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Pulmonary and Generalized Lysosomal Storage Induced by Amphiphilic Drugs

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Administration of amphiphilic drugs to experimental animals causes formation of myelinoid bodies in many cell types, accumulation of foamy macrophages in pulmonary alveoli and pulmonary alveolar proteinosis. These changes are the result of an interaction between the drugs and phospholipids which leads to an alteration in physicochemical properties of the phospholipids. Impairment of the digestion of altered pulmonary secretions in phagosomes of macrophages results in accumulation of foam cells in pulmonary alveoli. Impairment of the metabolism of altered phospholipids removed by autophagy induces an accumulation of myelinoid bodies. The administration of amphiphilic compounds thus causes pulmonary intra-alveolar histiocytosis which is a part of a drug-induced lysosomal storage or generalized lipidosis.

The accumulation of drug-lipid complexes in myelinoid bodies and in pulmonary foam cells may lead to alteration of cellular functioning and to clinical disease. Currently over 50 amphiphilic drugs are known. Unique pharmacological properties necessitate clinical use of some of these drugs. The occurrence and severity of potential clinical side effects depend on the nature of each drug, dosage and duration of treatment, simultaneous administration of other drugs and foods, individual metabolic pattern of the patient and other factors. Further studies on factors preventing and potentiating adverse effects of amphiphilic drugs are indicated.

In recent years it has become apparent that certain drugs administered systematically to man have serious side effects because of their affinity for the lungs. The pulmonary pathology produced by these drugs has received relatively little clinical attention because of the insidious and chronic nature of its development. With increasing awareness that a large variety of seemingly harmless drugs can induce such lung changes, it is imperative that more rigorous studies be carried out before such drugs are put to clinical use. The purpose of this report is to review a group of drugs which lead to intra-alveolar histiocytosis and to generalized lysosomal storage.

Foam Cells

In 1966, Greselin reported (*1*) that chronic administration of a drug which inhibits cholesterol synthesis, *trans*-1,4-bis(2-chlorobenzylaminomethyl)cyclohexane dichloride, also called AY-9944, induces accumulation of foam cells in pulmonary alveoli of experimental animals. In the past 15 years other drugs with a variety of pharmacological effects were shown to produce similar pulmonary side effects (Table 1).

These drugs induce essentially similar histological and ultrastructural changes in the lung, although the time required for the appearance of the foam cells and their quantity and size may be quite different in various animal species (*1–4*). The lungs of the treated animals increase in weight (*1,5*) and contain whitish plaques and nodules on gross examination (*1,6*). Microscopically these plaques consist of intra-alveolar accumulations of foam cells (*1,7*).

The foam cells are between 20 and 80 μm in diameter (*4,8–10*) and have a centrally placed nucleus. The cytoplasm is abundant, pale, and finely reticulated in hematoxylin-eosin stained sections (Fig. 1). In toluidine blue-stained Epon sections, the foam cells are filled with numerous round inclusions. Staining of foam cells with Sudan Black B and with Baker's acid hematein for phospholipids are positive, while staining with Sudan III and by the periodic acid-Schiff method are usually negative (*5,7,10,11*). Examination of fresh tissues in polarized light identifies both the inclusions in foam cells and myelinoid bodies as Maltese cross figures (*11,12*). Histochemical studies reveal high activities of acid phosphatase and β-glucuronidase, implicating the foam cells as macrophages (*4,10,13,14*).

The time sequence of pulmonary changes associated with foam cell accumulation has been studied at light and electron microscopic levels. The first change observed in iprindole-treated rats is interstitial pulmonary edema associated with degenerative changes in capillary endothelia (*14*). Subsequently endothelia and alveolar epithelia become swollen and the septa infil-

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Table 1. Inducers of intra-alveolar foam cells.[a]

	Alveolar lumen			Type II cells		Myelinoid bodies						
	Secretions	Foam cells	Proteinosis	Hypertrophy	Hyperplasia	Type I cells	Clara cells	Other cells	Affinity for lung	Chlorphentermine binding inhibited	Other effects	References
Amiodarone		+						+				(*243*)
Amitriptyline		0								+		(*3,41,118,244*)
AY-9944	+	+		+		+	+		+			(*1,8,144*)
Boxidine		+										(*26,7*)
Chlorcyclizine	+	+		+	+	+	+	+	+	+		(*7,26,118,221,245*)
1-Chloroamitriptyline		+		+		+		+				(*3,41*)
1-Chloro-10,11-dehydro-amitriptyline		+		+		+		+				(*3,41*)
Chloroquine		+								+		(*7,26,118*)
Chlorphentermine		+	+	+	+	+	+	+	+	+	A	(*3,10,19,21,114,118, 145,245,248,249,250*)
Chlorpromazine		0							+		B	(*3,41,244,245*)
Cloforex		+							+			(*5,17,246*)
Clomipramine		+		+		+		+				(*3,41,113*)
Cyclizine		+							+			(*7,26,221,245*)
4,4'-Diethylamino-ethoxyhexestrol	+	+				+		+				(*33,205*)
Erythromycin	+	+							+			(*212*)
Ethyl fluclozepate		+										(*247*)
Fenfluramine		+										(*2*)
Fluoxetine		+										(*24*)
Haloperidol		+										(*7,26*)
Homochlorcyclizine		+										(*7,26*)
Hydroxyzine		+										(*7,26*)
Imipramine		+		+		+		+	+	+	C	(*3,41,118,221,244,245,251*)
Iprindole		+	+			+	+	+				(*3,14,16,20,41*)
Meclizine		+										(*7,26*)
Norchlorcyclizine		+							+			(*7,26,112*)
Noxiptiline		0										(*3,41*)
Perhexiline		+										(*123*)
Phentermine		0									A	(*145,248*)
Quinacrine									+			(*245*)
RMI 10.393		+										(*11*)
Thioridazine		0										(*3,41*)
Triparanol		+		+			+	+				(*7,9,26*)
Zimelidine		+						+				(*243*)

[a]Legend: +, present; 0, absent; A, induces pulmonary hypertension in man (*206*); B, induces cytochrome P-450 (*221*); C, metabolized in lung (*221*).

trated by interstitial macrophages (*14*). The lungs of chlorphentermine-treated rats show hyperemia, aggregation of leucocytes in venules and perivascular infiltration by monocytes during the first week of treatment (*4*). In general, a few intra-alveolar macrophages appear early and become progressively larger, binucleated, and more numerous (*5,7,10,15*). These macrophages are derived from interstitial macrophages (*10,16*), which in turn originate from blood monocytes (*4,17*). In histological sections the alveolar lumina contain abundant amorphous material. On ultrastructural examination the material is identified as secretions derived from secretory vacuoles of granular pneumocytes (Figs. 2 and 3). It has been shown (*7,18,19*) that the intra-alveolar macrophages phagocytize the secretions, which are rich in dipalmitoyllecithin (*9*), and become foam cells (Fig. 4). After 3–6 weeks of treatment, the foam cells are numerous (*4,7,8,16*).

A marked decrease in the secretory activity of Type II pneumocytes is observed after 9 months of treatment (*20*). After 12 months of iprindole feeding, the accumulations of foam cells are replaced by pale eosinophilic granular material in the intra-alveolar spaces as a result of cellular breakdown, and the histological picture is that of alveolar proteinosis (*20*). Chronic administration of chlorphentermine and of AY-9944 will lead to similar changes (*1,21*). If the administration of the drug is withdrawn after several weeks of treatment, the size, the number of foam cells, the ultrastructure and enzyme activities will normalize in 2–5 weeks (*7,10,22–24*). During this process the secretions in phagosomes of macrophages are replaced by electron dense heterogeneous material (*7*). The current knowledge of the alveolar macrophage in drug-induced lipidoses has been reviewed by Reasor (*23*).

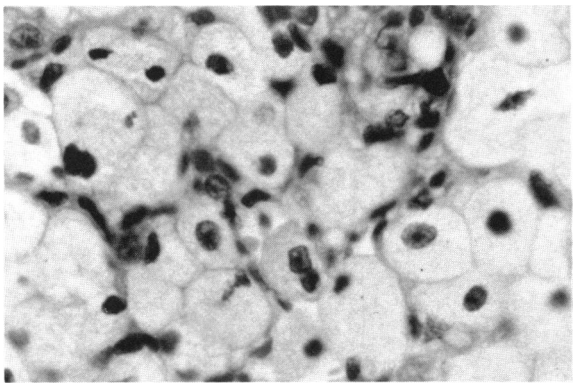

FIGURE 1. Densely packed foam cells in alveolar lumina of a rat fed chlorcyclizine. Hematoxylin-eosin, ×590.

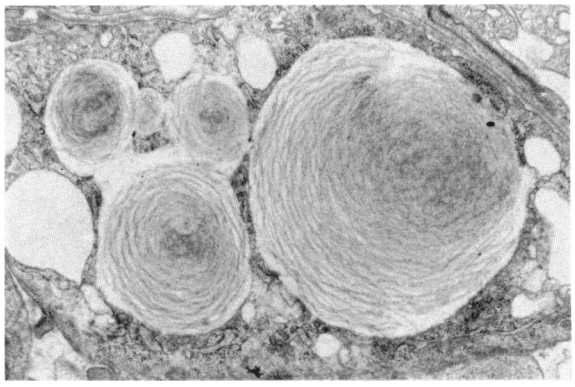

FIGURE 3. Secretion of a granular pneumocyte from a rat treated with chlorcyclizine (*302*). ×5600.

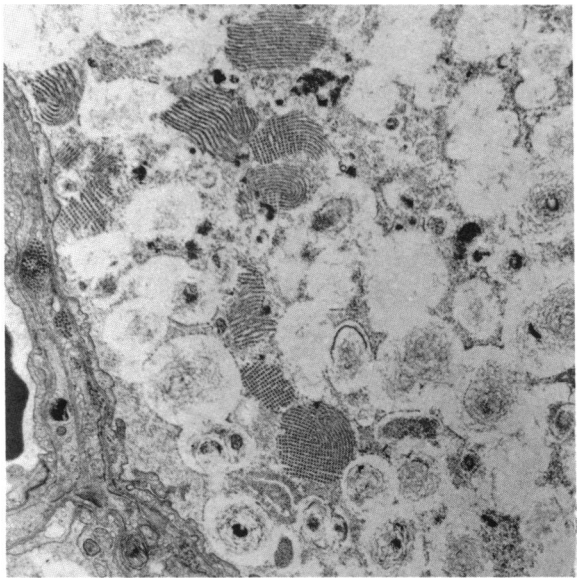

FIGURE 2. Portion of an alveolus filled with concentric and tubular secretions from a rat treated with chlorcyclizine. ×6900.

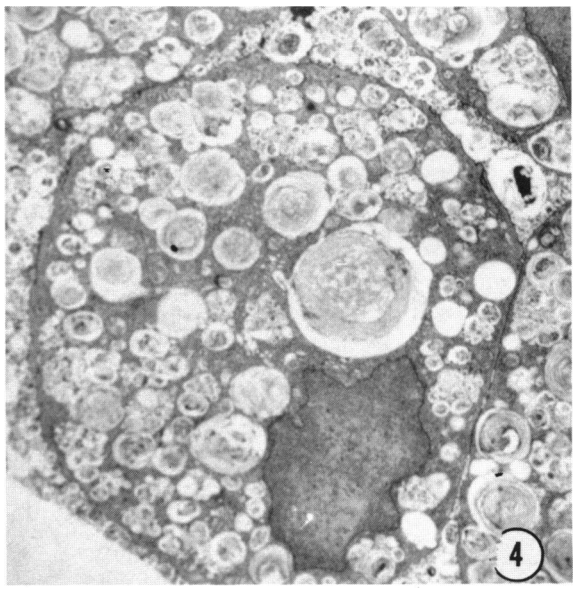

FIGURE 4. Foamy alveolar macrophage with phagocytized secretions from a rat treated wtih chlorcyclizine. ×4000.

Myelinoid Bodies

Several pulmonary cells show striking changes following treatment with amphiphilic drugs (AP drugs). Type II pneumocytes become hypertrophic and hyperplastic after triparanol and chlorcyclizine treatment (*7,8*) but do not show changes after chlorphentermine treatment (*10*). The secretory vacuoles of Type II pneumocytes become enlarged (*7,14*). Myelinoid bodies (*25,26*) and heterogeneous dense bodies appear in the cytoplasm of Type I pneumocytes (Fig. 5), ciliated bronchiolar epithelia and Clara cells, smooth muscle cells, fibroblasts and capillary endothelia (Table 1).

Drug-induced myelinoid bodies (DIM bodies) are secondary lysosomes containing lamellar, reticular or crystalloid material (Figs. 6 and 7). The lamellae form concentric layers with a 40 to 45 A periodicity (*27*). Reticular or crystalloid myelinoid bodies are found in various pulmonary cells, but not in pulmonary macrophages (*90*). Heterogeneous dense bodies are secondary lysosomes filled with heterogeneous material.

Myelinoid bodies have received a variety of names. The original term myeloid body (*25,26,28*) should be, in the opinion of Ghadially (*29*), replaced by the more appropriate term myelinoid body. Other investigators prefer to use terms such as body, inclusion or lysosome preceded by adjectives such as lamellar, lamellate, multilamellate, honeycomblike and membranous. Names which do not differentiate between membrane-bound myelinoid bodies and myelin figures without limiting membranes should be avoided.

The drugs which induce accumulations of pulmonary

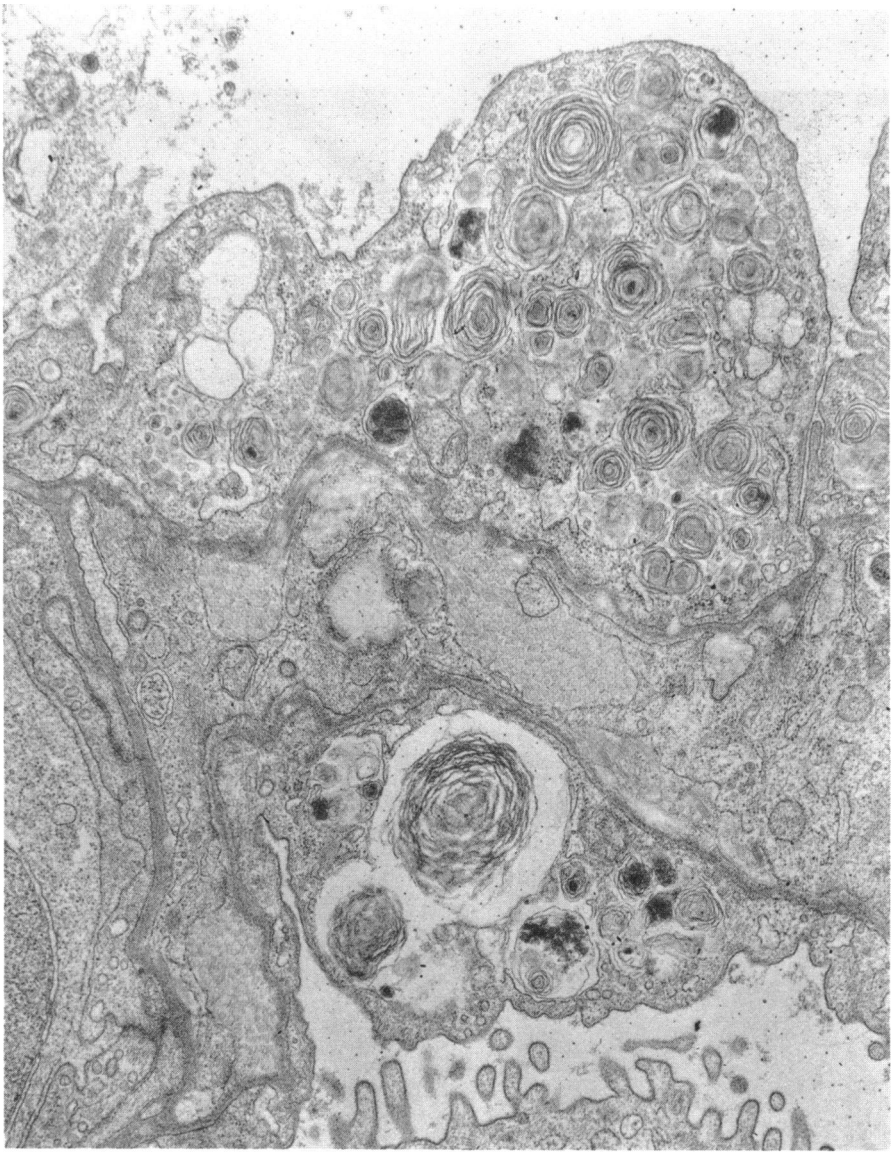

FIGURE 5. Type I pneumocytes from a rat fed chlorcyclizine for 5 weeks. The upper cell contains numerous myelinoid bodies. The lower cell contains heterogeneous dense bodies and material resembling alveolar secretions. ×15,600.

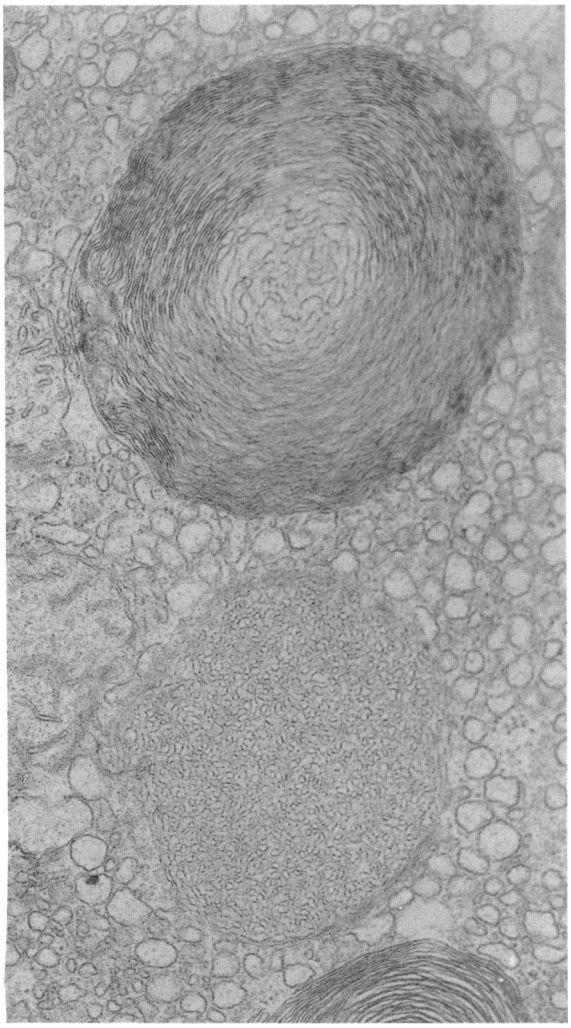

FIGURE 6. Myelinoid bodies induced in a rat hepatocyte by chlorcyclizine. The upper body is of the reticular type, the lower body is of the mixed type. ×23,400.

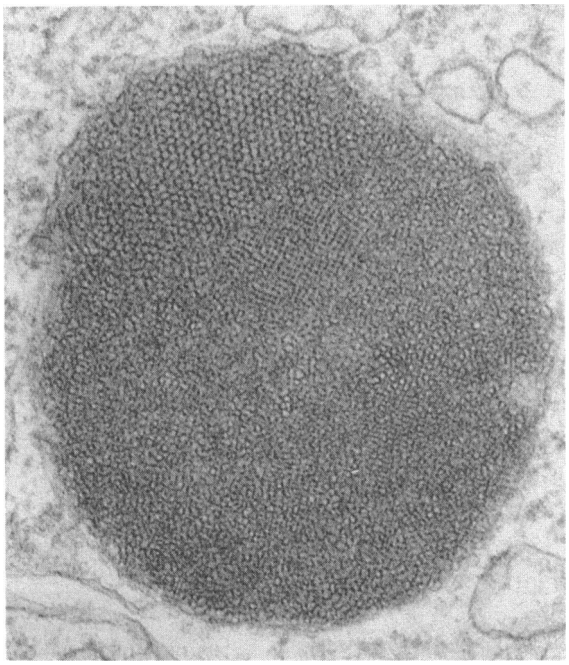

FIGURE 7. Crystalloid type of a myelinoid body from the corpus luteum of a chlorcyclizine-treated rat. ×22,400.

foam cells also induce the formation of myelinoid bodies in many other cell types of extrapulmonary tissues (Fig. 8) both *in vivo* (Table 2) and *in vitro* (Table 3). High doses of chlorphentermine, chloramitryptiline, RM1 10.393, and erythromycin induce formation of foam cells at extrapulmonary sites particularly in lymph nodes, spleen and thymus (*11,30*). Patients treated with diethylaminoethoxyhexestrol (DEAEH) have foamy cells with deep blue granules in their bone marrow (*31,32*), spleen and lymph nodes (*33*). Foam cells do not, however, appear in similarly treated rats (*34*).

Because the inclusions in foam cells and the DIM-bodies are modified lysosomes, knowledge of lysosome formation by heterophagy and by autophagy is necessary to understand their nature (*26,35*). In autophagy, sequestering cisternae surround a portion of the cytoplasm containing organelles and form an autophagic vacuole. The thin membranes of the sequestering cisterna are then transformed into a thick limiting membrane of the lysosome. Hydrolytic enzymes formed in endoplasmic reticulum are brought to the autophagic vacuole within primary lysosomes. The sequestered organelles are broken down by the hydrolytic enzymes and the autophagic vacuole changes into a heterogeneous dense body (secondary lysosome). Further digestion leads to the appearance of smaller homogeneous bodies (residual bodies). In heterophagy, the extracellular material enters the cell within pinocytotic vesicles and phagocytic vacuoles. Primary lysosomes empty their enzymes into this vacuole, and the digestion proceeds as in autophagy.

If the degradation of substrates sequestered within lysosomes is impaired, the substrates will accumulate, and the lysosomes will become storage bodies. Lysosomal digestion may be impaired by several mechanisms (*36,37*). For example, each of the human storage diseases is caused by the absence of a specific lysosomal enzyme. Myelinoid bodies are storage bodies containing lipids of membranes whose digestion is impaired by drugs (*18*). The inclusions in foam cells are phagosomes containing phagocytized pulmonary secretions whose digestion is impaired by drugs.

The inclusions in foam cells (Fig. 4) and the DIM bodies (Fig. 6) should be differentiated from secretory granules of Type II pneumocytes (*38*) (Fig. 3). All three structures are limited by a 90 Å thick membrane and contain lamellar material. The lamellae within phagosomes of pulmonary macrophages are less densely packed and less orderly arranged than those of DIM bodies. Tangential cuts through myelinoid bodies can obscure the outlines of the limiting membrane, leading

Table 2. Inducers of myelinoid bodies *in vivo*.[a]

Drugs and chemicals: name, generic (brand)[b]	Therapeutic use[c]	Amphiphilic molecule	Myelinoid bodies *in vitro*	Myelinoid bodies in animal	Myelinoid bodies in man	Adverse effects in man	Alveolar foam cells[d]	Liver	Kidney	Central NS[e]	Peripheral NS[e]	Pigment epithelium, retina[f]	Muller cells[f]	Neurons of retina[f]	Visual cells[f]	Lens[g]	Cornea[h]	Lymphatic system[i]	Blood[j]	Striated muscle[k]	Adrenal	Testis	Fetus	Malformation, abortion	References
(2-*N*-Methylpiperazinomethyl-1,3-diazofluoro-anthen-1-oxide (AC-3579)	X	+		+				+																	(*60,62*)
Amiodarone (Cordarone)	E	+		++	+	+	+	±		0	+	++	0	+	0	+	+	+		+	+				(*243,252*)
Amitriptyline (Elavil)	H	+	+	±			0	0		0								+							(*3*)
1-Chloroamitriptyline, R044318	H	+	+	++			+	+		+	+	++		+				+		+					(*132,83,84,142*)
1-Chloro-10,11-dehydroamitriptyline	H	+		+			+	+										+							(*3*)
trans-1,4-bis(2-Chlorobenzylaminoethyl)-cyclohexane (AY 9944)	T	+	+	++			+			±	+	+		+							+	+	+		(*8,77,144,267*)
Azacosterol: 20,25 diazacholesterol	T	+		++						±	+										+	+			(*77,253*)
Bilirubin		0	+	+		+				+															(*254,255*)
Boxidine	T	+					++	0																	(*7*)
Chloroquine (Aralen)	M	+	+	++	++	+	+	+	+	±	+	+	++	++	+	+	+	+	+	+		+	+		(*6,7,26,58,202,268,269*)
Chlorphentermine (Pre-sate)	C	+	+	++			+	+	+	+	+	++		+		+	+	+	+	+	+	+	+		(*10,13,41,132*)
Phentermine (Phentermine)	C	+	+				0													0					(*145,256*)
Chlorpromazine (Thorazine)	V	+	+	+		+	0	0									+	±		0					(*8,188,270*)
Clindamycin (Cleocin)	F	0		+				+																	(*212,30*)
Cloforex	C			+			+												+						(*17*)
Clomipramine (Anafranil)	H	+		++			+	+		±	+	+		+				+							(*3,41*)
Clozapine	VX	+		+				+										+			+				(*257*)
Cyanochlorophenylamidinourea	M	+		±																					(*41*)
Cyclizine (Marezine)	JLT	+		+			+	+																+	(*86,7*)
Chlorcyclizine (Fedrazil)	LT	+		++			++	+				++	+	++	0	+				+	+	+	+	++	(*7,26,271*)
Homochlorcyclizine	LTY	+		++			++	+																	(*7,97*)
Hydroxizine (Atarax)	TX	+		+			+	+																+	(*7*)
Meclizine (Bonine)	JL	+		+			+	+															0	+	(*7*)
Norchlorcyclizine	T	+		++			++	+																+	(*7*)
4,4′-Diethylaminoethoxyhexestrol	E	+	+	++	++	+	+	+	+	0		+		++				+	+	+			+		(*28,31,33,34,96,103,205*)
Erythromycin (Ilotycin)	F	0		+			+	+										+							(*212,30*)
Ethyl fluclozepate	H	0		+			+																		(*247*)
Fenfluramine (Pondimin)	C	+		+			+	+										+	+		+				(*41*)
Fluoxetine, [*N*-methyl-3-phenyl(α,α,α-trifluororo-*p*-tolyl)oxypropylamine hydrochloride]	Y		+				+														+				(*24*)
Gentamycin (Garamycin)	F	0	+	+	+	+			+																(*92,183,210,272*)
Haloperipol (Haldol)	OX	+					+	0																	(*7*)
6-Hydroxydopamine,5-hydroxydopamine		0	+	+																	+	+			(*211*)
IA3, 8-chloro-5-methyl-2-[2-(diethylamino)-ethyl]-2H-(1)benzothiopyranone[4,3,2-c,d]indazole	W	+		+				+										+			+				(*257*)
Imipramine (Tofranil)	H	+		++			+	+				+		+				+		+					(*3,41*)
Indoramine	A	+		+				+																	(*257*)
Iprindole (Prondol)	H	+	+	++			+	+		+	+	++		+		+		+	+	+					(*3,14,16,20*)
Maprotiline (Ludiomil)	H	+		+			+	+																	(*101,102*)
Nortriptyline (Aventyl)	H	+	+	+																					(*258*)

Table 2. Inducers of myeloid bodies *in vivo*.[a] (continued)

Drugs and chemicals: name, generic (brand)[b]	Therapeutic use[c]	Amphiphilic molecule	Myelinoid bodies *in vitro*	Myelinoid bodies in animal	Myelinoid bodies in man	Adverse effects in man	Alveolar foam cells[d]	Liver	Kidney	Central NS[e]	Peripheral NS[e]	Pigment epithelium, retina[f]	Muller cells[f]	Neurons of retina[f]	Visual cells[f]	Lens[g]	Cornea[h]	Lymphatic system[i]	Blood[j]	Striated muscle[k]	Adrenal	Testis	Fetus	Malformation, abortion	References
Noxiptiline (Agedal)	H	+	+	±			0	0		0								±							(*222*)
Paraquat	S	0		+					+																(*185*)
Perhexiline (Pexid)	ET	+	+	++	++	+	+	±		±	+	++		+				±	±	+	+				(*40,61,73,87,123–125, 273–275*)
Phenacetin, Acetophenetidine	B	0		+																					(*42*)
Prenylamine	E	+		±				±																	(*97*)
Quinacrine	M	+		++			+	+									+			+					(*87,259,12*)
R-800, *cis*-7-fluoro-1-phenyl-3-isochroman-methylamine	C	+		++																					(*27*)
RMI 10.393, 5-[*p*-(fluoren-9-ylidenemethyl)-phenyl]-2-piperidineethanol	G	+		+			+											+							(*132,84*)
SKF 14336-D, 9-(3-dimethylaminopropyl)-2-chloroacridane	X	+		+															+						(*260*)
Tamoxifen (Nolvadex)	K	+		++			+			+		+		+					+		+				(*41,303*)
Thioridazine (Mellaril)	VX	+		±		+	0	0				+						+							(*222*)
Tilorone	F	+		+	+			+	+					+			+		+						(*175,261,262,304*)
Triparanol (MER-29)	T	+	+	++		+	++	+	±	+	+	++	+	0	0					+	+	+		+	(*25,35,77,78,276–279*)
Zimelidine	H	+		++			+	±		±	±	+	0	0	0			+			+				(*243,22*)

[a] Legend: +, present; ++, abundant; ±, infrequent; 0, absent.
[b] Additional brand names are found in The Merck Index.
[c] Uses: A, adrenergic blocker, sympathicolytic; B, analgesic; C, anorectic; D, antagonist of serotonin; E, antianginal; F, antibacterial, antiviral; G, anticlotting; H, antidepressant; I, antidote; J, antiemetic, antinauseant; K, antestrogenic; L, antihistaminic; M, antimalarial, antihelmintic; N, antipruritic; O, antipsychotic; P, dye; Q, estrogenic; R, gonadal stimulating, ovulatory; S, herbicide; T, hypocholesterolemic; U, myocardial depressant; V, neuroleptic; W, schistosomicide; X, sedative, tranquilizer; Y, serotonin antagonist; Z, suppressant of lupus erythematosus, antirheumatic.
[d] See Table 1.
[e] Ref. (*263*).
[f] Refs. (*126,178,216,264*).
[g] Refs. (*39,201*).
[h] Ref. (*121*).
[i] Ref. (*41*).
[j] Refs. (*32,41,99,265*).
[k] Ref. (*266*).

Table 3. Inducers of myelinoid bodies *in vitro* systems.[a]

Drugs and chemicals: name, generic (brand)[b]	Therapeutic use[c]	Amphiphilic molecule	Culture of nervous tissue	Culture of macrophages	Culture of other cells	Other systems	References
Acridine orange					+		(*280*)
1-Amino-4-octylpiperazine, AP22	F	+	+				(*281*)
1,7-bis(*p*-Aminophenoxy)heptane, 153C51	W	+				[d,e]	(*282,108*)
Amitriptyline	H	+		+			(*283*)
AY 9944	T	+	+				(*215*)
Benzylidine-1-aminopiperazine, AP8	F	+	+				(*281*)
Bilirubin		0	+				(*284,285*)
Brompheniramine	L	+		+			(*257*)
Chloroquine	M	+	+	+	+	[f]	(*107,290–292*)
Chlorpheniramine (Teldrin)	L	+		+			(*257*)
Chlorpromazine (Thorazine)	V	+	+	+		[g]	(*188,283,293*)
Clociguanil	M	+			+		(*41*)
Diethylaminoethoxyhexestrol	E	+			+		(*286*)
Gentamycin	F	0			+		(*210*)
6-Hydroxydopamine		0			+		(*211*)
Lysergide	HXY	+	+				(*172*)
Mesoridazine (Serentil)	OX	+	+				(*258*)
Mianserine (Tolvin)	LNY	+			+		(*257*)
Myoinositol		0	+				(*287*)
Nortriptyline	H	+	+				(*258*)
Perhexiline	ET	+	+		+		(*73,294,295*)
Pheniramine	L	+		+			(*257*)
Phentermine	C	+		+			(*283*)
Promethazine (Phenergan)	JL	+	+				(*288*)
Trifluperazine (Stelazine)	OX	+	+				(*288*)
Trimeprazine (Temaril)	LN	+	+				(*288*)
Triparanol (MER-29)	T	+			+		(*100*)
Tunicamycin	F				+		(*289*)

[a] Legend: +, present; 0, absent.
[b] Additional brand names are found in The Merck Index.
[c] See Table 2.
[d] Schistosomes contain myelinoid bodies.
[e] Retinotoxic.
[f] Lysosomes of malarial parasites altered, no myelinoid bodies.
[g] In perfused rat liver.

to the misinterpretation that they are lacking a limiting membrane (*39–42*).

Drug-induced myelinoid bodies should be clearly differentiated from other cellular structures containing concentrically arranged lamellae (*26*). Structures simulating DIM bodies can be grouped into categories of cytoplasmic organelles, secretory granules (*43,44*), pigmented granules of neurons (*45*), storage granules (*46*), autophagic vacuoles in cells rich in phospholipids (*47*), phagocytic vacuoles oversupplied with phospholipids (*42*), and secondary lysosomes with a slow phospholipid breakdown (*48,49*). The term myelinoid bodies should not be applied to secondary lysosomes or vacuoles containing a few membrane fragments or an occasional myelin figure.

DIM bodies show a superficial resemblance to smooth fingerprints (*50,51*) and to whorls formed by smooth portions of rough cisternae (*52*), both of which may be also induced by amphiphilic drugs. Myelinoid bodies should be distinguished from myelin figures lying free in the cytoplasm or on the surface of organelles (*26,53*). Myelin figures represent bilayered lamellae of amphiphilic lipids which may arise from altered cellular membranes, in neutral lipids during lipolysis (*54,55*) or from altered myelin (*56*). Most often they are artifacts seen in tissue fixed in aldehydes followed by osmium tetroxide (*57*). Extracellular and intraluminal myelin figures may represent extruded contents of myelinoid bodies (Fig. 8) (*42,58,59*).

Biochemical Studies

Since the establishment of the lipid nature of the material stored within the foam cells and within myelinoid bodies, various investigators have analyzed the biochemical composition of organs (*60–62*), tumor cells (*63*), isolated alveolar macrophages and isolated DIM bodies derived from animals and people treated with amphiphilic drugs (AP drugs). As reviewed by Lüllmann-Rauch (*41*), the tissues show a marked increase of total phospholipids (PLs) and variable increases of cholesterol, triglycerides and gangliosides. The absolute increase in PLs is usually due to an increase of phosphatidylcholine and in decreasing per-

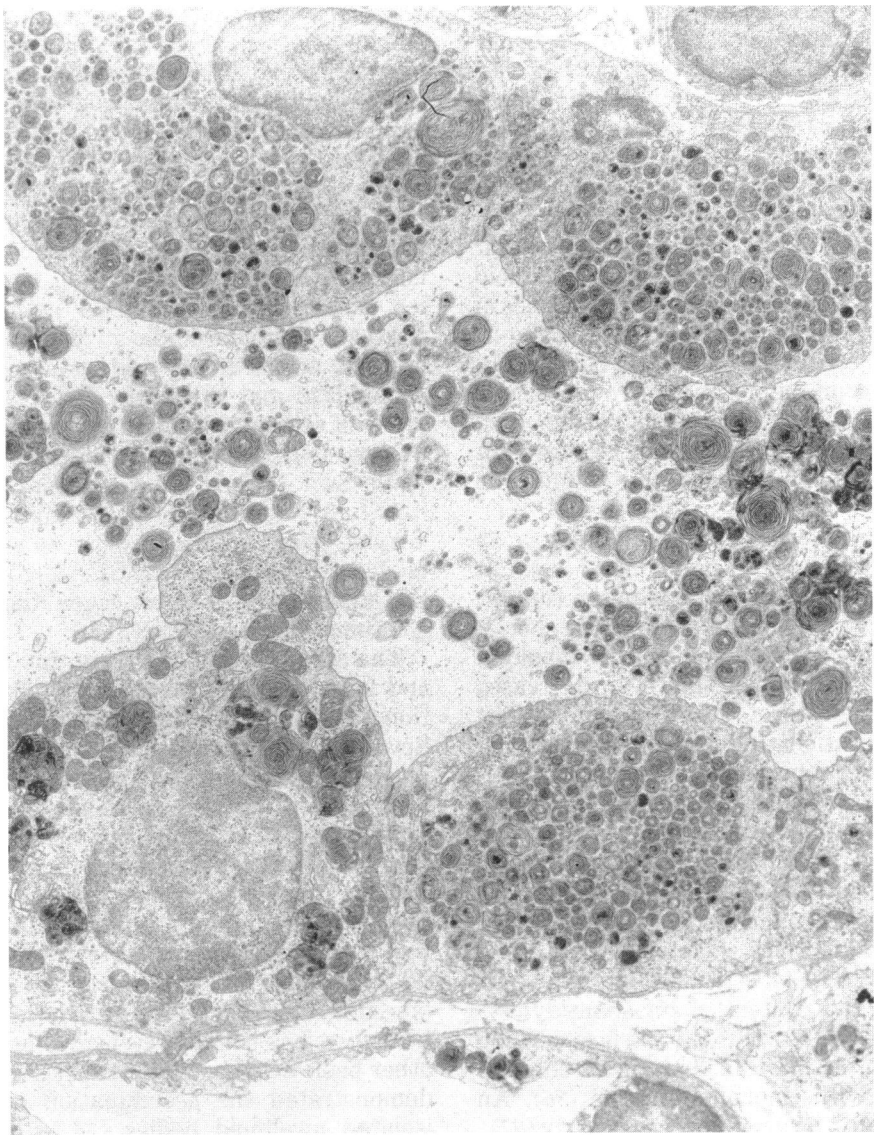

FIGURE 8. Renal collecting tubule from a rat treated with chloroquine for 6 weeks. The cells contain numerous myelinoid bodies. The lumen contains cellular debris with numerous myelinoid bodies and a few mitochondria derived from ruptured proximal cells. ×4,000.

centages to phosphatidylinositol, phosphatidylethanolamine, bis(monoacylglycero)phosphate (BMGP), sphingomyelin and phosphatidylserine.

Chloroquine and DEAEH increase the incorporation of glycerol into lysosomal phospholipids, but decrease its incorporation into microsomal phospholipids. These drugs greatly increase the synthesis of phosphatidylglycerol in rat liver (*64*). Homochlorcyclizine induces accumulation of glycolipids, phosphatidylcholine and BMGP in the liver (*65*). The chlorphentermine-induced accumulation of glycoproteins and mucopolysaccharides in culture of intestinal cells is interpreted to be the consequence of crinophagy rather than endocytosis (*66*).

Excessive storage of gangliosides is demonstrable in miniature pigs treated with chloroquine. In the brain, GM_2 ganglioside increases while phospholipids and cholesterol are unchanged (*67*). Skeletal muscle GM_2 ganglioside increases 100-fold, BMGP 50-fold and phospholipids 3-fold (*68*). Liver, spleen and lungs show a marked increase of glucosylceramide, GM_2 ganglioside and BMGP (*69*). Chlorphentermine induces a 14% increase of GM_1 ganglioside in rat brain (*70*). The incorporation of phosphorus into phosphatidylcholine is reduced and into phosphatidic acid increased by several amphiphilic drugs studied in cerebral cortex mince (*71*). Perhexiline induces the accumulation of gangliosides in human liver (*72*) and peripheral nerve (*73*) as well as that of GM_3 ganglioside in cultured fibroblasts (*74*).

The composition of DIM bodies and of tissues containing these bodies depends on the type of tissue examined, the animal species, diet (*75*), duration of treatment and

the type of the drug. The excess of hepatic phospholipids can be explained by the increase of PLs in myelinoid bodies alone (*76*). Several investigators studied the composition of cellular fractions rich in DIM bodies (*33,77,78*). The composition of smooth microsomal membranes from livers of rats treated with AC 3579 for 4 days is altered. The phospholipid/protein ratio is markedly increased while the cholesterol/phospholipid ratio is decreased. The isolated DIM bodies have a similar composition, suggesting that the content of myelinoid bodies could be derived from sequestered membranes of smooth endoplasmic reticulum. The labeled drug is found to be selectively concentrated in DIM bodies (*79*). The effect of this drug on membrane microviscosity is cholesterol-like (*80*). The low cholesterol/phospholipid ratio in DIM bodies could be the result of replacement of free cholesterol in membranes by the amphiphilic drugs (*76*).

Biochemical studies performed on whole lungs or on isolated alveolar macrophages obtained from animals treated with AP drugs reveal alterations in the content and composition of lipids. Cloforex increases the cholesterol content of rat lung by 50% and the phospholipid content five times (*5*). Perhexiline, however, decreases the concentration of cholesterol, PLs and gangliosides in rat lungs (*61*). Alterations induced in the lungs by chlorphentermine were reported by several investigators. Seiler and Wasserman (*81*) demonstrated a marked increase of phosphatidylcholine, and an increase in sphingomyelin, free cholesterol and cholesterol ester. Other investigators observed an increase in total PLs, phosphatidylcholine, phosphatidylinositol, phosphatidylglycerol, sphingomyelin, free cholesterol and triglycerides (*11,82–84*). The fatty acids of phospholipids were more saturated, the content of phosphatidylethanolamine was decreased (*82*) and the surface tension forces were reduced (*85*). RMI 10.393 produces changes similar to those seen with chlorphentermine (*86*). An increase of PLs in the lung lavage fluid occurs early (*87*).

The alveolar macrophages of rats treated with chlorphentermine and RMI 10.393 show an increase in total PLs, phosphatidylcholine, phosphatidylinositol, phosphatidylglycerol, phosphatidic acid, sphingomyelin and free cholesterol (*11,83,84,88,89*). 1-Chloramitryptiline, on the other hand, leads to a slight accumulation of lecithin and of phosphatidic acid in the lung, while the foam cells accumulate cholesterol, cholesterol esters and free fatty acids. The authors conclude that chlorphentermine and RMI 10.393 impair secretory capacity of pneumocytes, while chloramitryptiline does not. The alveolar macrophages induced by chlorphentermine show an increased lipid peroxidation, probably occurring within lysosomes, as well as augmented antioxidant defense mechanisms (*54,90*).

A marked increase of the levels of total PLs, total sterols, BMGP and desmosterol is demonstrable in the lamellar body fraction isolated from lungs of rats treated with DEAEH (*33*). Desmosterol is also found in fractions containing myelinoid bodies induced by inhibitors of cholesterol synthesis (*91,92*).

Tissues of animals and patients treated with various amphiphilic drugs contain an unusual phospholipid, bis(monoacylglycero)phosphate, or BMGP (*33,93–97*). It forms a much greater proportion of phospholipids in human tissues than in tissues of animals (*41,96*), probably because of a difference in drug metabolism (*98*).

The presence of lysosomal enzymes within DIM bodies in cells of different organs and species, after the administration of various AP drugs, has been repeatedly demonstrated (*25,32,41,99–102*). Quantitative studies usually reveal increased activities of acid phosphatase, β-glucuronidase, β-galactosidase, and decreased activities of acid esterase, β-*N*-acetylglucosaminidase and cathepsin D (*62,72,88,103–108*). The levels of several lysosomal enzymes (particularly that of β-*N*-acetylglucosaminidase) of foam cells are increased, while acid esterase and α-manosidase are decreased (*23,88,109,110*). Chlorcyclizine inhibits the supernatant enzyme steryl ester hydrolase *in vitro* (*111*). Myelinoid bodies of chloroquine and DEAEH-treated rats accumulate cholesterol ester because these drugs block its lysosomal degradation (*76*).

The accumulation of PLs within tissues, DIM bodies and foam cells has been correlated with the accumulation of amphiphilic drugs and of their metabolites. Several AP drugs and/or their metabolites are localized mostly in the lung and spleen, and moderately in the liver, kidney, heart, muscle, adrenals and fat (*112–116*). The number of DIM bodies appears to be related to the concentration of the drug in a tissue. Correlation between the concentration of acidic PLs and accumulation of the drug and its metabolites suggesting formation of a stable complex is reported by Matsuzawa et al. (*98,117*) in livers of patients treated with DEAEH. The binding of chlorphentermine to phospholipid-rich subcellular fractions is inhibited by desmethylimipramine and other basic amines (*118*) (Table 1). Several investigators demonstrated the accumulation of AP drugs within isolated myelinoid bodies (*76,78,119*). In addition to their accumulation within DIM bodies, some AP drugs form reversible complexes with phospholipids of the smooth endoplasmic reticulum (*120*). Such binding may decrease the activity of microsomal enzymes.

Preferential Organ Involvement

The number of DIM bodies in a tissue will depend on the speed with which a given AP drug is metabolized, the duration of treatment and the dosage of the drug (*121*). Potent AP drugs can induce DIM bodies in all tissues, but the quantity of DIM bodies will depend on the cell type. Weak AP drugs induce DIM bodies in a few cell types only, which usually include the lymphocytes. The sensitivity of lymphocytes may be related to the rapid turnover of glycerolipids in these cells (*122*). Perhexiline exemplifies a drug which induces DIM bodies in an unusual distribution pattern: Myelinoid bodies are commonly found in the retina, dorsal root ganglia, adrenal gland and muscle cells of the rat, while they are few in the hepatocytes and lymphocytes, and

foam cells in the lung are scarce (*123*). The same drug is, however, associated with the cirrhosis of the liver in man (*124,125*).

The difference in the amounts of DIM bodies in specific organs after treatment with individual AP drugs is probably related to the lipid composition of the tissue, binding of the drug by the tissue, metabolism and excretion of the drug. Certain cell types may contain specific phospholipids for which certain AP drugs have selective affinities. Thus the absence or presence of a specific phospholipid may decide whether an AP drug will induce myelinoid bodies in one or another cell type in a given tissue, such as a neuron or pigment epithelium of the retina (*126*). The binding of AP drugs to liposomes made of different lipids occurs in this increasing order: sphingomyelin and phosphatidylcholine, phosphatidylethanolamine, and phosphatidylserine (*127*). The divalent chloroquine has a very high affinity for phosphatidylserine and gangliosides which may explain its tendency to affect ganglionic cells. The positively charged adriamycin shows a high affinity for cardiolipin, which may be related to its selective toxicity for mitochondria (*128*) and its failure to induce typical myelinoid bodies.

The involvement of the central nervous system depends on the efficiency of the blood-brain barrier (*87,129*). The accumulation of AP bodies in liver cells may be facilitated by a slow metabolic inactivation of the drug, fast metabolism of the drug into an active metabolite and/or by passage of the drug through the hepatocytes during excretion of the drug in bile. Several AP drugs are excreted as bile salt-lecithin-drug micelles (*130*). The lungs also contain drug-metabolizing enzymes (*131,132*).

Uptake of Amphiphilic Drugs by the Lungs

The uptake of AP drugs has been studied in isolated perfused lungs of rabbits and rats. The accumulation has a saturable component and a linear nonsaturable component. The saturable component is attributed to specific binding sites or to a carrier-mediated transport. The linear component is attributed to diffusion to intracellular and extracellular fluid and to nonspecific binding to cellular components. The uptake of the drug is directly related to the degree of protonation of the nitrogen atom and the accumulation is reversible (*133*). Minchin et al. (*134*) suggested that the transport saturability could be explained either as a carrier-mediated transport or as an alteration of diffusion because of drug-induced changes in the fluid state of membranes. Uptake of chlorphentermine is a Na^+-dependent, carrier-mediated transport process (*133*). Methadone forms a slowly effluxable pool in the lung comparable to chlorphentermine and may be expected to induce phospholipidosis (*135*). The uptake of chloroquine by pancreatic islets requires neither energy-dependent active transport nor pinocytosis (*136*). Lungs of chlorphentermine-pretreated rats accumulate chlorphentermine more rapidly than control lungs (*137*).

Pathogenesis

The storing of phospholipids and of amphiphilic drugs in both myelinoid bodies and vacuoles of alveolar foam cells suggests that the pathogenesis of both lesions is similar. The two main factors which should be considered in the pathogenesis of phospholipid accumulation within myelinoid bodies are: an increased supply of PLs to secondary lysosome through membrane or product flow (*33*) and a decreased removal or catabolism of the contents of secondary lysosomes. Decreased catabolism of lysosomal contents could be associated with formation of cholesterol precursors (*1,7,8,28,77,78*), inhibition of the fusion between primary and secondary lysosomes (*58*), direct inactivation of certain lysosomal enzymes (*10,28,33,121*) and formation of drug–lipid complexes with altered physicochemical properties (*7,9,10,28,81*).

The factors to be considered in the pathogenesis of the accumulation of phospholipids within intra-alveolar foam cells are similar to those just listed. The pulmonary PLs are found in the pulmonary surfactant. Accumulation of foam cells could result from an increased production of the surfactant, decreased catabolism of the surfactant within pulmonary macrophages or decreased removal of the macrophages from the lungs (*8,20,26*). The pulmonary surfactant has been shown to be synthesized in Type II pneumocytes (*138,139*). It is catabolized in alveolar macrophages (*140*) and in Type I and II pneumocytes (*141*). The phospholipids of the surfactant contain about 76% of lecithin (particularly dipalmitoylphosphatidylcholine), and 11% of phosphatidylglycerol. Lamellar inclusion bodies of Type II pneumocytes have a similar composition. Studies on the incorporation of labeled palmitic acid into pulmonary PLs showed that phospholipid storage after chlorphentermine and RMI 10.393 is the result of decreased degradation, while the slight storage of PLs induced by chloramitriptyline is the result of marked increase of synthesis in spite of an increased degradation of PLs (*142*).

Fetal lungs of animals treated with AP drugs contain alveolar macrophages (*143*) or show hyperplasia of Type II pneumocytes (*144*). The neonatal lung is, however, less susceptible to chlorphentermine-induced alveolar foam cell formation than is the lung of adult rats (*11,23,145,146*).

Drug–Lipid Interactions

The majority of drugs which induce pulmonary intra-alveolar histiocytosis and generalized formation of myelinoid bodies (generalized lipidosis) are cationic amphiphilic compounds. They contain a hydrophobic region and a primary or substituted amine group which can bear a net positive charge. Such compounds interact with anionic groups of acidic phospholipids (such as phosphatidate, phosphatidylinositol, phosphatidylserine) of membranes. The hydrophobic regions of the drugs partition into the membrane. The interaction leads to neutralization of the charges on the phosphate

groups and to the expulsion of the tightly bound divalent cations such as calcium. All this leads to changes in the movement, fusion, permeability, transport and receptor functions of membranes (*147–150*). The interaction between various AP drugs and phospholipids was demonstrated by means of nuclear magnetic resonance (*151,152*).

Several authors (*41,121*) have pointed out that the AP drugs exist in a protonized and in a nonprotonized form. The nonprotonized forms permeate through the plasma membrane and through lysosomal membranes. The protonized forms are bound to plasma membrane, membranes of endoplasmic reticulum and other cytomembranes. Nonprotonized molecules enter the lysosomes, where they are protonized because of the strongly acid milieu, increase intralysosomal pH, form complexes with polar lipids of lysosomal contents and are thus trapped within the lysosomes (*41,121,153*).

The administration of several cationic AP drugs leads to quantitative alterations of phospholipids in various tissues (*84,96,97,122,154–156*). In general, the tissues and lysosomes will contain increased proportions of anionic phospholipids (phosphatidate, phosphatidylinositol, phosphatidylglycerol, lysobisphosphate) and decreased proportions of triglycerides, and of cationic phospholipids phosphatidylcholine and phosphatidylethanolamine (*157*). The quantitative changes in PLs and the hypotriglyceridemic effects can be explained as the result of the observed inhibition of the enzymes phosphatidate phosphohydrolase (*91,122,147,158*) and phospholipase, and stimulation of phosphatidate cytidylyltransferase (*159*) resulting in diversion of phospholipid synthesis from one to another pathway (*147, 149*).

The accumulation of phospholipids (PLs) within lysosomes can be explained as the result of impaired degradation of PLs by the lysosomal phospholipase (*121,122,149*). The presence of the enzyme phospholipase A has been demonstrated in the plasma membrane, and in microsomal and lysosomal fractions (*160*). The lysosomal phospholipase cleaves both fatty acid ester linkages of lecithin and of phosphatidylethanolamine without formation of lyso-forms (*161*). Various *in vitro* and *in vivo* studies show that the enzyme phospholipase A (which acts on the hydrophobic group of the PL) but not phospholipase C (which acts on the hydrophilic part of the PL molecule) is inhibited by several amphiphilic drugs (*91,119,120,162–164*). Following the formation of a complex between AP drugs and PLs, the hydrophilic group of the drug prevents the formation of the enzyme–substrate complex, while the hydrophobic group allows penetration of the drug into the lipid layer and determines the stability of the drug–lipid complex. Thus, e.g., the hydrophobic group of AC 3579 is larger than that of AP 22, the AC 3579–lipid complex is more stable and the enzyme inactivation is more complete than are those of AP 22 (*91*). Both lysosomal phospholipases have been found inhibited by chloroquine, DEAEH and aminoglycoside antibiotics (*165,166*). Depression of lysosomal phospholipase activities may be also due to the drug-induced increase of intralysomal pH (*153*).

The above alterations in enzymes do not explain the lysosomal accumulation of the anionic phospholipid bis(monoacylglycero)phosphate (BMGP) also called lysobisphosphatidic acid. BMGP contains very high amounts of polyenoic fatty acids, particularly docasahexaenoic acid (*167,168*). It is synthesized in lysosomes (*169,170*) by the BMGP synthetase by transfer of acyl groups from phosphatidylinositol to phosphatidylglycerol or lysophosphatidylglycerol (*76*). BMGP is resistant to degradation by lysosomal hydrolases (*76*). It is a normal component of lysosomal PLs, where it may account for 6 to 28% of total PLs (*76,167,171*). Some of the lysosomal BMGP could have its origin in the plasma membrane (*167*).

The lipid composition of myelinoid bodies and consequently also that of tissues is thus determined in part by the type of lipid reaching the lysosomes either by heterophagy or by autophagy. The formation of myelinoid bodies induced by lysergide has been attributed to increased endocytosis (*172*) which supplies lipids of plasma membrane to lysosomes. Autophagy of normal (*173*) or hyperplastic smooth endoplasmic reticulum will supply the lysosomes with excessive lipids characteristic of this organelle. Proliferation of smooth endoplasmic reticulum (*3,26,62,120,174*) associated with enhanced drug metabolism of some AP drugs (*112,174*) has been observed. Other drugs, such as tilorone and DEAEH, are, however, known to decrease drug metabolism and phospholipid content of the microsomal fraction (*103,175*).

Structural Types of Myelinoid Bodies

Myelinoid bodies are secondary lysosomes arising from the processes of autophagy and heterophagy. Sequestered and phagocytosed proteins and carbohydrates are degraded, while certain lipids resist digestion, because they formed complexes with drugs either within the lysosomes or prior to their internalization into the lysosome. The drug–lipid complexes inside the lysosome are rearranged into lamellar, reticular or crystalloid structures to form concentric lamellar, reticular and crystalloid myelinoid bodies (*26*) (Figs. 6 and 7). Fusion of unicentric lamellar myelinoid bodies gives origin to multicentric myelinoid bodies. Myelinoid bodies containing parallel lamellae, also called "zebra bodies," are rarely induced by drugs but are common in lysosomal storage diseases (*176*). Concentric lamellae, reticular patterns and amorphous dense material may be present in the complex myelinoid body. The crystalloid myelinoid bodies contain phospholipids in regular densely spaced patterns, which are different (square, rectangular, linear, etc.) according to the plane of section (Fig. 7). They represent PLs in hexagonal phase (*177*). Their formation is favored by a high lysosomal content of phosphatidylethanolamine and of highly unsaturated fatty acids (*126,177,178*). Studies using *in vitro* models showed that the structural patterns of a

phospholipid depend on the chemical nature of the PL, the presence of fusogenic lipids, the temperature and hydration (*179,180*). Increased hydration is associated with a loose packing of lamellae.

Myelinoid bodies induced by chloroquine contain abundant clear matrix in addition to lamellae. The formation of such vacuolated myelinoid bodies has been attributed to osmotic swelling due to a rapid intralysosomal accumulation of drugs which are not easily protonized and therefore not absorbed to endoplasmic reticulum (*41*).

Myelinoid Bodies Unrelated to Cationic Amphiphilic Drugs

The epithelial cells of renal proximal tubules are known to accumulate heterogeneous dense bodies rich in myelin figures in response to a variety of stimuli which lead to an increased intake of PLs. Thus, e.g., an excessive internalization of plasma membrane is induced by resorption of proteins from the glomerular filtrate of old rats (*181*). Membranes of hemolyzed erythrocytes are incorporated by heterophagy (*42*). The strongly cationic aminoglycosides gentamycin and netilmicin bind to the brush border and are reabsorbed by endocytosis, accumulate in lysosomes, induce myelinoid bodies and accumulation of phospholipids (*182–184*). Paraquat is cationic in its dissolved form and may be similarly bound to acidic phospholipids to form renal DIM bodies (*185*). Lysosomes resembling myelinoid bodies are found in the cells of the renal papilla and inner medulla of potassium depleted rats and man (*186*) as a consequence of an inadequate intralysosomal metabolism of PLs.

Pathology

The accumulation of pulmonary foam cells and of myelinoid bodies may be associated with serious alterations of cellular functions and lead to clinical diseases. The pathological effect of AP drugs will depend on the type of cellular membranes to which the drugs are attached. Thus the formation of drug–lipid complexes in the plasma membrane may be expected to alter the membrane flow (*187*), inhibit membrane internalization (*188*) and phagocytosis (*189*). Chlorpromazine, triparanol and gentamycin inhibit ($Na^+ + K^+$) ATPase activity (*190–192*). AP drugs alter permeability of membranes (*193,194*). The properties of membranes are changed by an increase in the fluidity of the lipid (*190,195–197*). AP drugs cause transition of lipid acyl chain from organized gel to randomized liquid crystalline phase. The phase transition is associated with a lateral expansion, decrease in thickness and density of a membrane, and with altered function of membrane-bound proteins.

Attachment of the drug to endoplasmic reticulum may result in the most important functional changes (*28*). The alteration of activities of enzymes associated with membranes were discussed earlier. Presence of the un-ionized drug in the membrane may be responsible for stabilization of lysosomes and of erythrocytes (*157,198*). Additional damage to membranes will depend on the metabolism of AP drugs into either stable epoxides or less stable arene oxides (*199*). Membranes containing drug–lipid complexes are recognized by the cell as abnormal, and are sequestered by the process of autophagy leading to the formation of DIM bodies.

Small numbers of myelinoid bodies are well tolerated by the cell. Large numbers may interfere with functional associations between organelles and impair metabolic processes. Cellular death may result for several reasons. The cell may be compressed in a limited space. The available pools of phospholipids needed for cell function and survival may be exhausted (*200,201*). Finally the cell may rupture into the lumen of a hollow structure, as seen in renal tubules (Fig. 8). Presence of myelin figures in the absence of cellular organelles, however, does not indicate cell rupture, but it represents the contents of myelinoid bodies extruded from the cell (*202*).

Functional impairment of overloaded macrophages may lead to a decreased resistance to infections (*25*). On the other hand, administration of amphiphilic drugs may be beneficial in controlling infections. Isolated alveolar macrophages from animals treated with AP drugs show an enhanced phagocytic activity and are more effective in killing bacteria (*23*). Chloroquine inhibits infections by enveloped viruses by preventing their uncoating within lysosomes (*203*). Chlorpromazine and trifluoperazine kill even phagocytized protozoa (*204*).

Amphiphilic drugs are known to induce adverse side effects in man. The foam cell syndrome was known to occur in Japanese patients since 1965. Yamamoto et al. (*156*) established that the syndrome is related to the intake of diethylaminoethoxyhexestrol and reproduced it in rats by the same drug. The term "drug-induced phospholipidosis" was introduced by Shikata et al. (*205*) and was popularized by Lüllmann-Rauch (*41*). It indicates a generalized lysosomal storage of phospholipids. The drug-induced lysosomal storage differs from inborn lysosomal storage diseases (*27,67,76,101*). It has not been established whether administration of AP drugs to patients with lysosomal storage diseases will have adverse effects because of an additional increase in lysosomal volume. A patient with a subclinical enzyme deficiency may be expected to develop a clinically significant disease.

Other clinical adverse effects induced by AP drugs in man are summarized in Table 4. Some of the serious adverse effects were discovered only after the drugs were used by man. The anorectic drugs have been associated with pulmonary hypertension in patients with familial predisposition (*206*). These vascular effects are related to an altered metabolism of serotonin rather than to foam cell accumulation (*207*). Chlorphentermine was shown to decrease pulmonary clearance of 5-hydroxytryptamine (*208*). Most probably other AP drugs will have clinical side effects. It is therefore

imperative to search for the ability of each newly developed drug to induce myelinoid bodies in specific locations when given in large doses.

In animal experiments, massive accumulation of pulmonary foam cells is an excellent indicator of a drug-induced lysosomal storage. It should be remembered, however, that foam cells occur in other pathological entities (*1*) and in old normal rats (*209*). Preclinical screening of drugs in intact animals may not identify a drug as a myelinoid body inducer, if the drug is rapidly metabolized to an inactive form. This drug may, however, have adverse effects in a few patients who are unable to metabolize it. Such a drug may be recognized in *in vitro* systems. In performing *in vitro* studies, we should be aware of the fact that gentamycin used in cell cultures has been shown to be an inducer of DIM bodies (*210*). The work of Unsicker et al. (*211*) with lizards suggests, that screening methods utilizing cold-blooded animals are feasible.

Unique pharmacological properties of some AP drugs will necessitate their clinical use in spite of induction of DIM bodies. The adverse effects of such drugs will be more predictable and the clinical use will be safer provided that the principles of myelinoid body formation and degradation will be established in animal experiments. At first we need studies at cellular level on the interactions between AP drugs as well as studies on interactions of AP drugs with other drugs, food components and environmental contaminants. Only a few structural studies were reported on AP drug interactions (*212–214*). The type of dietary lipids in the food may affect the resorption, distribution, retention and metabolism of AP drugs. Thus, for example, cholesterol has been shown to antagonize the phospholipid–drug interaction *in vitro* (*152*).

Equally needed are studies on factors affecting the disappearance of myelinoid bodies after the discontinuation of treatment. DIM bodies in animal experiments and *in vitro* systems usually disappear in 1 to 10 weeks (*33,62,178,212,215*). The recovery in monkeys (*216*) and in man (*33,72*) may take years to be complete. While it is known that simultaneous administration of phenobarbital and chlorphentermine reduces the formation of alveolar foam cells and DIM bodies (*132,146*) experimental studies on factors enhancing the resolution of already accumulated DIM bodies and inclusions in alveolar foam cells are lacking.

Pulmonary histiocytosis induced by AP drugs deserves special consideration of additional factors, such as the amount of the surfactant available for phagocytosis, the metabolism of drugs by Clara cells (*217*) and the localization of drugs in the lung. The accumulation of foam cells could be enhanced by simultaneous administration of drugs and hormones (*L*-thyroxin) which increase the amounts of the surfactant within alveoli either by stimulating the secretion (*218*) or the proliferation of Type II pneumocytes (*219*). In this regard it is of interest that AP drugs are more toxic in hyperthyroid mice (*220*).

Drug interactions could also result from the mutual inhibition of amine accumulation in the lung, and reversible storage of drugs in the lung could precipitate toxic effects (*133*). Pathological investigations are needed to establish whether the adverse effects of AP drugs on the lungs are potentiated by simultaneous treatment with drugs known to localize and/or accumulate in the lung, such as amphetamine, chloramphetamine, desipramine, diphenhydramine, fluphenazine, methadone, propranolol and tripelenamine (*221*), and with drugs which inhibit the binding of chlorphen-

Table 4. Clinical adverse reactions associated with the administration of known inducers of myelinoid bodies.[a]

	Reactions[a]												
Drug	Keratopathy	Retinopathy	Cataract	Neuropathy	Myopathy	Hepatomegaly	Splenomegaly	Liver fibrosis or cirrhosis	Hyperlipidemia	Pulmonary foam cells	Nephropathy	Malabsorption	References
Amiodarone	+			+						+			(*41,121,252,296,305,306*)
Chloroquine	+	+			+								(*41,121*)
Chlorpromazine	+		+										(*121,297*)
Diethylamino-ethoxyhexestrol						+	+	+	+	+			(*33,95,156,205,242*)
Gentamycin											+		(*184,298*)
Perhexiline				+		+		+					(*124,125,275,307*)
Quinacrine	+												(*259*)
Tamoxifen	+	+											(*299,303,308*)
Tilorone	+	+											(*261,262*)
Triparanol			+									+	(*280,287,300,301*)

[a] + denotes reported.

termine to the lung, such as pronethalol, pyrilamine, *d*-propoxyphene and quinidine (*134*).

The chemicals which should be studied for their ability to modify the adverse effects of AP drugs and for their potential to induce myelinoid bodies under special circumstances include: the basic dyes, such as acridine orange or methylene blue; the lipophilic basic amines (*221*); and drugs with amphiphilic molecules, which were not fully studied. Priority should be given to drugs currently on the market such as the expectorant bromhexine; the antihistaminics carbinoxamine, cyproheptadine, diphenhydramine, diphenylpyraline, methapyriline, pyrilamine and tripelenamine; the anticholinergics chlorphenoxamine and clofenetamine; the antidepressants butriptyline, desipramine, doxepine, protriptyline, trimipramine and zimelidine; the tranquilizers fluphenazine, promazine and triflupromazine; the analgesics methadone and *d*-propoxyphene; the gonad stimulating agents clomiphene and zuclomiphene; the suppressant of lupus erythematosus hydroxychloroquine; the anorectics phenpentermine and norfenfluramine; and the adrenergic blockers pronethacol and propranolol.

In clinical trials the peripheral blood is easily accessible for light microscopic and ultrastructural studies. Lymphocytes and plasma cells of animals and man respond to AP drugs by formation of vacuoles which correspond to myelinoid bodies (*2,31,32,222*). Some AP drugs such as perhexiline are, however, poor inducers of myelinoid bodies in lymphocytes (*123*).

The intra-alveolar accumulation of foamy macrophages is a form of pulmonary histiocytosis (*7,20*). Experimentally, alveolar foam cells can be induced by inhalation of aerosols of nickel oxide (*223*). Large PAS-positive cells can be induced by Freund's adjuvant (*224*) and are seen in tuberculous pneumonia of man (Fig. 9). These cells have a granular cytoplasm. Cells seen in lipid pneumonia, on the other hand, contain vacuoles of different sizes (Fig. 10). Massive accumulation of intra-alveolar histiocytes and hyperplasia of granular pneumocytes are found also in human and experimental desquamative interstitial pneumonia (*225–230*). These macrophages are, however, smaller, lack foamy appearance, and contain PAS-positive granules.

The drug-induced pulmonary histiocytosis (*20*) and desquamative pneumonia in man (*231*) may progress to alveolar proteinosis. The alveoli in alveolar proteinosis are filled with amorphous, proteinaceous, PAS-positive material which is rich in lipids and contains phospholipids (*232–234*). For this reason, the term alveolar lipoproteinosis is more exact (*232*). The intra-alveolar material seen in proteinoses of different origin is mostly derived from disintegrated macrophages (*235–237*) and from pneumocytes (*232,233,238*). Although the alveolar proteinosis induced by AP drugs in animals did not result in fibrosing alveolitis (*21*), cholesterol granulomata were observed in lungs of dogs treated with AY-9944 (*1*). Alveolar proteinosis is also observed in acute silicosis (*238,239*) and as a response to a variety of nonspecific chemical irritants (*235*).

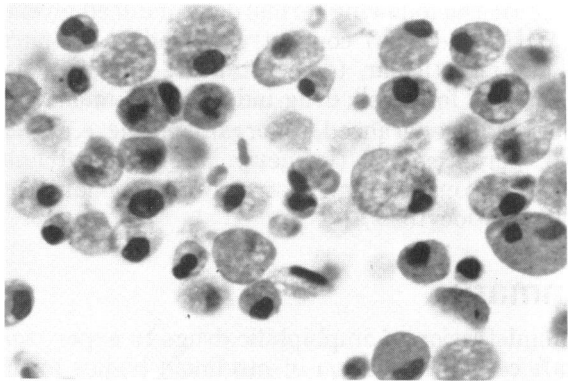

FIGURE 9. Alveolar macrophages from a patient with tuberculous pneumonia. ×590.

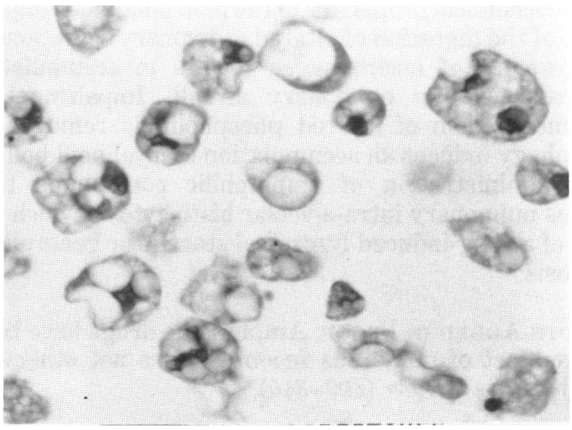

FIGURE 10. Alveolar macrophage from a patient with lipid pneumonia. ×590.

Diagnosis and Treatment

The alveolar proteinosis in man can be diagnosed in the electron microscope by examination of the sputum and of lung washings (*240*). Controlled volume bronchial lavage gives a good clinical response in treatment of alveolar proteinosis (*240*). Such treatment could be applied to clinically diagnosed cases of drug-induced alveolar histiocytosis. The degree of hepatic involvement in generalized lysosomal storage and the recovery can be followed by the levels of serum transaminases (*72,124,212,241,242*). The treatment of symptomatic generalized drug-induced lysosomal storage is discontinuation of the drug.

Terminology

Blohm (*157*) stressed the need for a standard nomenclature to facilitate indexing of drug-induced lipidoses.

We propose the following terms: drug-induced myelinoid body, DIM body: (a) concentric lamellar, (b) parallel lamellar, (c) reticular, (d) crystalloid, (e) mixed type; drug-induced foam cell; drug-induced lysosomal storage (lipidosis): (a) generalized, (b) organ-specific, e.g., renal, retinal, cerebrospinal (formerly cerebrospinal lipodystrophy, neuronal storage dystrophy), pulmonary (intra-alveolar histiocytosis).

Summary

Administration of amphiphilic drugs to experimental animals causes formation of myelinoid bodies in many cell types, accumulation of foamy macrophages in pulmonary alveoli, and pulmonary alveolar proteinosis. These changes are the result of an interaction between the drugs and phospholipids which leads to an alteration in physicochemical properties of the phospholipids. Impairment of the digestion of altered pulmonary secretions in phagosomes of macrophages results in accumulation of foam cells in pulmonary alveoli. Impairment of the metabolism of altered phospholipids removed by autophagy induces an accumulation of myelinoid bodies. The administration of amphiphilic compounds thus causes pulmonary intra-alveolar histiocytosis which is a part of a drug-induced lysosomal storage or generalized lipidosis.

NOTE ADDED IN PROOF: Amphiphilic drugs have been the subject of numerous recent studies not otherwise cited in this review (*309–340*).

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