?,

sive efforts by the pharmaceutical industry have led to

the synthesis of several such agents which are currently

be * Key: $++$, pronounced effect; $+$, moderate effect; \pm , uncertain effect; ?, is
sive efforts by the pharmaceutical industry have led to
the synthesis of several such agents which are currently
being tested in asthma. O sive efforts by the pharmaceutical industry have led to the synthesis of several such agents which are currently being tested in asthma. Of course, any conclusions drawn from such studies must depend on the degree of selec sive efforts by the pharmaceutical industry have led to
the synthesis of several such agents which are currently
being tested in asthma. Of course, any conclusions drawn
uri
from such studies must depend on the degree of s the synthesis of several such agents which are currently
being tested in asthma. Of course, any conclusions drawn
from such studies must depend on the degree of selectiv-
ity of the antagonist. The dose of antagonist must being tested in asthma. Of course, any conclusions drawn
from such studies must depend on the degree of selectiv-
ity of the antagonist. The dose of antagonist must also
fobe adequate to block endogenously generated mediat from such studies must depend on the degree of selectiv-
ity of the antagonist. The dose of antagonist must also
be adequate to block endogenously generated mediators
and, at the very least, should be shown to block the
ef ity of the antagonist. The dose of antagonist must also
be adequate to block endogenously generated mediators
and, at the very least, should be shown to block the
effects of exogenously delivered mediator. Examples of
the be adequate to block endogenously generated mediators and, at the very least, should be shown to block the imeffects of exogenously delivered mediator. Examples of net the specific antagonists currently available are given and, at the very least, should be shown to block the imerfects of exogenously delivered mediator. Examples of network the specific antagonists currently available are given for each mediator. The search for even more pote effects of exogenously delivered mediator. Examples of net
the specific antagonists currently available are given for
each mediator. The search for even more potent and B ,
specific antagonists may be beneficial to unrav the specific antagonists currently available are given for
each mediator. The search for even more potent and
specific antagonists may be beneficial to unravelling the
components of asthma, but may not necessarily have a
 each mediator. The search for even more potent a specific antagonists may be beneficial to unravelling to components of asthma, but may not necessarily have major clinical impact, since blocking a single mediator unlikely

II. Histamine

as the same involved.

The started in the pathogenesis of asthma shortly after its discovery, when it was shown to

mimic anaphylactic bronchoconstriction in guinea pigs with **1. Histamine**
 1. Histamine
 1. Histamine
 1. Histamine
 1. A
 **1. Example and Solution in the pathogenesis of

1. 1. 1. Example a**
 1. Example a
 1. Example a
 1. Example a
 1. II. Histamine

Histamine was implicated in the pathogenesis of

asthma shortly after its discovery, when it was shown to

mimic anaphylactic bronchoconstriction in guinea pigs

(167). Intravenous histamine caused bronchoco Histamine was implicated in the pathogenesis of asthma shortly after its discovery, when it was shown to mimic anaphylactic bronchoconstriction in guinea pigs (167). Intravenous histamine caused bronchoconstriction in ast asthma shortly after its discovery, when it was shown to
mimic anaphylactic bronchoconstriction in guinea pigs
(167). Intravenous histamine caused bronchoconstriction
in asthmatic subjects (473), and inhaled histamine was
 mimic anaphylactic bronchoconstriction in guinea pigs (167). Intravenous histamine caused bronchoconstriction in asthmatic subjects (473), and inhaled histamine was demonstrated to cause bronchoconstriction in asthmatic b (167). Intravenous histamine caused bronchoconstriction
in asthmatic subjects (473), and inhaled histamine was
demonstrated to cause bronchoconstriction in asthmatic
but not in normal subjects (154). Histamine is probably in asthmatic subjects (473) , and inhaled histamine was
demonstrated to cause bronchoconstriction in asthmatic
but not in normal subjects (154) . Histamine is probably
the best characterized of all mediators of asthma; demonstrated to cause bronchoconstriction in asthmation but not in normal subjects (154). Histamine is probably the best characterized of all mediators of asthma; there is now a wealth of information about its effects on h but not in normal subjects (154). Histamine is probably
the best characterized of all mediators of asthma; there
is now a wealth of information about its effects on human
airways, and the recent introduction of specific an the best characterized of all mediators of asther is now a wealth of information about its effects airways, and the recent introduction of specific sedating antihistamines has made it possible to the role of histamine in a *A. Synthesis* and the recent introduction
 A. Synthesis and *Metabolism*
 A. Synthesis and Metabolism
 Histamine is formed by decarbor Histamine is formed and provide to evaluate
a role of histamine in asthma pathophysiology.
Synthesis and Metabolism
Histamine is formed by decarboxylation of histidine
d stored in preformed cytoplasmic granules of mast

From the role of histamine in asthma pathophysiology.
A. Synthesis and Metabolism
Histamine is formed by decarboxylation of histidine
and stored in preformed cytoplasmic granules of mast
cells and basophils in close associ cells and Metabolism
A. Synthesis and Metabolism
Histamine is formed by decarboxylation of histic
and stored in preformed cytoplasmic granules of n
cells and basophils in close association with proteo
cans which are predom A. Synthesis and Metabolism air

Histamine is formed by decarboxylation of histidine che

and stored in preformed cytoplasmic granules of mast

by cells and basophils in close association with proteogly-

cans which are pr Histamine is formed by decarboxylation of histidine
and stored in preformed cytoplasmic granules of mast
cells and basophils in close association with proteogly-
cans which are predominantly heparin in mast cells and
chron cells and basophils in close association with proteogly-
cans which are predominantly heparin in mast cells and
ceptors, it has been possible to demonstrate that there
chrondroitin 4-sulfates in human basophils. Histamine cans which are predominantly heparin in mast cells and ceptors, it has been possible to demonstrate that there
chrondroitin 4-sulfates in human basophils. Histamine are few "spare" histamine receptors (250).
forms 5 to 10 cans which are predominantly heparin in mast cells and cepto:
chrondroitin 4-sulfates in human basophils. Histamine are fe
forms 5 to 10% of the content of human mast cell The
granules. It is released from lung mast cells chrondroitin 4-sulfates in human basophils. Histamine are
forms 5 to 10% of the content of human mast cell
granules. It is released from lung mast cells or blood ac
basophils by an active secretory process which is calcium forms 5 to 10% expansions. It is related
basophils by an act dependent, and severognized (215).

Histamine is metabolized by two major enzymatic +

Present and the set of the set o wheter interestingly information not available.

Histamine is metabolized by two major enzymatic

pathways, and less than 3% is excreted unchanged in the

urine. Fifty to 70% of histamine is metabolized to N-

methyl-hista Histamine is metabolized by two major enzymatic
pathways, and less than 3% is excreted unchanged in the
urine. Fifty to 70% of histamine is metabolized to N-
methyl-histamine by N-methyl transferase which is
found in small Histamine is metabolized by two major enzymatic
pathways, and less than 3% is excreted unchanged in the
urine. Fifty to 70% of histamine is metabolized to N-
methyl-histamine by N-methyl transferase which is
found in small pathways, and less than 3% is excreted unchanged in the
urine. Fifty to 70% of histamine is metabolized to N-
methyl-histamine by N-methyl transferase which is
found in small intestine, liver, kidney, and leukocytes;
and urine. Fifty to 70% of histamine is metabolized to N-
methyl-histamine by N-methyl transferase which is
found in small intestine, liver, kidney, and leukocytes;
and the remainder by diamine oxidase (histamine) to
imidazole methyl-histamine by N-m
found in small intestine, liv
and the remainder by dian
imidazole acetic acid in sm
neutrophils, and eosinophils *B. Histamine Receptors*
B. Histamine Receptors
Histamine *Receptors*
Histamine produces if

major cincal impact, since blocking a single mediator is
unlikely to have a major effect if many different media-
tors are involved.
I. Histamine (mepyramine), was able to block some responses, such
as contraction of guin Histamine Receptors
Histamine produces its effects by interacting with
ecific receptors on target cells. The existence of more B. Histamine Receptors
B. Histamine produces its effects by interacting with
specific receptors on target cells. The existence of more
than one receptor subtype was suggested when Ash and B. Histamine Receptors

Histamine produces its effects by interacting with

specific receptors on target cells. The existence of more

than one receptor subtype was suggested when Ash and

Schild found that the classical a B. Histamine produces its effects by interacting with
specific receptors on target cells. The existence of more
than one receptor subtype was suggested when Ash and
Schild found that the classical antihistamine, pyrilamine Histamine produces its effects by interacting with
specific receptors on target cells. The existence of more
than one receptor subtype was suggested when Ash and
Schild found that the classical antihistamine, pyrilamine
(m specific receptors on target cells. The existence of more
than one receptor subtype was suggested when Ash and
Schild found that the classical antihistamine, pyrilamine
(mepyramine), was able to block some responses, such
 than one receptor subtype was suggested when Ash and
Schild found that the classical antihistamine, pyrilamine
(mepyramine), was able to block some responses, such
as contraction of guinea pig trachea, but not others such
 Schild found that the classical antihistamine, pyrilamine (mepyramine), was able to block some responses, such as contraction of guinea pig trachea, but not others such as gastric acid secretion (29). The existence of a s (mepyramine), was able to block some responses, such
as contraction of guinea pig trachea, but not others such
as gastric acid secretion (29). The existence of a second
histamine receptor subtype (H_2 -receptor) was conf as contraction of guinea pig trachea, but not others such
as gastric acid secretion (29). The existence of a second
histamine receptor subtype (H_2 -receptor) was confirmed
with the development of selective antagonists s as gastric acid secretion (29). The existence of a second
histamine receptor subtype $(H_2$ -receptor) was confirmed
with the development of selective antagonists such as
cimetidine and ranitidine. There is also a third sub th the development of selective antagonists such as
metidine and ranitidine. There is also a third subtype
receptor (H_3) for which selective agonists and antag-
ists have recently been developed (27).
1. H_1 -receptors cimetidine and ranitidine. There is also a third subtype
of receptor (H_3) for which selective agonists and antag-
onists have recently been developed (27).
1. H_1 -receptors. H_1 -receptors have been identified in
ani

of receptor (H_3) for which selective agonists and
onists have recently been developed (27).
1. H_1 -receptors. H_1 -receptors have been ident
animal and human lung homogenates by receptor
techniques (114, 115, 250). U onists have recently been developed (27).

1. H_1 -receptors. H_1 -receptors have been identified

animal and human lung homogenates by receptor bindi

techniques (114, 115, 250). Using an immunohistoche

ical technique 1. H_1 -receptors. H₁-receptors have been identified in
animal and human lung homogenates by receptor binding
techniques (114, 115, 250). Using an immunohistochem-
ical technique to study the distribution of cyclic gua animal and human lung homogenates by receptor binding
techniques (114, 115, 250). Using an immunohistochem-
ical technique to study the distribution of cyclic guano-
sine monophosphate, H_1 -receptors have been localized
 techniques (114, 115, 250). Using an immunohistochemical technique to study the distribution of cyclic guanosine monophosphate, H_1 -receptors have been localized to airway epithelial cells, macrophages, and alveolar cell ical technique to study the distribution of cyclic guano-
sine monophosphate, H_1 -receptors have been localized
to airway epithelial cells, macrophages, and alveolar cells
in guinea pig lung, with surprisingly little lo sine monophosphate, H_1 -receptors have been localized
to airway epithelial cells, macrophages, and alveolar cells
in guinea pig lung, with surprisingly little localization to
airway or vascular smooth muscle (520). In b to airway epithelial cells, macrophages, and alveolar cells
in guinea pig lung, with surprisingly little localization to
airway or vascular smooth muscle (520). In bovine tra-
cheal smooth muscle, H₁-receptors have been in guinea pig lung, with surprisingly little localization to airway or vascular smooth muscle (520). In bovine tracheal smooth muscle, H_1 -receptors have been determined by direct receptor binding using $[^3H]$ pyrilamine airway or vascular smooth muscle (520). In bovine tra-
cheal smooth muscle, H₁-receptors have been determined
by direct receptor binding using [³H]pyrilamine and,
using phenoxybenzamine to fractionally inactivate re-
c cheal smooth muscle, H_1 -receptors have been
by direct receptor binding using $[^3H]$ pyri
using phenoxybenzamine to fractionally in
ceptors, it has been possible to demonstrat
are few "spare" histamine receptors (250).
T using phenoxybenzamine to fractionally inactivate receptors, it has been possible to demonstrate that there

ceptors, it has been possible to demonstrate that there
are few "spare" histamine receptors (250) .
The intracellular pathways involved in H_1 -receptor
activation have recently been studied. In guinea pig
ileum, histam are few "spare" histamine receptors (250) .
The intracellular pathways involved in H_1 -recept
activation have recently been studied. In guinea p
ileum, histamine stimulates breakdown of PI (180), an
similarly in bovine The intracellular pathways involved in H_1 -receptor
activation have recently been studied. In guinea pig
ileum, histamine stimulates breakdown of PI (180), and
similarly in bovine tracheal smooth muscle, a corre-
spondi

aspet

INFLAMMATORY MED
between H₁-receptor occupancy and PI response (248).
The increase in cyclic guanosine monophosphate (GMP) INFLAMMATORY MEDI
between H_1 -receptor occupancy and PI response (248).
The increase in cyclic guanosine monophosphate (GMP)
which occurs in lung via H_1 -receptor activation (471) is INFLAMMATORY MEDIATE

between H₁-receptor occupancy and PI response (248). a 1

The increase in cyclic guanosine monophosphate (GMP) alt

which occurs in lung via H₁-receptor activation (471) is

probably secondary to between H_1 -receptor occupancy and PI response (248).
The increase in cyclic guanosine monophosphate (GMP)
which occurs in lung via H_1 -receptor activation (471) is
probably secondary to the increase in intracellular formation. inch occurs in lung via H_1 -receptor activation (471) is smotohably secondary to the increase in intracellular cal-
num, which occurs in response to PI hydrolysis and IP₃ mat
rmation.
2. H_2 -receptors. H₂-receptor

probably secondary to the increase in intracellular calcum, which occurs in response to PI hydrolysis and IP₃ m
formation.
2. H_2 -receptors. H₂-receptors have been identified in alung using [³H]tiotidine (213), bu cium, which occurs in response to PI hydrolysis and IP₃ mat
formation. suc
2. H_2 -receptors. H₂-receptors have been identified in ate
lung using [³H]tiotidine (213), but their localization has bro
not been documen formation.
2. H_2 -receptors. H_2 -receptors have been identified in
lung using [³H]tiotidine (213), but their localization has
not been documented. H_2 -receptor activation causes an
increase in cyclic adenosine mon cyclase. of the documented. H_2 -receptor activation causes an crease in cyclic adenosine monophosphate (AMP) controls of lung, and H_2 -receptors are coupled to adenylate clase.
3. H_3 -*receptors*. H_3 -receptors have been d

increase in cyclic adenosine monophosphate (AMP) contant of lung, and H_2 -receptors are coupled to adenylate (4 cyclase.

3. H_3 -receptors. H_3 -receptors have been differentiated the using the selective agonist α tent of lung, and H_2 -receptors are coupled to adenylate (42)
cyclase. ons
3. H_3 -receptors. H_3 -receptors have been differentiated that
using the selective agonist α -methyl histamine and the pail
antagonist thio cyclase. $3. H_3$ -receptors. H₃-receptors have been differentiated the using the selective agonist α -methyl histamine and the paintagonist thioperamide, but the role of H₃-receptors in vietinvay is not known; it is 3. H_3 -receptors. H₃-receptors have been differentiated that using the selective agonist α -methyl histamine and the paintagonist thioperamide, but the role of H₃-receptors in viet airway is not known; it is possi antagonist thioperamide, but the role of H_3 -receptors in view that there may be a defect in H_2 -receptors in hyper-
airway is not known; it is possible that they may be reactive airways (122).
involved in feedback in airway is not known; it is possible that they may be
involved in feedback inhibition of histamine release. An 2. Vascular effects. Histamine has a dual effect on
atyptical histamine receptor-mediating relaxation, which
is airway is not known; it is possible the
involved in feedback inhibition of histar
atyptical histamine receptor-mediating r
is not blocked by combined H_1 and H
been described in rabbit trachea (207). *C. Airway Effects*
C. Airway Effects
C. Airway Effects
Histamine has seven

en described in rabbit trachea (207) .

to
 $Airway$ Effects

Histamine has several actions on the airway which

imic the pathophysiology of asthma, and for many $C.$ Airway Effects

Histamine has several actions on the airway which

mimic the pathophysiology of asthma, and for many

years histamine was considered to be the major inflam-C. Airway Effects
Histamine has several actions on the airway wh
mimic the pathophysiology of asthma, and for ma
years histamine was considered to be the major infla
matory mediator involved in asthma. C. Airway Effects

Histamine has several actions on

mimic the pathophysiology of asthr

years histamine was considered to be

matory mediator involved in asthma.

1. Airway smooth muscle. Bronch *1. Airway smooth muscle.* Bronchoconstriction was one of the first properties of histamine was shown to contract humanized (167) and histamine was shown to contract humanized

years histamine was considered to be the major inflam-
matory mediator involved in asthma.
1. Airway smooth muscle. Bronchoconstriction was
one of the first properties of histamine which was rec-
ognized (167) and histamin matory mediator involved in asthma.
1. Airway smooth muscle. Bronchoconstriction was
one of the first properties of histamine which was rec-
ognized (167) and histamine was shown to contract hu-
man bronchi in vitro many y 1. Airway smooth muscle. Bronchoconstriction was
one of the first properties of histamine which was rec-
ognized (167) and histamine was shown to contract hu-
man bronchi in vitro many years ago, (511). Histamine
contracts (167) and histamine was shown to contract human smaller airways (195). Although it has not been possible on the first properties of histamine which was recognized (167) and histamine was shown to contract human bronchi in ognized (167) and histamine was shown to contract human bronchi in vitro many years ago, (511). Histamine microntracts both large and small human airways in vitro

(201) and, in animals, this contractile effect may be mod man bronchi in vitro many years ago, (511) . Histamine
contracts both large and small human airways in vitro
 (201) and, in animals, this contractile effect may be
modulated by the presence of intact airway epithelium
contracts both large and small human airways in vitro (201) and, in animals, this contractile effect may be modulated by the presence of intact airway epithelium (206, 159). In vivo infused histamine causes marked systemic (201) and, in animals, this contractile effect n
modulated by the presence of intact airway epit.
(206, 159). In vivo infused histamine causes n
systemic vasodilation but no bronchoconstriction
299), whereas infused hista modulated by the presence of intact airway epithelium (206, 159). In vivo infused histamine causes marked systemic vasodilation but no bronchoconstriction (473, 299), whereas infused histamine causes bronchoconstriction i (206, 159). In vivo infused histamine causes marked
systemic vasodilation but no bronchoconstriction (473,
299), whereas infused histamine causes bronchoconstric-
tion in asthmatic patients (313, 557). Similarly, inhaled
 systemic vasodilation but no bronchoconstriction (473, 299), whereas infused histamine causes bronchoconstriction in asthmatic patients (313, 557). Similarly, inhaled histamine causes bronchoconstriction in asthmatic patie 299), whereas infused histamine causes bronchoconstriction in asthmatic patients (313, 557). Similarly, inhaled histamine causes bronchoconstriction in asthmatic patients more readily than normal subjects, as a manifestati tion in asthmatic patients (313, 557). Similarly, inhaled
histamine causes bronchoconstriction in asthmatic pa-
tients more readily than normal subjects, as a manifes-
tation of bronchial hyperreactivity (89). In vitro ai histamine causes bronchoconstriction in asthmatic partients more readily than normal subjects, as a manifes-
tation of bronchial hyperreactivity (89). In vitro airways with
from asthmatics do not appear to be more responsi tients more readily than normal subjects, as a manifes-
tation of bronchial hyperreactivity (89). In vitro airways
from asthmatics do not appear to be more responsive to
histamine (119, 243), although there is one report o tation of bronchial hyperreactivity (89). In vitro airways
from asthmatics do not appear to be more responsive to
histamine (119, 243), although there is one report of an
increased maximal response to histamine (510). In from asthmatics do not appear to be more responsive to histamine (119, 243), although there is one report of an increased maximal responst to histamine (510). In animals, tachyphylaxis to the homchoconstrictor effect of s histamine (119, 243), although there is one report of an increased maximal response to histamine (510). In animals, tachyphylaxis to the hronchoconstrictor effect of histamine may be demonstrated in vitro and may be due to increased maximal response to histamine (510). In animals, tachyphylaxis to the hronchoconstrictor effect of histamine may be demonstrated in vitro and may be due to the generation of prostaglandins, since indomethacin pre mals, tachyphylaxis to the hronchoconstrictor effect of histamine may be demonstrated in vitro and may be due to the generation of prostaglandins, since indomethacin prevents its development (443). Tolerance to histamine c histamine may be demonstrated in vitro and may be due
to the generation of prostaglandins, since indomethacin
prevents its development (443). Tolerance to histamine
prevents its development (443). Tolerance to histamine
m to the generation of prostaglandins, since indomethaciprevents its development (443). Tolerance to histamine
challenge may also be found in mild asthmatic subject
with a reduced bronchoconstrictor response to a secon
hista prevents its development (443). Tolerance to histaminchallenge may also be found in mild asthmatic subject
with a reduced bronchoconstrictor response to a secon
histamine challenge, which is prevented by prior treat
ment w challenge may also be found in mild asthmatic subjects, The with a reduced bronchoconstrictor response to a second to histamine challenge, which is prevented by prior treat-
ment with indomethacin (388). Histamine releases with a reduced broncho
histamine challenge, wh
ment with indomethacin
taglandins from human
account for this effect.
There is some debate stamine challenge, which is prevented by prior treat-
ent with indomethacin (388). Histamine releases pros-
glandins from human lung in vitro (471), which may
count for this effect. (1
There is some debate as to whether

ment with indomethacin (388). Histamine releases pros-
taglandins from human lung in vitro (471), which may
account for this effect.
There is some debate as to whether H_2 -receptors are
present in human airways. In seve taglandins from human lung in vitro (471), which ma
account for this effect.
There is some debate as to whether H_2 -receptors ar
present in human airways. In several animal species, H_2
receptors which mediate broncho

The increase in cyclic guanosine monophosphate (GMP) although this could be an effect on pulmonary vascular
which occurs in lung via H₁-receptor activation (471) is smooth muscle rather than on airways. An H₂-selectiv lung using [³H]tiotidine (213), but their localization has bronchoconstrictors in normal or asthmatic subjects
not been documented. H₂-receptor activation causes an (571, 432, 96), although there is one report that ci ATORS AND ASTHMA

a relaxant response to histamine, via H_2 -receptors (589),

although this could be an effect on pulmonary vascular ATORS AND ASTHMA

a relaxant response to histamine, via H_2 -receptors (589),

although this could be an effect on pulmonary vascular

smooth muscle rather than on airways. An H_2 -selective smooth muscle rather muscle rather wis H₂-receptors (589),
although this could be an effect on pulmonary vascular
smooth muscle rather than on airways. An H₂-selective
agonist, impromidine, has no effect on normal or a relaxant response to histamine, via H_2 -receptors (589 although this could be an effect on pulmonary vascula smooth muscle rather than on airways. An H_2 -selective agonist, impromidine, has no effect on normal or as a relaxant response to histamine, via H_2 -receptors (589),
although this could be an effect on pulmonary vascular
smooth muscle rather than on airways. An H_2 -selective
agonist, impromidine, has no effect on normal or although this could be an effect on pulmonary vascus smooth muscle rather than on airways. An H_2 -selectiagonist, impromidine, has no effect on normal or ast matic airways in vivo (609a), and H_2 -selective blocke such smooth muscle rather than on airways. An H_2 -selective agonist, impromidine, has no effect on normal or asthmatic airways in vivo (609a), and H_2 -selective blockers, such as cimetidine and ranitidine, have not been as agonist, impromidine, has no effect on normal or asthmatic airways in vivo (609a), and H_2 -selective blockers, such as cimetidine and ranitidine, have not been associated with bronchoconstriction or increased sensitivit matic airways in vivo $(609a)$, and H_2 -selective blocks such as cimetidine and ranitidine, have not been associed with bronchoconstriction or increased sensitivity bronchoconstrictors in normal or asthmatic subje $(571$ such as cimetidine and ranitidine, have not been associated with bronchoconstriction or increased sensitivity to bronchoconstrictors in normal or asthmatic subject $(571, 432, 96)$, although there is one report that cimet ated with bronchoconstriction or increased sensitivity thronchoconstrictors in normal or asthmatic subject $(571, 432, 96)$, although there is one report that cimetidine potentiates histamine-induced bronchoconstrictio $($ bronchoconstrictors in normal or asthmatic subjects (571, 432, 96), although there is one report that cimeti-
dine potentiates histamine-induced bronchoconstriction (425). A defect in H_2 -receptor function has been demo (571, 432, 96), although there is one report that cimeti-
dine potentiates histamine-induced bronchoconstriction
(425). A defect in H_2 -receptor function has been dem-
onstrated in allergic sheep (10), and there is evid dine potentiates histamine-induced bronchoconstriction (425). A defect in H_2 -receptor function has been demonstrated in allergic sheep (10), and there is evidence that H_2 -receptor-mediated gastric secretion may be i (425). A defect in H₂-receptor function has been de onstrated in allergic sheep (10), and there is evider that H₂-receptor-mediated gastric secretion may be i paired in asthmatic patients (246), which supports t view onstrated in allergic sh
that H_2 -receptor-mediat
paired in asthmatic pat
view that there may be a
reactive airways (122).
2. Vascular effects. Fi at H₂-receptor-mediated gastric secretion may be im-

ired in asthmatic patients (246), which supports the

ew that there may be a defect in H₂-receptors in hyper-

active airways (122).

2. *Vascular effects*. Histam

paired in asthmatic patients (246), which supports the view that there may be a defect in H_2 -receptors in hyper-
reactive airways (122).
2. *Vascular effects*. Histamine has a dual effect on human pulmonary vessels in view that there may be a defect in H_2 -receptors in hypreactive airways (122).
2. Vascular effects. Histamine has a dual effect
human pulmonary vessels in vitro, with constrict
mediated by H_1 -receptors and vasodilati reactive airways (122).

2. Vascular effects. Histamine has a dual effect on

human pulmonary vessels in vitro, with constriction

mediated by H₁-receptors and vasodilation via H₂-recep-

tors (86). Histamine increase 2. Vascular effects. Histamine has a dual effect on human pulmonary vessels in vitro, with constriction mediated by H_1 -receptors and vasodilation via H_2 -receptors (86). Histamine increases bronchial blood flow in sh human pulmonary ve
mediated by H_1 -recept
tors (86). Histamine is
sheep and dogs, an e
receptors (369, 333).
Histamine also cau ediated by H_1 -receptors and vasodilation via H_2 -receptrs (36). Histamine increases bronchial blood flow in
eep and dogs, an effect which is mediated via H_2 -
ceptors (369, 333).
Histamine also causes microvascular

tors (86). Histamine increases bronchial blood flow in sheep and dogs, an effect which is mediated via H_2 -
receptors (369, 333). Histamine also causes microvascular leakage in the bronchial microvasculature (507, 462), sheep and dogs, an effect which is mediated via H_i
receptors (369, 333).
Histamine also causes microvascular leakage in th
bronchial microvasculature (507, 462), which is presume
to be due to contraction of endothelial receptors (369, 333).
Histamine also causes microvascular leakage in the
bronchial microvasculature (507, 462), which is presumed
to be due to contraction of endothelial cells in post-
capillary venules (462). This effect Histamine also causes microvascular leakage in the
bronchial microvasculature (507, 462), which is presumed
to be due to contraction of endothelial cells in post-
capillary venules (462). This effect is mediated via H_1 bronchial microvasculature (507, 462), which is presumed
to be due to contraction of endothelial cells in post-
capillary venules (462). This effect is mediated via H_1 -
receptors and appears to be greater in larger rat to be due to contraction of endothelial cells in post-
capillary venules (462). This effect is mediated via H_1 -
receptors and appears to be greater in larger rather than capillary venules (462). This effect is mediated via H_1 -
receptors and appears to be greater in larger rather than
smaller airways (195). Although it has not been possible
to study the effect of histamine on human bron receptors and appears to be greater in larger rather than
smaller airways (195). Although it has not been possible
to study the effect of histamine on human bronchial
microvasculature, it is likely that similar effects to smaller airways (195). Although it has not been possible
to study the effect of histamine on human bronchia
microvasculature, it is likely that similar effects to those
seen in animals will occur. Intradermal injection of tamine in humans causes immediate weal formation, 557). view that there may be a defect in H_2 -receptors in hyper-
reactive airways (122).
 2. Vascular effects. Histamine has a dual effect on

2. Vascular effects. Histamine increases bronchial blood flow in

neuman pulmona

tamine in humans causes immediate weal formation,
which is completely inhibited by an H_1 -antagonist (20,
557).
3. Airway secretions. Histamine increases secretion of
mucus glycoproteins from human airways in vitro, and which is completely inhibited by an H_1 -antagonist (20,
557).
3. Airway secretions. Histamine increases secretion of
mucus glycoproteins from human airways in vitro, and
this effect is mediated by H_2 -receptors since 557).
3. Airway secretions. Histamine increases secretion of mucus glycoproteins from human airways in vitro, and this effect is mediated by H_2 -receptors since the effect is blocked by cimetidine and stimulated by dima 3. Airway secretions. Histamine increases secretion of mucus glycoproteins from human airways in vitro, and this effect is mediated by H_2 -receptors since the effect is blocked by cimetidine and stimulated by dimaprit (mucus glycoproteins from human airways in vitro, and
this effect is mediated by H_2 -receptors since the effect is
blocked by cimetidine and stimulated by dimaprit (524).
The effect of histamine is rather weak when compa blocked by cimetidine and stimulated by dimaprit (524). The effect of histamine is rather weak when compared with other secretagogs. In canine airways, histamine also increases ion transport and water secretion via H_1 blocked by c
The effect c
with other s
increases ion
tors (392).
4. Neural the effect of histamine is rather weak when computed the other secretagogs. In canine airways, histamine creases ion transport and water secretion via H_1 -re (392).
4. *Neural effects*. In many species, the bronchocon-

account for this effect. (118). It is likely that the vagal component of broncho-
There is some debate as to whether H_2 -receptors are
present in human airways. In several animal species, H_2 - comes relatively less im with other secretagogs. In canine airways, histamine also
increases ion transport and water secretion via H_1 -recep-
tors (392).
4. *Neural effects*. In many species, the bronchocon-
strictor effect of histamine is part increases ion transport and water secretion via H_1 -receptors (392).
4. Neural effects. In many species, the bronchoconstrictor effect of histamine is partially mediated by a vagal reflex, and histamine has been shown t tors (392).
4. Neural effects. In many species, the bronchoconstrictor effect of histamine is partially mediated by a vagal reflex, and histamine has been shown to increase action potentials in intrapulmonary vagal affere 4. Neural effects. In many species, the bronchoconstrictor effect of histamine is partially mediated by a vagal reflex, and histamine has been shown to increase action potentials in intrapulmonary vagal afferent nerves, an strictor effect of histamine is partially mediated by a vagal reflex, and histamine has been shown to increase action potentials in intrapulmonary vagal afferent nerves, an effect which is mediated by H_1 -receptors (506 vagal reflex, and histamine has been shown to increase
action potentials in intrapulmonary vagal afferent
nerves, an effect which is mediated by H_1 -receptors (506).
The role of cholinergic reflexes in the bronchial res action potentials in intrapulmonary vagal afferences, an effect which is mediated by H_1 -receptors (
The role of cholinergic reflexes in the bronchial resp
to histamine in humans is less certain, since some gr
have repo nerves, an effect which is mediated by H_1 -receptors (5)
The role of cholinergic reflexes in the bronchial respo
to histamine in humans is less certain, since some gro
have reported a significant reduction in the bronch The role of cholinergic reflexes in the bronchial response
to histamine in humans is less certain, since some groups
have reported a significant reduction in the bronchocon-
strictor response to inhaled histamine following to histamine in humans is less certain, since some gro
have reported a significant reduction in the bronchoc
strictor response to inhaled histamine following antic
linergic treatment (524, 187), whereas others have
(118). have reported a significant reduction in the bronchoconstrictor response to inhaled histamine following anticho-
linergic treatment (524, 187), whereas others have not
(118). It is likely that the vagal component of bronch strictor response to inhaled histamine following anticholinergic treatment (524, 187), whereas others have not (118). It is likely that the vagal component of bronchoconstriction may be greater in normal subjects but becom

EXTERN S4
Ance of small-molecular-weight compounds such as ⁹⁹Tc
diethylene triamine pentaacetate (Tc-DTPA) from hu BARNES, CHU
ance of small-molecular-weight compounds such as ⁹⁹Tc-
diethylene triamine pentaacetate (Tc-DTPA) from hu-
man lungs, suggesting that it increases lung epithelial BARNES, CHU
ance of small-molecular-weight compounds such as ⁹⁹Tc-
diethylene triamine pentaacetate (Tc-DTPA) from hu-
man lungs, suggesting that it increases lung epithelial
permeability, an effect mediated via H_2 -r ance of small-molecular-weight compounds such as ⁹⁹Tc-
diethylene triamine pentaacetate (Tc-DTPA) from hu-
man lungs, suggesting that it increases lung epithelial
permeability, an effect mediated via H₂-receptors (96). ance of small-molecular-weight compounds such as ⁹⁹Tc-
diethylene triamine pentaacetate (Tc-DTPA) from human lungs, suggesting that it increases lung epithelial me
permeability, an effect mediated via H_2 -receptors (9 diethylene triamine pentaacetate (Tc-DTPA) from human lungs, suggesting that it increases lung epithelial permeability, an effect mediated via H_2 -receptors (96). The site of the increased clearance is not certain, but thelium. The site of the increased clearance is not certain, but is
more likely to be at the alveolar level than airway epi-
thelium.
Histamine is also chemotactic to inflammatory cells.

The site of the increased clearance is not certain, but is pro
more likely to be at the alveolar level than airway epi-
thelium.
Histamine is also chemotactic to inflammatory cells, am
such as eosinophils (137, 577) and ne more likely to be at the alveolar level than airway epi-
thelium.
Histamine is also chemotactic to inflammatory cells,
such as eosinophils (137, 577) and neutrophils (515), and
may, therefore, amplify the inflammatory reac the lium.

Histamine is also chemotactic to inflammatory cells,

such as eosinophils (137, 577) and neutrophils (515), and

may, therefore, amplify the inflammatory reaction, al-

though the effects are small when compared Histamine is also chemotactic to inflammatory ce
such as eosinophils (137, 577) and neutrophils (515), i
may, therefore, amplify the inflammatory reaction,
though the effects are small when compared to ot
mediators. His such as eosinophils (137, 577) and neutrophils (515), and fourth fough the effects are small when compared to other momentiators. Histamine stimulates T-lymphocyte suppressor cell function via H_2 -receptors, and this fu may, therefore, amplify the inflammator
though the effects are small when com
mediators. Histamine stimulates T-lympl
sor cell function via H_2 -receptors, and thi
be depressed in atopic individuals (69).
IgE-mediated re ough the effects are small when compared to othe
ediators. Histamine stimulates T-lymphocyte suppres
r cell function via H_2 -receptors, and this function ma
depressed in atopic individuals (69).
IgE-mediated release of

mediators. Histamine stimulates T-lymphocyte supposor cell function via H_2 -receptors, and this function r
be depressed in atopic individuals (69).
IgE-mediated release of histamine from human be
phils is inhibited by h sor cell function via H_2 -receptors, and this function may
be depressed in atopic individuals (69).
IgE-mediated release of histamine from human baso-
phils is inhibited by histamine itself, acting on H_2 -recep-
tors, be depressed in atopic individuals (69). the IgE-mediated release of histamine from human baso-
phils is inhibited by histamine itself, acting on H_2 -receptors, so that H_2 -antagonists could theoretically enhance
hist IgE-mediated release of histamine from human bases phils is inhibited by histamine itself, acting on H_2 -recetors, so that H_2 -antagonists could theoretically enhan histamine release (365), but H_2 -receptors have no pins is inhibited by histors, so that H₂-antago
histamine release (365)
demonstrated on mast
D. Role in Asthma
There is a wealth of Stamine release (365) , but H_2 -receptors have not been monstrated on mast cells in human airways (312) .

Role in Asthma

There is a wealth of evidence which implicates histaine in asthma, and the recent introduction

minumerated on mast cells in human airways (312).

D. Role in Asthma

There is a wealth of evidence which implicates his

mine in asthma, and the recent introduction of non-

dative antihistamines has made it possible to d $D.$ Role in Asthma
There is a wealth of evidence which implicates hista-
mine in asthma, and the recent introduction of nonse-
dative antihistamines has made it possible to determine
more precisely its contribution to as D. Hole in Asthma
There is a wealth of evidence which implicates l
mine in asthma, and the recent introduction of n
dative antihistamines has made it possible to deter
more precisely its contribution to asthma pathophy
 ogy. ine in asthma, and the recent introduction of nonsetive antihistamines has made it possible to determine clicit
precisely its contribution to asthma pathophysiol-
y.
1. *Histamine release*. Measurements of histamine have i dative antihistamines has made it possible to determine
more precisely its contribution to asthma pathophysiol-
ogy.
1. Histamine release. Measurements of histamine have
been made in asthma since the first assays were deve

more precisely its contribution to asthma pathophysiol-
ogy.
1. Histamine release. Measurements of histamine have
ificen made in asthma since the first assays were devel-
oped in the 1940s. Fluorimetric assays, which lacke ogy.

1. Histamine release. Measurements of histamine have

been made in asthma since the first assays were devel-

oped in the 1940s. Fluorimetric assays, which lacked

specificity and sensitivity, gave conflicting result 1. Histamine release. Measurements of histamine have
been made in asthma since the first assays were devel-
oped in the 1940s. Fluorimetric assays, which lacked
specificity and sensitivity, gave conflicting results, but
r been made in asthma since the first assays were devel-
oped in the 1940s. Fluorimetric assays, which lacked b
specificity and sensitivity, gave conflicting results, but
refinement of radioenzymatic assays has made it poss oped in the 1940s. Fluorimetric assays, which lacked
specificity and sensitivity, gave conflicting results, but
refinement of radioenzymatic assays has made it possible
to detect low concentrations of histamine in plasma
(specificity and sensitivity, gave conflicting results, but
refinement of radioenzymatic assays has made it possible
to detect low concentrations of histamine in plasma
(101). Several studies reported an elevated base-line refinement of radioenzymatic assays has made it possible to detect low concentrations of histamine in plasma was too irritant, a more potent H₁-antagonist, clemas-
(101). Several studies reported an elevated base-line con-
centration of plasma histamine in severe asthma (102, (101). Several studies reported an elevated base-line con-
centration of plasma histamine in severe asthma (102,
126, 533), but the concentrations reported were very high,
and it seems unlikely that they reported release centration of plasma histamine in severe asthma (102, 126, 533), but the concentrations reported were very high, and it seems unlikely that they reported release from mast cells in lung, since such elevations should have c 126, 533), but the concentrations reported were very high,
and it seems unlikely that they reported release from
mast cells in lung, since such elevations should have
in caused marked cardiovascular effects (299). With im and it seems unlikely that they reported release from and tells in lung, since such elevations should have caused marked cardiovascular effects (299) . With improved sensitivity of the assay, it was shown that even mild mast cells in lung, since such elevations should have
caused marked cardiovascular effects (299). With im-
proved sensitivity of the assay, it was shown that even
mild asthmatic subjects had elevated values of plasma
hista proved sensitivity of the assay, it was shown that even
mild asthmatic subjects had elevated values of plasma
induced bronchoconstriction (474) . proved sensitivity of the assay, it was shown that even
mild asthmatic subjects had elevated values of plasma
histamine (59, 49), which has been interpreted as mast
cell "leakiness." Several conflicting results of plasma
h mild asthmatic subjects had elevated values of plasma
histamine (59, 49), which has been interpreted as mast
cell "leakiness." Several conflicting results of plasma
histamine measurements have been reported with var-
ious histamine (59, 49), which has been interpreted as mast
cell "leakiness." Several conflicting results of plasma
histamine measurements have been reported with var-
ious bronchoconstrictor challenges in asthma. Elevated
plas cell "leakiness." Several conflicting results of planetal
histamine measurements have been reported with
ious bronchoconstrictor challenges in asthma. Elev
plasma histamine has been reported in exercise-ind
bronchoconstric histamine measurements have been reported with various bronchoconstrictor challenges in asthma. Elevated
plasma histamine has been reported in exercise-induced
bronchoconstriction, but not in matched bronchocon-
striction ious bronchoconstrictor challenges in asthma. Elevated
plasma histamine has been reported in exercise-induced
bronchoconstriction, but not in matched bronchocon-
striction produced by hyperventilation (49), and it seems
ca plasma histamine has been reported in exercise-induced
bronchoconstriction, but not in matched bronchocon-
striction produced by hyperventilation (49), and it seems
likely that the increase with exercise might be due to t bronchoconstriction, but not in matched bronchoconstriction produced by hyperventilation (49), and it seems
likely that the increase with exercise might be due to the
increase in basophil counts which occurs during exercis striction produced by hyperventilation (49) , and it seems
likely that the increase with exercise might be due to the
increase in basophil counts which occurs during exercise
 (412) . Plasma histamine accounts for only likely that the increase with exercise might be due to the
increase in basophil counts which occurs during exercise
of histamine "tone" (144), and partially protects against
(412). Plasma histamine accounts for only 0.5% (412). Plasma histamine accounts for only 0.5% of total reported to be increased in allergen challenge in asth-
matic subjects (285), and there may be a secondary rise
associated with the late response (421) and also increases blood histamine, the remainder being contained in ba-
sophils, so any contamination of plasma is likely to give (1)
marked discrepancies (298). Plasma histamine is also breported to be increased in allergen challenge in a sophils, so any contamination of plasma is likely to give marked discrepancies (298). Plasma histamine is also reported to be increased in allergen challenge in asthmatic subjects (285), and there may be a secondary rise a marked discrepancies (298) . Plasma histamine is also brother
ported to be increased in allergen challenge in asth-
matic subjects (285) , and there may be a secondary rise role
associated with the late response (421)

G, AND PAGE
the time of maximum bronchoconstriction (57). Whether
these increases in plasma histamine are a reflection of G, AND PAGE
the time of maximum bronchoconstriction (57). Whether
these increases in plasma histamine are a reflection of
mediator release from airway mast cells is uncertain, G, AND PAGE
the time of maximum bronchoconstriction (57). Whether
these increases in plasma histamine are a reflection of
mediator release from airway mast cells is uncertain
however, and sampling blood from a peripheral v the time of maximum bronchoconstriction (57). Whether
these increases in plasma histamine are a reflection of
mediator release from airway mast cells is uncertain,
however, and sampling blood from a peripheral vein is
prob the time of maximum bronchoconstriction (57). Whether
these increases in plasma histamine are a reflection of
mediator release from airway mast cells is uncertain,
however, and sampling blood from a peripheral vein is
prob these increases in plasma histamine are a reflection of
mediator release from airway mast cells is uncertain,
however, and sampling blood from a peripheral vein is
probably unlikely to closely reflect the relatively small
 mediator release from airway mast cells is uncertain,
however, and sampling blood from a peripheral vein is
probably unlikely to closely reflect the relatively small
amount of histamine release in airways, particularly in
 however, and sampling blood from a peripheral vein is
probably unlikely to closely reflect the relatively small
amount of histamine release in airways, particularly in
hyperresponsive patients where a comparatively small
a probably unlikely to closely
amount of histamine release
hyperresponsive patients wh
amount of histamine release
found bronchomotor effect.
Recent studies have ther nount of histamine release in airways, particularly in
perresponsive patients where a comparatively small
nount of histamine released locally may have a pro-
und bronchomotor effect.
Recent studies have therefore measured

hyperresponsive patients where a comparatively sma
amount of histamine released locally may have a pro
found bronchomotor effect.
Recent studies have therefore measured histamin
more locally in bronchoalveolar lavage fluid amount of histamine released locally may have a pro-
found bronchomotor effect.
Recent studies have therefore measured histamine
more locally in bronchoalveolar lavage fluid from asth-
matics and demonstrated an elevated c found bronchomotor effect.

Recent studies have therefore measured histamine

more locally in bronchoalveolar lavage fluid from asth-

matics and demonstrated an elevated concentration in

comparison with nonasthmatic subj Recent studies have therefore measured histamine
more locally in bronchoalveolar lavage fluid from asth-
matics and demonstrated an elevated concentration in
comparison with nonasthmatic subjects (208, 116), al-
though in more locally in bronchoalveolar lavage fluid from asthmatics and demonstrated an elevated concentration in comparison with nonasthmatic subjects (208, 116), although in another study, no such elevation was found in mild st matics and demonstrated an elevated concentration in
comparison with nonasthmatic subjects (208, 116), al-
though in another study, no such elevation was found in
mild stable asthmatics (481). While the above studies
indic comparison with nonasthmatic subjects (208, 116), a
though in another study, no such elevation was found
mild stable asthmatics (481). While the above studie
indicate that histamine may be released in asthma are
thus provi though in another study, no such elevation was found in
mild stable asthmatics (481). While the above studies
indicate that histamine may be released in asthma and
thus provide indirect evidence of mast cell degranulation, mild stable asthmatics (481). While the above studies
indicate that histamine may be released in asthma and
thus provide indirect evidence of mast cell degranulation,
they do not give information about the contribution of
 thus provide indirect evidence of mast cell degranulation,
they do not give information about the contribution of
histamine to pathophysiology; this information can only
be provided by the use of specific antagonists.

they do not give information about the contribution of
histamine to pathophysiology; this information can only
be provided by the use of specific antagonists.
2. Antihistamines. If histamine is important in
asthma, then an histamine to pathophysiology; this information can obe provided by the use of specific antagonists.
2. Antihistamines. If histamine is important asthma, then antihistamines should be effective in clinical management. Previ be provided by the use of specific antagonists.

2. Antihistamines. If histamine is important in

asthma, then antihistamines should be effective in its

clinical management. Previous experience with antihis-

tamines has 2. Antihistamines. If histamine is important is
asthma, then antihistamines should be effective in it
clinical management. Previous experience with antihis
tamines has not been encouraging in asthma (314), al
though the H clinical management. Previous experience with antihistamines has not been encouraging in asthma (314) , although the H_1 -antagonists used have often lacked specificity, and sedative effects have limited the dosage.
Chl tamines has not been encouraging in asthma (314) , although the H₁-antagonists used have often lacked specificity, and sedative effects have limited the dosage.
Chlorpheniramine, given i.v. in a high dose, causes bronc

Example 12. Antihistamics (481). While the above studies ideated asthmatics (481). While the above studies didate that histamine may be released in asthma and us provide indirect evidence of mast cell degranulation, ey d tamines has not been encouraging in asthma (314) , although the H_1 -antagonists used have often lacked specificity, and sedative effects have limited the dosage.
Chlorpheniramine, given i.v. in a high dose, causes bron though the H₁-antagonists used have often lacked specificity, and sedative effects have limited the dosage.
Chlorpheniramine, given i.v. in a high dose, causes
bronchodilatation in asthmatic but not in normal sub-
jects ificity, and sedative effects have limited the dosage.
Chlorpheniramine, given i.v. in a high dose, causes
bronchodilatation in asthmatic but not in normal sub-
jects (474, 188), although the sedative side effects would
pr Chlorpheniramine, given i.v. in a high dose, caus
bronchodilatation in asthmatic but not in normal st
jects (474, 188), although the sedative side effects work
preclude clinical use. While inhaled chlorpheniramine
was too bronchodilatation in asthmatic but not in normal sub-
jects (474, 188), although the sedative side effects would
preclude clinical use. While inhaled chlorpheniramine
was too irritant, a more potent H_1 -antagonist, clem preclude clinical use. While inhaled chlorpheniramine preclude clinical use. While inhaled chlorpheniramine
was too irritant, a more potent H_1 -antagonist, clemas-
tine, given by inhalation caused bronchodilatation in
some asthmatic patients (433, 571), confirming the ex-
 was too irritant, a more potent H_1 -antagonist, clemastine, given by inhalation caused bronchodilatation in some asthmatic patients (433, 571), confirming the existence of histamine "tone" in asthmatic airways and sugge some asthmatic patients $(433, 571)$, confirming the existence of histamine "tone" in asthmatic airways and suggesting that there is some basal release of histamine in asthma.
H₁-antagonists have also been shown to part istence of histamine "tone" in asthmatic airways and suggesting that there is some basal release of histamine

tect against exercise-induced asthma (268) and antigen-
induced bronchoconstriction (474).
The recent introduction of potent and selective nonasthma.
H₁-antagonists have also been shown to partially pro-
ct against exercise-induced asthma (268) and antigen-
duced bronchoconstriction (474).
The recent introduction of potent and selective non-
dative antihistami

 H_1 -antagonists have also been shown to partially pitect against exercise-induced asthma (268) and antige induced bronchoconstriction (474) .
The recent introduction of potent and selective no sedative antihistamines, tect against exercise-induced asthma (268) and antigen-
induced bronchoconstriction (474).
The recent introduction of potent and selective non-
sedative antihistamines, such as terfenadine and astem-
izole, has made it pos induced bronchoconstriction (474) .
The recent introduction of potent and selective non-
sedative antihistamines, such as terfenadine and astem-
izole, has made it possible to more easily evaluate the
role of histamine i The recent introduction of potent and selective non-
sedative antihistamines, such as terfenadine and astem-
izole, has made it possible to more easily evaluate the
role of histamine in asthma, since it is possible to ach sedative antihistamines, such as terfenadine and astemizole, has made it possible to more easily evaluate the role of histamine in asthma, since it is possible to achieve a greater degree of H_1 -receptor blockade. Terfe izole, has made it possible to more easily evaluate the role of histamine in asthma, since it is possible to achieve a greater degree of H_1 -receptor blockade. Terfenadine causes a degree of bronchodilatation similar to role of histamine in asthma, since it is possible to achieve
a greater degree of H₁-receptor blockade. Terfenadine
causes a degree of bronchodilatation similar to that
achieved with a beta-agonist, confirming the existen a greater degree of H_1 -receptor blockade. Terfenadine causes a degree of bronchodilatation similar to that achieved with a beta-agonist, confirming the existence of histamine "tone" (144), and partially protects agains causes a degree of bronchodilatation similar to that
achieved with a beta-agonist, confirming the existence
of histamine "tone" (144), and partially protects against
exercise-induced asthma (452). Additionally, terfenadine achieved with a beta-agonist, confirming the existence
of histamine "tone" (144), and partially protects against
exercise-induced asthma (452). Additionally, terfenadine
has a small inhibitory effect against allergen chall of histamine "tone" (144), and partially protects against
exercise-induced asthma (452). Additionally, terfenadine
has a small inhibitory effect against allergen challenge
(121, 477), in doses which give a 30-fold shift in exercise-induced asthma (452). Additionally, terfenadine
has a small inhibitory effect against allergen challenge
(121, 477), in doses which give a 30-fold shift in the
bronchoconstrictor dose-response curves to histamine
 has a small inhibitory effect against allergen challenge (121, 477), in doses which give a 30-fold shift in the bronchoconstrictor dose-response curves to histamine (478), suggesting that histamine plays a relatively minor (121, 477), in doses which give a 30-fold shift in the bronchoconstrictor dose-response curves to histamine (478), suggesting that histamine plays a relatively minor role in immediate bronchoconstriction responses to alle bronchoconstrictor dose-response curves to histamine (478), suggesting that histamine plays a relatively minor role in immediate bronchoconstriction responses to allergen. Astemizole has a very long half-life and inhibits

PHARMACOLOGICAL REVIEW!

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INFLAMMATORY MEDIATOI
wk after discontinuing the drug (138, 282). Studies to (296
assess the long-term effects of nonsedative H₁-antago- acti INPLAMMATORY
wk after discontinuing the drug (138, 282). Studies
assess the long-term effects of nonsedative H_1 -anta
nists in asthma are currently underway. INFI
wk after discontinuing the drug (138,
assess the long-term effects of nonseder
inists in asthma are currently underway.
III. Cyclogy is an architecture assess the long-term effects of nonsedative H_1 -antagonists in asthma are currently underway.
III. Cyclooxygenase Products
Since the identification and isolation of the first pros-
taglandins in the 1960s, the cyclooxyg

III. **Cyclooxygenase Products**

mists in asthma are currently underway. $\frac{81}{100}$
III. Cyclooxygenase Products of the first prostaglandins in the 1960s, the cyclooxygenase products of harachidonic acid (AA) (which include prostaglandins and III. Cyclooxygenase Products

Since the identification and isolation of the first pros-

taglandins in the 1960s, the cyclooxygenase products of have

arachidonic acid (AA) (which include prostaglandins and H

thromboxane) Since the identification and isolation of the first pros-
taglandins in the 1960s, the cyclooxygenase products of have
arachidonic acid (AA) (which include prostaglandins and
thromboxane) have been implicated in asthma. Ma Since the identification and isolation of the first pros-
taglandins in the 1960s, the cyclooxygenase products of
arachidonic acid (AA) (which include prostaglandins and
thromboxane) have been implicated in asthma. Many
as taglandins in the 1960s, the cyclooxygenase products of have arachidonic acid (AA) (which include prostaglandins and
thromboxane) have been implicated in asthma. Many chy
aspects of the biochemistry and pharmacology of th aspects of the biochemistry and pharmacology of these compounds have been studied on lung tissue, which can generate, release, and inactivate them. Much information about the effects of cyclooxygenase products on the airways has been obtained in man.
A. Synthesis and Metaboli From the Second Security of the September of the about the effects of cyclooxygenase

ways has been obtained in man.
 A. Synthesis and Metabolism

Prostaglandins (PGs) are forme

out the effects of cyclooxygenase products on the air-
ys has been obtained in man.
Synthesis and Metabolism
Prostaglandins (PGs) are formed from arachidonic
id (AA), and initiation of PG biosynthesis occurs with Prostaglandins (PGs) are formed from arachidonic specific response to smooth muscle contraction.
acid (AA), and initiation of PG biosynthesis occurs with Enriched or purified human lung mast cells undergoing
its formation pholipase A_2 , which appears to be the rate-limiting step Prostaglandins (PGs) are formed from arachidonic special (AA), and initiation of PG biosynthesis occurs with
its formation from cell membrane phospholipids by phos-
pholipase A_2 , which appears to be the rate-limiting s Prostaglandins (PGs) are formed from arachidonic acid (AA), and initiation of PG biosynthesis occurs with its formation from cell membrane phospholipids by phos-
pholipase A_2 , which appears to be the rate-limiting step acid (AA), and initiation of PG biosynthesis occurs with
its formation from cell membrane phospholipids by phos-
pholipase A_2 , which appears to be the rate-limiting step
that determines the amount of substrate availabl its formation from cell membrane phospholipids by phos-
pholipase A_2 , which appears to be the rate-limiting step
that determines the amount of substrate available for
 PG synthesis (336). Arachidonic acid is oxidized b pholipase A_2 , which appears to be the rate-limiting ste
that determines the amount of substrate available for
PG synthesis (336). Arachidonic acid is oxidized by cy
clooxygenase to the cyclic endoperoxide, PGG₂, whic that determines the amount of substrate available for me

PG synthesis (336). Arachidonic acid is oxidized by cy-

clooxygenase to the cyclic endoperoxide, PGG₂, which is In

rapidly reduced to another unstable endopero PG synthesis (336). Arachidonic acid is oxidized by
clooxygenase to the cyclic endoperoxide, PGG₂, which
rapidly reduced to another unstable endoperoxi
 $PGH₂$, which then gives rise to $PGF_{2\alpha}$, $PGE₂$, a clooxygenase to the cyclic endoperoxide, PGG_2 , which is
rapidly reduced to another unstable endoperoxide,
 PGH_2 , which then gives rise to $PGF_{2\alpha}$, PGE_2 , and PGD_2
(fig. 3). Other enzymatic pathways for cyclic endo rapidly reduced to another unstable endoperoxide, all PGH_2 , which then gives rise to $PGF_{2\alpha}$, PGE_2 , and PGD_2 $P(Gig. 3)$. Other enzymatic pathways for cyclic endoper-
oxides lead to the formation of thromboxane A_2 PGH₂, which then gives rise to PGF_{2a} , PGE_2 , and PGD_2 PG (fig. 3). Other enzymatic pathways for cyclic endoper-
oxides lead to the formation of thromboxane A_2 (TxA₂) lated
and prostacylin (PGI₂), which are (fig. 3). Other enzymatic
oxides lead to the formatic
and prostacylin (PGI₂), wh
rapidly hydrolyzed to the
6-keto-PGF_{1a}, respectively
The main enzyme respo ides lead to the formation of thromboxane A_2 (Tx.
d prostacylin (PGI₂), which are both unstable and indly hydrolyzed to the inactive but stable TxB_2 and R is the prosectively.
The main enzyme responsible for pulm

and prostacylin $(PGI₂)$, which are both unstable and are
rapidly hydrolyzed to the inactive but stable $TxB₂$ and
6-keto-PGF_{1a}, respectively.
The main enzyme responsible for pulmonary metabo-
lism of PGs is the rapidly hydrolyzed to the inactive but stable TxB_2 and 6 -keto-PGF_{1a}, respectively.

The main enzyme responsible for pulmonary metabolism of PGs is the 15-OH-PG dehydrogenase (PGDH) and, within one transit through th 6-keto-PGF_{1a}, respectively.
The main enzyme responsible for pulmonary metabo-
lism of PGs is the 15-OH-PG dehydrogenase (PGDH)
and, within one transit through the lung, inactivation of
exogenous PGE₂ and PGF_{2a} is al The main enzyme responsible for pulmonary metabolism of PGs is the 15-OH-PG dehydrogenase (PGDH) and, within one transit through the lung, inactivation of exogenous PGE_2 and $PGF_{2\alpha}$ is almost complete (402, 469), but

AIRWAYS INFLAMMATION
Fig. 3. Synthetic pathways leading to the synthesis of prostaglar
dins, leukotrienes, and platelet-activating factor from membrane pho
pholipids. pholipids.

TORS AND ASTHMA
(296). This inactivation is a function of a selective and
active uptake of PGs by capillary endothelial plasma TORS AND ASTHMA
(296). This inactivation is a function of a selective and
active uptake of PGs by capillary endothelial plasma
membranes (80) and may be blocked by PG inhibitors TORS AND ASTHMA
(296). This inactivation is a function of a selective and
active uptake of PGs by capillary endothelial plasma
membranes (80) and may be blocked by PG inhibitors
such as indomethacin (80, 81). PGD_2 is a (296). This inactivation is a function of a selective and active uptake of PGs by capillary endothelial plasma membranes (80) and may be blocked by PG inhibitors such as indomethacin (80, 81). PGD_2 is a poor substrate f (296). This inactivation is a function of a selective and active uptake of PGs by capillary endothelial plasma membranes (80) and may be blocked by PG inhibitors such as indomethacin (80, 81). PGD₂ is a poor substrate f active uptake of PGs by capillary endothelial plasma
membranes (80) and may be blocked by PG inhibitors
such as indomethacin (80, 81). PGD₂ is a poor substrate
for PGDH and, when infused i.v. in man, is metabolized
to P membranes (80) and may be blocked b
such as indomethacin (80, 81). PGD_2 is
for PGDH and, when infused i.v. in mai
to PGF-9 derivatives (67, 367), which
have bronchoconstrictor actions (67).
 PGD_2 and PGI_2 are release ch as indomethacin (80, 81). PGD_2 is a poor substrate $PGDH$ and, when infused i.v. in man, is metaboliz $PGF-9$ derivatives (67, 367), which may themselve bronchoconstrictor actions (67).
 PGD_2 and PGI_2 are released fr

thromboxane) have been implicated in asthma. Many chyma during anaphylaxis, with smaller amounts of aspects of the biochemistry and pharmacology of these TxA_2 , PGE_2 , and PGF_{2a} ; by contrast, in the airway, compounds for PGDH and, when infused i.v. in man, is metabolized
to PGF-9 derivatives (67, 367), which may themselves
have bronchoconstrictor actions (67).
 PGD_2 and PGI_2 are released from human lung paren-
chyma during anaphyla to PGF-9 derivatives (67, 367), which may themselves
have bronchoconstrictor actions (67).
 PGD_2 and PGI_2 are released from human lung paren-
chyma during anaphylaxis, with smaller amounts of
 TxA_2 , PGE₂, and PGF_{2a} have bronchoconstrictor actions (67).

PGD₂ and PGI₂ are released from human lung parenchyma during anaphylaxis, with smaller amounts of TxA_2 , PGE₂, and PGF_{2a}; by contrast, in the airway,

PGI₂, PGF_{2a}, and P PGD₂ and PGI₂ are released from human lung parenchyma during anaphylaxis, with smaller amounts of TxA_2 , PGE₂, and PGE_{2a}; by contrast, in the airway, PGI₂, PGF_{2a}, and PGE₂ are released in the greatest amoun chyma during anaphylaxis, with smaller amounts of TxA_2 , PGE_2 , and PGF_{2a} ; by contrast, in the airway, PGI_2 , PGF_{2a} , and PGE_2 are released in the greatest amount (7, 513, 514). Steel et al. (549) suggest that p TxA₂, PGE₂, and PGF_{2a}; by contrast, in the airway,
PGI₂, PGF_{2a}, and PGE₂ are released in the greatest
amount (7, 513, 514). Steel et al. (549) suggest that
prostaglandin generation accompanying anaphylaxis
may PGI₂, PGF_{2*a*}, and PGE₂ are released in the greater amount (7, 513, 514). Steel et al. (549) suggest the prostaglandin generation accompanying anaphylax may result from a combination of factors, includin direct rele amount (7, 513, 514). Steel et al. (549) suggest that
prostaglandin generation accompanying anaphylaxis
may result from a combination of factors, including
direct release from mast cells, stimulation of H₁ hista-
mine re direct release from mast cells, stimulation of H_1 histamine receptors in lung parenchymal cells, and as a non-
specific response to smooth muscle contraction.
Enriched or purified human lung mast cells undergoing
IgE-d

mine receptors in lung parenchymal cells, and as a non-
specific response to smooth muscle contraction.
Enriched or purified human lung mast cells undergoing
IgE-dependent activation release PGD_2 as the major
cyclooxyge mine receptors in lung parenchymal cells, and as a non-
specific response to smooth muscle contraction.
Enriched or purified human lung mast cells undergoing
IgE-dependent activation release PGD_2 as the major
cyclooxyge specific response to smooth muscle contraction.

Enriched or purified human lung mast cells undergoing

IgE-dependent activation release PGD₂ as the major

cyclooxygenase product (281, 364, 512). Human alveolar

macroph Enriched or purified human lung mast cells undergoing
IgE-dependent activation release PGD_2 as the major
cyclooxygenase product (281, 364, 512). Human alveolar
macrophages also release PGD_2 (380) in addition to
measur measurable quantities of PGE_2 , $PGF_{2\alpha}$, and TxB_2 (235).
In vivo, local instillation of antigen in the airways of allergic asthmatics results in the immediate release of cyclooxygenase product (281, 364, 512). Human alveolar
macrophages also release PGD_2 (380) in addition to
measurable quantities of PGE_2 , $PGF_{2\alpha}$, and TxB_2 (235).
In vivo, local instillation of antigen in the airwa macrophages also release PGD_2 (380) in addition to
measurable quantities of PGE_2 , $PGF_{2\alpha}$, and TxB_2 (235).
In vivo, local instillation of antigen in the airways of
allergic asthmatics results in the immediate rele measurable quantities of PGE_2 , $PGF_{2\alpha}$, and TxB_2 (23
In vivo, local instillation of antigen in the airways
allergic asthmatics results in the immediate release
 PGD_2 in bronchoalveolar lavage fluid (420). PGE_2
re In vivo, local instillation of antigen in the airways of allergic asthmatics results in the immediate release of PGD_2 in bronchoalveolar lavage fluid (420). PGE_2 is released from canine airway epithelial cells when st allergic asthmatics results in the immediate release of PGD_2 in bronchoalveolar lavage fluid (420). PGE_2 is released from canine airway epithelial cells when stimulated with bradykinin (353), and human pulmonary vascu PGD_2 in bronchoalveolar lavage fluid (420). PGE_2 is
released from canine airway epithelial cells when stimu-
lated with bradykinin (353), and human pulmonary vas-
cular endothelial cells are an important source of PGI released from canine airway epithelial cells when stimulated with bradykinin (353), and human pulmonary vascular endothelial cells are an important source of PGI_2 (301). Furthermore, circulating cells, such as platelets lated with bradykinin (353), and human pulmonary vas-
cular endothelial cells are an important source of PGI_2
(301). Furthermore, circulating cells, such as platelets
and neutrophils, may also contribute to the produ 427). **B. Receptor**
B. Receptors
B. Receptors
Classification direct release from mast cells, stimulation of H_1 histamine receptors in lung parenchymal cells, and as a non-
specific response to smooth muscle contraction.
Enriched or purified human lung mast cells undergoing
IgE-d

B. Receptors

Classification of the prostanoid receptors has been

based primarily on comparisons of the rank orders of

agonist potency (232, 322). Receptor classes have been and B. Receptors

Classification of the prostanoid receptors has been

based primarily on comparisons of the rank orders of

agonist potency (232, 322). Receptor classes have been

identified according to their prostanoid B. Receptors
Classification of the prostanoid receptors has been
based primarily on comparisons of the rank orders of
agonist potency (232, 322). Receptor classes have been
identified according to their prostanoid effect, Classification of the prostanoid receptors has been
based primarily on comparisons of the rank orders of
agonist potency (232, 322). Receptor classes have been
identified according to their prostanoid effect, such as
contr identified according to their prostanoid effect, such as contractile/stimulant, relaxant/inhibitory, and irritant/
coughing actions (232). On the other hand, Coleman et
al. (140) have proposed that receptors exist for each agonist potency (232, 322). Receptor classes have been
identified according to their prostanoid effect, such as
contractile/stimulant, relaxant/inhibitory, and irritant/
coughing actions (232). On the other hand, Coleman identified according to their prostanoid effect, such as

contractile/stimulant, relaxant/inhibitory, and irritant/

coughing actions (232). On the other hand, Coleman et

al. (140) have proposed that receptors exist for contractile/stimulant, relaxant/inhibitory, and irritant/
coughing actions (232). On the other hand, Coleman et
al. (140) have proposed that receptors exist for each of
the natural prostanoids (i.e., the PGs D_2 , E_2 , coughing actions (232). On the other hand, Coleman et al. (140) have proposed that receptors exist for each of the natural prostanoids (i.e., the PGs D_2 , E_2 , $F_{2\alpha}$, and I_2 and TxA_2). At each receptor type, o al. (140) have proposed that receptors exist for each of the natural prostanoids (i.e., the PGs D_2 , E_2 , $F_{2\alpha}$, and I_2 and TxA_2). At each receptor type, one of these natural prostanoids is most active, with t the natural prostanoids (i.e., the PGs D_2 , E_2 , $F_{2\alpha}$, and I_2 and TxA_2). At each receptor type, one of these natural prostanoids is most active, with the others being substantially weaker. With the use of sel and TxA_2). At each receptor type, one of these
prostanoids is most active, with the others bein
stantially weaker. With the use of selective anta
and agonists of prostanoid contractile effects, G
(231) has proposed 3 su prostanoids is most active, with the others being substantially weaker. With the use of selective antagonists and agonists of prostanoid contractile effects, Gardiner (231) has proposed 3 subtypes of the contractile/stimu stantially weaker. With the use of selective antagonists
and agonists of prostanoid contractile effects, Gardiner
(231) has proposed 3 subtypes of the contractile/stimu-
lant receptor with the following agonists (TxA₂, and agonists of prostanoid contractile effects, Gardiner (231) has proposed 3 subtypes of the contractile/stimu-
lant receptor with the following agonists (TxA_2 , PGF_{2a} , or PGD_2 and PGE_2), and Coleman et la. (140) (231) has proposed 3 subtypes of the contractile/stimu-
lant receptor with the following agonists (TxA_2 , $PGF_{2\alpha}$,
or PGD_2 and PGE_2), and Coleman et la. (140) suggest
that there may be receptor subtypes for the PGE lant receptor with the following agonists $(TxA_2, PGF_{2\alpha},$
or PGD_2 and PGE_2), and Coleman et la. (140) suggest
that there may be receptor subtypes for the PGE_2 and
 TxA_2 receptors. In human lung strips, all prostanoi or PGD_2 and PGE_2), and Coleman et la. (140) suggest
that there may be receptor subtypes for the PGE_2 and
 TxA_2 receptors. In human lung strips, all prostanoid
contractile agonists appear to exert their effects via that there may be receptor subtypes for the PGE_2 and TxA_2 receptors. In human lung strips, all prostanoid contractile agonists appear to exert their effects via the thromboxane receptor; however, contraction of human TxA_2 receptors. In human lung strips, all prostanoid contractile agonists appear to exert their effects via the thromboxane receptor; however, contraction of human bronchioles may be mediated via a novel prostanoid rece contractile agonists appear to exert their effects via the
thromboxane receptor; however, contraction of human
bronchioles may be mediated via a novel prostanoid
receptor which remains to be identified (403). $PGI₂$ thromboxane receptor; however, contraction of human
bronchioles may be mediated via a novel prostanoid
receptor which remains to be identified (403). PGI_2 re-
ceptors have been identified in lung homogenates by
direct r

EXECUTE:
 receptors and the characteristics and distribution of in

other prostanoid receptors have not been determined. cy BARNES, (BARNES, 1999)

proceptors and the characteristics and distribution

other prostanoid receptors have not been determined **Figure 15 and the contract and the contract of the C.**
C. Airway Effects
1. Airway smooth

1. Airway Effects
1. Airway Effects
1. Airway smooth muscle. The prostanoids PGD₂,
The prostanoids PGD₂,
The prostanoids PGD₂,
The prostanoids PGD₂, C. Airway Effects

1. Airway smooth muscle. The prostanoids PGD_2 ,
 $PGF_{2\alpha}$, and TxA_2 contract human airway smooth muscle

in vitro (83, 232, 560); PGE_1 (2, 523) and PGI_2 relax C. Airway Effects

1. Airway smooth muscle. The prostanoids PGD_2 ,
 $PGF_{2\alpha}$, and TxA_2 contract human airway smooth muscle

in vitro (83, 232, 560); PGE_1 (2, 523) and PGI_2 relax

human smooth muscle (292), but thi 1. Airway smooth muscle. The prostanoids PGD_2 ,
PGF_{2a}, and TxA_2 contract human airway smooth muscle
in vitro (83, 232, 560); PGE₁ (2, 523) and PGI₂ relax
human smooth muscle (292), but this effect is small
when c *I. Airway smooth muscle.* The prostanoids PGD_2 , $PGF_{2\alpha}$, and TxA_2 contract human airway smooth muscle in vitro (83, 232, 560); PGE_1 (2, 523) and PGI_2 relax human smooth muscle (292), but this effect is small wh PGF_{2*a*}, and TxA₂ contract human airway smooth muscle
in vitro (83, 232, 560); PGE₁ (2, 523) and PGI₂ relax
human smooth muscle (292), but this effect is small
when compared to that of isoproterenol. PGE₂ can ei in vitro (83, 232, 560); PGE₁ (2, 523) and PGI₂ relax
human smooth muscle (292), but this effect is small
when compared to that of isoproterenol. PGE₂ can either
increase or decrease basal tone of isolated human air human smooth muscle (292) , but this effect is small
when compared to that of isoproterenol. PGE₂ can either
increase or decrease basal tone of isolated human airway
muscle preparations (230) . In contrast to the guin when compared to that of isoproterenol. PGE_2 can either increase or decrease basal tone of isolated human airway muscle preparations (230). In contrast to the guinea pig, endogenous prostanoids neither modulate the basa increase or decrease basal tone of isolated human airwa
muscle preparations (230). In contrast to the guinea pi
endogenous prostanoids neither modulate the basal to
of isolated human airway smooth muscle (98, 169, 270
nor muscle preparations (230). In contrast to the guinea pig,
endogenous prostanoids neither modulate the basal tone
of isolated human airway smooth muscle (98, 169, 270),
mor the contractile responses to acetylcholine or his endogenous prostanoids neither modulate the basal tone
of isolated human airway smooth muscle (98, 169, 270),
nor the contractile responses to acetylcholine or hista-
mine (98, 270). This is also true of airways obtained f of isolated human airway smooth muscle (98, 169, 270), nor the contractile responses to acetylcholine or histamine (98, 270). This is also true of airways obtained from asthmatic patients (119). Adcock and Garland (5) repo nor the contractile responses to acetylcholine or histamine (98, 270). This is also true of airways obtained from asthmatic patients (119). Adcock and Garland (5) reported a potentiation of histamine-induced contraction of mine (98, 270). This is also true of airways obtained from
asthmatic patients (119). Adcock and Garland (5) re-
ported a potentiation of histamine-induced contractions
of small human bronchial muscle preparations by indo-
 asthmatic patients (119). Adcock and Garland
ported a potentiation of histamine-induced cont
of small human bronchial muscle preparations is
methacin, but this must be interpreted with
because no appropriate controls were rted a potentiation of histamine-induced contract small human bronchial muscle preparations by interpreted with cause no appropriate controls were performed.
Inhaled PGF_{2 α} causes a dose-dependent bronchocon-indiction

of small human bronchial muscle preparations by independent, but this must be interpreted with cautio because no appropriate controls were performed.
Inhaled $PGF_{2\alpha}$ causes a dose-dependent bronchocon striction associat methacin, but this must be interpreted with cauti
because no appropriate controls were performed.
Inhaled PGF_{2*a*} causes a dose-dependent bronchoconstriction associated with coughing (430, 451, 538). Ast
matics are more because no appropriate controls were performed.
Inhaled $PGF_{2\alpha}$ causes a dose-dependent bronchocostriction associated with coughing (430, 451, 538). As
matics are more responsive to the bronchoconstrice
effect of $PGF_{2\$ striction associated with coughing (430, 451, 538). A
matics are more responsive to the bronchoconstrict
effect of PGF_{2a} than normal subjects (398, 430). Th
son et al. (572) found a good correlation between
airway respo matics are more responsive to the bronchoconstrict
effect of PGF_{2 α} than normal subjects (398, 430). Thor
son et al. (572) found a good correlation between thairway responsiveness to PGF_{2 α} and that to methach
lin effect of PGF_{2*a*} than normal subjects (398, 430). Thom-
son et al. (572) found a good correlation between the
airway responsiveness to PGF_{2*a*} and that to methacho-
line, with PGF_{2*a*} begin 100-fold more potent tha son et al. (572) found a good correlation between th
airway responsiveness to PGF_{2a} and that to methacho
line, with PGF_{2a} begin 100-fold more potent than meth
acholine; aspirin-sensitive asthmatics were less sensiti airway responsiveness to PGF_{2a} and that to methacho-
line, with PGF_{2a} begin 100-fold more potent than meth-
acholine; aspirin-sensitive asthmatics were less sensitive
to PGF_{2a} . Tachyphylaxis to the bronchoconstri line, with PGF_{2*a*} begin 100-fold more potent than meth-
acholine; aspirin-sensitive asthmatics were less sensitive
to PGF_{2*a*}. Tachyphylaxis to the bronchoconstrictor ef-
has been reported in animal tissues. Using th to PGF_{2a}. Tachyphylaxis to the bronchoconstrictor effects of PGF_{2a} has been reported in asthmatics (204, 398) but not in normal subjects. Sequential administration of high doses of PGF_{2a} may paradoxically result in fects of $\text{PGF}_{2\alpha}$ has been reported in asthmatics (204, 398)
but not in normal subjects. Sequential administration of
high doses of $\text{PGF}_{2\alpha}$ may paradoxically result in bron-
chodilation, predominantly in the larg cts of PGF_{2*x*} has been reported in asthmatics (204, 398) sh
t not in normal subjects. Sequential administration of see
the doses of PGF_{2*x*} may paradoxically result in bron-
odilation, predominantly in the large airw

but not in normal subjects. Sequential administration of seeight doses of $PGF_{2\alpha}$ may paradoxically result in broncholilation, predominantly in the large airways (204). Con a molar basis, PGD_2 is approximately 3-fold high doses of PGF_{2a} may paradoxically result in broncholilation, predominantly in the large airways (204). On a molar basis, PGD_2 is approximately 3-fold m potent than PGF_{2a} and 30 times more than histami chodilation, predominantly in the large airways (204).
On a molar basis, PGD_2 is approximately 3-fold mo
potent than $PGF_{2\alpha}$ and 30 times more than histamine
a bronchoconstrictor agent, and the duration of bronch
cons On a molar basis, PGD_2 is approximately 3-fold more
potent than $PGF_{2\alpha}$ and 30 times more than histamine as
a bronchoconstrictor agent, and the duration of broncho-
constriction is more prolonged (266). Its effect is potent than $PGF_{2\alpha}$ and 30 times more than histamine as
a bronchoconstrictor agent, and the duration of broncho-
constriction is more prolonged (266). Its effect is inhib-
ited by a thromboxane receptor antagonist, sugg a bronchoconstrictor agent, and the duration of broncho-
constriction is more prolonged (266). Its effect is inhib-
ited by a thromboxane receptor antagonist, suggesting P
that PGD₂ may act via the thromboxane recepto constriction is more prolonged (266). Its effect is inhibited by a thromboxane receptor antagonist, suggesting that PGD₂ may act via the thromboxane receptor (68). There are no data in humans on the airway effects of T ited by a thromboxane receptor antagonist, suggestin
that PGD_2 may act via the thromboxane receptor (68
There are no data in humans on the airway effects TxA_2 or of its stable metabolite TxB_2 , although in dog
 TxB_2 that PGD₂ may act via the thromboxane receptor (68). There are no data in humans on the airway effects of eden
TxA₂ or of its stable metabolite TxB₂, although in dogs, ygen
TxB₂ is slightly less potent than PGF_{2*}* TxA_2 or of its stable metabolite TxB_2 , although in dogs,
 TxB_2 is slightly less potent than $PGF_{2\alpha}$ in causing bron-
chonconstriction (598). TxA_2 has been implicated in
bronchial hyper-responsiveness in dogs, sin TxA_2 or of its stable metabolite TxB_2 , although in dog TxB_2 is slightly less potent than $PGF_{2\alpha}$ in causing bronchonconstriction (598). TxA_2 has been implicated is bronchial hyper-responsiveness in dogs, since a TxB₂ is slightly less potent than PGF_{2a} in causing bronchines chonconstriction (598). TxA₂ has been implicated in due
bronchial hyper-responsiveness in dogs, since a throm-
boxane synthetase inhibitor prevents the chonconstriction (598). T
bronchial hyper-responsive
boxane synthetase inhibito
chial reactivity due to PA
ozone (11) in this species.
Both PGE₁ and PGE₂ onchial hyper-responsiveness in dogs, since a throm-

xane synthetase inhibitor prevents the increased bron-

ial reactivity due to PAF (131), allergen (130), and

one (11) in this species.

Both PGE₁ and PGE₂ are bro

boxane synthetase inhibitor prevents the increased bronchial reactivity due to PAF (131), allergen (130), and ozone (11) in this species.
Both PGE₁ and PGE₂ are bronchodilators in both normal and asthmatic subjects an chial reactivity due to PAF (131), allergen (130), α ozone (11) in this species.
Both PGE₁ and PGE₂ are bronchodilators in b
normal and asthmatic subjects and can reverse the br
choconstrictor effect of PGF_{2*a*} (ozone (11) in this species.

Both PGE₁ and PGE₂ are bronchodilators in both

normal and asthmatic subjects and can reverse the bronchoconstrictor effect of PGF_{2*a*} (161, 317, 537). Bronchoconstrictor responses to bo Both PGE₁ and PGE₂ are bronchodilators in both ry-
normal and asthmatic subjects and can reverse the bron-
choconstrictor effect of PGF_{2*a*} (161, 317, 537). Broncho-
constrictor responses to both PGE₁ and PGE₂ h normal and asthmatic subjects and can reverse the bron-
choconstrictor effect of $PGF_{2\alpha}$ (161, 317, 537). Broncho-
constrictor responses to both PGE_1 and PGE_2 have also
been reported (277, 398, 536), possibly by sti choconstrictor effect of $PGF_{2\alpha}$ (161, 317, 537). Bronchoconstrictor responses to both PGE_1 and PGE_2 have also been reported (277, 398, 536), possibly by stimulation of airway afferent vagal C-fibers (491). Even bip constrictor responses to both PGE₁ and PGE₂ have also
been reported (277, 398, 536), possibly by stimulation of
airway afferent vagal C-fibers (491). Even biphasic re-
sponse to PGE₂ has been reported (591). Intraven

G, AND PAGE
inhibit platelet aggregation (77, 562) and increase plasma
cyclic AMP (265). However, PGI₂ can prevent the bron-G, AND PAGE
inhibit platelet aggregation (77, 562) and increase plasm
cyclic AMP (265). However, PGI₂ can prevent the bron
choconstrictor effect of ultrasonic mist and exercise (77 G, AND PAGE
inhibit platelet aggregation (77, 562) and increase plasma
cyclic AMP (265). However, PGI₂ can prevent the bron-
choconstrictor effect of ultrasonic mist and exercise (77),
and PGD₂ (264), in asthmatic subj inhibit platelet aggregation $(77, 562)$ and cyclic AMP (265) . However, PGI₂ can p
choconstrictor effect of ultrasonic mist and PGD₂ (264) , in asthmatic subjects.
The bronchoconstrictor effect of hist hibit platelet aggregation (77, 562) and increase plasma
clic AMP (265). However, PGI_2 can prevent the bron-
oconstrictor effect of ultrasonic mist and exercise (77),
d PGD₂ (264), in asthmatic subjects.
The bronchoco

cyclic AMP (265). However, PGI_2 can prevent the bron-
choconstrictor effect of ultrasonic mist and exercise (77),
and PGD_2 (264), in asthmatic subjects.
The bronchoconstrictor effect of histamine, when ad-
ministered choconstrictor effect of ultrasonic mist and exercise (77),
and PGD_2 (264), in asthmatic subjects.
The bronchoconstrictor effect of histamine, when ad-
ministered immediately after $PGF_{2\alpha}$, is transiently po-
tentiate and PGD₂ (264), in asthmatic subjects.
The bronchoconstrictor effect of histamine, when ad-
ministered immediately after PGF_{2 α}, is transiently po-
tentiated in normal subjects (272, 593); similarly, both
histamine The bronchoconstrictor effect of histamine, when administered immediately after $PGF_{2\alpha}$, is transiently potentiated in normal subjects (272, 593); similarly, both histamine and methacholine responsiveness are enhanced b ministered immediately after PGF_{2 α}, is transiently potentiated in normal subjects (272, 593); similarly, both histamine and methacholine responsiveness are enhanced by PGD₂ in asthmatic subjects (224). However, PGF tentiated in normal subjects (272, 593); similarly, both
histamine and methacholine responsiveness are en-
hanced by PGD_2 in asthmatic subjects (224). However,
 $PGF_{2\alpha}$ reduces the subsequent response to histamine
afte histamine and methacholine responsiveness are hanced by PGD_2 in asthmatic subjects (224). However $PGF_{2\alpha}$ reduces the subsequent response to hist after the base-line tone has returned to normal 2 later (203). Potentia hanced by PGD_2 in asthmatic subjects (224). However, $PGF_{2\alpha}$ reduces the subsequent response to histamine after the base-line tone has returned to normal 20 min later (203). Potentiation of cholinergic neurotransmissi PGF_{2*a*} reduces the subsequent response to histamine after the base-line tone has returned to normal 20 min later (203). Potentiation of cholinergic neurotransmission by a TxA₂ mimetic (U46619) has been demonstrated in after the base-line tone has returned to normal 20 min
later (203). Potentiation of cholinergic neurotransmis-
sion by a TxA_2 mimetic (U46619) has been demonstrated
in canine airways (135), but it is not known whether t later (203). Potentiation of cholinergic neurotransmis-
sion by a $T x A_2$ mimetic (U46619) has been demonstrated
in canine airways (135), but it is not known whether this
facilitating effect is seen in human airways. A si sion by a TxA₂ mimetic (U46619) has been demonstrated
in canine airways (135), but it is not known whether this
facilitating effect is seen in human airways. A similar
effect has been demonstrated with $PGF_{2\alpha}$ (350, 5 in canine airways (135), but it is not known whether this facilitating effect is seen in human airways. A similar effect has been demonstrated with $PGF_{2\alpha}$ (350, 528). By contrast, PGE_2 depresses cholinergic neurotran facilitating effect has been
contrast, PGE
(592) and, the
nine airways.
2. Secretion (592) and, therefore, cholinergic reflex responses in ca-

Inhaled PGF_{2*a*} causes a dose-dependent bronchocon-lease (394, 485), while PGE₂ inhibits its release in one
striction associated with coughing (430, 451, 538). Asth-
study (394) but not in another (485). In normal sub *2. Secretion.* In the mass of the secretion in the mass of the secretion. In the secretion, the secretion. In human airways. A similar effect has been demonstrated with PGF_2 . (350, 528). By contrast, PGE_2 depresses c (592) and, therefore, cholinergic reflex responses in ca-
nine airways.
2. Secretion. In human airway tissue explants, PGD₂
and $F_{2\alpha}$ significantly increase mucous glycoprotein re-
lease (394, 485), while PGE₂ inhi nine airways.

2. Secretion. In human airway tissue explants, PGD_2

and $F_{2\alpha}$ significantly increase mucous glycoprotein re-

lease (394, 485), while PGE_2 inhibits its release in one

study (394) but not in another 2. Secretion. In human airway tissue explants, PGD₂, and $F_{2\alpha}$ significantly increase mucous glycoprotein re-
lease (394, 485), while PGE₂ inhibits its release in one
study (394) but not in another (485). In normal study (394) but not in another (485). In normal subjects, lease (394, 485), while PGE₂ inhibits its release in one study (394) but not in another (485). In normal subjects,
inhalation of PGF_{2 α} causes increased airway secretions,
with the production of mucous glycoproteins study (394) but not in another (485). In normal subjects,
inhalation of PGF_{2*a*} causes increased airway secretions,
with the production of mucous glycoproteins (370). The
increase in mucous glycoprotein output induced b inhalation of PGF_{2*x*} causes increase in mucous glycoprotein
increase in mucous glycoprotein
and $F_{2\alpha}$ in feline airways was
rather than goblet cells (489).
The effect of cyclooxygenase j th the production of mucous glycoproteins (370). The crease in mucous glycoprotein output induced by PGE_1 d $F_{2\alpha}$ in feline airways was from submucosal glands ther than goblet cells (489). The effect of cyclooxygenas

increase in mucous glycoprotein output induced by PGE₁
and $F_{2\alpha}$ in feline airways was from submucosal glands
rather than goblet cells (489).
The effect of cyclooxygenase products on ion transport
has been reported i and $F_{2\alpha}$ in feline airways was from submucosal glands
rather than goblet cells (489).
The effect of cyclooxygenase products on ion transport
has been reported in animal tissues. Using the Ussing
short-circuit techniqu rather than goblet cells (489).

The effect of cyclooxygenase products on ion transport

has been reported in animal tissues. Using the Ussing

short-circuit technique, $\text{PGF}_{2\alpha}$ increased net chloride

secretion, but has been reported in animal tissues. Using the Ussing
short-circuit technique, PGF₂_{*a*} increased net chloride
secretion, but PGE₁ decreased both chloride and sodium
secretion in canine trachea (13). Bradykinin stimul short-circuit technique, $\text{PGF}_{2\alpha}$ increased net chloride secretion, but PGE_1 decreased both chloride and sodium secretion in canine trachea (13). Bradykinin stimulates chloride secretion in the same tissue via th secretion, but PGE_1 decreased both chloride and sodium
secretion in canine trachea (13). Bradykinin stimulates
chloride secretion in the same tissue via the release of
 PGE_2 from airway epithelial cells (353). In bovin secretion in canine trachea (13). Bradyk
chloride secretion in the same tissue via
 PGE_2 from airway epithelial cells (353).
chea, indomethacin reversed net basal
flow of sodium and chloride ions (338).
3. Inflammatory e *3. Inflammatory effects.* The effects of *353*. In bovine tra-
3. In domethacin reversed net basal transepithelial
3. Inflammatory effects. The effect of cyclooxygenase
oducts on airway vascular permeability is poorly

PGE₂ from airway epithelial cells (353). In bovine trachea, indomethacin reversed net basal transepithelial flow of sodium and chloride ions (338).
3. *Inflammatory effects*. The effect of cyclooxygenase products on air chea, indomethacin reversed net basal transepithelial
flow of sodium and chloride ions (338).
3. *Inflammatory effects*. The effect of cyclooxygenase
products on airway vascular permeability is poorly doc-
umented. In the flow of sodium and chloride ions (338).
3. *Inflammatory effects*. The effect of cyclooxygens
products on airway vascular permeability is poorly do
umented. In the skin, PGE₁ and E₂ are poor inducers
edema but are pot 3. Inflammatory effects. The effect of cyclooxygena
products on airway vascular permeability is poorly do
umented. In the skin, PGE₁ and E₂ are poor inducers
edema but are potent vasodilators. However, the cycloo
ygen products on airway vascular permeability is poorly
umented. In the skin, PGE₁ and E₂ are poor induc
edema but are potent vasodilators. However, the cyc
ygenase products, PGE₁, E₂, F_{2*a*}, D₂, and I₂, can in
ed umented. In the skin, PGE_1 and E_2 are poor inducers of edema but are potent vasodilators. However, the cycloox-
ygenase products, PGE_1 , E_2 , $F_{2\alpha}$, D_2 , and I_2 , can mark-
edly potentiate histamine-, PAF edema but are potent vasodilators. However, the cycloox-
ygenase products, PGE_1 , E_2 , $F_{2\alpha}$, D_2 , and I_2 , can mark-
edly potentiate histamine-, PAF -, and bradykinin-in-
duced skin edema in several species inc ygenase products, PGE_1 , E_2 , $F_{2\alpha}$, D_2 , and I_2 , can markedly potentiate histamine-, PAF -, and bradykinin-in-
duced skin edema in several species including man (21,
63, 209, 610, 611). PGD_2 induces a wheal edly potentiate histamine-, PAF-, and bradykinin-in-
duced skin edema in several species including man $(21, 63, 209, 610, 611)$. PGD₂ induces a wheal and flare
response when injected into human skin, and histological
e duced skin edema in several species including man (21, 63, 209, 610, 611). $PGD₂$ induces a wheal and flare response when injected into human skin, and histological examination reveals a perivascular neutrophil infil 63, 209, 610, 611). PGD₂ induces a wheal and flare
response when injected into human skin, and histological
examination reveals a perivascular neutrophil infiltrate
as early as 30 min (545); this local cutaneous infiltr response when injected into human skin, and histological
examination reveals a perivascular neutrophil infiltrate
as early as 30 min (545); this local cutaneous infiltrate is
potentiated by leukotriene B_4 (LTB₄) (545 examination reveals a perivascular neutrophil infiltrate
as early as 30 min (545); this local cutaneous infiltrate is
potentiated by leukotriene B_4 (LTB₄) (545). Some in
vitro chemokinetic activity of PDC_2 (241) an as early as 30 min (545); this local cutaneous infiltrate is
potentiated by leukotriene B_4 (LTB₄) (545). Some in
vitro chemokinetic activity of PDG_2 (241) and of TxA_2
(547) for neutrophils has been reported. By c potentiated by leukotriene B_4 (LTB₄) (545). Some in
vitro chemokinetic activity of PDG_2 (241) and of TxA_2
(547) for neutrophils has been reported. By contrast,
 PGD_2 and PGI_2 are both inhibitors of platelet fu vitro chemokinetic activi
(547) for neutrophils ha
PGD₂ and PGI₂ are both
(391, 539). PGD₂ enhance
human basophils (465).
D. Role in Asthma (047) for neutropins
PGD₂ and PGI₂ are bo
(391, 539). PGD₂ enhar
human basophils (465)
D. Role in Asthma
Increased plasma co 191, 539). PGD₂ enhances the release of histamine from
man basophils (465).
Role in Asthma
Increased plasma concentrations of a circulating me-
bolite of PGF_{2*a*} and TxB₂ have been observed imme-

the main basephils (465).

D. Role in Asthma

Increased plasma concentrations of a circulating me-

tabolite of $PGF_{2\alpha}$ and TxB_2 have been observed imme-

PHARMACOLOGICAL REVIEW!

INFLAMMATORY MEDIATORS AND ASTHMA ⁵⁷

INFLAMMATORY MEDIATOI
diately after antigen-induced bronchoconstriction in The
asthmatic subjects (252, 527). In addition, increased lev-INFLAMMATORY MEI
diately after antigen-induced bronchoconstriction in
asthmatic subjects (252, 527). In addition, increased lev-
els of PGD₂ in bronchoalveolar lavage fluid have been INFLAMMATORY MEDIATO
diately after antigen-induced bronchoconstriction in The
asthmatic subjects (252, 527). In addition, increased lev-
les of PGD₂ in bronchoalveolar lavage fluid have been but
detected during the acute diately after antigen-induced bronchoconstriction in T
asthmatic subjects (252, 527). In addition, increased lev-
tels of PGD₂ in bronchoalveolar lavage fluid have been b
detected during the acute response (420). Raised diately after antigen-induced bronchoconstriction in The
asthmatic subjects (252, 527). In addition, increased lev-
tand
els of PGD₂ in bronchoalveolar lavage fluid have been butic
detected during the acute response (42 els of PGD_2 in bronchoalveolar lavage fluid have been
detected during the acute response (420). Raised plasma
levels of $PGF_{2\alpha}$ and PGE_1 have also been reported in
asthma (428, 442).
Cyclooxygenase inhibition with a Gyptheodor is dependent of PGD₂ in bronchoalveolar lavage fluid have been tected during the acute response (420). Raised plasmarels of PGF_{2*a*} and PGE₁ have also been reported in thma (428, 442). Cyclooxygenase inhi

detected during the acute response (420). Raised plasma
levels of PGF₂^a and PGE₁ have also been reported in
asthma (428, 442).
Cyclooxygenase inhibition with aspirin or nonsteroidal ucts
antiinflammatory agents, suc levels of PGF_{2*a*} and PGE₁ have also been reported in
asthma (428, 442).
Cyclooxygenase inhibition with aspirin or nonsteroidal
antiinflammatory agents, such as indomethacin, has no
effect on resting pulmonary functio normal subjects (223, 442).

Cyclooxygenase inhibition with aspirin or nonsteroidal

antiinflammatory agents, such as indomethacin, has no

effect on resting pulmonary function of asthmatic and

normal subjects (202, 440). Cyclooxygenase inhibition with aspirin or nonsteroidal
antiinflammatory agents, such as indomethacin, has no
effect on resting pulmonary function of asthmatic and
normal subjects (202, 440). However, there is a distinct
su antiinflammatory agents, such as indomethacin, has infect on resting pulmonary function of asthmatic an
normal subjects (202, 440). However, there is a distingubgroup comprising approximately 5% of asthmatic
"aspirin-sensi effect on resting pulmonary function of asthmatic and
normal subjects (202, 440). However, there is a distince
subgroup comprising approximately 5% of asthmatics
("aspirin-sensitive asthmatics") who experience symp
tomatic normal subjects (202, 440). However, there is a distint
subgroup comprising approximately 5% of asthmatitive asthmatics") who experience sym
tomatic worsening after ingesting aspirin or nonsteroid
antiinflammatory agents. subgroup comprising approximately 5% of asthmat
("aspirin-sensitive asthmatics") who experience syntomatic worsening after ingesting aspirin or nonsteroi
antiinflammatory agents. The bronchoconstrictor me
anism is unclear, ("aspirin-sensitive asthmatics") who experience symptomatic worsening after ingesting aspirin or nonsteroidal
antiinflammatory agents. The bronchoconstrictor mechanism is unclear, but appears to be related to cyclooxy-
ge tomatic worsening after ingesting aspirin or nonsteroida
antiinflammatory agents. The bronchoconstrictor mech
anism is unclear, but appears to be related to cyclooxy
genase inhibition (561), and there is also evidence for
 antiinflammatory agents. The bronchoconstrictor me
anism is unclear, but appears to be related to cycloo
genase inhibition (561), and there is also evidence
platelet activation with aspirin (15). A minority of ne
aspirin-s anism is unclear, but appears to be related to cycloor
genase inhibition (561), and there is also evidence
platelet activation with aspirin (15). A minority of no
aspirin-sensitive asthmatics are improved by cycloor
genase genase inhibition (561), and there is also evidence fo
platelet activation with aspirin (15). A minority of non
aspirin-sensitive asthmatics are improved by cyclooxy
genase inhibitors (326, 484, 563). Inhibition of throm
b platelet activation with aspirin (15). A minority of non-
aspirin-sensitive asthmatics are improved by cyclooxy-
genase inhibitors (326, 484, 563). Inhibition of throm-
boxane synthetase by OKY-046 (see table 1), an imidaspirin-sensitive asthmatics are improved by cyclooxy-
genase inhibitors (326, 484, 563). Inhibition of throm-
boxane synthetase by OKY-046 (see table 1), an imid-
azole derivative (297), has been reported to improve
bronc genase inhibitors (326, 484, 563). Inhibition of throm-
boxane synthetase by OKY-046 (see table 1), an imid-
azole derivative (297), has been reported to improve
bronchial hyper-responsiveness in asthmatics (220), but
this boxane synthetase by OKY-046 (see table 1), an imid-
azole derivative (297), has been reported to improve (H
bronchial hyper-responsiveness in asthmatics (220), but
this study needs to repeated with thromboxane receptor (azole derivative (297) , has been reported to improve
bronchial hyper-responsiveness in asthmatics (220) , but
this study needs to repeated with thromboxane receptor
blockers $(267, 441)$, because of the possible shunti pronchial hyper-responthis study needs to rep
blockers (267, 441), be
 PGH_2 metabolism tow
clooxygenase products.
Cyclooxygenase inhi is study needs to repeated with thromboxane receptor
ockers (267, 441), because of the possible shunting of
 δH_2 metabolism towards the synthesis of other cy-
oxygenase products.
Cyclooxygenase inhibition with indometh

Cyclooxygenase inhibition with indomethacin or as-
pirin does not influence the early acute response induced
by inhaled antigen in asthmatic subjects (196, 202, 527),
despite suppressing the early rise in plasma TxB_2 (5 clooxygenase products.
Cyclooxygenase inhibition with indomethacin or as-
pirin does not influence the early acute response induced
by inhaled antigen in asthmatic subjects (196, 202, 527),
despite suppressing the early r Cyclooxygenase inhibition with indomethacin or as-
pirin does not influence the early acute response induced
by inhaled antigen in asthmatic subjects (196, 202, 527), file
spite suppressing the early rise in plasma TxB_2 pirin does not influence the early acute response induced
by inhaled antigen in asthmatic subjects (196, 202, 527),
despite suppressing the early rise in plasma $T \mathbf{x} B_2$ (527).
However, the late-phase response to antig by inhaled antigen in asthmatic subjects (196, 202, 527), from
despite suppressing the early rise in plasma TxB_2 (527). 5-1
However, the late-phase response to antigen is inhibited cat
by indomethacin, aspirin, or benox despite suppressing the early rise in plasma TxB_2 (527).
However, the late-phase response to antigen is inhibited
by indomethacin, aspirin, or benoxaprofen (196, 527),
and there is evidence that suppression of TxA_2 an However, the late-phase response to antigen is inhibited
by indomethacin, aspirin, or benoxaprofen (196, 527),
and there is evidence that suppression of ${\rm TxA}_2$ and the
production of ${\rm PGI}_2$ may contribute to this effec by indomethacin, aspirin, or benoxaprofen (196, 527)
and there is evidence that suppression of TxA_2 and the
production of PGI_2 may contribute to this effect (527)
These results, however, are not confirmed by a recen
s and there is evidence that suppression of TxA_2 and the production of PGI_2 may contribute to this effect (527).
These results, however, are not confirmed by a recent study, where an inhibitory effect on indomethacin an production of $PGI₂$ may contribute to this effect (52
These results, however, are not confirmed by a rece
study, where an inhibitory effect on indomethacin ar
gen-induced airway hyper-responsiveness in asthmat
has b These results, however, are not confirmed by a recent
study, where an inhibitory effect on indomethacin anti-
gen-induced airway hyper-responsiveness in asthmatics
has been observed (324). These various clinical observa-
t study, where an inhibitory effect on indomethacin anti-
gen-induced airway hyper-responsiveness in asthmatics
has been observed (324). These various clinical observa-
tions made with NSAIDs (see table 1) in antigen-induced gen-induced airway hyper-responsiveness in asthma
has been observed (324). These various clinical obser
tions made with NSAIDs (see table 1) in antigen-indu
asthmatics bring into question the precise relations
between late sponsiveness. tions made with NSAIDs (see table 1) in antigen-induced
asthmatics bring into question the precise relationship
between late-onset responses and bronchial hyper-re-
sponsiveness.
In vitro studies of passively sensitized hu

asthmatics bring into question the precise relationship
between late-onset responses and bronchial hyper-re-
sponsiveness.
In vitro studies of passively sensitized human bron-
chial strips have demonstrated an enhanced con between late-onset responses and bronchial hyper-responsiveness.

In vitro studies of passively sensitized human bronchial strips have demonstrated an enhanced contractile

effect of antigen by indomethacin, due to an augm sponsiveness.
In vitro studies of passively sensitized human bron-
chial strips have demonstrated an enhanced contractile
effect of antigen by indomethacin, due to an augmented
release of histamine, and perhaps of other me In vitro studies of passively sensitized human bronchial strips have demonstrated an enhanced contractile
effect of antigen by indomethacin, due to an augmented
release of histamine, and perhaps of other mediators
such as chial strips have demonstrated an enhanced contractile
effect of antigen by indomethacin, due to an augmented
release of histamine, and perhaps of other mediators
such as leukotrienes (4). Although indomethacin does
not in effect of antigen by indomethacin, due to an augment
release of histamine, and perhaps of other mediate
such as leukotrienes (4). Although indomethacin do
not influence exercise-induced bronchoconstrictic
(502), it prevent release of histamine, and perhaps of other m
such as leukotrienes (4). Although indometha
not influence exercise-induced bronchocon
(502), it prevents the tachyphylactic bronchoco
response to successive bouts of exercise (not influence exercise-induced bronchoconstriction (502), it prevents the tachyphylactic bronchoconstrictor response to successive bouts of exercise (434).
Overall, there is reasonable evidence to suggest that cyclooxygena

not influence exercise-induced bronchoconstriction (502), it prevents the tachyphylactic bronchoconstrictor response to successive bouts of exercise (434).

Overall, there is reasonable evidence to suggest that cyclooxygen (502), it prevents the tachyphylactic bronchoconstrictor variable response to successive bouts of exercise (434). gerally developed approaches overall, there is reasonable evidence to suggest that the cyclooxygenase produ response to successive bouts of exercise (434).
Overall, there is reasonable evidence to suggest that
cyclooxygenase products play a modulatory role in sev-
eral aspects of airway function. Whether this role is
beneficial Overall, there is reasonable evidence to suggest the cyclooxygenase products play a modulatory role in several aspects of airway function. Whether this role is
beneficial or detrimental to the asthmatic airway depends on t cyclooxygenase products play a modulatory role in several aspects of airway function. Whether this role is
beneficial or detrimental to the asthmatic airway depends on the predominance of the cyclooxygenase product
because

ATORS AND ASTHMA
The availability of more specific antagonists of the pros-
- tanoids may help dissect their precise individual contri TORS AND ASTHMA
The availability of more specific antagonists of the pr
tanoids may help dissect their precise individual contr
bution to asthma. INFLAMMATORY MEDIATORS AND ASTHMA
nchoconstriction in The availability of more specific antagonists of the pros-
dition, increased lev-
ranoids may help dissect their precise individual contri-
rage fluid have been bution

IV. Lipoxygenase Products
Lipoxygenation of arachidonic acid gives rise to prod-Lipoxygenation of arachidonic acid gives rise to prod-
Lipoxygenation of arachidonic acid gives rise to prod-
ucts with potent inflammatory effects which may be
relevant to the pathophysiology of asthma. In particular, IV. Lipoxygenase Products
Lipoxygenation of arachidonic acid gives rise to products
with potent inflammatory effects which may be
relevant to the pathophysiology of asthma. In particular
the leukotrienes, although identifi IV. Lipoxygenase Products
Lipoxygenaion of arachidonic acid gives rise to prod-
ucts with potent inflammatory effects which may be
relevant to the pathophysiology of asthma. In particular,
the leukotrienes, although identi Lipoxygenation of arachidonic acid gives rise to products with potent inflammatory effects which may be relevant to the pathophysiology of asthma. In particular, the leukotrienes, although identified in the late 1970s, wer ucts with potent inflammatory effects which may be
relevant to the pathophysiology of asthma. In particular,
the leukotrienes, although identified in the late 1970s,
were recognized as being biologically important in the
1 relevant to the pathophysiology of asthma. In particular, the leukotrienes, although identified in the late 1970s, were recognized as being biologically important in the 1930s when they were isolated in lung perfusates and the leukotrienes, although identified in the late 1970s,
were recognized as being biologically important in the
1930s when they were isolated in lung perfusates and
named slow-reacting substance of anaphylaxis (SRS-A).
The were recognized as being biologically important in the 1930s when they were isolated in lung perfusates and named slow-reacting substance of anaphylaxis (SRS-A). The role of lipoxygenase products in human asthma is still u 1930s when they were isolated in lung perfusates and
named slow-reacting substance of anaphylaxis (SRS-A).
The role of lipoxygenase products in human asthma is
still undergoing evaluation, and the current availability
of s named slow-reacting substance of anaphylaxis (SI
The role of lipoxygenase products in human ast
still undergoing evaluation, and the current avail
of several leukotriene antagonists for human us
sparked further interest in A. Synthesis and Metabolism
A. Synthesis and Metabolism
A. Synthesis and Metabolism
A. Synthesis and Metabolism
Arachidonic acid may be oxygena

PGH₂ metabolism towards the synthesis of other cy-
clooxygenase products.
are the most common derivatives of arachidonic acid to
Cyclooxygenase inhibition with indomethacin or as-
pirin does not influence the early acut several leukotriene antagonists for human use has
arked further interest in lipoxygenase products.
Synthesis and Metabolism
Arachidonic acid may be oxygenated at different sites
specific lipoxygenases, initiating the forma sparked further interest in lipoxygenase products.

A. Synthesis and Metabolism

Arachidonic acid may be oxygenated at different sites

by specific lipoxygenases, initiating the formation of

leukotrienes (LTs), lipoxins, A. Synthesis and Metabolism
Arachidonic acid may be oxygenated at different sites
by specific lipoxygenases, initiating the formation of
leukotrienes (LTs), lipoxins, and several hydroxyacids
(HETEs) (fig. 4). The initial A. Synthesis and Metabolism

Arachidonic acid may be oxygenated at different sites

by specific lipoxygenases, initiating the formation of

leukotrienes (LTs), lipoxins, and several hydroxyacids

(HETEs) (fig. 4). The ini by specific lipoxygenases, initiating the formation of leukotrienes (LTs), lipoxins, and several hydroxyacids (HETEs) (fig. 4). The initial compounds generated from arachidonic acid are hydroperoxyeicosatetraenoic acids (H by specific lipoxygenases, initiating the formation of leukotrienes (LTs), lipoxins, and several hydroxyacids (HETEs) (fig. 4). The initial compounds generated from arachidonic acid are hydroperoxyeicosatetraenoic acids (H leukotrienes (LTs), lipoxins, and several hydroxyacids
(HETEs) (fig. 4). The initial compounds generated from
arachidonic acid are hydroperoxyeicosatetraenoic acids
(HPETEs), which may either be reduced by peroxidases
to c (HETEs) (fig. 4). The initial compounds generated from
arachidonic acid are hydroperoxyeicosatetraenoic acids
(HPETEs), which may either be reduced by peroxidases
to corresponding monohydroxy acids (mono-HETEs), or
be meta arachidonic acid are hydroperoxyeicosatetraenoic acids

(HPETEs), which may either be reduced by peroxidases

to corresponding monohydroxy acids (mono-HETEs), or

be metabolized via other pathways. The mono-HETEs

are the (HPETEs), which may either be reduced by peroxidases
to corresponding monohydroxy acids (mono-HETEs), or
be metabolized via other pathways. The mono-HETEs
are the most common derivatives of arachidonic acid to
be detected to corresponding monohydroxy acids (mono-HETEs), or
be metabolized via other pathways. The mono-HETEs
are the most common derivatives of arachidonic acid to
be detected in the lungs, with 15-HETE being the most
predominant be metabolized via other pathways. The mono-HETEs
are the most common derivatives of arachidonic acid to
be detected in the lungs, with 15-HETE being the most
predominant (163, 259). Both the formation of 5-HPETE
from arac are the most common derivatives of arachidonic acid to
be detected in the lungs, with 15-HETE being the most
predominant (163, 259). Both the formation of 5-HPETE
from arachidonic acid and the subsequent conversion of
5-HP predominant (163, 259). Both the formation of 5-HPETE
from arachidonic acid and the subsequent conversion of
5-HPETE to LTA₄ (see table 1 for abbreviations) are
catalyzed by 5-lipoxygenase, which is selectively acti-
va predominant (163, 259). Both the formation of 5-HPETE
from arachidonic acid and the subsequent conversion of
5-HPETE to LTA₄ (see table 1 for abbreviations) are
catalyzed by 5-lipoxygenase, which is selectively acti-
vat from arachidonic acid and the subsequent conversion of 5-HPETE to LTA₄ (see table 1 for abbreviations) are catalyzed by 5-lipoxygenase, which is selectively actuated by challenge with antigen or the calcium ionophon A23 5-HPETE to LTA₄ (see table 1 for abbreviations) are catalyzed by 5-lipoxygenase, which is selectively activated by challenge with antigen or the calcium ionophore A23187 (501). LTA₄ is unstable and is hydrolyzed enzycatalyzed by 5-lipoxygenase, which is selectively actuated by challenge with antigen or the calcium ionophore A23187 (501). LTA₄ is unstable and is hydrolyzed enzy matically to the dihydroxyacid, LTB₄, or converted no vated by challenge with antigen or the calcium ionopho
A23187 (501). LTA₄ is unstable and is hydrolyzed enz
matically to the dihydroxyacid, LTB₄, or converted n
nenzymatically into isomers of LTB₄. Alternativel
LTA A23187 (501). LTA₄ is unstable and is hydrolyzed enzy
matically to the dihydroxyacid, LTB₄, or converted no
nenzymatically into isomers of LTB₄. Alternatively
LTA₄ may be conjugated with glutathione to the pepti
d matically to the dihydroxyacid, LTB₄, or converted no-
nenzymatically into isomers of LTB₄. Alternatively,
LTA₄ may be conjugated with glutathione to the pepti-
dolipid LTC₄, first identified as a component of slo nenzymatically into isomers of LTB₄. Alternatively,
LTA₄ may be conjugated with glutathione to the pepti-
dolipid LTC₄, first identified as a component of slow-
reacting substance (SRS) in mouse mastocytomas (419).
 LTA₄ may be conjugated with glutathione to the pepti-
dolipid LTC₄, first identified as a component of slow-
reacting substance (SRS) in mouse mastocytomas (419).
LTC₄ may be converted to LTD₄, a cysteinyl glyciny dolipid LTC₄, first identified as a component of slow-
reacting substance (SRS) in mouse mastocytomas (419).
LTC₄ may be converted to LTD₄, a cysteinyl glycinyl
derivative, by the action of γ -glutamyl transpeptid reacting substance (SRS) in mouse mastocytomas (419).
LTC₄ may be converted to LTD₄, a cysteinyl glycinyl
derivative, by the action of γ -glutamyl transpeptidase
(444). LTD₄ is further metabolized to the cysteinyl LTC₄ may be converted to LTD₄, a cysteinyl glycinyl derivative, by the action of γ -glutamyl transpeptidase (444). LTD₄ is further metabolized to the cysteinyl derivative, LTE₄, by the action of a dipeptidase (4 derivative, by the action of γ -glutamyl transpeptidase (444). LTD₄ is further metabolized to the cysteinyl derivative, LTE₄, by the action of a dipeptidase (450).
Conversion of LTE₄ to LTF₄ with the reincorpora (444). LTD₄ is further metabolized to the cysteinyl de-
rivative, LTE₄, by the action of a dipeptidase (450).
Conversion of LTE₄ to LTF₄ with the reincorporation of
glutamic acid by γ -glutamyl transpeptidase ha rivative, LTE₄, by the action Conversion of LTE₄ to LTF₄ with glutamic acid by γ -glutamyl transported (16), but there is no released from the human lung. The generation of leukotrien by proversion of LTE₄ to LTF₄ with the reincorporation of utamic acid by γ -glutamyl transpeptidase has also been ported (16), but there is no evidence that LTF₄ is leased from the human lung.
The generation of le reported (16), but there is no evidence that $LTF₄$ is

glutamic acid by γ -glutamyl transpeptidase has also been reported (16), but there is no evidence that LTF₄ is released from the human lung.
The generation of leukotrienes has been described from a number of tissues o released from the human lung.
The generation of leukotrienes has been described
from a number of tissues or purified cells (182, 358, 468).
Among the human cell types that are of potential rele-
vance to asthma, the profil The generation of leukotrienes has been described
from a number of tissues or purified cells (182, 358, 468).
Among the human cell types that are of potential rele-
vance to asthma, the profile and quantity of leukotrienes from a number of tissues or purified cells $(182, 358, 46)$
Among the human cell types that are of potential revance to asthma, the profile and quantity of leukotries
generated in vitro are dependent upon the cell type a
 Among the human cell types that are of potential relevance to asthma, the profile and quantity of leukotrienes generated in vitro are dependent upon the cell type and the stimulus applied. For example, circulating neutrop vance to asthma, the profile and quantity of leukotrienes
generated in vitro are dependent upon the cell type and
the stimulus applied. For example, circulating neutro-
phils produce approximately 5 to 10 times more LTB₄ generated in vitro are dependent upon the cell type and
the stimulus applied. For example, circulating neutro-
phils produce approximately 5 to 10 times more LTB₄
than LTC₄ when activated with the calcium ionophore
A2 the stimulus applied. For example, circulating neutro-
phils produce approximately 5 to 10 times more LTB₄
than LTC₄ when activated with the calcium ionophore
A23187, but the ratios and quantities are reversed with
no phils produce approximately 5 to 10 times more LTB₄
than LTC₄ when activated with the calcium ionophore
A23187, but the ratios and quantities are reversed with
normal eosinophils (609, 522). Even more LTC₄ is gen-
e

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BRONCHIAL HYPERRESPONSIVENESS

FIG. 4. Possible mechanism of bronchial hyper-responsiveness in-

duced by platelet-activating factor (PAF). PAF may attract and activate

eosinophils, which release basic proteins such as FIG. 4. Possible mechanism of bronchial hyper-responsiveness in-
duced by platelet-activating factor (PAF). PAF may attract and activate
eosinophils, which release basic proteins such as major basic protein
(*MBP*), eosino **neuron interactivating factor (PAF). PAF may attraction of the cosinophils, which release basic proteins such as majo (***MBP***), eosinophil cationic protein (***ECP***), and eoshid meurotoxin (***EDN***) which are toxic to airway e** discount by pattern at the mattern state has the mattern state processor (*MBP*), eosinophil cationic protein (*ECP*), and eosinophil-den
neurotoxin (*EDN*) which are toxic to airway epithelium.
in addition, eosinophils ca

(*MBP*), eosinophil cationic protein (*ECP*), and eosinophil-derive
neurotoxin (*EDN*) which are toxic to airway epithelium.
in addition, eosinophils can also activate the 15-lipoxy
genase pathway (274). On the other hand neurotoxin (*EDN*) which are toxic to airway epithelium.

in addition, eosinophils can also activate the 15-lipoxy-

genase pathway (274). On the other hand, alveolar mac-

rophages generate 20 times more LTB_4 than $LTC_$ in addition, eosinophils can also activate the 15-lip genase pathway (274). On the other hand, alveolar rephages generate 20 times more LTB₄ than LTC₄ (396). Human lung fragments release mostly sulfidoptide leukotrien in addition, eosinophils can also activate the 15-lipoxy
genase pathway (274). On the other hand, alveolar macrophages generate 20 times more LTB_4 than LTC_4 (19
396). Human lung fragments release mostly sulfidoper
tid genase pathway (274). On the other hand, alveolar mac-
rophages generate 20 times more LTB_4 than LTC_4 (199,
396). Human lung fragments release mostly sulfidopep-
tide leukotrienes when activated by IgE-dependent
mecha rophages generate 20 times more LTB_4 than LTC_4 (199,
396). Human lung fragments release mostly sulfidopeptide
leukotrienes when activated by IgE-dependent
mechanisms, but stimulation with the calcium ionophore
also re 396). Human lung fragments release mostly sulfidopeptide leukotrienes when activated by IgE-dependent mechanisms, but stimulation with the calcium ionophore also results in the formation of LTB_4 (354, 467). Highly given tide leukotrienes when activated by IgE-depende
mechanisms, but stimulation with the calcium ionopho
also results in the formation of LTB₄ (354, 467). High
purified human lung mast cells release less than 4 ng
LTB₄ pe mechanisms, but stimulation with the calcium ionophore
also results in the formation of LTB_4 (354, 467). Highly
purified human lung mast cells release less than 4 ng of
 LTB_4 per million mast cells after IgE-mediated a also results in the formation of LTB_4 (354, 467). Hi
purified human lung mast cells release less than 4 n
 LTB_4 per million mast cells after IgE-mediated act
tion compared to 10 ng of LTC_4 (358, 381); only s
quantiti purified human lung mast cells release less than 4 ng of LTB₄ per million mast cells after IgE-mediated activation compared to 10 ng of LTC₄ (358, 381); only small quantities of LTD₄ and LTE₄ are generated. Sulfid LTB₄ per million mast cells after IgE-mediated activation compared to 10 ng of LTC₄ (358, 381); only small quantities of LTD₄ and LTE₄ are generated. Sulfidopeptide leukotrienes are released in vivo into nasal sec tion compared to 10 ng of LTC₄ (358, 381); only small
quantities of LTD₄ and LTE₄ are generated. Sulfidopep-
tide leukotrienes are released in vivo into nasal secretions
of antigen-challenged allergic subjects (151) quantities of LTD_4 and LTE_4 are generated. Sulfidopeptide leukotrienes are released in vivo into nasal secretions and and and and and and and allergic subjects (151). In vitro, the allergen challenge of lung tissue fr tide leukotrienes are released in vivo into nasal secretions and LTD₄, since their molar ratios needed to elicit iden-
of antigen-challenged allergic subjects (151). In vitro, tical biological effects differ markedly in of antigen-challenged allergic subjects (151). In vitro
allergen challenge of lung tissue from asthmatic subject
results in the release of LTC_4 , D_4 , and E_4 (163). Huma
monocytes can also generate substantial amoun allergen challenge of lung tissue from asthmatic subjects (36 results in the release of LTC_4 , D_4 , and E_4 (163). Human pig monocytes can also generate substantial amounts of to l LTB_4 and LTC_4 on stimulation wi

3, AND PAGE
and human airways have been shown to generate LTB₄
and 15-lipoxygenase products (284, 291). 3, AND PAGE
and human airways have been shown to g
and 15-lipoxygenase products (284, 291).
5-Hydroxyeicosatetraenoic acid (5-HET

AND PAGE
d human airways have been shown to generate LTB_4
d 15-lipoxygenase products (284, 291).
5-Hydroxyeicosatetraenoic acid (5-HETE) and other
ono-HETEs are produced by stimulated neutrophils, and human airways have been shown to generate LTB
and 15-lipoxygenase products $(284, 291)$.
5-Hydroxyeicosatetraenoic acid (5-HETE) and othe
mono-HETEs are produced by stimulated neutrophils
together with LTB₄ $(239$ and human airways have been shown to generate LTB_4
and 15-lipoxygenase products (284, 291).
5-Hydroxyeicosatetraenoic acid (5-HETE) and other
mono-HETEs are produced by stimulated neutrophils,
together with LTB_4 (239) and 15-lipoxygenase products (284, 291).
5-Hydroxyeicosatetraenoic acid (5-HETE) and other
mono-HETEs are produced by stimulated neutrophils,
together with LTB_4 (239). A whole series of di-HETEs
and mono-HETEs are forme 5-Hydroxyeicosatetraenoic acid $(5$ -HETE) and other mono-HETEs are produced by stimulated neutrophils, together with LTB₄ (239). A whole series of di-HETEs and mono-HETEs are formed by eosinophils, but when stimulated b together with LTB₄ (239). A whole series of di-HETE and mono-HETEs are formed by eosinophils, but whe stimulated by calcium ionophore A23187, 15-HETE be comes the predominant eicosanoid released by eosinophils (576). 12stimulated by calcium ionophore A23187, 15-HETE becomes the predominant eicosanoid released by eosinophils (576). 12-HETE is the primary lipoxygenase product of platelets (330). The transformation of LTC_4 to LTD_4 and imulated by calcium ionophore A23187, 15-HETE be-
mes the predominant eicosanoid released by eosino-
ils (576). 12-HETE is the primary lipoxygenase prod-
t of platelets (330).
The transformation of LTC_4 to LTD_4 and L

comes the predominant eicosanoid released by eosino-
phils (576). 12-HETE is the primary lipoxygenase prod-
uct of platelets (330).
The transformation of LTC_4 to LTD_4 and LTE_4 rep-
resents a bioconversion rather tha phils (576). 12-HETE is the primary lipoxygenase product of platelets (330).

The transformation of LTC₄ to LTD₄ and LTE₄ represents a bioconversion rather than catabolism of leukotrienes and is an extremely efficie uct of platelets (330).

The transformation of LTC_4 to LTD_4 and LTE_4 represents a bioconversion rather than catabolism of leukotrienes and is an extremely efficient process (260).

Catabolism of LTE_4 may occur at The transformation of LTC_4 to LTD_4 and LTE_4 represents a bioconversion rather than catabolism of leukotrienes and is an extremely efficient process (260).
Catabolism of LTE_4 may occur at extrapulmonary sites, but resents a bioconversion rather than catabolism of leu-
kotrienes and is an extremely efficient process (260).
Catabolism of LTE₄ may occur at extrapulmonary sites,
but LTE₄ can be partly excreted unchanged from the
ki kotrienes and is an extremely efficient process (260).
Catabolism of LTE₄ may occur at extrapulmonary sites,
but LTE₄ can be partly excreted unchanged from the
kidneys (445). Alterations in the peptide portion of LTC Catabolism of LTE₄ may occur at extrapulmonary sites,
but LTE₄ can be partly excreted unchanged from the
kidneys (445). Alterations in the peptide portion of LTC₄
do not usually result in a major loss of its biologi kidneys (445). Alterations in the peptide portion of $LTC₄$ do not usually result in a major loss of its biological activity (164). The sulfidopeptide leukotrienes released from neutrophils activated by phorbol myris do not usually result in a major loss of its biological activity (164). The sulfidopeptide leukotrienes released from neutrophils activated by phorbol myristate acetate are rapidly metabolized extracellularly by the concom activity (164). The sulfidopeptide leukotrienes released activity (164). The sulfidopeptide leukotrienes released
from neutrophils activated by phorbol myristate acetate
are rapidly metabolized extracellularly by the concomi-
tant formation of hypochlorous acid; this effect is p from neutrophils activated by phorbol myristate acetate are rapidly metabolized extracellularly by the concomitant formation of hypochlorous acid; this effect is prevented by the presence of a scavenger of hypochlorous aci are rapidly metabolized extracellularly by the concomitant formation of hypochlorous acid; this effect is prevented by the presence of a scavenger of hypochlorous acid, such as L-serine (341, 342). Eosinophils from hypereo tant formation of hypochlorous acid; this effect is prevented by the presence of a scavenger of hypochlorous acid, such as L-serine $(341, 342)$. Eosinophils from hypereosinophilic patients can spontaneously inactivate LT acid, such as L-serine (341, 342). Eosinophils from hypereosinophilic patients can spontaneously inactivate LTC₄ also through the generation of hypochlorous acid (609). Inactivation of LTB₄ occurs mostly intracellular pereosinophilic patients can spontaneously inactivate pereosinophilic patients can spontaneously inactive LTC₄ also through the generation of hypochlorous a (609) . Inactivation of LTB₄ occurs mostly intracellula in neutrophils by beta-oxidation with the involvement a c LTC₄ also through the generation of hypochlorous acia (609). Inactivation of LTB₄ occurs mostly intracellularly
in neutrophils by beta-oxidation with the involvement of
a cytochrome P-450-like system (521), but the me (609). Inactivation of LTB₄ occurs mostly intracellularly
in neutrophils by beta-oxidation with the involvement of
a cytochrome P-450-like system (521), but the metabo-
lites thus formed are still biologically active (2 in neutrophils by beta-oxidation with the involvement of
a cytochrome P-450-like system (521), but the metabo-
lites thus formed are still biologically active (282). Inac-
tivation by ω -oxidation may occur in vivo (516 a cytochrome P-450-like system (521), but the metabolities thus formed are still biologically active (282). Inactivation by ω -oxidation may occur in vivo (516). There is evidence to suggest that HPETEs and HETEs may in zymes (530, 584a). tivation by ω -oxidation may occur in vivo (516). There
is evidence to suggest that HPETEs and HETEs may
inhibit the 5-lipoxygenase as well as cyclooxygenase en-
zymes (530, 584a).
Lipoxins are a newly described series

is evidence to suggest that HPETEs and HETEs may
inhibit the 5-lipoxygenase as well as cyclooxygenase en-
zymes (530, 584a).
Lipoxins are a newly described series of oxygenated
derivatives of AA formed from interaction of inhibit the 5-lipoxygenase as well as cyclooxygenase en-
zymes (530, 584a).
Lipoxins are a newly described series of oxygenated
derivatives of AA formed from interaction of the 5- and
15-lipoxygenase pathways, which were zymes (530, 584a).

Lipoxins are a newly described series of oxygen

derivatives of AA formed from interaction of the 5-

15-lipoxygenase pathways, which were first isolated in

neutrophils incubated with 15-HETE (517). Eo Lipoxins are a newly described series of oxygenated
derivatives of AA formed from interaction of the 5- and
15-lipoxygenase pathways, which were first isolated from
neutrophils incubated with 15-HETE (517). Eosinophil-
enr derivatives of AA formed from interaction
15-lipoxygenase pathways, which were first
neutrophils incubated with 15-HETE (517)
enriched leukcoytes also generate lipoxin A
stimulated with calcium ionophore (518). enriched leukcoytes also generate lipoxin A (LXA) when stimulated with calcium ionophore (518).
B. Receptors

The structural determinants of LTC_4 and LTD_4 for its contractile effects on guinea pig trachea and parenchy-
mal strips have been studied (164, 106, 184, 361, 328). B. Receptors
The structural determinants of LTC_4 and LTD_4 fo
contractile effects on guinea pig trachea and parenc
mal strips have been studied (164, 106, 184, 361, 3 B. Receptors
The structural determinants of LTC_4 and LTD_4 for its
contractile effects on guinea pig trachea and parenchy-
mal strips have been studied (164, 106, 184, 361, 328).
Studies of isomers of LTC_4 have demon The structural determinants of LTC_4 and LTD_4 for its contractile effects on guinea pig trachea and parenchymal strips have been studied (164, 106, 184, 361, 328).
Studies of isomers of LTC_4 have demonstrated that di The structural determinants of LTC_4 and LTD_4 for its
contractile effects on guinea pig trachea and parenchy-
mal strips have been studied (164, 106, 184, 361, 328).
Studies of isomers of LTC_4 have demonstrated that
 contractile effects on guinea pig trachea and parenchy-
mal strips have been studied (164, 106, 184, 361, 328).
Studies of isomers of LTC_4 have demonstrated that
differences in binding correspond closely with difference mal strips have been studied $(164, 106, 184, 361, 328)$.
Studies of isomers of LTC_4 have demonstrated that differences in binding correspond closely with differences
in contractile potency, supporting the concept that Studies of isomers of LTC_4 have demonstrated that differences in binding correspond closely with differences in contractile potency, supporting the concept that the lung binding site is a specific receptor (329). Functi differences in binding correspond closely with difference
in contractile potency, supporting the concept that the
lung binding site is a specific receptor (329). Functiona
studies suggest that these are discrete receptors in contractile potency, supporting the concept that the lung binding site is a specific receptor (329) . Functional studies suggest that these are discrete receptors for LTC_4 and LTD_4 , since their molar ratios needed lung binding site is a specific receptor (329). Functional
studies suggest that these are discrete receptors for LTC_4
and LTD_4 , since their molar ratios needed to elicit iden-
tical biological effects differ mar studies suggest that these are discrete receptors for LTC_4
and LTD_4 , since their molar ratios needed to elicit iden-
tical biological effects differ markedly in different tissues
(360, 107), and since the contra and LTD₄, since their molar ratios needed to elicit identical biological effects differ markedly in different tissues (360, 107), and since the contractile response of guinearly pig lung parenchymal strips is biphasic t tical biological effects differ markedly in different tissues
(360, 107), and since the contractile response of guinea
pig lung parenchymal strips is biphasic to LTD₄ but not
to LTC₄ (183). In addition, the compound F (360, 107), and since the contractile response of guino pig lung parenchymal strips is biphasic to LTD_4 but n to LTC_4 (183). In addition, the compound FPL 557 (see table 1) selectively antagonizes the effect of LTI on

INFLAMMATORY MEDIAT
its the conversion of LTC₄ to LTD₄, FPL 55712 is unable
to inhibit LTC₄-induced smooth muscle contraction di INFLAMMATORY MEDIA
its the conversion of LTC_4 to LTD_4 , FPL 55712 is unable
to inhibit LTC_4 -induced smooth muscle contraction
(411). (411). to inhibit LTC_4 -induced smooth muscle contraction (411).
Radioligand studies have also demonstrated two distinct binding sites in guinea pig lung homogenates, cor-

its the conversion of LTC_4 to LTD_4 , FPL 55712 is unable
to inhibit LTC_4 -induced smooth muscle contraction
(411).
Radioligand studies have also demonstrated two dis-
tinct binding sites in guinea pig lung ho to inhibit LTC_4 -induced smooth muscle contraction (411).

(411). Radioligand studies have also demonstrated two direct binding sites in guinea pig lung homogenates, corresponding with the function of LTC_4 and LTD_4 r (411). to calculate two dis-

Radioligand studies have also demonstrated two dis-

tinct binding sites in guinea pig lung homogenates, cor-

lung responding with the function of LTC_4 and LTD_4 recep-

tors (280, 104). Radioligand studies have also demonstrated two dis-
tinct binding sites in guinea pig lung homogenates, cor-
responding with the function of LTC_4 and LTD_4 recep-
effectors (280, 104). Autoradiographic studies have map tinct binding sites in guinea pig lung homogenates, cor-
responding with the function of LTC_4 and LTD_4 receptors (280, 104). Autoradiographic studies have mapped bre
the distribution of LTC_4 and LTD_4 binding sites responding with the function of LTC_4 and LTD_4 receptors (280, 104). Autoradiographic studies have mapped brothe distribution of LTC_4 and LTD_4 binding sites in closuries pig lung, with LTC_4 receptors being more w tors (280, 104). Autoradiographic studies have mapped the distribution of LTC_4 and LTD_4 binding sites in compute pure pure pure evidence that a proportion distributed and present in higher density than LTD_4 receptor guinea pig lung, with LTC₄ receptors being more widely distributed and present in higher density than LTD₄ receptors (51). There is some evidence that a proportion of LTC₄ binding is to the enzyme glutathione-S-tran distributed and present in higher density than LTD_4 receptors (51). There is some evidence that a proportion of LTC_4 binding is to the enzyme glutathione-S-transferase (558). However, pharmacological studies suggest t distributed and present in higher density than LTD_4 receptors (51). There is some evidence that a proportion of LTC_4 binding is to the enzyme glutathione-S-transferase (558). However, pharmacological studies suggest t receptors (51). There is some evidence that a proportion last of LTC₄ binding is to the enzyme glutathione-S-trans-
ferase (558). However, pharmacological studies suggest vithat normal human bronchi may not contain diff of LTC₄ binding is to the enzyme glutathione-S-trans-
ferase (558). However, pharmacological studies suggest vitre
that normal human bronchi may not contain different 142)
receptors for LTC₄ and LTD₄ (106). It has b ferase (558). However, pharmacological studies suggest vitre
that normal human bronchi may not contain different 142)
receptors for LTC_4 and LTD_4 (106). It has been suggested muc
that the majority of leukotriene recep that normal human bronchi may not contain α receptors for LTC_4 and LTD_4 (106). It has been st that the majority of leukotriene receptors may n an intracellular pool and that they may be recretive plasma membr ceptors for LTC_4 and LTD_4 (106). It has been suggested
at the majority of leukotriene receptors may reside in
intracellular pool and that they may be recruited to
e plasma membrane during activation (358).
The selecti

that the majority of leukotriene receptors may reside in
an intracellular pool and that they may be recruited to
the plasma membrane during activation (358).
The selective suppression of the chemotactic responses
of neutro an intracellular pool and that they may be recruited to
the plasma membrane during activation (358) .
The selective suppression of the chemotactic responses
of neutrophils to mono-HETEs by esters of mono-
HETEs gives sup the plasma membrane during activation (358).
The selective suppression of the chemotactic responses
of neutrophils to mono-HETEs by esters of mono-
HETEs gives support for a receptor-mediated interaction
between neutrophil The selective suppression of the chemotactic responses In
of neutrophils to mono-HETEs by esters of mono-
HETEs gives support for a receptor-mediated interaction Ii
between neutrophils and mono-HETEs (240). Cellular a
rec of neutrophils to mono-HETEs by esters of mono-
HETEs gives support for a receptor-mediated interaction
between neutrophils and mono-HETEs (240). Cellular
receptors to LTB₄ have also been postulated on the basis
of func HETEs gives support for a receptor-mediated interaction
between neutrophils and mono-HETEs (240) . Cellular
receptors to LTB₄ have also been postulated on the basis
of functional and radioligand binding studies. Specif between neutrophils and mono-HETEs (240). Cellular are
receptors to LTB₄ have also been postulated on the basis ve
of functional and radioligand binding studies. Specificity ul
of LTB₄ as a chemotactic agent for human receptors to LTB₄ have also been postulated on the basis of functional and radioligand binding studies. Specificity of LTB₄ as a chemotactic agent for human neutrophils is supported by the fact that it is 30 - to 30 of functional and radioligand binding studies. Specificity ulteration of LTB₄ as a chemotactic agent for human neutrophils and is supported by the fact that it is 30- to 300-fold more potent as compared with naturally o of LTB₄ as a chemotactic agent for human neutrophils
is supported by the fact that it is 30- to 300-fold more
potent as compared with naturally occurring isomers
(211, 362). In two studies, there was saturation of the
b is supported by the fact that it is 30- to 300-fold more
potent as compared with naturally occurring isomers
(211, 362). In two studies, there was saturation of the
binding of $[^{3}H]LTB_{4}$ to human neutrophils (244, 327) potent as compared with naturally occurring isomers (211, 362). In two studies, there was saturation of the chinding of $[^{3}H]LTB_{4}$ to human neutrophils (244, 327), got the dissociation constant and number of specific m (211, 362). In
binding of $[^{3}H]$
but the disso
binding sites
these studies. binding sites reported differed significantly between these studies.
 C. Airway Effects

C. Airway Effects

1. Airway smooth muscle. The contractile effect of

sulfidopeptide leukotrienes on human bronchial muscle

has been carefully documented (165, 261, 303, 163, 510, C. Airway Effects
1. Airway smooth muscle. The contractile effect of
sulfidopeptide leukotrienes on human bronchial muscle
has been carefully documented (165, 261, 303, 163, 510,
106). Leukotrienes C_4 and D_4 are app 1. Airway smooth muscle. The contractile effect of
sulfidopeptide leukotrienes on human bronchial muscle
has been carefully documented (165, 261, 303, 163, 510,
106). Leukotrienes C_4 and D_4 are approximately 1000-
f sulfidopeptide leukotrienes on human bronchial muscle
has been carefully documented (165, 261, 303, 163, 510,
106). Leukotrienes C_4 and D_4 are approximately 1000-
fold more potent than histamine in contracting human has been carefully documented (165, 261, 303, 163, 510,
106). Leukotrienes C_4 and D_4 are approximately 1000-
fold more potent than histamine in contracting human
isolated bronchus (165), but are less active in human 106). Leukotrienes C_4 and D_4 are approximately 1000-
fold more potent than histamine in contracting human
isolated bronchus (165), but are less active in human
parenchymal strips (505). LTE₄ is less potent than LT fold more potent than histamine in contracting human isolated bronchus (165), but are less active in human parenchymal strips (505). LTE₄ is less potent than L and LTD₄, but its effects are more prolonged. LTB₄ cont isolated bronchus (165), but are less active in human
parenchymal strips (505). LTE₄ is less potent than LTC₄
and LTD₄, but its effects are more prolonged. LTB₄ also
contracts human isolated bronchus, but rapid ta parenchymal strips (505). LTE₄ is less potent than LTC₄ and LTD₄, but its effects are more prolonged. LTB₄ also contracts human isolated bronchus, but rapid tachyphy-laxis develops (505). 5- and 15-HETE cause modes contracts human isolated bronchus, but
laxis develops (505). 5- and 15-HET
contraction of human bronchial muscl
LXA causes long-lasting contraction of
strip, but is inactive on trachea (166).
In vivo, the effects of aeroso In the effects of aerosols of LTC₄, D₄, and E₄ ability of the effects of aerosols of LTC₄, D₄, and E₄ ability we been studied in normal and asthmatic subjects (283, 4.

contraction of human bronchial muscle in vitro (145) .
LXA causes long-lasting contraction of guinea pig lung
strip, but is inactive on trachea (166) .
In vivo, the effects of aerosols of LTC_4 , D_4 , and E_4
have b LXA causes long-lasting contraction of guinea pig lung creative, but is inactive on trachea (166) .

In vivo, the effects of aerosols of LTC₄, D₄, and E₄ abileable in normal and asthmatic subjects $(283, 4.606, 607$ strip, but is inactive on trachea (166).

In vivo, the effects of aerosols of LTC_4 , D_4 , and E_4

have been studied in normal and asthmatic subjects (283,

606, 607, 78, 41, 540, 323, 254, 168). As observed in

anim In vivo, the effects of aerosols of LTC_4 , D_4 , and E_4 ability have been studied in normal and asthmatic subjects (283, 4606, 607, 78, 41, 540, 323, 254, 168). As observed in anominals, leukotrienes constrict both l have been studied in normal and asthmatic subjects (283, 606, 607, 78, 41, 540, 323, 254, 168). As observed in animals, leukotrienes constrict both large and small airways (41, 540, 323). Inhaled LTC_4 and LTD_4 a 606, 607, 78, 41, 540, 323, 254, 168). As observed in
animals, leukotrienes constrict both large and small air-
ways (41, 540, 323). Inhaled LTC₄ and LTD₄ and 1000
to 5000 times more potent than histamine, with a long animals, leukotrienes constrict both large and small air ways (41, 540, 323). Inhaled LTC₄ and LTD₄ and 100 to 5000 times more potent than histamine, with a longeduration of action (606, 607, 41). LTE₄ is approximat ways (41, 540, 323). Inhaled LTC₄ and LTD₄ and 1000
to 5000 times more potent than histamine, with a longer
duration of action (606, 607, 41). LTE₄ is approximately
one-tenth as potent as LTD₄ (168), with a longer to 5000 times more potent than histamine, with a longer
duration of action (606, 607, 41). LTE₄ is approximately
one-tenth as potent as LTD₄ (168), with a longer dura-
tion of action, is agreement with its in vitro ef

kotrienes (540, 78, 6, 168). In one study (254), asthmatics
kotrienes (540, 78, 6, 168). In one study (254), asthmatics
did not display the same degree of hyper-responsiveness ATORS AND ASTHMA
kotrienes (540, 78, 6, 168). In one study (254), asthmat
did not display the same degree of hyper-responsivene
to LTD₄ as they did to histamine, but the measureme to LTD4 as they did not display the same degree of hyper-responsivenes
to LTD₄ as they did to histamine, but the measurement
of responsiveness to leukotrienes may depend upon the kotrienes (540, 78, 6, 168). In one study (254), asthmatics
did not display the same degree of hyper-responsiveness
to LTD₄ as they did to histamine, but the measurement
of responsiveness to leukotrienes may depend upon kotrienes (540, 78, 6, 168). In one study (254), asthmatics
did not display the same degree of hyper-responsiveness
to LTD₄ as they did to histamine, but the measurement
of responsiveness to leukotrienes may depend upon did not display the same degree of hyper-responsiveness
to LTD₄ as they did to histamine, but the measurement
of responsiveness to leukotrienes may depend upon the
lung function test chosen (6, 168). In contrast to their to LTD₄ as they did to histamine, but the measurement
of responsiveness to leukotrienes may depend upon the
lung function test chosen (6, 168). In contrast to their
effect in the guinea pig, leukotrienes do not mediate lung function test chosen (6, 168). In contrast to their effect in the guinea pig, leukotrienes do not mediate their bronchoconstrictor effects through the release of cyclooxygenase products, in particular TxA_2 (163, 303). Fect in the guinea pig, leukotrienes do not mediate the onchoconstrictor effects through the release of α oxygenase products, in particular $T \mathbf{x} A_2$ (163, 64).
2. *Secretion*. Both LTC₄ and LTD₄ are potent stimu

bronchoconstrictor effects through the release of cy-
clooxygenase products, in particular $T x A_2$ (163, 607,
303).
2. Secretion. Both LTC₄ and LTD₄ are potent stimu-
lants of mucus release as measured by the output o 303).

2. Secretion. Both LTC₄ and LTD₄ are potent stimu-

lants of mucus release as measured by the output of

mucus glycoprotein secretion from human airways in

vitro, being 10-fold more potent than methacholine (3 2. Secretion. Both LTC₄ and LTD₄ are potent stimulants of mucus release as measured by the output of mucus glycoprotein secretion from human airways in vitro, being 10-fold more potent than methacholine (393, 142). Th lants of mucus release as measured by t
mucus glycoprotein secretion from huma
vitro, being 10-fold more potent than metha
142). The mono-HETEs are less effectiv
mucus secretion in human airways (394).
In vivo, LTC₄ and In a given than methacholine (393, and the methacholine (393, a). The mono-HETEs are less effective in causing 20 . The mono-HETEs are less effective in causing 204 .
In vivo, LTC_4 and LTD_4 enhance mucus secretion i

142). The mono-HETEs are less effective in causing
mucus secretion in human airways (394).
In vivo, LTC_4 and LTD_4 enhance mucus secretion in
the trachea of the dog (302); however, no effect was
observed in the c observed in the cat, except at extremely high doses (488). mucus secretion in human airways (394).
In vivo, LTC_4 and LTD_4 enhance mucus secretion in
the trachea of the dog (302); however, no effect was
observed in the cat, except at extremely high doses (488).
In the canine t In vivo, LTC_4 and LTD_4 enhance mucus secretion
the trachea of the dog (302); however, no effect v
observed in the cat, except at extremely high doses (48
In the canine trachea, LTC_4 , D_4 , and E_4 (but not l
stim the trachea of the dog (302); however, no effect was
observed in the cat, except at extremely high doses (488).
In the canine trachea, LTC_4 , D_4 , and E_4 (but not B_4)
stimulate increased chloride secretion across observed in the cat, except at extremely high doses (488).
In the canine trachea, LTC_4 , D_4 , and E_4 (but not B_4)
stimulate increased chloride secretion across the epithe-
lium (354). Release of SRS-A during expe In the canine trachea, LTC_4 , D_4 , and E_4 (but not B_4
stimulate increased chloride secretion across the epithe
lium (354). Release of SRS-A during experimental canin
anaphylaxis may be responsible for the slowing lium (354). Release of SRS-A during experimental canine anaphylaxis may be responsible for the slowing of mucus velocity caused by antigen inhalation (595). LTC₄ stimulates ciliary beat frequency of sheep airways in vit anaphylaxis m
velocity cause
ulates ciliary
an effect med
PGE₂ (594).
3. Vascular locity caused by antigen inhalation (595). LTC₄ stim-
ates ciliary beat frequency of sheep airways in vitro,
 ι effect mediated by cyclooxygenase products, possibly
 $3E_2$ (594).
3. *Vascular effects*. Leukotrienes C

these studies.

1. *Airway Effects*

1. *Airway smooth muscle*. The contractile effect of a phase of vasoconstriction (162), and the potentiation

1. *Airway smooth muscle*. The contractile effect of a phase of vasoconstri 106). Leukotrienes C_4 and D_4 are approximately 1000-
fold more potent than histamine in contracting human
isolated bronchus (165), but are less active in human
metal and flare responses at low concentrations (79, 10 and LTD₄, but its effects are more prolonged. LTB₄ also effect that probably depends on the emigration and in-
contracts human isolated bronchus, but rapid tachyphy-
laxis develops (505). 5- and 15-HETE cause modest v ulates ciliary beat frequency of sheep airways in vitro,
an effect mediated by cyclooxygenase products, possibly
 PGE_2 (594).
3. Vascular effects. Leukotrienes C_4 , D_4 , and E_4 in-
crease microvascular permeabilit an effect mediated by cyclooxygenase products, possibly PGE_2 (594).
3. Vascular effects. Leukotrienes C_4 , D_4 , and E_4 increase microvascular permeability in the airways of guinea pigs (612, 286), being at least PGE₂ (594).

3. Vascular effects. Leukotrienes C₄, D₄, and E₄ increase microvascular permeability in the airways of

guinea pigs (612, 286), being at least 100 to 1000 times

more active than histamine (612), prob 3. Vascular effects. Leukotrienes C_4 , D_4 , and E_4 increase microvascular permeability in the airways of guinea pigs (612, 286), being at least 100 to 1000 times more active than histamine (612), probably through a crease microvascular permeability in the airways of guinea pigs (612, 286), being at least 100 to 1000 times more active than histamine (612), probably through a direct action at the postcapillary venular endothelial cell guinea pigs (612, 286), being at least 100 to 1000 times
more active than histamine (612), probably through a
direct action at the postcapillary venular endothelial cell
(162, 306). A leukotriene antagonist largely inhibit more active than histamine (612), probably through a
direct action at the postcapillary venular endothelial cell
(162, 306). A leukotriene antagonist largely inhibits al-
lergen-induced microvascular leakage in guinea pig ways (194). This effect of the leukotrienes is preceded by lergen-induced microvascular leakage in guinea pig airlergen-induced microvascular leakage in guinea pig air-
ways (194). This effect of the leukotrienes is preceded by
a phase of vasoconstriction (162), and the potentiation
of the microvascular leakage by vasodilator prosta ways (194). This effect of the leukotrienes is preceded by
a phase of vasoconstriction (162), and the potentiation
of the microvascular leakage by vasodilator prostaglan-
dins, such as PGE_2 and PGI_2 (458), may be rela a phase of vasoconstriction (162), and the potentiation
of the microvascular leakage by vasodilator prostaglan-
dins, such as PGE_2 and PGI_2 (458), may be related to
inhibition of vasoconstriction. However, in the huma of the microvascular leakage by vasodilator prostaglandins, such as PGE_2 and PGI_2 (458), may be related to inhibition of vasoconstriction. However, in the human skin, LTC_4 and D_4 are potent vasodilators, producin dins, such as PGE₂ and PGI₂ (458), may be related to
inhibition of vasoconstriction. However, in the human
skin, LTC₄ and D₄ are potent vasodilators, producing
wheal and flare responses at low concentrations (79, skin, LTC₄ and D_4 are potent vasodilators, producing skin, LTC₄ and D₄ are potent vasodilators, produci
wheal and flare responses at low concentrations (79, 10)
LTB₄ also increases microvascular permeability (97),
effect that probably depends on the emigration and i
t wheal and flare responses at low concentrations (79, 109).
LTB₄ also increases microvascular permeability (97), an
effect that probably depends on the emigration and in-
teraction of neutrophils through the endothelial LTB₄ also increases microvascular permeability (97), an effect that probably depends on the emigration and interaction of neutrophils through the endothelial microvasculature (97, 82, 604) and, in human skin, the increa effect that probably depends on the emigration and in-
teraction of neutrophils through the endothelial micro-
vasculature (97, 82, 604) and, in human skin, the increase
in microvascular permeability induced by LTB₄ is i in microvascular permeability induced by $LTB₄$ is in-

4. *Effects of cells.* LTB₄ is the most potent chemotactic and chemokinetic lipoxygenase product for neutrophils creased by the vasodilator PGE_2 (21). LXA causes arte-
riolar dilation, but has no effect on microvascular perme-
ability (166).
4. Effects of cells. LTB₄ is the most potent chemotactic
and chemokinetic lipoxygenase p riolar dilation, but has no effect on microvascular perme-
ability (166).
4. Effects of cells. LTB₄ is the most potent chemotactic
and chemokinetic lipoxygenase product for neutrophils
in vitro (161, 211), but is less ef ability (166).
4. Effects of cells. LTB₄ is the most potent chemotactic
and chemokinetic lipoxygenase product for neutrophils
in vitro (161, 211), but is less effective for eosinophils
(597). This action is not shared b 4. Effects of cells. LTB₄ is the most potent chemotactic
and chemokinetic lipoxygenase product for neutrophils
in vitro (161, 211), but is less effective for eosinophils
(597). This action is not shared by the sufidopep and chemokinetic lipoxygenase product for neutrophils
in vitro (161, 211), but is less effective for eosinophils
(597). This action is not shared by the sufidopeptide
leukotrienes. Intradermal injection of LTB_4 results in vitro (161, 211), but is less effective for eosinophils (597). This action is not shared by the sufidopeptide leukotrienes. Intradermal injection of LTB_4 results in neutrophil accumulation into human skin, associated (597). This action is not shared by the sufidopeptide leukotrienes. Intradermal injection of LTB_4 results in neutrophil accumulation into human skin, associated with a slow-onset tenderness and induration (545, 109). Le neutrophil accumulation into human skin, associated
with a slow-onset tenderness and induration (545, 109).
Leukotriene B_4 also stimulates the release of lysosomal
enzymes (198) and enhances the release of oxygen radi-

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EXARNES, CHUNG,

cals from human neutrophils (519). It enhances the other

expression of surface complement (C3b) receptors on (58 EXAMPLES, CHUNG, A

expression of surface complement (C3b) receptors on (586

human neutrophils and eosinophils (421). Mono-HETEs cau BARNES, CHU

cals from human neutrophils (519). It enhances the

expression of surface complement (C3b) receptors on

human neutrophils and eosinophils (421). Mono-HETEs

also have been reported to stimulate the chemotaxis cals from human neutrophils (519). It enhances the offerences of surface complement (C3b) receptors on (5
human neutrophils and eosinophils (421). Mono-HETEs calso have been reported to stimulate the chemotaxis of su
human cals from human neutrophils (519). It enhances the
expression of surface complement (C3b) receptors on
human neutrophils and eosinophils (421). Mono-HETEs
also have been reported to stimulate the chemotaxis of
human eosino expression of surface complement $(C3b)$ receptors on $(58$
human neutrophils and eosinophils (421) . Mono-HETEs cau
also have been reported to stimulate the chemotaxis of sub
human eosinophils and neutrophils, with maxim human neutrophils and eosinophils (421). Mono-HETEs cause also have been reported to stimulate the chemotaxis of sub-
human eosinophils and neutrophils, with maximal re-
formyl-methionyl peptides (242, 238), with 5-HETE pr also have been reported to stimulate the chemotaxis of subjecture human eosinophils and neutrophils, with maximal re- LTD_4 , sponses similar in magnitude to those evoked by C5a and tiinfla formyl-methionyl peptides $(242$ human eosinophils and neutrophils, with maximal responses similar in magnitude to those evoked by C5a and formyl-methionyl peptides (242, 238), with 5-HETE being the most potent. 5- and 12-HETEs and LXA induce degranulatio sponses similar in magnitude to those evoked by C5a and
formyl-methionyl peptides (242, 238), with 5-HETE
being the most potent. 5- and 12-HETEs and LXA
induce degranulation of human neutrophils (551, 517).
5-HPETE potenti formyl-methionyl pep
being the most poter
induce degranulation
5-HPETE potentiates
man basophils (466).
5. Effect on bronchia Fraction of human neutrophils (551, 517). (4

induce degranulation of human neutrophils (551, 517). (4

5. Effect on bronchial responsiveness. Leukotrienes can

increase the responsiveness of guinea pig tracheal muscle

to

5-HPETE potentiates the release of histamine from human basophils (466).

mointing the effect on *bronchial responsiveness*. Leukotrienes can

increase the responsiveness of guinea pig tracheal muscle

tato histamine in vi man basophils (466) .
5. Effect on bronchial responsiveness. Leukotrienes can
increase the responsiveness of guinea pig tracheal muscle
to histamine in vitro, although the effects seem to vary
between the different sulfi 5. *Effect on bronchial responsiveness*. Leukotrienes can increase the responsiveness of guinea pig tracheal muscle to histamine in vitro, although the effects seem to vary between the different sulfidopeptide leukotriene increase the responsiveness of guinea pig tracheal muscle
to histamine in vitro, although the effects seem to vary
between the different sulfidopeptide leukotrienes (150,
345). This property may also be shared by 5-HETE (between the different sulfidopeptide leukotrienes (150, 345). This property may also be shared by 5-HETE (145). LTB₄ has been shown to augment bronchial responsiveness to acetylcholine in dogs (435). However, in man, pr 345). This property may also be shared by 5-HETE (145). the LTB₄ has been shown to augment bronchial responsive-
ness to acetylcholine in dogs (435). However, in man, T
prior inhalation of LTD₄ failed to increase the LTB₄ has been shown to augment bronchial responsive- (24) ness to acetylcholine in dogs (435). However, in man, T prior inhalation of LTD₄ failed to increase the broncho-kotr constrictor effect of histamine (40), alth ness to acetylcholine in dogs (435) . However, in r
prior inhalation of LTD₄ failed to increase the bronc
constrictor effect of histamine (40) , although LTE₄
increase histamine airway responsiveness transientl
man prior inhalation of LTD₄ failed to increase the bronconstrictor effect of histamine (40), although LTE, increase histamine airway responsiveness transient man (348). LTB₄ has no effect on bronchial responsioness in ma increase histamine air
man (348). LTB₄ has
ness in man, even in t
D. Role in Asthma
1. Leukotriene relea 1. *Leukotriene release.* Sulfidopeptide leukotrienes can allow the discussed in mass is the *Leukotriene release*. Sulfidopeptide leukotrienes can allow the discussed discussed in mass decretions after all ergen challenge

mess in man, even in the presence of PGD_2 (83a).

D. Role in Asthma

1. Leukotriene release. Sulfidopeptide leukotrienes can

be detected in nasal secretions after allergen challenge

in vivo (151) and in pooled plasma munited and in the matter of the matter of the matter of the matter of the detected in nasal secretions after allergen challenge che
in vivo (151) and in pooled plasma from subjects with acute asthma (616). Using a bioassa D. Role in Asthma
1. Leukotriene release. Sulfidopeptide leukotrienes can
be detected in nasal secretions after allergen challenge
in vivo (151) and in pooled plasma from subjects with
acute asthma (616). Using a bioassay 1. Leukotriene release. Sulfidopeptide leukotrienes can
be detected in nasal secretions after allergen challenge
in vivo (151) and in pooled plasma from subjects with
acute asthmat (616). Using a bioassay system, SRS-A be detected in nasal secretions after allergen challenge chivation in vivo (151) and in pooled plasma from subjects with acute asthma (616). Using a bioassay system, SRS-A has been measured in the sputum of allgeric asthma in vivo (151) and in pooled plasma from subjects with
acute asthma (616). Using a bioassay system, SRS-A has
been measured in the sputum of allgeric asthmatic sub-
jects (578), but there is doubt about the specificity of
s

jects (578), but there is doubt about the specificity of
such an assay.
2. Inhibitors. Several studies have now examined the
effect of pharmacological inhibition of lipoxygenase ac-
tion or inhibition of leukotriene effec such an assay.

2. *Inhibitors*. Several studies have now examined

effect of pharmacological inhibition of lipoxygenase

tion or inhibition of leukotriene effects. Inhibition

LTC₄ and LTD₄ synthesis through an effect 2. Inhibitors. Several studies have now examined the undertext of pharmacological inhibition of lipoxygenase action or inhibition of leukotriene effects. Inhibition of of LTC₄ and LTD₄ synthesis through an effect on g effect of pharmacological inhibition of lipoxygenase action or inhibition of leukotriene effects. Inhibition of LTC₄ and LTD₄ synthesis through an effect on glutathione S-transferase by U-60,257 (Piriprost) (37) blocks tion or inhibition of leukotriene effects. Inhibition of LTC_4 and LTD_4 synthesis through an effect on glutathione S-transferase by U-60,257 (Piriprost) (37) blocks the atomobilistaminic component of airway smoot LTC₄ and LTD₄ synthesis through an effect on glutathindrone S-transferase by U-60,257 (Piriprost) (37) blocks the admonitration induced by allergen in the bronchi of atopic but had no effect on allergen challenge in a one S-transferase by U-60,257 (Piriprost) (37) blocks the nonhistaminic component of airway smooth muscle contraction induced by allergen in the bronchi of atopic asthmatic subjects in vitro, but had no effect on allergen nonhistaminic component of airway smooth muscle con-
traction induced by allergen in the bronchi of atopic
asthmatic subjects in vitro, but had no effect on allergen
challenge in asthmatic subjects in vivo (387). FPL 55712 traction induced by allergen in the bronchi of atopic
asthmatic subjects in vitro, but had no effect on allergen
challenge in asthmatic subjects in vivo (387). FPL 55712,
the first recognized leukotriene antagonist (33), a asthmatic subjects in vitro, but had no effect on allergen
challenge in asthmatic subjects in vivo (387). FPL 55712,
the first recognized leukotriene antagonist (33), also
attenuates allergen-induced bronchial contraction challenge in asthmatic subjects in vivo (387). FPL 55712,
the first recognized leukotriene antagonist (33), also
attenuates allergen-induced bronchial contraction of hu-
man airways in vitro (3). In vivo, L-649,923 (see ta the first recognized leukotriene antagonist (33), also hattenuates allergen-induced bronchial contraction of human airways in vitro (3). In vivo, L-649,923 (see table 1) ry (304), an LTD₄ receptor antagonist, had only a attenuates allergen-induced bronchial contraction of human airways in vitro (3). In vivo, L-649,923 (see table 1)
 (304) , an LTD₄ receptor antagonist, had only a marginal,

nonsignificant effect on the early response man airways in vitro (3). In vivo, L-649,923 (see table 1) rylcholine. PAF has a number of synonyms, including (304), an LTD₄ receptor antagonist, had only a marginal, Paf-acether (75), acetyl glyceryl ether phosphorylc (304), an LTD₄ receptor antagonist, had only a marginal, nonsignificant effect on the early response to antigen and no effect on the late bronchoconstrictor response after antigen challenge (99). However, it is likely t nonsignificant effect on the early response to antigen (AG.

and no effect on the late bronchoconstrictor response lary

after antigen challenge (99). However, it is likely that, at ertie

the dose used, L-649,923 is only and no effect on the late bronchoconstrictor response lary
after antigen challenge (99). However, it is likely that, at ertic
the dose used, L-649,923 is only weakly effective against intu
LTD₄-induced bronchoconstricti after antigen challenge (99). However, it is likely that, at the dose used, L-649,923 is only weakly effective against LTD₄-induced bronchoconstriction in vivo (42). FPL 55712, when inhaled by asthmatic subjects, had on LTD₄-induced bronchoconstriction in vivo (42). FPL induce several characteristic features of asthma (415, 52, 55712, when inhaled by asthmatic subjects, had only a $53, 95$).
week bronchodilator effect in 2 of 4 subject LTD₄-induced bronchoconstriction in vivo (42). FPL 10 mdu 55712, when inhaled by asthmatic subjects, had only a 53 , s week bronchodilator effect in 2 of 4 subjects studied; however, this antagonist has only a sh 55712, when inhaled by asthmatic subjects, had only a week bronchodilator effect in 2 of 4 subjects studied; however, this antagonist has only a short half-life and is also a phosphodiesterase inhibitor (349) . Short-ter week bronchodilator effect in 2 of 4 showever, this antagonist has only a shouled also a phosphodiesterase inhibitor (3 treatment of asthmatic subjects with the inhibitor, 2,3,5-Trimethyl-6-(12-hydroxynyl)-1,4-benzoquinone however, this antagonist has only a short half-life and is
also a phosphodiesterase inhibitor (349). Short-term 1.
treatment of asthmatic subjects with the 5-lipoxygenase to c
inhibitor, 2,3,5-Trimethyl-6-(12-hydroxy-5,10 treatment of asthmatic subjects with the 5-lipoxygenase
inhibitor, 2,3,5-Trimethyl-6-(12-hydroxy-5,10-dodecadi-
ynyl)-1,4-benzoquinone (AA-361) (615), had no effect on
the airways hyper-responsiveness of asthma (220). An-

G, AND PAGE
other 5-lipoxygenase inhibitor, REV 5901 (see table 1)
(585), which is also a leukotriene receptor antagonist, (585), AND PAGE
(585), which is also a leukotriene receptor antagonist
(585), which is also a leukotriene receptor antagonist
caused no bronchodilatation when inhaled by asthmatic G, AND PAGE
other 5-lipoxygenase inhibitor, REV 5901 (see table 1)
(585), which is also a leukotriene receptor antagonist,
caused no bronchodilatation when inhaled by asthmatic
subjects (189), and there was no antagonism a subjects (189), which is also a leukotriene receptor antagonist,

(585), which is also a leukotriene receptor antagonist,

caused no bronchodilatation when inhaled by asthmatic

subjects (189), and there was no antagonism other 5-lipoxygenase inhibitor, REV 5901 (see table 1) (585), which is also a leukotriene receptor antagonist, caused no bronchodilatation when inhaled by asthmatic subjects (189), and there was no antagonism against LTD₄ (585), which is also a leukotriene receptor antagonist,
caused no bronchodilatation when inhaled by asthmatic
subjects (189), and there was no antagonism against
 LTD_4 -induced bronchoconstriction. Colchicine, an an-
tiin caused no bronchodilatation when inhaled by asthmatic
subjects (189), and there was no antagonism against
LTD₄-induced bronchoconstriction. Colchicine, an an-
tiinflammatory agent, has been shown to inhibit LTB₄
produc subjects (189), and there was no antagonism against
LTD₄-induced bronchoconstriction. Colchicine, an an-
tiinflammatory agent, has been shown to inhibit LTB₄
production from human neutrophils in vivo, yet has no
effect (464). tiinflammatory agent, has been shown to inhibit $LTB₄$
production from human neutrophils in vivo, yet has no
effect on either early or late-phase response to allgergen
 (464) .
The use of dietary supplementation with

effect on either early or late-phase response to allgergen (464).

The use of dietary supplementation with eicosapentae-

noic acid (fish oil) to decrease the formation of lipoxy-

genase products by diversion to the less genase products by diversion to the less active eicosapen-(464).
The use of dietary supplementation with eicosapentaenoic acid (fish oil) to decrease the formation of lipoxy-
genase products by diversion to the less active eicosapen-
taenoic derivatives, such as LTB_5 , C_5 , a The use of dietary supplementation with eicosapentae-
noic acid (fish oil) to decrease the formation of lipoxy-
genase products by diversion to the less active eicosapen-
taenoic derivatives, such as LTB_6 , C_6 , and D noic acid (fish oil) to decrease the formation of lipor
genase products by diversion to the less active eicosape
taenoic derivatives, such as LTB_6 , C_5 , and D_5 (346), h
also been studied in asthma. Despite the fact genase products by diversion to the less active eicosapentaenoic derivatives, such as LTB_5 , C_5 , and D_5 (346), has also been studied in asthma. Despite the fact that leukocyte function was attenuated in terms of L (24). so been studied in asthma. Despite the fact that leucyte function was attenuated in terms of LTB_4 biosynesis and chemotaxis, no clinical benefit was observed 4).
The role of the lipoxygenase products, including leutrien kocyte function was attenuated in terms of $LTB₄$ biosynthesis and chemotaxis, no clinical benefit was observed (24) .
The role of the lipoxygenase products, including leukotrienes, in asthma, therefore, still remai

thesis and chemotaxis, no clinical benefit was observed (24).

The role of the lipoxygenase products, including leu-

kotrienes, in asthma, therefore, still remains unclear,

perhaps largely through the difficulty in obtai (24).
The role of the lipoxygenase products, including leukotrienes, in asthma, therefore, still remains unclear,
perhaps largely through the difficulty in obtaining con-
vincing pharmacological inhibition of their effects The role of the lipoxygenase products, including leukotrienes, in asthma, therefore, still remains unclear, perhaps largely through the difficulty in obtaining convincing pharmacological inhibition of their effects. Althou kotrienes, in asthma, therefore, still remains unclear,
perhaps largely through the difficulty in obtaining con-
vincing pharmacological inhibition of their effects. Al-
though the leukotrienes are potent in causing smooth perhaps largely through the difficulty in obtaining convincing pharmacological inhibition of their effects. Although the leukotrienes are potent in causing smooth muscle contraction, airway microvascular leakage, and mucus vincing pharmacological inhibition of their effects. Although the leukotrienes are potent in causing smooth muscle contraction, airway microvascular leakage, and mucus secretion, they are not capable of inducing persisten though the leukotrienes are potent in causing smooth
muscle contraction, airway microvascular leakage, and
mucus secretion, they are not capable of inducing per-
sistent bronchial hyper-responsiveness. Apart from
LTB₄, t mucus secretion, they are not capable of inducing per-
sistent bronchial hyper-responsiveness. Apart from
LTB₄, the other leukotrienes do not possess significant
chemotactic activity for eosinophils. sistent bronchial hyper-responsiveness. Apart from LTB₄, the other leukotrienes do not possess significant chemotactic activity for eosinophils.
V. Platelet Activating Factor

In 1966 it was observed that there was a complement-**1. Platelet Activating Factor**

In 1966 it was observed that there was a complement-

independent release of histamine into plasma (in rabbits

undergoing an acute allergic response) (39). As platelets

had previously bee In 1966 it was observed that there was a complement-
independent release of histamine into plasma (in rabbits
undergoing an acute allergic response) (39). As platelets
had previously been demonstrated to be the major sourc independent release of histamine into plasma (in rabbits
undergoing an acute allergic response) (39). As platelets
had previously been demonstrated to be the major source
of histamine in this species (290), this suggested undergoing an acute allergic response) (39). As platelets
had previously been demonstrated to be the major source
of histamine in this species (290), this suggested the
formation of a mediator capable of inducing platelet
 had previously been demonstrated to be the major source
of histamine in this species (290), this suggested the
formation of a mediator capable of inducing platelet
activation in the allergic response. This histamine releas of histamine in this species (290), this suggested the formation of a mediator capable of inducing platelet activation in the allergic response. This histamine release was the consequence of an IgE-dependent activation of formation of a mediator capable of inducing platelet activation in the allergic response. This histamine release was the consequence of an IgE-dependent activation of basophils, which in turn released a soluble product cap activation in the allergic response. This histamine release
was the consequence of an IgE-dependent activation of
basophils, which in turn released a soluble product ca-
pable of eliciting platelet activation (74). This ba was the consequence of an IgE-dependent activation of basophils, which in turn released a soluble product capable of eliciting platelet activation (74). This basophil product was termed platelet activating factor (PAF) and basophils, which in turn released a solul
pable of eliciting platelet activation (74).
product was termed platelet activating face
has been chemically characterized as a
phospholipid, 1-O-alkyl-2-acetyl-sn-glyce
rylcholine pable of eliciting platelet activation (74). This basophil
product was termed platelet activating factor (PAF) and
has been chemically characterized as an ether-linked
phospholipid, 1-O-alkyl-2-acetyl-sn-glyceryl-3-phospho product was termed platelet activating factor (PAF) and
has been chemically characterized as an ether-linked
phospholipid, 1-O-alkyl-2-acetyl-sn-glyceryl-3-phospho-
rylcholine. PAF has a number of synonyms, including
Paf-a has been chemically characterized as an ether-line
phospholipid, 1-O-alkyl-2-acetyl-sn-glyceryl-3-phosphylcholine. PAF has a number of synonyms, inclu
Paf-acether (75), acetyl glyceryl ether phosphorylcho
(AGEPC) (172), or phospholipid, 1-O-alkyl-2-acetyl-sn-glyceryl-3-phosphorylcholine. PAF has a number of synonyms, includin
Paf-acether (75), acetyl glyceryl ether phosphorylcholine
(AGEPC) (172), or anti-hypertensive polar renomedu
lary lip rylcholine. PAF has a number of synonyms, including
Paf-acether (75), acetyl glyceryl ether phosphorylcholine
(AGEPC) (172), or anti-hypertensive polar renomedul-
lary lipid (APRL) (84). PAF has many biological prop-
ertie Paf-acether (75), acetyl glyceryl ether phosphorylcholine (AGEPC) (172), or anti-hypertensive polar renomedul-
lary lipid (APRL) (84). PAF has many biological properties in addition to platelet activation and is particular (AGEPC) (172), or anti-hypertensive polar renomedul-
lary lipid (APRL) (84). PAF has many biological prop-
erties in addition to platelet activation and is particularly
interesting as a putative mediator of asthma, since i lary lipid
erties in a
interestin
induce sev
53, 95). induce several characteristic features of asthma $(415, 52, 52)$

duce several characteristic teatures of asthma (415, 52,
 1. Synthesis. The synthesis of PAF is not secondary

cell damage or physical disruption (568), suggesting 53, 95).
A. *Origin*
1. Synthesis. The synthesis of PAF is not secondary
to cell damage or physical disruption (568), suggesting
that PAF is neither preformed nor stored but rather A. Origin
1. Synthesis. The synthesis of PAF is not secondary
to cell damage or physical disruption (568), suggesting
that PAF is neither preformed nor stored but rather
synthesized denovo. Two distinct synthetic pathways state of PAF is not secondary
it of cell damage or physical disruption (568), suggesting
that PAF is neither preformed nor stored but rather
synthesized denovo. Two distinct synthetic pathways
have been described for PAF (1. Synthesis. The synthesis of PAF is not secondary
to cell damage or physical disruption (568), suggesting
that PAF is neither preformed nor stored but rather
synthesized denovo. Two distinct synthetic pathways
have been

PHARMACOLOGICAL REVIEWS

aspet

INFLAMMATORY MEDIAT
two-step pathway which has been demonstrated in a h
number of inflammatory cell types in vitro, including p
macrophages (404, 431, 14), neutrophils (371, 309), eo- a INFLAMMATORY MED
two-step pathway which has been demonstrated in a
number of inflammatory cell types in vitro, including
macrophages (404, 431, 14), neutrophils (371, 309), eo-
sinophils (344), and platelets (73, 125), and two-step pathway which has been demonstrated in a
number of inflammatory cell types in vitro, including
macrophages (404, 431, 14), neutrophils (371, 309), eo-
sinophils (344), and platelets (73, 125), and which in-
volves two-step pathway which has been demonstrated in
number of inflammatory cell types in vitro, includin
macrophages (404, 431, 14), neutrophils (371, 309), e
sinophils (344), and platelets (73, 125), and which in
volves the p number of inflammatory cell types in vitro, including pha
macrophages (404, 431, 14), neutrophils (371, 309), eo-
sinophils (344), and platelets (73, 125), and which in-
the
volves the production of the biologically inact macrophages (404, 431, 14), neutrophils (371, 309), eo-
sinophils (344), and platelets (73, 125), and which in-
volves the production of the biologically inactive inter-
osa
mediate, lyso-PAF, from ether-linked phospholip sinophils (344), and platelets (73, 125), and which in-
volves the production of the biologically inactive inter-
mediate, lyso-PAF, from ether-linked phospholipids by p
the action of phospholipase A_2 (PLA₂) (fig. 3) volves the production of the biologically inactive inter-
mediate, lyso-PAF, from ether-linked phospholipids by
the action of phospholipase A_2 (PLA₂) (fig. 3). This step
is in common with the liberation of arachidoni mediate, lyso-PAF, from ether-linked phospholipids by ph
the action of phospholipase A_2 (PLA₂) (fig. 3). This step cel
is in common with the liberation of arachidonic acid for
sythe subsequent formation of cyclooxyge the action of phospholipase A_2 (PLA₂) (fig. 3). This st
is in common with the liberation of arachidonic acid i
the subsequent formation of cyclooxygenase and lipor
genase metabolites (fig. 3). Formation of lyso-PAF
a is in common with the liberation of arachidonic acid for
the subsequent formation of cyclooxygenase and lipoxy-
genase metabolites (fig. 3). Formation of lyso-PAF is
abolished by PLA₂ inhibitors, such as bromophenacytyl the subsequent formation of cyclooxygenase and lipoxy-
genase metabolites (fig. 3). Formation of lyso-PAF is ocy
abolished by PLA₂ inhibitors, such as bromophenacytyl (
bromide (586), hydrocortisone, and macrocortin (44 genase metabolites (fig. 3). Formation of lyso-PAF is
abolished by PLA₂ inhibitors, such as bromophenacytyl
bromide (586), hydrocortisone, and macrocortin (449).
In order to synthesise PAF, a second enzyme has to be
con abolished by PLA_2 inhibitors, such as bromophenacytyl
bromide (586), hydrocortisone, and macrocortin (449).
In order to synthesise PAF, a second enzyme has to be
concomitantly activated with the PLA_2 , namely an bromide (586), hydrocortisone, and macrocortin (449).
In order to synthesise PAF, a second enzyme has to be
concomitantly activated with the PLA₂, namely an acetyl
coenzyme A (CoA)-dependent acetyltransferase enzyme,
wh concomitantly activated with the PLA₂, namely an acetyl
coenzyme A (CoA)-dependent acetyltransferase enzyme,
which has been described in a number of inflammatory
cell types and is the rate-limiting step for PAF produc-
 coenzyme A (CoA)-dependent acetyltransferase enzyme,
which has been described in a number of inflammatory
cell types and is the rate-limiting step for PAF produc-
tion by this pathway (542, 543).
A second synthetic pathway enzyme A (CoA)-dependent acetyltransferase enzyme, typuch has been described in a number of inflammatory lay

Il types and is the rate-limiting step for PAF produc-

or by this pathway (542, 543).

A second synthetic path

which has been described in a number of inflammat
cell types and is the rate-limiting step for PAF prod
tion by this pathway (542, 543).
A second synthetic pathway for PAF involves
enzyme, cholinephosphotransferase, which cell types and is the rate-limiting step for PAF production by this pathway (542, 543).
A second synthetic pathway for PAF involves the
enzyme, cholinephosphotransferase, which can synthe-
size PAF directly from ether-link tion by this pathway (542, 543).

A second synthetic pathway for PAF involves the

enzyme, cholinephosphotransferase, which can synthe-

size PAF directly from ether-linked phospholipids (542,

543). The levels of this enz enzyme, cholinephosphotransferase, which can synthe-
size PAF directly from ether-linked phospholipids (542, enzyme, cholinephosphotransferase, which can syn
size PAF directly from ether-linked phospholipids (
543). The levels of this enzyme are generally much high
than the comparable acetyl transferase levels, and
icularly so in size PAF directly from ether-linked phospholipids $(542, 543)$. The levels of this enzyme are generally much higher than the comparable acetyl transferase levels, and particularly so in lung. The cholinephosphotransferase 543). The levels of this enzyme are generally much higher $\frac{3. \text{ Metabolism}}{3. \text{ Metabolism}}$. PAF is very rapidly metabolized by the than the comparable acetyl transferase levels, and particular action of the enzyme phosphatidyl-2ticularly so in lung. The cholinephosphotransferase which removes acetate and leads to the formation of pathway may be required to maintain physiological levels lyso-PAF (197). Thus, the primary metabolite of PAF is of PAF iccularly so in lung. The cholinephosphotransferase pathway may be required to maintain physiological levels of PAF for normal cell function, particularly in the regulation of blood pressure, whereas the rate-limiting ace pathway may be required to maintain physiological lev
of PAF for normal cell function, particularly in t
regulation of blood pressure, whereas the rate-limiti
acetyl transferase pathway is only activated in respon
to infla of PAF for normal cell function, particularly in the regulation of blood pressure, whereas the rate-limiting $\frac{t}{t}$ acetyl transferase pathway is only activated in response to inflammatory signals such as phagocytosis acetyl transferase pathway is only activated in response
to inflammatory signals such as phagocytosis or chemo-
taxis (543). Most of these data originate from in vitro
observations and, to what extent these two synthetic acetyl transferase pathway is only activated in response
to inflammatory signals such as phagocytosis or chemo-
taxis (543). Most of these data originate from in vitro
observations and, to what extent these two synthetic
p to inflammatory signals such as phagocytosis or chemotaxis (543). Most of these data originate from in vitro observations and, to what extent these two synthetic pathways contribute to PAF formation in vivo, remains to be taxis (543). Most of these data originate from in vitro
observations and, to what extent these two synthetic incl-
pathways contribute to PAF formation in vivo, remains
to be elucidated. The availability of a number of ac observations and, to what extent these two synthetic increased pathways contribute to PAF formation in vivo, remains the to be elucidated. The availability of a number of acetyl $\frac{1}{2}$ m transferase inhibitors, such as pathways contribute to PAF formation in viv
to be elucidated. The availability of a number
transferase inhibitors, such as L-648-611, m
elucidate the precise role of this synthetic p
both phyisology and pathophysiology (49 be elucidated. The availability of a number of acetyl
ansferase inhibitors, such as L-648-611, may help to
ucidate the precise role of this synthetic pathway in
th phyisology and pathophysiology (490).
2. Cellular origin.

transferase inhibitors, such as L-648-611, may help to
elucidate the precise role of this synthetic pathway in
both phyisology and pathophysiology (490).
2. Cellular origin. Although PAF was originally de-
scribed as a pr elucidate the precise role of this synthetic pathway in
both phyisology and pathophysiology (490).
2. Cellular origin. Although PAF was originally de-
scribed as a product of rabbit basophils, it can also be
produced by a both phyisology and pathophysiology (490).

2. Cellular origin. Although PAF was originally described as a product of rabbit basophils, it can also produced by a number of other inflammatory cells. If

terestingly, in man 2. Cellular origin. Although PAF was originally described as a product of rabbit basophils, it can also be produced by a number of other inflammatory cells. Interestingly, in man PAF does not appear to be an extracellular scribed as a product of rabbit basophils, it can also be
produced by a number of other inflammatory cells. In-
terestingly, in man PAF does not appear to be an extra-
cellular product of basophils or mast cells and, althou produced by a number of other inflammatory cells. In-
terestingly, in man PAF does not appear to be an extra-
cellular product of basophils or mast cells and, although
pulmonary mast cells have the capacity to synthesize
 terestingly, in man PAF does not appear to be an ext cellular product of basophils or mast cells and, althou
pulmonary mast cells have the capacity to synthes
PAF, it appears to be retained intracellularly (366). T
phenome cellular product of basophils or mast cells and, although
pulmonary mast cells have the capacity to synthesize
 PAF , it appears to be retained intracellularly (366). This
phenomenon has also been observed in human neutropulmonary mast cells have the capacity to synthesize PAF , it appears to be retained intracellularly (366). This increment on has also been observed in human neutro-
phils, but the precise role of the intracellular PAF i PAF, it appears to be retained intracellularly (366). This phenomenon has also been observed in human neutro-
phils, but the precise role of the intracellular PAF is
uncertain (378). Three to 4% of the synthesized PAF is
r phenomenon has also been observed in human neutro
phils, but the precise role of the intracellular PAF i
uncertain (378). Three to 4% of the synthesized PAF i
released within a few minutes of activation of neutrophil
by tr phils, but the precise role of the intracellular PAF is
uncertain (378). Three to 4% of the synthesized PAF is
released within a few minutes of activation of neutrophils
by triggers such as opsonized zymosan or calcium io released within a few minutes of activation of neutrophils
by triggers such as opsonized zymosan or calcium iono-
phore. Human platelets produce lesser amounts of PAF
than neutrophils but approximately 50 times more lyso-
 than neutrophils but approximately 50 times more lyso-
PAF, presumably associated with the production of ara-
chidonic acid metabolites following PLA_2 activation. Eoby triggers such as opsonized zymosan or calcium iono-
phore. Human platelets produce lesser amounts of PAF
than neutrophils but approximately 50 times more lyso-
PAF, presumally associated with the production of ara-
chid phore. Human platelets produce lesser amounts of PAF
than neutrophils but approximately 50 times more lyso-
PAF, presumally associated with the production of ara-
chidonic acid metabolites following PLA_2 activation. Eothan neutrophils but approximately 50 times more lyso-
PAF, presumaltly associated with the production of ara-
chidonic acid metabolites following PLA_2 activation. Eo-
sinophils isolated from patients with eosinophilia PAF, presumably associated with the production of a chidonic acid metabolites following PLA_2 activation. is
inophilic isolated from patients with eosinophilia rele
PAF following stimulation with various chemotactic f
to chidonic acid metabolites following PLA_2 activation. Eosinophils isolated from patients with eosinophilia release
PAF following stimulation with various chemotactic factors, including eosinophilic chemotatic factor of a sinophils isolated from patients with eosinophilia release

PAF following stimulation with various chemotactic fac-

tors, including eosinophilic chemotatic factor of anaphy-

laxis (ECF-A) and f-Met-Leu-Phe, suggesting th

INFLAMMATORY MEDIATORS AND ASTHMA
two-step pathway which has been demonstrated in a human eosinophils (344, 531). Human alveolar macro-
number of inflammatory cell types in vitro, including phage obtained by bronchoalveola human eosinophils (344, 531). Human alveolar macro-STORS AND ASTHMA
human eosinophils (344, 531). Human alveolar macro-
phage obtained by bronchoalveolar lavage of allergic 61
human eosinophils (344, 531). Human alveolar macro-
phage obtained by bronchoalveolar lavage of allergic
asthmatics also release PAF following stimulation with
the appropriate antigen in vitro (26). Interestingly, zymthe appropriate antigen in Vienna alveolar macrophage obtained by bronchoalveolar lavage of allergic asthmatics also release PAF following stimulation with the appropriate antigen in vitro (26). Interestingly, zym-
osan do phage obtained by bronchoalveolar lavage of allergic asthmatics also release PAF following stimulation with the appropriate antigen in vitro (26). Interestingly, zymosan does not release PAF from human alveolar macrophages asthmatics also release PAF following stimulation with
the appropriate antigen in vitro (26). Interestingly, zym-
osan does not release PAF from human alveolar macro-
phages, despite an increase in phagocytic activity in s the appropriate antigen in vitro (26). Interestingly, zy
osan does not release PAF from human alveolar mac
phages, despite an increase in phagocytic activity in s
cells. However, it remains possible that PAF is be
synthesi osan does not release PAF from human alveolar macre
phages, despite an increase in phagocytic activity in succells. However, it remains possible that PAF is bein
synthesized in these cells but is being retained intrace
lul cells. However, it remains possible that PAF is being
synthesized in these cells but is being retained intracel-
lularly in an analogous manner to that observed in phag-
ocytosing neutrophils.
Cultured human vascular endot

synthesized in these cells but is being retained intracel-
lularly in an analogous manner to that observed in phag-
ocytosing neutrophils.
Cultured human vascular endothelial cells also release
PAF following stimulation wi lularly in an analogous manner to that observed in phag-
ocytosing neutrophils.
Cultured human vascular endothelial cells also release
PAF following stimulation with thrombin, calcium ion-
ophore, leukotrienes, histamine, ocytosing neutrophils.
Cultured human vascular endothelial cells also release
PAF following stimulation with thrombin, calcium ion-
ophore, leukotrienes, histamine, bradykinin, ATP, or
monocyte-derived interleukin 1 (475). Cultured human vascular endothelial cells also releaved PAF following stimulation with thrombin, calcium is ophore, leukotrienes, histamine, bradykinin, ATP, monocyte-derived interleukin 1 (475). As with other c types, som PAF following stimulation with thrombin, calcium ion-
ophore, leukotrienes, histamine, bradykinin, ATP, or
monocyte-derived interleukin 1 (475). As with other cell
types, some of the PAF formed by endothelial cell mono-
la ophore, leukotrienes, histamine, bradykinin, ATP, or
monocyte-derived interleukin 1 (475). As with other cell
types, some of the PAF formed by endothelial cell mono-
layers remains cell associated rather than being releas monocyte-derived interleukin 1 (475). As with other a types, some of the PAF formed by endothelial cell molayers remains cell associated rather than being releasextracellularly in situations where PGI_2 production of the types, some of the PAF formed by endothelial cell mono-
layers remains cell associated rather than being released
extracellularly in situations where PGI₂ production can
be detected. Preliminary data show that PAF is syn layers remains cell associated rather than being releasextracellularly in situations where $PGI₂$ production of the detected. Preliminary data show that PAF is synther sized by human epidermal cells obtained from ps extracellularly in situations where
be detected. Preliminary data sho
sized by human epidermal cells of
lesions (153), but whether airway
size PAF has not been determined
3. Metabolism. PAF is very rapion *3. Metabolism.* Phaliminary data show that PAF is synthe-
 3. Metabolism. PAF is very rapidly metabolized by the
 3. Metabolism. PAF is very rapidly metabolized by the

tion of the enzyme phosphatidyl-2-acetyl-hydrola

sized by human epidermal cells obtained from
lesions (153), but whether airway epithelial cells
size PAF has not been determined.
3. Metabolism. PAF is very rapidly metaboliza
action of the enzyme phosphatidyl-2-acetyl-h
w lesions (153), but whether airway epithelial cells synthe-
size PAF has not been determined.
3. Metabolism. PAF is very rapidly metabolized by the
action of the enzyme phosphatidyl-2-acetyl-hydrolase,
which removes acetate size PAF has not been determined.
3. Metabolism. PAF is very rapidly metabolized by the
action of the enzyme phosphatidyl-2-acetyl-hydrolase,
which removes acetate and leads to the formation of
lyso-PAF (197). Thus, the pr 3. Metabolism. PAF is very rapidly metabolized by the action of the enzyme phosphatidyl-2-acetyl-hydrolase, which removes acetate and leads to the formation of lyso-PAF (197) . Thus, the primary metabolite of PAF is also action of the enzyme phosphatidyl-2-acetyl-hydrolase,
which removes acetate and leads to the formation of
lyso-PAF (197). Thus, the primary metabolite of PAF is
also its precursor in some situations, and in some cell
types lyso-PAF (197). Thus, the primary metabolite of PAF is lyso-PAF (197). Thus, the primary metabolite of PAF
also its precursor in some situations, and in some c
types there is a constant cycle of PAF synthesis a
metabolism (575). The acetylhydrolase enzyme respo
sible for the i also its precursor in some situations, and in some cell
types there is a constant cycle of PAF synthesis and
metabolism (575). The acetylhydrolase enzyme respon-
sible for the initial metabolism of PAF has been identi-
fie types there is a constant cycle of PAF synthesis and
metabolism (575). The acetylhydrolase enzyme respon-
sible for the initial metabolism of PAF has been identi-
fied in the plasma of a number of mammalian species,
inclu metabolism (575). The acetylhydrolase enzyme responsible for the initial metabolism of PAF has been identified in the plasma of a number of mammalian species, including man, and is extremely active. From studies in the rab sible for the initial metabolism of PAF has been identi-
fied in the plasma of a number of mammalian species,
including man, and is extremely active. From studies in
the rabbit, 70% of the PAF is metabolized to lyso-PAF
1 fied in the plasma of a number of mammalian species,
including man, and is extremely active. From studies in
the rabbit, 70% of the PAF is metabolized to lyso-PAF
1 min after i.v. injection (339). An acetylhydrolase en-
zy including man, and is extremely active. From studies in
the rabbit, 70% of the PAF is metabolized to lyso-PAF
1 min after i.v. injection (339). An acetylhydrolase en-
zyme (which is capable of metabolizing PAF) has also
be the rabbit, 70% of the PAF is metabolized to lyso-PAF
1 min after i.v. injection (339). An acetylhydrolase en-
zyme (which is capable of metabolizing PAF) has also
been reported to be present on the surface of platelets,
w 1 min after i.v. injection (339). An acetylhydrolase en zyme (which is capable of metabolizing PAF) has also
been reported to be present on the surface of platelets
which is released following activation with PAF (559)
Ace zyme (which is capable of metabolizing PAF) has also
been reported to be present on the surface of platelets
which is released following activation with PAF (559)
Acetylhydrolase activity in plasma from asthmatic chil-
dre been reported to be present on the surface of platelets,
which is released following activation with PAF (559).
Acetylhydrolase activity in plasma from asthmatic chil-
dren is significantly reduced compared with healthy co which is released following activation with PAF (559).
Acetylhydrolase activity in plasma from asthmatic chil-
dren is significantly reduced compared with healthy con-
trols, suggesting that PAF may have protracted biologi types, some of the PAF formed by endothelial cell mono-
layers remains cell associated rather than being released
extracellularly in situations where PGI₂ production can
be detected. Preliminary data show that PAF is sy dren is significantly reduced compared with health
trols, suggesting that PAF may have protracted bio
activity in these subjects (409). Lyso-PAF can be f
metabolized by the removal of the O-alkyl group
enzyme similar to th trols, suggesting that PAF may have protracted biological
activity in these subjects (409). Lyso-PAF can be further
metabolized by the removal of the O-alkyl group by an
enzyme similar to the well-characterized tetrahydrop activity in these subjects (409). Lyso-PAF can be further
metabolized by the removal of the O-alkyl group by an
enzyme similar to the well-characterized tetrahydropter-
idine-dependent alkyl monooxygenase enzyme isolated
f metabolized by the removal of the O-alkyl group by an
enzyme similar to the well-characterized tetrahydropter-
idine-dependent alkyl monooxygenase enzyme isolated
from hepatic tissue, which metabolizes lyso-PAF to a
fatty idine-dependent alkyl monooxygenase enzyme isolated
from hepatic tissue, which metabolizes lyso-PAF to a
fatty aldehyde and glyceryl-3-phosphorylcholine (343).
B. Receptors
There are a number of indications that PAF exer

There are a number of indications that PAF exerts its
ological effects via specific membrane receptors. PAF biological effects via specific membrane receptors.
B. Receptors
Diological effects via specific membrane receptors. PAF
is both highly potent, acting on some tissues in concen-B. Receptors
There are a number of indications that PAF exerts
biological effects via specific membrane receptors. P
is both highly potent, acting on some tissues in concentrations as low as 10^{-8} M, and is stereoselect There are a number of indications that PAF exerts its
biological effects via specific membrane receptors. PAF
is both highly potent, acting on some tissues in concen-
trations as low as 10^{-8} M, and is stereoselective (9 There are a number of indications that PAF exerts its
biological effects via specific membrane receptors. PAF
is both highly potent, acting on some tissues in concen-
trations as low as 10^{-8} M, and is stereoselective (9 biological effects via specific membrane receptors. PAF
is both highly potent, acting on some tissues in concen-
trations as low as 10^{-8} M, and is stereoselective (94). PAF
also exhibits specific tachyphylaxis, which ag is both highly potent, acting on some tissues in concentrations as low as 10^{-8} M, and is stereoselective (94). PAl also exhibits specific tachyphylaxis, which again suggest an action via specific receptors (334). There trations as low as 10^{-8} M, and is stereoselective (94). PAF also exhibits specific tachyphylaxis, which again suggests an action via specific receptors (334). There have also been a number of studies using $[^{3}H]PAF$ a also exhibits specific tachyphylaxis, which again suggests
an action via specific receptors (334). There have also
been a number of studies using [³H]PAF as a radioligand,
which have demonstrated high affinity, saturable an action via specific receptors (334). There have also
been a number of studies using [³H]PAF as a radioligand,
which have demonstrated high affinity, saturable binding
sites for PAF on human platelets (583), neutrophil

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62
is inhibited by a number of PAF antagonists, but there of
is a high degree of nonspecific binding which makes these be 62

BARNES, CHUNG,

is inhibited by a number of PAF antagonists, but there

is a high degree of nonspecific binding which makes these

experiments difficult to interpret. Recently, labeled PAF fu experiments difficult to interpret. Recently, labeled PAF antagonists, but there other is a high degree of nonspecific binding which makes these best experiments difficult to interpret. Recently, labeled PAF functagonists antagonists, but there of
is a high degree of nonspecific binding which makes these best
experiments difficult to interpret. Recently, labeled PAF fund
antagonists, such as [³H]kadsurenone and [³H]WEB In
2086 (see tabl is inhibited by a number of PAF antagonists, but the
is a high degree of nonspecific binding which makes the
experiments difficult to interpret. Recently, labeled P.
antagonists, such as $[^{3}H]$ kadsurenone and $[^{3}H]W$
 is a high degree of nonspecific binding which makes these be
experiments difficult to interpret. Recently, labeled PAF fun
antagonists, such as $[^{3}H]$ kadsurenone and $[^{3}H]WEB$
2086 (see table 1), have proved more usefu experiments difficult to interpret. Recently, labeled PAF fun
antagonists, such as $[^{3}H]$ kadsurenone and $[^{3}H]WEB$ I
2086 (see table 1), have proved more useful as radioli-
brogands (294, 580). Although none of the abo antagonists, such as $[$ ³H]kadsurenone and $[$ ³H]WEB 2086 (see table 1), have proved more useful as radioli-
gands (294, 580). Although none of the above evidence is idefinitive proof of the existence of a PAF recepto 2086 (see table 1), have proved more useful as radioli-
gands (294, 580). Although none of the above evidence is recover
definitive proof of the existence of a PAF receptor, a effect (1
number of studies have reported tha gands (294, 580). Although none of the above evidence is definitive proof of the existence of a PAF receptor, a number of studies have reported that the binding of PAF appears to correlate with its biological effects (95). definitive proof of the existe
number of studies have report
appears to correlate with its
protein has been isolated cor
from human platelets (582).
Experiments showing diffe mber of studies have reported that the binding of PAF
pears to correlate with its biological effects (95). A
otein has been isolated containing the PAF receptor
om human platelets (582).
Experiments showing different affin

appears to correlate with its biological effects (95). A spotein has been isolated containing the PAF receptor bet
from human platelets (582). chore from human platelets (582).
Experiments showing different affinities of t protein has been isolated containing the PAF receptor be
from human platelets (582). ch
Experiments showing different affinities of the PAF co
antagonist, kadsurenone, in peritoneal macrophages and hi
blood leukocytes, hav from human platelets (582) . ch
Experiments showing different affinities of the PAF
antagonist, kadsurenone, in peritoneal macrophages and
blood leukocytes, have suggested the existence of more
contain one receptor subty Experiments showing different affinities of the PAF
antagonist, kadsurenone, in peritoneal macrophages and
blood leukocytes, have suggested the existence of more
than one receptor subtype (335), although in this study
cell antagonist, kadsurenone, in peritoneal macrophages and hist
blood leukocytes, have suggested the existence of more corr
than one receptor subtype (335), although in this study in a
cells obtained from two different specie blood leukocytes, have suggested the existence of more compared than one receptor subtype (335), although in this study in cells obtained from two different species were compared. Moreover all adhesion are not blocked by P than one receptor subtype (335), although in this study cells obtained from two different species were compared.
Another study has reported that certain effects of PAF (e.g., induction of neutrophil adhesion) are not block cells obtained from two different species were compared.
Another study has reported that certain effects of PAF
(e.g., induction of neutrophil adhesion) are not blocked
by PAF antagonists at concentrations which clearly an Another study has reported that certain effects of PAF (e.g., induction of neutrophil adhesion) are not blocked
by PAF antagonists at concentrations which clearly an-
tagonize other biological activities of PAF (590).
Whet (e.g., induction of neutrophil adhesion) are not blocked
by PAF antagonists at concentrations which clearly an-
tagonize other biological activities of PAF (590). inc
Whether PAF-receptor subtypes exist is still not certa by PAF antagonists at α
tagonize other biolog
Whether PAF-receptor
but is an important issue
all the effects of PAF.
 C Airvoy Effects *C. Airway Effects*
C. Airway Effects
C. Airway Effects
L. Airway smooth i is an important issue since antagonists may not block
the effects of PAF.
Airway Effects
1. Airway smooth muscle. PAF is as one of the most
tent inducers of bronchoconstriction in both experi-

potential the effects of PAF.

C. Airway Effects

1. Airway smooth muscle. PAF is as one of the mediator in ducers of bronchoconstriction in both experiental animals and man (416, 160, 501a). However, P. C. Airway Effects

1. Airway smooth muscle. PAF is as one of the most

protent inducers of bronchoconstriction in both experi-

mental animals and man (416, 160, 501a). However, PAF

does not posess direct contractile eff C. Airway Effects
1. Airway smooth muscle. PAF is as one of the most
potent inducers of bronchoconstriction in both experi-
mental animals and man (416, 160, 501a). However, PAF
does not posess direct contractile effects o 1. Airway smooth muscle. PAF is as one of the most
potent inducers of bronchoconstriction in both experi-
mental animals and man (416, 160, 501a). However, PAF
does not posess direct contractile effects on human air-
way s potent inducers of bronchoconstriction in both experi-
mental animals and man (416, 160, 501a). However, PAF
does not posess direct contractile effects on human air-
way smooth muscle preparations in vitro, yet may elicit
 mental animals and man (416, 160, 501a). However, PAF
does not posess direct contractile effects on human air-
way smooth muscle preparations in vitro, yet may elicit
contraction of airway smooth muscle preparations pro-
v does not posess direct contractile effects on hum-
way smooth muscle preparations in vitro, yet may
contraction of airway smooth muscle preparation
vided platelets are present in the organ bath (509
In experimental animals contraction of airway smooth muscle preparations provided platelets are present in the organ bath (509, 120).
In experimental animals, PAF-induced bronchoconstriction is secondary to platelet activation, since broncho-cons contraction of airway smooth muscle preparations provided platelets are present in the organ bath (509, 120).
In experimental animals, PAF-induced bronchoconstriction is secondary to platelet activation, since bronchocons vided platelets are present in the organ bath $(509, 120)$.
In experimental animals, PAF-induced bronchoconstric-
tion is secondary to platelet activation, since broncho-
constriction is abrogated in animals previously re In experimental animals, PAF-induced bronchoconstriction is secondary to platelet activation, since bronchoconstriction is abrogated in animals previously rendered thrombocytopenic by the use of a selective cytotoxic antib tion is secondary to platelet activation, since broncho-constriction is abrogated in animals previously rendered thrombocytopenic by the use of a selective cytotoxic antibody (587, 258). The nature of the platelet-derived constriction is abrogated in animals previously rendered
thrombocytopenic by the use of a selective cytotoxic
antibody (587, 258). The nature of the platelet-derived
spasmogen is not known, and there is controversy about
 thrombocytopenic by the use of a selective cytotoxic
antibody (587, 258). The nature of the platelet-derived
spasmogen is not known, and there is controversy about
the effects of antihistamines, 5-hydroxytryptamine (5-
HT) antibody (587, 258). The nature of the platelet-derived
spasmogen is not known, and there is controversy about
the effects of antihistamines, 5-hydroxytryptamine (5-
HT) antagonists, and inhibitors of arachidonic acid me-
 spasmogen is not known, and there is controversy about
the effects of antihistamines, 5-hydroxytryptamine (5-
HT) antagonists, and inhibitors of arachidonic acid me-
tabolism (both cyclooxygenease and lipoxygenase) (587,
8 the effects of antihistamines, 5-hydroxytryptamine (5-

HT) antagonists, and inhibitors of arachidonic acid me-

tabolism (both cyclooxygenease and lipoxygenase) (587, 587, 357). Neutrophils have also been implicated in P HT) antagonists, and inhibitors of arachidonic acid metabolism (both cyclooxygenease and lipoxygenase) (587
87, 357). Neutrophils have also been implicated in PAF-
induced bronchoconstriction (325), and there is a very
clo tabolism (both cyclooxygenease and lipoxygenase) (587, 87, 357). Neutrophils have also been implicated in PAF-
induced bronchoconstriction (325), and there is a very
close anatomical relationship between platelets and neu-87, 357). Neutrophils have also been implicated in PAF-
induced bronchoconstriction (325), and there is a very
close anatomical relationship between platelets and neu-
trophils observed throughout the pulmonary vasculature induced bronchoconstriction (325) , and there is a very
close anatomical relationship between platelets and neu-
trophils observed throughout the pulmonary vasculature
of experimental animals following systemic treatment close anatomical relationship between platelets and netrophils observed throughout the pulmonary vasculature of experimental animals following systemic treatme with PAF (174). As neutrophils and platelets have be observed trophils observed throughout the pulmonary vasculature
of experimental animals following systemic treatment
with PAF (174). As neutrophils and platelets have been
observed to cooperate in the formation of novel biolog-
ica of experimental animals following systemic treature with PAF (174). As neutrophils and platelets have observed to cooperate in the formation of novel bically active materials (382, 390), it is conceivable such products con striction. served to cooperate in the formation of novel biolog-

illy active materials (382, 390), it is conceivable that

ch products contribute to PAF-induced bronchocon-

gion.

PAF induces contraction of rabbit (110) and guinea
 ically active materials (382, 390), it is conceivable that the such products contribute to PAF-induced bronchocon-
striction. his PAF induces contraction of rabbit (110) and guinea very pig lung strip preparations in vitro

such products contribute to PAF-induced bronchoconstriction.

PAF induces contraction of rabbit (110) and guinea

pig lung strip preparations in vitro, which may depend

in part upon the release of acetylcholine from choli striction.

PAF induces contraction of rabbit (110) and guinea

pig lung strip preparations in vitro, which may depend

in part upon the release of acetylcholine from cholinergic

nerves (556) or on the release of thrombox PAF induces contraction of rabbit (110) and guinea value of pig lung strip preparations in vitro, which may depend flume part upon the release of acetylcholine from cholinergic on nerves (556) or on the release of thrombox prig lung strip preparations in vitro, which may depend flow
in part upon the release of acetylcholine from cholinergic or l
nerves (556) or on the release of thromboxane (351). in t
However, in addition to airway smooth m

G, AND PAGE
other contractile elements and are not necessarily the
best preparations for studying airway smooth muscle G, AND PAGE
other contractile elements and are not necessarily the
best preparations for studying airway smooth muscle
function. function. The contractile elements and are not necessarily the st preparations for studying airway smooth muscle notion.
In humans, PAF administered by inhalation is a potent onchoconstrictor, having a rapid onset of action and

other contractile elements and are not necessarily the
best preparations for studying airway smooth muscle
function.
In humans, PAF administered by inhalation is a potent
bronchoconstrictor, having a rapid onset of action best preparations for studying airway smooth muscle
function.
In humans, PAF administered by inhalation is a potent
bronchoconstrictor, having a rapid onset of action and
recovery over 2 h, whereas lyso-PAF has no signific function.
In humans, PAF administered by inhalation is a potent
bronchoconstrictor, having a rapid onset of action and
recovery over 2 h, whereas lyso-PAF has no significant
effect (160). The bronchoconstriction induced by In humans, PAF administered by inhalation is a potent
bronchoconstrictor, having a rapid onset of action and
recovery over 2 h, whereas lyso-PAF has no significant
effect (160). The bronchoconstriction induced by PAF in
ma bronchoconstrictor, having a rapid onset of action and
recovery over 2 h, whereas lyso-PAF has no significant
effect (160). The bronchoconstriction induced by PAF in
man is tachyphylactic, preventing cumulative dose-re-
sp recovery over 2 h, whereas lyso-PAF has no significant
effect (160). The bronchoconstriction induced by PAF in
man is tachyphylactic, preventing cumulative dose-re-
sponse studies. Surprisingly, there is no relationship
be effect (160). The bronchoconstriction induced by PAF in
man is tachyphylactic, preventing cumulative dose-re-
sponse studies. Surprisingly, there is no relationship
between the airway responsiveness to PAF and that to a
ch man is tachyphylactic, preventing cumulative dose-re-
sponse studies. Surprisingly, there is no relationship
between the airway responsiveness to PAF and that to a
cholinergic agonist in normal subjects (160). This is in
c sponse studies. Surprisingly, there is no relationship
between the airway responsiveness to PAF and that to a
cholinergic agonist in normal subjects (160). This is in
contrast to all other bronchconstrictor stimuli, such cholinergic agonist in normal subjects (160). This is in contrast to all other bronchconstrictor stimuli, such as histamine, LTs, and PGs, in which there is a good correlation with the sensitivity to methacoline (89). Eve contrast to all other bronchconstrictor stimuli, such as
histamine, LTs, and PGs, in which there is a good
correlation with the sensitivity to methacoline (89). Even
in asthmatic patients showing hyperresponsiveness to
me histamine, LTs, and PGs, in which there is a good correlation with the sensitivity to methacoline (89). Even in asthmatic patients showing hyperresponsiveness to metacholine, the airway responsiveness to inhaled PAF is sim rrelation with the sensitivity to methacoline (89). Even
asthmatic patients showing hyperresponsiveness to
etacholine, the airway responsiveness to inhaled PAF
similar to that observed in normal subjects (134, 501a).
2. Ai

cholinergic agonist in normal subjects (160). This is in
contract to all other bronchonstrictor simuli, such as
histamine, LTs, and PGs, in which there is a good
correlation with the sensitivity to methacoline (89). Even
 in asthmatic patients showing hyperresponsiveness to
metacholine, the airway responsiveness to inhaled PAF
is similar to that observed in normal subjects (134, 501a).
2. Airway secretions. There are few reported studies
i metacholine, the airway responsiveness to inhaled PAF
is similar to that observed in normal subjects (134, 501a).
2. Airway secretions. There are few reported studies
investigating the effect of PAF on airway secretion. P is similar to that observed in normal subjects (134, 501a).
2. Airway secretions. There are few reported studies
investigating the effect of PAF on airway secretion. PAF
increases mucus secretion in the trachea of ferrets 2. At the secretions. There are lew reported statues
investigating the effect of PAF on airway secretion. PAF
increases mucus secretion in the trachea of ferrets both
in vitro and in vivo (337), and also weakly stimulates increases mucus secretion in the trachea of ferrets both
in vitro and in vivo (337), and also weakly stimulates
mucus glycoprotein from explants of human airways in
witro (247). PAF induces an increase in the protein
cont in vitro and in vivo (337), and also weakly stimulates
mucus glycoprotein from explants of human airways in
vitro (247). PAF induces an increase in the protein
content of airway secretions, although no alternation in
mucus mucus glycoprotein from explants of human airways
vitro (247). PAF induces an increase in the prot
content of airway secretions, although no alternation
mucus output (499, 463). It is likely that the increa
protein content vitro (247). PAF induces an increase in the protein
content of airway secretions, although no alternation in
mucus output (499, 463). It is likely that the increased
protein content is secondary to plasma protein extrava-
 effects on airway secretions, attiough no attenuation in
mucus output (499, 463). It is likely that the increased
protein content is secondary to plasma protein extrava-
sation into the airways, as PAF is known to have mar protem content is secondary to plasma protem extrave
sation into the airways, as PAF is known to have marke
effects on airway microvascular permeability (see below
Recent studies in isolated porcine trachea have demon
stra effects on airway microvascular permeability (see below).
Recent studies in isolated porcine trachea have demonstrated increased mucus secretion following PAF administration, which was unaffected by antagonists of hista-
m effects on airway microvascular permeability (see below).

Recent studies in isolated porcine trachea have demon-

strated increased mucus secretion following PAF admin-

istration, which was unaffected by antagonists of Recent studies in isolated porcine trachea have demon-
strated increased mucus secretion following PAF admin-
istration, which was unaffected by antagonists of hista-
mine, acetylcholine, and LTD, or by inhibitors of PG
a strated increased mucus secretion following PAr administration, which was unaffected by antagonists of histamine, acetylcholine, and LTD₄ or by inhibitors of PG and LT synthesis (550). Also, PAF has been observed to stim mine, acetylcholine, and LTD₄ or by inhibitors of PG
and LT synthesis (550). Also, PAF has been observed to
stimulate secretion of mucus in explants of rodent air-
ways in organ culture (8). PAF, administered intratra-
c and LT synthesis (550). Also, PAF has been observed to
stimulate secretion of mucus in explants of rodent air-
ways in organ culture (8). PAF, administered intratra-
cheally or intravenously, slows mucociliary transport,
w stimulate secretion of mucus in explants of rodent air-
ways in organ culture (8). PAF, administered intratra-
cheally or intravenously, slows mucociliary transport,
which may result from an effect on ciliated respiratory
 ways in organ culture
cheally or intraveno
which may result fro
epithelial cells, or fi
airway lumen (35).
3. Vascular effects. eally or intravenously, slows mucociliary transport,
hich may result from an effect on ciliated respiratory
ithelial cells, or from exudation of plasma into the
rway lumen (35).
3. *Vascular effects*. PAF induces microvasc

which may result from an effect on ciliated respiratory
epithelial cells, or from exudation of plasma into the
airway lumen (35).
3. *Vascular effects*. PAF induces microvascular leakage
in several tissues including skin (epithelial cells, or from exudation of plasma into the
airway lumen (35).
3. Vascular effects. PAF induces microvascular leakage
in several tissues including skin (453, 454, 289, 19–23)
and airways (191, 436) at doses over airway lumen (35).

3. Vascular effects. PAF induces microvascular leakage

in several tissues including skin (453, 454, 289, 19-23)

and airways (191, 436) at doses over 1000 times lower

than that of histamine. In man, 3. Vascular effects. PAF induces microvascular leakage
in several tissues including skin $(453, 454, 289, 19-23)$
and airways $(191, 436)$ at doses over 1000 times lower
than that of histamine. In man, the effect of PAF in several tissues including skin $(453, 454, 289, 19-23)$
and airways $(191, 436)$ at doses over 1000 times lower
than that of histamine. In man, the effect of PAF on
microvascular permeability has been studied in the and airways (191, 436) at doses over 1000 times lowe
than that of histamine. In man, the effect of PAF o
microvascular permeability has been studied in the skin
where PAF elicits a classical acute wheal and flare re
spons than that of histamine. In man, the effect of PAF on microvascular permeability has been studied in the skin, where PAF elicits a classical acute wheal and flare response (64, 23, 408, 133). The wheal response is unaffect microvascular permeability has been studied in the skin,
where PAF elicits a classical acute wheal and flare re-
sponse (64, 23, 408, 133). The wheal response is unaf-
fected by prior treatment with H_1 -antagonists (alt where PAF elicits a classical acute wheal and flare re-
sponse (64, 23, 408, 133). The wheal response is unaf-
fected by prior treatment with H_1 -antagonists (although
the flare response is) or cyclooxygenase inhibitors sponse (64, 23, 408, 133). The wheal response is unaf-
fected by prior treatment with H_1 -antagonists (although
the flare response is) or cyclooxygenase inhibitors, sug-
gesting that this effect is not secondary to libe fected by prior treatment with H_1 -antagonists (although
the flare response is) or cyclooxygenase inhibitors, sug-
gesting that this effect is not secondary to liberated
histamine or cyclooxygenase metabolites (20). Inc the flare response is) or cyclooxygenase inhibitors, suggesting that this effect is not secondary to liberated
histamine or cyclooxygenase metabolites (20). Increased
vascular permeability is partly dependent on local bloo histamine or cyclooxygenase metabolites (20). Increased
vascular permeability is partly dependent on local blood
flow, and the addition of local vasodilators, such as PGE_1
or PGE_2 , potentiates $\mathrm{PAF}\text{-induced}$ vasc histamine or cyclooxygenase metabolites (20). Increased
vascular permeability is partly dependent on local blood
flow, and the addition of local vasodilators, such as PGE_{1}
or PGE_{2} , potentiates $\mathrm{PAF}\text{-induced}$ va vascular permeability is partly dependent on local blood
flow, and the addition of local vasodilators, such as PGE_{1}
or PGE_{2} , potentiates $\mathrm{PAF}\text{-induced}$ vascular permeability
in the skin (19). It is less certain flow, and the addition of local
or PGE₂, potentiates PAF-ind
in the skin (19). It is less certa
is important in the bronchial
has a high basal blood flow.

PHARMACOLOGICAL REVIEWS

INFLAMMATORY MED
PAF-induced vascular permeability appears to be in-
pendent of platelet or neutrophil activation (414, 454, INFLAMMATORY MEDL

PAF-induced vascular permeability appears to be in-

dependent of platelet or neutrophil activation (414, 454,

470), despite the fact that PAF induces sequestration of INFLAMMATORY MEDIAT

PAF-induced vascular permeability appears to be in-

dependent of platelet or neutrophil activation (414, 454, of

470), despite the fact that PAF induces sequestration of subth platelets and neutrophi PAF-induced vascular permeability appears to be idependent of platelet or neutrophil activation (414, 45470), despite the fact that PAF induces sequestration both platelets and neutrophils in the cutaneous microsaculature PAF-induced vascular permeability appears to be in-
dependent of platelet or neutrophil activation (414, 454,
470), despite the fact that PAF induces sequestration of
both platelets and neutrophils in the cutaneous micro-
 dependent of platelet or neutrophil activation (414, 454, 470), despite the fact that PAF induces sequestration of both platelets and neutrophils in the cutaneous microvasculature (174). Since endothelial cells have PAF re 470), despite the fact that PAF induces sequestration of both platelets and neutrophils in the cutaneous micro-
vasculature (174). Since endothelial cells have PAF re-
ceptors (108), it is quite likely that PAF has a direc both platelets and neutrophils in the cutaneous micro
vasculature (174). Since endothelial cells have PAF re
ceptors (108), it is quite likely that PAF has a direc
contractile effect on endothelial cells. PAF-induced vas
c vasculature (174). Since endothelial cells have PAF receptors (108), it is quite likely that PAF has a direct contractile effect on endothelial cells. PAF-induced vascular permeability can be inhibited in both experimental ceptors (108), it is quite likely that PAF has a direct contractile effect on endothelial cells. PAF-induced vas-
cular permeability can be inhibited in both experimental
animals and man by PAF antagonists, suggesting that contractile effect on endothelial cells. PAF-induced v.
cular permeability can be inhibited in both experimen
animals and man by PAF antagonists, suggesting th
PAF is acting via specific PAF receptors (133, 273, 19
PAF has cular permeability can be inhibited in both experimental continuals and man by PAF antagonists, suggesting that in PAF is acting via specific PAF receptors (133, 273, 192). m
PAF has potent effects on airway microvascular animals and man by PAF antagonists, suggesting that in
PAF is acting via specific PAF receptors (133, 273, 192). m
PAF has potent effects on airway microvascular perme-
ability; as little as 1 ng/kg administered i.v. to gu PAF is acting via specific PAF receptors (133, 273, 192).
PAF has potent effects on airway microvascular perme-
ability; as little as 1 ng/kg administered i.v. to guinea
pigs induces a rapid extravasation of Evans blue dye PAF has potent effects on airway microvascular perme-
ability; as little as 1 ng/kg administered i.v. to guinea
pigs induces a rapid extravasation of Evans blue dye (as
a marker of plasma-albumin) in central and peripheral ability; as little as 1 ng/kg administered i.v. to guinea
pigs induces a rapid extravasation of Evans blue dye (as
a marker of plasma-albumin) in central and peripheral
airways (191, 436). As in the skin, this is a direct pigs induces a rapid extravasation of Evans blue dye (as
a marker of plasma-albumin) in central and peripheral
airways (191, 436). As in the skin, this is a direct effect
of PAF, since it is not reduced by platelet depleti a marker of plasma-albumin) in central and peripheral
airways (191, 436). As in the skin, this is a direct effect
of PAF, since it is not reduced by platelet depletion,
cyclooxygenase inhibition, or antagonists of histamin airways (191, 436). As in the skin, this is a direct effect
of PAF, since it is not reduced by platelet depletion,
cyclooxygenase inhibition, or antagonists of histamine
or leukotrienes (191), but is inhibited by PAF antag of PAF, since it is not reduced by platelet depletion cyclooxygenase inhibition, or antagonists of histaminor leukotrienes (191), but is inhibited by PAF antagonist. (191, 192). PAF induces delayed leakage of plasma pro te cyclooxygenase innotion, or antagonists of installine
or leukotrienes (191), but is inhibited by PAF antagonists
(191, 192). PAF induces delayed leakage of plasma pro-
teins into the airways, which may be inhibited by anti (462). 194, 192). FAF induces delayed leakage of plasma pro-
teins into the airways, which may be inhibited by anti-
asthma drugs such as cromolyn sodium and theophylline
(462).
4. Inflammatory cell activation. PAF activates a wi

asthma drugs such as cromolyn sodium and theophyll

(462).

4. Inflammatory cell activation. PAF activates a w

range of inflammatory cells, both in vitro and in vivo.

vitro, PAF induces aggregation of platelets (74), neu (462).
4. Inflammatory cell activation. PAF activates a wide
range of inflammatory cells, both in vitro and in vivo. In
vitro, PAF induces aggregation of platelets (74), neutro-
phils (210, 439), and monocytes (614), with 4. Inflammatory cell activation. PAF activates a wide
range of inflammatory cells, both in vitro and in vivo. In
witro, PAF induces aggregation of platelets (74) , neutro-
chils $(210, 439)$, and monocytes (614) , with range of inflammatory cells, both in vitro and in vivo. In vitro, PAF induces aggregation of platelets (74), neutro-
phils (210, 439), and monocytes (614), with subsequent release of secondary inflammatory mediators, inclu vitro, PAF induces aggregation of platelets (74), neutro-
chils (210, 439), and monocytes (614), with subsequent has
release of secondary inflammatory mediators, including tai
lipoxygenase and cyclooxygenase products, oxyg phils (210, 439), and monocytes (614), with subsequent
release of secondary inflammatory mediators, including
lipoxygenase and cyclooxygenase products, oxygen radi-
cals, and lysosomal enzymes. PAF also induces the
chemota lipoxygenase and cyclooxygenase products, oxygen radi-

cals, and lysosomal enzymes. PAF also induces the yet to be fully elucidated, but platelet depletion inhibits

chemotaxis of neutrophils (439, 597) and eosinophils b lipoxygenase and cyclooxygenase products, oxygen radi-
cals, and lysosomal enzymes. PAF also induces the yet
chemotaxis of neutrophils (439, 597) and eosinophils botl
(344, 531, 564, 597). The response of eosinophils to PA cals, and lysosomal enzymes. PAF also induces the
chemotaxis of neutrophils (439, 597) and eosinophils
(344, 531, 564, 597). The response of eosinophils to PAF
is of particular interest in the context of asthma, as PAF
rep chemotaxis of neutrophils (439, 597) and eosinophils (344, 531, 564, 597). The response of eosinophils to PAF is of particular interest in the context of asthma, as PAF represents the most potent chemotactic stimuli for hu (344, 531, 564, 597). The response of eosinophils to PAF the lis of particular interest in the context of asthma, as PAF brond represents the most potent chemotactic stimuli for huplate man eosinophils so far described (3 is of particular interest in the context of asthma, as PAF
represents the most potent chemotactic stimuli for hu-
man eosinophils so far described (344, 531, 564, 597).
Other eosinophil chemotactic stimuli, such as ECF-A
a represents the most potent chemotactic stimuli for human eosinophils so far described (344, 531, 564, 597). such the release of PAF may act via the release of PAF, suggesting that PAF may (40 play a central role in the che man eosinophils so far described (344, 531, 564, 597
Other eosinophil chemotactic stimuli, such as ECF-
and formyl-methionyl-leucyl-phenylalanine (FMLF
may act via the release of PAF, suggesting that PAF ma
play a central Other eosinophil chemotactic stimuli, such as ECF-A cand formyl-methionyl-leucyl-phenylalanine (FMLP), comay act via the release of PAF, suggesting that PAF may (play a central role in the chemotactic response of eosinophi and formyl-methionyl-leucyl-phenylalanine (FMLP),
may act via the release of PAF, suggesting that PAF may
play a central role in the chemotactic response of eosin-
ophils (344, 531). In addition, PAF induces the formation
 may act via the release of PAF, suggesting that PAF may (4
play a central role in the chemotactic response of eosin-
ophils (344, 531). In addition, PAF induces the formation im
of LTC₄ from eosinophils (103), and PAF an play a central role in the chemotactic response of eosin-
ophils (344, 531). In addition, PAF induces the formation import LTC₄ from eosinophils (103), and PAF antagonists not
inhibit IgE-dependent activation and releas ophils (344, 531). In addition, PAF induces the formation
of LTC₄ from eosinophils (103), and PAF antagonists
inhibit IgE-dependent activation and release of oxygen
radicals from eosinophils, suggesting that PAF may be
i of LTC₄ from eosinophils (103), and PAF antagonists nonselusibility LgE-dependent activation and release of oxygen per-respradicals from eosinophils, suggesting that PAF may be man. Finvolved in allergic stimulation of miniont ige-dependent activation and release of oxygen per-
radicals from eosinophils, suggesting that PAF may be man
involved in allergic stimulation of this cell type (112). resp
PAF causes much greater activation of eos involved in allergic stimulation of this cell type (112) . res

PAF causes much greater activation of eosinophils from dogethmatic patients than from other atopic patients (124) , 501

and human eosinophils have a high PAF causes much greater activation of eosinophils from
asthmatic patients than from other atopic patients (124),
and human eosinophils have a high density of PAF
receptors (580). PAF also activates macrophages, with
releas thmatic patients than from other atopic patients (124),
d human eosinophils have a high density of PAF
ceptors (580). PAF also activates macrophages, with
lease of oxygen radicals (269).
In vivo, PAF results in the recruit and human eosinophils have a high density of PAF creeptors (580). PAF also activates macrophages, with speeds of oxygen radicals (269).
In vivo, PAF results in the recruitment of various (inflammatory cells into tissues fo

receptors (580). PAF also activates macrophages, with
release of oxygen radicals (269).
In vivo, PAF results in the recruitment of various
inflammatory cells into tissues following either systemic
or local administration. release of oxygen radicals (269).
In vivo, PAF results in the recruitment of various
inflammatory cells into tissues following either systemic
or local administration. After intradermal administration
of PAF in normal volu In vivo, PAF results in the recruitment of various
inflammatory cells into tissues following either systemic
or local adminstration. After intradermal administration
of PAF in normal volunteers, there is a substantial
infl or local administration. After intradermal administration
of PAF in normal volunteers, there is a substantial
inflammatory cell infiltrate characterized at 4 h by neu-
trophils, and at 24 h by a mixed cellular infiltrate or local adminstration. After intradermal administration
of PAF in normal volunteers, there is a substantial
inflammatory cell infiltrate characterized at 4 h by neu-
trophils, and at 24 h by a mixed cellular infiltrate co of PAF in normal volunteers, there is a substantial neinflammatory cell infiltrate characterized at 4 h by neutrophils, and at 24 h by a mixed cellular infiltrate comprising both neutrophils and mononuclear cells $(22$

CHATORS AND ASTHMA
Characterized by activated eosinophils and is reminiscent
of antigen-induced eosinophil infiltration in the same TORS AND ASTHMA

characterized by activated eosinophils and is reminiscent

of antigen-induced eosinophil infiltration in the same

subjects (275). This suggests that allergic subjects resubjects (275). This suggests that allergic subjects (275). This suggests that allergic subjects re-
spond differently to PAF in comparison with healthy characterized by activated eosinophils and is reminiscent
of antigen-induced eosinophil infiltration in the same
subjects (275). This suggests that allergic subjects re-
spond differently to PAF in comparison with healthy
 characterized by activated eosinophils and is reminiscent
of antigen-induced eosinophil infiltration in the same
subjects (275). This suggests that allergic subjects re-
spond differently to PAF in comparison with healthy
 subjects (275). This suggests that allergic subjects re-
spond differently to PAF in comparison with healthy
individuals. Since the rate-limiting acetyltransferase en-
zyme involved in PAF production is switched on in
eosi subjects (275). This suggests that allergic subjects re-
spond differently to PAF in comparison with healthy
individuals. Since the rate-limiting acetyltransferase en-
zyme involved in PAF production is switched on in
eosi spond differently to PAF in comparison with healthy
individuals. Since the rate-limiting acetyltransferase en-
zyme involved in PAF production is switched on in
eosinophils obtained from individuals with eosinophilia
compa individuals. Since the rate-limiting acetyltransferase en-
zyme involved in PAF production is switched on in
eosinophils obtained from individuals with eosinophilia
compared with healthy subjects (344), these observations
 zyme involved in PAF production is switched on in
eosinophils obtained from individuals with eosinophilia
compared with healthy subjects (344), these observations
indicate that PAF should be considered as a primary
mediato eosinophils obtained from individuals with eosinophilia
compared with healthy subjects (344), these observations
indicate that PAF should be considered as a primary
mediator involved in the induction and maintenance of
the indicate that PAF should be considered as a primary mediator involved in the induction and maintenance of the eosinophilic infilitration observed in allergic patients. Thus, PAF antagonists inhibit antigen-induced eosino-
 ediator involved in the induction and maintenance of
e eosinophilic infilitration observed in allergic patients.
nus, PAF antagonists inhibit antigen-induced eosino-
il infilitration in sensitized animals (149, 148, 356).
 the eosinophilic infilitration observed in allergic patients.
Thus, PAF antagonists inhibit antigen-induced eosino-
phil infilitration in sensitized animals (149, 148, 356).
Preliminary studies indicate that inhalation of

Preliminary studies indicate that inhalation of PAF Thus, PAF antagonists inhibit antigen-induced eosino-
phil infilitration in sensitized animals (149, 148, 356).
Preliminary studies indicate that inhalation of PAF
by normal volunteers results in an increased recovery of
n phil infilitration in sensitized animals (149, 148, 356).
Preliminary studies indicate that inhalation of PAF
by normal volunteers results in an increased recovery of
neutrophils in bronchoalveolar lavage fluid at 6 hr ac-Preliminary studies indicate that inhalation of PAF
by normal volunteers results in an increased recovery of
neutrophils in bronchoalveolar lavage fluid at 6 hr ac-
companied by activation of neutrophils in the circulatio sy normal volumeers results in an increased recovery of
neutrophils in bronchoalveolar lavage fluid at 6 hr ac-
companied by activation of neutrophils in the circulation
(596). In animals, PAF, administered both locally an mpanied by activation of neutrophils in the circulation
96). In animals, PAF, administered both locally and
stemically, induces an eosinophilic-rich infiltrate in
elungs (25, 148, 149).
PAF also induces an extravascular re

(396). In animals, PAF, administered both locally and
systemically, induces an eosinophilic-rich infiltrate in
the lungs (25, 148, 149).
PAF also induces an extravascular recruitment of
platelets into pulmonary tissue, whe the lungs (25, 148, 149).

PAF also induces an extravascular recruitment of

platelets into pulmonary tissue, where they are observed

to be in close apposition to both airway smooth muscle

and infiltrating eosinophils (3 FAF also middes an extravascular recruitment of
platelets into pulmonary tissue, where they are observed
to be in close apposition to both airway smooth muscle
and infiltrating eosinophils (355). Such pathological
changes to be in close apposition to both airway smooth muscle
and infiltrating eosinophils (355). Such pathological
changes have also been reported in allergic animals and
have been identified in bronchoalveolar lavage fluid ob-
 and infiltrating eosinophils (355). Such pathological
changes have also been reported in allergic animals and
have been identified in bronchoalveolar lavage fluid ob-
tained from allergic asthmatics (407). The contribution have been identified in bronchoalveolar lavage fluid obtained from allergic asthmatics (407). The contribution have been identified in bronchoalveolar lavage fluid obtained from allergic asthmatics (407). The contribution of extravascular platelets to the pathology of asthma has get to be fully elucidated, but platelet depletion i tained from allergic asthmatics (407). The contribution
of extravascular platelets to the pathology of asthma has
yet to be fully elucidated, but platelet depletion inhibits
both PAF and antigen-induced eosinophil infilitr of extravascular platelets to the pathology of asthma has
yet to be fully elucidated, but platelet depletion inhibits
both PAF and antigen-induced eosinophil infilitration in
the lungs of animals (356) and reduces PAF-indu both PAF and antigen-induced eosinophil infilitration in
the lungs of animals (356) and reduces PAF-induced
bronchial hyperreactivity in the guinea pig (400). As
platelets are a good source of smooth muscle mutogens,
such the lungs of animals (356) and reduces PAF-induced
bronchial hyperreactivity in the guinea pig (400). As
platelets are a good source of smooth muscle mutogens,
such as platelet-derived growth factor (500), they may
contrib bronchial hyperreactivity in the guinea pig (400). As
platelets are a good source of smooth muscle mutogens,
such as platelet-derived growth factor (500), they may
contribute to the hyperplasia of bronchial smooth muscle
 platelets are a good source of smooth muscle mutdsuch as platelet-derived growth factor (500), they contribute to the hyperplasia of bronchial smooth m
observed both in animals chronically treated with
(405) and in asthmat ch as platelet-derived growth factor (500), they may
ntribute to the hyperplasia of bronchial smooth muscle
served both in animals chronically treated with PAF
05) and in asthmatic patients at autopsy (271).
5. *Bronchial*

contribute to the hyperplasia of bronchial smooth muscle

observed both in animals chronically treated with PAF

(405) and in asthmatic patients at autopsy (271).

5. Bronchial hyper-responsiveness. One of the most

impor observed both in animals chronically treated with PA
(405) and in asthmatic patients at autopsy (271).
5. Bronchial hyper-responsiveness. One of the mos-
important properties of PAF is its ability to induce
nonselective an (405) and in asthmatic patients at autopsy (271).

5. Bronchial hyper-responsiveness. One of the most

important properties of PAF is its ability to induce a

nonselective and long-lasting increase in bronchial hy-

per-r important properties of PAF is its ability to induce a
nonselective and long-lasting increase in bronchial hy-
per-responsiveness in both experimental animals and
man. PAF has been shown to elicit increased bronchial
respo nonselective and long-lasting increase in bronchial hyper-responsiveness in both experimental animals and man. PAF has been shown to elicit increased bronchial responsiveness in guinea pigs (400, 58, 494, 495, 205), dogs (per-responsiveness in both experimental animals and
man. PAF has been shown to elicit increased bronchial
responsiveness in guinea pigs (400, 58, 494, 495, 205),
dogs (131), sheep (128), and normal human subjects (160,
501 man. PAF has been shown to elicit increased bronchial
responsiveness in guinea pigs (400, 58, 494, 495, 205),
dogs (131), sheep (128), and normal human subjects (160,
501a). In guinea pigs, the increased responsiveness is
 responsiveness in guinea pigs (400, 58, 494, 495, 205), dogs (131), sheep (128), and normal human subjects (160, 501a). In guinea pigs, the increased responsiveness is dependent upon the presence of circulating platelets, dogs (131), sheep (128), and normal human subjects (16
501a). In guinea pigs, the increased responsiveness
dependent upon the presence of circulating platele
since platelet depletion with a specific cytotoxic antibo
abroga (400), 501a). In guinea pigs, the increased responsiveness is
dependent upon the presence of circulating platelets,
since platelet depletion with a specific cytotoxic antibody
abrogates PAF-induced bronchial hyper-responsi nce platelet depletion with a specific cytotoxic antibulary responsive may be matched bronchial hyper-responsive 00), whereas selective depletion of neutrophils is we teffect (413).
In man, the maximal increase in bronchia

abrogates PAF-induced bronchial hyper-responsivenes (400), whereas selective depletion of neutrophils is with out effect (413).
In man, the maximal increase in bronchial responsiveness to methacholine occurs 3 days after a (400), whereas selective depletion of neutrophils is with-
out effect (413).
In man, the maximal increase in bronchial responsiv-
ness to methacholine occurs 3 days after a single expo-
sure to PAF and may persist in some out effect (413).
In man, the maximal increase in bronchial responsiv-
ness to methacholine occurs 3 days after a single expo-
sure to PAF and may persist in some individuals for up
to 4 wk. Because PAF is rapidly inactiva In man, the maximal increase in bronchial responsiveness to methacholine occurs 3 days after a single exposure to PAF and may persist in some individuals for up to 4 wk. Because PAF is rapidly inactivated in the airways, s

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PHARMACOLOGICAL REVIEWS

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gation. Although PAF elicits airway hyper-responsivne
to a wide range of spasmogens, including histamin EXTRES, CHE
gation. Although PAF elicits airway hyper-responsivness
to a wide range of spasmogens, including histamine,
acetylcholine, serotonin, and substance P, the increased BARNES, CHUNG
gation. Although PAF elicits airway hyper-responsivness
to a wide range of spasmogens, including histamine,
acetylcholine, serotonin, and substance P, the increased a
responsiveness is not secondary to altera gation. Although PAF elicits airway hyper-responsivness
to a wide range of spasmogens, including histamine,
acetylcholine, serotonin, and substance P, the increased
responsiveness is not secondary to alterations in recepto gation. Although PAF elicits airway hyper-responsivne
to a wide range of spasmogens, including histamin
acetylcholine, serotonin, and substance P, the increas
responsiveness is not secondary to alterations in recept
number to a wide range of spasmogens, including histamine, use
acetylcholine, serotonin, and substance P, the increased aver
responsiveness is not secondary to alterations in receptor
anisms (at least for acetylcholine and histam acetylcholine, serotonin, and substance P, the increased avaint responsiveness is not secondary to alterations in receptor antinumber, affinities, or post-receptor transduction mechanisms (at least for acetylcholine and hi responsiveness is not secondary to alterations in receptor
number, affinities, or post-receptor transduction mech-
anisms (at least for acetylcholine and histamine in the
guinea pig) (495). PAF has, however, been observed anisms (at least for acetylcholine and histamine in the (597) , bronchoconstriction (173, 526), bronchial hyperguinea pig) (495). PAF has, however, been observed to responsiveness (149, 279), and airway edema (191, 192). anisms (at least for acetylcholine and histamine in t
guinea pig) (495). PAF has, however, been observed
elicit a down-regulation of beta-adrenoceptors in 1
brain (92) and human lung in vitro (9), a phenomena
which may con guinea pig) (495). PAF has, however, been observed to
elicit a down-regulation of beta-adrenoceptors in rat
brain (92) and human lung in vitro (9), a phenomenon
which may contribute to bronchial hyper-responsiveness
and wh elicit a down-regulation of beta-adrenoceptors in rat P
brain (92) and human lung in vitro (9), a phenomenon re
which may contribute to bronchial hyper-responsiveness go
and which is a feature of astmatic airways in vitro. brain (92) and human lung in vitro (9), a phenome
which may contribute to bronchial hyper-responsive
and which is a feature of astmatic airways in v
However, in guinea pigs made hyper-responsive follow
treatment with i.v. which may contribute to bronchial hyper-responsiveness goland which is a feature of astmatic airways in vitro. inclose the induced the induced streament with i.v. PAF, there is a reduced bronchodiant lator response to isop and which is a feature of astmatic airways in vi
However, in guinea pigs made hyper-responsive follow
treatment with i.v. PAF, there is a reduced bronch
lator response to isoproterenol in vivo, but the in v
responsiveness However, in guinea pigs made hyper-responsive following (9
treatment with i.v. PAF, there is a reduced bronchodi-
lator response to isoproterenol in vivo, but the in vitro
geographic responsiveness of tracheal smooth muscl treatment with i.v. PAF, there is a reduced bronch
lator response to isoproterenol in vivo, but the in v
responsiveness of tracheal smooth muscle to isopro
enol and tracheal and lung beta-receptor density ren
unchanged (58 lator response to isoproterenol in vivo, but the in vitro
responsiveness of tracheal smooth muscle to isoproter-
enol and tracheal and lung beta-receptor density remain obst
unchanged (58). This suggests the impaired bronc responsiveness of tracheal smooth muscle to isoproter-
enol and tracheal and lung beta-receptor density remain obtunchanged (58). This suggests the impaired bronchodi-
lator response to a beta-agonist in vivo is not due to enol and tracheal and lung beta-receptor density remain unchanged (58). This suggests the impaired bronchodilator response to a beta-agonist in vivo is not due to impaired beta-adrenoceptor function and is more likely to b unchanged (58).
lator response t
impaired beta-agonis
by a beta-agonis
PAF-induced or response to a beta-agonist in vivo is not due to PA
paired beta-adrenoceptor function and is more likely me
be due to airway edema, which would not be reversible gui
a beta-agonist.
PAF-induced bronchial hyper-responsiv

impaired beta-adrenoceptor function and is more likely meto be due to airway edema, which would not be reversible guy a beta-agonist.

PAF-induced bronchial hyper-responsiveness may be infinite a consequence of eosinophil to be due to airway edema, which would not be reversible gut by a beta-agonist.

PAF-induced bronchial hyper-responsiveness may be infancement of eosinophil infiltration (fig. 4), and the take degree of blood eosinophilia by a beta-agonist.

PAF-induced bronchial hyper-responsiveness may be

a consequence of eosinophil infiltration (fig. 4), and the

degree of blood eosinophilia is closely related to the

degree of bronchial hyper-responsiv FAF-induced bronchial hyper-responsiveness may be into
a consequence of eosinophili infiltration (fig. 4), and the tab
degree of blood eosinophilia is closely related to the nisi
degree of bronchial hyper-responsiveness (2 degree of blood eosinophilia is closely related to the negree of bronchial hyper-responsiveness (216, 567). Eosinophils release cytotoxic materials, such as major basic a protein (MBP), eosinophil cationic protein (ECP), a degree of bronchial hyper-responsiveness (216, 567). Eo-
sinophils release cytotoxic materials, such as major basic ate
protein (MBP), eosinophil cationic protein (ECP), and with
eosinophil peroxidase (EPO) which may lead sinophils release cytotoxic materials, such as major basic ate
protein (MBP), eosinophil cationic protein (ECP), and wit
eosinophil peroxidase (EPO) which may lead to damage obs
of airway epithelium (216). Epithelial disru protein (MBP), eosinophil cationic protein (ECP), and with eosinophil peroxidase (EPO) which may lead to damage obsof airway epithelium (216). Epithelial disruption is a PAI common feature of asthma, and loss of epithelium eosinophil peroxidase (EPO) which may lead to damage
of airway epithelium (216). Epithelial disruption is a
common feature of asthma, and loss of epithelium may
contribute to airway hyper-responsiveness by loss of an
epith of airway epithelium (216). Epithelial disruption is a P
common feature of asthma, and loss of epithelium may in
contribute to airway hyper-responsiveness by loss of an sl
epithelial-derived relaxant factor (206, 55, 159), common feature of asthma, and loss of epithelium may
contribute to airway hyper-responsiveness by loss of an
epithelial-derived relaxant factor (206, 55, 159), by ex-
posure of sensory nevre endings (43), or by the loss of contribute to airway hyper-responsiveness by loss of a
epithelial-derived relaxant factor (206, 55, 159), by en
posure of sensory nerve endings (43), or by the loss of
enzymes which metabolize sensory neuropeptides (219
Lo epithelial-derived relaxant factor (206, 55, 159), by ex-
posure of sensory nerve endings (43), or by the loss of
enzymes which metabolize sensory neuropeptides (219).
Loss of epithelium could also explain the impaired bro posure of sensory nerve endings (43), or by the loss contains enzymes which metabolize sensory neuropeptides (219)
Loss of epithelium could also explain the impaired bronchodilator response to beta-agonists in vivo followi enzymes which metabolize sensory heuropeptues (215) .
Loss of epithelium could also explain the impaired bron-
chodilator response to beta-agonists in vivo following
administration of PAF in the guinea pig, since beta-
a Loss of epithelium could also explain the impaired bron
chodilator response to beta-agonists in vivo followin
administration of PAF in the guinea pig, since beta
agonists have a reduced effect on airway smooth muscl
prepar **Exaministration** of 11
agonists have a reduce
D. Role in Asthma
1. Rolesse of *DAE* is

in asthma remains unknown, although PAF may repro-
duce many features of asthma. The detection of PAF in D. Role in Asthma

1. Release of PAF in asthma. The precise role of PAF

in asthma remains unknown, although PAF may repro-

duce many features of asthma. The detection of PAF in

biological fluids has been hampered by the Branch Fig. 3. How write

in asthma remains unknown, although PAF may repro-

in asthma remains unknown, although PAF may repro-

induce many features of asthma. The detection of PAF in

biological fluids has been hampere 1. Release of PAF in asthma. The precise role of PAF mat
in asthma remains unknown, although PAF may repro-
duce many features of asthma. The detection of PAF in
biological fluids has been hampered by the lack of a
prop
s in asthma remains unknown, although PAF may repro-
duce many features of asthma. The detection of PAF in
biological fluids has been hampered by the lack of a
pimple assay system. Most attempts to measure PAF in
biological duce many features of asthma. The detection of PAF in habiological fluids has been hampered by the lack of a presimple assay system. Most attempts to measure PAF in biological fluids have relied upon the bioassay developed biological fluids has been hampered by the lack of a
simple assay system. Most attempts to measure PAF in
biological fluids have relied upon the bioassay developed
by Henson and Pinckard (276), which is based upon the
fact simple assay system. Most attempts to measure PAF in
biological fluids have relied upon the bioassay developed A .
by Henson and Pinckard (276), which is based upon the
fact that PAF is able to selectively desensitize pl biological fluids have relied upon the bioassay developed A .
by Henson and Pinckard (276), which is based upon the
fact that PAF is able to selectively desensitize platelets nin
to itself in vitro. A number of investiga by Henson and Pinckard (276), which is based upon fact that PAF is able to selectively desensitize plate
to itself in vitro. A number of investigators have u
their technique to show that a PAF-like material
released into t to itself in vitro. A number of investigators have used genases) which are produced by the liver (plasma kalli-
their technique to show that a PAF-like material is krein) and by other tissues (tissue kallikrein). In addi-
 to itself in vitro. A number of investigators have use
their technique to show that a PAF-like material is
released into the circulation concomitantly with antigen
induced bronchoconstriction (570, 70). PAF has als
been de their technique to show that a PAF-like material is kreendesed into the circulation concomitantly with antigen-
induced bronchoconstriction (570, 70). PAF has also kince detected in bronchoalveolar lavage fluid of asth-
ma released into the circulation concomitantly with antigen-
induced bronchoconstriction (570, 70). PAF has also
been detected in bronchoalveolar lavage fluid of asth-
matics using this bioassay technique (146) and in blooc
o induced bronchoconstri
been detected in bronc
matics using this bioass
of allergic asthmatics us
onset responses (423).

EXARNES, CHUNG, AND PAGE
 2. PAF antagonists. A more feasible approach is the
 2. PAF antagonists. Several of which are now G, AND PAGE
2. PAF antagonists. A more feasible approach is the
use of specific PAF antagonists, several of which are now
available and some are undergoing clinical trials. PAF G, AND PAGE
2. PAF antagonists. A more feasible approach is the
use of specific PAF antagonists, several of which are now
available and some are undergoing clinical trials. PAF
antagonists inhibit several of the effects of 2. PAF antagonists. A more feasible approach is the use of specific PAF antagonists, several of which are now available and some are undergoing clinical trials. PAF antagonists inhibit several of the effects of PAF which a 2. PAF antagonists. A more feasible approach is the use of specific PAF antagonists, several of which are now available and some are undergoing clinical trials. PAF antagonists inhibit several of the effects of PAF which a use of specific PAF antagonists, several of which are no
available and some are undergoing clinical trials. P_/
antagonists inhibit several of the effects of PAF whi
are relevant to asthma, including eosinophil activati
(available and some are undergoing clinical trials. PAF
antagonists inhibit several of the effects of PAF which
are relevant to asthma, including eosinophil activation
(597), bronchoconstriction (173, 526), bronchial hyperantagonists inhibit several of the effects of PAF which
are relevant to asthma, including eosinophil activation
(597), bronchoconstriction (173, 526), bronchial hyper-
responsiveness (149, 279), and airway edema (191, 192) are relevant to asthma, including eosinophil activatio
(597), bronchoconstriction (173, 526), bronchial hype
responsiveness (149, 279), and airway edema (191, 192
PAF-antagonists also inhibit certain aspects of allerg
resp (597), bronchoconstriction $(173, 526)$, bronchial hyp
responsiveness $(149, 279)$, and airway edema $(191, 19)$
PAF-antagonists also inhibit certain aspects of aller
responses in both experimental animals and man. Gi
gol responsiveness (149, 279), and airway edema (191, 192).
PAF-antagonists also inhibit certain aspects of allergic
responses in both experimental animals and man. Gink-
golida B (BN 52021) and WEB 2086 inhibit allergen-
indu PAF-antagonists also inhibit certain aspects of allergic
responses in both experimental animals and man. Gink-
golida B (BN 52021) and WEB 2086 inhibit allergen-
induced bronchoconstriction in sensitized guinea pigs
(93, 1 responses in both experimental animals and man. Gink
golida B (BN 52021) and WEB 2086 inhibit allergen
induced bronchoconstriction in sensitized guinea pig
(93, 117), and BN 52021 reduces the eosinophil activatio
and bronc golida B (BN 52021) and WEB 2086 inhibit allenduced bronchoconstriction in sensitized guinea (93, 117), and BN 52021 reduces the eosinophil active and bronchial hyper-responsiveness resulting from a gen-challenge (149, 356 induced bronchoconstriction in sensitized guinea pigs (93, 117), and BN 52021 reduces the eosinophil activation and bronchial hyper-responsiveness resulting from allergen challenge (149, 356). Furthermore, in ragweed-sensi (93, 117), and BN 52021 reduces the eosinophil active and bronchial hyper-responsiveness resulting from gen challenge $(149, 356)$. Furthermore, in ragweed sitized rabbits, BN 52021 inhibits late-onset air obstruction and and bronchial hyper-responsiveness resulting from allergen challenge (149, 356). Furthermore, in ragweed-sensitized rabbits, BN 52021 inhibits late-onset airways obstruction and the increased bronchial hyper-responsiveness gen challenge (149, 356). Furthermore, in ragweed-sen
sitized rabbits, BN 52021 inhibits late-onset airway
obstruction and the increased bronchial hyper-respon
siveness following allergen challenge (148). However
PAF antag sitized rabbits, BN 52021 inhibits late-onset airways
obstruction and the increased bronchial hyper-respon-
siveness following allergen challenge (148). However,
PAF antagonists do not inhibit propranolol- or indo-
methac obstruction and the
siveness following
PAF antagonists d
methacin-induced
guinea pigs (179).
Clinical studies w veness following allergen challenge (148). However,
AF antagonists do not inhibit propranolol- or indo-
ethacin-induced bronchial hyperresponsiveness in
inea pigs (179).
Clinical studies with PAF antagonists are still in t

PAF antagonists do not inhibit propranolol- or indo-
methacin-induced bronchial hyperresponsiveness in
guinea pigs (179).
Clinical studies with PAF antagonists are still in their
infancy (132), but the ginkoglide mixture, methacin-induced bronchial hyperresponsiveness
guinea pigs (179).
Clinical studies with PAF antagonists are still in th
infancy (132), but the ginkoglide mixture, BN 52063 (
table 1), appears to function as a selective PAF guinea pigs (179).
Clinical studies with PAF antagonists are still in their
infancy (132), but the ginkoglide mixture, BN 52063 (see
table 1), appears to function as a selective PAF antago-
nist in man (133) and inhibits t Clinical studies with PAF antagonists are still in th
infancy (132), but the ginkoglide mixture, BN 52063 (s
table 1), appears to function as a selective PAF antag
nist in man (133) and inhibits the late-phase cutanec
resp table 1), appears to function as a selective PAF antagonist in man (133) and inhibits the late-phase cutaneous response to allergen in atopic subjects, which is associated with eosinophil infiltration and has some similari with the pathology of the late-onset airways obstruction nist in man (133) and inhibits the late-phase cutaneous
response to allergen in atopic subjects, which is associ-
ated with eosinophil infiltration and has some similarity
with the pathology of the late-onset airways obstr response to allergen in atopic subjects, which is associated with eosinophil infiltration and has some similarity with the pathology of the late-onset airways obstruction observed in allergic subjects (493). This suggests ated with eosinophil infiltration and has some similarity
with the pathology of the late-onset airways obstruction
observed in allergic subjects (493). This suggests that
PAF may be involved in the late-onset allergic resp with the pathology of the late-onset airways obstruction
observed in allergic subjects (493). This suggests that
PAF may be involved in the late-onset allergic response
in man. BN 52063, when taken orally, has recently bee observed in allergic subjects (493). This suggests th PAF may be involved in the late-onset allergic respon
in man. BN 52063, when taken orally, has recently bee
shown to be only a modest antagonist of PAF-induce
bronchoco PAF may be involved in the late-onset allergic response
in man. BN 52063, when taken orally, has recently beer
shown to be only a modest antagonist of PAF-induce
bronchoconstriction in human airways (492), and there
fore m in man. BN 52063, when taken orally, has recently been
shown to be only a modest antagonist of PAF-induced
bronchoconstriction in human airways (492), and there-
fore more potent antagonists may be necessary to eval-
uate shown to be only a modest antagonishonchoconstriction in human airway
fore more potent antagonists may be
uate airway disease. Clinical trials of E
are currently under way (255, 132). In Haman an Wagonists may be
gonists may be
ay (255, 132).
VI. Kinins
ted kinins are i

1. *Role in Asthma*
1. *Release of PAF in asthma*. The precise role of PAF may reproduce the servent vasoactive peptides in asthma.
1. *Release of PAF in asthma*. The precise role of PAF matic treatment of blood (497), and te airway disease. Clinical trials of BN 52063 in asthma

e currently under way (255, 132).
 VI. Kinins

Bradykinin and related kinins are formed from plasma

ecursors as part of the inflammatory response, yet are currently under way (255, 132).

VI. Kinins

Bradykinin and related kinins are formed from plasma

precursors as part of the inflammatory response, yet

there is relatively little information about the involve-VI. Kinins
Bradykinin and related kinins are formed from plass
precursors as part of the inflammatory response,
there is relatively little information about the involve-
ment of these potent vasoactive peptides in asthr V1. **AIRINS**
Bradykinin and related kinins are formed from plasma
precursors as part of the inflammatory response, yet
there is relatively little information about the involve-
ment of these potent vasoactive peptides in a Bradykinin and related kinins are formed from plasm
precursors as part of the inflammatory response, yethere is relatively little information about the involve
ment of these potent vasoactive peptides in asthma
Bradykinin precursors as part of the inflammatory response, yet
there is relatively little information about the involve-
ment of these potent vasoactive peptides in asthma.
Bradykinin itself was first isolated in 1949 from enzy-
mat there is relatively little information about the involvement of these potent vasoactive peptides in asthma.
Bradykinin itself was first isolated in 1949 from enzy-
matic treatment of blood (497), and later shown to be a
ni ment of these potent vasoactive peptides in asthical
Bradykinin itself was first isolated in 1949 from en
matic treatment of blood (497), and later shown to b
nine amino acid peptide. Lysine-bradykinin (kallid
has also bee mine amino acid peptide. Lysine

has also been identified and has a

properties (483).
 A. Formation and metabolism
 Bradykinin is generated from a

Show also been identified and has similar pharmacological
operties (483).
Formation and metabolism
Bradykinin is generated from α -2-globulins, called ki-
nogens, in plasma by the action of enzymes (kininoproperties (483).

A. Formation and metabolism

Bradykinin is generated from α -2-globulins, called

ninogens, in plasma by the action of enzymes (kinin

genases) which are produced by the liver (plasma ka A. Formation and metabolism
Bradykinin is generated from α -2-globulins, called kinino
ninogens, in plasma by the action of enzymes (kinino
genases) which are produced by the liver (plasma kalli
krein) and by other tiss A. Formation and metabolism
Bradykinin is generated from α -2-globulins, called ki
ninogens, in plasma by the action of enzymes (kinino
genases) which are produced by the liver (plasma kalli
krein) and by other tissues Bradykinin is generated from α -2-globulins, called kininogens, in plasma by the action of enzymes (kininogenases) which are produced by the liver (plasma kallikrein) and by other tissues (tissue kallikrein). In additio ninogens, in plasma by the action of enzymes (kinino-
genases) which are produced by the liver (plasma kalli-
krein) and by other tissues (tissue kallikrein). In addi-
tion, human lung mast cells and basophils release a
ki genases) which are produced by the liver (plasma kallikrein) and by other tissues (tissue kallikrein). In addition, human lung mast cells and basophils release
kininogenase, which is distinct from kallikreins (476)
and whi krein) and by other tissues (tissue kallikrein). In a
tion, human lung mast cells and basophils releas
kininogenase, which is distinct from kallikreins (4
and which may be identical to tryptase. Both a h
molecular-weight k tion, human lung mast cells and basophils release
kininogenase, which is distinct from kallikreins (476
and which may be identical to tryptase. Both a high
molecular-weight kininogen (HMWK) and a low-molec
ular-weight kini kininogenase, which is distinct from kallikreins (476), and which may be identical to tryptase. Both a high-molecular-weight kininogen (HMWK) and a low-molecular-weight kininogen are recognized, the former probably acting

INFLAMMATORY MEDIATORS AND ASTHMA
latter for tissue kallikrein, since it is formed extravas- nin causes bronchoc cularly.

INFLAMMATORY ME
ter for tissue kallikrein, since it is formed extravas-
larly.
Bradykinin and lys-bradykinin are inactivated by var-
is proteolytic enzymes, but the major pathways involve latter for tissue kallikrein, since it is formed extravas-
cularly. a
Bradykinin and lys-bradykinin are inactivated by var-
ious proteolytic enzymes, but the major pathways involve
kininase I (carboxypeptidase N) and kinin latter for tissue kallikrein, since it is formed extrava
cularly.
Bradykinin and lys-bradykinin are inactivated by ve
ious proteolytic enzymes, but the major pathways invol
kininase I (carboxypeptidase N) and kininase II (a s

cularly. a a symple of the major pathways involve

ious proteolytic enzymes, but the major pathways involve

kininase I (carboxypeptidase N) and kininase II (angio-

tensin converting enzyme; ACE), the latter enzyme b Bradykinin and lys-bradykinin are inactivated by var-

ious proteolytic enzymes, but the major pathways involve

kininase I (carboxypeptidase N) and kininase II (angio-

tensin converting enzyme; ACE), the latter enzyme be ious proteolytic enzymes, but the major pathways involve
kininase I (carboxypeptidase N) and kininase II (angio-
tensin converting enzyme; ACE), the latter enzyme being
localized to endothelial cells. ACE inhibitors, such kininase I (carboxypeptidase N) and kininase II (angio
tensin converting enzyme; ACE), the latter enzyme being
localized to endothelial cells. ACE inhibitors, such a
captopril and enalapril, by preventing the action of kin tensin converting enzyme; ACE), the latter enzyme bei
localized to endothelial cells. ACE inhibitors, such
captopril and enalapril, by preventing the action of kini
ase II may enhance the effects of endogenous bradykin
Thu localized to endothelial cells. ACE inhibitors, such as captopril and enalapril, by preventing the action of kinin-
ase II may enhance the effects of endogenous bradykinin.
Thus, enalapril increases the vascular effects of kinin in human skin (228). However, another potent
ACE-inhibitor (ramipril) has no effect on the broncho-
constrictor effect of bradykinin (178), suggesting that ase II may enhance the effects of endogenous bradykinin.
Thus, enalapril increases the vascular effects of brady-
kinin in human skin (228). However, another potent
ACE-inhibitor (ramipril) has no effect on the broncho-
co Thus, enalapri increases the vascular enects of brady-
kinin in human skin (228). However, another potent of
ACE-inhibitor (ramipril) has no effect on the broncho-
constrictor effect of bradykinin (178), suggesting that v
 kinin in human skin (228). However, another potent
ACE-inhibitor (ramipril) has no effect on the broncho-
constrictor effect of bradykinin (178), suggesting that
ACE is not an important mechanism for degradation of
bradyki ACE-inhibitor (ramipril) has no effect on the broncho-
constrictor effect of bradykinin (178), suggesting that vas
ACE is not an important mechanism for degradation of dir
bradykinin in human airways. Nor is the effect of constrictor effect of bradykinin (178), suggesting th
ACE is not an important mechanism for degradation
bradykinin in human airways. Nor is the effect of br
dykinin on human bronchi enhanced by captopril in vit
(223). Furt ACE is not an important mechanism for degradation of din
bradykinin in human airways. Nor is the effect of bra-
dykinin on human bronchi enhanced by captopril in vitro
 (223) . Furthermore, there is no evidence that ACE i bradykinin in human airways. Nor is the effect of bradykinin on human bronchi enhanced by captopril in vitr (223). Furthermore, there is no evidence that ACE inhitiors cause any deterioration in asthma, although the do pro dykinin on human bronchi enhanced by captopril in vitro B
(223). Furthermore, there is no evidence that ACE inhib-
itors cause any deterioration in asthma, although they redo
produce a dry cough in some patients, which is (223). Furthermore, there is no evidence that ACE inhibitors cause any deterioration in asthma, although they do produce a dry cough in some patients, which is unrelated to asthma (602) . These kinases are less active ag itors cause any deterioration in asthe produce a dry cough in some paties and the set of each may have more prolonged effects. deted to asthma (602). These kinases are less active
against lys-bradykinin than against bradykinin, so that
it may have more prolonged effects.
B. Receptors
Kinins activate specific receptors, which have been

Minist rys-bradykinin than against bradykinin, so that the

may have more prolonged effects.

Receptors
 $\begin{array}{c}\n\text{Kinins active specific receptors, which have been
\ntected in some tissues using ¹²⁵I-labeled bradykinin\n\end{array}$ detected in some protonged effects.

B. Receptors
 $\frac{1}{2}$ Kinins activate specific receptors, which have been

detected in some tissues using $\frac{1}{2}$ I-labeled bradykinin

(438), and in intestine, high-affinity bindi B. Receptors

Kinins activate specific receptors, which have been

detected in some tissues using ¹²⁵I-labeled bradykinin

(438), and in intestine, high-affinity binding sites have

been found in epithelial cells (147). Examples Entity School Entity School and the detected in some tissues using 125 I-labeled bradykinin all (438), and in intestine, high-affinity binding sites have been found in epithelial cells (147). Using a series of Kinins activate specific receptors, which have been
detected in some tissues using 125 I-labeled bradykinin
(438), and in intestine, high-affinity binding sites have
been found in epithelial cells (147). Using a series the distinguish two types of receptors are more potently stimulates ion transport across canine tracheal epi-
detected in some tissues using ¹²⁵I-labeled bradykinin and this is inhibited by cyclooxygenase blockade
been (438), and in intestine, high-affinity binding sites
been found in epithelial cells (147). Using a serie
bradykinin fragments and analogs, it has been pos
to distinguish two types of receptor; B_1 -receptors
selectively been found in epithelial cells (147). Using a series
bradykinin fragments and analogs, it has been possit
to distinguish two types of receptor; B_1 -receptors a
selectively activated by lys-bradykinin and des-Arg-bi
dyki bradykinin fragments and analogs, it has been possit
to distinguish two types of receptor; B_1 -receptors a
selectively activated by lys-bradykinin and des-Arg-br
dykinin, whereas B_2 -receptors are more potently stim
l selectively activated by lys-bradykinin and des-Arg-bra-
dykinin, whereas B_2 -receptors are more potently stimu-
lated by bradykinin itself (483). Selective peptide antag-
onists have now been synthesized for each recep selectively activated by lys-bradykinin and des-Arg-bra-
dykinin, whereas B_2 -receptors are more potently stimulated by bradykinin itself (483). Selective peptide antag-
onists have now been synthesized for each recepto dykinin, whereas B_2 -receptors are more potently stimulated by bradykinin itself (483). Selective peptide antagonists have now been synthesized for each receptor type.
While most responses to kinins appear to be mediate lated by bradykinin itself (483). Selective peptide antag-

onists have now been synthesized for each receptor type.

While most responses to kinins appear to be mediated

wia B₂-receptors, there is some evidence that B onists have now been synthesize While most responses to kinii
via B_2 -receptors, there is some experimental
might increase in experimental
so may be relevant to asthma. might increase in experimental inflammation (389), and

so may be relevant to asthma.
 C. Airway Effects
 1. Airway smooth muscle. Bradykinin is a potent bron-

gnt increase in experimental infiammation (389), and

may be relevant to asthma.
 Airway Effects
 1. Airway smooth muscle. Bradykinin is a potent bron-

oconstrictor in guinea pigs in vivo, which is prevented so may be relevant to asthma.
 $c. Airway Effects$
 $1. Airway smooth muscle. Bradykinin is a potent bron-
choconstructor in guinea pigs in vivo, which is prevented
by cyclooxygenase inhibitors (143), and probably me-$ C. Airway Effects
1. Airway smooth muscle. Bradykinin is a potent bron-
choconstrictor in guinea pigs in vivo, which is prevented
by cyclooxygenase inhibitors (143), and probably me-
diated by the generation of thromboxane deltary *diversion-muscle*. Bradykinin is a potent bronchoconstrictor in guinea pigs in vivo, which is prevented
by cyclooxygenase inhibitors (143), and probably me-
diated by the generation of thromboxane. In humans,
both 1. Airway smooth muscle. Bradykinin is a potent bronchoconstrictor in guinea pigs in vivo, which is prevented by cyclooxygenase inhibitors (143), and probably mediated by the generation of thromboxane. In humanishoth intra choconstrictor in guinea pigs in vivo, which is prevented
by cyclooxygenase inhibitors (143), and probably me-
diated by the generation of thromboxane. In humans,
both intravenous and inhaled bradykinin causes bron-
chocon by cyclooxygenase inhibitors (143), and probably me-
diated by the generation of thromboxane. In humans, inental inflammation (483), there is little direct evidence
both intravenous and inhaled bradykinin causes bron-
chat effect on human airways, even in the presence of capto-
pril (223), suggesting that its bronchoconstrictor action both intravenous and inhaled bradykinin causes bron-
choconstriction in asthmatic but not in normal subjects dif
(278, 535, 429, 223). In vitro bradykinin has almost no
caffect on human airways, even in the presence of cap choconstriction in asthmatic but not in normal subjects (278, 535, 429, 223). In vitro bradykinin has almost no
effect on human airways, even in the presence of capto-
pril (223), suggesting that its bronchoconstrictor act (278, 535, 429, 223). In vitro bradykinin has almost no effect on human airways, even in the presence of capto-
pril (223), suggesting that its bronchoconstrictor action
is indirect. In contrast to the guinea pig, aspirin effect on human airways, even in the presence of capto-
pril (223), suggesting that its bronchoconstrictor action
is indirect. In contrast to the guinea pig, aspirin does not
reduce its bronchoconstrictor effect in human s pril (223), suggesting that its bronchoconstrictor action sum simulative. In contrast to the guinea pig, aspirin does not reduce its bronchoconstrictor effect in human subjects, the but cholinergic antagonists partially in is indirect. In contrast to the guinea pig, aspirin does not reduce its bronchoconstrictor effect in human subjects, the the cholinergic antagonists partially inhibit the response, and suggesting that a vagal reflex mechan reduce its bronchoconstrictor effect in human subjects,
but cholinergic antagonists partially inhibit the response,
suggesting that a vagal reflex mechanism is involved
(535, 223). In dogs, bradykinin is a potent stimulant but cholinergic antagonists partially inhibit the response, suggesting that a vagal reflex mechanism is involved (535, 223). In dogs, bradykinin is a potent stimulant of bronchial C-fibers (316), and in other tissues produ suggesting that a vagal reflex mechanism is involet (535, 223). In dogs, bradykinin is a potent stimulant bronchial C-fibers (316), and in other tissues production from consider that brady sensitive nerves (579). It is pos

ntial only a struck of the TORS AND ASTHMA
nin causes bronchoconstriction in asthmatic patients by
a similar action and activates axon reflex mechanisms
(43). (43). n causes bronchoconstriction in asthmatic patients by
similar action and activates axon reflex mechanisms
3).
There is no evidence that bradykinin causes bronchial
per-responsiveness in man, since inhalation of brady-

nin causes bronchoconstriction in asthmatic patients
a similar action and activates axon reflex mechaniss
(43).
There is no evidence that bradykinin causes bronch
hyper-responsiveness in man, since inhalation of brackinin a similar action and activates axon reflex mechanis
(43).
There is no evidence that bradykinin causes bronch
hyper-responsiveness in man, since inhalation of bra
kinin does not increase responsiveness to other bronc
constr (43). There is no evidence that bradykinin causes bronchial
hyper-responsiveness in man, since inhalation of brady-
kinin does not increase responsiveness to other broncho-
constrictor mediators (223), and even reduces the hyper-responsiveness in man, since inhalation of brady-
kinin does not increase responsiveness to other broncho-
constrictor mediators (223), and even reduces the re-
sponse to histamine, possibly because of release of bro chodilator prostaglandins (223)

2. *Vascular effects*. Bradykinin is a potent vasodilator of canine bronchial vessels and also increases airway mucosal thickness (333). The effects of bradykinin on constrictor mediators (223), and even reduces the response to histamine, possibly because of release of bronchodilator prostaglandins (223).
2. Vascular effects. Bradykinin is a potent vasodilator of canine bronchial vesse sponse to histamine, possibly because of release of bron-
chodilator prostaglandins (223).
2. *Vascular effects*. Bradykinin is a potent vasodilator
of canine bronchial vessels and also increases airway
mucosal thickness (chodilator prostaglandins (223).

2. Vascular effects. Bradykinin is a potent vasodil

of canine bronchial vessels and also increases ain

mucosal thickness (333). The effects of bradykinin

vascular smooth muscle may be m 2. Vascular effects. Bradykinin is a potent vasouria
of canine bronchial vessels and also increases airv
mucosal thickness (333). The effects of bradykinin
vascular smooth muscle may be mediated via prostagl
dins, and brad of canine bronchial vessels and also increases airway
mucosal thickness (333). The effects of bradykinin on
vascular smooth muscle may be mediated via prostaglan-
dins, and bradykinin has been shown to release prosta-
cyli mucosal thickness (333). The effects of bradykinin on
vascular smooth muscle may be mediated via prostaglan-
dins, and bradykinin has been shown to release prosta-
cylin also after intravenous infusion in humans (62).
Brad vascular smooth muscle may be mediated via prostaglandins, and bradykinin has been shown to release prostacylin also after intravenous infusion in humans (62).
Bradykinin also causes microvascular leakage in guinea pig air dins, and bradykinin has been shown to release prostacylin also after intravenous infusion in humans (62).
Bradykinin also causes microvascular leakage in guinea pig airways (507, 177) and produces a wheal and flare respon cylin also after intravenous infusion in humans (62).
Bradykinin also causes microvascular leakage in guinea
pig airways (507, 177) and produces a wheal and flare
response in human skin (228). Injection of kallikrein into
 Bradykinin also causes microvascular leakage in guinea
pig airways (507, 177) and produces a wheal and flare
response in human skin (228). Injection of kallikrein into
human skin causes a late reaction, suggesting that bra pig airways (507, 177) and produces a wheal and flare
response in human skin (228). Injection of kallikrein into
human skin causes a late reaction, suggesting that bra-
dykinin may contribute to this inflammatory response
 response in human skin (228) . Injection of kallikrein into
human skin causes a late reaction, suggesting that bra-
dykinin may contribute to this inflammatory response
 (181) , and raises the possibility that it may pla man skin causes a late reaction, suggesting that bra-
kinin may contribute to this inflammatory response
81), and raises the possibility that it may play a similar
le in the late response to allergens in the airways.
3. Ai

(181), and raises the possibility that it may play a similar role in the late response to allergens in the airways.
3. $Airway$ secretions. Bradykinin is a potent stimulant of ion transport in intestinal mucosa, which may rel of ion transport in intestinal mucosa, which may relate role in the late response to allergens in the airways.
3. Airway secretions. Bradykinin is a potent stimulant
of ion transport in intestinal mucosa, which may relate
to the high density of binding sites (147). Bradykinin
a 3. Airway secretions. Bradykinin is a potent stimulant
of ion transport in intestinal mucosa, which may relate
to the high density of binding sites (147) . Bradykinin
also stimulates ion transport across canine tracheal of ion transport in intestinal mucosa, which may relate
to the high density of binding sites (147). Bradykinin
also stimulates ion transport across canine tracheal epi-
thelium, and this is inhibited by cyclooxygenase bloc the ingit density of binding sites (147) . Bradykinin
also stimulates ion transport across canine tracheal epi-
thelium by bradykinin.
Less is known about the effects of bradykinin on mucus
secretion, although lys-bradyk

secretion, and this is inhibited by cyclocxygenase blockade (353). Furthermore, PGE_2 is released from tracheal epithelium by bradykinin.
Less is known about the effects of bradykinin on mucus secretion, although lys-bra to be found in gland tissue) is released from trachear-
the fium by bradykinin.
Less is known about the effects of bradykinin on mu
secretion, although lys-bradykinin (the kinin most lil
to be found in gland tissue) stimu the field by bradykinin.

Less is known about the effects of bradykinin on mucus

secretion, although lys-bradykinin (the kinin most likely

to be found in gland tissue) stimulates mucus glycopro-

tein release from canine

secretion, although lys-bradykinin (the kinin most likely
to be found in gland tissue) stimulates mucus glycopro-
tein release from canine airways in vitro (38).
4. Effect on nerves. Bradykinin stimulates sensory
nerve end to be found in gland tissue) stimulates mucus glycopro
tein release from canine airways in vitro (38).
4. Effect on nerves. Bradykinin stimulates sensory
nerve endings in airways (316) and in human subject
produces pronoun tein release from canine airways in vitro (38).
4. Effect on nerves. Bradykinin stimulates sensory
nerve endings in airways (316) and in human subjects
produces pronounced dyspnea (223). This effect is rem-
iniscent of the 4. Effect on nerves. Bradykinin stimulates sensory
nerve endings in airways (316) and in human subjects
produces pronounced dyspnea (223). This effect is rem-
iniscent of the pain produced by bradykinin application
to blis nerve endings in airways (316) and in human subjects
produces pronounced dyspnea (223). This effect is rem-
iniscent of the pain produced by bradykinin application
to blister burns in human skin (310). It is possible that
 asthma. to blister burns in human skin (310). It is possible that
bradykinin may therefore contribute to the symptoms of
asthma.
D. Role in Asthma

Despite the evidence that kinins are released in exper-D. Role in Asthma
Despite the evidence that kinins are released in exper-
imental inflammation (483), there is little direct evidence
that they are involved in asthma. This is because of D. Role in Asthma
Despite the evidence that kinins are released in exper-
imental inflammation (483), there is little direct evidence
that they are involved in asthma. This is because of
difficulties of measurement in biol Despite the evidence that kinins are released in experimental inflammation (483), there is little direct evidence that they are involved in asthma. This is because of difficulties of measurement in biological fluids, and b Despite the evidence that kinins are released in experimental inflammation (483), there is little direct evidence that they are involved in asthma. This is because of difficulties of measurement in biological fluids, and b ental inflammation (483), there is little direct evidence
at they are involved in asthma. This is because of
ficulties of measurement in biological fluids, and be-
use of the lack of specific antagonists for clinical use.

that they are involved in asthma. I his is because of
difficulties of measurement in biological fluids, and be-
cause of the lack of specific antagonists for clinical use.
HMWK is consumed during human anaphylaxis (541),
s difference of the lack of specific antagonists for clinical use.

HMWK is consumed during human anaphylaxis (541),

suggesting that kinins are produced. Plasma kinins are

reported to be increased during asthma attacks (1) HMWK is consumed during human anaphylaxis (541), suggesting that kinins are produced. Plasma kinins are reported to be increased during asthma attacks (1), but there are considerable doubts about the assay procedures, and suggesting that kinins are produced. Plasma kinins are reported to be increased during asthma attacks (1), buthere are considerable doubts about the assay procedures and the high values reported may represent spontaneou ki

there are considerable doubts about the assay procedu
and the high values reported may represent spontane
kinin formation in plasma.
Recent studies have demonstrated that allergen cl
lenge leads to production of bradykinin whinin formation in plasma.

Kecent studies have demonstrated that allergen chal-

Recent studies have demonstrated that allergen chal-

lenge leads to production of bradykinin and lys-brady-

kinin in nasal washings of at kinin formation in plasma.
Recent studies have demonstrated that allergen chal-
lenge leads to production of bradykinin and lys-brady-
kinin in nasal washings of atopic individuals (476). Fur-
thermore, HMWKs could also be

BARNES, C
albumin (66), suggesting that increased vascular perm
ability allows entry of HMWK from which kinins BARNES, CHUNG,
albumin (66), suggesting that increased vascular perme-
ability allows entry of HMWK from which kinins are me
formed by local tissue kallikreins. Such measurements bro BARNES, CHU
albumin (66), suggesting that increased vascular perme-
ability allows entry of HMWK from which kinins are
formed by local tissue kallikreins. Such measurements
have not been made in the lower respiratory tract albumin (66), suggesting that increased vascular perme-
ability allows entry of HMWK from which kinins are
formed by local tissue kallikreins. Such measurements
have not been made in the lower respiratory tract, but
recent ability allows entry of HMWK from which kinins are formed by local tissue kallikreins. Such measurements have not been made in the lower respiratory tract, but recently tissue kallikrein has been detected in bronchoal-veol ability allows entry of HMWK from which kind
formed by local tissue kallikreins. Such measu
have not been made in the lower respiratory trecently tissue kallikrein has been detected in bro
veolar lavage fluid of asthmatic rmed by local tissue kallikreins. Such measurements browe not been made in the lower respiratory tract, but to cently tissue kallikrein has been detected in bronchoal-
olar lavage fluid of asthmatic subjects (127). man The

have not been made in the lower respiratory tract, recently tissue kallikrein has been detected in bronchoveolar lavage fluid of asthmatic subjects (127).
There are currently no bradykinin antagonists where suitable for cl recently tissue kallikrein has been detected in bronch
veolar lavage fluid of asthmatic subjects (127).
There are currently no bradykinin antagonists wh
are suitable for clinical use, but several potent compo
tive antagoni veolar lavage fiuld of asthmatic subjects (127) .
There are currently no bradykinin antagonists which the should prove suitable for clinical use, but several potent competitive antagonists, which are peptide analogs of b are suitable for clinical use, but several potent competi-
tive antagonists, which are peptide analogs of bradyki-
nin, have been developed which should prove suitable for
animal studies (588).
VII. Adenosine tive antagonists, which are peptide analogs of bradykinin, have been developed which should prove suitable for
animal studies (588).
VII. Adenosine
Recently there has been increasing interest in the

metrical studies (588).
 $\begin{array}{rcl}\n\textbf{WII.} \textbf{Adenosine} & \textbf{a} \\
\textbf{Recently there has been increasing interest in the} & \textbf{eff} \\
\textbf{Fesible involvement of the purine nucleoside, adenosine,} & \textbf{ref} \\
\end{array}$ animal studies (588).

VII. Adenosine

Recently there has been increasing interest in the

possible involvement of the purine nucleoside, adenosine,

in asthma, since it may be released by allergen challenge VII. Adenosine

Recently there has been increasing interest in the

possible involvement of the purine nucleoside, adenosine,

in asthma, since it may be released by allergen challenge

(385) and may cause bronchoconstrict VII. Adenosine

Recently there has been increasing interest

possible involvement of the purine nucleoside, ade

in asthma, since it may be released by allergen characteristic

(385) and may cause bronchoconstriction (156) in asthma, since it may be released by allergen challenge (385) and may cause bronchoconstriction (156).
A. Origin

Adenosine is generated extracellularly by dephosphorylation of AMP by the membrane-associated enzyme 5'-nucleotidase. Adenosine is therefore formed under A. Origin

Adenosine is generated extracellularly by dephospho-

rylation of AMP by the membrane-associated enzyme

5'-nucleotidase. Adenosine is therefore formed under

thich has recently received attention is its effect A. Origin
Adenosine is generated extracellularly by dephospho-
rylation of AMP by the membrane-associated enzyme
5'-nucleotidase. Adenosine is therefore formed under
conditions in which AMP is generated within the cell, Adenosine is generated extracellularly by dephosphorylation of AMP by the membrane-associated enzyme 5'-nucleotidase. Adenosine is therefore formed under conditions in which AMP is generated within the cell, such as excess such as excessive stimulation or under the conditions in which AMP is generated within the conditions in which AMP is generated within the cosuch as excessive stimulation or under hypoxic condions. Adenosine may then be ta tylation of AMP by the membrane-associated enzyme
5'-nucleotidase. Adenosine is therefore formed under
conditions in which AMP is generated within the cell,
such as excessive stimulation or under hypoxic condi-
facilitate such as excessive stimulation or under hypoxic condi-
tions. Adenosine may then be taken up into the cells by
facilitated transport (which is specifically blocked by
dipyridamole), where it is converted back to AMP or
bro facilitated transport (which is specifically blocked by tions. Adenosine may then be taken up into the cells
facilitated transport (which is specifically blocked
dipyridamole), where it is converted back to AMP
broken down by adenosine deaminase to the inacti
inosine. Extracell facilitated transport (which is specifically blocked by
dipyridamole), where it is converted back to AMP or
broken down by adenosine deaminase to the inactive
inosine. Extracellular adenosine is also rapidly inacti-
vated dipyridamole), where it is converted back to AMF
broken down by adenosine deaminase to the inac
inosine. Extracellular adenosine is also rapidly ina
vated by adenosine deaminase, and therefore adenos
has a very short durat broken down by adenosine deaminase to the inactive D
inosine. Extracellular adenosine is also rapidly inacti-
vated by adenosine deaminase, and therefore adenosine
has a very short duration of action. Thus, the cardiova inosine. Extracellular adenosine is also rapidly inactivated by adenosine deaminase, and therefore adenosine
has a very short duration of action. Thus, the cardiovas-
cular effects of adenosine decay within 1 min of stoppi vated by adenosine deaminase, and therefore adenosine
has a very short duration of action. Thus, the cardiovas-
cular effects of adenosine decay within 1 min of stopping
an infusion (226). This suggests that adenosine func (395). as a local hor
variety of cells
(395).
B. Receptors
Adenosine

riety of cells, including leukocytes (386), and mast cel
95).
Receptors
Adenosine interacts with specific cell surface rece
rs, which either inhibit (A₁) or stimulate (A₂) adenyla (395).

B. Receptors

Adenosine interacts with specific cell surface receptors, which either inhibit (A₁) or stimulate (A₂) adenylate

cyclase, which may be distinguished by selective agonists B. Receptors
Adenosine interacts with specific cell surface recep-
tors, which either inhibit (A_1) or stimulate (A_2) adenylate
cyclase, which may be distinguished by selective agonists
(368). Thus, for A_1 -receptors B. Receptors

Adenosine interacts with specific cell surface receptors, which either inhibit (A_1) or stimulate (A_2) adenylat

cyclase, which may be distinguished by selective agonist

(368). Thus, for A_1 -receptors, Adenosine interacts with specific cent surface recep-
tors, which either inhibit (A_1) or stimulate (A_2) adenylate
cyclase, which may be distinguished by selective agonists
(368). Thus, for A_1 -receptors, N_e -phenyl cyclase, which may be distinguished by selective agonists

(368). Thus, for A_1 -receptors, N_e -phenylisopropyl aden-

osine (PIA) is more potent than N-ethylcarboximide

adenosine (NECA), whereas for A_2 -receptors, t

osine (PIA) is more potent than N-ethylcarboximide
adenosine (NECA), whereas for A_2 -receptors, the order
of potency is reversed.
While adenosine receptors have been identified in lung
by direct receptor binding studies adenosine (NECA), whereas for A_2 -receptors, the order of potency is reversed.

While adenosine receptors have been identified in lung ay

by direct receptor binding studies (581), the cellular

localization of the rece of potency is reversed.

While adenosine receptors have been identified in lung

by direct receptor binding studies (581), the cellular

localization of the receptors is not known, although

adenosine appears to be active **by direct re**
localization
adenosine ap
C. Actions
When ad

aspet

adenosine appears to be active on a wide range of cells.

C. Actions

C. Actions

C. Actions

When administered by aerosol, adenosine induces

THI. Sensory Neuropeptides

rapid bronchoconstriction in asthmatic subjects, bu rapid bronchoconstriction in asthmatic subjects, but has Recently there has been considerable interest in the
no effect on normal subjects (156), but the mechanism possible involvement of axon reflex mechanisms and the
of C. Actions
When administered by aerosol, adenosine induces
rapid bronchoconstriction in asthmatic subjects, but has
no effect on normal subjects (156), but the mechanism
of bronchoconstriction is not yet certain. Adenosine When administered by aerosol, adenosine induces
rapid bronchoconstriction in asthmatic subjects, but has
no effect on normal subjects (156), but the mechanism
of bronchoconstriction is not yet certain. Adenosine has
ittle

Form that the bronchoconstrictor effect is indirect. Pretreat
that the bronchoconstrictor effect is indirect. Pretreat-
ment-with an anticholinergic drug does not inhibit Frank AND PAGE
that the bronchoconstrictor effect is indirect. Pretreat-
ment with an anticholinergic drug does not inhibit the
bronchoconstriction (384), suggesting that it is not due Broad S. AND PAGE
that the bronchoconstrictor effect is indirect. Pretreat-
ment with an anticholinergic drug does not inhibit the
bronchoconstriction (384), suggesting that it is not due
to an irritant effect of the inhal that the bronchoconstrictor effect is indirect. Pretreatment with an anticholinergic drug does not inhibit the bronchoconstriction (384), suggesting that it is not due to an irritant effect of the inhalation, but it is inh that the bronchoconstrictor effect is indirect. Pretreatment with an anticholinergic drug does not inhibit the bronchoconstriction (384), suggesting that it is not due to an irritant effect of the inhalation, but it is inh ment with an anticholinergic drug does not inhibit the bronchoconstriction (384), suggesting that it is not due
to an irritant effect of the inhalation, but it is inhibited
by cromolyn, raising the possibility that mediato bronchoconstriction (384), suggesting that it is not due
to an irritant effect of the inhalation, but it is inhibited
by cromolyn, raising the possibility that mediator release
may be important (155). Adenosine is known to to an irritant effect of the inhalation, but it is inhibited
by cromolyn, raising the possibility that mediator release
may be important (155). Adenosine is known to enhance
the release of histamine from human lung mast ce may be important (155). Adenosine is known to enhance
the release of histamine from human lung mast cells
under certain conditions (288), and in rodent mast cells
selectively enhances the secretion of histamine, rather
th may be important (155). Adenosine is known to enhance
the release of histamine from human lung mast cells
under certain conditions (288), and in rodent mast cells
selectively enhances the secretion of histamine, rather
th the release of histamine from human lung mast c
under certain conditions (288), and in rodent mast c
selectively enhances the secretion of histamine, rat
than that of newly formed mediators (395). The
antagonist, terfenadi under certain conditions (288), and in rodent mast cells
selectively enhances the secretion of histamine, rather
than that of newly formed mediators (395). The H_1 -
antagonist, terfenadine, markedly inhibits the broncho selectively enhances the secretion of histamine, rath
than that of newly formed mediators (395). The F
antagonist, terfenadine, markedly inhibits the bronch
constriction to inhaled AMP (which is converted
adenosine) (477), than that of newly formed mediators (395). The H_1 -
antagonist, terfenadine, markedly inhibits the broncho-
constriction to inhaled AMP (which is converted to
adenosine) (477), suggesting that the bronchoconstrictor
eff antagonist, terfenadine, markedly inhibits the bronch
constriction to inhaled AMP (which is converted
adenosine) (477), suggesting that the bronchoconstrict
effect of adenosine in asthma may be due to selecti
release of hi since adenosine in and a minimal converted
adenosine) (477), suggesting that the bronchoconstrict
fefect of adenosine in asthma may be due to selec
release of histamine from airway mast cells. The ade
sine receptor mediat adenosine) (477), suggesting that the bronchoconstrictor
effect of adenosine in asthma may be due to selective
release of histamine from airway mast cells. The adeno-
sine receptor mediating bronchoconstriction paradoxi-
 effect of adenosine in asthma may be due to selective
release of histamine from airway mast cells. The adeno-
sine receptor mediating bronchoconstriction paradoxi-
cally appears to be the A_2 -receptor, since NECA is mor release of histamine from airway mast cells. The adenosine receptor mediating bronchoconstriction paradoxically appears to be the A_2 -receptor, since NECA is more potent than PIA in causing bronchoconstriction in rats i sine receptor metalling bronchoconstriction paradoxi-
cally appears to be the A_2 -receptor, since NECA is more
potent than PIA in causing bronchoconstriction in rats
in vivo (455), and presumably this receptor is locali

In vivo (455), and presumably this receptor is localized
to airway mast cells.
Another effect of adenosine on airway smooth muscle
which has recently received attention is its effect on
beta-adrenoceptors. Adenosine appea Another effect of aden
which has recently rece
beta-adrenoceptors. Ader
receptor tachyphylaxis is
through the A_1 -receptors
The effect of adenosine inch has recently received attention is its effect on ta-adrenoceptors. Adenosine appears to enhance beta-
ceptor tachyphylaxis in airway smooth muscle (399)
rough the A_1 -receptors.
The effect of adenosine on airway se beta-adrenoceptors. Adenosine appears to enhance
receptor tachyphylaxis in airway smooth muscle
through the A_1 -receptors.
The effect of adenosine on airway secretions and
target cells of the airway has not been investi

The effect of adenosine on airway secretions and other target cells of the airway has not been investigated.

chose of histamine from airway mast cells. The adeno-
energetor mediatrine from airway mast cells. The adeno-
sine receptor mediating bronchoconstriction paradoxi-
cally appears to be the A_2 -receptor, since NECA is mor The effect of adenosine on airway secretions and other
rget cells of the airway has not been investigated.
Role in Asthma
After allergen challenge, plasma concentrations of
enosine increase in asthmatics in parallel with b target cells of the airway has not been investigated.

D. Role in Asthma

After allergen challenge, plasma concentrations of

adenosine increase in asthmatics in parallel with bron-

choconstriction, but no increase is see After allergen challenge, plasma concentrations of adenosine increase in asthmatics in parallel with bronchoconstriction, but no increase is seen after similar bronchoconstriction induced by methacholine (385). The increas adenosine increase in asthmatics in parallel with bron-
choconstriction, but no increase is seen after similar
bronchoconstriction induced by methacholine (385). The
increase in plasma concentrations is unexpected, since
t choconstriction, but no increase is seen after similar
bronchoconstriction induced by methacholine (385). The
increase in plasma concentrations is unexpected, since
the half-life of adenosine is so short, and may suggest
t bronchoconstriction induced by methacholine (385). The increase in plasma concentrations is unexpected, since the half-life of adenosine is so short, and may suggest that adenosine is generated secondarily from other cells

ince a related methylxanthine, enprofylline, has even
enosine (NECA), whereas for A_2 -receptors, the order
potency is reversed.
While adenosine receptors have been identified in lung
while adenosine receptors (460). Thu increase in plasma concentrations is unexpected, since
the half-life of adenosine is so short, and may suggest
that adenosine is generated secondarily from other cells.
Theophylline, at concentrations which are within the The nan-lie of adenosine is so short, and may suggest
that adenosine is generated secondarily from other cells.
Theophylline, at concentrations which are within the
therefore, therefores, and its anti-asthma effects have, Theophylline, at concentrations which are within t
therapeutic range $(55 \text{ to } 110 \mu\text{M})$, is an antagonist
adenosine receptors, and its anti-asthma effects have
therefore, been ascribed to adenosine antagonism $(21$
The therapeutic range (55 to 110 μ M), is an antagonist of adenosine receptors, and its anti-asthma effects have, therefore, been ascribed to adenosine antagonism (214). Theophylline selectively inhibits the bronchoconstric adenosine receptors, and its anti-asthma effects have
therefore, been ascribed to adenosine antagonism (214
Theophylline selectively inhibits the bronchoconstrict
action of inhaled adenosine (157), but it is unlikely the
i therefore, been ascribed to adenosine antagonism (214) .
Theophylline selectively inhibits the bronchoconstrictor
action of inhaled adenosine (157) , but it is unlikely that
its anti-asthma effects are due to adenosine its anti-asthma effects are due to adenosine antagonism, its anti-astima effects are due to adenosine antagonism,
since a related methylxanthine, enprofylline, has even
more potent bronchodilator effects, but is not an effective
antagonist of adenosine receptors (460). Thus, the more potent bronchodilator effects, but is not an effective
antagonist of adenosine receptors (460). Thus, theoph-
ylline cannot be used as a probe to examine the role of
endogenous adenosine in asthma, since it has many o antagonist of adenosine receptors (460). Thus, theoph-
ylline cannot be used as a probe to examine the role of
endogenous adenosine in asthma, since it has many other
effects (44). Until specific adenosine antagonists, whi punne cannot be used as a probe to examine the rolendogenous adenosine in asthma, since it has many offects (44). Until specific adenosine antagonists, which not have other actions, can be used clinically, the of adenosine effects (44). Until specific adenosine antagonists, which
do not have other actions, can be used clinically, the role
of adenosine in asthma remains difficult to evaluate.
VIII. Sensory Neuropeptides

rapid bronchoconstriction in asthmatic subjects, but has Recently there has been considerable interest in the
no effect on normal subjects (156), but the mechanism possible involvement of axon reflex mechanisms and the
of not have other actions, can be used clinically, the role
adenosine in asthma remains difficult to evaluate.
VIII. Sensory Neuropeptides
Recently there has been considerable interest in the
ssible involvement of axon reflex possible in asthma remains difficult to evaluate.
 VIII. Sensory Neuropeptides

Recently there has been considerable interest in the

possible involvement of axon reflex mechanisms and the

role of sensory neuropeptides VIII. Sensory Neuropeptides
Recently there has been considerable interest in the
possible involvement of axon reflex mechanisms and the
role of sensory neuropeptides in airway pathophysiology
(43, 45, 46, 375, 376). These INFLAMMATORY MEDIATORS AND ASTHMA
proinflammatory and may be involved in neurogenic CGRP may inhibit t
inflammation and exaggerating the inflammatory re-
therefore, directly po INFLAMMATORY MED
proinflammatory and may be involved in neurogenic
inflammation and exaggerating the inflammatory re-
sponse in asthmatic airways. Several neuropeptides have INFLAMMATORY MEDIATURED INFORTED INTERTS INTERTAINMATORY MEDIATURE INTERTAINMENT CONTINUIT AIR SUPPOSE in asthmatic airways. Several neuropeptides have now been localized to sensory nerves, including the taproinflammatory and may be involved in neurogenic
inflammation and exaggerating the inflammatory re-
sponse in asthmatic airways. Several neuropeptides have
now been localized to sensory nerves, including the ta-
chykinins proinflammatory and may be involved in neurogenic
inflammation and exaggerating the inflammatory re-
sponse in asthmatic airways. Several neuropeptides have
now been localized to sensory nerves, including the ta-
chykinins inflammation and exaggerating the inflammatory re-
sponse in asthmatic airways. Several neuropeptides have
now been localized to sensory nerves, including the ta-
chykinins substance P (SP), neurokinin A (NKA, pre-
k le
v sponse in asthmatic airways. Several neuropeptides have
now been localized to sensory nerves, including the ta-
chykinins substance P (SP), neurokinin A (NKA, pre-
viously known as substance K), and neuropeptide K
(NPK), now been localized to sensory nerves, including the tachykinins substance P (SP), neurokinin A (NKA, previously known as substance K), and neuropeptide K
(NPK), as well as calcitonin gene-related peptide
(CGRP). Neurokinin chykinins substance P (SP), neurokinin A (NK
viously known as substance K), and neuroper
(NPK), as well as calcitonin gene-related
(CGRP). Neurokinin B (NKB, previously known
romedin L) has not yet been identified in lung. *A. Origin*
A. Origin
A. Origin
A. Origin

medin L) has not yet been identified in lung.

Origin

Sensitive neuropeptides are localized to capsaicin

ive C-fiber afferents in airways. The peptide A. Origin
Sensitive neuropeptides are localized to capsaicin-sensitive C-fiber afferents in airways. The peptides are
synthesized in sensory neurones in the nodose and jug-
ular ganglia and transported peripherally (376). for example in the sensitive neuropeptides are localized to capsaicin-sen-
sitive C-fiber afferents in airways. The peptides are h
synthesized in sensory neurones in the nodose and jug-
sular ganglia and transported periph Sensitive neuropeptides are localized to capsaicin-sensitive C-fiber afferents in airways. The peptides are synthesized in sensory neurones in the nodose and jug ular ganglia and transported peripherally (376). There may a sitive C-fiber afferents in airways. The peptides are has synthesized in sensory neurones in the nodose and jug-
sular ganglia and transported peripherally (376). There clearly also be sensory neuropeptides in nerves which synthesized in sensory neurones in the nodose and jug-SP is ular ganglia and transported peripherally (376) . There cle of may also be sensory neuropeptides in nerves which orig-chiomete within the airway itself. Histoch may also be sensory neuropeptides in nerves which originate within the airway itself. Histochemical studies have demonstrated that SP immunoreactivity is localized to fine nerves within and beneath airway epithelium, aroun may also be sensory neuropeptides in nerves which originate within the airway itself. Histochemical studies have demonstrated that SP immunoreactivity is localized to fine nerves within and beneath airway epithelium, aroun inate within the airway itself. Histochemical studies have airdemonstrated that SP immunoreactivity is localized to prime nerves within and beneath airway epithelium, izat around blood vessels and ganglia and, to a lesser demonstrated that SP immunoreactivity is localized fine nerves within and beneath airway epithe around blood vessels and ganglia and, to a lesser exertinin airway smooth muscle (372). These nerves be found peripherally as fine nerves within and beneath airway epithelium, incound blood vessels and ganglia and, to a lesser extent, twithin airway smooth muscle (372) . These nerves may be found peripherally as well as centrally. SP-immuno-rea around blood vessels and ganglia and, to a lesser extent
within airway smooth muscle (372). These nerves may
be found peripherally as well as centrally. SP-immuno
reactive nerves are less numerous in human airways (372
and within airway smooth muscle (372). These nerves may muscle found peripherally as well as centrally. SP-immuno-
reactive nerves are less numerous in human airways (372) C
and, in some studies, have not been convincingly dem be found peripherally as well as centrally. SP-immuno-
reactive nerves are less numerous in human airways (372) (and, in some studies, have not been convincingly dem-
ideonstrated (332). However, rapid degradation of SP in reactive nerves are less numerous in human airways (372) C
and, in some studies, have not been convincingly dem-
identificant difficulty demonstrated (332). However, rapid degradation of SP in (424
airways, and the fact th and, in some studies, have not been convincingly demonstrated (332). However, rapid degradation of SP in airways, and the fact that SP may decrease with age and possibly with smoking, might explain the difficulty in demons resection. the same decrease with age and be saibly with smoking, might explain the difficulty in a monstrating this peptide in lungs obtained at surgical losection.
NKA is coded by the same gene as SP (426) and is in serefore coloc

possibly with smoking, might explain the difficulty in automonstrating this peptide in lungs obtained at surgical loc-
resection.
NKA is coded by the same gene as SP (426) and is in laterefore colocalized within sensory n demonstrating this peptide in lungs obtained at surgives
resection.
NKA is coded by the same gene as SP (426) and
therefore colocalized within sensory nerves (287). CGI
is frequently colocalized with tachykinins, and CGR
i resection.

NKA is coded by the same gene as SP (426) and is

therefore colocalized within sensory nerves (287). CGRP

is frequently colocalized with tachykinins, and CGRP-

immunoreactive nerves have been demonstrated in NKA is coded by the same gene as SP (426) and is in therefore colocalized within sensory nerves (287) . CGRP is frequently colocalized with tachykinins, and CGRP-
immunoreactive nerves have been demonstrated in human a therefore colocalized within sensory nerves (287). CG
is frequently colocalized with tachykinins, and CG
immunoreactive nerves have been demonstrated in
man airways (447). In some animal species, CGR
also localized to neur

sensory nerve endings by a calcium-dependent mechaman airways (447). In some animal species, CGRP is duest also localized to neuroendocrine cells in the airway. Si
Sensory neuropeptides are released by capsaicin from bisensory nerve endings by a calcium-dependent mecha-
h also localized to neuroendocrine cells in the airway.

Sensory neuropeptides are released by capsaicin from

sensory nerve endings by a calcium-dependent mecha-

hism, and this has recently been demonstrated in isolated

i Sensory neuropeptides are released by capsaicin from bracknown were endings by a calcium-dependent mecha-
nism, and this has recently been demonstrated in isolated is
perfused guinea pig lungs (508). Agents that activate h sensory nerve endings by a calcium-dependent mecha-
nism, and this has recently been demonstrated in isolated
is equal the release of sensory neuropeptides from lung
to induce the release of sensory neuropeptides from lung (508). perrused guinea pig lungs (508). Agents that activate
sensory nerves, such as bradykinin, have also been shown
to induce the release of sensory neuropeptides from lung
(508).
Less is known about the metabolism of sensory n

to induce the release of sensory neuropeptides from lung (508).

Less is known about the metabolism of sensory neuropeptides, but it seems likely that tachykinins are rap-

idly degraded by peptidases. In guinea pig lung s (508).
Less is known about the metabolism of sensory neu-
ropeptides, but it seems likely that tachykinins are rap-
idly degraded by peptidases. In guinea pig lung strips,
SP causes contraction only in the presence of capt Less is known about the metabolism of sensory neu-
ropeptides, but it seems likely that tachykinins are rap-
idly degraded by peptidases. In guinea pig lung strips, little
SP causes contraction only in the presence of capt ropeptides, but it seems likely that tachykinins are rap-
idly degraded by peptidases. In guinea pig lung strips, litt
SP causes contraction only in the presence of captopril, str
suggesting that, in this preparation, meta idly degraded by peptidases. In guinea pig lung strips Causes contraction only in the presence of captoprosuggesting that, in this preparation, metabolism by A(
is critical (603) and, in vivo, captopril enhances to broncho Sr causes contraction only in the presence of captopril, stricting suggesting that, in this preparation, metabolism by ACE infusion critical (603) and, in vivo, captopril enhances the sult bronchoconstrictor effect of SP (is critical (603) and, in vivo, captopril enhances the bronchoconstrictor effect of SP (529). Neutral metal-loendopeptidase (enkephalinase) may be a more important degrading enzyme in airways, and inhibition by thiorphan o bronchoconstrictor effect of SP (529). Neutral metal-
loendopeptidase (enkephalinase) may be a more impor-
tant degrading enzyme in airways, and inhibition by pot
hiorphan or phosphoramidon greatly enhances the air-
way ef loendopeptidase (enkephalinase) may be a more impor-
tant degrading enzyme in airways, and inhibition by po
thiorphan or phosphoramidon greatly enhances the air-
way effects of SP in animals (529, 88) and in human
mairways tant degrading enzyme in airways, and inhibition by
thiorphan or phosphoramidon greatly enhances the air-
way effects of SP in animals (529, 88) and in human
airways (218). CGRP is presumed to be more slowly
metabolized, s thiorphan or phosphoramidon greatly enhances the air-
way effects of SP in animals (529, 88) and in human
airways (218). CGRP is presumed to be more slowly
metabolized, since its effects may be very prolonged (91),
and deg

67 ATORS AND ASTHMA
CGRP may inhibit the breakdown of SP (352) and may, TORS AND ASTHMA
CGRP may inhibit the breakdown of SP (352
therefore, directly potentiate its effect (90). *CGRP* may in
therefore, dire
B. Receptors
At least 3 re

A. Origin

Sensitive neuropeptides are localized to capsaicin-sen-

sitive C-fiber afferents in airways. The peptides are has been studied in guinea pig and human lung (113).

synthesized in sensory neurones in the nodose GRP may inhibit the breakdown of SP (352) and may,
erefore, directly potentiate its effect (90).
 $Receptors$
At least 3 receptor subtypes for tachykinins have now
en recognized (105, 340). NK_1 receptors (previously therefore, directly potentiate its effect (90) .
 B. Receptors

At least 3 receptor subtypes for tachykinins have now

been recognized $(105, 340)$. NK₁ receptors (previously

known as SP-P receptors) are selectively B. Receptors

At least 3 receptor subtypes for tachykinins have now

been recognized (105, 340). NK₁ receptors (previously

known as SP-P receptors) are selectively activated by

SP, NK₂ (previously SP-E) receptors by B. Receptors

At least 3 receptor subtypes for tachykinins have now

been recognized (105, 340). NK₁ receptors (previously

known as SP-P receptors) are selectively activated by

SP, NK₂ (previously SP-E) receptors by At least 3 receptor subtypes for tachykinins have now
been recognized $(105, 340)$. NK₁ receptors (previously
known as SP-P receptors) are selectively activated by
SP, NK₂ (previously SP-E) receptors by NKA, and NK₃ been recognized (105, 340). NK₁ receptors (previously known as SP-P receptors) are selectively activated by SP, NK₂ (previously SP-E) receptors by NKA, and NK₃ (previously SP-N) receptors by NKB. This suggests that, shown as ST - F receptors) are selectively activated if SP , NK_2 (previously SP - E) receptors by NKA , and NH (previously SP - N) receptors by NKB . This suggests the although different tachykinins may be released S F, N N₂ (previously S F-E) receptors by NKB. This suggests that, although different tachykinins may be released from the same nerves, they may regulate different physiological functions, as discussed below for airw atthough unferent tachy knims may be released from the
same nerves, they may regulate different physiological
functions, as discussed below for airway effects. Using
the autoradiographic approach, SP receptor distribution
 the autoradiographic approach, SP receptor distribution
has been studied in guinea pig and human lung (113).
SP receptors are predominantly localized to smooth mus-
cle of airway cells from trachea down to terminal bronthe autoradiographic approach, SP receptor distribution
has been studied in guinea pig and human lung (113).
SP receptors are predominantly localized to smooth mus-
cle of airway cells from trachea down to terminal bron-
c has been studied in guinea pig and human lung (113).
SP receptors are predominantly localized to smooth mus-
cle of airway cells from trachea down to terminal bron-
chioles, with less labeling of epithelial cells. In human SP receptors are predominantly localized to smooth musicle of airway cells from trachea down to terminal bronchioles, with less labeling of epithelial cells. In huma airways, submucosal glands were also labeled (48). Suppr cle of airway cells from trachea down to terminal bronchioles, with less labeling of epithelial cells. In human airways, submucosal glands were also labeled (48). Surprisingly, labeled NKA does not show significant localiz chioles, with less labeling of epithelial cells. In human
airways, submucosal glands were also labeled (48). Sur-
prisingly, labeled NKA does not show significant local-
ization to guinea pig trachea (601). As in other org airways, submucosal glands were also labeled (48). Sur-
prisingly, labeled NKA does not show significant local-
ization to guinea pig trachea (601). As in other organs,
tachykinins stimulate PI turnover in airway smooth
mu ization to guinea pig trachea (601). As in other organs,
tachykinins stimulate PI turnover in airway smooth
muscle and, in keeping with functional data, NKA is
more potent than SP in this respect (251).
CGRP binds to speci SP receptors are predominantly localized to smooth mus-
cloid sate of airway cells from traches down to terminal bron-
chicles, with less labeling of epitheiial cells. In human
airways, submucosal glands were also labeled muscle and, in keeping with functional data, NKA is

muscle and, in keeping with functional data, NKA is
more potent than SP in this respect (251).
CGRP binds to specific receptors which have been
identified in several peripheral organs, including lung
(424). Recently the di more potent than SP in this respect (251).

CGRP binds to specific receptors which have been

identified in several peripheral organs, including lung

(424). Recently the distribution of CGRP receptors has

been determined CGRP binds to specific receptors which have been
identified in several peripheral organs, including lung
(424). Recently the distribution of CGRP receptors has
been determined in guinea pig and human lung using
autoradiogr identified in several peripheral organs, including lung
(424). Recently the distribution of CGRP receptors has
been determined in guinea pig and human lung using
autoradiography. In airways, CGRP binding sites are
localize (424). Recently the distribution of CORF Feceptors has
been determined in guinea pig and human lung using
autoradiography. In airways, CGRP binding sites are
localized predominantly to bronchial vessels, with only
scanty l been determined in gotal
autoradiography. In ailocalized predominantl
scanty labeling of airway
in both species (383). localized predominantly to bronchial vessels, with only scanty labeling of airway smooth muscle and epithelium in both species (383). whist parameter and epithelium

1. *Airway Effects*

1. *Airway smooth muscle*. In animals, tachykinins pro-

1. *Airway smooth muscle*. In animals, tachykinins pro-

1. *Airway smooth muscle*. In animals, tachykinins pro-

is frequently colocalized with tachykinins, and CGRP-

Sensitively are the minimum oreactive nerves have been demonstrated in human airways (447). In some animal species, CGRP is duce bronchoconstriction both in vitro and in both species (383).

C. Airway Effects

1. Airway smooth muscle. In animals, tachykinins pro-

duce bronchoconstriction both in vitro and in vivo (375).

Since tachykinin receptors are found even on terminal C. Airway Effects
1. Airway smooth muscle. In animals, tachykinins pro-
duce bronchoconstriction both in vitro and in vivo (375).
Since tachykinin receptors are found even on terminal
bronchioles, this suggests that tachyk 1. Airway smooth muscle. In animals, tachykinins produce bronchoconstriction both in vitro and in vivo (375).
Since tachykinin receptors are found even on terminal
bronchioles, this suggests that tachykinins may regulate
b duce bronchoconstriction both in vitro and in vivo (375).
Since tachykinin receptors are found even on terminal
bronchoides, this suggests that tachykinins may regulate
bronchomotor tone in peripheral airways (113), and t Since tachykinin receptors are found even on terminal
bronchioles, this suggests that tachykinins may regulate
bronchomotor tone in peripheral airways (113), and this
is confirmed by functional studies (218). SP contracts bronchioles, this suggests that tachykinins may regulate
bronchomotor tone in peripheral airways (113), and this
is confirmed by functional studies (218). SP contracts
human bronchi in vitro (373), but NKA is significantl bronchomotor tone in peripheral airways (113), and this
is confirmed by functional studies (218). SP contracts
human bronchi in vitro (373), but NKA is significantly
more potent, suggesting an NK₂ receptor on human
airw human bronchi in vitro (373), but NKA is significantly
more potent, suggesting an NK_2 receptor on human
airway smooth muscle (397, 446). Neuropeptide K is also
a potent bronchoconstrictor in animals (287) and conhuman bronchi in vitro (373), but NKA is significantly
more potent, suggesting an NK₂ receptor on human
airway smooth muscle (397, 446). Neuropeptide K is also
a potent bronchoconstrictor in animals (287) and con-
tract more potent, suggesting an NK_2 receptor on human
airway smooth muscle (397, 446). Neuropeptide K is also
a potent bronchoconstrictor in animals (287) and con-
tracts human airways in vitro (397). Infusion of SP in
human tracts human airways in vitro (397). Infusion of SP in human subjects has profound cardiovascular effects but little effect on airway function with a small bronchoconstrictor effect, followed by bronchodilatation at higher a potent bronchoconstrictor in animals (287) and contracts human airways in vitro (397). Infusion of SP in human subjects has profound cardiovascular effects but little effect on airway function with a small bronchoconstri tracts human airways in vitro (397). Infusion of SP in
human subjects has profound cardiovascular effects but
little effect on airway function with a small bronchocon-
strictor effect, followed by bronchodilatation at high numan subjects has proround cardiovascular effects but
little effect on airway function with a small bronchocon-
strictor effect, followed by bronchodilatation at higher
infusion doses. This may reflect reduced vagal tone strictor effect, followed by bronchodilatation at hight million doses. This may reflect reduced vagal tone sulting from systemic vasodilatation (227). Even given in subjects with mild asthma who are hyperponsive to histami infusion doses. This may reflect reduced vagal tone resulting from systemic vasodilatation (227). Even give by inhalation, SP has no significant effect on airwa
function in subjects with mild asthma who are hyperree ponsiv sulting from systemic vasodilatation (227). Even given
by inhalation, SP has no significant effect on airway
function in subjects with mild asthma who are hyperres-
ponsive to histamine (227). This could be due to enzy-
ma by inhalation, SP has no significant effect on airwarfunction in subjects with mild asthma who are hyperresponsive to histamine (227). This could be due to enzy matic degradation of SP in the airway. NKA has less marked ca function in subjects with mild asthma who are hyperres-
ponsive to histamine (227) . This could be due to enzy-
matic degradation of SP in the airway. NKA has less
marked cardiovascular effects than SP, but causes bron-
 ponsive to nistamine (227). This could be due to enzy-
matic degradation of SP in the airway. NKA has less
marked cardiovascular effects than SP, but causes bronchoconstriction at higher infused doses (193) and is
reported matic degradation of SP in the airway
marked cardiovascular effects than SP,
choconstriction at higher infused dos
reported to cause bronchoconstriction
inhalation to asthmatic subjects (305).

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BARNES, CHUNG, AND PAGE
There is now considerable evidence that tachykinins cular leakage
released from sensory nerves can account for nonadre-sory peptides EXEMPLES
There is now considerable evidence that tachykin
released from sensory nerves can account for nonadre-
nergic, noncholinergic (NANC) bronchoconstrict BARNES, CHU

There is now considerable evidence that tachykinine

released from sensory nerves can account for nonadre-

nergic, noncholinergic (NANC) bronchoconstriction

after vagal stimulation in rodents (18). Capsaicin There is now considerable evidence that tachykinins cureleased from sensory nerves can account for nonadre-
nergic, noncholinergic (NANC) bronchoconstriction po
after vagal stimulation in rodents (18). Capsaicin, which ma
 There is now considerable evidence that tachykiveleased from sensory nerves can account for non-
nergic, noncholinergic (NANC) bronchoconstriater vagal stimulation in rodents (18). Capsaicin, we
releases sensory neuropepti released from sensory nerves can account for nonadresting and the energic, noncholinergic (NANC) bronchoconstriction post after vagal stimulation in rodents (18). Capsaicin, which may releases sensory neuropeptides, also c mergic, indichalmergic (NANC) bronchoconstriction potenties after vagal stimulation in rodents (18). Capsaicin, which meleases sensory neuropeptides, also causes bronchoconstriction is a capsaicin, which depletes sensory n releases sensory neuropeptides, also causes bronchoconstriction in these species, and chronic treatment with capsaicin, which depletes sensory neuropeptides, results in loss of NANC bronchoconstriction (376). In human surw striction in these species, and chronic treatment with capsaicin, which depletes sensory neuropeptides, results in loss of NANC bronchoconstriction (376). In human airways, capsaicin also causes contraction in vitro, sugge capsaicin, which depletes sensory neuropeptides, results that
in loss of NANC bronchoconstriction (376). In human C
airways, capsaicin also causes contraction in vitro, sug-
prox
gesting that it is releasing sensory neurop in loss of NANC bronchoconstriction (376). In human
airways, capsaicin also causes contraction in vitro, sug-
gesting that it is releasing sensory neuropeptides (373)
In vivo inhaled capsaicin causes intense coughing in
hu airways, capsaicin also causes contraction in vitro, suggesting that it is releasing sensory neuropeptides (373).
In vivo inhaled capsaicin causes intense coughing in human subjects, but only transient bronchoconstriction In vivo inhaled caps:
human subjects, but o
which is prevented by
gesting a vagal refler
neuropeptides (222).
Tachykinins, while man subjects, but only transient bronchoconstriction
nich is prevented by anticholinergic treatment, sug-
sting a vagal reflex rather than release of sensory
uropeptides (222).
Tachykinins, while having a direct effect on

which is prevented by anticholinergic treatment,
gesting a vagal reflex rather than release of sen
neuropeptides (222).
Tachykinins, while having a direct effect on recep
in airway smooth muscle, may also produce broncho
s gesting a vagal reflex rather than release of sen
neuropeptides (222).
Tachykinins, while having a direct effect on recep-
in airway smooth muscle, may also produce bronchocon-
striction indirectly. Thus, in rabbits, the b neuropeptides (222).

Tachykinins, while having a direct effect on receptors completed by atropic indirectly. Thus, in rabbits, the bronchocon-

striction indirectly. Thus, in rabbits, the bronchocon-

strictor response is Tachykinins, while having a direct effect on receptors cally if
in airway smooth muscle, may also produce bronchocon-
striction indirectly. Thus, in rabbits, the bronchocon-
rabbit s
strictor response is inhibited by atrop in airway smooth muscle, may also produce bronchocon-
striction indirectly. Thus, in rabbits, the bronchocon-
strictor response is inhibited by atropine, suggesting (54)
release of acetylcholine from cholinergic nerves striction indirectly. Thus, in rabbits, the bronchoconstrictor response is inhibited by atropine, suggesting release of acetylcholine from cholinergic nerves (565). A similar effect is seen in guinea pig airways, where a f strictor response is inhibited by atropine, suggesting release of acetylcholine from cholinergic nerves (565). A similar effect is seen in guinea pig airways, where a facilitating action on postganglionic cholinergic nerve release of acetylcholine from cholinergic nerves (565). A guinding effect is seen in guinea pig airways, where a breading facilitating action on postganglionic cholinergic nerves, therefore than preganglionic, has been fou similar enect is seen in gamea pig an ways, where a
facilitating action on postganglionic cholinergic nerves,
rather than preganglionic, has been found (60). However,
similar studies have not shown such an effect on human
 rather than preganglionic, has been found (60). However,
similar studies have not shown such an effect on human
airways in vitro (K. Rhoden and P. J. Barnes, unpub-
lished results). Epithelial removal markedly enhances
the similar studies have not shown such an effect on hum
airways in vitro (K. Rhoden and P. J. Barnes, unplished results). Epithelial removal markedly enhan
the contractile effect of tachykinins in guinea pig a
ways, which mig airways in vitro (K. Rhoden and P. J. Barnes, unpub-
lished results). Epithelial removal markedly enhances
the contractile effect of tachykinins in guinea pig air-
ways, which might be explained either by loss of "epithelished results). Epithelial removal markedly enhances
the contractile effect of tachykinins in guinea pig air-
ways, which might be explained either by loss of "epithe-
lium-derived relaxant factor" (EpDRF) or removal of
m the contractile effect of tachykinins in guide,
ways, which might be explained either by los
lium-derived relaxant factor" (EpDRF) or
metabolizing enzymes, since phosphoramido
the effect of epithelial removal (251, 219).
2 given the explained either by loss of "epithe-
 2. Secretion. SP is one of the most potent known
 $\frac{1}{2}$. Secretion. SP is one of the most potent known
 $\frac{1}{2}$. Secretion. SP is one of the most potent known
 $\frac{1$

metabolizing enzymes, since phosphoramidon eliminates
the effect of epithelial removal (251, 219).
2. Secretion. SP is one of the most potent known
stimulants of mucus secretion in animal airways (38,
141). Similarly, in h metabolizing enzymes, since phosphoramidon eliminates the effect of epithelial removal $(251, 219)$.

2. Secretion. SP is one of the most potent known tide

stimulants of mucus secretion in animal airways $(38, 141)$. Sim the effect of epithelial removal (251, 219).

2. Secretion. SP is one of the most potent known

stimulants of mucus secretion in animal airways (38,

141). Similarly, in human airways in vitro, SP is an

effective stimulan 2. Secretion. SP is one of the most potent known
stimulants of mucus secretion in animal airways (38,
141). Similarly, in human airways in vitro, SP is an
effective stimulant of mucus secretion (56), which cor-
relates wit stimulants of mucus secretion in anii 141). Similarly, in human airways in effective stimulant of mucus secretion relates with the demonstration of SP-
man airway submucosal glands (113). Tachykinins also transiently incre 1). Similarly, in human airways in vitro, SP is an ective stimulant of mucus secretion (56), which cor-
ates with the demonstration of SP-receptors on hu-
an airway submucosal glands (113).
Tachykinins also transiently inc

effective stimulant of mucus secretion (56), which correlates with the demonstration of SP-receptors on human airway submucosal glands (113).
Tachykinins also transiently increase conductance in across canine airway epith relates with the demonstration of SP-receptors on hu-
man airway submucosal glands (113).
Tachykinins also transiently increase conductance
across canine airway epithelium and, since SP is more
potent than neurokinins, th man airway submucosal glands (113).

Tachykinins also transiently increase conductance in

across canine airway epithelium and, since SP is more

potent than neurokinins, this suggests that an NK₁ re-

receptor is invol Tachykinins also transiently increase condu
across canine airway epithelium and, since SP is
potent than neurokinins, this suggests that an N
receptor is involved (480). In the guinea pig, the ef
epithelial removal is also across canine airway epithelium and, since SP is more
potent than neurokinins, this suggests that an NK_1 re-
potent is involved (480). In the guinea pig, the effect of perithelial removal is also greater for the broncho potent than neurokinins, this suggests that an NK_1 receptor is involved (480). In the guinea pig, the effect of epithelial removal is also greater for the bronchoconstrictor effect of SP than for NKA, suggesting that NK receptor is involved (480). In the guinea pig, the effect of μ epithelial removal is also greater for the bronchoconstric-
tor effect of SP than for NKA, suggesting that NK₁ der
receptors may be important in the epit epithelial removal is also greater for the bronchoconstric-
tor effect of SP than for NKA, suggesting that NK₁ d
receptors may be important in the epithelial modulation
of airway smooth muscle tone (251). Whether this i tor effect of SP than for NKA, suggesting that NK_1 defectors may be important in the epithelial modulation spot airway smooth muscle tone (251). Whether this is also Intrue for human airways is not yet certain. The effe receptors may be important in the epithelial modulation specified for airway smooth muscle tone (251). Whether this is also In rod true for human airways is not yet certain. The effect of broncl CGRP on airway secretion is of airway smooth muscle tone (251). Whether this is also
true for human airways is not yet certain. The effect of
CGRP on airway secretion is also unknown, but, since
CGRP is a potent vasodilator, the increase in blood flo is the formular properties in the subset of SRP on airway secretion is also unknown, but, since $3RP$ is a potent vasodilator, the increase in blood flow airway glands might be expected to increase secretion.
3. Vascular e CGRP on airway secretion is also unknown, but, since
CGRP is a potent vasodilator, the increase in blood flow
to airway glands might be expected to increase secretion.
3. Vascular effects. SP is a potent systemic vasodila

CGRP is a potent vasodilator, the increase in blood flow
to airway glands might be expected to increase secretion
3. Vascular effects. SP is a potent systemic vasodilato
in human subjects (227) , and in animals it increa to airway glands might be expected to increase secretion.

3. Vascular effects. SP is a potent systemic vasodilator Ne

in human subjects (227), and in animals it increases are

bronchial flow (333). SP also causes microv 3. Vascular effects. SP is a potent systemic vasodilator Ne
in human subjects (227), and in animals it increases are
bronchial flow (333). SP also causes microvascular leak-
invage in guinea pig airways (507) and is more in human subjects (227), and in animals it increases
bronchial flow (333). SP also causes microvascular leak-
age in guinea pig airways (507) and is more potent than
NKA and NKB (34), suggesting that an NK₁ receptor is
 age in guinea pig airways (507) and is more potent than NKA and NKB (34), suggesting that an NK_1 receptor is involved. In animals treated with capsaicin, mechanical trauma and cigarette smoke no longer cause microvas-

G, AND PAGE
cular leakage in rodents, indicating that release of sen-
sory peptides is involved in this response (374). It is not s, AND PAGE
cular leakage in rodents, indicating that release of sen-
sory peptides is involved in this response (374). It is not
possible to study airway microvascular leakage in hu-For S, AND PAGE
cular leakage in rodents, indicating that release of sen-
sory peptides is involved in this response (374). It is not
possible to study airway microvascular leakage in hu-
mans, but, in skin, SP causes a wh cular leakage in rodents, indicating that release of sensory peptides is involved in this response (374). It is not possible to study airway microvascular leakage in humans, but, in skin, SP causes a wheal and flare respon suar leakage in rouents, indicating that release of sensory peptides is involved in this response (374). It is not possible to study airway microvascular leakage in humans, but, in skin, SP causes a wheal and flare respons possible to study airway microvascular lemans, but, in skin, SP causes a wheal and f
suggesting vasodilatation and increased va
ability (256). As in guinea pig airways, SP i
than NKA or NKB in this respect (221).
CGRP is a mans, but, in skin, Sr causes a wheat and hare response,
suggesting vasodilatation and increased vascular perme-
ability (256). As in guinea pig airways, SP is more potent
than NKA or NKB in this respect (221).
CGRP is a v

gesting that it is releasing sensory neuropeptides (373). guinea pig airways, CGRP does produce microvascular
In vivo inhaled capsaicin causes intense coughing in leakage (34), but presumably is a bronchial vasodilator
hum than NKA or NKB in this respect (221) .
CGRP is a very potent vasodilator in human skin, but
produces a wheal only at very high doses $(91, 221)$. In than NKA or NKB in this respect (221).
CGRP is a very potent vasodilator in human skin, but
produces a wheal only at very high doses (91, 221). In
guinea pig airways, CGRP does produce microvascular
leakage (34), but presu CGRP is a very potent vasodilator in human skin, but
produces a wheal only at very high doses (91, 221). In
guinea pig airways, CGRP does produce microvascular
leakage (34), but presumably is a bronchial vasodilator
in bot produces a wheal only at very high doses (91, 221). In guinea pig airways, CGRP does produce microvascular leakage (34), but presumably is a bronchial vasodilator in both guinea pig and human airways since a very high dens guinea pig airways, CGRP does produce microvascular
leakage (34), but presumably is a bronchial vasodilator
in both guinea pig and human airways since a very high
density of CGRP-receptors is localized to bronchial ves-
se in both guinea pig and human airways since a very high in both guinea pig and human airways since a very high density of CGRP-receptors is localized to bronchial vessels (383). Since CGRP is a vasodilator and SP increases leakage, it is possible that they may interact synergis density of CGRP-receptors is localized to bronchial vessels (383). Since CGRP is a vasodilator and SP increases leakage, it is possible that they may interact synergistically if released together. Potentiation of SP-induce sels (383). Since CGRP is a vasodilator and SP increases
leakage, it is possible that they may interact synergistically if released together. Potentiation of SP-induced
leakage with CGRP has been reported in guinea pig and leakage, it is possible that they may interact synergistically if released together. Potentiation of SP-induced
leakage with CGRP has been reported in guinea pig and
rabbit skin (229, 90), but not convincingly in human sk cally if released together. Potentiation of SP-induced
leakage with CGRP has been reported in guinea pig and
rabbit skin (229, 90), but not convincingly in human skin
(54). No potentiation of SP induced leak by CGRP in
gui rabbit skin $(229, 90)$, but not convincingly in human skin (54) . No potentiation of SP induced leak by CGRP in guinea pig airways has been found (34) , possibly because bronchial blood flow is already high and cannot rabbit skin (229
(54). No potent
guinea pig airwa
bronchial blood
ther potentiated
4. Inflammate 4). No potentiation of SP induced leak by CGRP in
inea pig airways has been found (34), possibly because
onchial blood flow is already high and cannot be fur-
er potentiated.
4. *Inflammatory cells*. The SP-induced wheal a

guinea pig airways has been found (34), possibly because
bronchial blood flow is already high and cannot be fur-
ther potentiated.
4. Inflammatory cells. The SP-induced wheal and flare
response in human skin is inhibited b bronchial blood flow is already high and cannot be fur-
ther potentiated.
4. *Inflammatory cells*. The SP-induced wheal and flare
response in human skin is inhibited by antihistamines
(212) and increases the release of his ther potentiated.
4. *Inflammatory cells*. The SP-induced wheal and flare
response in human skin is inhibited by antihistamines
(212) and increases the release of histamine into draining
veins (50). This suggests that SP d 4. Inflammatory cells. The SP-induced wheal and flare
response in human skin is inhibited by antihistamines
(212) and increases the release of histamine into draining
veins (50). This suggests that SP degranulates mast cel (212) and increases the release of histamine into draining veins (50) . This suggests that SP degranulates mast cells in human skin, but there is no direct evidence that this is so in human airway mast cells. Furthermo (212) and increases the release of histamine into draining
veins (50). This suggests that SP degranulates mast cells
in human skin, but there is no direct evidence that this
is so in human airway mast cells. Furthermore, veins (50). I his suggests that SP degrandiates mast cens
in human skin, but there is no direct evidence that this
is so in human airway mast cells. Furthermore, intrader-
mal capsaicin, which produces a flare in human ski is so in human airway mast cells. Furthermore, intradermal capsaicin, which produces a flare in human skin,
does not cause a wheal in the same way as antigen (50),
suggesting that release of endogenous sensory neuropep-
t mal capsaicin, which produces a flare in human skin, does not cause a wheal in the same way as antigen (50), suggesting that release of endogenous sensory neuropeptides may not degranulate mast cells. The effect of SP on m does not cause a wheal in the same way as antigen (50), suggesting that release of endogenous sensory neuropeptides may not degranulate mast cells. The effect of SP on mast cells may not be mediated by a classical SP-recep peptide. les may not degranulate mast cells. The effect of mast cells may not be mediated by a classical Sceptor (212), but may be due to the basic nature of t
ptide.
SP may also have effects on neutrophils and lymples and may, the

on mast cells may not be mediated by a classical SP-
receptor (212), but may be due to the basic nature of this
peptide.
SP may also have effects on neutrophils and lympho-
cytes and may, therefore, be involved in regulati receptor (212), but may be due to the basic nature of this peptide.

SP may also have effects on neutrophils and lympho-

cytes and may, therefore, be involved in regulation of

inflammatory reactions (457), although there peptide.
SP may also have effects c
cytes and may, therefore, bothis in airways.
evidence for this in airways.
D Role in Asthma cytes and may, there
 inflammatory reaction
 D. Role in Asthma

Although sensory 1 inflammatory reactions (457) , although there is no direct
evidence for this in airways.
D. Role in Asthma
Although sensory neuropeptides have several effects
which might indicate a role in asthma (45) , direct evi-

evidence for this in airways.

D. Role in Asthma

Although sensory neuropeptides have several effects

which might indicate a role in asthma (45), direct evi-

dence for their involvement is lacking, since there are no D. Role in Asthma

Although sensory neuropeptides have several effects

which might indicate a role in asthma (45), direct evi-

dence for their involvement is lacking, since there are no

specific antagonists which are s D. Role in Asthma
Although sensory neuropeptides have several effects
which might indicate a role in asthma (45), direct evi-
dence for their involvement is lacking, since there are no
specific antagonists which are suitab Although sensory neuropeptides have several effects
which might indicate a role in asthma (45) , direct evi-
dence for their involvement is lacking, since there are no
specific antagonists which are suitable for clinical which might indicate a role in asthma (45), direct evidence for their involvement is lacking, since there are no specific antagonists which are suitable for clinical use.
In rodents sensory neuropeptides may mediate NANC b dence for their involvement is lacking, since there are n
specific antagonists which are suitable for clinical us
In rodents sensory neuropeptides may mediate NAN
bronchoconstriction and airway vascular leakage aft
vagal s specific antagonists which are suitable for clinical use.
In rodents sensory neuropeptides may mediate NANC
bronchoconstriction and airway vascular leakage after
vagal stimulation, as discussed above. Furthermore,
stimulat In rodents sensory neuropeptides may mediate NANC
bronchoconstriction and airway vascular leakage after
vagal stimulation, as discussed above. Furthermore,
stimulation of sensory nerves by inflammatory mediators
causes rel bronchoconstriction and airway vascular leakage after
vagal stimulation, as discussed above. Furthermore,
stimulation of sensory nerves by inflammatory mediators
causes release of sensory neuropeptides from lung (508).
Neu vagal stimulation, as discussed above. Furthermore,
stimulation of sensory nerves by inflammatory mediators
causes release of sensory neuropeptides from lung (508).
Neurogenic inflammation and axon reflex mechanisms
are we stimulation of sensory nerves by inflammatory mediators
causes release of sensory neuropeptides from lung (508).
Neurogenic inflammation and axon reflex mechanisms
are well documented in the skin (459), axon reflexes are
i causes release of sensory neuropeptides from lung (508) .
Neurogenic inflammation and axon reflex mechanisms are well documented in the skin (459) , axon reflexes are involved in the skin response to antigen (377) , an Neurogenic inflammation and axon reflex mechanis
are well documented in the skin (459), axon reflexes
involved in the skin response to antigen (377), and i
possible that similar axon reflex mechanisms may op
ate in the air are well documented in the skin (459), axon reflexes are
involved in the skin response to antigen (377), and it is
possible that similar axon reflex mechanisms may oper-
ate in the airways in asthma (43). SP- and CGRP-
imm involved in the skin response to antigen (377), and it is
possible that similar axon reflex mechanisms may oper-
ate in the airways in asthma (43). SP- and CGRP-
immunoreactive nerves are certainly present in human
airways

Bedspet

PHARMACOLOGICAL REVIEWS

INFLAMMATORY MEDIATO
an axon reflex in asthma, since airway epithelium is wh
damaged and sensory nerve endings may be exposed of INFLAMMATORY MEDIAT
an axon reflex in asthma, since airway epithelium is w
damaged and sensory nerve endings may be exposed of
(331). Inflammatory mediators, such as bradykinin, may ao INFLAMMATORY MEDIATORY

an axon reflex in asthma, since airway epithelium is wh

damaged and sensory nerve endings may be exposed of

(331). Inflammatory mediators, such as bradykinin, may act

release sensory neuropeptide an axon reflex in asthma, since airway epitheliur
damaged and sensory nerve endings may be expo
(331). Inflammatory mediators, such as bradykinin, release sensory neuropeptides, as discussed above. A
reflex mechanisms migh damaged and sensory nerve endings may be expose (331). Inflammatory mediators, such as bradykinin, marelease sensory neuropeptides, as discussed above. Axcelex mechanisms might, therefore amplify inflammation in asthmatic (331). Inflammatory mediators, such as bradykinin, marelease sensory neuropeptides, as discussed above. Axceptex mechanisms might, therefore amplify inflammation in asthmatic airways, leading to exaggerated brough no sele release sensory neuropeptides, as discussed above. Axon
reflex mechanisms might, therefore amplify inflamma-
tion in asthmatic airways, leading to exaggerated bron-
choconstriction and mucosal edema. Although no selec-
tiv reflex mechanisms might, therefore amplify inflammation in asthmatic airways, leading to exaggerated bron-
choconstriction and mucosal edema. Although no selective tachykinin antagonists are yet available for clinical C
us tion in asthmatic airways, leading to exaggerated bron-
choconstriction and mucosal edema. Although no selec-
tive tachykinin antagonists are yet available for clinical
use, it might be possible to study the contribution o choconstriction and mucosal edema. Although no selective tachykinin antagonists are yet available for clinical
use, it might be possible to study the contribution of
axon reflex mechanisms by inhibitory release of sensory
 tive tachykinin antagonists are yet available for clinical C-tuse, it might be possible to study the contribution of Argazon reflex mechanisms by inhibitory release of sensory the neuropeptides. In the guinea pig, clonidin axon reflex mechanisms by inhibitory release of sensory
neuropeptides. In the guinea pig, clonidine inhibits
NANC and cholinergic vagal bronchoconstriction via axon reflex mechanisms by inhibitory release of sensory the anaphylatoxins C3a and C5a, although still retaining
neuropeptides. In the guinea pig, clonidine inhibits chemotactic activity. Until the recent development of
N MANC and cholinergic vagal bronchoconstriction via care-
prejunctional alpha₂ receptors (17), and opioids selectively inhibit NANC bronchoconstriction both in vitro
(217) and in vivo (71), acting via μ -opioid recepto sensory and chollineight vagal biolicincularitation
prejunctional alpha₂ receptors (17), and opioids s
tively inhibit NANC bronchoconstriction both in
(217) and in vivo (71), acting via μ -opioid receptor
sensory nerv tively inhibit NANC bronchoconstriction both in vitro (217) and in vivo (71), acting via μ -opioid receptors on sensory nerves. Depletion of airway sensory neuropeptides by capsaicin does not alter base-line bronchial r (217) and in vivo (71), acting via μ -opioid receptors on (217) and in vivo (71), acting via μ -opioid receptors on sensory nerves. Depletion of airway sensory neuropeptides by capsaicin does not alter base-line bronchial responsiveness in animals (569). Capsaicin pretreatment sensory nerves. Depletion of airway sensory neuropeptides by capsaicin does not alter base-line bronchiin responsiveness in animals (569). Capsaicin pretreatment of guinea pigs has been reported to inhibit bronchiin hypertides by capsaicin does not alter base-line bronchia
responsiveness in animals (569). Capsaicin pretreatmen
of guinea pigs has been reported to inhibit bronchia
hyper-responsiveness induced by toluene diisocyanate
by mecha responsiveness in animals (569). Capsaicin pretreatme of guinea pigs has been reported to inhibit bronch hyper-responsiveness induced by toluene diisocyana by mechanisms that remain to be explored (569); ho ever, it is lik of guinea pigs has been reported to inhibit bronchial
hyper-responsiveness induced by toluene diisocyanate,
by mechanisms that remain to be explored (569); how-
ever, it is likely that the measurement of airways resist-
an hyper-responsiveness induced by toluene diisocyanate,
by mechanisms that remain to be explored (569); how-
ever, it is likely that the measurement of airways resist-
ance mainly reflects changes in nasal resistance. The
ed by mechanisms that remain to be explored (569); how-
ever, it is likely that the measurement of airways resist-
ance mainly reflects changes in nasal resistance. The
edema induced by cigarette smoke in guinea pig nasal
muc ever, it is likely that the measurement of airways resistance mainly reflects changes in nasal resistance. The
edema induced by cigarette smoke in guinea pig nasal
mucosa is inhibited by capsaicin pretreatment (374), guidi ance mainly renects changes in hasal redema induced by cigarette smoke in gu
mucosa is inhibited by capsaicin pretre
indicating that sensory neuropeptides are intrants
airway inflammatory response to irritants mucosa is inhibited by capsaicin pretreatment (374),
indicating that sensory neuropeptides are involved in the
airway inflammatory response to irritants.
IX. Complement
Over 100 yr ago, it was recognized that serum condicating that sensory neuropeptides are involved in the

way inflammatory response to irritants.
 IX. Complement

Over 100 yr ago, it was recognized that serum con-

ined soluble and heat-labile proteins which could lyse

airway inflammatory response to irritants. C5

IX. Complement from the could lyse

over 100 yr ago, it was recognized that serum con-

tained soluble and heat-labile proteins which could lyse isolaterial cells. It is now a IX. Complement
Over 100 yr ago, it was recognized that serum con
tained soluble and heat-labile proteins which could lyse
bacterial cells. It is now apparent that the complemen
cascade represents a complex system consistin **cascade represents a complement** from tained soluble and heat-labile proteins which could lyse isoluterial cells. It is now apparent that the complement depeascade represents a complex system consisting of a tion range of Over 100 yr ago, it was recognized that serum contained soluble and heat-labile proteins which could lyse is
bacterial cells. It is now apparent that the complement defensed represents a complex system consisting of a tra bacterial cells. It is now apparent that the complement cascade represents a complex system consisting of a range of plasma proteins that play a role in host defense and in a number of pathological disorders of both im-
mu bacterial cells. It is now apparent that the compleme cascade represents a complex system consisting of range of plasma proteins that play a role in host deferend in a number of pathological disorders of both is munologica cascade represents a complex system consisting of a
range of plasma proteins that play a role in host defense
and in a number of pathological disorders of both im-
munological and nonimmunological origin. The activa-
tion range of plasma proteins that play a role in host defense brand in a number of pathological disorders of both im-
munological and nonimmunological origin. The activa-duation sequence and generation of the various componen and in a number of pathological disorders of both im-
munological and nonimmunological origin. The activa-
tion sequence and generation of the various components
complement components, C3a and
involvement of two complement munological and nonimmunological origin. The activa-
tion sequence and generation of the various components
are complex (100), and we have concentrated on the
compoly involvement of two complement components, C3a and
c5a (effects. involvement of two complement components, C3a and C5a (anaphylatoxins), which have documented airway effects.
 A. Origin and metabolism

The anaphylatoxins are fragments of the complement cascade that play little part in the further activation of effects.

A. Origin and metabolism

The anaphylatoxins are fragments of the complement

is cascade that play little part in the further activation of

the cascade itself, although they may regulate the further

b A. Origin and metabolism
The anaphylatoxins are fragments of the complement
cascade that play little part in the further activation of
the cascade itself, although they may regulate the further
production of the C2 compone A. *Origin and metabolism*
The anaphylatoxins are fragments of the complem
cascade that play little part in the further activation
the cascade itself, although they may regulate the furth
production of the C2 component, bu The anaphylatoxins are fragments of the complement
cascade that play little part in the further activation of
the cascade itself, although they may regulate the further
production of the C2 component, but may have inflam-
 the cascade itself, although they may regulate the further bed production of the C2 component, but may have inflaminometry effects. C3a and C5a are generated following his activation of the complement pathways by both the production of the C2 component, but may have inflam-
matory effects. C3a and C5a are generated following
activation of the complement pathway by both the clas-
sical and the alternative pathways. The complete amino
acid se matory effects. C3a and C5a are generated following his activation of the complement pathway by both the classical and the alternative pathways. The complete amino rolacid sequence of the anaphylatoxins has now been elu-
c activation of the complement pathway by both the classical and the alternative pathways. The complete amino rolacid sequence of the anaphylatoxins has now been elu-
acid sequence of the anaphylatoxins has now been elu-
cid sical and the alternative pathways. The complete amino rol
acid sequence of the anaphylatoxins has now been elu-
cidated in several species, including man, and there is uni
considerable homology. C5a has 74 amino acids and acid sequence of the anaphylatoxins has now been elu-
cidated in several species, including man, and there is
considerable homology. C5a has 74 amino acids and
contains an oligosaccharide attached at position 64 with
the a cidated in several species, including man, and there is considerable homology. C5a has 74 amino acids and remains an oligosaccharide attached at position 64 with the active site being the carboxy-terminal pentapeptide Metconsiderable homology. C5a has 74 amino acids and contains an oligosaccharide attached at position 64 with the active site being the carboxy-terminal pentapeptide Met-Glu-Leu-Gly-Arg. The remainder of the molecule is requi

INFLAMMATORY MEDIATORS AND ASTHMA ⁶⁹ INFLAMMATORY MEDIATORS AND ASTHMA

irway epithelium is which is not so with C3a, although the carboxyterminal

gs may be exposed of this molecule is again the active site. C3a has 77 amino of this molecule is again the active site. C3a has 77 amino
of this molecule is again the active site. C3a has 77 amino
acids with the carboxy-terminal pentapeptide Leu-Gly-
Leu-Ala-Arg. Leu-Ala-Arg.

The anaphylatoxins are rapidly inactivated in plasma
by the so-called anaphylatoxin inactivator (AI) which of this molecule is again the active site. C3a has 77 amino
acids with the carboxy-terminal pentapeptide Leu-Gly-
Leu-Ala-Arg.
The anaphylatoxins are rapidly inactivated in plasma
by the so-called anaphylatoxin inactivator acids with the carboxy-terminal pentapeptide Leu-Gly-
Leu-Ala-Arg.
The anaphylatoxins are rapidly inactivated in plasma
by the so-called anaphylatoxin inactivator (AI) which
expresses a carboxypeptidase B function removing Leu-Aia-Arg.

The anaphylatoxins are rapidly inactivated in plasma

by the so-called anaphylatoxin inactivator (AI) which

expresses a carboxypeptidase B function removing the

C-terminal arginine, leaving C3a des Arg and by the so-called anaphylatoxin inactivator (AI) which
expresses a carboxypeptidase B function removing the
C-terminal arginine, leaving C3a des Arg and C5a des
Arg, products devoid of much of the biological activity of
the expresses a carboxypeptidase B function removing the C-terminal arginine, leaving C3a des Arg and C5a des Arg, products devoid of much of the biological activity of the anaphylatoxins C3a and C5a, although still retaining C-terminal arginine, leaving C3a des Arg and C5a des Arg, products devoid of much of the biological activity of the anaphylatoxins C3a and C5a, although still retaining chemotactic activity. Until the recent development of chemotactic activity. Until the recent development of phylatoxins have been difficult to measure. rboxy-peptidase inhibitors, the in vivo levels of ana-
sylatoxins have been difficult to measure.
Receptors
Specific membrane receptors have been identified
aich bind C3 and its various components. C3a receptors

phylatoxins have been difficult to measure.

B. Receptors

Specific membrane receptors have been identified

which bind C3 and its various components. C3a receptors

have been identified on leukocytes and mast cells, while B. Receptors

Specific membrane receptors have been identified

which bind C3 and its various components. C3a receptors

have been identified on leukocytes and mast cells, while

C5a receptors have been identified on mast B. Receptors
Specific membrane receptors have been identified which bind C3 and its various components. C3a receptor
have been identified on leukocytes and mast cells, mono-
C5a receptors have been identified on mast cells specific membrane receptors have been identified
which bind C3 and its various components. C3a receptors
have been identified on leukocytes and mast cells, while
C5a receptors have been identified on mast cells, mono-
cyte have been identified on leukocytes and mast cells, while C5a receptors have been identified on mast cells, monocytes, platelets, and leukocytes (482). To date, specific receptors for anaphylatoxins have not been demonstrat have been identified on leukocytes and mast cells, while
C5a receptors have been identified on mast cells, mono-
cytes, platelets, and leukocytes (482). To date, specific
receptors for anaphylatoxins have not been demon-
s Coa receptors have been identified on mast cens, monicytes, platelets, and leukocytes (482). To date, specifical receptors for anaphylatoxins have not been demonstrated in airway preparations, but C5a is able to contra bro tes, platelets, and leukocytes (482). To date, specific
ceptors for anaphylatoxins have not been demon-
rated in airway preparations, but C5a is able to contract
onchial smooth muscle preparations in vitro (482).
1. Smooth

explores for anaphylatoxins have not been demon-
strated in airway preparations, but C5a is able to contract
bronchial smooth muscle preparations in vitro (482).
1. Smooth muscle contraction. Intravenous injection of
guine strated in an way preparations, but Coa is able to contract
bronchial smooth muscle preparations in vitro (482).
1. Smooth muscle contraction. Intravenous injection of
guinea pigs with C5a causes bronchoconstriction (85),
 1. Smooth muscle contruction. Intravenous injection of
guinea pigs with C5a causes bronchoconstriction (85),
but the mechanisms involved are unknown, although
C5a and C5a des Arg induce the release of histamine
(498, 503), guinea pigs with C5a causes bronchoconstriction (65),
but the mechanisms involved are unknown, although
C5a and C5a des Arg induce the release of histamine
(498, 503), prostaglandins (504), and leukotrienes (554)
from guin C5a and C5a des Arg induce the release of histamine (498, 503), prostaglandins (504), and leukotrienes (554) from guinea pig lung. C5a elicits airway smooth muscle contraction in both perfused guinea pig lungs (503) and is (498, 503), prostaglandins (504), and leukotrienes (554) from guinea pig lung. C5a elicits airway smooth muscle contraction in both perfused guinea pig lungs (503) and isolated tracheal smooth muscle preparations (482), i from guinea pig lung. Coa encits arrway smooth muscle
contraction in both perfused guinea pig lungs (503) and
isolated tracheal smooth muscle preparations (482), in-
dependently of histamine release. The precise contribu-
 isolated tracheal smooth muscle preparations (482), in
dependently of histamine release. The precise contribution of arachidonic acid metabolites to C5a-induce
bronchoconstriction is not clear, although both cycloo:
ygenas tion of arachidonic acid metabolites to C5a-induced
bronchoconstriction is not clear, although both cycloox-
ygenase and lipoxygenase metabolites inhibit C5a-in-
duced contraction of airway smooth muscle preparations.
C3a bronchoconstriction is not clear, although both cycloox-
ygenase and lipoxygenase metabolites inhibit C5a-in-
duced contraction of airway smooth muscle preparations.
C3a is a less potent inducer of airway smooth muscle
con ygenase and lipoxygenase metabolites inhibit C5
duced contraction of airway smooth muscle preparat
C3a is a less potent inducer of airway smooth mu
contraction than C5a in the guinea pig (555). This e
appears to be mediate duced contraction of airway smooth muscle preparations.
C3a is a less potent inducer of airway smooth muscle
contraction than C5a in the guinea pig (555). This effect
appears to be mediated predominantly via a cyclooxygenappears to be mediated predominantly via a cyclooxygen-
ase product, despite the release of histamine (555). Both
C3a and C5a induce marked tachyphylaxis in airway
smooth muscle preparations, although there is no cross-
de B. Receptors

Specific membrane receptors have been identified

specific membrane receptors have been identified on mast cells, while

CSa receptors have been identified on leukocytes and mast cells, while

CSa receptors smooth muscle preparations, although there is no cross-

2. Vascular effects. Complement activation has long been recognized as a trigger of increased vascular perme-
ability in skin, which was believed to be secondary to smooth muscle preparations, although there is no cro
desensitization between them, indicating that they is
likely to activate discrete receptors (482).
2. Vascular effects. Complement activation has lo
been recognized as a desensitization between them, indicating that they are likely to activate discrete receptors (482).
2. Vascular effects. Complement activation has long been recognized as a trigger of increased vascular perme-
ability in s 2. Vascular effects. Complement activation has long
been recognized as a trigger of increased vascular perme-
ability in skin, which was believed to be secondary to
histamine release (175). C5a and C3a induce vascular
perm been recognized as a trigger of increased vascular permeability in skin, which was believed to be secondary to histamine release (175). C5a and C3a induce vascular permeability through neutrophil activation, although the r ability in skin, which was believed to be secondary to
histamine release (175). C5a and C3a induce vascular
permeability through neutrophil activation, although the
role of the neutrophil has not been fully elucidated (604 histamine release (175). C5a and C3a induce vascular
permeability through neutrophil activation, although the
role of the neutrophil has not been fully elucidated (604).
Although C5a releases PAF from neutrophils (605), it permeability through neutrophil activation, although the role of the neutrophil has not been fully elucidated (604).
Although C5a releases PAF from neutrophils (605), it is unlikely that PAF is the mediator responsible for role of the neutrophil has not been fully elucidated (604).
Although C5a releases PAF from neutrophils (605), it is
unlikely that PAF is the mediator responsible for the
neutrophil-dependent vascular permeability induced b Although C5a releases PAF from neutrophils (605), it is
unlikely that PAF is the mediator responsible for the
neutrophil-dependent vascular permeability induced by
C5a as PAF antagonists do not inhibit C5a-induced
edema fo unlikely that PAF is the mediator responsible for the neutrophil-dependent vascular permeability induced b C5a as PAF antagonists do not inhibit C5a-induce edema formation (273). In man, C5a produces immediat wheal and fla neutrophil-dependent vascular permeability induced by
C5a as PAF antagonists do not inhibit C5a-induced
edema formation (273). In man, C5a produces immediate
wheal and flare reactions in skin; an H1-antihistamine
reduced t

addition, biopsies of skin showed neutrophil infiltration, endothelial cell edema, and mast cell degranulation
endothelial cell edema, and mast cell degranulation.
There is little work in the role of C5a in airways, althoug BARNES, CHUNG
addition, biopsies of skin showed neutrophil infiltration, c
endothelial cell edema, and mast cell degranulation. to
There is little work in the role of C5a in airways, although (
preliminary studies have sho addition, biopsies of skin showed neutrophil infiltration,
endothelial cell edema, and mast cell degranulation.
There is little work in the role of C5a in airways, although (
preliminary studies have shown that C5a is asso endothelial cell edema, and mast cell degranulation.
There is little work in the role of C5a in airways, although
preliminary studies have shown that C5a is associated
with neutrophil recruitment in airways (300).

There is little work in the role of C5a in airways, although
preliminary studies have shown that C5a is associated
with neutrophil recruitment in airways (300).
3. Mucus secretion. Little is known about the effects
of the preliminary studies have shown that C5a is associated the with neutrophil recruitment in airways (300). a
3. Mucus secretion. Little is known about the effects of the anaphylatoxins on airway secretion or mucociliary a
cle with neutrophil recruitment in airways (300).
3. Mucus secretion. Little is known about the effects
of the anaphylatoxins on airway secretion or mucociliary
clearance. C3a stimulates mucus glycoprotein secretion
from human 3. Mucus secretion. Litt
of the anaphylatoxins on a
clearance. C3a stimulates
from human airways in vite
effect on secretory cells.
4. Chemotaxis and cell from human airways in vitro (393a), probably via a direct
effect on secretory cells.
4. Chemotaxis and cell activation. One of the most

clearance. C3a stimulates mucus glycoprotein secretion refrom human airways in vitro (393a), probably via a direct leneffect on secretory cells.
4. Chemotaxis and cell activation. One of the most widely studied effects of from human airways in vitro $(393a)$, probably via a direct
effect on secretory cells.
4. Chemotaxis and cell activation. One of the most
widely studied effects of anaphylatoxins is their ability
to induce activation of i effect on secretory cells.
4. Chemotaxis and cell activation. One of the most
widely studied effects of anaphylatoxins is their ability
to induce activation of inflammatory cells. C5a and C5a
sid
des Arg have chemotactic a 4. Chemotaxis and cell activation. One of the most
widely studied effects of anaphylatoxins is their ability
to induce activation of inflammatory cells. C5a and C5a
sides Arg have chemotactic activity for neutrophils, wit widely studied effects of anaphylatoxins is their ability
to induce activation of inflammatory cells. C5a and C5a
des Arg have chemotactic activity for neutrophils, with
a potency even greater than that of LTB4 (417). C5a
 to induce activation of inflammatory cells. C5a and C5a des Arg have chemotactic activity for neutrophils, with a potency even greater than that of LTB4 (417). C5a also has chemotactic activity for macrophages (486), basop des Arg have chemotactic activity for neutrophils, with
a potency even greater than that of LTB4 (417). C5a
its
also has chemotactic activity for macrophages (486),
basophils (319), and eosinophils (318). In contrast, hu-
 a potency even greater than that of LTB4 (417). C5a it
also has chemotactic activity for macrophages (486),
basophils (319), and eosinophils (318). In contrast, hu-
man C3a is devoid of chemotactic activity (200). Both
C5 also has chemotactic activity for macrophages (48
basophils (319), and eosinophils (318). In contrast, h
man C3a is devoid of chemotactic activity (200). Bo
C5a and C5a des Arg also stimulate the adhesion
inflammatory cell basophils (319), and eosinophils (318). In contrast, hu-

man C3a is devoid of chemotactic activity (200). Both

C5a and C5a des Arg also stimulate the adhesion of

inflammatory cells and elicit the release of other mediaman C3a is devoid of chemotactic activity (200). Both C5a and C5a des Arg also stimulate the adhesion of inflammatory cells and elicit the release of other mediators, including lysosomal enzymes (401), free oxygen radicals C5a and C5a des Arg also stimulate the adhesion of inflammatory cells and elicit the release of other mediators, including lysosomal enzymes (401), free oxygen radicals (72), both lipoxygenase and cyclooxygenase products inflammatory cells and elicit the release of other metors, including lysosomal enzymes (401), free oxy
radicals (72), both lipoxygenase and cyclooxygen
products of arachidonic acid metabolism (136), and I
from both neutrop **Frame in the CFA** including lysosomal enzymes (401) , free oxygen $\frac{1}{100}$
dicals (72) , both lipoxygenase and cyclooxygenase need
oducts of arachidonic acid metabolism (136) , and PAF
tom both neutrophils (110)

radicals (72), both lipoxygenase and cyclooxygenase
products of arachidonic acid metabolism (136), and PAF
from both neutrophils (110) and eosinophils (344).
5. Bronchial hyper-responsiveness. Inhalation of C5a
des Arg cau products of arachidonic acid metabolism (136), and PAI
from both neutrophils (110) and eosinophils (344).
5. Bronchial hyper-responsiveness. Inhalation of C5
des Arg causes increased airway responsiveness to his
tamine 4 h from both neutrophils (110) and eosinophils (344) .
5. Bronchial hyper-responsiveness. Inhalation of C5a
des Arg causes increased airway responsiveness to his-
tamine 4 h later (300) , at a time when neutrophil infil-5. Bronchial hyper-responsiveness. Inhalation of C5 des Arg causes increased airway responsiveness to his tamine 4 h later (300), at a time when neutrophil infil tration occurs in the airways. The increased airway responsi des Arg causes increased airway responsiveness to his-
tamine 4 h later (300), at a time when neutrophil infil-
tration occurs in the airways. The increased airway re-
sponsiveness is reduced in animals rendered neutropeni tamine 4 h later (300), at a time when neut
tration occurs in the airways. The increased
sponsiveness is reduced in animals rendered r
suggesting that neutrophils contribute to the
of bronchial hyper-responsiveness by C5a **Example 19 Sponsiveness is reduced suggesting that neutrost suggesting that neutrost D. Role in Asthma**
D. Role in Asthma Little is known of the

asthma, since studies with inhibitors of complement D. Role in Asthma
Little is known of the role of anaphylatoxins in hun
asthma, since studies with inhibitors of complem
activation have not yet been reported in man. Measure-
ment of C5a and C3a have proved to be difficult D. Role in Asthma

Little is known of the role of anaphylatoxins in human

asthma, since studies with inhibitors of complement stim

activation have not yet been reported in man. Measure-

eral

ment of C5a and C3a have p Little is known of the role of anaphylatoxins in human
asthma, since studies with inhibitors of complement
activation have not yet been reported in man. Measure-
ment of C5a and C3a have proved to be difficult in
plasma, a asthma, since studies with inhibitors of complement stinuarition have not yet been reported in man. Measure-
ment of C5a and C3a have proved to be difficult in sele-
plasma, and their release has not yet been demonstrated activation have not yet been reported in man. Measure-
ment of C5a and C3a have proved to be difficult in see
plasma, and their release has not yet been demonstrated ge
in asthma. The potent effects of these mediators on
 ment of C5a and C3a have proved to be difficult in splasma, and their release has not yet been demonstrated gines as a subtraction of these mediators on microvascular leakage and bronchial smooth muscle have not been conf plasma, and their release has not yet been demonstrated
in asthma. The potent effects of these mediators on
microvascular leakage and bronchial smooth muscle have
not been confirmed in human subjects, and no specific
antag in asthma. The potent effects of these mediators on microvascular leakage and bronchial smooth muscle have not been confirmed in human subjects, and no specific antagonists are available. Several clinical investigations c microvascular leakage and bronchial smooth muscle have
not been confirmed in human subjects, and no specific
antagonists are available. Several clinical investigations cie
have reported the activation of the complement cas not been confirmed in human subjects, and no specific
antagonists are available. Several clinical investigations
have reported the activation of the complement cascade
buring asthma. Plasma C4 concentrations have been
foun antagonists are available. Several clinical investigations
have reported the activation of the complement cascade
during asthma. Plasma C4 concentrations have been
found to be elevated in childhood asthma and depressed
in mave reported the activation of the complement cascade
during asthma. Plasma C4 concentrations have been
found to be elevated in childhood asthma and depressed
in non-atopic adult asthmatics (321), although other
investiga found to be elevated in childhood asthma and depressed (47
in non-atopic adult asthmatics (321), although other bro
investigators have not confirmed this observation (263, but
236, 574, 176). Furthermore, no changes in com in non-atopic adult asthmatics (321), although other
investigators have not confirmed this observation (263,
236, 574, 176). Furthermore, no changes in complement
are detected in allergic asthmatics following either early
 investigators have not confirmed this observation (263
236, 574, 176). Furthermore, no changes in complement
are detected in allergic asthmatics following either early
or late reactions to allergen provocation (293, 315, 1 236, 574, 176). Furthermore, no changes in complement are detected in allergic asthmatics following either earlor late reactions to allergen provocation (293, 315, 12). A few patients develop reduced hemolytic complement a are detected in allergic asthmatics following either early $(573, 158)$.

or late reactions to allergen provocation $(293, 315, 12)$. In dogs, serotonin enhances vagal nerve but not ace-

A few patients develop reduced he or late reactions to allergen provocation (293, 315, 12).
A few patients develop reduced hemolytic complement
activity or C4 in arterial or venous blood following aller-
gen provocation (548), whereas others have reported A few patients develop reduced hemolytic complementivity or C4 in arterial or venous blood following all gen provocation (548), whereas others have reported increase (65). The role of complement in aspirin-sentive asthma i activity or C4 in arterial or venous blood following allergen provocation (548), whereas others have reported an increase (65). The role of complement in aspirin-sensitive asthma is equally controversial, since some invest gen provocation (548), whereas others have reported an increase (65). The role of complement in aspirin-sensitive asthma is equally controversial, since some investigators have reported decreased complement levels after or

There is little work in the role of C5a in airways, although (472). These studies do not exclude the possibility that

preliminary studies have shown that C5a is associated there may be local complement activation within t G, AND PAGE
changes in hemolytic complement activity or C4 in ar-
terial or venous blood following aspirin provocation The NAMI PAGE
Thanges in hemolytic complement activity or C4 in ar-
terial or venous blood following aspirin provocation
(472). These studies do not exclude the possibility that G, AND PAGE

changes in hemolytic complement activity or C4 in ar-

terial or venous blood following aspirin provocation

(472). These studies do not exclude the possibility that

there may be local complement activation w changes in nemotytic complement activity or C4 in ar-
terial or venous blood following aspirin provocation
(472). These studies do not exclude the possibility that
there may be local complement activation within the
airway terial or venous blood following aspirin provocat (472). These studies do not exclude the possibility t
there may be local complement activation within
airways in asthma. The use of specific inhibitors of
complement cascad (472). These studies do not exclude the possibility that
there may be local complement activation within the
airways in asthma. The use of specific inhibitors of the
complement cascade, such as N-acetyl-aspartyl-glutamic
a there may be local complement activation within the airways in asthma. The use of specific inhibitors of the complement cascade, such as N-acetyl-aspartyl-glutamic acid (NAAGA), may be useful in asthma, and preliminary res e airways in asthma. The complement cascade, acid (NAAGA), may be results have already in the series of the se acid (NAAGA), may be useful in asthma, and preliminary
results have already indicated a beneficial effect in al-
lergic rhinitis (233).
X. Serotonin

lergic rhinitis (233).
 **X. Serotonin

Serotonin (5-hydroxytryptamine, 5-HT) was once con-

sidered to be an important mediator of asthma, since it** sidered to be an important mediator of asthma, since considered to be an important mediator of asthma, since it
caused bronchoconstriction in several animal species, but X. Serotonin
Serotonin (5-hydroxytryptamine, 5-HT) was once considered to be an important mediator of asthma, since it
caused bronchoconstriction in several animal species, but
its relevance to human asthma now seems doubt Serotonin (5-hydroxytryptamine, 5-HT) was once
sidered to be an important mediator of asthma, sincaused bronchoconstriction in several animal species
its relevance to human asthma now seems doubtful *A. Origin*
A. Origin
A. Origin
A. Origin

used bronchoconstriction in several animal species, but
relevance to human asthma now seems doubtful.
Origin
Serotonin is formed by decarboxylation of tryptophan
the diet and stored in secretory granules. In rodents, A. Origin

Serotonin is formed by decarboxylation of tryptophan

in the diet and stored in secretory granules. In rodents,

serotonin is present in mast cell granules, but this is not

the case in humans. Serotonin in man Serotonin is formed by decarboxylation of tryptophan
in the diet and stored in secretory granules. In rodents,
serotonin is present in mast cell granules, but this is not
the case in humans. Serotonin in man is localized Serotonin is formed by decarboxylation of tryptoph
in the diet and stored in secretory granules. In roder
serotonin is present in mast cell granules, but this is is
the case in humans. Serotonin in man is localized
neuroen in the diet and stored in secretory granules. In rodents,
serotonin is present in mast cell granules, but this is not
the case in humans. Serotonin in man is localized to
neuroendocrine cells of the gastrointestinal and r serotonin is present in mast cell granules, but this is not
the case in humans. Serotonin in man is localized to
neuroendocrine cells of the gastrointestinal and respira-
tory tract, to certain nerves, and to secretory gr the case in humans. Serotonin in man is localized to
neuroendocrine cells of the gastrointestinal and respira-
tory tract, to certain nerves, and to secretory granules in
platelets. The possible involvement in platelets in rotonin. platelets. The possible involvement in platelets in asthma (416) has, therefore, reawakened interest in serotonin.
B. Receptors

Expositences in collection in initiality contribute to the induction
of bronchial hyper-responsiveness by C5a.
D. Role in Asthma
D. Role in Asthma
Interesponsiveness by C5a.
Little is known of the role of anaphylatoxins i thma (416) has, therefore, reawakened interest in se-
tonin.
Receptors
The development of specific antagonists has made it
ssible to recognize at least three types of serotonin potonin.
 B. Receptors

The development of specific antagonists has made it

possible to recognize at least three types of serotonin

receptor. 5-HT₁-receptors are usually inhibitory, 5-HT₂-B. Receptors
The development of specific antagonists has made it
possible to recognize at least three types of serotonin
receptor. 5-HT₁-receptors are usually inhibitory, 5-HT₂-
receptors are excitatory and mediate smo The development of specific antagonists has made it possible to recognize at least three types of serotonin receptor. $5\text{-}HT_1\text{-receptors}$ are usually inhibitory, $5\text{-}HT_2\text{-receptors}$ are excitatory and mediate smooth muscle cont The development of specific antagonists has made it
possible to recognize at least three types of serotonin
receptor. $5\text{-}HT_1\text{-}receptors$ are usually inhibitory, $5\text{-}HT_2\text{-}receptors$ are excitatory and mediate smooth muscle conpossible to recognize at least times types or serotonin
receptor. 5-HT₁-receptors are usually inhibitory, 5-HT₂-
receptors are excitatory and mediate smooth muscle con-
traction, and 5-HT₃-receptors are present on ne receptors are excitatory and mediate smooth muscle contraction, and 5-HT₃-receptors are present on nerves a
stimulate neurotransmitter release from certain peripral nerves (487). The development of more and moselective a stimulate neurotransmitter release from certain peripheral nerves (487). The development of more and more selective antagonists has provided evidence for heterogeneity within 5-HT₁- and 5-HT₃-receptor subtypes.
C. Air *Selective antagonists has provided evidence for heterogeneity within 5-HT₁- and 5-HT₃-receptor subtypes.
C. Airway Effects
Serotonin causes bronchoconstriction in several spe-*

geneity within 5-HT₁- and 5-HT₃-receptor subtypes.
C. Airway Effects
Serotonin causes bronchoconstriction in several spe-
cies, including the guinea pig, cat, rat, dog, and monkey; C. Airway Effects

C. Airway Effects

Serotonin causes bronchoconstriction in several spe-

cies, including the guinea pig, cat, rat, dog, and monkey;

but there is considerable doubt about its effect in human

airways. Se C. Atrway Effects
Serotonin causes bronchoconstriction in several species, including the guinea pig, cat, rat, dog, and monkey;
but there is considerable doubt about its effect in human
airways. Serotonin even relaxes huma Serotonin causes bronchoconstriction in several species, including the guinea pig, cat, rat, dog, and monkey;
but there is considerable doubt about its effect in human
airways. Serotonin even relaxes human airways in vitro but there is considerable doubt about its effect in hu
airways. Serotonin even relaxes human airways in
(479). In vivo inhaled serotonin was reported to c
bronchoconstriction in some asthmatic patients (
but other studies airways. Serotonin even relaxes human airways in vitro (479). In vivo inhaled serotonin was reported to cause bronchoconstriction in some asthmatic patients (448), but other studies have found no consistent bronchoconstric (479) . In vivo inhaled serotonin was reported to cause
bronchoconstriction in some asthmatic patients (448) ,
but other studies have found no consistent bronchocon-
strictor response in either normal or asthmatic subje

tylcholine-induced bronchoconstriction, suggesting that strictor response in either normal or asthmatic subjects (573, 158).

In dogs, serotonin enhances vagal nerve but not ace-

tylcholine-induced bronchoconstriction, suggesting that

it may facilitate release of acetylcholin In dogs, serotonin ennances vagar nerve out not ace-
tylcholine-induced bronchoconstriction, suggesting that
it may facilitate release of acetylcholine from airway
nerves (257, 525). Whether this occurs in human airways
ha

It may facilitate release of acetylcholine from airway
nerves (257, 525). Whether this occurs in human airways
has not been determined.
Serotonin is a potent constrictor of human pulmonary
vessels (479), but it is not know vessels (479), but it is not known whether it constricts bronchial vessels. It also causes microvascular leakage in

aspet

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INFLAMMATORY MEDI
guinea pig airways (507) and could have a similar effect
in man since it causes a wheal response in human skin INFLAMMATORY MEDIATC
guinea pig airways (507) and could have a similar effect
in man since it causes a wheal response in human skin des
and stimulates an axon reflex (487). eos IN
guinea pig airways (507) and could ha
in man since it causes a wheal respor
and stimulates an axon reflex (487).
Few studies have been performed v inea pig airways (507) and could have a similar effect
man since it causes a wheal response in human skin
d stimulates an axon reflex (487).
Few studies have been performed with antagonists of
protonin in asthma. Ketanser guinea pig airways (507) and could have a similar effection man since it causes a wheal response in human skip and stimulates an axon reflex (487).
Few studies have been performed with antagonists of serotonin in asthma.

In man since it causes a wheat response in numan skin and stimulates an axon reflex (487) .
Few studies have been performed with antagonists of serotonin in asthma. Ketanserin, a 5-HT₂ antagonist, has no protective act (544). nave been performed with an
insthma. Ketanserin, a 5-HT₂
WI. Chemotactic Factors
mediators discussed above. has no protective action against exercise-induced asthma (544).
 XI. Chemotactic Factors

Many of the mediators discussed above, and particu-

(544).
 XI. Chemotactic Factors

Many of the mediators discussed above, and partic

larly LTB₄, 15-HETE, PAF, and C5a, have potent chem

otactic activity. In addition, a number of poorly defin **XI. Chemotactic Factors**
Many of the mediators discussed above, and particu-
larly LTB₄, 15-HETE, PAF, and C5a, have potent chem-
otactic activity. In addition, a number of poorly defined
large molecules have been ident Al. Chemotactic ractors
Many of the mediators discussed above, and particularly LTB₄, 15-HETE, PAF, and C5a, have potent chemotactic activity. In addition, a number of poorly define
large molecules have been identified a Many of the mediators discussed above, and particu-
larly LTB₄, 15-HETE, PAF, and C5a, have potent chem-
otactic activity. In addition, a number of poorly defined
large molecules have been identified as chemoattractants larly LTB₄, 15-HETE, PAF, and C5a, have potent chem-
otactic activity. In addition, a number of poorly defined
having the sequence Val-Gly-Ser-Glu and Ala-Gly-Ser-
large molecules have been identified as chemoattractant large molecules have been identified as chemoattractants
and investigated for their potential contribution to al-
lergic inflammation. However, almost all the work in this
area has relied upon in vitro observations of chem and investigated for their potential contribution to aland investigated for their potential contribution to al-
lergic inflammation. However, almost all the work in this
area has relied upon in vitro observations of chemo-
attractant activity, and no conclusive proof of the in lergic inflammation. However, almost all the work in this
area has relied upon in vitro observations of chemo-
attractant activity, and no conclusive proof of the in-
volvement of these materials in vivo has been obtained. area has relied upon in vitro observations of chemo-
attractant activity, and no conclusive proof of the in-
volvement of these materials in vivo has been obtained.
Materials displaying chemotactic activity by neutrophils
 attractant activity, and no conclusive proof of the in-
volvement of these materials in vivo has been obtained.
Materials displaying chemotactic activity by neutrophils
in vitro have been identified as products released fr volvement of these materials in vivo has been obtained.
Materials displaying chemotactic activity by neutrophils
in vitro have been identified as products released from
human leukemic basophils (363), rat mast cells (565), Materials displaying chemotactic activity by neutrophils
in vitro have been identified as products released from
human leukemic basophils (363), rat mast cells (565),
and extracts of lung tissue (437). Neutrophil chemotact in vitro have been identified as products released fr
human leukemic basophils (363), rat mast cells (56
and extracts of lung tissue (437). Neutrophil chemota
activity has also been detected in the serum of patie
undergoin human leukemic basophils (363), rat mast cells (565), and extracts of lung tissue (437). Neutrophil chemotactic activity has also been detected in the serum of patients undergoing experimentally induced physical and temper and extracts of lung tissue (437). Neutrophil chemotactic inity activity has also been detected in the serum of patients eoundergoing experimentally induced physical and temper-
ature-induced urticaria (600, 32), allergic activity has also been detected in the serum of patients
undergoing experimentally induced physical and temper-
ature-induced urticaria (600, 32), allergic and nonallergic
bronchoconstriction (546, 30). However, many of th undergoing experimentally induced physical and temperature-induced urticaria (600, 32), allergic and nonallergic (bronchoconstriction (546, 30). However, many of the adefined low-molecular-weight chemotactic factors (e.g. ature-matced urticaria (600, 32), allergic and nonaliergic
bronchoconstriction (546, 30). However, many of the
defined low-molecular-weight chemotactic factors (e.g., 1
LTB₄ and PAF) avidly bind to plasma proteins, and i defined fow-molecular-weight chemotactic factors (e.g.,
LTB₄ and PAF) avidly bind to plasma proteins, and it
still remains plausible that such chemotactic activity
could be secondary to these low-molecular-weight mate-
r still remains plausible that such chemotactic activity
could be secondary to these low-molecular-weight mate-
rials bound to plasma proteins. Neutrophil chemotactic
activity cannot be attributed to the complement frag-
me could be secondary to these low-molecular-weight mate-
rials bound to plasma proteins. Neutrophil chemotactic
activity cannot be attributed to the complement frag-
ments C3 or C5 as a high-molecular-weight, heat-stable
pr rials bound to plasma proteins. Neutrophil chemotactic ent
activity cannot be attributed to the complement frag-
ittl ments C3 or C5 as a high-molecular-weight, heat-stable airv
protein $(M_r \sim 600,000)$ having neutrophil c activity cannot be attributed to the complement frag-
ments C3 or C5 as a high-molecular-weight, heat-stable airv
protein $(M_r \sim 600,000)$ having neutrophil chemotactic σ
activity (NCA) has been shown to be unaffected b ments C3 or C5 as a high-molecular-weight, heat-stable
protein $(M_r \sim 600,000)$ having neutrophil chemotactic
activity (NCA) has been shown to be unaffected by
preincubation with an antibody to human C3 or C;
complement fr activity (NCA) has been shown to be unaffected by
preincubation with an antibody to human C3 or C5
complement fragments (347). NCA is released in a vari-
ety of inflammatory conditions, including urticaria (600,
32), and activity (NCA) has been shown to be unaffected by
preincubation with an antibody to human C3 or C5
complement fragments (347). NCA is released in a vari-
ety of inflammatory conditions, including urticaria (600,
32), and f complement fragments (347). NCA is released in a varicomplement fragments (347). NCA is released in a vari-
ety of inflammatory conditions, including urticaria (600,
32), and following challenge of asthmatics by exercise e
(347) or with an appropriate antigen (31, 422). Howe ety of inflammatory conditions, including urticaria (60
32), and following challenge of asthmatics by exerci
(347) or with an appropriate antigen (31, 422). However
the specificity of this molecule as a marker of aller
res 32), and following challenge of asthmatics by exercise en (347) or with an appropriate antigen $(31, 422)$. However, gethe specificity of this molecule as a marker of allergic stresponses is highly dubious, because simi the specificity of this molecule as a marker of allergic
responses is highly dubious, because similar NCA chem-
otactic activity has been reported in patients with active
bronchitis and pneumonia (152). It seems likely tha the specificity of this molecule as a marker of aller
responses is highly dubious, because similar NCA che
otactic activity has been reported in patients with act
bronchitis and pneumonia (152). It seems likely t
NCA may r responses is highly dubious, because similar NCA chem-
otactic activity has been reported in patients with active (61
bronchitis and pneumonia (152). It seems likely that mu
NCA may represent an indication that an acute i otactic activity has been reported in p
bronchitis and pneumonia (152). It
NCA may represent an indication th
matory process has taken place in n
as acute plasma proteins are utilized.
Another problem with the various onchitis and pneumonia (152). It seems likely that CA may represent an indication that an acute inflam-
atory process has taken place in much the same way
acute plasma proteins are utilized.
Another problem with the variou

NCA may represent an indication that an acute inflam-
matory process has taken place in much the same way
as acute plasma proteins are utilized.
Another problem with the various NCA activities de-
scribed experimentally an matory process has taken place in much the same way
as acute plasma proteins are utilized.
Another problem with the various NCA activities de-
scribed experimentally and clinically is that they rely on
the use of a bioassa as acute plasma proteins are utilized.

Another problem with the various NCA activities descave

scribed experimentally and clinically is that they rely on

the use of a bioassay based on movement of neutrophils (61).

in scribed experimentally and clinically is that they rely on
the use of a bioassay based on movement of neutrophils (witro and, as such, all current measurements of NCA
merely reflect a general activity rather than a defined the use of a bioassay based on movement of neutrophils
in vitro and, as such, all current measurements of NCA
merely reflect a general activity rather than a defined
chemical entity. As mentioned earlier, until specific
ch in vitro and, as such, all current measurements of NCA
merely reflect a general activity rather than a defined
chemical entity. As mentioned earlier, until specific
chemical quantification of the proposed NCA activities
is chemical entity. As ment
chemical quantification of
is developed, all such chem
tributed to the release of low
binding to plasma proteins.

ORS AND ASTHMA

A second group of chemotactic factors have also been

scribed that share the property of being selective for TORS AND ASTHMA
A second group of chemotactic factors have also been
described that share the property of being selective for
eosinophils (318). Eosinophil chemotactic factor of ana-TORS AND ASTHMA

A second group of chemotactic factors have also been

described that share the property of being selective for

eosinophils (318). Eosinophil chemotactic factor of ana-

phylaxis (ECF-A) has been identifie A second group of chemotactic factors have also been
described that share the property of being selective for
eosinophils (318). Eosinophil chemotactic factor of ana-
phylaxis (ECF-A) has been identified in supernatants
fr basophils (318). Eosinophil chemolactic factor of an
phylaxis (ECF-A) has been identified in supernatar
from IgE-challenged tissue extracts of human lung (3)
and isolated cell preparations, such as human leuker
basophils (from IgE-challenged tissue extracts of human lung (320)
and isolated cell preparations, such as human leukemic
basophils (363) and human mast cells (30) . Furthermore,
ECF activity has been identified in the serum of nom igen-changed ussue extracts of human lung (520)
and isolated cell preparations, such as human leukemic
basophils (363) and human mast cells (30). Furthermore,
ECF activity has been identified in the serum of patients
u and isolated ten preparations, such as human reukemic
basophils (363) and human mast cells (30). Furthermore,
ECF activity has been identified in the serum of patients
undergoing antigen-induced bronchoconstriction (406)
a and with urticarias produced by physical challenge (600). and with diricatias produced by physical changing (600).
ECF-A was originally described as two tetrapeptides,
having the sequence Val-Gly-Ser-Glu and Ala-Gly-Ser-
Glu (237), but it is now clear that such tetrapeptides onl ECF-A was originally described as two tetrapept
having the sequence Val-Gly-Ser-Glu and Ala-Gly-
Glu (237), but it is now clear that such tetrapeptides
form a very small component of the original EC
(599). ECF-A is far les Having the sequence val-cry-Ser-Critical Ana-Cry
Glu (237), but it is now clear that such tetrapeptide
form a very small component of the original E
(599). ECF-A is far less potent than PAF as a chen
tic agent from human e **x** Is now clear that such tetra

and component of the of

far less potent than PAF a

uman eosinophils, howeve
 XII. Oxygen Radicals

als are generated as part 99). ECF-A is far less potent than PAF as a chemot:

expect from human eosinophils, however (597).

XII. Oxygen Radicals

Oxygen radicals are generated as part of the inflam-

atory reaction and are therefore likely to be

Glu (237), but it is now clear that such tetrapeptides only form a very small component of the original ECF-A (599). ECF-A is far less potent than PAF as a chemotactic agent from human eosinophils, however (597).
 XII. O ic agent from human eosinophils, however (597).
 XII. Oxygen Radicals

Oxygen radicals are generated as part of the inflam-

matory reaction and are therefore likely to be involved

in the pathophysiology of asthma. Acti XII. Oxygen Radicals
Oxygen radicals are generated as part of the inflam-
matory reaction and are therefore likely to be involved
in the pathophysiology of asthma. Activation of various
inflammatory cells, including macrop Oxygen radicals are generated as part of the inflamentory reaction and are therefore likely to be involvin the pathophysiology of asthma. Activation of vario inflammatory cells, including macrophages, neutrophileosinophils Experimentally are generated as part of the minar matory reaction and are therefore likely to be involved in the pathophysiology of asthma. Activation of vario inflammatory cells, including macrophages, neutrophileosinoph matory reaction and are therefore likely to be involved
in the pathophysiology of asthma. Activation of various
inflammatory cells, including macrophages, neutrophils,
eosinophils, and mast cells, generates the oxygen int in the pathophysiology of asthma. Activation of variinflammatory cells, including macrophages, neutroph
eosinophils, and mast cells, generates the oxygen int
mediates superoxide anion (O_2^+) and hydrogen perox
 (H_2O_2) inflammatory cells, including macrophages, neutrophils,
eosinophils, and mast cells, generates the oxygen inter-
mediates superoxide anion (O_2^{\top}) and hydrogen peroxide
 (H_2O_2) (36); the hydroxyl radical (OH) is forme eosinophils, and mast cells, generates the oxygen inter-
mediates superoxide anion (O_2^+) and hydrogen peroxide
 (H_2O_2) (36); the hydroxyl radical (OH) is formed nonen-
zymatically as a secondary reaction. Oxygen radi inediates superoxide amon (O_2) and nydrogen peroxid (H_2O_2) (36); the hydroxyl radical (OH) is formed noner zymatically as a secondary reaction. Oxygen radicals make various toxic effects on cellular function, includ (1.1202) (30); the hydroxyl radical (OH) is formed nonen-
zymatically as a secondary reaction. Oxygen radicals may
have various toxic effects on cellular function, including
inhibition of certain enzymes (especially th zymatically as a secondary reaction. Oxygen radicals make various toxic effects on cellular function, includin
inhibition of certain enzymes (especially those dependen
on SH groups), damage to DNA, and the formation c
lipi have various toxic effects on cellular function, including
inhibition of certain enzymes (especially those dependent
on SH groups), damage to DNA, and the formation of
lipid peroxides from the polyunsaturated fatty acids on SH groups), damage to DNA, and the formation of lipid peroxides from the polyunsaturated fatty acids present in the cell membrane (311). It is surprising that so little is known about the effects of oxygen radicals on a lipid peroxides from the polyunsaturated fatty acids present in the cell membrane (311). It is surprising that so little is known about the effects of oxygen radicals on airway function.
Oxygen radicals have effects on air bid peroxides from the polyunsaturated fatty acids pres-
t in the cell membrane (311). It is surprising that so
tle is known about the effects of oxygen radicals on
way function.
Oxygen radicals have effects on airway smo

in the cen membrane (311). It is surprising that so
little is known about the effects of oxygen radicals on
airway function.
Oxygen radicals have effects on airway smooth muscle
in vitro. H_2O_2 is the oxygen radical wh the oxygen radicals have effects on airway smooth muscle
in vitro. H_2O_2 is the oxygen radical which appears to
have the major effect on airway tone and causes contrac-
tion both in bovine (552) and guinea pig airways Uxygen radicals have errects on airway smooth muscle
in vitro. H_2O_2 is the oxygen radical which appears to
have the major effect on airway tone and causes contrac-
tion both in bovine (552) and guinea pig airways (61) mave the major effect on airway tone and causes contion both in bovine (552) and guinea pig airways $(6$ the guinea pig, the contractile effect of H_2O_2 is genhanced by removal of epithelium, suggesting that gen radi tion both in bovine (352) and guinea pig alrways (61). In
the guinea pig, the contractile effect of H_2O_2 is greatly
enhanced by removal of epithelium, suggesting that oxy-
gen radicals release a relaxant factor. The b emanced by removal of epithenum, suggesting that oxy-
gen radicals release a relaxant factor. The bronchocon-
striction is also reduced by indomethacin, suggesting that
 H_2O_2 also releases constrictor cyclooxygenase pro gen radicals release a relaxant factor. The bronchocon
striction is also reduced by indomethacin, suggesting tha
H₂O₂ also releases constrictor cyclooxygenase product
(61). Oxygen radicals may also affect airway smootl striction is also reduced by indometriacin, suggesting that H_2O_2 also releases constrictor cyclooxygenase products (61). Oxygen radicals may also affect airway smooth muscle by an action on beta-adrenoceptor function. H_2O_2 also releases constrictor cyclooxygenase produced (61). Oxygen radicals may also affect airway smomuscle by an action on beta-adrenoceptor function Thus, alveolar macrophages incubated with guinea trachea lead to (61). Oxygen radicals may also arrect airway smooth
muscle by an action on beta-adrenoceptor function.
Thus, alveolar macrophages incubated with guinea pig
trachea lead to reduced relaxation responses to isopro-
terenol, a Thus, alveolar macrophages incubated with guinea pig
trachea lead to reduced relaxation responses to isopro-
terenol, an effect which is prevented by free radical
scavengers (189). However, direct incubation of oxygen
radi (61). terenol, an effect which is prevented by free radical
scavengers (189). However, direct incubation of oxygen
radicals with airways fails to alter beta-receptor function
(61). Oxygen radicals may also have potent vascular e radicals with airways fails to alter beta-receptor function

radicals with alrways lates to atter beta-receptor function (61).
 $Oxygen$ radicals may also have potent vascular effects.
 H_2O_2 potently relaxes pulmonary vascular smooth mus-

cle in vitro (253) and also causes increas or typen radicals may also have potent vascular effects.
 H_2O_2 potently relaxes pulmonary vascular smooth mus-
cle in vitro (253) and also causes increased vascular
permeability, possibly via a direct basic effect to v H_2O_2 potently relaxes pulmonary vascular smooth mus-
cle in vitro (253) and also causes increased vascular
permeability, possibly via a direct basic effect to vascular
endothelial cells (170). It is therefore possible H_2O_2 potently relaxes pulmonary vascular smooth mus-
cle in vitro (253) and also causes increased vascular
permeability, possibly via a direct basic effect to vascular
endothelial cells (170). It is therefore possible cie in vitro (253) and also
permeability, possibly via a c
endothelial cells (170). It is
gen radicals might contrib
edema in asthmatic airways.

BARNES, CHUNG,
The role of oxygen-derived free radicals in asthma is ⁶
Il not certain, but perhaps studies using antioxidants BARNES, CHU

The role of oxygen-derived free radicals in asthma is

still not certain, but perhaps studies using antioxidants

or free radical scavengers might show some benefit.

Ascorbic acid is an effective antioxidant The role of oxygen-derived free radicals in asthma is
still not certain, but perhaps studies using antioxidants
or free radical scavengers might show some benefit.
Ascorbic acid is an effective antioxidant and reduces
meth The role of oxygen-derived free radicals in asthma is
still not certain, but perhaps studies using antioxidants
or free radical scavengers might show some benefit.
Ascorbic acid is an effective antioxidant and reduces
meth still not certain, but perhaps studies using antioxidants
or free radical scavengers might show some benefit.
Ascorbic acid is an effective antioxidant and reduces
methacholine-induced bronchoconstriction in asthmatic
subj or free radical scavenge
Ascorbic acid is an effect
methacholine-induced bro
subjects (410), although t
an alternative mechanism **Example 18 Second Second Lie Conclusions**
 XIII. Conclusions
 XIII. Conclusions

Many different mediators have now been implicated

Many different med an alternative mechanism.

XIII. Conclusions

Many different mediators have now been implicated

in asthma, and we have discussed the evidence for their

involvement in asthma. In most cases the evidence is XIII. Conclusions
Many different mediators have now been implicated
in asthma, and we have discussed the evidence for their
involvement in asthma. In most cases the evidence is
circumstantial, and it will be necessary to d Many different mediators have now been implicated
in asthma, and we have discussed the evidence for their
involvement in asthma. In most cases the evidence is
circumstantial, and it will be necessary to develop more
poten in asthma, and we have discussed the evidence for their
involvement in asthma. In most cases the evidence is
circumstantial, and it will be necessary to develop more
potent and selective antagonists before the role of each involvement in asthma. In most cases the evidence is circumstantial, and it will be necessary to develop more potent and selective antagonists before the role of each mediator in a complex inflammatory disease, such as ast circumstantial, and it will be necessary to develop more
potent and selective antagonists before the role of each
mediator in a complex inflammatory disease, such as
asthma, can be elucidated. There is increasing evidence
 potent and selective antagonists before the role of each
mediator in a complex inflammatory disease, such as
asthma, can be elucidated. There is increasing evidence
that there are complex interactions between mediators
wit asthma, can be elucidated. There is increasing evidence that there are complex interactions between mediators with amplification or modification of their effects, which may make it even more difficult to determine the cont that there are complex interactions between mediators
with amplification or modification of their effects, which
may make it even more difficult to determine the contri-
bution of a single mediator. The therapeutic implica is that there are complex interactions between mediators
with amplification or modification of their effects, which
may make it even more difficult to determine the contri-
bution of a single mediator. The therapeutic impl may make it even more difficult to determine the conclusion of a single mediator. The therapeutic implicat
is that an antagonist of a single mediator is unlikely
have a major clinical effect. Thus, even potent antil
tamine is that an antagonist of a single mediator is unlikely to
have a major clinical effect. Thus, even potent antihis-
tamines have not proved to be effective in the manage-
ment of clinical asthma. Perhaps PAF might prove to is that an antagonist of a single mediator is unlikely to have a major clinical effect. Thus, even potent antihis-
tamines have not proved to be effective in the management of clinical asthma. Perhaps PAF might prove to be have a major clinical effect. Thus, even potent antihis-
tamines have not proved to be effective in the manage-
ment of clinical asthma. Perhaps PAF might prove to be
the exception, since this mediator most closely mimics
 tamines have not proved to be effective in the manage
ment of clinical asthma. Perhaps PAF might prove to b
the exception, since this mediator most closely mimic
the pathological features of asthma, and the imminen
availab ment of clinical asthma. Perhaps PAF might prove to be
the exception, since this mediator most closely mimics
the pathological features of asthma, and the imminent
availability of specific PAF antagonists for clinical stud the exception, since this mediator most closely mimics
the pathological features of asthma, and the imminent
availability of specific PAF antagonists for clinical stud-
ies should shortly answer this question. It seems lik the pathological features of asthma, and the imminent
availability of specific PAF antagonists for clinical stud-
ies should shortly answer this question. It seems likely
that other mediators will be described in the futur availability of specific PAF antagonists for clinical studies should shortly answer this question. It seems likely that other mediators will be described in the future and may contribute to the inflammatory reaction of ast

ies should shortly answer this question. It seems likely
that other mediators will be described in the future and
may contribute to the inflammatory reaction of asthma.
We have emphasized human studies where possible,
sin that other mediators will be described in the future and may contribute to the inflammatory reaction of asthma.
We have emphasized human studies where possible, since there appear to be marked differences between species i may contribute to the inflammatory reaction of asthma.
We have emphasized human studies where possible,
since there appear to be marked differences between
species in production of and response to inflammatory
mediators. F We have emphasized human studies where possible,
since there appear to be marked differences between
species in production of and response to inflammatory
mediators. Furthermore, there is no animal model which
duplicates a since there appear to be marked differences between
species in production of and response to inflammatory
mediators. Furthermore, there is no animal model which
duplicates all the features of human asthma, although
animal mediators. Furthermore, there is no animal model which
duplicates all the features of human asthma, although
animal studies have provided important information
about the processes involved in asthma, such as micro-
vascula mealators. Furthermore, there is no animal model which
duplicates all the features of human asthma, although
animal studies have provided important information
about the processes involved in asthma, such as micro-
vascula animal studies have provided important information
about the processes involved in asthma, such as micro-
vascular leakage, which cannot yet be measured in hu-
man airways. In the future, there should be greater
emphasis about the processes involved in asthma, such as microvascular leakage, which cannot yet be measured in human airways. In the future, there should be greater emphasis on human studies, and particularly studies in asthmatic vascular leakage, which cannot yet be measured in human airways. In the future, there should be greater emphasis on human studies, and particularly studies in asthmatic patients, in order to unravel the complexities of th man airways. In the emphasis on human asthmatic patients,
asthmatic patients,
of the inflammators.
Ashawisdreamts, W.

careful **and** detailed **preparation of the manuscript.**

REFERENCES

- 1. ABE, K., WATANABE, N., KUMAGAI, L., MOUMI, T., STEKI, T., AND YOSUNGA, K.: Circulating plasma kinin in patients with bronchial asthma.
Experientia 22: 626-627, 1967. EXPERENCES

2. ABE, K., WATANABE, N., KUMAGAI, L., MOUMI, T., STEKI, T., AND YO-

2. ADAIKAN, K.: Circulating plasma kinin in patients with bronchial asthma.

2. ADAIKAN, P. G., AND KARIM, S. M. M.: Effects of some prostag
- analogues on guinea pig and human respirators. T., STEKI, T., AND YO-SUNGA, K.: Circulating plasma kinin in patients with bronchial asthma.
Experientia 22: 626-627, 1967.
DAIKAN, P. G., AND KARIM, S. M. M.: Effects of some Experientia 22: 626-627, 1967.

2. ADAIKAN, P. G., AND KARIM, S. M. M.: Effects of some prostaglandin

analogues on guinea pig and human respiratory tract. Prostaglandins 18:

787-791, 1979.

3. ADAMs, G. K., AND LICHTENST
- **contraction of guinea pig and human airways. Nature (Lond.) 270: 255-** 257, 1977. The Training on guinee pig and human respiratory tract. Prostaglandina 18:

787-791, 1979.

3. ADAMS, G. K., AND LICHTENSTEIN, L. M.: Antagonism of antigen-induced

contraction of guinea pig and human airways. N
-
- c.: Lond., **2.1, ADCOCK,** *S.I.*, AND LICHENSTEIN, L. M.: Indomethacin enhances response of human bronchus to antigen. Am. Rev. Respir. Dis. 131: 8-10, 1985.
 ADAMS, G. K., AND LICHENSTEIN, L. M.: Indomethacin enhances r
- BARNES, CHUNG, AND PAGE

in asthma is 6. ADELROTH, E., MORRIS, M. M., HARGREAVE, F. E., AND O'BYRNE, P. M.:

antioxidants antioxidants patients with asthma and normal controls. N. Engl. J. Med. 315: 480-

anna hanact 484, 444, 1986.

6. ADELROTH, E., MORRIS, M. M., HARGREAVE, F. E., AND O'BYRNE, P. Nairway responsiveness to leukotrienes C₄ and D₄ and to methacholine

484, 1986.

484, 1986.

7. ADKINSON, N. F., NEWBALL, H. H., FINDLAY, S Airway responsiveness to leukotrienes C, and D, and to methacholine in
patients with asthma and normal controls. N. Engl. J. Med. 315: 480-484, 1996.
484, 1996.
DKNSON, N. F., NEWBALL, H. H., FINDLAY, S., ADAMS, K., AND LI
	- patients with asthma and normal controls. N. Engl. J. Med. 315: 480-
484, 1986.
7. ADKINSON, N. F., NEWBALL, H. H., FINDLAY, S., ADAMS, K., AND LICH-
TENSTEIN, L. M.: Anaphylactic release of prostaglandins from human
human
	-
	- TENSTEIN, L. M.: Anaphylactic release of prostaglandins from human
hung in vitro. Am. Rev. Respir. Dis. 121: 911-920, 1980.
8. ADLER, K. B., SCHWARTZ, J. E., ANDERSON, W. H., AND WELTON, A. F.:
Platelet activating factor s **143: 1-6, 1987.** 10. **AHMED,** 10. **AHMED,** 10. **ACRAWAL,** D. K., AND TOWNLEY, R. G.: Effect of platelet activating factor on beta-adrenoreceptors in human lung. Biochem. Biophys. Res. Commun. 143: 1-6, 1987.

	0. AHMED, T.
	- Clin. Immunol. 72: 311-3, 1987.

	143: 1-6, 1987.

	143: 1-6, 1987.

	10. AHMED, T., KRAINSON, J., AND YERGER, L.: Functional depression of H_{ap}histamine receptors in sheep with experimental allergic asthma. J. Allergy

	Clin
	- bistamine receptors in sheep with experimental allergic asthma. J. Allergy
Clin. Immunol. 72: 310-320, 1983.
11. AIZAWA, H., CHUNG, K. F., LEIKAUF, G. D., UEKI, I., BETHEL, R. A.,
O'BYRNE, P. M., HIROSE, T., AND NADEL, J. In allergen-induced bronchospasm in house dust RAST negative as in dogs.
J. Appl. Physiol. 59: 1936–1940, 1986.
J. Appl. Physiol. 59: 1936–1940, 1986.
L. Appl. Physiol. 59: 1936–1940, 1986.
LAM, R., ROZENINISCKA, A., AND K
	-
	- boxane generation in ozone-induced airway hyperresponsiveness in dogs.

	J. Appl. Physiol. 59: 1936–1940, 1986.

	12. ALAM, R., ROZNNIECKI, J., SWATKO, A., AND KUZMINSKA, B.: Complement

	in allergen-induced bronchospasm in h in allergen-induced bronchospean
patients. Allergol. Immunopatho:
-BAZZAZ, F. J., YADAVA, V. P., A
Na and Cl transport in canine true
Physiol. 240: F101-105, 1981.
LEERT, D. H., AND SNYDER, F.: B. patients. Allergol. Immunopathol. 11: 431–433, 1983.

	13. AL-BAZZAZ, F. J., YADAVA, V. P., AND WESTENFELDER, C.: Modification of

	Na and Cl transport in canine tracheal mucosa by prostaglandins. Am. J.

	Physiol. 240: F101–
	- 3-BAZZAZ, F. J., YADAVA, V. P., AND WESTENFELDER, C.: Modification of Na and Cl transport in canine tracheal mucosa by prostaglandins. Am. J. Physiol. 240: F101-105, 1981.

	caregive. D. H., AND SNYDER, F.: Biosynthesis of
	- 14. ALBERT, D. H., AND SNYDER, F.: Biosynthesis of 1-alkyl-2-acetyl *sn*-glycero
3-phosphocholine (platelet activating factor) from 1-alkyl-2-acyl *sn*-glycero
3-phosphocholine (platelet activating factor) from 1-alkyl-2-a
	- sensitive asthma: abnormal platelet response to drugs inducing asthmatic
sensitive asthma: abnormal platelet response to drugs inducing asthmatic
attacks; diagnostic and physiopathological implications. Int. Arch. Allergy

	- **by stimulation of anticents Callenge.** Pays 2.17. ANDERSSON, R. G. G., FUGNER, A., LUNDGREN, B. R., AND MUACEVIC, G.:
17. ANDERSSON, R. G. G., FUGNER, A., LUNDGREN, B. R., AND MUACEVIC, G.:
1nhibitory effects of clonidine Inhibitory effects of clonidine on bronchospesm induced in guinea-pigs
by vagal stimulation or antigen challenge. Eur. J. Pharmacol. 123: 181-
185, 1986.
18. ANDERSSON, R. G. G., AND GRUNDSTROM, N.: The excitatory non-chol
	- ergic, non-adrenergic nervous system of the guinea-pig airways. Eur. J. Respir. Dis. 64 (suppl. 131): 141-157, 1983.
	- **MORRSSON, R. G. G., AND GRUNDSTROM, N.: The excitatory non-cholinergic, non-adrenergic nervous system of the guinea-pig airways. Eur. J. Respir. Dis. 64 (suppl. 131): 141–157, 1983.
RCHER, C. B., FROEHLICH, W., PAGE, C. P** Experiment of the sum of the MACDONALD, D. M.: Synergistic interaction between prostaglandins and Paf-acether in experimental animals and man. Prostaglandin
	- Paf-acether in experimental animals and man. Prostaglandins 27: 495-501, 1984.
601, 1984.
RCHER, C. B., MACDONALD, D. M., MORLEY, J., PAGE, C. P., PAUL, W.,
AND SANJAR, S.: Effects of eerum albumin, indomethacin, and hista **21. ARCHER,** C. B., PAGE, C. P., JUHLIN, L., MORLEY, J., AND MACDONALD, 1985.
21. ARCHER, C. B., PAGE, C. P., JUHLIN, L., MORLEY, J., AND MACDONALD, 1985.
21. AECHER, C. B., PAGE, C. P., JUHLIN, L., MORLEY, J.,
	- skin. of experimental animals and man. Br. J. Pharma
akin. of experimental animals and man. Br. J. Pharma
1985.
D. M.: Delayed-onset synergiam between leukotriene B4.
E₂ in human skin. Prostaglandins 33: 799-807, 1987.
a
	- 1985.

	21. ARCHER, C. B., PAGE, C. P., JUHLIN, L., MORLEY, J., AND MACDONALD,

	D. M.: Delayed-onset synergism between leukotriene B₄ and prostaglandin

	E₃ in human akin. Prostaglandins 33: 799-807, 1987.

	22. ARCHER, C **22. ARCHER,** C. B., PAGE, C. P., MORLEY, J., AND MACDONALD, D. M.:

	Accumulation of inflammatory cells in response to intracutaneous plate-

	let-activating factor (Paf-acether) in man. Br. J. Dermatol. 112: 285-

	290, 198
- **Acknowledgments.** We are very grateful to Madeleine Wray for her
Acknowledgments. Br. D. D. M.: Inflammatory characteristics of platelet activating factor (PAF-
Acknowledgments. We are very grateful to Madeleine Wray f
- let-activating factor (Paf-acether) in man. Br. J. Dermatol. 112: 285-
290, 1985.
29. RECHER, C. B., PAGE, C. P., PAUL, W., MORLEY, J., AND MACDONALD, D.
M.: Inflammatory characteristics of platelet activating factor (PAF-M.: Inflammatory characteristics of platelet activating factor (PAF-
acether) in human skin. Br. J. Dermotol. 110: 45-50, 1984.
24. ARM, J. P., HORTON, C. E., EISER, N. M., CLARK, T. J. H., SPUR, B., AND
LEE, T. H.: The ef
	-
	- **by ketotifel.** Am. Rev. Respir. 205. ARNOUX, B., DENVERAIR, A., PAGE, C. P., MORLEY, J., AND BENVENISTE, J.:

	Pulmonary effects of platelet-activating factor in a primate are inhibited

	by ketotifen. Am. Rev. Respir. Dis. Pulmonary effects of platelet-activating factor in a primate are inhibited
by ketotifen. Am. Rev. Respir. Dis. 131: A2, 1985.
26. ARNOUX, B., JOSEPH, M., SIMOES, M. H., TONNEL, A. B., DUROUX, P.,
CAPRON, A., AND BENVENISTE CAPRON, A., AND BENVENISTE, J.: Antigenic release of Paf-acether and
	- beta-glucuronidase from alveolar macrophages of asthmatics. Bull. Eur.
Physiopathol. Respir. 23: 119-124, 1987.
RRANG, J. M., GARBARG, M., LANCELOT, J. C., LECOMTE, J-M., POLLARD,
H., ROBBA, M., SCHUNACK, W., AND SCHWARTZ, 123, 1987. 27. ARRANG, J. M., GARBARG, M., LANCELOT, J. C., LECOMTE, J.-M., POLLARD,
H., ROBBA, M., SCHUNACK, W., AND SCHWARTZ, J.-C.: Highly potent and
selective ligands for histamine H₃-receptors. Nature (Lond.) 327: 117-
123, 19
	- Patients. Clin. Allergy *7*: 173-182, 1977. II., VAUGHAN, J. H., AND TAN, E. M.: Plasma complement changes during bronchospasm produced in asthmatic patients. Clin. Allergy 7: 173-182, 1977.

	29. AsH, A. S. P., AND SCHILD,
	-

spet

- **INFLAMMATORY MEDIATORS AND ASTHMA**

30. ATKINS, P. C., NORMAN, M., WEINER, H., AND ZWEIMAN, B.: Release of

1990: 138P, 1987.

1997. tions in humans. Ann. Intern. Med. 86: 415-418, 1977.

31. ATKINS, P. C., NORMAN, M. E.,
- neutrophil chemotactic activity in man: correlation with bronchospasm 1987.
and inhibition by disodium cromoglycate. J. Allergy Clin. Immunol. 62: 62. BARROW, S. E., DOLLERY, C. T., HEAVEY, D. J., HICKLING, N. C., RITTER, **IRENT CONSTRAINT WEINTER, H., AND ZWEIMAN, B.: Release of neutrophil chemotactic activity during immediate hypersensitivity reactions in humans. Ann. Intern. Med. 86: 415-418, 1977.

IKINS, P. C., NORMAN, M. E., AND ZWEI** neutrophil chemotactic activity during immediate hypersensitivity reactions in humans. Ann. Intern. Med. 86: 415-418, 1977.
TKINS, P. C., NORMAN, M. E., AND ZWEIMAN, B.: Antigen induced
neutrophil chemotactic activity in m 31. ATKINS, P. C., NORMAN, M. E., AND ZWEIMAN, B.: Antigen induced
neutrophil chemotactic activity in man: correlation with brohchospasm
and inhibition by disodium cromoglycate. J. Allergy Clin. Immunol. 62:
149-155, 1978.
-
- 149-155, 1978.
 M. A. L.: S. AND ZWEIMAN, B.: Mediator release in local heat urticaria.
 M. L.: E.: S. A. L. B., LEE, T. B., SHEARD, P., AND TATTERSALL.
 M. L.: Selective inhibitor of alow reacting substance of anaphy 32. ATKINS, P. C., AND ZWEIMAN, B.: Mediator release in local heat urticaria.

J. Allergy Clin. Immunol. 68: 286-289, 1981.

33. AUGSTEIN, J., FARMER, J. B., LEE, T. B., SHEARD, P., AND TATTERSALL,

M. L.: Selective inhibi
- M. L.: Selective inhibitor of slow reacting substance of anaphylaxis.
Nature (Lond.) 245: 215-217, 1973.
34. AURSUDKIJ, B., BARNES, P. J., BELVISI, M. G., DIJK, S., EVANS, T. W.,
AND ROGERS, D. F.: Effect of substance P, n AND ROGERS, D. F.: Effect of substance P, neurokinins, and calcitonin gene-related peptide on microvascular permeability in guinea pig airways.
J. Physiol. **398**: 51P, 1968.
35. AURSUDKLI, B., ROGERS, D. F., EVANS, T. W.,
- 55. AURSUDKIJ, B., ROGERS, D. F., Evans, T. W., ALTON, E. W. F. W., CHUNG,
K. F., AND BARNES, P. J.: Reduced tracheal mucus velocity in guinea-pig
in vivo by platelet activating factor. Am. Rev. Respir. Dis. 35: A160, 1967
- **36. BABIOR, B. M.: The respiratory burst of phagocytes. J. Clin. Invest. 73:** 599-601. 1984.
- ABIOR, B. M.: The respiratory burst of phagocytes. J. Clin. Invest. 73:
599–601, 1964.
NCH, M. K., BRASHLER, J. R., SMITH, H. W., FITZPATRICK, F. A., SUN, 67. E.
F. F., AND MCGUIRE, J. C.: 6,9-Deexpoxy-6,9-(phenylimino)-de 599-601, 1964.

37. BACH, M. K., BRASHLER, J. R., SMITH, H. W., FITZPATRICK, F. A., SUN,

F. F., AND MCGUIRE, J. C.: 6,9-Deexpoxy-6,9-(phenylimino)-delta 6,8-

prostaglandin I₁ (U-60,257), a new inhibitor of leukotriene
-
- prostaglandin I_1 (U-60,257), a new inhibitor of leukotriene C and D
synthesis: in vitro studies. Prostaglandins 23: 759-770, 1982.
38. BAKER, A. P., HILLEGASS, L. M., HOLDEN, D. A., AND SMITH, W. J.: Effect
of kallidin of kallidin, substance P, and other basic polypeptides on the production
of respiratory macromolecules. Am. Rev. Respir. Dis. 115: 811-817, 1977.
39. BARBARO, J. F., AND ZVAIFLER, N. J.: Antigen induced histamine release
f 1999. BARBARO, J. F., AND ZVAIFLER, N. J.: Antigen induced histamine release from platelets and rabbits producing homologous PCA antibody. Proc. Soc. Exp. Biol. Med. 122: 1245-1247, 1966. **41.** BARNES, N. C., PIPER, P. J.,
-
- EXERUS, N. C., PIPER, P. J., AND COSTELLO, J. F.: Actions of inhaled 6

elukotrienes and their interactions with other allergic mediators. Prosta-

glandins 28: 629-631, 1984.

RENES, N. C., PIPER, P. J., AND COSTELLO, J. subsects. Thorax **39: 500-504, 1984.**

41. BARNES, N. C., PIPER, P. J., AND COSTELLO, J. F.: Comparative effects of an oral black others on C., leads to the effects. Thorax 39: 500-504, 1984.

42. BARNES, N. C., PIPER, P.
- RENES, N. C., PIPER, P. J., AND COSTELLO, J. F.: Comparative effects of inhaled leukotriene C₄, leukotriene D₄, and histamine in normal human subjects. Thorax 39: 500-504, 1984.
RENES, N. C., PIPER, P. J., AND COSTELLO 816-821, 1987. The effect of an oral and Levis and The effect of an oral and the puise of th (suppl. 144): 217-265, 1986. 44. BARNES, P. J.: Asthma as an axon reflex. Lancet 1: 242-245, 1986.

44. BARNES, P. J.: Asthma therapy: basic mechanisms. Eur. J. Respir. Dis. 68

(suppl. 144): 217-265, 1986.

46. BARNES, P.
-
-
- (suppl. 144): 217-265, 1986.

RNES, P. J.: Airway neuropeptides and asthma. Trends Pharm. Sci. 8:

24-27, 1987.

RNES, P. J.: Neuropeptides in the lung: localization, function, and patho-

RNES, P. J.: Inflammatory mediato
-
- **45. BARNES, P. J.: Airway neuropeptides and asthma. Trends Pharm.** Sci. 8:

24–27, 1987.

46. BARNES, P. J.: Neuropeptides in the lung: localization, function, and patho-

47. BARNES, P. J.: Inflammatory mediator receptor 24-27, 1987.

46. BARNEs, P. J.: Neuropeptides in the lung: localization, function, and patho-

physiologic implications. J. Allergy Clin. Immunol. 79: 285-295, 1987.

47. BARNES, P. J.: Inflammatory mediator receptors and **implications.** J. Allergy Clin. Immunol. 79: 285-295, 1987.
 47. BARNES, P. J.: Inflammatory mediator receptors and asthma. Am. Rev.
 Respir. Dia. 135: S26-31, 1987.
 48. BARNES, P. J.: Neuropeptides in human airways
-
- Respir. Dis. 138: S26-31, 1987.

Respir. Dis. 138: S26-31, 1987.

Implications. Am. Rev. Respir. Dis. 136: S77-S83, 1988.

REVENTES, P. J., AND BROWN, M. J.: Venous plasma histamine in exercise

and hyperventilation induce
- implications. Am. Rev. Respir. Dis. 136: S77-S83, 1988.
49. BARNES, P. J., AND BROWN, M. J.: Venous plasma histamine in exercise
and hyperventilation induced asthma in man. Clin. Sci. 61: 159-162,
1981.
50. BARNES, P. J., and hyperventilation induced asthma in man. Clin. Sci. 61: 159-162,
1981.
50. BARNES, P. J., BROWN, M. J., DOLLERY, C. T., FULLER, R. W., HEAVEY,
50. BARNES, P. J., BROWN, M. J., DOLLERY, C. T., FULLER, R. W., HEAVEY,
D. J
-
- 52. BARNES, P. J., AND CHUNG, K. F.: PAF closely mimics pathology of asthma.
Tranda Pharmacol. Sci. 8: 285-287. 1987.
-
- trachea. Am. Rev. Respir. Dis. 131: A29, 1985.

52. BARNES, P. J., AND CHUNG, K. F.: PAF closely mimics pathology of asthma.

Trends Pharmacol. Sci. 8: 285-287, 1987.

53. BARNES, P. J., CHUNG, K. F., AND PAGE, C. P.: Plat calcitonin gene-related peptide in man. J. Physiol. 374: 22P, 1986.
 53. BARNES, P. J., CONRADSON, T.-B., DDXON, C. M. S., AND FULLER, R. W.:

A comparison of the cutaneous actions of substance P, neurokinin A, and

calc
-
-
- 54. BARNES, P. J., CONRADSON, T.-B., DIXON, C. M. S., AND FULLER, R. W.:

A comparison of the cutaneous actions of substance P, neurokinin A, and

calcitonin gene-related peptide in man. J. Physiol. 374: 22P, 1986.

55. BA
- effect of substance P, muscarinic and adrenergic stimulation in vitro. Br.
J. Pharmacol. 89: 767P, 1986.
57. BARNES, P., FITZGERALD, G., BROWN, M., AND DOLLERY, C.: Nocturnal
asthma and changes in circulating epinephrine, **Br. Advises and changes in circulating epinephrine, histamine and cortisol.**
N. Engl. J. Med. 303: 263-267, 1980.

83. BARNES, P. J., GRANDORDY, B. M., PAGE, C. P., RHODEN, K. J., AND ROBERTSON, D. N.: The effect of plate catecholamines in stable asthmatic subjects. C. P., RHODEN, K. J., AND ROBERTSON, D. N.: The effect of platelet activating factor on pulmonary beta-adrenoceptors. Br. J. Pharmacol. 90: 709–715, 1987.

59. BARNES, P. J., IN
-
-

on cholinergic neural responses in guinea-pig trachea. Br. J. Pharmacol.
190: 138P, 1987.
190: 138P, 1987.

- 90: 138P, 1987. TORS AND ASTHMA

on cholinergic neural responses in guinea-pig trachea. Br. J. Pharmacol.

90: 138P, 1987.

61. BARNES, P. J., AND RHODEN, K. J.: The effect of oxygen-derived free

radicals on airway smooth on cholinergic neural responses in guinea-pig trachea. Br. J. Pharmacol.
90: 138P, 1987.
RRNES, P. J., AND RHODEN, K. J.: The effect of oxygen-derived free
radicals on airway smooth muscle responses. Br. J. Pharmacol. 90
- J. M., AND VIAL, J.: Effect of vasoactive peptides on prostacylin synthesis in man. Br. J. Pharmacol. 87: 243–248, 1986.
- radicals on airway smooth muscle responses. Br. J. Pharmacol. 90: 142P,
1987.
62. BARROW, S. E., DOLLERY, C. T., HEAVEY, D. J., HICKLING, N. C., RITTER,
J. M., AND VIAL, J.: Effect of vasoactive peptides on prostacylin syn **a. M., AND VIAL, J.: EITECT OF VEROESCUTE PEPLIGES ON PROBECTAIN SYNTHERE.**
 and BASRAN, G. S., MORLEY, J., PAUL, W., AND TURNER-WARWICK, M.: Evidence in man for synergistic interactions between putative mediators of acu factor a possible mediator of the dual response to allergen. Clin. Allergence in man for synergistic interactions between putative mediators of acute inflammation and asthma. Lancet 1: 935-937, 1982.
ASRAN, G. S., PAGR,
- dence in man for synergistic interactions between putative mediators of
acute inflammation and asthma. Lancet 1: 935-937, 1982.
64. BASRAN, G. S., PAGE, C. P., PAUL, W., AND MORLEY, J.: Platelet activating
factor: a possib
- **human servest Serverum during immediate and late asthmatic reactions factor:** a possible mediator of the dual response to allergen. Clin. Allergy 14: 75-79, 1984.
14: 75-79, 1984.
NUER, X., DORSCH, W., AND BECKER, T.: Lev factor: a possible mediator of the dual response to allergen. Clin. Allergy
14: 75-79, 1984.
65. BAUER, X., DORSCH, W., AND BECKER, T.: Levels of complement factors in
human serum during immediate and late asthmatic reacti
- human serum during immediate and late asthmatic reactions and during acute hypersensitivity pneumonitis. Allergy 35: 383–390, 1980.
NUMGARTEN, C. R., TOGIAS, A. G., NACLERIO, R. M., LICHTENSTEIN, L.
M., NORMAN, P. S., AND 66. BAUMGARTEN, C. R., TOGIAS, A. G., NACLERIO, R. M., LICHTENSTEIN, L.
M., NORMAN, P. S., AND PROUD, D.: Influx of kininogens into nasal
secretions after antigen challenge of allergic individuals. J. Clin. Invest.
67. BEA
- **secretions after antigen challenge of allergic individuals. J. Clin. Invest.**
76: 191-197, 1965.
HARDY, C. R. W., ROBINSON, C., FEATHERSTONE, R. L., VARLEY, J. G.,
HARDY, C. C., CHURCH, M. K., AND HOLGATE, S. T.: 9-Alpha, 76: 191-197, 1965.
RASLEY, C. R. W., ROBINSON, C., FEATHERSTONE, R. L., VARLEY, J. G., HARDY, C. C., CHURCH, M. K., AND HOLGATE, S. T.: 9-Alpha, 11-beta-
prostaglandin F₂, a novel metabolite of prostaglandin D₂, is a p 978-983, 1987. HARDY, C. C., CHURCH, M. K., AND HOLGATE, S. T.: 9-Alpha, 11-beta-
prostaglandin F_a , a novel metabolite of prostaglandin D_a , is a potent
contractile agonist of human and guinea pig airways. J. Clin. Invest. 79:
878-983
- 68. **BEASLEY, R., FEATHERST0NE, R., CHURCH, M.,** RAFFERTY, **P., FARLEY,** J., of bronchoconstrictor prostanoida in vitro **and in** vivo by GR 32191: induced bronchoconstriction in asthma. J. Appl. Physiol. in press, 1988. **induced bronchoconstriction in asthma.** J. Apple Theorem in the method of the conduction of the contribution of the endiator is in vivo by GR 32191:

implication for the contribution of these mediators to immediate alle **ROCKLIN, Inc. about the contribution of these mediators to immediate allergenization** for the contribution of these mediators to immediate allergenization in the contribution in asthma. J. Appl. Physiol. in press, 1988.

- atomic subjects. N. Englished and a subjects. N. Englished and a subject of the subjects. N. E., McCAFFREY, R. P., SOTER, N. A., AND

ROCKLIN, R. E.: Abnormal histamine-induced suppresence suppresence cell function in

acc 69. BEER, D. J., OSBAND, M. E., MCCAFFREY, R. P., SOTER, N. A., AND
ROCKLIN, R. E.: Abnormal histamine-induced suppressor-cell function in
atopic subjects. N. Engl. J. Med. 306: 454-458, 1982.
70. BEER, H. J.: Wirkungen de
-
-
- The BENDER, M. G., CHUNG, K. F., JACKSON, D. M., AND BARNES, P. J.: Opioid

27. BELVISI, M. G., CHUNG, K. F., JACKSON, D. M., AND BARNES, P. J.: Opioid

28. D. Pharmacol. 92: 566P, 1987.

29. BENDER, J. G., AND VAN EPPS, D
- control of non-cholinergic bronchoconstriction in the guinea-pig in vivo.
Br. J. Pharmacol. 92: 596P, 1987.
T. Exhuals interactions in release of
superoxide anions (O₃-7) from human neutrophila. Further evidence for
supe superoxide anions (O_3^-) from human neutrophils. Further evidence for multiple pathways of activation. Inflammation 9: 67-79, 1985.

73. BENVENISTE, J., CHIGNARD, M., LE COUEDIC, J. P., AND VARGAFIG, B.

B.: Biosynthesis multiple pathways of activation. Inflammation 9: 67-79, 1985.

73. BENVENISTE, J., CHIGNARD, M., LE COUEDIC, J. P., AND VARGAFTIG, B.

B.: Biosynthesis of platelet-activating factor (PAF-acether). II. Involvement of phosph
- ment of phospholipese A_2 in the formation of PAF-acether and lyso-PAF-acether from rabbit platelets. Thromb. Res. 25: 375-385, 1982.
74. BENVENISTE, J., HENSON, P. M., AND COCHEANE, C. G.: Leukocyte dependent histamine
- **ENVENISTE, J., HENSON, P. M., AND COCHEANE, C. G.: Loukocyte dependent histamine release from rabbit platelets.: the role of IgE, basophila, and a platelet activating factor. J. Exp. Med. 136: 1356–1377, 1972.

RNVENISTE** pendent histamine release from rabbit platelets.: the role of IgE, basoph
and a platelet activating factor. J. Exp. Med. 136: 1356–1377, 1972.
RNVENISTE, J., TENCE, M., VARENNE, P., BIDAULT, J., BOULLET, C., A
POLONSKY, J. photidylcholine. C. R. Acad. Sci. 289: 1037-1040, 1979.

To BENVENISTE, J., TENCE, M., VARENNE, P., BIDAULT, J., BOULLET, C., AND

POLONSKY, J.: Semi-synthese et structure proposee du facteur activant

les plaquettes (PAF) POLONSKY, J.: Semi-synthese et structure proposee du facteur activant
les plaquettes (PAF): PAF-acether, un alkyl ether analogue de la lysophos-
photidylcholine. C. R. Acad. Sci. 289: 1037-1040, 1979.
76. BERRIDGE, M. J.,
-
- 77. **BIANC0,** 5., **ROBUSCHI, M., CESARANI, R., GANPOLDI, C., AND KAMBUROFF, P.: Prevention of aspecifically induced bronchoconstriction by PGI, and** messenger in cellular signal transduction. Nature (Lond.) 312: 315-321, 1984.
1984.
ANCO, S., ROBUSCHI, M., CESARANI, R., GANPOLDI, C., AND KAMBUROPP,
P.: Prevention of aspecifically induced bronchoconstriction by PGI, and 77. BIANCO, S., ROBUSCHI, M., CESARANI, R., GANFOLDI, C., AND KAMBUROFF,
P.: Prevention of aspecifically induced bronchoconstriction by PGI₂ and
20-methyl-PGI₂ in asthmatic patients. Pharm. Res. Commun. 10: 657-
675, 1 1. Devention of aspecifically induced bronchoconstriction by PGI_s and
20-methyl-PGI_s in asthmatic patients. Pharm. Res. Commun. 10: 657-
675, 1978.
78. BISGAARD, H., GROTH, S., AND MADSEN, F.: Bronchial hyperreactivity
- T8. BISGAARD, H., GROTH, S., AND MADSEN, F.: Bronchial hyperreactivity of
leukotriene D, and histamine in exogenous asthma. Br. Med. J. 290:
1468–1471, 1985.
T9. BISGAARD, H., KRISTENSEN, J., AND SONDERGAARD, J.: The effec
- 53. BARNES, P. J., CHUNG, K. F., AND PAGE, C. P.: Platelet-activating factor leukotriene C₄ and D₄ on cutaneous blood flow in humans. Prostaglandins as a mediator of allergic disease. J. Allergy Clin. Immunol. in press BGAARD, H., KRISTENSEN, J., AND SONDERGAARD, J.: The eleukotriene C₄ and D₄ on cutaneous blood flow in humans. Prostage 23: 797-801, 1982.
23: 797-801, 1982.
by some rabbit tissues in vitro. J. Physiol. 221: 371-387, 1 Benkotriene C₄ and D₄ on cutaneous blood flow in humans. Prostaglandins

23: 797-801, 1982.

80. Brro, L. Z.: Accumulation and apparent active transport of prostaglandins

by some rabbit tissues in virto. J. Physiol. 2
	-
	- prostagandin metabolism and apparent active transport of prostaglandins by some rabbit tissues in vitro. J. Physiol. 221: 371-387, 1972.
Tro, L. Z., BAROODY, R. A., AND RETTZ, M. E.: Dependence of pulmonary
prostaglandin m 82. By some rabbit tissues in vitro. J. Physiol. 221: 371-387, 1972.

	81. Brro, L. Z., BAROODY, R. A., AND REITZ, M. E.: Dependence of pulmon protaglandin metabolism on carrier-mediated transport processes. A

	J. Physiol.
	- by L. Z., BAROODY, R. A., AND RETTZ, M. E.: Dependence of pulmonary
prostaglandin metabolism on carrier-mediated transport processes. Am.
J. Physiol. 51: 382-387, 1977.
IORK, J., HEDQVIST, P., AND AFORS, K.-E.: Increase of prostaglandin metabolism on carrier-mediated transport processes. Am.

	J. Physiol. 51: 382-387, 1977.

	82. BJORK, J., HEDQVIST, P., AND AFORS, K.-E.: Increase of vascular permea-

	bility induced by leukotriene B_s and the FORK, J., HEDQVIST, P., AND AFORS, K.-E.: Increase of vascular permeability induced by leukotriene B₄ and the role of polymorphonuclear leukocytes. Inflammation 6: 189–200, 1982.
kocytes. Inflammation 6: 189–200, 1982.
L
	-
	- bility induced by leukotriene B, and the role of polymorphonuclear leu-

	kocytes. Inflammation 6: 189-200, 1982.

	83. BLACK, J. L., ARMOUR, C. L., VINCENC, K. S., AND JOHNSON, P. R. A.: A

	comparison of the contractile act 83a. BLACK, P. N., FULLER, R. W., TAYLOR, G. W., BARNES, P. J., AND DOLLERY, C. T.: Bronchial reactivity is not increased after inhalation of leukotriene B₄ and prostaglandin D₂. Br. J. Clin. Pharmacol. 25: 667P, 1988.
	- leukotriene B₄ and prostaglandin D₃. Br. J. Clin. Pharmacol. 25: 667P, 1988.

	84. BLANK, M. L., SNYDER, F., BYERS, W. L., BROOKS, B., AND MUIRHEAD, E.

	E.: Antihypertensive activity of an alkyl ether analog of phosphat

2012

ARMACOLO

spet

 $\overline{\mathbb{O}}$

- **BARNES, CHUNC**

85. BODAMMER, G., AND VOGT, W.: Actions of anaphylatoxins on circulation

and respiration in the guinea-pig. Int. Arch. Allerg. Appl. Immunol. 32:

417–428, 1967. **EXERT COMMARISE AND SIMURE AND VOOT, W.: Actions of anaphylatoxins on circulation**
and respiration in the guinea-pig. Int. Arch. Allerg. Appl. Immunol. 32:
417-428, 1967.
86. Bor, J., Bor, M.-A., AND SIMONSSON, B. G.: A d EXECTION PULLER AND VOGT, W.: Actions of anaphylatoxins on circulation
and respiration in the guinea-pig. Int. Arch. Allerg. Appl. Immunol. 32:
417-428, 1967.
B.C. A., AND SIMONSSON, B. G.: A dual action of histamine on
is
-
- 17–428, 1967.

or, J., Bor, M.-A., AND SIMONSSON, B. G.: A dual action of histamine on

isolated human pulmonary arteries. Respiration 40: 117–122, 1980.

oNNET, J., THEAUDEAN, D., AND BESSIN, P.: Dependency of PAF-acether 86. Bor, J., Bor, M.-A., AND SIMONSSON, B. G.: A dual action of histamine on isolated human pulmonary arteries. Respiration 40: 117-122, 1980.
87. BONNET, J., THEAUDEAN, D., AND BESSIN, P.: Dependency of PAF-acether induce
- **CAUGHEY, G., THIBAUDEAN, D., AND BESSIN, P.: Dependency of PAF-acether induced bronchospasm on the lipoxygenase pathway in the guinea-pig.
Prostaglandins 26: 457-466, 1983.
CAUGHEY, G., CORRALES, R., VARSANO, S., GOLD, M.** induced bronchospasm on the lipoxygenase pathway in the guinea-pig.
Prostaglandina 26: 457–466, 1983.
88. BORSON, D. B., CORRALES, R., VARSANO, S., GOLD, M., VIRO, N., CAUGHEY, G., RAMACHANDRAN, J., AND NADEL, J. A.: Enkep
-
- 89. BOUSHEY, H. A., HOLTZMAN, M. J., SHELLER, J. R., AND NADEL, J. A.:
Bronchial hyperreactivity. Am. Rev. Respir. Dis. 121: 389–413, 1980.
90. BRAIN, S. D., AND WILLIAMS, T.: Inflammatory oedema induced by syner-
giam bet
- 91. Brain, S. D., Williams, T. J., Tippins, J. R., Morris, H. R., and **91. BRAIN, S. D., AND WILLIAMS, T.: Inflammatory oedema induced by syner-**

90. BRAIN, S. D., AND WILLIAMS, T.: Inflammatory oedema induced by syner-

116.

116.

116.

118. J. Pharmacol. 86: 856–860, 1985.

91. BRAIN, S. giam between CGRP and mediator.
Br. J. Pharmacol. 86: 855-860, 1985.
RAIN, S. D., WILLIAMS, T. J., Tin
MacINTYRE, I.: Calcitonin gene-rel.
Nature (Lond.) 313: 54-56, 1985.
RAQUET, P., ETIENNE, A., AND CLO. BRAIN, S. D., WILLIAMS, T. J., TIPPINS, J. R., MORRIS, H. R., AND
MACINTYRE, I.: Calcitonin gene-related peptide is a potent vasodilator.
Nature (Lond.) 313: 54–56, 1985.
92. BRAUET, P., ETIENNE, A., AND CLOSTRE, F.: Down-
- MACINTYRE, I.: Calcitonin gene-related peptide is a potent vasodilator.

Nature (Lond.) 313: 54-56, 1985.

92. BRAQUET, P., ETIENNE, A., AND CLOSTRE, F.: Down-regulation of beta 2-

adrenergic receptors by PAF-acether and
- Nature (Lond.) 313: 54-56, 1985.

92. BRAQUET, P., ETIENNE, A., AND CLOSTRE, F.: Down-regulation of beta 2-

adrenergic receptors by PAF-acether and its inhibition by the PAF-

acether antagonist BN 52021. Prostaglandins 3 adrenergic receptors by PAF-acether and its inhibition by the PAF-acether antagonist BN 52021. Prostaglandins 30: 721-726, 1985.
RAQUET, P., ETIENNE, A., TOUVAY, C., BOURGAIN, R., LEFORT, J., AND VARGAFTIG, B. B. Involveme acether antagonist BN 52021. Prostaglandins 30: 721-726, 1985.

93. BRAQUET, P., ETIENNE, A., TOUVAY, C., BOURGAIN, R., LEFORT, J., AND

VARGAFTIG, B. B.: Involvement of platelet activating factor in respiratory

anaphylax 93. BRAQUET, P., BTIENNE, A., TOUVAY, C., BOURGAIN, R., LEFORT, J., AND VARGAFTIG, B. B.: Involvement of platelet activating factor in respiratory anaphylaxis, demonstrated by Paf-acether inhibitor BN 5202i. Lancet 1: 1501 v. Design of specific antagonists. 2. Design of specific antagonists. Ten of specific antagonists. Trends Pharm. Sci. 7: 397-403, 1986.

96. BRAQUET, P., AND GODFROID, J. J.: Platelet activating factor (Paf-acether)

96. S
- 1941 BRAQUET, P., AND GODFROID, J. J.: Platelet activating factor (Paf-acether)
specific binding sites. 2. Design of specific antagonists. Trends Pharm.
Sci. 7: 397-403, 1986.
95. BRAUDE, P., SHEN, T. Y., TOUQUI, L, AND VA
- Sci. 7: 397-403, 1986.

95. BRAQUET, P., SHEN, T. Y., TOUQUI, L, AND VARGAFTIG, B. B.: Perspectives

in platelet-activating factor research. Pharmacol. Rev. 39: 97-145, 1987.

96. BRAUDE, S., ROVSTON, D., COB, C., AND BARN
-
- in platelet-activating factor research. Pharmacol. Rev. 39: 97-145, 1987.

96. BRAUDE, S., ROYSTON, D., COE, C., AND BARNES, P. J.: Histamine increases

lung permeability by an H₂-receptor mechanism. Lancet 2: 372-374, 1 **BRAY, M. A., CUNNINGHAM, F. M., FORD-HUTCHINSON, A. W., AND SMITH,**
M. J. H.: Leukotriene B.: a mediator of vascular permeability. Br. J.
Pharmacol. 72: 483-486, 1981.
98. BRINK, C., GRIMAUD, C., GUILLOT, C., AND OREHEK,
-
- **EXAMPLE ANTIFUL ANTIFUL ANTIFUL ANTIFUL ANTIFUL ANTIFUL ANTIFUL ANTIFUL DETERMINED DETERMINED BY THE RESPONSE DETERMINED AT ANTIFUL ANTIFUL OR DATA L-649,923 on the response to inhaled antigen in asthma. J. Allergy Clin.**
-
- between indomethacin and contractile agents on human isolated airway
muscle. Br. J. Pharmacol. 69: 383-388, 1980.
99. BRITTON, J. R., HANLEY, S. P., AND TATTERSFIELD, A. E.: The effect of an
oral leukotriene D_e antagonis York, 1984.

York, 1984.

101. BROWN, M. J., IND, P. W., CAUSON, R., AND LEE, T. H.: A novel double-

isotope technique for the enzymatic assay of plasma histamine. Applica-

tion of mast cell activation assessed by antige
-
- mine levels in plasma, blood, and urine in severe asthma and the effectricosteroid treatment. Thorax 31: 724-729, 1976.
LRUJNZEEL, P. L. B., KOENDERMAN, L., KOK, P. T. M., HAMELINICAL L., AND VERHAGEN, J. L.: Platelet acti corticosteroid treatment. Thorax 31: 724-729, 1976.

103. BRUIJNZEEL, P. L. B., KOENDERMAN, L., KOK, P. T. M., HAMELINK, M.

L., AND VERHAGEN, J. L.: Platelet activating factor (PAF-acether) in-

duced leukotriene C₄ for
- and guantine nucleotides. Life Sci. **31:** AND BUCK, S. H., Thomas Science of human sosinophils. Pharm. Res. Commun. 18: 61-69, 1986.

104. BEUNS, R. F., THOMSEN, W. J., AND PUGSLEY, T. A.: Binding of leukotrienes C₄ and
-
- 104. BRUNS, R. F., THOMSEN, W. J., AND PUGSLEY, T. A.: Binding of leuko-
trienes C₄ and D₄ to membranes from guinea pig lungs: regulation by ions
and guanine nucleotides. Life Sci. 33: 645-653, 1983.
105. BUCK, S. H., ICK, S. H., AND BURCHER, E.: The tachykinins: a family of peptides with a brood of "receptors." Trends Pharmacol. Sci. 7: 65-68, 1986.

UCKNER, C. K., KRELL, R. D., LARAVUSO, R. B., COURSIN, D. B., BERN-STRIN, P. R., AND W 106. BUCKNER, C. K., KRELL, R. D., LARAVUSO, R. B., COURSIN, D. B., BERN-

STEIN, P. R., AND WILL, J. A.: Pharmacological evidence that human

intralobar airways do not contain different receptors that mediate con-

tracti
-
- FRICAL SURISH 108. HUMA, I.EVI, R., GUO, Z.-G., AND COREY, E. J.: Leukotrienes C., D.,

2., CHUNG, K. F., AND BARNES, P. J.: PAF antagonists: their therapeutic role

and E.; effects on human and guinea-pig cardiac preparat PESCARMONA, G., SANAVIO, F., D'URSO, N., AND MARCHISIO, P. C.: **PESCARMONA, G., SANAVIO, F., D'URSO, N., AND MARCHISIO, P.** C.:

Human endothelial cells are targets for platelet activating factor (PAF).

I. PAF induces changes in cytoskeleton structures. J. Immunol., in press,

1988.

-
- I. PAF induces changes in cytoakeleton structures. J. Immunol., in press,
1988.
109. CAMP, R. D. R., COUTTS, A. A., GREAVES, M. W., KAY, A. B., AND
WALFORT, M. J.: Responses of human skin to intradermal injection of
buckgr WALPORT, M. J.: Responses of human skin to intradermal injection of leukotrienes C_4 , D_4 , and B_4 . Br. J. Pharmacol. 80: 497-502, 1983.
AMUSSI, G., MONTRUCCHIO, G., ANTRO, C., TETTA, C., BUSSOLINO, F., AND EMANUELL 110. CAMUSSI, G., MONTRUCCHIO, G., ANTRO, C., TETTA, C., BUSSOLINO, F., AND EMANUELLI, G.: In vitro spassmogenic effect on rabbit lung tissue of 1-O-octadecyl-2-an-glyceryl-3-phosphorylcholine (platelet activating factor):
-

- G, AND PAGE

LINO, F.: Neutropenia induced by platelet-activating factor (PAF-acether)

released from neutrophils: the inhibitory effect of prostacyclin (PGI₃).

Agents Actions 11: 550–552, 1981.

112. CAPRON, M., BENVE Agents Actions 11: 550–552, 1981.

112. CAPRON, M., BENVENISTE, J., BRAQUET, P., AND CAPRON, A.: Role of PAF-

acether in IgE-dependent activation of eosinophils. J. Lipid Med. in press,

133. CARSTAIRS, J. R., AND BARNES,
-
- 113. CARSTAIRS, J. R., AND BARNES, P. J.: Autoradiographic mapping of substance P receptors in lung. Eur. J. Pharmacol. 127: 295-296, 1986.
114. CARSWELL, H., AND NAHORSKI, S. R.: Distribution and characteristics of histam **EXECUTE:** H,, AND NAHORSKI, S. R.: Distribution and characteristics of histamine H₁-receptors in guinea-pig airways identified by [³H]mepyramine. Eur. J. Pharmacol. 81: 301-307, 1982.
Mas.LE, T. B., RODBARD, D., AND K
-
- mine. Eur. J. Pharmacol. 81: 301-307, 1982.

115. CASALE, T. B., RODBARD, D., AND KALINER, M.: Characterization of histamine H₁-receptors in human peripheral lung. Biochem. Pharmacol. 34:

3285-3292, 1985.

116. CASALE, 217. CASALA, D., AND HUNNINGHAKE, G. W.: Elevated bronchoalveolar lavage
fluid histamine levels in allergic asthmatics are associated with metha-
choline bronchial hyperresponsiveness. J. Clin. Invest. 79: 1197-1203,
1987. fluid histamine levels in allergic asthmatics are associated with metha-
- **3:** 117. CASALS-STENZEL, J.: Effects of WEB 2086, a novel antagonist of platelet-

3. 1987.

117. CASALS-STENZEL, J.: Effects of WEB 2086, a novel antagonist of platelet-

activating factor in active and passive anaphylax
- **Allergy Clin. Immunol. 58: 607-613, 1976.**
 Allergy Clin. Immunol. 58: 607-613, 1976.
- **BRINK, C. L., EVANS, R., AND WARD, G. W.: The effect of atropine** and albuterol aerosols on the human bronchial response to histamine. J. Allergy Clin. Immunol. 58: 607–613, 1976.
ERRINA, J., LADURIE, M. L., LABAT, C., RA Respir. Distribution States of States of States of Companion of the CERRINA, J., LADURIE, M. L., LABAT, C., RAFFESTIN, B., BAYOL, A., AND BRINK, C.: Comparison of human bronchial muscle responses to histamine
in vivo with
- BRINK, C.: Comparison of human bronchial muscle responses to histamine
in vivo with histamine and isoprotenerol agonists in vitro. Am. Rev.
Respir. Dis. 134: 57-61, 1976.
RRINNA, J., RAPAT, S., LABAT, C., BOULLET, C., BAYO **Respir. Dis. 134:** 57-61, 1976.
 **INSERM SPACE AND SERM SYMPOSIUM SYMPOSIUM INTERFERM SPACE AND BRINK, C.: Effects of PAF-acether on isolated muscle preparations

C., AND BRINK, C.: Effects of PAF-acether on isolated musc** 2005-212, Elsevier Science Pub. B.V., 1983. 121. CHAN, P.C., BAYOL, A. GATEAU, O., AND BRINK, C.: Effects of PAF-acether on isolated muscle preparations from the rat, guinea-pig, and human lung. In Platelet-Activating Fact receptor antagonistics, term and a burnan lung. In Platelet-Activating Factor, INSERM Symposium No. 23, ed. by J. Benveniste and B. Arnoux, pp 206-212, Elsevier Science Pub. B.V., 1983. 121. CHAN, T. B., SHELTON, D. M., AN scienting active and passive analphylaxis. Immunopharmacology

16. CA-7781, 1987.

118. Gasemathe, C. L., Evany M. M. D. W. H. P. (Fig. effect of attenpine

Allergy Clin, Immunol, 581: 697-613, 1976.

119. CERMINA, J., LA
- receptor antagonist, terfenadine, on antigen-induced asthma. Br. J. Dis.

Chest 80: 375-384, 1986.

22. CHAND, N.: Is airway hyperreactivity in asthma due to histamine H₂-

123. CHAND, N.: Is airway hyperreactivity in as receptor antagonist, terfenadine, on antigen-induced asthma. Br. J. Dis.
Chest 80: 375-384, 1986.
122. CHAND, N.: Is airway hyperreactivity in asthma due to histamine H_rreceptor deficiency? Med. Hypotheses 6: 1105-1112,
-
-
- 122. CHAND, N.: Is airway hyperreactivity in asthma due to histamine H_2
receptor deficiency? Med. Hypotheses 6: 1105-1112, 1980.
123. CHAND, N., AND EYRE, P.: Classification and biological distribution of
histamine rec
- 14. Character considers to plate the activating factor in

Increased cosinophil responsiveness to plate the activating factor in

asthma. Clin. Sci. 74 (suppl. 18): 5P, 1988.

125. CHAP, H., MAUCO, G., SIMON, M. F., BENVEN
-
- CHINES, T. J., WILLIAMS, S. J., SEATON, A., BRUCE, C., AND TAYLOR, W.

H.: Histamine, basophils, and eosinophils in severe asthma. Clin. Sci. 57:

127. CHRISTIANSEN, S. C., PROUD, D., AND COCHRANE, C. G.: Detection of tiss
- **Extra factor on aerosol histamine responses in awake sheep. Am. Rev.**
 Clin. Invest. 79: 188-197, 1987.
 REP. 197. 1987.
 REP. 197. 1987.
 **REP. 202. CHUNG, K. F.: Role of inflammation in the hyperreactivity of the EXECUTE 128. CHULT THAN, B. W., LEFTERTS, P. L., AND SNAPPER, J. R.: Effect of platelet activating factor on aerosol histamine responses in awake sheep. Am. Rev.

Respir.** Dis. 135: 1267-1270, 1987.
 129. CHUNG, K. F.:
-
- Respir. Dis. 135: 1267–1270, 1987.

HUNG, K. F.: Role of inflammation in the hyperreactivity of the airways

in asthma. Thorax 41: 657–662, 1986.

HUNG, K. F., AIzAWA, H., BECKER, A. B., FRICK, O., GOLD, W. M., AND

NADEL, I.es. Catology, 11. The Rev. Respired. The respired in the allowing of the allways

in asthma. Thorax 41: 657-662, 1986.

NADEL, J. A.: Inhibition of antigen-induced airway hyperresponsiveness

by a thromboxane synthetase
- NADEL, J. A.: Inhibition of antigen-induced airway hyperresponsiveness

by a thromboxane synthetase inhibitor (OKY-046) in allergic dogs. Am.

Rev. Respir. Dis. 134: 258-261, 1986.

HUNG, K. F., AIzAWA, H., LEKAUF, G. D., 131. CHUNG, K. F., AIZAWA, H., LEIKAUF, G. D., UEKI, I. F., EVANS, T. W., AND
NADEL, J. A.: Airway hyperresponsiveness induced by platelet-activating
factor: role of thromboxane generation. J. Pharmacol. Exp. Ther. 236:
58
-
- NADEL, J. A.: Airway hyperresponsiveness induced by platelet-activating
factor: role of thromboxane generation. J. Pharmacol. Exp. Ther. 236:
580–584, 1986.
132. CHUNG, K. F., AND BARNES, P. J.: PAF antagonists: their ther 248-251, 1987. 134. CHUNG, K. F., DENT, G., McCUSKER, M., GUINOT, P., PAGE, C. P., AND

BARNES, P. J.: Effect of a ginkgolide mixture (BN 52063) in antagonising

skin and platelet responses to platelet activating factor in BARNES, P. J.: Effect of a ginkgolide mixture (BN 52063) in antagonising
gkin and platelet responses to platelet activating factor in man. Lancet 1:
248-251, 1987.
HUNG, K. F., DIXON, C. M. S., AND BARNES, P. J.: Platelet-
- **and circulating cells. Am. Rev. Respir. Dis. 135: A159, 1987.** 248-251, 1987.

134. CHUNG, K. F., DIXON, C. M. S., AND BARNES, P. J.: Platelet-activating

factor (PAF) and asthmatic airways: effects of caliber, responsiveness,

and circulating relation and increase and containing cell
-
- 134. CHUNG, K. F., DIXON, C. M. S., AND BARNES, P. J.: Platelet-activating
factor (PAF) and asthmatic airways: effects of caliber, responsiveness,
and circulating cells. Am. Rev. Respir. Dis. 135: A159, 1987.
135. CHUNG, K of cholinergic neurotransmission in canine airways by thromboxane-
mimetic U 46619. Eur. J. Pharmacol. 117: 373-375, 1985.
136. CLANCY, R. M., DAHNDEN, C. A., AND HUGLI, T. E.: Arachidonate metab-
olism of human polymorpho
- Met-Leu-Phe or complement component C5a is independent of phospho-
lipase activation. Proc. Natl. Acad. Sci. USA 80: 7200–7204, 1983.
137. CLARK, R. A., GALLIN, J. I., AND KAPLAN, A. P.: The selective eosinophil
chemotacti

ARMACOLO

spet

 $\overline{\mathbb{O}}$

- INFLAMMATORY MEDIA[.]
138. CLEE, M. D., INGRAM, C. G., REID, P. C., AND ROBERTSON, A. S.: The effect of astemizole on exercise-induced asthma. Br. J. Dis. Chest 78: EER, M. D., INGRAM, C. G., REID, P. C., AND ROBERTSON, A. S.: The
effect of astemizole on exercise-induced asthma. Br. J. Dis. Chest 78:
180–183, 1984.
OCKROFT, D. W., AND MURDOCK, K. Y.: Comparative effects of inhaled 139. CLER, M. D., INGRAM, C. G., REID, P. C., AND ROBERTSON, A. S.: The effect of astemizole on exercise-induced asthma. Br. J. Dis. Chest 78: 180-183, 1984.
139. COCKROPT, D. W., AND MURDOCK, K. Y.: Comparative effects of
- SER, M. D., INGRAM, C. G., REID, P. C., AND ROBERTSON, A. S.: The effect of astemizole on exercise-induced asthma. Br. J. Dis. Chest 78:
180–183, 1984.
salbutamol, sodium cromoglycate, and beclomethasone diproprionate on
a 180–183, 1984.

189. COCKROFT, D. W., AND MURDOCK, K. Y.: Comparative effects of inhaled

salbutamol, sodium cromoglycate, and beclome
thasone diproprionate on allergen-induced early asthmatic responses, late asthmatic res
- 140. COLEMAN, R. A., HUMPHREY, P. P. A., KENNEDY, I., AND LUMLEY, P.: 1
Prostanoid receptors. The development of a working classification. Trends
Pharmacol. Sci. 5: 303-306, 1984.
141. COLES, S. J., NEILL, K. H., AND REID,
-
- 141. COLES, S. J., NEILL, K. H., AND REID, L. M.: Potent stimulation of glycoprotein secretion in canine trachea by substance P. J. Appl. Physiol.
67: 1323-1327, 1984.
201ES, S. J., NEILL, K. H., REID, L. M., AUSTEN, K. F. and lysozyme secretion in canine traches by substance P. J. Appl. Physiol. 169. DAVIS, C., KANNAN, M. S., JONES, T. R., AND DANIEL, E. E.: Control of the colles, J. Appl. Physiol. 53: 1080-
142. Colles, S. J., NEIL, K. H., E. J., AND LEWIS, R. A.: Effects of leukotrienes C4 and D4 on glycoprotein 170
and lysozyme secretion by human bronchial mucosa. Prostaglandins 25:
155-170, 1983.
143. COLLIER, H. O. J., AND SHORLEY, P. G.: Analgesic antip
-
-
-
- 144. COOKSON, W. O. C. M.: Bronchodilator action of the antihistamine terfen-
adine. Br. J. Clin. Pharmacol. 24: 120-121, 1987.
145. COPAS, J. L., BORGEAT, P., AND GARDINER, P. J.: The actions of 5, 12, and
15-HETE on trac **bronchoalveolar lavage fluid from asthmatic patients. Bronchoal J. J. J. Co. 114, 1982.**
8: 105-114, 1982.
 9: 105-114, 1982.

W. STENTON, S. C., AND WALTERS, B. H.: Platelet-activating factor

M. STENTON, S. C., AND 8: 105-114, 1982.

146. COURT, E. N., GOADBY, P., HENDRICK, D. J., KELLY, C. A., KINGSTON,

W., STENTON, S. C., AND WALTERS, E. H.: Platelet-activating factor in

honchoalveolar lavage fluid from asthmatic patients. Br. J.
-
- bronchoalveolar lavage fluid from asthmatic patients. Br. J. Clin. Pharmacol. 24: 258, 1987.
macol. 24: 258, 1987.
147. COX, H. M., MUNDAY, K. A., AND POAT, J. A.: Identification of selective,
high affinity ¹³⁸I-angioten **tivity** by BN 52021, and the same of the same of the magnetonic and the intertinal epithelia. Br. J. Pharmacol. 87: 201–209, 1986.
 tivity by BN 52021, a platelet activating factor antagonist. Clin. Res. in

L.; Modific
- 148. COYLE, A., SJOERDSMA, K., PAGE, C. P., BROWN, L., AND METZGER, W.

J.: Modification of the late asthmatic response and bronchial hyperreac-

tivity by BN 52021, a platelet activating factor antagonist. Clin. Res. in
 The Same Corollation. Here is 1988.

149. Covins, A. J., URWIN, S. C., Page, C. P., Touvay, C., VILLAIN, B., AND

BRAQUET, P.: The effect of the selective antagonist BN 52021 on PAF

and antigen-induced bronchial hyperreac **EXAMPLET, P.: The effect of the selective antagonist BN 52021 on PAF** and antigen-induced bronchial hyperreactivity and eosinophil accumulation. Eur. J. Pharmacol. in press, 1983.
150. CREESSE, B. R., AND BACH, M. K.: Hyp
-
- WEBER, B. R., AND BACH, M. K.: Hyperreactivity of airways smooth muscle produced in vitro by leukotrienes. Prostagland. Leuk. Med. 11: 161–169, 1983.
RETCOS, P. S., PETERS, S. P., ADKINSON, N. F., NACLERIO, R. M., RTAYES, produced in vitro by leukotrienes. Prostagland. Leuk. Med. 11: 161-169,
1983.
151. CRETICOS, P. S., PETERS, S. P., ADKINSON, N. F., NACLERIO, R. M.,
1983.
151. CRETICOS, P. S., PETERS, S. P., ADKINSON, N. F., NACLERIO, R.
-
- **platelet activating factor** (PAF) by human epidermal cells. Br. J. Phar-
 PAYS CUNDELL, D. R., MORGAN, D. J. R., AND DAVIS, R. J.: N. C. F.—a mast

cell specific chemotactic factor? Clin. Sci. 66: 50P, 1984.
 153. CUN 152. CURDELL, D. R., MORGAN, D. J. R., AND DAVIS, R. J.: N. C. F.—a mast
cell specific chemotactic factor? Clin. Sci. 66: 50P, 1984.
153. CUNNINGHAM, F. M., LEIGH, I., AND MALLET, A. I.: The production of
platelet activati and asthmatic subjects. J. Clin. I. AND MALLET, A. I. The product platelet activating factor (PAF) by human epidermal cells. Br. J. macol. 90: 117P, 1987.
154. CURRY, J. J.: The action of histamine on the respiratory tract
-
-
- macol. 90: 117P, 1987.

164. CURRY, J. J.: The action of histamine on the respiratory tract in normal

and asthmatic subjects. J. Clin. Invest. 25: 785-791, 1946.

165. CUSHLEY, M. J., AND HOLGATE, S. T.: Adenosine-induced
-
- adenoine and guanosine on airway resistance in normal and asthmatic
adenoine and guanosine on airway resistance in normal and asthmatic
subjects. Br. J. Clin. Pharmacol. 15: 161-165, 1983.
157. CUSHLEY, M. J., TATTERSFIELD 159. Cuss, F. M., J., WEE, L. H., AND HOLGATE, S. T.: The effect of inhaled 5-
hydroxytryptamine (5-HT, serotonin) on airway calibre in man. Br. J.
Cuss, F. M., AND BARNES, P. J.: Epithelial mediators. Am. Rev. Respir.
Dis
-
- bydroxytryptamine (5-HT, serotonin) on airway calibre in man. Br. J.
Clin. Pharmacol. 22: 487-490, 1966.
159. Cuss, F. M., AND BARNES, P. J.: Epithelial mediators. Am. Rev. Respir.
Dis. 136: 842-845, 1967.
160. Cuss, F. M.
-
- Dis. 136: 542-545, 1987.

160. CUSS, F. M., DIXON, C. M. S., AND BARNES, P. J.: Effects of inhaled platelet

activating factor on pulmonary function and bronchial responsiveness in

man. Lancet 2: 189-192, 1986.

161. CUTH 161. CUTHBERT, M. F.: Bronchodilatory activity of aerosols of prostaglandins E_1
and E_2 in asthmatic subjects. Proc. R. Soc. Med. 64: 15-16, 1971.
162. DAHLEN, S. E., BJORK, J., HEDQVIST, P., ARFORS, K.-E., HAMMARSTR
- USA 78: 3887-3891, 1981.

USA 78: 3887-3891, 1981.

ISS. DAHLEN, S.-E., HANSSON, G., HEDQVIST, P., BJORK, T., GRANSTROM, E.,

AND DAHLEN, B.: Allergen challenge of lung tissue from asthmatics elicits

bronchial contraction
-
- 176. **DAHLEN, S.-E., HEDQVIST, P., HAMMERSTROM, B., AND SAMUELSSON, B.:**

Leukotrienes are potent constrictors of human bronchi. Nature (Lond.)

288: 484–486, 1980. **288: 484-486, 1980.**
 28. Biological activities of lipoxin RHLEN, S.-E., HEDQVIST, P., HAMMERSTROM, B., AND SAMUELSSON, B.:
Leukotrienes are potent constrictors of human bronchi. Nature (Lond.)
B.B.: 484–486, 1980.
RHLEN, S.-E., RAUD, J., SERHAN, C. N., BJORK, B., AND SAMUELSS 165. DAHLEN, S.-E., HEDQVIST, P., HAMMERSTROM, B., AND SAMUELSSON, B.:
 Loukottienes are potent constrictors of human bronchi. Nature (Lond.)
 288: 484-486, 1980.

166. DAHLEN, S.-E., RAUD, J., SERHAN, C. N., BJORK, B.
-
-
- B.: Biological activities of lipoxin A include lung strip contraction and
dilation of arterioles in vivo. Acta Physiol. Scand. 130: 643–648, 1987.
167. DALE, H. H., AND LAIDLAW, P. P.: Histamine shock. J. Physiol. 52: 355, 188. DAVIDSON, A. B., LEE, T. H., SCAMON, P. D., SOLWAY, J., MCFADDEN, E.
R., INGRAM, R. H., COREY, E. J., AUSTEN, K. F., AND DRAZEN, J. M.:
Bronchoconstrictor effects of leukotriene E4 in normal and asthmatic
subjects. Am
-
- Bronchoconstrictor effects of leukotriene E4 in normal and asthmatic subjects. Am. Rev. Respir. Dis. 135: 333-337, 1987.
169. DAVIS, C., KANNAN, M. S., JONES, T. R., AND DANIEL, E. E.: Control of human airwy smooth muscle: vivo study. Rae. 22: 239-254, 1981.

170. DEL MAESTRO, R. F., BJORK, J., AND ARFORS, K. E.: Increase in microvascular permeability induced by enzymatically generated free radicals. I. In vivo study. Microvasc. Res. 22: 239
- I. MAESTRO, R. F., BJORK, J., AND ARFORS, K. E.: Increase in microvascular permeability induced by enzymatically generated free radicals. I. Invivo study. Microvasc. Res. 22: 239-254, 1981.
B. MONCHY, J. G. R., KAUFFMAN, H cuar permeabury manced by enzymanically generated free radicals. I. in
171. DE MONCHV, Microvasc. Res. 22: 239-254, 1981.
171. DE MONCHY, J. G. R., KAUFFMAN, H. F., VENGE, P., KOETER, G. H.,
JANSEN, H. M., SLUITER, H. J.,
- sosinophilia curing allergen-included late asthmatic reactions. Am. Rev.

Respir. Dis. 131: 373-376, 1985.

DEMOPOULOS, C. A., PINCKARD, R. N., AND HANAHAN, D. J.: Platelet

activating factor: evidence for 1-O-alkyl-2-acet
- activating factor: evidence for 1-O-alkyl-2-acetyl-an-giyceryl-3-phosphorylcholine as the active component (a new class of lipid chemical media-
tors). J. Biol. Chem. 254: 9355-9358, 1979.
ESQUAND, S., Touvay, C., RANDON, purs). J. Biol. Chem. 254: 9355-9358, 1979.

RSQUAND, S., TOUVAY, C., RANDON, J., LAGENTE, V., VILAIN, B., MARI-DONNEAU-PARINI, I., ETIRENIS, A., LEFORT, J., BRAQUET, P., AND VAR-GAFTIG. B. B.: Interference of BN 52021 (gi 174. DEWARD PARINI, I., ETIENNE, A., LEPORT, J., BRAQUET, P., AND VAR-
GAFTIG, B. B.: Interference of BN 52021 (ginkgolide B) with the broncho-
pulmonary effects of PAF-acether in the guinea pig. J. Pathol. 144: 25-
34, 19 **Bandyining International C, and Exercise C, and in the statistic increases (i. a)**
Bandyining factor reddences for 1:0 alby 2-acety-an-glyceryl-3-phosphotome, cm/s.
Bandyining factor reddences for 1:0 alby 2-acety-an-
- pulmonary effects of PAF-acether in the guinea pig. J. Pathol. 144: 25-34, 1984.

174. DEWAR, A., ARCHER, C. B., PAUL, W., PAGE, C. P., MACDONALD, D. M.,

175. DIAS MORLEY, J.: Cutaneous and pulmonary histopathological res AND MORLEY, J.: Cutaneous and pulmonary histopathological response to platelet activating factor (Paf-acether) in the guinea-pig. J. Pathol. 144: 25-34, 1984.
144: 25-34, 1984.
inflammation. II. Biological properties of an
- to platelet activating factor (Paf-acether) in the guinea-pig. J. Pathol.
144: 25-34, 1984.
175. DIAS DA SILVA, W., AND LEPOW, I. H.: Complement as a mediator of
inflammation. II. Biological properties of anaphylotoxin pre
- inflammation. II. Biological properties of anaphylotoxin prepared with
purified components of human complement. J. Exp. Med. 125: 921-946,
1967.
Disz, P. D., GALLEGUILLOS, F. R., GONZALEZ, M. C., PANTIN, C. F. A.,
AND KAY,
- AND KAY, A. B.: Bronchoalveolar lavage in asthma: the effect of disodium
cromoglycate on leukocyte counts, immunoglobulins, and complement. J.
Allergy Clin. Immunol. 74: 41–48, 1984.
177. DLIK, S., ROGERS, D. F., AND BARNE fractor. **Clin.** Immunol. 74: 41-48, 1984.

177. DIJK, S., ROGERS, D. F., AND BARNES, P. J.: Bradykinin-induced microvascular leakage in guinea-pig airways: involvement of platelet-activating factor. Clin. Sci. 74: 29P, 19
- IT. S., ROGERS, D. F., AND BARNES, P. J.: Bradykinin-induced microvascular leakage in guinea-pig airways: involvement of platelet-activating factor. Clin. Sci. 74: 29P, 1988.

IXON, C. M. S., FULLER, R. W., AND BARNES, P. cuar learage in guinea-pig airways: involvement or platelet-activating
178. DKoN, C. M. S., FULLER, R. W., AND BARNES, P. J.: The effect of an
angiotensin converting enzyme inhibitor, ramipril, on bronchial responses
to in
- **methacin and propries and propries in press, 1988.**
 Methacin and propranology and propranology Breat C. P.: PAF does not contribute to bronchial hyperreactivity induced by indo-
 Methacin and propranolol. Br. J. Pharm
- **PRODUGINAL SMOOTH MUSCLE OF ALCT MUSCLE OF ALCT PART AND FACT PART does not contribute to bronchial hyperreactivity induced by indomethacin and propranolol. Br. J. Pharmacol. in press, 1988. 180. DONALDSON, J., AND HILL,**
- methacin and propranolol. Br. J. Pharmacol. in press, 1988.

180. DONALDSON, J., AND HILL, S. J.: Histamine-induced inositol phospholipid

breakdown in the longitudinal smooth muscle of guinea pig ileum. Br. J.

181. DOR, inveakdown in the longitudinal smooth muscle of guinea pig ileum. Br. J. Pharmacol. 85: 499-512, 1985.

181. Dor, P. J., VERVOLET, D., SARENE, M., ANDRAC, L., BUNERANDI, J. J., AND CHARPIN, J.: Induction of late cutaneous 181. DOR, P. J., VERVOLET, D., SARENE, M., ANDRAC, L., BUNERANDI, J. J., AND CHARPIN, J.: Induction of late cutaneous reaction by kallikrein injection: comparison with allergic-like late response to compound 48/80.
182. DR
-
- 183. DRAZEN, J. M., AUSTEN, K. F., LEWIS, R. A., CLARK, D. A., GOTO, G., MARFAT, A., AND COREY, E. J.: Comparative airway and vascular activities of leukotrienes C, and D in vivo and in vitro. Proc. Natl. Acad. Sci. USA 77 77: 4354-4358, 1980. 184. **DRAFTAT, A., AUSTEN, B. A., CLARK, D. A., GOTO, G.,** MARFAT, A., AND COREY, E. J.: Comparative sirway and vascular activities of leukotrienes C., and D in vivo and in vitro. Proc. Natl. Acad. Sci MARFAT, A., AND COREY, E. J.: Comparative airway and vascular activities of leukotrienes C₁ and D in vivo and in vitro. Proc. Natl. Acad. Sci. USA 77: 4354–4358, 1980.
A.R.ZEN, J. M., LEWISS, R. A., AUSTEN, K. F., TODA,
- of leukotrienes C_1 and D in vivo and in vitro. Proc. Natl. Acad. Sci. USA
77: 4354-4358, 1980.
184. DRAZEN, J. M., LEWIS, R. A., AUSTEN, K. F., TODA, M., BRION, F., MARFAT,
A., AND COREY, E. J.: Contractile activities A., AND COREY, E. J.: Contractile activities of structural analogues of leukotrienes C and D: necessity of a hydrophobic region. Proc. Natl. Acad.
Sci. USA 78: 3195-3196, 1981.
Sci. USA 78: 3195-3196, 1981.
antigen-induced
- J. Pharmacol. 59: 475, 1978. 1981.

J. Pharmacol. Sci. USA 78: 3195-3198, 1981.

185. DUNLOP, L. S., AND SMITH, A. P.: The effect of histamine antagonists on

antigen-induced contractions of sensitized human bronchus in vi
-
- antigen-induced contractions of sensitized human bronchus in vitro. Br.

J. Pharmacol. 59: 475, 1977.

186. DUNNILL, M. S.: The pathology of asthma with special reference to changes

in the bronchial mucosa. J. Clin. Patho airway obstruction in man. Bull. Eur. Physiopathol. Respir. **18:** 449-460, **1982.** 188. EISER, N. M., AND GUZ, A.: Effect of atropine on experimentally-induced

187. EISER, N. M., AND GUZ, A.: Effect of atropine on experimentally-induced

1982.

1982.

1982. EISER, N. M., MILLS, J., SNASHALL, P. D., AND
-
- 189. Eust way obstruction in man. Bull. Eur. Physiopathol. Respir. 18: 449–460, 1982.

189. Eusta, N. M., MILLS, J., SNASHALL, P. D., AND GUZ, A.: The role of histamine receptors in asthma. Clin. Sci. 60: 363–370, 1981.

1 **iSER, N. M., MILLS, J., SNASHALL, P. D., AND GUZ, A.: The role of histamine receptors in asthma. Clin. Sci. 60: 363-370, 1981.
NGEL, F., OOSTING, R. S., AND NIJKAMP, F. P.: Pulmonary macrophages induce deterioration of gu**

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 $\overline{\mathbb{O}}$

PHARM
REV

- **EVANS, J. M., BARNES, N. C., PIPER, P. J., AND COSTELLO, J. F.: The effect** J. Allergy C
of REV5901 on histamine and leukotriene D₄ induced bronchoconatriction 217. FROSSARD, N
in man. Br. J. Clin. Pharmacol. 25: 111P,
-
- platelet-activating factor on airway vascular permeability: possible mechanisms. J. Appl. Physiol. 63: 479-484, 1987.
192. EVANS, T. W., DENT, G., ROGERS, D. F., AURSUDKIJ, B., CHUNG, K. F., AND BARNES, P. J.: Effect of a platelet-activating factor on airway vascular permeability: possible mech-
nisms. J. Appl. Physiol. 63: 479-484, 1987.
192. EVANS, T. W., DENT, G., ROGERS, D. F., AURSUDKIJ, B., CHUNG, K. F.,
AND BARNES, P. J.: Effect of a
- ARNES, P. J.: Effect of a PAF antagonist, WEB 2086, on airway microvascular leakage in the guinea pig and platelet aggregation in man. Br. J. Pharmacol. 94: 164-168, 1988.
ARS, T. W., DIXON, C. M. S., CLARKE, B., CONRADSON 193. EVANS, T. W., DIXON, C. M. S., CLARKE, B., CONRADSON, T.-B., AND BARNES, P. J.: Comparison of airway and cardiovascular effects of substance P and neurokinin A in man. Br. J. Clin. Pharmacol. 25: 273-275, 1988.

1988.
-
-
- permeability in different parts of the guinea-pig airways. Clin. Sci. 74:
46P, 1968.
196. FAIRFAX, A. J., HANSON, J. M., AND MORLEY, J.: The late reaction following
bronchial provocation with house dust mite allergen: depe
- 196. FAIRFAX, A. J., HANSON, J. M., AND MORLEY, J.: The late reaction following 1084, 1985.

bronchial provocation with house dust mite allergen: dependence on 223. FULLER, R. W., DIXON, C. M. S., CUSS, F. M. C., AND BARNE var, A.J., HANSON, J. M., AND MORLEY, J.: The late reaction following
bronchial provocation with house dust mite allergen: dependence on
arachidonic acid metabolism. Clin. Exp. Immunol. 52: 393-398, 1983.
RR, R. S., COX, C honochial provocation with house dust mite allergen: dependence on arachidonic acid metabolism. Clin. Exp. Immunol. 52: 393–396, 1983.
RRR, R. S., COX, C. P., WARDLOW, M. L., AND JORENSON, R.: Preliminary
studies of an aci arachidonic acid metabolism. Clin. Exp. Immunol. 52: 393-398, 1983.

197. FARR, R. S., Cox, C. P., WARDLOW, M. L., AND JORENSON, R.: Preliminary

studies of an acid labile factor (ALF) in human sera that inactivates

plate
- **SAMUELS OF AN UNIVERSON, STIMULATION**
 SAMUELS Of an acid labile factor (ALF) in human sera that inactivates

platelet-activating factor (PAF). Clin. Immunol. Immunopathol. 15: 318-
 SAMUELSSON, B.: Stimulation of huma 199. FELNMARK, S. J., LINDGREN, J. A., CLAESSON, H.-E., MALMSTEN, C., AND

SAMUELSSON, B.: Stimulation of human leukocyte degranulation by leu-

kotriene B_A and its omega-oxidized metabolites. FEBS Lett 186: 141-

144, 1
-
- kotriene B₄ and its omega-oxidized metabolites. FEBS Lett 136: 141-
144, 1981.
199. FELS, A. O. S., PAWLOWSKI, N. A., CRAMER, E. B., KING, T. K. C., COHN,
2. A., AND SCOTT, W. A.: Human alveolar macrophages produce leuko
-
- C3a and C5a leukotaxis in vitro and under simulated in vivo conditions.

J. Immunol. 120: 109-115, 1978.

201. FINNEY, M. J. B., KARLSSON, J.-A., AND PERSSON, C. G. A.: Effects of

bronchoconstrictors and bronchodilators o Indemethacin modification of immediate-type immunologic airway responses in allergic sathmatic and nonasthmatic subjects. Am. Rev. Respir.
Dis. 123: 609-614, 1981.
SH, J. E., JAMESON, L. S., ALBRIGHT, A., AND NORMAN, P. S.
- **in asthmatic subjects. Am. Rev. Respiration and STATE SUPPOSE IN AMERICAL SUPPOSE IN A. S., JAMESON, L. S., ALBRIGHT, A., AND NORMAN, P. S.: Modu of the bronchomotro reffects of chemical mediators by prostagland in asthma**
- Dia. 123: 609-614, 1981.

203. FISH, J. E., JAMESON, L. S., ALBRIGHT, A., AND NORMAN, P. S.: Modulation

of the bronchomotor effects of chemical mediators by prostaglandin F₃m

in asthmatic subjects. Am. Rev. Respir. Dis of the bronchomotor effects of chemical mediators by prostaglandin F₃.
in asthmatic subjects. Am. Rev. Respir. Dis. 130: 571-574, 1984.
204. FIBH, J. E., NEWBALL, H. H., NORMA, P. S., AND PETERMAN, V. E.: Novel
effects o **to Paffram Construction Induces and Pat-acether agent and Paffram AN, V. E.: Novel effects of PGF_{as} in airway function in asthmatic subjects. J. Appl. Physiol. 232.
54:** 105-122, 1983. L.W., PARENTE, L., AND PAYNE, A.
-
- effects of PGF_{as} in airway function in asthmatic subjects. J. Appl. Physiol. 232
54: 105-122, 1983.
205. FrrzessALD, M. F., LEES, I. W., PARENTE, L., AND PAYNE, A. N.: Exposure 233
to Paf-acether aerosol induces airway h to Paf-acether aerosol induces airway hyperresponsiveness to 5-HT in guinea-pigs. Br. J. Pharmacol. 90: 112P, 1987.
208. FLAVAHAN, N. A., AARHUS, L. L., RIMELE, T. J., AND VANHOUTTE, P. M.: Respiratory epithelium inhibits Sponsee of rabbits trachea **and bronchus. J. L., RIMELE, T. J.**, AND VANHOUTTE, P. M.:
Respiratory epithelium inhibits bronchial smooth muscle tone. J. Appl.
Physiol. 58: 834-838, 1985.
207. FLEISCH, J. H., AND CHALKINS,
-
- F. Physiol. 58: 334-338, 1985.
 ERNAGO SPACE AND CHALKINS, P. J.: Comparisons of drug-induced responses of rabbit traches and bronchus. J. Appl. Physiol. 41: 61-66, 1976.

INT, K. C., LEUNG, K. B. P., HUDSPITH, B. N., BR 207. FLEISCH, J. H., AND CHALKINS, P. J.: Comparisons of drug-induced responses of rabbit traches and bronchus. J. Appl. Physiol. 41: 61-66, 1976.
208. FLINT, K. C., LEUNG, K. B. P., HUDSPTH, B. N., BROSTOFF, J., PEARCE, F Soon Have, H. D., L., AND JOHNSON, N. M.: Bronchoalveolar mast cells in extrinsic
asthma: a mechanism for the initiation of antigen specific bronchocon-
striction. Br. Med. J. 291: 923-926, 1986.
209. FLOWER, R. J., HARVEY
-
-
- 233, 1976.

210. Form-Hurchmson, A. W.: Neutrophil aggregating properties of PAF-
 acether and leukotriene B₄. Int. J. Immunopharmacol. 5: 17–21, 1983.

211. FORD-HUTCHINSON, A. W., BRAY, M. A., DOIG, M. V., SHIPLEY, M accether and leukotriene B., Int. J. Immunopharmacol. 5: 17-21, 1983.

211. FORD-HUTCHINSON, A. W., BRAY, M. A., DOIG, M. V., SHIPLEY, M. E.,

AND SMITH, M. J. H.: Leukotriene B., a potent chemokinetic and aggre-

gating s
-
- **214. FREMAN, J. C., NORRIS, D. B., RISING, T. J., AND WEBBER, S. E.: The binding of [¹H] tiotidine to homogenates of guinea-pig lung parenchyma.
B. B. J. Pharmacol. 86: 475-482, 1985.
Br. J. Pharmacol. 86: 475-482, 1985**
- **145-147,** 1980. binding of [⁸H]tiotidine to homogenates of guinea-pig lung parenchyma.

Br. J. Pharmacol. **86:** 475–482, 1986.

214. FREDHOLM, B. B., AND SYDBOM, A.: Are the anti-allergic actions of the

ylline due to antagonism at the
-
-

- **J.** Allergy Clin. Immunol. 77: 527-537, 1986.
217. **FROSSARD, N., AND BARNES, P. J.:** μ **-Opioid receptors modulate non-**
cholinergic constrictor nerves in guinea-pig airways. Eur. J. Pharmacol Cholinergy Clin. Immunol. 77: 527-537, 1986.

COSSARD, N., AND BARNES, P. J.: µ-Opioid receptors modulate non-

cholinergic constrictor nerves in guinea-pig airways. Eur. J. Pharmacol.

147: 519-521, 1987. **1. Allergy Clin. Immun**
1088ARD, N., AND B.
cholinergic constrictor
147: 519-521, 1987.
1088ARD, N., AND BAB **217. FROSSARD, N., AND BARNES, P. J.:** μ **-Opioid receptors modulate non-cholinergic constrictor nerves in guinea-pig airways. Eur. J. Pharmacol.
218. FROSSARD, N., AND BARNES, P. J.: Effect of tachykinins on small human**
- 219. FROSSARD, N., AND BARNES, P. J.: Effect of tachykinins on small human airways and the influence of thiorphan. Am. Rev. Respir. Dis. 137: 196, 1988.
REGISTER AND BARNES, P. J.: Effect of tachykinins on small human
19
- **removal, endopeptidase and cyclooxygenase inhibition on airway re-**
removal, endopeptidase and cyclooxygenase inhibition on airway re-
Respires and endogenous and endogenous tachykinins. Am. Rev. Respir. Dis.
137: 2
- BARNES, P. J.: Comparison of airway and cardiovascular effects of sub-

1988. The manner Br. J. Clin. Pharmacol. 25: 273-275,

1988. The Manneson and House and Development and Br. J. Clin. Pharmacol. 25: 273-275,

1988. th 219. FROSSARD, N., KHODEN, K. J., AND BARNES, P. J.: Effect of epithelium
removal, endopeptidase and cyclooxygenase inhibition on airway re-
sponses to exogenous and endogenous tachykinins. Am. Rev. Respir. Dis.
137: 208, 137: 206, 1988.

JIMURA, M., SASAKI, F., NAKATSUMI, Y., TAKAHASHI, Y., HIPUMI, S., TAGA, K., MIPUNE, J. I., TANAKA, T., AND MATSUDA, T.: Effects of

thromboxane synthetase inhibitor (OKY-046) and a lipoxygenase inhibitor (**EXECUTE:** THORA, M., SASAKI, F., NAKATSUMI
TAGA, K., MIFUNE, J. I., TANAKA, '
thromboxane synthetase inhibitor (OF
tor (AA-861) on bronchial responsive
subjects. Thorax 41: 955-959, 1986.
iller, R. W., Conradson, T.-B., D TAGA, K., MIFUNE, J. I., TANAKA, T., AND MATSUDA, T.: Effects of thromboxane synthetase inhibitor (OKY-046) and a lipoxygenase inhibitor (AA-961) on bronchial responsiveness to acetylcholine in asthmatic subjects. Thorax 4
	- tor (AA-861) on bronchial responsiveness to acetylcholine in asthmatic subjects. Thorax 41: 955-959, 1966.

	221. Fuller, R. W., Conradson, T.-B., Dixon, C. M. S., Crossman, D. C., and

	Barnes, P. J.: Sensory neuropeptide e
	-
	-
	-
	- 221. Fuller, R. W., Conradson, T.-B., Dixon, C. M. S., Crossman, D. C., and
Barnes, P. J.: Sensory neuropeptide effects in human skin. Br. J. Pharmacol. 92: 781-788, 1987.
222. Fuller, R. W., DIXoN, C. M. S., AND BARNES, Prostaglandin D₃ potentiates airway responsiveness to histamine and
methacholine. Am. Rev. Respir. Dis. 133: 252-254, 1986.
225. FULLER, R. W., KELSEY, C. R., COLE, P. J., DOLLERY, C. T., AND MAC-
DERMOT, J.: Dexamethaso
	-
	- 225. FULLER, R. W., KELSEY, C. R., COLE, P. J., DOLLERY, C. T., AND MAC-
DERMOT, J.: Dexamethasone inhibits the production of thromboxane B₂
and leukotriene B₄ by human alveolar and perioneal macrophages in
culture. Cl Physiol. **62: 1473-1479,** 1987. 227. FULLER, R. W., MAXWELL, D. L., DIXON, C. M. S., MCGREGOR, G. P.,
BARNES, V. F., BLOOM, S. R., AND BARNES, P. J.: The effects of substance
P on cardiovascular and respiratory function in human subjects. J. Appl.
Physio
	- protein F. W., WARREN, J. B., MCCUSKER, M., AND DOLLERY, C. T.:
Effect of enalapril on skin responses to bradykinin in man. Br. J. Clin.
Pharmacol. 23: 88-90, 1987.
MSE, R., AND SARIA, A.: Potentiation of tachykinin-induce
	- Pharmacol. 23: 88-80, 1987.

	229. GAMSE, R., AND SARIA, A.: Potentiation of tachykinin-induced plasma

	protein extravastion by calcitonin gene-related peptide. Eur. J. Pharmacol. 114: 61-66, 1965.

	230. GARDINER, P. J.: T
	-
	- macol. 114: 61-66, 1986.

	ARDINER, P. J.: The effects of some natural prostaglandins on isolated

	human circular bronchial muscle. Prostaglandins 10: 607-616, 1975.

	ARDINER, P. J.: Characterisation of prostanoid relaxant/ **231. GARDINER, P. J.: Characterisation of prostaglandins 10: 607-616, 1975.**

	231. GARDINER, P. J.: Characterisation of prostancid relaxant/inhibitory receptors $($ a) using a highly selective agonist, TR4979. Br. J. Pharm
	-
	- 231. GARDINER, P. J.: Characterisation of prostanoid relaxant/inhibitory receptors (μ) using a highly selective agonist, TR4979. Br. J. Pharmacol. 87:
45-56, 1986.
45-56, 1986.
45-56, 1986.
45-56, 1986.
232. GARDINER, P and a mixed in the preliminary evaluation of the effect of N-acetyl aspartyl
glutanate on pollen nasal challenge and measured by rhinomanometry
and symptomatology. Allergy 42: 626-630, 1967.
234. GLVNN, A. A., AND MICHAELS
	-
	- and symptomatology. Allergy 42: 626-630, 1987.

	LYNN, A. A., AND MICHAELS, L.: Bronchial biopsy in chronic bronchitis

	and asthma. Thorax 15: 142-153, 1960.

	CRASTES DE PAULET, A., AND MICHEL, F. B.: Functional assessment subjects. **J.** Allergy Chin. Immunol. 70: 88-93, 1982.

	236. GODARD, P., CHAINTREUIL, J., DAMON, M., COUPE, M., FLANDRE, O., CRASTES DE PAULET, A., AND MICHEL, F. B.: Functional assessment of

	alwolar macrophages: comparis CRASTES DE PAULET, A., AND MICHEL, F. B.: Functional assessment alveolar macrophages: comparison of cells from asthmatics and norm subjects. J. Allergy Clin. Immunol. 70: 88-93, 1982.
236. GODFREY, R. C., AND HAWKEEL, F. B
	-
	- philotactic tetrapeptides of human lung tissue: identification of bronchial asthma. Lancet 1: 464-465, 1975.
 philotactic factor is a sected. 1464-465, 1975.
 philotactic factor philotactic factor of anaphylaxis. Proc. 237. **GOETZL, E. J., AND AUSTEN, K. F.: Purification and synthesis of eosimphilotactic tetrapeptides of human lung tissue: identification as eosinoply chemotactic factor of anaphylaxis. Proc. Natl. Acad. Sci. 72: 4123-4123**
	- the motactic factor of anaphylaxis. Proc. Natl. Acad. Sci. 72: 4123-4127, 1975.

	238. GOETZL, E. J., AND PICKETT, W. C.: The human PMN leukocyte chemotactic activity of complex hydroxy-eicosatetraenoic acids (HETEs). J.
 238. GOETZL, E. J., AND PICKETT, W. C.: The human PMN leukocyte chemotactic activity of complex hydroxy-eicosatetraenoic acids (HETEs). J.

	239. GOETZL, E. J., AND SUN, F. F.: Generation of unique mono-hydroxy-

	eicosatetr
	-
	- Immunol. 128: 1789-1791, 1980.

	239. GOBTEL, E. J., AND SUN, F. F.: Generation of unique mono-hydroxy-

	eicosatetraenoic acid from arachidonic acid by human neutrophils. J. Exp.

	Med. 150: 406-411, 1979.

	240. GOBTEL, E. J 240. GOETZL, E. J., VALONE, F. H., REINHOLD, V. N., AND GORMAN, R. R.:
Specific inhibition of the PMN leukocyte characteristic response to hydroxy-fatty acid metabolites of arachidonic acid by methyl ester deriva-
tives. J
	- Specific inhibition of the PMN leukocyte characteristic response to hydroxy-fatty acid metabolites of arachidonic acid by methyl ester derivatives. J. Clin. Invest. 63: 1181-1186, 1979.

	OETZL, E. J., WELLER, P. F., AND VA droxy-fatty acid metabolites of arachidonic acid by methyl ester deriva-
tives. J. Clin. Invest. 63: 1181-1186, 1979.
241. Goneral, E. J., WELLER, P. F., AND VALONE, F. H.: Biochemical and
functional bases of the regulator B. Samuelsson, and R. Paoletti, vol. 1, pp. 157-167, Raven Press, New
	-

PHARM
REV

REV

ARMACOLO

- INFLAMMATORY MEDIATORS AND ASTHMA

(HETE). J. Clin. Invest. 59: 179-183, 1977.

243. GOLDIE, R. G., SPINA, D., HENRY, P. J., LULICH, K. M., AND PATERSON, 268. HARTLEY, J. P. R., AND

J. W.: In vitro responses of human asth
- **human, beta-receptor agonists, and theophylline. Br. J. Clin. Pharmacol. 22: 669-676; 1986.**

macol. 22: 669-676; 1986.
 pharmacol. 23: 669-676; 1986.
 buman neutrophils for the chemotactic mediator 5,12-dihydroxy-6,1
- 244. GOLDMAN, D. W., AND GOBTZL, E. J.: Characterization of a receptor on
human neutrophils for the chemotactic mediator 5,12-dihydroxy-6,14-cis-
8,10-trans-eicosatetreenoic acid (leukotriene B_a). J. Immunol. 129: 1600-
 Exp. Med. 148: 787-792, 1978.

245. GOLDSTEIN, I. M., MALMSTEN, C. L., KINDAHL, H., KAPLAN, H. B., RADMARK, O., SAMURLESDN, B., AND WEISSMANN, G.: Thrombozane

generation by human peripheral blood polymorphonuclear leukocy RADMARK, O., SAMUELSSON, B., AND WEISSMANN, G.: Thromboxane 271
generation by human peripheral blood polymorphonuclear leukocytes. J.
Exp. Med. 148: 787-792, 1978.
246. GONEALEZ, H., AND AHMED, T.: Suppression of gastric H
-
-
-
- 247. GOSWAMI, S. K., OHASHI, M., PANAGIOTIS, S., AND MAROM, Z.: Platelet 27.
activating factor enhances mucous glycoprotein release from human air-
ways in vitro. Am. Rev. Respir. Dia. 135: A159, 1987.
248. GRANDORDY, B. M 248. GRANDORDY, B. M., AND BARNES, P. J.: Phosphoinositide turnover in
airway smooth muscle. Am. Rev. Respir. Dis. 136: 832-35, 1967.
249. GRANDORDY, B. M., CUSS, F. M., SAMPSON, A. S. PALMER, J. B., AND
BARNES, P. J.: Pho
- BARNES, P. J.: Phosphatidylinositol response to cholinergic agonists in airway smooth muscle: relationship to contraction and muscarinic receptors in human lung correlation. Exp. There. 238: 273-279, 1986.

250. GRANDORDY,
- Am. Rev. Respir. Die. Rev. Respir. Die. 135: A274, 1987. 250. GRANDORDY, B. M., RHODEN, K., AND BARNES, P. J.: Histamine H., receptors in human lung: correlation of receptor binding and function.
Am. Rev. Respir. Dis. 136: Reeptors in human lung: correlation of receptor binding and function.

Am. Rev. Respir. Dis. 135: A274, 1987.

251. GRANDORDY, B. M., RHODEN, K. J., FROSSARD, N., AND BARNES, P. J.:

Tachykinin receptors and phosphoinositi
- Tachykinin receptors and phosphoinositide turnover in airways. Am. Re

Respir. Dis. 135: A87, 1987.

252. GREEN, K., HEDQVIST, P., AND SVANBORG, N.: Increased plasma levels

15-keto-13,14-dihydro-prostaglandin F_{ar} after
- 252. GREEN, K., HEDQVIST, P., AND SVANBORG, N.: Increased plasma levels of
15-keto-13,14-dihydro-prostaglandin F_{2n} after allergen-provoked asthma
in man. Lancet 1: 1419-1421, 1974.
253. GREENBERG, B., RHODEN, K., AND B
-
- cules generated by electrical stimulation affect vascular smooth muscle.
J. Mol. Cell Cardiol. 18: 975-981, 1986.
254. GRIFFIN, M., WEISS, J. W., LEITCH, A. G., MCFADDEN, E. R., COREY, E.
J., AUSTEN, K. F., AND DRAZEN, J. J., AUSTEN, K. F., AND DRAZEN, J. M.: Effect of leukotriene D., on the airways in asthma. N. Engl. J. Med. 308: 436-439, 1983.
UINOT, P., DUCHIER, J., PIN, I., BRAMBILLA, C. H., AND BRAQUET, P.: DINOT, P., DUCHIER, J., PIN 255. GUINOT, P., DUCHIER, J., PIN, I., BRAMBILLA, C. H., AND BRAQUET, P.:
Effect of BN 52063, a specific PAF-acether antagonist, on the bronchial
stimulation by allergen in asthmatic patients. Clin. Exp. Pharmacol. Phys.
i
-
- R. Appl. Physiol. 44: 144-149, 1978. Interaction and the induced by substance P in human skin. J. Invest. Dermatol. 71: 233-235, 1978.

257. HAHN, H. L., WILSON, A. G., GRAF, P. D., FISCHER, S. P., AND NADEL, J. 282.

4.:
- **PINCKARD, R. N.:** Respiratory and circulatory alterations induced by **acetyl glyceryl ether phoephorylcholine, a mediator of** IgE anaphylaxis in J. Appl. Physiol. 44: 144-149, 1978.
258. HALONEN, M., PALMER, J. D., LOHMAN, I. C., MCMANUS, L. M., AND
PINCKARD, R. N.: Respiratory and circulatory alterations induced by
acetyl glyceryl ether phosphorylcholine, a mediat
- PINCKARD, R. N.: Respiratory and circulatory alterations induced by
acetyl giveryl ether phosphorylcholine, a mediator of IgE anaphylaxis in
259. HAMBERG, M., Rev. Respir. Dis. 122: 915-924, 1980.
HAMMARSTROM, S., HEDQV18T **hydroxy-5,8,11,13-eicosatetraenoic acid (15-HETE) as the major metabolite of arachidonic acid in human lung. Acta Physiol. Scand. 110: 219-221, 1960.
221, 1960.
ANMARSTROM, S., BERNSTROM, K., ORNING, L., DAHLEN, S. E., H**
- olite of arachidonic acid in human lung. Acta Physiol. Scand. 110: 219-221, 1980.
 AMMARSTROM, S., BERNSTROM, K., ORNING, L., DAHLEN, S. E., HEDQV-AMMARSTROM, G., AND REVENAS, B.: Rep. in the monkey, *Mocaca ivus.* **Bioche** 221, 1980.

221, 1980.

MMARSTROM, S., BERNSTROM, K.,

187, P., SMEDEGARD, G., AND REVIS

Johnnun. 101: 1109-1115, 1981.

Commun. 101: 1109-1115, 1981.

ANNAH, C. J., BACH, M. K., PARE 260. HAMMARSTROM, S., BERNSTROM, K., ORNING, L., DAHLEN, S. E., HEDQV-
18T, P., SMEDEGARD, G., AND REVENAS, B.: Rapid in vivo metabolism of
leukotriene C₃ in the monkey, *Macaca iuus*. Biochem. Biophys. Res.
Commun. 101:
- 261. HANNAH, C. J., BACH, M. K., PARE, P. D., AND SCHELLENBERG, R. R.:
Slow-reacting substances (leucotrienes) contract human airway and pulmonary vascular smooth muscle in vitro. Nature (Lond.) 290: 343-344,
1981.
282. HA
- UELS80N, B.: Identification and biological activities of novel onega-
oridized metabolites of leukotriene B₄ from human leukocytes. FEBS
Lett. 130: 107-112, 1981.
263. HANS80N, L. O., KJELLMAN, N. I. M., AND LEIJON, I.:
-
-
- bronchial asthma. Lancet 2: 874, 1975.

264. HARDY, C., ROBINSON, C., BRADDING, P., AND HOLGATE, S. T.: Prostacy-

clin: a functional antagonist of prostaglandin D_r-induced bronchoconstric-

tion. Thorax 39: 696, 1964.
 clin: a functional antagonist of prostaglandin D_x-induced bronchoconstric289. HUMPHREY, D. M., MCMANUS, L. M., HANAHAN, D. J., AND PINCKARD, R.

tion. Thorax 39: 696, 1964.

1965. HARDY, C., ROBINSON, C., LEWIS, R. A.,
-
- cyclin in normal and asthmatic subjects. Am. Rev. Respir. Dis. 131: 18-
21, 1985.
286. HARDY, C. C., ROBINSON, C., TATTERSFIELD, A. E., AND HOLGATE, S. T.: 291. F
The bronchoconstrictor effect of inhaled prostaglandin D₃ The bronchoconstrictor effect of inhaled prostaglandin D₂ in normal and
asthmatic man. N. Engl. J. Med. 311: 209-213, 1984.
ARRIS, D. N., GREENBERG, R., PHILLIPS, M. B., MICHEL, I. M., GOLDEN-
BERG, H. J., HASLANGER, M.

- isolated **smooth muscle. Eur. J. Pharmacol. 103: 9-18,** 1984. 268. **HARTLEY,** J. P. R., **AND NOGRADY,** 5. G.: Effect of inhaled antihistamine
- histamine, beta-receptor agonists, and theophylline. Br. J. Clin. Phar-
macol. 22: 669-676, 1986. **AND HADDING, U.: Platelet activating factor (PAF)** induces the oxidative
244. GOLDMAN, D. W., AND GOETZL, E. J.: Characteri AND HADDING, U.: Platelet activating factor (PAF) induces the oxidative burst in macrophages. Int. J. Immunopharmacol. 5: 115-121, 1983.
- ARTUNG, H. P., PARNHAM, M. J., WINKLEMAN, J., ENGLEBERGER, W.,

AND HADDING, U.: Platelet activating factor (PAF) induces the oxidative

burst in macrophages. Int. J. Immunopharmacol. 5: 115-121, 1983.

AYSE-LEGRAND, I., C Pharmacol. Exp. Ther. **239: 536-541, 1986.**

270. HAYE-LEGRAND, I., CERRINA, J., RAFFESTIN, B., LABAT, C., BOULLET, C., BAYOL, A., BENVENISTE, J., AND BRINK, C.: Histamine contraction of isolated human airway muscle prepar BAYOL, A., BENVENISTE, J., AND BRINK, C.: Histamine contraction of
isolated human airway muscle preparations: role of prostaglandins. J.
Pharmacol. Exp. Ther. 239: 536-541, 1986.
272. HEARD, B. E., AND HUSAIN, S.: Hyperpla
	-
	- **EARD, B. E., AND HUSAIN, S.: Hyperplasia of bronchial smooth muscle in asthma. J. Pathol. 110: 319, 1973.**
 EATON, R. W., HENDERSON, A. F., DUNLOP, L. S., AND COSTELLO, J. F.:
 The influence of pretreatment with prosta 271. HEARD, B. E., AND HUSAIN, S.: Hyperplasia of bronchial smooth muscle in asthma. J. Pathol. 110: 319, 1973.

	272. HEATON, R. W., HENDERSON, A. F., DUNLOP, L. S., AND COSTELLO, J. F.: The influence of pretreatment with The influence of pretreatment with prostagland
in F_{2n} on bronchial sensitivity to inhaled histamine and methacholine in normal subjects. Br. J.
Dis. Chest 78: 168-174, 1984.
ELEWELL, P. G., AND WILLIAMS, T. J.: A spec
	- not oedema induced by leukocyte chemoattractants in rabbit skin. J. Immunol. 137: 302-307, 1986.
274. HENDERSON, W. R., HARLEY, J. B., AND FAUCI, A. S.: Arachidonic acid **IMMUNOL 137: 108-174, 1984.**
 IMMUNOL 137: 302-307, AND WILLIAMMS, T. J.: A specific antagonist of platelet-

	activating factor suppresses oederna formation in an Arthus reaction but

	not oederna induced by leukocyte ch
	- not oedema induced by leukocyte chemoattractants in rabbit skin.
Immunol. 137: 302-307, 1986.
RNDERSON, W. R., HARLEY, J. B., AND FAUCI, A. S.: Arachidonic antertabolism in normal and hypereosinophilic syndrome eosinophils 137: 302-307, 1986.

	274. HENDERSON, W. R., HARLEY, J. B., AND FAUCI, A. S.: Arachidonic acid

	metabolism in normal and hypereosinophilic syndrome eoeinophils: gen-

	eration of leukotrienes B., C₄, D₄, and 15-lipoxygen metabolism in normal and hypereosinophilic syndrome eosinophils: generation of leukotrienes B₄, C₄, D₄, and 15-lipoxygenase products. Immu-
nology 51: 679-686, 1984.
RNOC₉, E₂, AND VARGAFTIG, B. B.: Accumulation
	- nology 51: 679-686, 1984.

	275. HENGCQ, E., AND VARGAFTIG, B. B.: Accumulation of eosinophils in response to intracutaneous PAF-acether and allergens in man. Lancet 1:

	1378–1379, 1986.

	276. HENSON, P. M., AND PINCKARD, R
	- ENOCQ, E., AND VARGAFTIG, B. B.: Accumulation of eosinophils in sponse to intracutaneous PAF-acether and allergens in man. Lancet 1378-1379, 1986.
ENSON, P. M., AND PINCKARD, R. N.: Basophil-derived platelet-activat
factor sponse to intracutaneous PAF-acether and allergens in man. Lancet 1:
1378–1379, 1986.
ENSON, P. M., AND PINCKARD, R. N.: Basophil-derived platelet-activating
factor (PAF) as an in vivo mediator of acute allergic reactions: 276. HENSON, P. M., AND PINCKARD, R. N.: Basophil-derived platelet-activating
factor (PAF) as an in vivo mediator of acute allergic reactions: demonstration of specific desensitization follatelets to PAF during IgE-induced factor (PAF) as an in vivo mediator of acute allergic reactions: demonstration of specific desensitization of platelets to PAF during IgE-induced
anaphylaxis in the rabbit. J. Immunol. 119: 2179-2184, 1977.
277. HERXHEIMER
	-
	-
	- guinea. H., AND ROSTSCHER, I.: Effects of prostaglandin E₁ on lung
function in bronchial asthma. Eur. J. Clin. Pharmacol. 3: 123-125, 1971.
278. HERXHEIMER, H., AND STRESEMAN, E.: The effect of tradykinin aerosol in
guin Exp. Pharmacol. Phys. in press, 1988. 280. HERXHEIMER, H., AND STRESEMAN, E.: The effect of bradykinin aeror guinea-pigs and in man. J. Physiol. 158: 38P, 1981.

	279. HEUER, H., AND CASALS-STENEEL, J.: Effects of the beta-
	- 279. HEUER, H., AND CASALS-STENZEL, J.: Effects of the beta-2 agonist fenoterol (Berotec) and PAF on bronchial hypersensitivity in the guinea-pig. Clin.
Exp. Pharmacol. Phys. in press, 1988.
280. HOGABOOM, G. K., MONG, S.,
	- DGABOOM, G. R., MONG, S., WU, H., AND CROOKE, S. T.: Peptacoleumo-
trienes: distinct receptors for leukochiene C₄ and D₄ in the guinea-pig lung.
Biochem. Biophys. Res. Commun. 116: 1136, 1983.
DLGATE, S. T., BURNS, G. release. J. Immunol. 133: 2138, 1984. 282. Hotelstown, D. H. Anaphylactic and calcium-dependent generation of prostaglandin D₁ (PGD₂), thromboxane B₂, and other cyclooxygenase products of arachidonic acid by disperse
	- (PGD₃), thromboxane B_2 , and other cyclooxygenase products of arachionic acid by dispersed human lung cells and relationship to histamine
clease. J. Immunol. 133: 2138, 1984.
HoLGATE, S. T., EMMANUEL, M. B., AND HOWAR
	- ELLIOTT, E. V.: BRANANUEL, M. B., AND HOWART, P. H.: Astemizole and
other H₁-antihistaminic drug treatments of asthma. J. Allergy Clin. Im-
munol. 76: 375–380, 1985.
DLROYDE, M. C., COLE, M., ALTOUNYAN, R. E. C., DIXON,
	-
	- colour H₁-antihistaminic drug treatments of asthma. J. Allergy Clin. Immunol. 76: 375-380, 1985.
283. HOLROVDE, M. C., COLE, M., ALTOUNYAN, R. E. C., DIXON, M., AND ELLOTT, E. V.: Bronchoconstriction produced in man by l **generation of leukotriene B**, by tracheal epithelial cells from dogs.
Biochem. Biophys. Res. Commun. 114: 1071-1076, 1983.
285. HOWARTH, P. H., DURHAM, S. R., LEE, T. H., KAY, A. B., CHURCH, M. K.,
AND HOLGATE, S. T.: Inf Biochem. Biophys. Res. Commun. 114: 1071-1076, 1983.
285. HOWARTH, P. H., DURHAM, S. R., LEE, T. H., KAY, A. B., CHURCH, M. K.,
AND HOLGATE, S. T.: Influence of albuterol, cromolyn sodium, and ipra-
tropium bromide on the
	- plasma extravalsation in asthma. Am. Rev. Respir. Dis. 132:

	986-992, 1985.

	286. HUA, X. Y., DAHLEN, S. E., LUNDBERG, J. M., HAMMERSTROM, S., AND

	HEDQVIST, P.: Leukotrienes C₄ and E₄ cause widespread and extensive

	p
	- AND HEDQVIST, P.: Leukotrienes C₄ and E₄ cause widespread and extensive plasma extravasation in the guinea-pig. Naunyn-Schmiedeberg's Arch.
Pharmacol. 330: 136-141, 1965.

	UA, X. Y., THEODORSSON-NORHEIM, E., BRODIN, E. Pharmacol. 330: 136-141, 1985.

	287. HUA, X. Y., THEODORSSON-NORHEIM, E., BRODIN, E., LUNDBERG, J. M.,

	AND HOKFELT, T.: Multiple tachykinins (neurokinin A, neuropeptide K,

	and substance P) in capsaicin-sensitive sensory
	- and substance P) in capacicin-sensitive sensory neurons in the guinear-
pig. Regul. Pept. 13: 1-19, 1985.
288. HUGHES, P. J., HOLGATE, S. T., AND CHURCH, M. K.: Adenosine inhibits
and potentiates IgE-dependent histamine re and potentiates IgE-dependent histamine release from human lung mast
cells by an A₃-purinoceptor mediated mechanism. Biochem. Pharmacol.
83: 3847–3852, 1984.
UMPHREY, D. M., MCMANUS, L. M., HANAHAN, D. J., AND PINCKARD,
	-
	-
	- Physiol. HUNTER, J. A., FINKBEINER, W. E., NADEL, J. A., GOETZL, E. J., AND HOLTZMAN, M. J.: Predominant generation of 15-lipoxygenase metabo-
lites of arachidonic acid by epithelial cells from human trachea. Proc.
Natl. A
	- 292. HUTAS, I., HADHAZY, P., DEBRECZENI, L., AND VIZI, E. S.: Relaxation of human isolated bronchial amooth muscle: role of prostacyclin and pros-

ARMAC

spet

 \mathbb{O}

- taglandin F₂, on muscle tone. Lung 159: 153-161, 1981. [293. HUNG, AND PAGE taglandin F₂, on muscle tone. Lung 159: 153-161, 1981.

293. HUTCHCROFT, B. J., *AND* Guz, A.: Levels of complement components during 321. KAY
- BARNES, CHUNG

taglandin F₂ on muscle tone. Lung 159: 153-161, 1981.

293. HUTCHCROFT, B. J., AND GUZ, A.: Levels of complement components during

allergen-induced asthma. Clin. Allergy 8: 59-64, 1978.

294. HWANG, S. B.
- platelet activating factor. J. Biol.

Chem. 261: 13720-13726, 1986.

295. Hwang, S. B., Lam, M. H., AND SHEN, T. Y.: Specific binding sites for

platelet activating factor in human lung tissues. Biochem. Biophys. Res.

Com 295. HWANG, S. B., LAM, M. H., AND SHEN, T. Y.: Specific binding sites for
platelet activating factor in human lung tissues. Biochem. Biophys. Res.
Commun. 128: 972-979, 1985.
296. HYMAN, A. L., AND KADOWITZ, P. J.: Pulmon
-
-
-
- **J. Med. Chem. 24: 1139-1148, 1981.**

ID, P. W., BARNES, P. J., BROWN, M. J., CAUSON, R., AND DOLLERY, C.

T.: Measurement of plasma histamine. Clin. Allergy 13: 61-67, 1983.

ID, P. W., BROWN, M. J., LHOSTE, F. J. M., AND 298. IND, P. W., BARNES, P. J., BROWN, M. J., CAUSON, R., AND DOLLERY, C.
T.: Measurement of plasma histamine. Clin. Allergy 13: 61–67, 1983.
299. IND, P. W., BROWN, M. J., LHOSTE, F. J. M., MACQUIN, I. M., AND
DOLLERY, C. 299. IND, P. W., BROWN, M. J., LHOSTE, F. J. M., MACQUIN, I. M., AND
DOLLERY, C. T.: Concentration effect relationships of infused histamine
in normal volunteers. Agents Actions 12: 12-15, 1982.
300. IRVN, C. G., BEREND, N
-
- Research Politics C. R.: Concentration effect relationships of infused histamine
in normal volunteers. Agents Actions 12: 12-15, 1982.
300. IRVIN, C. G., BEREND, N., AND HENSON, P. M.: Airways hyperreactivity
and inflammat Xev. Respir. Dis. 134: 777-783, 1986.

301. JOHNSON, A. R.: Human pulmonary endothelial cells in culture: activities

of cells from arteries and cells from veins. J. Clin. Invest. 65: 841-850,

1980.

302. JOHNSON, H. G.,
- of cells from arteries and cells from veins. J. Clin. Invest. 65: 841-850,

202. JoHNSON, H. G., AND MCNEE, M. L.: Secretagogue responses of leukotriene
 C_4 , D.: comparison of potency in canine traches in vivo. Prostagl CHOSON, H. G., AND MCNEE, M. L.: Secretagogue responses of leukotriene C_4 , D_4 : comparison of potency in canine traches in vivo. Prostaglandins $25: 237-243$, 1983.

25: 237-243, 1983.

contractile activity of leukot
-
- C., D.; comparison of potency in canine traches in vivo. Prostaglandina
25: 237-243, 1983.
303. JONES, T. R., DAVIES, C., AND DANIEL, E. E.: Pharmacological study of the
contractile activity of leukotriene C₄ and D₄ on Example contractile activity of leukotriene C₄ and D₄ on isolated
contractile activity of leukotriene C₄ and D₄ on isolated
smooth muscle. Can. J. Physiol. Pharmacol.'60: 638-643,
FORD-HUTCHIMAON, A. W., FRENETTE, 3 -hydroxy-prophylphenoxy)propylthio)-hydroxy- β -methylbenzenebutan-oate: a selective, orally active leukotriene receptor antagonist. Can. J. smooth muscle. Can. J. Physiol. Pharmacol. $60: 638-643$, 1982.
304. JONES, T. R., YOUNG, R., CHAMPION, E., CHANETTE, L., DENNIS, D., FORD-HUTCHINSON, A. W., FRENETTE, R., GAULTIER, J. Y., GUINDON, K., KAKUSHIMA, M., ET A R., KARUSHIMA, M., ET AL.: L-649,923, sodium (BS*, R*)-4-(3-(4-acetyl-332. LATTINEN, L. A., LATTINEN, A., PANULA, P. A., PARTANEN, M., TERVO, K.,
3-hydroxy-prophylphenoxy)propylthio)-hydroxy-β-methylbensenebutan-
oate: a
- substance P and neurokinin A on the airways of normal and asthmatic
- 306. JORIS, I., MAJNO, G., COREY, E. J., AND LEWIS, R. A.: The mechanism of vascular leakage induced by leukotriene E₄: endothelial contraction. Am.
J. Pathol. 126: 19–24, 1987.
307. JOSEPH, M., AURIAULT, C., CAPRON, A., Source Books, 1987. In the sixtence P and neurokinin A on the airways of normal and asthmatic subjects. Thorax 42: 779–783, 1987.
306. JORIS, I., MAJNO, G., COREY, E. J., AND LEWIS, R. A.: The mechanism of 334. Jack Heakag brus, I., MAJNO, G., COREY, E. J., AND LEWIS, R. A.: The mechanism of vascular leakage induced by leukotriene E₄: endothelial contraction. Am.
J. Pathol. 126: 19–24, 1987.
SEPH, M., AURIAULT, C., CAPRON, A., VORNG, H., A
-
- vascular leakage induced by leukotriene E₄: endothelial contraction. Am.
J. Pathol. 126: 19-24, 1987.
307. JOSEPH, M., AURIAULT, C., CAPRON, A., VORNG, H., AND VIENS, P.: A new
function for platelets: IgE-dependent killi
- Sol. Solar function for platelets: IgE-dependent killing of schistozomes. Nature
(Lond.) 303: 310-312, 1983.
308. JOSEPH, M., TONNEL, A. B., TARPIER, G., AND CAPRON, A.: Involvement
of immunoglobulin E in the secretory pro bod immunoglobulin E in the secretory process of alveolar macrophages
from asthmatic patients. J. Clin. Invest. 71: 221-230, 1983.
UVIN-MARCHER, E., NINIO, E., BEURAIN, G., AND BENVENISTE, J.: Bio-
synthesis of Paf-acether mund. 133: 892-898, 1984. 310. JuHLIN, L, AND MICHAELSSON, G., Cutaneous reactions of Paf-acether and acetyl-transferase activity in human leukocytes. J. Im munol. 133: 892-898, 1984.
310. JuHLIN, L, AND MICHAELSSON, G.: C
- bradykinin, and histamine in healthy subjects and patients with urticaria. **Acta Dermatovenereol. 48: 26-36,** 1969. 311. JUNOD, **A. P.: Effects of oxygen intermediates on cellular functions. Am.** THEIN, L, AND MICHAELSSON, G.: Cuthraline in healthy sub-
Diedykinin, and histamine in healthy sub-
Acta Dermatovenereol. 48: 26-36, 1969.
Nev. Respir. Dis. 135: 32S-34S, 1987.
ALINER, M.: Human lung tissue and anap bradykinin, and histamine in healthy subjects and patients with urticaria.
Acta Dermatovenereol. 48: 26–36, 1969.
311. JUNOD, A. P.: Effects of oxygen intermediates on cellular functions. Am.
Rev. Respir. Dis. 136: 325–345
-
- Acta Dermatovenereol. 48: 26–36, 1969.

NOD, A. P.: Effects of oxygen intermediates on cellular functions. Am.

Rev. Respir. Dis. 135: 325–348, 1987.

ALINER, M.: Human lung tissue and anaphylaxis. The effects of histamine 312. KALINER, M.: Human lung tissue and anaphylaxis. The effects of histamine
312. KALINER, M.: Human lung tissue and anaphylaxis. The effects of histamine
312. KALINER, M.: Human lung tissue and anaphylaxis. The effects o NAINER, M.: Human lung tissue and anaphylaxis. The effects of histamine
on the immunologic release of mediators. Am. Rev. Respir. Dis. 118:
1015–1022, 1978.
MAINER, M.: SHELHAMER, J. H., AND OTTESEN, E. A.: Effects of infu
- on the immunologic release of mediators. Am. Rev. Respir. Dis. 118:
1015–1022, 1978.
ALINER, M., SHELHAMER, J. H., AND OTTESEN, E. A.: Effects of infused
histamine: correlation of plasma histamine levels and symptoms. J. A 313. KALINER, M., SHELHAMER, J. H., AND OTTESEN, E. A.: Effects of infused histamine: correlation of plasma histamine levels and symptoms. J. Allergy Clin. Immunol. **69:** 283-289, 1982.
314. KARLIN, J. M.: The use of antih
-
- 315. KAUFFMAN, H. F., VAN DER HEIDE, S., H. BIEC.S OF INICAL PRESS, D. All-
lergy Clin. Immunol. **69:** 283–289, 1982.
314. KARLIN, J. M.: The use of antihistamines in asthma. Ann. Allergy 30: 342–
347, 1972.
315. KAUFFMAN, during house dust mite-produced bronchial obstructive reactions. Clin. WRIES, K.: Plasma histamine concentrations and complement activation during house dust mite-produced bronchial obstructive reactions. Clin. Allergy 13:
- D. G.: Bradykinin stimulates afferent vagal C-fibers in intrapulmonary airways of dogs. J. C. G., and Bakractive reactions. Clin.
Allergy 13: 219-228, 1983.
316. KAUFMAN, M. P., COLERIDGE, H. M., COLERIDGE, J. C. G., AND BAKER,
D. G.: Bradykinin stimulates afferent vagal C-fibers in intrapulm
- aterosols of prostaglandine E, and B, as bronch
- AWAKAMI, Y., UCHIYAMA, K., IRIE, T., AND MURAO, M.: Evaluation of aerosols of prostaglandins E₁ and E₂ as bronchodilators. Eur. J. Clin.
Pharmacol. 6: 127–132, 1973.
AV, A. B.: Studies on eoeinophil leucocyte migratio servedes. 6 prostaglandine E₁ and E₂ as bronchodilators. Eur. J. Clin.
Pharmacol. 6: 127-132, 1973.
318. KAY, A. B.: Studies on eosinophil leucocyte migration. I. Factors specifically
chemotactic for eosinophils and ne clin. Exp. Immunol. Clin. Exp. Immunol. T. Takes one of an eosinophile and neutrophile generated from guinea-pig
serum by antigen-antibody complexes. Clin. Exp. Immunol. 7: 723-737,
1970.
319. KAY, A. B., AND AUSTEN, K. F.
-
-

903, 1971.

- 321. KAY, A. B., **BACON,** G. D., **MERCER, B. A., SIMPSON, H., AND GRArFON,** J. W.: Complement components and IgE in bronchial asthma. Lancet 2: 916-920, 1974. 903, 1971.

221. KAY, A. B., BACON, G. D., MERCER, B. A., SIMPSON, H., AND GRAFTON, J.

W.: Complement components and IgE in bronchial asthma. Lancet 2:

916–920, 1974.

222. KENNEDY, I., COLEMAN, R. A., HUMPHREY, R. P. A.
- proposed classification. Provided as the set of the SNC Complement components and IgE in bronchial asthma
916–920, 1974.
LENNEDY, I., COLEMAN, R. A., HUMPHREY, R. P. A., LEVY,
LUMLEY, P.: Studies on the characterisation of
- 322. KERN, R., COLEMAN, R. A., HUMPHREY, R. P. A., LEVY, G. P., AND
LUMLEY, P.: Studies on the characterisation of prostancial receptors: a
proposed classification. Prostaglandins 24: 667–689, 1982.
323. KERN, R., SMITH, L in 1993. Here, R. S. Rev. Rev. Rev. Rev. Rev. Rev. R. R. R. D., AND BERNSTEIN,

132. KERN, R., SMITH, L. J., PATTERSON, R., KRELL, R. D., AND BERNSTEIN,

P. R.: Characterization of the airway response to inhaled leukotrien
- inhibits allergen-induced airway hyperresponsiveness but not allergen-
- 297. IIZUKA, K., AKAHANE, K., MOMOSE, D., AND NAKAZAWA, M.: Highly induced asthmatic responses. Am. Rev. Respir. Dis. 135: A312, 1987.

selective inhibitors of thromboxane synthetase. 1. Imidazole derivatives. 325. KLIMEK, P. R.: Characterization of the airway response to inhaled leukotriene D,
in normal subjects. Am. Rev. Respir. Dis. 133: 1127-1132, 1986.
324. KIRBY, J. G., HARGREAVE, F. E., AND O'BYRNE, P. M.: Indomethacin
inhibits allerg induced asthmatic responses. Am. Rev. Respir. Dis. 135: A312, 1987.

325. KLIMEK, J. J., WINSLOW, C. M., AND SAUNDERS, R. N.: Platelet and

neutrophil interactions in platelet-activating factor (PAF)-induced

changes in va
	-
	-
	- 628-641, 1983. 328. KRELL, R. A., AND PARKER, C. W.: Specific binding of leukotriene B. to a receptor on human polymorphonuclear leukocytes. J. Exp. Med. 157:
628-641, 1983.
628-641, 1983.
628-641, 1983.
628. KRELL, R. D., a receptor on human polymorphonuclear leukocytes. J. Exp. Med. 157:
628-641, 1983.
329. KRELL, R. D., TsAI, B. S., BERDOULAY, A., BARONE, M., AND GILES, R. E.:
Heterogeneity of leukotriene receptors in guinea-pig trachea.
	- RELL, R. D., Tsal, B. S., BERDOULAY, A., BARONE, M., AND GILES, R. E.:
Heterogeneity of leukotriene receptors in guinea-pig trachea. Prostaglandins 25: 171–178, 1983.
UEHL, F. A., DE HAVEN, R. N., AND PONG, S. S.: Lung tis dins 25: 171-178, 1983.

	329. KUEHL, F. A., DE HAVEN, R. N., AND PONG, S. S.: Lung tissue receptors

	for sulfidopeptide leukotrienes. J. Allergy Clin. Immunol. 74: 378-381,

	330. KUEHL, F. A., AND EGAN, R. W.: Prostaglandi UBHL, F. A., DE HAVEN, R. N., AND PONG, S. S.: Lung
for sulfidopeptide leukotrienes. J. Allergy Clin. Immund
1984.
UEHL, F. A., AND EGAN, R. W.: Prostaglandins, arachi
inflammation. Science (Wash. DC) 210: 978-986, 1980.
A
	-
	- 330. KUEHL, F. A., AND EGAN, R. W.: Prostaglandins, arachidonic acid, and inflammation. Science (Wash. DC) 210: 978-986, 1980.
331. LAITINEN, A., AND EGAN, R. W.: Prostaglandins, arachidonic acid, and inflammation. Science F. A., AND EGAN, R. W.: Prostaglandins, arinflammation. Science (Wash. DC) 210: 978–986, 19

	NATINEN, L. A., HEINO, M., LATINEN, A., KAVA, T., .

	Damage of the airway epithelium and bronchial reaction

	asthma. Am. Rev. Res 331. LAITINEN, L. A., HEINO, M., LAITINEN, A., KAVA, T., AND HAAHTELA, T.:
Damage of the airway epithelium and bronchial reactivity in patients with
asthma. Am. Rev. Respir. Dis. 131: 599–606, 1985.
332. LAITINEN, L. A., L
	- **AND TERVO, M.: LATTINEN, A., KAVA, T., AND HAAHTELA, T.:**
Damage of the airway epithelium and bronchial reactivity in patients with
asthma. Am. Rev. Respir. Dis. 131: 599–606, 1985.
AND TERVO, K., LATTINEN, A., PANULA, P.
	- 333. **LAITINEN, L. A., LAITINEN, A., AND WIDDICOMBE,** J. G.: Effects of inflam- matory and other mediators on airway vascular beds. Am. Rev. Respir. the lower respiratory tract of the rabbit and not of man. Thorax 38: 531-
536, 1983.
333. LATHINEN, A., AND WIDDICOMBE, J. G.: Effects of inflam-
matory and other mediators on airway vascular beds. Am. Rev. Respir.
Dis. 13
	-
	- 334. LALAU-KERALY, C., AND BENVENISTE, J.: Specific desensitisation of rabbit
platelets by platelet activating factor (PAF-acether) and derivatives. Br.
J. Haematol. 51: 313-325, 1982.
335. LAMBRECHT, G., AND PARNHAM, M. J glandins. Biochim. Biophys. Acts 164: 126: Maxwell different platelet activating factor receptor subtypes on macrophages and polymorphonuclear leucocytes. Br. J. Pharmacol. 87: 287-299, 1986.
LANDS, W. M., AND SAMUELSSON,
	-
	- configuration and contractions in the photometric produced changes in much secretion and in respirations. Bicohim. Biophys. Acts 164: 426-430, 1968.
ANDS, W. M., AND SAMUELS80N, B.: Phospholipid precursor of prostaglandins Actions (suppl. 21): 245-251, 1987.

	337. LANG, M., HANSEN, D., AND HAHN, H. L.: Effect of the PAF antagonist

	CV-3988 on PAF-induced changes in mucus secretion and in respiratory

	and circulatory variables in ferret. PAF, CV-3988 on PAF-induced changes in mucus secretion and in respiratory
cV-3988 on PAF-induced changes in mucus secretion and in respiratory
and circulatory variables in ferret. PAF, platelet, and asthma. Agents
Actions (supp
	- Actions (suppl. 21): 245–251, 1987.

	338. LANGRIDGE-SMITH, J. E., RAO, M. C., AND FIELD, M.: Chloride and sodium

	transport across bovine tracheal epithelium: effects of secretagogues and

	indomethacin. Pflugers Arch.-Eur.
	- REAGRIDGE-SMITH, J. E., KAO, M. C., AND FIELD, M.: Chloride and sodium
indomethacin. Pflugers Arch.-Eur. J. Physiol. 402: 42-47, 1984.
 BERGER, MATTEI, C., GODENECHE, D., CHABARD, J. L., PETIE, J., AND
 BERGER, J. A.: P tration in the rabbit and proteins principle and proteins and proteins and proteins Arch. Eur. J. Physiol. 402: 42-47, 1984.
ATRIGUE-MATTEI, C., GODENECHE, D., CHABARD, J. L., PETIE, J., AND
BERGER, J. A.: Pharmacokinetic **LEE, C.-M., CAMPBELL, N. J., WILLIAMS, B. J., AND IVERSEN, L. L.:**
Comparison with ⁵H-labeled lyso-Paf-acether after intravenous administration in the rabbit and protein binding. Agents Actions 15: 643-648, 1984.

	240.
	-
	- J. Pharmacol. 130: 2002-217, 1986. 1986. 341. LEE, C.-M., CAMPBELL, N. J., WILLIAMS, B. J., AND IVERSEN, L. L.:
Multiple tachykinin binding sites in peripheral tissues and in brain. Eur.
J. Pharmacol. 130: 209-217, 1986.
3 stimulated human polymorphonuclear leukocytes. Proc. Natl. Acad. Sci. J., Pharmacol. 130: 209-217, 1986.
J. Pharmacol. 130: 209-217, 1986.
E. C. W., LEWIS, R. A., COREY, E. J., BARTON, A., OH, H., TAUBER, A.
I., AND AUSTEN
	- 341. LEE, C. W., LEWIS, R. A., COREY, E. J., BARTON, A., OH, H., TAUBER, A.
I., AND AUSTEN, K. A., COREY, E. J., BARTON, A., OH, H., TAUBER, A.
I., AND AUSTEN, K. F.: Oxidative inactivation of leukotriene C. by
stimulated AND AUSTEN, K. F.: The myeloperoxidase dependent metabolism of
leukotrienes C₄, D₄, and E₄ to 6-*trans*-leukotriene B₄ distereoisomers and
the subclass-specific s-distereoisomeric sulfoxides. J. Biol. Chem. 258:
15
	- AND AUSTEN, K. F.: The myeloperoxidase dependent metabolism of leukotrienes C_4 , D_4 , and E_4 to 6-*trans*-leukotriene B_4 distereoisomers and the subclass-specific s-distereoisomeric sulfoxides. J. Biol. Chem. 25 the subclass-specific s-distereoisomeric sulfoxides. J. Biol. Chem. 258:
15004-15010, 1983.
343. LEE, T. C., BLANK, M. L., FITZGERALD, V., AND SNYDER, F.: Substrate
specificity in the biocleavage of the O-alkyl-2-acetyl-sn
	- 344. LEE, T. C., LENIHAN, D. J., MALONE, B., RODDY, L. L., AND WASSERMAN,
S. I.: Increased biosynthesis of platelet-activating factor in activated
human eosinophils. J. Biol. Chem. 259: 5530, 1984.
345. LEE, T. H., AUSTEN,
	- incur and EU MALONE, B., RODDY, L. L., AND WASSERMAN,
S. I.: Increased biosynthesis of platelet-activating factor in activated
human eosinophils. J. Biol. Chem. 259: 5526-5530, 1984.
EE, T. H., AUSTEN, K. F., COREY, E. J., S. I.: Increased biosynthesis of platelet-activating factor in activated
human eosinophils. J. Biol. Chem. 259: 5526-5530, 1984.
345. **LEE, T. H., AUSTEN, K. F., COREY, E. J., AND DRAZEN, J. M.: LTE4-**
induced airway hyper
	-

PHARM
REV

spet

 $\overline{\mathbb{O}}$

INFLAMMATORY MEDIATO

J., SPUR, B. W., ROBINSON, D. R., COREY, E. J., LEWIS, R. A., AND

AUSTEN, K. F.: Effect of distary enrichment with eicosapertaenoic and

docosahexaenoic acids on in vitro neutrophil and monocyte leuk AUSTEN, K. F.: Effect of dietary enrichment with eicosapentaenoic and
docosahexaenoic acids on in vitro neutrophil and monocyte leukotriene
generation and neutrophil function. N. Engl. J. Med. 312: 1217-1224,
1985.
T.E.E.,

- phil function. N. Engl. J. Med. 312: 1217-1224,
1985.
347. Lee, T. H., NAGY, L., NAGAKURA, T., WALPORT, M. J., AND KAY, A. B.:
Identification and partial characterisation of an exercise-induced neutro-
phil chemotactic fac
- Identification and partial characterisation of an exercise-induced neutro-
phil chemotactic factor in bronchial asthma. J. Clin. Invest. 69: 889-899,
1982.
E.R., T. H., SHORE, S., COREY, E. J., AUSTEN, K. F., AND DRAZEN,
-
- phil chemotactic factor in bronchial asthma. J. Clin. Invest. 69: 889-899,
1982.
1982. LEE, T. H., SHORE, S., COREY, E. J., AUSTEN, K. F., AND DRAZEN, J. M.:
Leukotriene E_q-induced airway hyperresponsiveness to histamine AND KAY, A. B.: Slow-reacting substance of anaphylaxis antagonist FPL55712 in chronic asthma. Lancet 2: 304–305, 1981.
FPL55712 in chronic asthma. Lancet 2: 304–305, 1981.
Augmentation of parasympathetic contraction in tra 350. LEFF, A. R., MUNOZ, N. M., TALLET, J., CAVIGELLI, M., AND DAVID, A. C.:

Augmentation of parasympathetic contraction in tracheal and bronchial

airways by prostaglandin F_{2a} in situ. J. Appl. Physiol. 58: 1558-1564
- mechanisms distinct from those from those for leukotriene C4 and bradykinin. Br. J. Appl. Physiol. 58: 1558-1564,
351. LEFORT, J., ROTILIO, D., AND VARGAFTIG, B. B.: The platelet-independent
release of thromboxene A₃ by 1985.

1985.

LEFORT, J., ROTILIO, D., AND VARGAFTIG, B. B.: The platelet-independent

release of thromboxane A₈ by PAF-acether for guinea-pig lungs involves

mechanisms distinct from those for leukotriene C₄ and brady Felesse of thromboxane A_s by PAF-acether for guinea-pig lungs involves
mechanisms distinct from those for leukotriene C₄ and bradykinin. Br. J.
Pharmacol. 82: 525-531, 1984.
352. LE GREVES, P., NYBERO, F., TERENIUS, L.
-
-
- gene-related peptide is a potent inhibitor of substance P degradation. Eur.
J. Pharmacol. 115: 309-311, 1985.
353. LEIKAUP, G. D., UEKI, I. F., NADEL, J. A., AND WIDDICOMBE, J. H.:
Bradykinin stimulates chloride secretion lipoxygenaee products of arechidonic acid. J. Appl. 248: F48-F55, 1985.
 354. LERLAUP, G. D., UERLI, I. F., WIDDIOMERS, J. H., AND NADEL, J. A.:
 Alteration of chloride secretion across canine tracheal epithelium by

l
- Alteration of chloride secretion across canine tracheal epithelium by
lipoxygenase products of arachidonic acid. J. Appl. Physiol. 250: F47-53,
1986.
ELLOUCH-TUBIANA, A., LEFORT, J., PIROTZKY, E., VARGAFIIG, B. B., AND
PrI ipoxygenase products of arachidonic acid. J. Appl. Physiol. 200: F47-b3,
1986.
ELOUCH-TUBIANA, A., LEFORT, J., PIROTZKY, E., VARGAFTIG, B. B., AND
PFISTER, A.: Ultrastructural evidence for extravascular platelet recruit-
m 1950.

ISO. LELLOUCH-TUBIANA, A., LEPORT, J., PIROTZKY, E., VARGAFTIG, B. B., AND

PFISTER, A.: Ultrastructural evidence for extravascular platelet recruit-

ment in the lung upon intravenous injection of platelet activati
- ment in the lung upon intravenous injection of platelet activating it (Paf-acether) to guinea-pigs. Br. J. Enp. Pathol. 66: 345–355, 1985.
ELLOUCH-TUBIANA, A., LEFORT, J., SIMON, M. T., PrisTER, A., DA ID.
C., AND VARGAFTI
- E., AND VARGAFTIG, B. B.: PAF-acether antagonists and platelet suppression block eosinophil recruitment into lungs of allergen or PAF-acether-injected guinea-pigs. Clin. Exp. Pharmacol. Phys. in press, 1988.
WWES, A. J., D bronchoepasm and platelet aggregation. Agents Actions **15: 636-641,** 1984.
-
- 358. LEWIS, R. A., AND AUSTEN, K. F.: The biologically active leukotrienes. J.
Clin. Invest. 73: 889-897, 1984.
359. LEWIS, R. A., AUSTEN, K. F., DRAZEN, J. M., CLARK, D. A., MARFAT, A.,
AND COREY, E. J.: Slow reacting sub 359. LEWIS, R. A., AUSTEN, K. F., DRAZEN, J. M., CLARK, D. A., MARFAT, A.,
AND COREY, E. J.: Slow reacting substances of anaphylaxis: identification
of leukotrienes C₁ and D from human and rat sources. Proc. Natl. Acad.

- of leukotrienes C₁ and D from human and rat sources. Proc. Natl. Acad.
Sci. USA 77: 3710–3714, 1980.
EWAS. R. A., DRAZEN, J. M., AUSTEN, K. F., CLARK, D. A., AND COREY,
E. J.: Identification of the C(6)-S-conjugate of Sci. USA 77: 3710–3714, 1980.
 IWIS, R. A., DRAZEN, J. M., AUSTEN, K. F., CLARK, D. A., AND COREY
 E. J.: Identification of the C(6)-S-conjugate of leukotriene A with cysteines a naturally occurring slow reacting substa
- phys. Res. Commun. 96: 271-277, 1980.
361. LEWIS, R. A., DRAEEN, J. M., AUSTEN, K. F., TODA, M., BRION, F., MARFAT,
A., AND COREY, E. J.: Contractile activities of structural analogs of
leukotrienes C and D: role of the po
-
- 363. LEWIS, R. A., GOETZL, E. J., WASSERMAN, S. I., VALONE, F. H., RUBIN,
R., AND AUSTEN, K. F.: The release of four mediators of immediate
hypersensitivity from human leukaemic basophils. J. Immunol. 114: 87-
- 362. LEWIS, R. A., GOETZ, E. J., DRAZEN, J. M., SOTER, N. A., AUSTEN, K. F.,

AND COREY, E. J., DRAZEN, J. M., SOTER, N. A., AUSTEN, K. F.,

AND COREY, E. J.: Functional characterization of synthetic leukotriene B

and its 364. LEWIS, R. A., SOTER, N. A., DIAMOND, N., AUSTEN, K. F., OATES, J. A., AND ROBERTS, L. J. II.: Prostaglandin D₂ generation after activation of rat and human mast cells with anti-1gE. J. Immunol. 129: 1627–1631, 1862.
- mine. J. Pharmacol. Exp. There. 192: 441-450, 1975.

365. LICHTENSTEIN, L. M., AND GILLESPIE, E.: The effects of H₁ and H₂ antihistanines on allergic histanine release and its inhibition by histanines. J. Pharmacol. Ex
- **and Treatment, pp. 1-15, Academic Press, Inc., New York, 1984.**
 and Treatment, A.: In vitro and in vivo studies of mediator release

from human mast cells. In Asthma: Physiology, Immunopharmacology,

and Treatment, pp. Procession D, in a normal human volution of mediator release from human mast cells. In Asthma: Physiology, Immunopharmacology, and Treatment, pp. 1-15, Academic Press, Inc., New York, 1984.
Bron, T. E., AND ROBERTS, L. J.,
- and Treatment, pp. 1-15, Academic Press, Inc., New York, 1984.
367. LISTON, T. E., AND ROBERTS, L. J., II.: Metabolic fate of radiolabelled
-
-

INFLAMMATORY MEDIATORS AND ASTHMA

v, E. J., LEWIS, R. A., AND bronchial artery blood flow and bronchomotor tone. J. Appl. Physiol 59:

int with eicosapentaenoic and 254–261, 1985.

iil and monocyte leukotriene 370. LOPEZ-

- 254-261, 1985.

254-261, 1985.

254-261, 1985.

370. **LOPEZ-VIDREIRO, M. I., DAS, I., SMITH, A. P., PICOT, R., AND REID, L.:**

Bronchial secretion from normal human airways after inhalation of pros-

taglandin F_{2n} , ace bronchial artery blood flow and bronchomotor tone. J. Appl. Physiol 59:
254–261, 1985.
Bronchial secretion from normal human airways after inhalation of pros-
Bronchial secretion from normal human airways after inhalation 254–261, 1985.

370. LOPEZ-VIDREIRO, M. I., DAS, I., SMITH, A. P., PICOT, R., AND REID, L.:

Bronchial secretion from normal human airways after inhalation of prostaglandin F_{2m} acetylcholine, histamine, and citric acid
- 139, 1977.
 371. LOTNER, G. Z., LYNCH, J. M., BETZ, S. J., AND HENSON, P. M.: Human

neutrophil-derived platelet activating factor. J. Immunol. 124: 676–684,

1980.

272. LUNDBERG, J. M., HOKFELT, T., MARTLING, C.-R., SA
- 371. LOTNER, G. Z., LYNCH, J. M., BETZ, S. J., AND HENSON, P. M.: Human
neutrophil-derived platelet activating factor. J. Immunol. 124: 676-684,
1980.
372. LUNDBERG, J. M., HOKFELT, T., MARTLING, C.-R., SARIA, A., AND CUEL neutrophil-derived platelet activating ractor. J. Immunol. 124: 676–684,
1980.
JNDBERG, J. M., HOKFELT, T., MARTLING, C.-R., SARIA, A., AND CUELLO,
C.: Substance P-immunoreactive sensory nerves in the lower respiratory
tra 372. LUNDBERG, J. M., HOKFELT, T., MARTLING, C.-R., SARIA, A., AND CUELLO,
C.: Substance P-immunoreactive sensory nerves in the lower respiratory
tract of various mammals including man. Cell Tissue Res. 235: 251-261,
1984.
- tract of various mammals including man. Cell Tissue Res. 235: 251-261,
1984.
373. LUNDBERG, J. M., MARTLING, C.-R., AND SARIA, A.: Substance P and
capsaicin-induced contraction of human bronchi. Acta Physiol. Scand.
119: 4
- tract of various mammals including man. Cell Tissue Res. 235: 251-261,
1984.

1984.

273. LUNDBERG, J. M., MARTLING, C.-R., AND SARIA, A.: Substance P and

capsaicin-induced contraction of human bronchi. Acta Physiol. Scan
-
- Nature (Lond.) 302: 251-253, 1983.

375. LUNDBERG, J. M., AND SARIA, A.: Polypeptide-containing neurons in airway

smooth muscle. Annu. Rev. Physiol. 49: 557-572, 1987.

376. LUNDBERG, J. M., SARIA, A., LUNDBLAD, L., ANGAA INDBERG, J. M., AND SARIA, A.: Polypeptide-containing neurons in airway
smooth muscle. Annu. Rev. Physiol. 49: 557–572, 1987.
INDBERG, J. M., SARIA, A., LUNDBLAD, L., ANGAARD, A., MARTLING, C.-
R., THEODORSSON-NORHEIM, E., R., THEODORSSON-NORHEIM, E., STJARNE, P., AND HOKPELT, T.: Bioactive pepticles in capsacin-sensitive C-fiber afferents of the airways: functional and pathophysiological implications. In The Airways: Neural Control in Healt
- STT. LUNDBLAD, L., LUNDBERG, L., ANGGARD, A., AND ZETTERSTROM, O.:

Capsaicin pretreatment inhibits the flare component of the cutaneous

allergic reaction in man. Eur. J. Pharmacol. 113: 461–462, 1986.

378. LYNCH, J. M.,
-
- **BLAIR, I. A.: Pharmacol. 113: 461-462, 1985.**

ANCH, J. M., AND HENSON, P. M.: The intracellular retention of newly-

synthetized platelet-activating factor. J. Immunol. 137: 2653-2661, 1986.

ACDERMOT, J. M., BARNES, P.
- ment in the lung upon intravenous injection of platelet activating lactor and particles of and protects of the set of anticlosed curio SIG. LIVENCH, 3. M., AND THENSON, F. M.: 1 DE BILIGACHILLY TWENTIES and the synthetized platelet-activating factor. J. Immunol. 137: 2653-2661, 1986.
379. MACDERMOT, J. M., BARNES, P. J., WADELL, K., DOLLERY, C. T., AND BL BLAIR, I. A.: Prostacyclin binding to guinea pig pulmonary receptors. Eur. J. Pharmacol. 68: 127-130, 1981.
IACDERMOT, J., KELSEY, C. R., WADDELL, K. A., RICHMOND, R., KNIGHT, R. K., COLE, P. J., DOLLERY, C. T., LANDON, D. 380. MACDERMOT, J., KELSEY, C. R., WADDELL, K. A., RICHMOND, R., KNIGHT,
R. K., COLE, P. J., DOLLERY, C. T., LANDON, D. N., AND BLAIR, I. A.:
Synthesis of leukotriene B₄ and prostanoids by human alveolar macro-
phages: a
	- dins 27: 163-179, 1984.

	381. MACGLASHAN, D. W., SCHLEIMER, R. P., PETERS, S. P., SCHULMAN, E. S.

	ADAMS, G. K., NEWBALL, H. H., AND LICHTENSTEIN, L. M.: Generation

	of leukotrienes by purified human lung mast cells. J. Cl
	- ADAMS, G. K., NEWBALL, H. H., AND LICHTENSTEIN, L. M.: Generation of leukotrienes by purified human lung mast cells. J. Clin. Invest. 70: 747–751, 1982.
ACLOUF, J., 92.
ACLOUF, J., DE LACLOS, B. F., AND BORGEAT, P.: Stimul 382. MACLOUF, J., DE LACLOS, B. F., AND BORGEAT, P.: Stimulation of leuko
triene biosynthesis in human blood leukocytes by platelet-derived 12
hydroxy-eicosatetraenoic acid. Proc. Natl. Acad. Sci. USA 79: 6042-6046
1982.
3 triene biosynthesis in human blood leukocytes by platelet-derived 12-
hydroxy-eicosatetraenoic acid. Proc. Natl. Acad. Sci. USA 79: 6042-6046,
1982.
AK, J. C. W., AND BARNES, P. J.: Autoradiographic localisation of calci-

	-
	- nyary-elecosatetraenoic acid. Proc. Natl. Acad. Sci. USA 78: 0042-0046,
1982.

	MAK, J. C. W., AND BARNES, P. J.: Autoradiographic localisation of calcitonin gene-related peptide binding sites in guinea-pig and human lung.

	- bronchoconstriction in asthma. Role of parasympathetic stimulation and
adrenergic inhibition. Am. Rev. Respir. Dis. 132: 1-6, 1985.
385. MANN, J. S., HOLGATE, S. T., RENWICK, A. G., AND CUSHLEY, M. J.:
Airway effects of pu
- E. 3.: Contractive activities of structural analogs of a S86. MANN, J. S., RENWICK, A. G., AND HOLGATE, S. T.: Release of adenoaine USA 78: 4679-4583, 1981.
USA 78: 4679-4583, 1981.
USA 78: 4679-4583, 1981.
USA 78: 468, 19 **386. MANN, J. S., HOLGATE, S. T., RENWICK, A. G., AND CUSHLEY, M. J.:**
Airway effects of purine nucleosaides and nucleotides and its metabolites from activated human J. Appl. Physiol. **61:** 1676, 1986.
386. MANN, J. S., R
	- bronchial provocation in asthma. J. Appl. Physiol. 61: 1667-1676, 1986.

	386. MANN, J. S., RENWICK, A. G., AND HOLGATE, S. T.: Release of adenosine

	and its metabolites from activated human leucocytes. Clin. Sci. 70: 461-4
	- Solution in asthma. Thorax 41: 746-752, 1986.

	388. MARING, P. J., JONES, G. L., AND O'BYRNE, P. M.: Indomethacin prevents

	histamine tachyphylaxis in asthmatica. Am. Rev. Respir. Dis. 135: A313,

	389. MARCEAU, F., BARABÉ,
	-
- S. LIGHTENTEIN, L. M., AND GILLESPIE, E.: The effects of H₁ and H₂ 390. MARCUS, A. J., SAFIER, L. B., ULLMAN, H. L., BROEKMAN, M. J., ISLAM, antihistamines on allergic histamine release and its inhibition by hista-
ant histamine tachyphylaxis in asthmatics. Am. Rev. Respir. Dis. 135: A313, 1987.

MARCEAU, F., BARABÉ, J., ST-PIERRE, S., AND REGOLI, D.: Kinin receptors

in experimental inflammation. Can. J. Physiol. Pharmacol. 58: 536-542, in experimental inflammation. Can. J. Physiol. Pharmacol. 08: 836–8
1980.
ARCUS, A. J., SAFIER, L. B., ULLMAN, H. L., BROEKMAN, M. J., ISLARCUS
N., OGLESBY, T. D., AND GORMAN, R. R.: 12*S₋20*-Dihydroxyeicoeatetr
noic aci S90. MARCUS, A. J., SAFIER, L. B., ULLMAN, H. L., BROEKMAN, M. J., ISLAM,
N., OGLESBY, T. D., AND GORMAN, R. R.: 12S,20-Dihydroxyeicosatetrae-
noic acid: a new eicosanoid synthesized by neutrophils from 12S-hydrox-
yeicosa
	-
	- veicosatetraenoic acid produced by thrombin or collagen-stimulated plate-
lets. Proc. Natl. Acad. Sci. USA 81: 903-907, 1984.
391. MARCUS, A. J., WERSLER, B. B., JAPFR, E. A., AND BROEKMAN, M. J.:
Synthesis of prostacyclin Synthesis of prostacyclin from platelet derived endoperoxides by cultured
human endothelial cells. J. Clin. Invest. **66:** 979-986, 1980.
392. MARIN, M. G., DAVIS, B., AND NADEL, J. A.: Effect of histamine on electrical
and
- 367. LISTON, T. E., AND ROBERTS, L. J., II.: Metabolic fate of radiolabelled 392. MARIN, M. G., DAVIS, B., AND NADEL, J. A.: Effect of histamine on electrical
prostaglandin D₃ in a normal human volunteer. J. Biol. Chem. KARIN, M. G., DAVIS, B., AND NADEL, J. A.: Effect of histamine on electrical
and ion transport properties of tracheal epithelium. J. Appl. Physiol. 42:
735–738, 1977.
KALINER, M.: Slow reacting substances LTC₄ and D₄ i

REV

- 451, 1982. **393a. MAROM,** Z., **SHELHAMER, J., BERGER, M.,** FRANK, M., **AND KALINER,** M.: **Anaphylatoxin C3a enhances mucous glycoprotein release** from **human** 451, 1982.
Marom, Z., Shelhamer, J., Berger, M., Frank, M.
Anaphylatoxin C3a enhances mucous glycoprotein
airways in vitro. J. Exp. Med. 161: 657–668, 1985.
AROM, Z., SHELHAMER, J. H., AND KALINER, M.: T
- 393a. MAROM, Z., SHELHAMER, J., BERGER, M., FRANK, M., AND KALINER, M.: Anaphylatoxin C3a enhances mucous glycoprotein release from human airways in vitro. J. Exp. Med. 161: 657–668, 1985.
394. MAROM, Z., SHELHAMER, J. H., Anaphylatoxin C3a enhances mucous glycoprotein release from human airways in vitro. J. Exp. Med. 161: 657–668, 1985.
AROM, Z., SHELHAMER, J. H., AND KALINER, M.: The effects of arachidonic acid, monohydroxyeicosatetraenoic Extra Saint Theory Saint Control of the AROM, Z., SHELHAMER, J. H., Gonic acid, monohydroxyeicosa
Invest. 67: 1695-1703, 1981.
Invest. 67: 1695-1703, 1981.
ARQUARDT, D. L., GRUBER, H 394. MAROM, Z., SHELHAMER, J. H., AND KALINER, M.: The effects of arachionic acid, monohydroxyeicosatetraenoic acid, and prostaglandins on the release of mucus glycoproteins from human airways in vitro. J. Clin.
Invest. 67
-
- release from stimulated mast cells. Proc. Natl. Acad. Sci. USA 81: 6192-6196, 1984.
 MARTIN, T. R., ALTMAN, L. C., ALBERT, R. K., AND HENDERSON, W. R.: Leukotriene B₄ production by the human alveolar macrophage: a pote 398. MARTIN, T. R., ALTMAN, L. C., ALBERT, R. K., AND HENDERSON, W. R.:
Leukotriene B₄ production by the human alveolar macrophage: a potential
mechanism for lung amplification. Am. Rev. Respir. Dis. 129: 106-111,
1984.

- M, neuropeptide K in human lower airways. Life Sci. 106-111, 1984.

297. MARTLING, C.-R., THEORDORSSON-NORHEIM, E., AND LUNDBERG, J. M.:

Cocurrence and effects of multiple tachykinins: substance P, neuropehinin

A, neurop
- ARTLING, C.-R., THEORDORSSON-NORHEIM, E., AND LUNDBERG, J. M.:
Occurrence and effects of multiple tachykinins: substance P, neurokinin
A, neuropeptide K in human lower airways. Life Sci. 40: 1633–1643, 1987.
ATHE, A. A., A
- Occurrence and effects of multiple tachykinins: substance P, neurokinin
A, neuropeptide K in human lower airway. Life Sci. 40: 1633-1643, 1987.
MATHE, A. A, AND HEDQVIST, P.: Effect of prostaglandin F₃, and E₃ on
airwa interactions between bealthy subjects and asthmatic patients. Am. Rev.

Subsequire. Dis. 11: 313-320, 1975.

399. MATRAN, R., NALINE, E., ADVENIER, C., AND DUROUX, P.: In vitro deeen-

sitzation of beta-adrenergic receptor Respir. Dis. 11: 313-320, 1975.

399. MATRAN, R., NAD DUROUX, P.: In vitro desenting a situation of beta-adrenergic receptors on isolated guinea-pig trachea:

interactions between beta-adrenergic receptors on isolated guin
- interactions betwee
other drugs. J. Allen
AzzONI, L., MORLE
hyper-reactivity by
365: 107P, 1985.
CCARTHY, K., AND
- **401. MCCARTHY, K., AND HENSON,** P. M.: Induction of lysosomal enzyme 400. MAZZONI, L., MORLEY, J., PAGE, C. P., AND SANJAR, S.: Induction of airway
hyper-reactivity by platelet activating factor in the guinea-pig. J. Physiol.
365: 107P, 1985.
401. MCCARTHY, K., AND HENSON, P. M.: Induction CCARTHY, K., AND HENSON, P. M.: Induction of lysosomal enzyme secretion by alveolar macrophages in response to the purified complement fragments C5a and C5a des Arg. J. Immunol. 123: 2511-2517, 1979. C., TERRAGNO, N. A., S
-
-
- **human airways. Br. J. M., AND BENVENISTE, J.: Platelet activating factor** (PAF-acether) and macrophages: phagocytosis-associated release of PAF-acether from rat peritoneal macrophages. Cell Immunol. 57: 281-292, CKENNIFF, M., RODGER, I. W., NORMAN, P., AND GARDINER, P. J.:
Characterisation of the contractile prostanoid receptors in guinea pig and
human sirways. Br. J. Pharmacol. 93: 567, 1988.
ENCIA-HUERTA, J. M., AND BENVENISTE, **404. MENCIA-HUERTA, J. M., AND BENVENISTE, J.: Platelet activating factor** (PAF-acether) and macrophages: phagocytosis-associated release of PAF-acether from rat peritoneal macrophages. Cell Immunol. 57: 281-292, 1981.
19 S., (PAF-acether) and macrophages: phagocytosis-associated release of PAF-acether from rat peritoneal macrophages. Cell Immunol. 57: 281-292, 1981.
1981.
ENCIA-HUERTA, J. M., PIGNOL, B., TOUVAY, C., VILLAIN, B., HENANE, EN
- And Browns, and Britoneal macrophages. Cell Immunol. 57: 281-292, 1981.
AND BRACUET AT MAND BRACT CONSTRANT PROPERTY AND BRAQUET, PASS, COVLE, A. J., PAGE, C. P., PITSTER, A., ROLA-PLESZCZYNSKI, M., AND BRAQUET, P.: Effec factor (PAF-acether) in two mammalian species. Chin. Exp. Pharmacol.

S. Covins, A. J., PAGE, C. P., Prister, A., Rolla-PLESZCZYNSKI, M.

AND BRAQUET, P.: Effect of long term treatment with platelet activating

factor (PAF **406. MENCIA-HUERTA, J. M., PIGNOL, B., TOUVAY, C., VILLAIN, B., HENANE, S., COYLE, A. J., PAGE, C. P., PFISTER, A., ROLA-PLESECZYNSKI, M., AND BRAQUET, P.: Effect of long term treatment with platelet activating factor (PA**
- AND BRAQUET, P.: Effect of long term treatment with platelet activating Phys. in press, 1988.
 Phys. in press, 1988.
 ETZGER, W. J., RICHERSON, H. B., AND WASSERMAN, S. I.: Generation

and partial characterization of e Sactor (PAF-acether) in two mammalian species. Clin. Exp. Pharmacol.

Phys. in press, 1988.

406. METZGER, W. J., RICHERSON, H. B., AND WASSERMAN, S. I.: Generation

and partial characterization of eosinophil chemotactic a
- P., MONICK, M., SJOERSDMA, K., AND HUNNINGHAKE, G. W.: Local
allergen challenge and bronchoalveolar lavage of allergic asthmatic lungs. and partial characterization of eosinophil chemotactic activity and neutrophil chemotactic activity during early and late phase airway responses.

J. Allergy Clin. Immunol. 78: 282-290, 1966.

407. METZGER, W. J., ZAVALA,
-
- allergen challenge and bronchoalveolar lavage of allergic asthmatic lungs.
And. Rev. Respir. Dis. 135: 433-440, 1987.
408. MicHEL, L., MENCIA-HEUETA, J. M., BENVENISTE, J., AND DUBERTRET,
L.: Biologic properties of LTB4 an J. Invest. Dermatol. 88: 675-681, 1987.

109. MIWA, M., MIYAKE, T., SUGATANI, J., SUZUKI, Y., AND MATSUMOTO, M.:

PAF acetylhydrolase activities in the sera of wheezy children. Clin. Exp.

Pharmacol. Phys. in press, 1988.

- FAF acetylhydrolase activities in the PAF acetylhydrolase activities in the Pharmacol. Phys. in press, 1988.
OHSENIN, V., DUBOIS, A. B., AND I On responses to methodoline challenges to the Respir. Dis. 127: 143-147, 1983.

- Fharmacol. Phys. in press, 1988.

410. MoHSENIN, V., DUBOIS, A. B., AND DOUGLAS, J. S.: Effect of ascorbic acid

on responses to methacholine challenge in asthmatic subjects. Am. Rev.

Respir. Dis. 127: 143-147, 1983.

411 Respir. Dis. 127: 143-147, 1983.

411. Mong, S., Wu, H. L., Scorr, M. O., LEWIS, M. A., CLARK, M. A., WEICHMAN, B. M., KINEIG. C. M., GLARK, M. A., WEICHMAN, B. M., KINEIG. (C.M., GLARK) M. G., AND CROOKE, S. T.:

Molecula
- muscle contraction and radioligand binding in guinea-pig lung. J. Pharmacol. Exp. Ther. 234: 316-322, 1985.

412. MORGAN, D. J. R., MOODLEY, I., PHILLIPS, M. J., AND DAVIES, R. J.:

Plasma histamine in asthmatic and contro macol. Exp. Ther. 234: 316-322, 1985.

412. MORGAN, D. J. R., MOODLEY, I., PHILLIPS, M. J., AND DAVIES, R. J.:
 Plasma histamine in asthmatic and control subjects following exercise:

influence of circulating basophils a
-
- involvement in hypereactivity induced by platelet activating factor (PAF,
AGEPC). Ann. Allergy 55: 329, 1985.
414. MORLEY, J., PAGE, C. P., AND PAUL, W.: Inflammatory actions of platelet
activating factor (Paf-acether) in
-
-
- **in vivo effector. Prog. Resp. Res. 19:** 117–123, 1985.
 in vivo effector. Prog. Resp. Res. 19: 117–123, 1985.
 in Vivo effect of leukocytes and the microcirculation. Lancet 2: 1142–1144, 1984.
 in vivo effect of leuk

- BARNES, CHUNG, AND PAGE
and enhancement of prostaglandin E₂. Am. J. Pathol. 115: 233-244, 1984.
AND KALINER, M.: 418. MURPHY, K. R., MARSH, W. R., GLEZEN, L. S., IRVIN, C. G., WILSON, M.
lease from human C., AND LARSEN, **C., AND LARSEN, G. L.: Inflammation and the late phase reaction M.**

C., AND LARSEN, G. L.: Inflammation and the late phase reaction in

asthma: the effect of polymorphonuclear leukocyte depletion on airways

obstruction Sional Resp. 22: 48-53, 1980. In CLEZEN, L. S., IRVIN, C. G., WILSON, M.
C., AND LARSEN, G. L.: Inflammation and the late phase reaction in
asthma: the effect of polymorphonuclear leukocyte depletion on airways
obstruction
	- asthma: the effect or polymorphonuclear leukocyte depletion on airways
siopathol. Resp. 22: 48-53, 1980.
URPHY, R. C., HAMMARSTROM, S., AND SAMUELSSON, B.: Leukotriene C:
a slow-reacting substance from murine mastocytoma c
	- 420. MURRAY, R. C., HAMMARSTROM, S., AND SAMUELSSON, B.: Leukotriene C:
a slow-reacting substance from murine mastocytoma cells. Proc. Natl.
Acad. Sci. USA 76: 4275-4279, 1979.
420. MURRAY, J. J., TONNEL, A. B., BRASH, A. a slow-reacting substance from murine mastocytoma cells. Proc. Natl. Acad. Sci. USA 76: 4275-4279, 1979.
URRAY, J. J., TONNEI, A. B., BRASH, A. R., ROBERTS, L. J., GOSSET, P., URRAY, J. J., CAPRON, A., AND OATES, J. A.: Re **420. MURRAY, J. J., TONNEL, A. B., BRASH, A. R., ROBERTS, L. J., GOSSET, P., WORKMAN, R., CAPRON, A., AND OATES, J. A.: Release of prostaglandin D₂ into human airways during acute antigen challenge. N. Engl. J. Med. 315**
	- D₂ into human airways during acute antigen challenge. N. Engl. J. Med.
 421. NAGY, L., LEE, T. H., GOETZL, E. J., PICKETT, W., AND KAY, A. B.: Complement receptor enhancement and chemotaxis of human neutrophils

	and ot Complement receptor enhancement and chemotaxis of human neutrophils
and eosinophils by leukotrienes and other lipoxygenase products. Clin.
Exp. Immunol. 47: 541-547, 1982.
422. NAGY, L., LER, T. H., AND KAY, A. B.: Neutrop
	-
	- antigen-induced late asthmatic reactions. N. Engl. J. Med. 306: 497-501,
1982.

	AZAMURA, T., MORITA, Y., KURIYAMA, M., ISHIHARA, K., ITO, K., AND

	MIYAMOTO, T.: Platelet activating factor in late asthmatic responses. Int.

	- MIYAMOTO, T.: Platelet activating factor in late asthmatic responses. Int.
Arch. Allergy Appl. Immunol. 82: 57-61, 1987.
424. NAKAMUTA, H., FUKUDA, Y., KOIDA, M., ET AL.: Binding sites of calcitonin
form-related peptide (C
	- AKAMUTA, H., FUKUDA, Y., ROIDA, M., ET AL.: Binding sites of calcitonin
Jpn. J. Pharmacol. 42: 175–180, 1986.
Jpn. J. Pharmacol. 42: 175–180, 1986.
ATHAN, R. A., SEGALL, N., GLOVER, G. C., AND SCHOCKET, A. L.: The
effects
	- **426. NATHAN, R. A., SEGALL, N., GLOVER, G. C., AND SCHOCKET, A. L.: The**

	effects of H₁ and H₃ antihistamines on histamine inhalation challenges

	in asthmatic patients. Am. Rev. Respir. Dis. 120: 1251-1259, 1979.
 42 Nucleotide sequences of cloned cDNAs for two types of bovine brain
- NATURE (LOND.) 203. MCGIFF, J. C., TERRAGNO, N. A., STRAND, J. C., LEE, J. B., LONIGRO, A.

J., AND NG, K. K. F.: Selective peesses of proetaglandins by the lung.

Mature (Lond.) 203: 32-36, 1989.

Mature (Lond.) 203: 32-3 effects of H₁ and H₂ antihistamines on histamine inhalation challenges
in asthmatic patients. Am. Rev. Respir. Dis. 120: 1251-1259, 1979.
426. NAWA, H., HRROSE, T., TAKASHIMA, H., INAYAMA, S., AND NAKANISHI, S.:
Nucle substance P precursor. Nature (Lond.) 306: 32-36, 1983.

427. NEEDLEMAN, P., MONCADA, S., BUNTING, S., VANE, J. R., HAMBERG, M.,

AND SAMUELSSON, B.: Identification of an enzyme in platelet microsomes

which generates thro
	- Which generates thromboxane A₂ from prostaglandin endoperoxides. Nature (Lond.) 261: 558-560, 1976.

	428. NEMOTO, T., AOKI, H., IKE, A., YAMADA, K., KONDON, T., KOBAYASHI, S., AND INAGAWA, T.: Serum prostaglandin levels **and INCR, Physiol.** 22: 139-146, 1975.
 AND INAGAWA, T.: Serum prostaglandin levels in asthmatic patients. J.
 Allergy Clin. Immunol. 57: 89-94, 1976.
 429. NEWBALL, H. M., KEISER, H. R., AND PISANO, J. J.: Bradykini
	-
	- Allergy Clin. Immunol. 57: 89–94, 1976.
EWBALL, H. M., KEISER, H. R., AND PISANO, J. J.: Bradykinin and human
airways. Respir. Physiol. 24: 139–146, 1975.
EWBALL, H. H., AND LENFANT, C.: The influence of atropine and cro **RWBALL, H. M., KEISER, H. K., AND E**
airways. Respir. Physiol. 24: 139–14
EWBALL, H. H., AND LENPANT, C.: Th
on human bronchial hyper-reactivit
Respir. Physiol. 30: 125–136, 1977.
INIO, E. W., MENCIA-HUERTA, J. M.,
	- anways. Respir. Physiol. 24: 139-146, 1976.

	430. NEWBALL, H. H., AND LENFANT, C.: The influence of atropine and cromolyn

	on human bronchial hyper-reactivity to aerosolized prostaglandin F_{3n}.

	Respir. Physiol. 30: 125-1 Hyperreactivity in murine macrophages. Biochim. Biophys. Acta 710: 23-1982.
Associativity in murine macrophages. Biochim. Biophys. Acta 710: 23-1982.
068ADY, S. G., AND BEVAN, C.: H2 receptor blockade and bronclopperreacti
	-
	- ase activity in murine macrophages. Biochim. Biophys. Acta 710: 23-31,
1982. NoGRADY, S. G., AND BEVAN, C.: H2 receptor blockade and bronchial
hyperreactivity to histamine in asthma. Thorax 36: 268-271, 1981.
433. NOGRADY,
	- **induced broadcalled broncho- constrainer and refractoriness** and refractoriness and refractoriness after exercise-
 induced broncho- constriction and refractoriness after exercise. Am. Rev.
 Respir. Dis. 134: 69-72, 19
	- Thorax 33: 396-404, 1978.

	434. O'BYRNE, P. M., AND JONES, G. L.: The effect of indomethacin on exercise-

	induced broncho-constriction and refractoriness after exercise. Am. Rev.

	Respir. Dis. 134: 69-72, 1986.

	435. O'BY induced broncho-constriction and refractoriness after exercise. Am. Rev.
Respir. Dis. 134: 69-72, 1986.
435. O'BYRNE, P. M., LEIKAUF, G. D., AIZAWA, H., BETHEL, R. A., UEKI, I. F.,
HOLTZMAN, M. J., AND NADEL, J. A.: Leukot
	- AS5. O'BYRNE, P. M., LEIKAUF, G. D., AIZAWA, H., BETHEL, K. A., UEKI, I. F., HOLTYMAN, M. J., AND NADEL, J. A.: Leukotriene Ba invasion hyperresponsiveness in dogs. J. Appl. Physiol. 59: 1941-1946, 1985.
436. O'DONNELL, S. neutrophil chemotactic activation is all the model of the model activating factor in guinea-pig trachea and bronchi. Eur. J. Pharmacol.
138: 385-396, 1987.
138: 385-396, 1987.
neutrophil chemotactic activity from isolated
	- **Chin. Immunol 72: 695-701, 1982.**
 Chinese 296, 1987.
 Chin. E., LER, T. H., AND KAY, A. B.: Immunological release of
 Chin. Immunol. 72: 695-701, 1982.
 C. E., GOODFRIEND, T. L., AND PENA, C.: Bradykinin receptor-437. O'DRISCOLL, B. R., LEE, T. H., AND KAY, A. B.: Immunological release of neutrophil chemotactic activity from isolated lung fragments. J. Allergy Clin. Immunol. **72:** 695-701, 1982.
438. ODYA, C. E., GOODFRIEND, T.
	-
	- **C., L., GOODFRIEND, T. L., AND FENA, C.: Bradykinin receptor-libinding studied with iodinated analogues. Biochem. Pharmacol. 29: 17: FLAHERTY, J. T., LEES, C. J., MILLER, C. H., MCCALL, C. E., LEWIS, C., LOVE, S. H., AND** 183, 1980.
FLAHERTY, J. T., LEES, C. J., MILLER, C.
C., LOVE, S. H., AND WYKLE, R. L.: Sele
phils: further studies with 1-O-alkyl-sn-
logues. J. Immunol. 127: 731–737, 1981.
GILVY, C. S., DUBOIS, A. B., AND DOUGLA 183, 1980.

	439. O'FLAHERTY, J. T., LEES, C. J., MILLER, C. H., MCCALL, C. E., LEWIS, J.

	C., LOVE, S. H., AND WYKLE, R. L.: Selective desensitisation of neutro-

	phils: further studies with 1-0-alkyl-an-glycero-3-phosphoc
	-
	- 369, 1981.
GLETREE, M. L., HARRIS, D. H., GREENBERG, R., HASLANGER, M. F.,
AND NAKANE, M.: Pharmacological actions of SQ 29,548, a novel selective
thromboxane antagonist. J. Pharmacol. Exp. Ther. 243: 435–441, 1985.
- 503-509, 1983.

41. OGLETREE, M. L., HARRIS, D. H., GREENBERG, R., HASLANGER, M. F.,

41. OGLETREE, M. L., HARRIS, D. H., GREENBERG, R., HASLANGER, M. F.,

41. MORLEY, J., PAGE, C. P., AND SANJAR, S.: Pulmonary responses t without induced bronchoconstriction. J. Allergy Clin. Immunol. 67: 363-
369, 1981.
441. OGLETRER, M. L., HARRIS, D. H., GREENBERG, R., HASLANGER, M. F.,
AND NAKANE, M.: Pharmacological actions of SQ 29,548, a novel selecti **the guinear in vitro:** F. F., REIBMAN, K. E., ARBESMAN, C. E., AMIDDLETON, E.: Plasma prostaglandin concentrations in allergic brachea in the Arch. Allergy Appl. Immunol. 57: 279–281, 1978.
Chial asthma. Int. Arch. Allerg
	-

PHARM
REV

spet

 $\overline{\mathbb{O}}$

- INFLAMMATORY MEDIAT

drugs. J. Pharmacol. Exp. Ther. 194: 554-564, 1975.
 **444. ORNING, L., AND HAMMARSTROM, S.: Inhibition of leukotriene C and 47

leukotriene D biosynthesis. J. Biol. Chem. 255: 8023-8026, 1980.**
- leukotriene D biosynthesis. J. Biol. Chem. 255: 8023-8026, 1980.

444. ORNING, L., AND HAMMARSTROM, S.: Inhibition of leukotriene C and

445. ORNING, L., KAIJSER, L, AND HAMMARSTROM, S.: In vivo metabolism of

445. ORNING, drugs. J. Pharmacol. Exp. Ther. 194: 554-564, 1975.

RNING, L., AND HAMMARSTROM, S.: Inhibition of leukotriene C and
 Bukotriene D biosynthesis. J. Biol. Chem. 255: 8023-8026, 1980.
 Biochem. L., KAUSER, L., AND HAMMAR **446. PALMER, J. B. D., AND BARNES,** P. J.: Neuropeptidee and airway smooth muscle function. **Am. Rev. Respir.** Dis. 136: Sb-SM, 1987. 447. PALMER, **J. B. D.,** Cuss, F. M. C., MULDERRY, P. K., GHATEI, M. A.,
-
- Biophys, Res. Commun. 130: 214–217, 1985.

446. PALMER, J. B. D., AND BARNES, P. J.: Neuropeptides and airway smooth 475.

muscle function. Am. Rev. Respir. Dis. 136: S5-S54, 1987.

447. PALMER, J. B. D., CUSS, F. M. C., M
-
-
- J. Pharmacol. 91: 95-101, 1967.

448. PANZANI, R.: 5-Hydroxytryptamine (serotonin) in human bronchial asthma.

Ann. Allergy 20: 721-732, 1962.

449. PARNTE, L., AND FLOWER, R. J.: Hydrocortisone and "macrocortin" inhibit
 Life Sci. 36: 1225-1231, 1986.

450. PARKER, C. W., FALKENHEIN, S. F., AND HUBER, M. M.: Sequential conversion of the glutathionyl side chain of slow reacting substance (SRS) to cysteinyl-glycine and cysteine in rat basoph
- 451. PATEL, K. R.: Atropine, sodium cromoglycate, and thymoxamine in PGF₂-induced bronchoconstriction in extrinsic asthma. Br. Med. J. 2880-362, 1975.
1975. K. R.: Terfenadine in exercise-induced asthma. Br. Med. J. 288:
-
- activating factor (PAF-acether) in the guinea-pig. Agents Actions 13: 1466-457, 1984.
 ACCELANTEL, W., AND PAGE, C. P.; Cutaneous responses to synthetic platelet activating factor (PAF-acether) in the guinea-pig. Agents
- 163. PAUL, W., AND PAGE, C. P.: Cutaneous responses to synthetic platelet

activating factor (PAF-acether) in the guinea-pig. Agents Actions 13:

48

465–457, 1983.

465–457, 1983.

47. PAGE, C. P., CUNNINGHAM, F. M., AND
-
- metabolism by human monocytes: studies with platelet-depleted cultures.
- and hypersensitivity by sensory neuropeptides. J. Immunol. 132: 1601–1604, 1984.
ECK, M. J., PIPER, P. J., AND WILLIAMS, T. J.: The effect of leukotrienes C_4 and D_4 on the microvasculature of guinea-pig skin. Prosta
- 458. PECK, M. J., PIPER, P. J., AND WILLIAMS, T. J.: The effect of leukotrienes **315,** 1981. 1604, 1984.

1604, 1984.

458. PECK, M. J., PIPER, P. J., AND WILLIAMS, T. J.: The effect of leukotrienes

C₄ and D₄ on the microvasculature of guinea-pig skin. Prostaglandins 21:

315, 1981.

459. PERNOW, B.: Role of
-
- C₄ and D₄ on the microvasculature of guinea-pig skin. Prostaglandins 21:

315, 1981.

459. PERNOW, B.: Role of tachykinins in neurogenic inflammation. J. Immunol.

135: 812-815, 1985.

460. PERNOW, C. G. A.: Developmen
-
-
- **461. PERSSON, C. G. A.: Role of plasma exudation in asthmatic airways. Lancet**
2: 1126-1128, 1986.
462. PERSSON, C. G. A.: Leakage of macromolecules from the tracheobronchial
circulation. Am. Rev. Respir. Dis. 135: S7 capsaicin (C. A.: Leakage of macromolecules from the tracheobronchial
circulation. Am. Rev. Respir. Dis. 135: S71-S75, 1987.
463. PERSSON, C. G. A., ERJEPALT, I., AND SUNDLER, F.: Airway microvacular
and optichelial leakag
- M., PROUD, D., P., P., AND SUNDLER, F.: Airway microvascular
and opithelial leakage of plasma induced by PAF-acether (PAF) and
capeaicin (CAP). Am. Rev. Respir. Dis. 135: A401, 1987.
TTERS, S. P., FREELAND, H. S., KELLY, S repeaicin (CAP). Am. Rev. Respir. Dis. 135: A401, 13
respeaicin (CAP). Am. Rev. Respir. Dis. 135: A401, 13
resp. S. P., FREELAND, H. S., KELLY, S. J., PIPKORM., PROUD, D., SCHLEIMER, R. P., LICHTENSTEIN, I
E.: Is leukotrie 464. PETERS, S. P., FREELAND, H. S., KELLY, S. J., PIPKORN, U., NACLERIO, K.

M., PROUD, D., SCHLEIMER, R. P., LICHTENSTEIN, L. M., AND FISH, F.

E.: Is leukotriene B, an important mediator in IgE-mediated allergic

reacti
-
- **466. PETERS, S. P., KAGEY-SOBOTKA, A., MACGLASHAN, D. W., AND LICHTEN-STEIN, L. M.: Effect of prostaglandin D_s in modulating histamine from human basophils. J. Pharmacol. Exp. Ther. 228: 400–406, 1984.
466. PETERS, S. P**
- STEIN, L. M.: Effect of prostaglandin D₃ in modulating histamine from
human basophils. J. Pharmacol. Exp. Ther. 228: 400–406, 1984.
466. PETERS, S. P., KAGEY-SOBOTKA, A., MACGLASHAN, D. W., SIEGEL, M. I.,
AND LICHTENSTRI vitro and in vivo function. R. P., NACLERIO, R. M., MACGLASHAN, D. W., Tous, A. G., PROUD, D., FREELAND, H. S., Fox, C., ADKINSON, N. F., AND LICHTENSTEIN, L. M.: The pathophysiology of human mast cells: in virto and in vi AND LICHTENSTEIN, L. M.: The pathophysiology of human mast cells: ir vitro and in vivo function. Am. Rev. Respir. Dis. 135: 1196-1200, 1967.
468. PIPER, P. J.: Formation and actions of leukotrienes. Physiol. Rev. 64: 744-

- **761,** 1984.
-
- vitro and in vivo function. Am. Hev. Hespir. Dis. 130: 1196-1200, 1987.

468. PIPER, P. J.: Formation and actions of leukotrienes. Physiol. Rev. 64: 744-761, 1984.

761, 1984.

469. PIPER, P. J., VANE, J. R., AND WYLLIE, J PER, P. J., VANE, J. R., AND WYLLEE, J. H.: Inactivation of prostaglandins thy the lungs. Nature (Lond.) 225: 600-605, 1970.
ROTZEY, E., PAGE, C. P., ROUBIN, R., PPISTER, A., PAUL, W., BONNET, E., AND. ENVERIER, J.: Paf-ac by the lungs. Nature (Lond.) 220: 600-600, 1970.
 470. PIROTERY, E., PAGE, C. P., ROUBIN, R., PEISTER, A., PAUL, W., BONNET,
 3., AND BENVENISTE, J.: Paf-acether-induced plasma exudation in rat

skin is independent of J., AND BENVENISTE, J.: Paf-acether-induced pla
kin is independent of platelets and neutrophils. M.
Lymphatics 1: 107-122, 1984.
ATSHON, L. F., AND KALINER, M. A.: The effects of
of histamine upon human lung cyclic nucleot
- **472. PLATSHON, L. F., AND KALINER, M. A.: The effects of immunologic release**
of histamine upon human lung cyclic nucleotide levels and prostaglandin
generation. J. Clin. Invest. **62**: 1113-1121, 1978.
PLESKOW, W. W., CH
- as pirin-sensitive asthmatic patients during aspirin-sensitive asthmatic patients during aspirin-sensitive aspirin-sensitive aspirin-sensitive aspirin-sensitive aspheric patients during aspirin challenge. J. Allergy

- Clin. Immunol. 72: 462-468, 1983.

64, 1975. Clin. Immunol. 72: 462-468, 1983.

bition of leukotriene C and 473. PLoy-SoNG-SANG, Y., CORBIN, R. P., AND ENGEL, L. A.: Effects of intra-

1655: 802-8026, 1970.

M. S.: In vivo Clin. Immunol. 73: 462–468, 1983.

473. PLOY-SONG-SANG, Y., CORBIN, R. P., AND ENGEL, L. A.: Effects of intra-

venous histamine on lung mechanics in man after beta-blockade. J. Appl.

Physiol. 44: 690–695, 1978.

474. POP
	- 474. POPA, V. T.: Effect of an H1 blocker, chlorpheniramine, on intubation tests
	- venous histamine on lung mechanics in man after beta-blockade. J. Appl.
Physiol. 44: 690-695, 1978.
474. POPA, V. T.: Effect of an H1 blocker, chlorpheniramine, on intubation tests
with histamine and allergen in allergic a
	- 474. POPA, V. T.: Effect of an H1 blocker, chlorpheniramine, on intubation tests
with histamine and allergen in allergic asthma. Chest 78: 442–451, 1980.
475. PRESCOTT, S. M., ZIMMERMAN, G. A., AND MCINTYRE, T. M.: Human
 176. Proc. Natl. Acad. Sci. USA 81: 3534-3538, 1984.

	176. PROUD, D., TOGIAS, A., NACLERIO, R. M., CRUSH, S. A., NORMAN, P. S.,

	1678. DEADLERTRISTEIN, L. M.: Kinins are generated in vivo following nasal

	airway challenge
	- airway challenge of allergic individuals with allergen. J. Clin. Invest. 72:
1678–1685, 1983.
AFFERTY, P., BEASLEY, R., AND HOLGATE, S. T.: The contribution of
histamine to immediate bronchoconstriction produced by inhaled 137. RAFFERTY, P., BEASLEY, R., AND HOLGATE, S. T.: The contribution of histamine to immediate bronchoconstriction produced by inhaled allergen and adenosine monophosphate in atopic asthma. Am. Rev. Respir. Dis. 136: 369-3
	-
	- 478. Rev. Respir. Die. 136: 17. Terrenadion (Seldano) is a potent and properties in a notice in the paper. Die. 136: 181-184, 1987.

	RAFFESTIN, B., **CERRINA,.,** BOULLET, C., LABAT, C., BENVENISTE, J., AND
Bruns, C., Respon **BRINK, P., AND HOLGATE, S. T.: Terfenadine (Seldane) is a potent and selective histamine H₁ receptor antagonist in asthmatic airways. Am. Rev. Respir. Dis. 135: 181-184, 1987.
Respir. Dis. 135: 181-184, 1987.
BRINK, C.:** eelective histamine H₁ receptor antagonist in asthmatic airways. Am. Rev.
Respir. Dis. 135: 181-184, 1987.
BRINK, C.: Response and sensitivity of isolated human pulmonary muscle
DRINK, C.: Response and sensitivity of iso **479. RAFFESTIN, B., CERRINA,J., BOULLET, C., LABAT, C., BENVENISTE, J., AND**

	BRINK, C.: Response and sensitivity of isolated human pulmonary muscle

	preparations to pharmacological agents. J. Pharmacol. Exp. Ther. 233:

	- study. Regal. 12: **9-19, 1985.** 186-194, 1985.

	186-194, 1985.

	186-194, 1985.

	1995. RANGACHARI, P. K., AND MCWADE, D.: Effects of tschykinins on the

	electrical activity of isolated cannie tracheal epithelium: an explora
	- 480. RANGACHARI, P. K., AND MCWADE, D.: Effects of tachykinins on the
electrical activity of isolated canine tracheal epithelium: an exploratory
study. Regul. Pept. 12: 9-19, 1985.
481. RANKIN, J. A., KALINER, M., AND REYN
	- **482. REGAL, J. F., EASTMAN, A. J., AND PICKERING, R. J.: C5a-induced tracheal**
contraction. A histamine independent mechanism. J. Immunol. 124:
2876-2878, 1980.
483. REGOLI, D., AND BARABE, J.: Pharmacology of bradykinin
	-
- **455. PAUWELS, R., AND VAN DER STRAETEN, M.: The bronchial effect of adenomine in the rat. Arch. Int. Pharmacodyn. Ther. 280: 229-239, 1986.**
 458. PAYAN, G. P., LEVINE, J.: Pharmacodyn. Ther. 280: 229-239, 1986.
 458. contraction. A histamine independent mechanism. J. Immunol. 124:

2876–2878, 1980.

483. REGOLI, D., AND BARABS, J.: Pharmacology of bradykinin and related

kinins. Pharmacology of bradykinin and related

484. RESTA, O., F Respiration **46: 121-127, 1984.**

ARESPIRA, O., FOSCHINO. BARBAR, O.M. P., AND CARWINEO, N.: Asthma re-

lieved by acetylsalicylic acid and non-steroid anti-inflammatory drugs.

Respiration 46: 121-127, 1984.

485. RICH, B
	-
	- browchi in vitro. Thorax 39: 420-423, 1984.
 Bronchi in vitro. Thorax 39: 420-423, 1984.
 BRICHARDSON, P. S.: Effects of prostaglanding E_B, E_B, and F_B, on mucin secretion from human bronchi in vitro. Thorax 39: 4 ponents. Infects of protestand as E₁, α_{23} , and τ_{2s} on much secretion from numan also. The HARMERSCHMIDT, D. E., AND HOIDAL, J. R.: Chemotactic and phagocytic responses of human alveolar macrophages to activated HAMMERSCHMIDT, D. E., AND HOIDAL, J. R.: Chemotactic and phagocytic
responses of human alveolar macrophages to activated complement com-
ponents. Infect. Immun. 43: 775-778, 1984.
487. RICHARDSON, B. P., AND ENGEL, G.: The
	-
	- responses of human alveolar macrophages to activated complement com-
ponents. Infect. Immun. 43: 775-778, 1964.
487. RICHARDSON, B. P., AND ENGEL, G.: The pharmacology and function of 5-
HT₃ receptors. Trends Neurol Sci. **489. RICHARDSON, P. S., PEATTELD, A. C., JACKSON, D. M., AND PIPER, P. J.:**
The effect of leukotrienes on the output of mucins from the cat traches.
 *In Le*ukotrienes and Other Lipoxygenase Products, ed. by P. J. Piper,
	- In Leukotrienes and Other Lipoxygenase Products, ed. by P. J. Piper, pp. 178-187, Wiley, New York, 1983.

	489. RICHARDSON, P. S., PHIPPS, R. J., BALFRE, K., AND HALL, R. L.: The roles

	of mediators, irritants, and allergen of mediators, irritants, and allergens in causing mucin secretion from the trachea. *In* Respiratory Tract Mucus, Ciba Foundation Symposium, vol. 54, pp. 111-131, Elsevier, 1978.

	54, pp. 111-131, Elsevier, 1978.

	DBBNNS,
	-
- trachea. *In* Respiratory Tract Mucus, Ciba Foundation Symposium, vol.
54, pp. 111-131, Elsevier, 1978.
490. ROBBINS, J. C., MACHOY, H., LAM, M. H., PONPIPOM, M. M., RUPPRECHT,
K. M., AND SHEN, T. Y.: A synthetic phospholi **the mass of the SHEN, T. Y.: A synthetic phospholipid inhibitor of PAF**
biosynthesis. Fed. Proc. 44: 1269, 1985.
BERRTS, A. M., SCHULTZ, H. O., GREEN, J. F., ARMSTRONG, D. J.,
KAUPMAN, M. P., COLERIDGE, H. M., AND COLERID **491. ROBERTS, A. M., SCHULTZ, H. O., GREEN, J. F., ARMSTRONG, D. J., KAUPMAN, M. P., COLERIDGE, H. M., AND COLERIDGE, J. C. G.: Reflex tracheal contraction evoked in dogs by bronchodilator prostaglandins E_r coles. Appl.** KAUFMAN, M. P., COLERIDGE, H. M., AND COLERIDGE, J. C. G.: Reflex
tracheal contraction evoked in dogs by bronchodilator prostaglandins E₃
and I₃. J. Appl. Physiol. 58: 1823–1831, 1985.
antagonist BN52063 on PAF-induced **globulin by snake venoms and by trypsin. Am. J. Physiol. 156: 261-273, 1949. 498. ROCHA E SILvA,** M., **BIER,** 0., **AND ARONSON,** M.: Histamine release **by** at Thammasart University on December 8, 2012 pharmrev.aspetjournals.org Downloaded from
	- tracheal contraction evoked in dogs by bronchodilator prostagiandins E_2
and I_3 . J. Appl. Physiol. 58: 1823-1831, 1985.
492. RoBERTS, N. M., MCCUSKER, M. T., AND BARNES, P. J.: Effect of a PAF
antagonist BN52063 on P
	- **PERTS, N. M., PAGE, C. P., CHUNG, K. F., AND BARNES, P. J.: The effect** of a specific PAF antagonists, BN 52063, on antigen-induced cutaneous responses in man. J. Allergy Clin. Immunol. in press, 1988. The press, 1988. Ph
	-
	- 105-11, 1987. The sponses in man. J. Allergy Clin. Immunol. in press, 1988.

	494. ROBERTSON, D. N., AND PAGE, C. P.: Effect of platelet agonists on airway

	reactivity and intrathoracic platelet accumulation. Br. J. Pharmac meactivity and intrathoracic platelet accumulation. Br. J. Pharmacol. 92:
105-111, 1987.
DBERTSON, D. N., RHODEN, K. J., GRANDORDY, B., PAGE, C. P., AND
BERTSON, D. J. The effect of platelet activating factor on histamine 105-111, 1987.

	496. ROBERTSON, D. N., RHODEN, K. J., GRANDORDY, B., PAGE, C. P., AND BARNES, P. J.: The effect of platelet activating factor on histamine and muscarinic receptor function in guinea-pig airways. Am. Rev. Re
	- muscarinic receptor function in guinea-pig airways. Am. Rev. Respir. Dis.
in press, 1988.
496. ROBINSON, C., AND HOLGATE, S. T.: Mast cell-dependent inflammatory
mediators and their putative role in bronchial asthma. Clin.
	- globulin by snake venoms and by trypsin. Am. J. Physiol. 156: 261-273,
	-

ARMACOLO

spet

 $\overline{0}$

- **BARNES, CHUN**
 anaphylatoxin. Nature (Lond.) 168: 465-466, 1951.
 499. ROGERS, D. F., AURSUDKIJ, B., EVANS, T. W., BELVISI, M. G., CHUNG, K.
 F., AND BARNES, P. J.: Platelet activating factor increases protein exu-
 anaphylatoxin. Nature (Lond.) 168: 465–466, 1951.
OGERS, D. F., AURSUDKLJ, B., EVANS, T. W., BELVISI, M. G., CHUNG, K.
F., AND BARNES, P. J.: Platelet activating factor increases protein exudation but not mucus secretion i anaphylatoxin. Nature (Lond.) 168: 465-466, 1951.

499. ROGERS, D. F., AURSUDKIJ, B., EVANS, T. W., BELVISI, M. G., CHUNG, K.

F., AND BARNES, P. J.: Platelet activating factor increases protein exudation but not mucus sec 499. ROGERS, D. F., AURSUDKIJ, B., EVANS, T. W., BELVISI, M. G., CHUNG, K.
F., AND BARNES, P. J.: Platelet activating factor increases protein exudation but not mucus secretion in guinea-pig trachea in vivo. Am. Rev.
Respi
-
-
- from human leukocytes possesses 5-lipoxygenase and leukotriene A synthase activities. Proc. Natl. Acad. Sci. USA 83: 857-861, 1986.
501a. RUBIN, A-H. E., SMITH, L. J., AND PATTERSON, R.: The bronchoconstrictor properties o thase activities. Proc. Natl. Acad. Sci. USA 83: 857-861, 1986.
RUBIN, A-H. E., SMITH, L. J., AND PATTERSON, R.: The bronchoor
properties of platelet-activating factor in humans. Am. Rev. R
136: 1145-1151, 1987.
UDOLF, M., 501a. RUBIN, A-H. E., SMITH, L. J., AND PATTERSON, R.: The bronchoconstrictor fola. RUBIN, A-H. E., SMITH, L. J., AND PATTERSON, R.: The bronchoconstripup properties of platelet-activating factor in humans. Am. Rev. Respir. 136: 1145-1151, 1987.
136: 1145-1151, 1987.
502. RUDOLF, M., GRANT, B. J. B.
-
- 136: 1145-1151, 1987.

502. RUDOLF, M., GRANT, B. J. B., AND SAUNDERS, K. B.: Aspirin in exercinduced asthma. Lancet 1: 450, 1975.

503. SACKEYFIO, A. C.: Definition of the histamine component of the bronch constructor and
- toxins **(AT)** and provides and provides and proposed and proposed and proposed and proposed and proposed and protocol. 43: 424, 1971.
 Br. J. Pharmacol. 43: 424, 1971.
 Br. J. Pharmacol. 55: 240, 1975.
 Br. J. Pharmac pays for the matter of anaphylocites. A comparison of the histopathological effect of anaphyloticins (AT) and prostaglandin E₂ (PGE₂) and PGF₂ in guinea-pig lung Br. J. Pharmacol. 55: 240, 1975.

MHOUN, M. N., AND PI
- toxins (AT) and prostaglandin E₂ (PGE₂) and PGF₂ in guinea-pig lungs.
Br. J. Pharmacol. 55: 240, 1975.
505. SAMHOUN, M. N., AND PIPER, P. J.: Comparative actions of leukotrienes in
lung from various species. *In* Leu
- STINGTH, M. N., AND PIPER, P. J.: Comparative actions of leukotrienes in
lung from various species. In Leukotrienes and Other Lipoxygenase Prod-
ucts, ed. by P. J. Piper, pp. 161–177, Wiley, New York, 1983.
MPSON, S. R., A
- lung from various species. In Leukotrienes and Other Lipoxygenase Prod-
ucts, ed. by P. J. Piper, pp. 161-177, Wiley, New York, 1983.
506. SAMPSON, S. R., AND VIDRUK, D. H.: The nature of the receptor mediating
stimulant e J. Physiol. 287: 509-518, 1979.

507. SARA, A., L. LUNDBERG, J. M., SKOFTTSCH, G., AND LEMBECK, F.: Vascular

protein leakage in various tissues induced by substance P, capsaicin,

bradykinin, serotonin, histamine, and by
- broadykinin, serotonin, histamine, and by antigen challenge. Naunyn-
Schmiedeberg's Arch. Pharmacol. 324: 212-218, 1983.
508. SARIA, A., THEODORSSON-NORHEIM, E., GAMSE, R., AND LUNDBERG, J.
M.: Release of substance P and s
-
- asthmatic airway and pulmonary vascular smooth muscle. Int. Arch. Rev. Respir. Dis. 136: S28-31, 1987.

510. SCHELLENBERG, R. R., AND FOSTER, A.: In vitro responses of human asthmatic airway and pulmonary vascular smooth m
- RELLENBERG, R. R., AND FOSTER, A.: In vitro responses of human asthmatic airway and pulmonary vascular smooth muscle. Int. Arch.
Allergy Appl. Immunol. 75: 237-241, 1984.
THELLENBERG, D. F., MONGAR, J. L., AND HERXHEIMER, 376-382, 1951.
- 511. SCHILD, H. O., HAWKINS, D. F., MONGAR, J. L., AND HERXHEIMER, H.:
Reactions of isolated human asthmatic lung and bronchial tissue to a
specific antigen. Histamine release and muscular contraction. Lancet 2:
376-382, 1 376–382, 1951.

612. SCHLEMMRR, R. P., MACGLASHAN, D. W., PETERS, S. P., PINCKARD, R. N.,

ADKINSON, N. F., AND LICHTENSTEIN, L. M.: Characterization of inflam-

matory mediator release from purified human lung mast cells.
-
- AND ADKINSON, N. F., JR., AND NEWBALL, H. H.: Cycloos
 ADMADKINSON, N. F., JR., AND NEWBALL, H. H.: Cycloos
 Appl. Physiol. 53: 589–595, 1982.

AND ADKINSON, N. F.: Anaphylactic release of thromboxane A₃, prostantly. genase metabolites in human lung anaphylaxis airway vs. parenchyma. J.
Appl. Physiol. 53: 589-595, 1982.
514. SCHULMAN, E. S., NEWBALL, H. H., DEMERS, L. M., FITZPATRICK, F. A.,
AND ADKINSON, N. F.: Anaphylactic release of Respir. Die. Die. 124: 514. SCHUD AND ADKINSON, N. F.: Anaphylactic release of thromboxane A₃, prosential SCHULMAN, B. S., NEWBALL, H. H., DEMERS, L. M., FTTZPATRICK, F. AND ADKINSON, N. F.: Anaphylactic release of throm LATION DENINSON, N. F.: Anaphylactic release of thromboxane A₃, proglandin D₃, and prostacyclin from human lung parenchyma. Am. l
Respir. Dis. 124: 402-406, 1981.
LIGMANN, B. E., FLETCHER, M. P., AND GALLIN, J. I.: Hi
- glandin D₃, and prostacyclin from human lung parenchyma. Am. Rev.
Respir. Dis. 124: 402-406, 1981.
LIGMANN, B. E., FLETCHER, M. P., AND GALLIN, J. I.: Histamine modulation of human neutrophil oridase metabolism, locomoti 515. SELIGMANN, B. E., FLETCHER, M. P., AND GALLIN, J. I.: Histamine modulation of human neutrophil oxidase metabolism, locomotion, degranulation, and membrane potential changes. J. Immunol. 130: 1902-1909, 1983.
1983. KRA
- **ion, and membrane potential changes. J. Immunol. 130: 1902-1909,**
1983.
IRAFIN, W., OATES, J., AND HUBBARD, W.: Metabolism of leukotriene B.
in the monkey. Identification of the principal non-volatile metabolite in
the 1983.
 **516. SERAFIN, W., OATES, J., AND HUBBARD, W.: Metabolism of leukotriene B₄

in the monkey. Identification of the principal non-volatile metabolite in

the urine. Prostaglandins 27: 899-908, 1984.

517. SERHAN, C.** series of compounds for compounds for compounds from architection of the principal non-volatile metabolite in the urine. Proctaglandins 27: 899-908, 1984.
517. SERHAN, C. N., HAMBERG, M., AND SAMUELSSON, B.: Lipoxins, a no
-
- the unit. I rosalganisms 21. 300–000, 1300–000, 1300–000, 1300–1300, B.: Lipoxins, a novel
series of compounds formed from arachidonic acid in human leukocytes.
Proc. Natl. Acad. Sci. USA 81: 5335–5339, 1984.
ERHAN, C. N., 211: 2427-246, 1997. Samman, 1997. Samman Samma
- FRANN, C. N., HIRBCH, U., PALMBLAD, J., AND SAMUELSSON, B.: Formation of lipoxin A by granulocytes from eosinophilic donors. FEBS Lett 217: 242-246, 1987.
217: 242-246, 1987.
B., RND WEISSMANN, G.: Leukotriene B₄ is a co tion of lipoxin A by granulocytes from eosinophilic donors. FEBS Lett 217: 242-246, 1987.

519. SERHAN, C. N., RADIN, A., SMOLEN, J. E., KORCHAK, H., SAMUELSSON, B., AND WEISSMANN, G.: Leukotriene B₄ is a complete secre 217: 242-246, 1987.

519. SERHAN, C. N., RADIN, A., SMOLEN, J. E., KORCHAK, H., SAMUELSSON,

B., AND WEISSMANN, G.: Leukotriene B₄ is a complete secretagogue in

human neutrophils: a kinetic analysis. Biochem. Biophys. R
- Somman neutrophils: a kinetic analysis. Biochem. Biophys. Res. Comman neutrophils: a kinetic analysis. Biochem. Biophys. Res. Comm
107: 1006-1012, 1982.
RETL, K., CASALE, T. B., WESCOTT, S. L., AND KALINER, M. A.: Imitohis 107: 1006-1012, 1982.

520. SERTL, K., CASALE, T. B., WESCOTT, S. L., AND KALINER, M. A.: Immunohistochemical localization of histamine-stimulated increases in cyclic

GMP in guinea pig lung. Am. Rev. Respir. Dis. 135: 456
- **for the catabolism of histemine-stimulated increases** in cyclic
cohistochemical localization of histamine-stimulated increases in cyclic
 GMP in guinea pig lung. Am. Rev. Respir. Dis. 135: 456–462, 1987.
521. SHAW, S., AN
- U. S., AND GOLDSTEIN, I. M.: Omega-oxidation is the major pathway for the catabolism of leukotriene B₄ in human polymorphonuclear leukocytes. J. Biol. Chem. 259: 10181-10187, 1984.
HAW, R. J., CROMWELL, O., AND KAY, A. B cytes. J. Biol. Chem. 259: 10181-10187, 1984.

522. SHAW, R. J., CROMWELL, O., AND KAY, A. B.: Preferential generation of

leukotriene C₄ by human eosinophils. Clin. Exp. Immunol. 56: 716-722,

1984.

523. SHEARD, P.: Th **56:** 716-722, 1984.
 524. SHEARD, P.: The effect of prostaglandin E₁ on isolated bronchial muscle
 524. SHEARMER, J., MAROM, Z., AND KALINER, M.: Immunologic and neuro-
 524. SHELHAMER, J., MAROM, Z., AND KALINER,
-
-

- BARNES, CHUNG, AND PAGE

airways in vitro. J. Clin. Invest. 66: 1400-1408, 1980.

M. G., CHUNG, K. 525. SHELLER, J. R., HOLTZMAN, M. J., SKOOGH, B.-E., AND NADEL, J. A.:

Interaction of serotonin with vagal and acetylcholi constriction in canine lungs. J. Appl. Physiol. 52: 964-966, 1982. airways in vitro. J. Clin. Invest. 66: 1400-1408, 1980.

525. SHELLER, J. R., HOLTZMAN, M. J., SKOOGH, B.-E., AND NADEL, J. A.:

Interaction of serotonin with vagal and acetylcholine-induced broncho-

constriction in canin
	- **WELLER, J. R., HOLTZMAN, M. J., SKOOGH, B.-E., AND NADEL, J. A.:**
Interaction of serotonin with vagal and acetylcholine-induced broncho-
constriction in canine lungs. J. Appl. Physiol. 52: 964–966, 1982.
HEN, T. Y., HUANG constriction in canine lungs. J. Appl. Physiol. 52: 964–966, 1982.
HEN, T. Y., HUANG, S.-B., CHANG, M. N., DOEBBER, T. W., LAM, M.-H.,
WU, M. S., WANG, X., HAN, G. Q., AND LI, R. Z.: Characterization of
platelet-activating platelet-activating factor receptor antagonist isolated for haifenteng (Piper futokadsura): specific inhibition of in vitro and in vivo platelet-activating factor-induced effects. Proc. Natl. Acad. Sci. USA 82: 672-676, 19
	- (Fiper futokadsura): specific inhibition of in vitro and in vivo platelet-
activating factor-induced effects. Proc. Natl. Acad. Sci. USA 82: 672-
676, 1985. G., MALON, L., MACFARLANE, C. M., MOUTON, W., AND
JOUBERT, J. R.
	- keto-prostagiandin F_{1m} beta-thromboglobulin in antigen-induced asthma
before and after indomethacin pretreatment. Br. J. Clin. Pharmacol. 19:
459–470, 1985.
10RE, S., COLLIER, B., AND MARTIN, J. G.: Effect of endogenou before and after indomethacin pretreatment. Br. J. Clin. Pharmacol. 19:
459–470, 1985.
528. SHORE, S., COLLIER, B., AND MARTIN, J. G.: Effect of endogenous prosta-
glandins on acetylcholine release from dog trachealis musc
	- FORE, S., COLLIER, B., AND MARTIN, J. G.: Effect of endogenous prosta-
glandins on acetylcholine release from dog trachealis muscle. J. Appl
Physiol. 62: 1837-1844, 1987.
M.: Substance P induced bronchoconstriction in guin glandins on acetylcholine release from dog trachealis muscle. J. Appl.

	Physiol. 62: 1837–1844, 1987.

	529. SHORE, S. A., STIMLER-GERRARD, N. P., COATES, S. R., AND DRAZEN, J.

	M.: Substance P induced bronchoconstriction i
	- **CUATRECASAS, P.: Regulation of arachidonate metabolism via hipoxygen- CUATRECASAS, P.: Regulation of arachidonate metabolism via hipoxygen-** CUATRECASAS, P.: Regulation of arachidonate metabolism via lipoxygen-
ase and
	- 531. SIGAL, C. E., VALONE, F. H., HOLTZMAN, J., AND GOETZL, E. J.: Preferential
human eosinophil chemotactic activity of the platelet activating factor
(PAF): 1-O-hexadecyl-2-acetyl-an-glyceryl-3-phosphocholine (AGEPC).
J. (PAY): 1-O-hexadecyl-3-phosphocholine (AGEPC). 1-O-hexadecyl-2-acetyl-3-phosphocholine (AGEPC). **J. Chin. Immunol.** 7: 179-188, 1987. **J.** The regulation of human eoeinophil chemotactic activity of the platelet activating function by cytokineer. Immunol. Total and the plate of the plate of text immunol. To cheracle of the plate of the plate of the plate of the section of the mean cosinophil function by cytokines. Immunol. Today 8: 380-385, 1913. State methods of the minimids of the state in the state of the state in the state of the state of the state in the state of the state in the state of the state of the state in the state of the state of the state of t
	-
	- relationship of plasma histamine to the activity of bronchial asthma histamine to the activity of bronchial asthma. J. The relationship of plasma histamine to the activity of bronchial asthma. J. Allergy Clin. Immunol. 60:
	- Fraction by cytokines. Immunol. Today 8: 330–385, 1987.

	533. SIMON, R. A., STEVENSON, D. D., ARROYAVE, C. M., AND TAN, E. M.: The

	relationship of plasma histamine to the activity of bronchial asthma. J.

	Allergy Clin. Im nervous system and the cough reflex in the increased responsiveness of **SUPPOSE TO A SUPPOSE TO A SUPPOSE THE STATE OF DETAILS ARE STATES AND MONESON, B. G., SKOOGH, B. E., BERGH, N. P., ANDERSON, R., AND MONSSON, B. G., SKOOGH, B. E., BERGH, N. P., ANDERSON, R., AND SVEDMYR, N.: In vivo and**
	- niversy in patients with obstructive airway disease. J. Clin. Invest. 4
1812–1818, 1967.
MONSSON, B. G., SKOOGH, B. E., BERGH, N. P., ANDERSON, R., Atlanta SVEDMYR, N.: In vivo and in vitro effect of bradykinin on bronchia 1812–1818, 1967.

	1812–1818, 1967.

	535. **SIMONSSON, B. G., SKOOGH, B. E., BERGH, N. P., ANDERSON, R., AND**

	SVEDMYR, N.: In vivo and in vitro effect of bradykinin on bronchial motor

	tone in normal subjects and in patient SVEDMYR, N.: In vivo and in vitro effect of bradykinin on bronchial motor
tone in normal subjects and in patients with airway obstruction. Respiration 30: 378-388, 1973.
ration 30: 378-388, 1973.
prostaglandins F_{2x} an
	- tone in normal subjects and in patients with airway obstruction. Respiration 30: 378–388, 1973.
536. SMITH, A. P.: The effects of intravenous infusion of graded doses of
prostaglandins F_{2x} and E_2 on lung resistance 536. SMITH, A. P.: The effects of intravenous infusion of graded doses of
prostaglandins F_{2n} and E_2 on lung resistance in patients undergoing
termination of pregnancy. Clin. Sci. 44: 17-19, 1973.
537. SMITH, A. P.,
	-
	- asthmatic man. Br. New Corressert, M. F.. Antagonistic action of aerosos,
3: 212-213, 1972.
538. SMITH, A. P., CUTHBERT, M. F., AND DUNLOP, L. S.: Effects of inha
prostaglandins E₁, E₂, and F₂, on the airway resistan
	- glam D, inhibits the aggregation of human platelets. Throm. Res. 5:

	S38. SMITH, A. P., CUTHBERT, M. F., AND DUNLOP, L. S.: Effects of inhaled

	asthmatic man. Clin. Sci. Mol. Med. 48: 421-430, 1975.

	539. SMITH, J. B., SIL
	-
	- 539. SMTH, J. B., SILVER, M. J., INGERMAN, C. M., AND KOCSIS, J. J.: Prosta-
glandin D₂ inhibits the aggregation of human platelets. Throm. Res. 5:
291–299, 1974.
540. SMTH, L. J., GREENBERGER, P. A., PATTERSON, R., KREL
	- LICHTENSTEIN, L. M.: Physiologic manifestations of human anaphylaxis.
J. Clin. Invest. **66:** 1072-1080, 1980.
542. SNYDER, F.: Chemical and biochemical aspects of platelet activating factor:
a novel class of acetylated eth LIGHTENSTEIN, L. M.: Physiologic manifestations of human anaphylaxis.
J. Clin. Invest. **66:** 1072-1080, 1980.
542. SNYDER, F.: Chemical and biochemical aspects of platelet activating factor:
a novel class of acetylated eth
	- NYDER, F.: Chemical and biochemical aspects of platelet activating factor:

	a novel class of acetylated ether-linked choline phospholipids. Med. Res.

	Rev. 5: 107-140, 1985.

	NYDER, F.: The significance of dual pathways fo platelet activating factor: 1-alkyl-2-lyso-*sn*-glycero-3-phosphate as a branchpoint. *In* New Horizons in Platelet Activating Factor Research, ed. by C. M. Winslow, and M. L. Lee, pp. 13–25, John Wiley & Sons, Ltd., New Y phaenchpoint. In New Horizons in Platelet Activating Factor Reby C. M. Winslow, and M. L. Lee, pp. 13–25, John Wiley & S. New York, 1987.
New York, 1987.
S. Y., LAM, W. K., AND KVENS, S.: Selective 5-HT₃ recepto.
S. Y.,
	-
	- 544. So. S. Y., Lam, W. K., AND KVENS, S.: Selective 5-HT_s receptor blockade
544. So, S. Y., Lam, W. K., AND KVENS, S.: Selective 5-HT_s receptor blockade
545. Sorrex, N. A., LEWIS, R. A., COREY, E. J., AND AUSTEN, K. F **J. Invest. Dermatol. 80: 115-119,** 1983. 546. **S0TER,** N. A., **WASSERMAN,** S. I., AUSTEN, K. F., **AND MCFADDEN,** E. R.: Release of mast cell mediators and alterations in lung function in patients
	- of synthetic leukotrienes (LTC., LTD., LTE., and LTB.) in human skin.
J. Invest. Dermatol. 80: 115-119, 1983.
546. SOTER, N. A., WASSERMAN, S. I., AUSTEN, K. F., AND MCFADDEN, E. R.:
Release of mast cell mediators and alte
	- **boxane A, mediates and alterations and alterations in lung function is prelease of mast cell mediators and alterations in lung function in patients with cholinergic articaria. N. Engl. J. Med. 302: 604–608, 1980. 547. SPA**
	- THE EFFECT OF ALLERGEN PROVIDED AND DUNN, M. J.: Throm-
boxane A₂ mediates augmented polymorphonuclear leukocyte adhesive-
ness. J. Clin. Invest. 66: 406-414, 1980.
MALENHEIM, S., AND MACHADO, L.: Late allergic bronchial ness. J. Clin. Invest. **66:** 406-414, 1980.
548. STALENHEIM, S., AND MACHADO, L.: Late allergic bronchial reactions and
the effect of allergen provocation on the complement system. J. Allergy
Clin. Immunol. 75: 508-512, 19
	-

ARMACOLO

spet

 $\overline{\mathbb{O}}$

spet

 $\, \mathbb G \,$

PHARM
REV

- **responses. J. Allergy Clin. Immunol. 64: 287-293, 1979.**

550. STEIGER, J., BRAY, M. A., AND SUBRAMANIAN, N.: Platelet activating factor

(PAF) is a potent stimulator of porcine tracheal fluid secretion in vitro. human and guinea pig lung tissue: comparison of parenchymal and airway
responses. J. Allergy Clin. Immunol. 64: 287–293, 1979.
TEIGER, J., BRAY, M. A., AND SUBRAMANIAN, N.: Platelet activating factor
(PAF) is a potent stim numan and guinea pig tung ussue: comparison of parencitymal and airway
responses. J. Allergy Clin. Immunol. 64: 287-293, 1979.
550. STENGER, J., BRAY, M. A., AND SUBRAMANIAN, N.: Platelet activating factor
(PAF) is a poten
- EIGER, J., BRAY, M. A., AND SUBRAMANIAN, N.: Platelet activating ractor
(PAF) is a potent stimulator of porcine tracheal fluid secretion in vitro.
Eur. J. Pharmacol. 142: 367-372, 1987.
ENSON, W. F., AND PARKER, C. W.: Mon 2100-2104, 1980. **552. STENSON, W. F., AND PARKER, C. W.: Monohydroxyeicosatetraenoic acids**

(HETEs) induce degranulation of human neutrophils. J. Immunol. 124:

2100-2104, 1980.

552. STEWART, R. M., WEIR, E. K., MONGOME
- **ENDOGENOUE MECHANISM.** THE SERVICE CHEFT CHEFT CHEFT CHANGED MET REWART, R. M., WEIR, E. K., MONGOMERY, M. R., AND NIE
D. E.: Hydrogen peroxide contracts airway smooth muscle:
D. E.: Hydrogen peroxide contracts airway smo
- guinea-pig lung parenchymal strips: sensitivity of the leukotriene-mediated component to cyclo-oxygenase inhibitors. Biochem. Biophys. Res. Soz. STEWART, R. M., WEIR, E. R., MONGOMERY, M. R., AND NIEWOEHNER,

D. E.: Hydrogen peroxide contracts airway smooth muscle: a possible

endogenous mechanism. Respir. Physiol. 45: 333-342, 1981.

553. STIMLER, N. P.: Spas
-
- bos. STIMLER, N. P., BACH, M. K., BLOUR, C. M., AND HUGLI, T. E.: Kelesse
of leukotrienes from guinea-pig lung stimulated by C5a des arg anaphy-
lotoxin. J. Immunol. 128: 2247-2252, 1982.
555. STIMLER, N. P., BLOUR, C. M.,
-
-
- 557. SUMMERS, R., SIGLER, R., SHELHAMER, J. H., AND KALINER, M.: Effects
of infused histamine on asthmatic and normal subjects: comparison of
skin test responses. J. Allergy Clin. Immunol. 67: 456–464, 1981.
558. SUN, F. F K. F.: Identification of a high affinity leukotriene C₄-binding protein in 558. SUN, F. F., CHAU, L. Y., SPUR, B., COREY, E. J., LEWIS, R. A., AND AUSTEN,
K. F.: Identification of a high affinity leukotriene C₄-binding protein in
rat liver cytosol as glututhione-S-transferase. J. Biol. Chem. 26 released from platelets on a high affinity leukotriene C₄-binding protein in
rat liver cytosol as glututhione-S-transferase. J. Biol. Chem. 261: 8540-
8546, 1986.
IZUKI, Y., MIWA, M., HARADA, M., AND MATSUMOTO, M.: Acety
- Exp. Pharmacol. Phys. in press, 1988.

8546, 1986.

8546, 1986.

8546, 1986.

8546, 1986.

859. SUZUKI, Y., MIWA, M., HARADA, M., AND MATSUMOTO, M.: Acetylhydolase

released from platelets on aggregation with platelet acti DUCT, T., MIWA, M., HARADA, M., AND MATSUMOTO, M.: *h*uman bronchial muscles on aggregation with platelet activation.
 Exp. Pharmacol. Phys. in press, 1988.
 human bronchial muscle. Nature (Lond.) 217: 69, 1968.
 czer 561. SZCZEKLIK, A., **GRYGLEWSKI,** R. J., **AND CZERNIAWSKA-MYSIK,** G.: Reha-
-
-
- Exp. Pharmacol. Phys. in press, 1988.

560. SWATMAN, W. J. F., AND COLLIER, H. O. J.: Effects of prostaglandins on

human bronchial muscle. Nature (Lond.) 217: 69, 1968.

561. SZCZEKLIK, A., GRYGLEWSKI, R. J., AND CZERNIAW ionahip of inhibition of prostaglandin biosynthesis by analgesics to asthma attacks in aspirin-sensitive patients. Br. Med. J. 1: 67-69, 1975. 562. SZCZEKLIK, A., GRYGLEWSKI, R. J., NIZANKOWSKA, E.; AISANKOWSKI, R., AND MU **562. SZCZEKLIK, A., GRYGLEWSKI, R. J., NIZANKOWSKA, E., NISANKOWSKI, R.,**
AND MUSIAL, J.: Pulmonary and anti-platelet effects of intravenous and
inhaled prostacyclin in man. Prostaglandina 16: 651-660, 1978.
563. SZCZEKL
-
- inhaled prostacyclin in man. Prostagiandins 16: 651-660, 1978.

563. Szczeskuk, A., AND NizANKOWSKA, E.: Asthma improved by aspirin-like

druga. Br. J. Dis. Chest 77: 153-158, 1983.

564. TAMURA, N., AGRAWAL, D. K., AND TO INDEA, N., AGRAWAL, D. K., AND TOWNLEY, R. G.: Effects of platelet activating factor on the chemotaxis of normodense eosinophils from normal subjects. Biochem. Biophys. Res. Commun. 142: 638-644, 1987.
NNAKA, D. T., AND GR
- 1561 TANAKA, D. T., AND GRUNSTEIN, M. M.: Mechanisms of substance P. 592. WALTERS, E. H., O'BYRNE, P. M., FABBRI, L. M., GRAF, P. D., HOLTZMAN,

induced contraction of rabbit sirway smooth muscle. J. Appl. Physiol. 57:
 biologic activity of mast cell granules. Immunology 125: 325-335, 1980.
 biologic activity of mast cell granules. Immunology 125: 325-335, 1980.
 biologic activity of mast cell granules. Immunology 125: 325-335, 1980
-
-
- 1551–1557, 1984.

566. TANNENBADU, S., OERTEL, H., HENDERSON, W., AND KALINER, M.: The

biologic activity of mast cell granules. Immunology 125: 325–335, 1980.

567. TAYLOR, K. J., AND LUKSZA, A. R.: Peripheral blood eosin 567. TAYLOR, K. J., AND LUKSZA, A. R.: Peripheral blood eoainophil counts and
bronchial responsiveness. Thorax 42: 452-456, 1987.
668. TENCE, M., POLONSKY, J., LECOUEDIC, J. P., AND BENVENISTE, J.: Release,
purification, a
-
-
- 571. THOMSON, N. C., AND KERR, J. W.: The effect of inhaled H_1 and H_2 -
receptor antagonists in normal and asthmatic subjects. Thorax 35: 428-
434, 1980.
434, 1980.
434, 1980.
435. C., ROBERTS, R., BANDENKAVIS, J.,
- 434, 1980.

572. THOMSON, N. C., ROBERTS, R., BANDENKAVIS, J., NEWBALL, H., AND

HARGREAVE, F. E.: Comparison of bronchial response to prostagland

F₃. and methacoline. J. Allergy Clin. Immunol. 68: 392–398, 1981.

573.
-
-
- **asthmatics. Allergy** 40: 136-140, 1985.
 asthma. Lancet 1: 813, 1976.
 asthma. Lancet 1: 8 ing factor in stimulated rabbit platelets. Evidence for an alkylacetylashma. Lancet 1: 813, 1976.

S75. TOUQUI, L., JACQUEMIN, C., DUMARRY, C., AND VARGAPTIG, B. B.: Alkyl-

2-acyl-an-glycero-3-phosphorylcholine is the precursor of platelet activating factor in stimulated rabbit platelet. Ev
- 1978. TURK, J., MAAS, R. L., BRASH, A. R., ROBERTS, L. J., AND OATES, J. A.: A and neurokinin B binding sites in guinea-pig trachea. Neurosci. Lett.
Arachidonic acid 15-lipoxygenase products from human eosinophils. J. 37:
- 577. TURNBULL, L. W., AND KAY, A. B.: Eosinophils and mediators of anaphy-
-

human and guinea pig lung tissue: comparison of parenchymal and airway KAY, A. B.: Mediators of immediate-type hypersensitivity in sputum from
1977. presponses. J. Allergy Clin. Immunol. 64: 287–293, 1979. http://www.patie k AND ASTHMA
KAY, A. B.: Mediators of immediate-type hypersensitivity in sputum from
patients with chronic bronchitis and asthma. Lancet 2: 526–529, 1977.

- patients with chronic bronchitis and asthma. Lancet 2: 526-529, 1977.

FAR, N., MARAMATSU, I., AND FUJIWARA, M.: Capsaicin and bradykin-

induced substance P-ergic responses in the iris sphincter muscle of the KAY, A. B.: Mediators of immediate-type hypersensitivity in sputum from
patients with chronic bronchitis and asthma. Lancet 2: 526-529, 1977.
579. UEDA, N., MARAMATSU, I., AND FUJIWARA, M.: Capsaicin and bradykin-
induced
- **EDA, N., MARAMATSU, 1., AND FUJIWARA, M.: Capeaicin and bradykin-
induced substance P-ergic responses in the iris sphinter muscle of the
rabbit. J. Pharmacol. Exp. Ther. 230: 469-473, 1984.
KENA, D., DENT, G., SYBRECHT, G** mouced substance P-ergic responses in the iris spinncter muscle of t
rabbit. J. Pharmacol. Exp. Ther. 230: 469–473, 1984.
580. UKENA, D., DENT, G., SYBRECHT, G. W., AND BARNES, P. J.: Radioliga
polymorphonuclear leukocytes
- binding of antagonists of platelet-activating factor to human platelets and
polymorphonuclear leukocytes. FASEB. J. 2: A1575, 1988.

KENA, D., SCHIRREN, C. G., AND SCHWABE, U.: Effect of xanthine deriv-

atives on adenosin 581. UKENA, D., SCHIRREN, C. G., AND SCHWABE, U.: Effect of xanthine deriv-591. UKENA, D., SCHIRREN, C. G., AND SCHWABE, U.: Effect of xanthine derivatives on adenosine-receptors of guinee pig lung. *In* Anti-asthma Xanthines and Adenosine, ed. by K-E. Anderseon, and C. G. A. Persson, pp. 390–398 actives on adenosine-receptors of guinea pig lung. In Anti-asthma Xanthines and Adenosine, ed. by K-E. Andersson, and C. G. A. Persson, pp. 390-398, Excerpta Medica, Amsterdam, 1985.
582. VALONE, F. H.: Isolation of a plat
-
- binding factor. Immunology 52: 169-174, 1984.

583. VALONE, F. H., COLES, E., REINHOLD, V. R., AND GOETZL, E. J.: Specific

binding of phospholipid platelet-activating factor by human platelets. J.

Immunol. 129: 1637-1641 platelet activating factor. Immunology 52: 169-174, 1984.
583. VALONE, F. H., COLES, E., REINHOLD, V. R., AND GOETZL, E. J.: Specific binding of phospholipid platelet-activating factor by human platelets
Immunol. 129: 1637
- **phonuclear leucocytes of the immunological mediator 1-O-hexadecyl/** binding of phospholipid platelet-activating factor by human platelets. J.
Immunol. 129: 1637-1641, 1982.
584. VALONE, F. H., AND GOETZL, E. J.: Specific binding by human polymor-
phonuclear leucocytes of the immunological
- of guinea-pig lung parenchyma. Role of cyclo-oxygenase metabolite. Im-
muchamacology 5: 251-257, 1983.
mutan-farencology 5: 251-257, 1983.
556. STMLER-GERARD, N. P.: Parasympathetic stimulation as a mechanism of 584a. VAND phonuclear leucocytes of the immunological mediator 1-O-hexadecyl₁
149, 1983.
149, 1983.
7ANDERHOEK, J. Y., TARE, N. S., BAILEY, J. M., GOLDSTEIN, A. L., AND
7ANDERHOEK, J. Y., TARE, N. S., BAILEY, J. M., GOLDSTEIN, A. L octadecyl-2-acetyl-sn-glycero-3-phosphoryicholine. Immunology 48: 141-
149, 1983.

140, 1983.

140, 1983.

264a. VANDERHORK, J. Y., TARE, N. S., BAILEY, J. M., GOLDSTEIN, A. L., AND

PLUZWIK, D. H.: New role for 15-hydroxy
	- 257: 12191-12195, 1982.

	585. VAN INWEGEN, R. G., KHANDWALA, A., GORDON, R., SONNIND, P., Courrs, S., AND JOLLY, S.: Rev 5901: an orally effective peptidoleuko-

	triene antagonist, detailed biochemical/pharmacological prof COUTTS, S., AND JOLLY, S.: Rev 5901: an orally effective peptidoleuko-
triene antagonist, detailed biochemical/pharmacological profile. J. Phar-
macol. Exp. Ther. 241: 117-124, 1987.
ARGAFTIG, B. B., CHIGNARD, M., AND BENV
	- triene antagonist, detailed biochemical/pharmacological profile. J. Phi
macol. Exp. Ther. 241: 117-124, 1987.
586. VARGAFTIG, B. B., CHIGNARD, M., AND BENVENISTE, J.: Present concer
on the mechanisms of platelet aggregatio
	- IREGATTIG, B. B., CHIGNARD, M., AND BENVENISTE, J.: Present concepts
on the mechanisms of platelet aggregation. Biochem. Pharmacol. 30: 263-271, 1981.
REGATTIG, B. B., LEFORT, J., CHIGNARD, M., AND BENVENISTE, J.: Plate-
R on the mechanisms of platelet aggregation. Biochem. Pharmacol. 30: 263-
271, 1981.
587. VARGAFTIG, B. B., LEPORT, J., CHIGNARD, M., AND BENVENISTE, J.: Plate-
let-activating factor induces a platelet-dependent bronchoconst
	-
	-
	- unrelated to the formation of prostaglandin derivatives. Eur. J. Pharma-
col. 65: 185-192, 1980.

	NREK, R. J., AND STEWART, J. M.: Competitive antagonists of bradykinin.

	Peptides 6: 161-164, 1985.

	VINCENC, K., BLACK, J., **MURTY, I. F., AND HENSON, P. M.: PAF antagonists: different effects of** Fharmacol. 84: 201-210, 1984.

	590. VOELKEL, N. F. CHANG, S. W., PFEFFER, K. D., WORTHEN, S. G., MC-

	MURTY, I. F., AND HENSON, P. M.: PAF antagonists: different effects of

	platelets, neutrophils, guinea-pig ileum, and PA
	-
	- MURTY, I. F., AND HENSON, P. M.: PAF antagonists: different effects of
platelets, neutrophils, guinea-pig ileum, and PAF-induced vasodilation in
isolated rat lung. Prostaglandins 32: 359-372, 1986.
591. WALTERS, E. H., AND **in cancine trachealis smooth muscle in vivo. Thorax 37: 918-922, 1982.**
 in cannot muscle. J. A., FABRIR, L. M., GRAF, P. D., HOLTZMAN, M. J., AND NADEL, J. A.: Control of neutraminamission by prostaglandins

	in canin
	- **M. J., AND NADEL, J. A.: Control of neurotransmission by prostaglandins**
in canine trachealis smooth muscle. J. Appl. Physiol. 57: 129–134, 1984.
ALTERS, E. H., PARRISH, R. W., BEVAN, C., AND SMITH, A. P.: Induction
of br in canine trachealis smooth muscle. J. Appl. Physiol. 57: 129–134, 1984.
593. WALTERS, E. H., PARRISH, R. W., BEVAN, C., AND SMITH, A. P.: Induction
of bronchial hypersensitivity: evidence for a role of prostaglandins. Tho
	- ALTERS, E. H., FARRISH, R. W., BEVAN, C., AND SMITH, A. P.: Induction
36: 571-574, 1981.
38: 571-574, 1981.
ANNER, A., SIELCZAK, M., MELLA, J. F., AND ABRAHAM, W. M.: Ciliary
ANNER, A., SIELCZAK, M., MELLA, J. F., AND ABRA 1967-1971, 1986.

	1986: 571-574, 1981.
 **ESPANNER, A., SIELCEAK, M., MELLA, J. F., AND ABRAHAM, W. M.: Ciliary

	1997-1971, 1986.

	1967-1971, 1986.

	595. WANNER, A., ZARZECKI, S., HIRSCH, J., AND EPSTEIN, S.: Tracheal mucou**
	- responsiveness in allergic and nonallergic airways. J. Appl. Physiol. 60:
1967–1971, 1986.
595. WANNER, A., ZARZECKI, S., HIRSCH, J., AND EPSTEIN, S.: Tracheal mucous
transport in experimental canine asthma. J. Appl. Physi
- receptor antagonists in normal and asthmatic subjects. Thorax 35: 428-

FOO. THOMPSON, P. J., HANSON, J. M., BILANI, H., TURNER-WARWICK, M.,

Rev. Respir. Dis. 129: 3A, 1984.

Rev. Respir. Dis. 129: 3A, 1984.

Rev. Respir. 1967-1971, 1986.

595. WANNER, A., ZARZECKI, S., HIRSCH, J., AND EPSTEIN, S.: Tracheal mucous

transport in experimental canine asthma. J. Appl. Physiol. 39: 950-957,

1975.

1975.

1976.

2008. WARDLAW, A. J., CHUNG, K. F spone in dependence after after a securities. C. Appl. 1 aysol. 09. 500–501, 1975.
1975.
1975. M., BARNES, P. J., COLLINS, J. V., AND KAY, A. B.: Cellular
changes in blood and broncholayelolar lavage (BAL) and bronchinal r CUSKER, M., BARWES, P. J., COLLINS, J. V., AND KAY, A. B.: Cellular
changes in blood and bronchoalveolar lavage (BAL) and bronchial re-
sponsiveness after inhaled PAF in man. Am. Rev. Respir. Dis. 137: 283,
1988.
697. WARD
	-
	-
	-
	- Immunol. 72: 101-115, 1983. **600.** WASSERMAN, S. I.: Mediators of immediate hypersensitivity. J. Allergy Clin.
 IMMUNOL AND AUSTEN, N. A. CENTER, D. M., AND AUSTEN, K. F.: Cold

	1699. WASSERMAN, S. I.: Mediators of immed 599. WASSERMAN, S. I.: Mediators of immediate hypersensitivity. J. Allergy Clin.

	Immuno. 72: 101-115, 1963.

	COO. WASSERMAN, S. I., SOTER, N. A., CENTER, D. M., AND AUSTEN, K. F.: Cold

	urticaria. Recognition and characte
	-
	-
	- **personal on the guineary of the guineary of the guinear ST. 136, 1987.**
 602. WEBB, D., BENJAMIN, N., COLLIER, J., AND ROBINSON, B.: Enalapri-
 604. WEBBER, S. E., AND FOREMAN, J. C.: The effect of substance P and rela
	-

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2012

Downloaded from pharmrev.aspetjournals.org at Thammasart University on December 8,

- **EARNES, CHUNG,**
by polymorphonuclear leucocytes in inflammation. Nature (Lond.) 289:
605. WEDMORE, C. V., AND WILLIAMS, T. J.: Platelet-activating factor (PAF), a
secretory product of polymorphonuclear leucocytes, increas secretory productions are inflammation. Nature (Lond.) 289:
Secretory product of polymorphonuclear leucocytes, increases vascular
secretory product of polymorphonuclear leucocytes, increases vascular
permeability in rabbit
- by polymorphonuclear leucocytes in inflammation. Nature (Lond.) 289:
605. WEDMORE, C. V., AND WILLIAMS, T. J.: Platelet-activating factor (PAF), a
secretory product of polymorphonuclear leucocytes, increases vascular
perme 606. WEISS, J. W., DRAZEN, J. M., COLES, N., MCFADDEN, E. K., WELLER, P.
W. COREY, E. J., LEWIS, R. A., AND AUSTEN, K. F.: Bronchoconstrictor
effects of leukotriene C in humans. Science (Wash. DC) 216: 196-199,
1962.
607. in Normal humans produced by inhalation of leukotriene D: potency, E. J., Lewis, R. A., AND AUSTEN, K. F.: Bronchoconstrictor of effects of leukotriene C in humans. Science (Wash. DC) 216: 196-199, 1982.
1982.
1982. W. DRA
- **608.** WEISS, J. W., DRAZEN, J. M., MCFADDEN, E. R., ET AL.: Airway constriction in normal humans produced by inhalation of leukotriene P.: potency, time, 614 ourse, and effect of aspirin therapy. JAMA 249: 2814–2817, 1983
- EISS, J. W., DRAZEN, J. M., MCFADDEN, E. R., ET AL.: Airway constriction
in normal humans produced by inhalation of leukotriene D: potency, time,
course, and effect of aspirin therapy. JAMA 249: 2814–2817, 1983.
EISS, S., **609.** WEISS, S., ROBB, G. P., AND BLUMGART, P.: The velocity of blood flow in health and disease as measured by the effect of histamine on the minute vessels. Am. Heart J. 4: 664, 1928.
609. WELLER, P. F., LEE, C. W., F
- 608. WEISS, S., ROBB, G. P., AND BLUMGART, P.: The velocity of blood flow in
health and disease as measured by the effect of histamine on the minute
vessels. Am. Heart J. 4: 664, 1928.
609. WELLER, P. F., LEE, C. W., FOST
- AND LEWIS, R. A.: Generation and metabolism of 5-lipoxygenase pathway
leukotrienes by human cosinophils: predominant production of leuko-
triene C₄. Proc. Natl. Acad. Sci. USA 80: 7626-7630, 1983.
609a. WHITE, J. P., MI
-

- changes of inflammation. Br. J. Pharmacol. 65: 517-524, 1979.
611. WILLIAMS, T. J., AND MORLEY, J.: Prostaglandins as potentiators of increased vascular permeability in inflammation. Nature (Lond.) 246: 215-217. 1973.
- 217, 1973. 612. WILLIAMS, T. J., AND MORLEY, J.: Prostaglandins as potentiators of increased vascular permeability in inflammation. Nature (Lond.) 246: 215-
217, 1973.
612. Woownap, D. F., WEICHMAN, B. M., GILL, C. A., AND **ability. Prostaghanding 25: 131, 1983.**
 ability. Prostaglandins 25: 131, 1983.
 ability. Pr
- A.: The effect of synthetic leukotrienes on tracheal microvas
ability. Prostaglandins 25: 131, 1983.
NNCRY, K. B., HAMMER, C. H., HARVATH, L., RENFER, L., F.
NNCRY, T. J.: Studies of human C5a as a mediator of inn normal h **614. Yake Strategins 25: 131, 1983.**
 613. YANCEY, K. B., HAMMER, C. H., HARVATH, L., RENFER, L., FRANK, M. M., AND LAWLEY, T. J.: Studies of human C5a as a mediator of inflammation in normal human skin. J. Clin. Invest.
- **SUPERT, K. B., HAMMER, C. H., HARVATH, L., KENFER, L., FRANK, M. M.,**

SUPERTY, T. J.: Studies of human C5a as a mediator of inflammation

in normal human skin. J. Clin. Invest. 75: 486–495, 1985.

1984KA, T., BOXER, L. A
- 615. **YOSHIMOTO, T., YOKOYAMA, C., OCHI, K., Er AL.:** 2,3,5-Trimethyh-6-(12 superoxide anion response to formyl-methionyl-ieucyl-phenylalanine (FMLP) and platelet-activating factor (PAF). J. Immunol. 128: 1939-1944, 1982.
1944, 1982.
09HIMOTO, T., YOKOYAMA, C., OCHI, K., ET AL.: 2,3,5-Trimethyl-6-1944, 1982.

615. YOSHIMOTO, T., YOKOYAMA, C., OCHI, K., ET AL.: 2,3,5-Trimethyl-6-(12-08HIMOTO, T., YOKOYAMA, C., OCHI, K., ET AL.: 2,3,5-Trimethyl-6-(12-

hydroxy-5,10-dodecadinyl)-1,4-benzoquinone (AA-861), a selective
-

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