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COMPARATIVE TOXICITY OF POLYCHLORINATED BIPHENYL AND POLYBROMINATED BIPHENYL IN THE RAT LIVER: LIGHT AND ELECTRON MICROSCOPIC ALTERATIONS AFTER SUBACUTE DIETARY EXPOSURE

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The comparative toxicity of polychlorinated biphenyl (PCB) and polybrominated biphenyl (PBB) in livers was studied in male Holtzman rats. Four-week-old animals were fed at dietary levels of 0, 5, 50, or 500 ppm for 5 weeks and then sacrificed. The mean liver-body weight ratios of the 50 and 500 ppm groups were increased. Histopathologic examination of the livers revealed fatty degenerative change associated with both compounds. This change was more marked at 500 than at 50 ppm. Various sized lamellar cytoplasmic inclusions were detected in livers of animals fed 500 ppm of either compound. However, the inclusions were more numerous in the PBB-treated rats. Several animals fed 50 ppm PBB had a few inclusions. In rats that received 500 ppm PBB, hypertrophic degenerative hepatocytes were present around the central veins. On the periphery of this change there were occasionally multinucleated hepatocytes. Electron microscopic examination at a dose level of 5 ppm in both the PCB and PBB groups showed a slight proliferation of smooth endoplasmic reticulum (SER), a moderate increase of lipid droplets and some liposomes, and a marked proliferation of Golgi condensing vesicles containing lipoprotein particles. A decreased number of mitochondria and lysosomes was also observed. At 50 ppm, similar but more marked ultrastructural alterations were seen. In addition, an increased number of branched and cup-shaped profiles of mitochondria and a decreased number of Golgi condensing vesicles containing lipoprotein particles were observed. Concentric membranous cytoplasmic whorls were encountered only in the 50 ppm PBB-treated rats. At 500 ppm the number of mitochondria decreased in both groups. There was also a marked increase in the number of SER and liposomes concomitant with a decreased number of Golgi condensing vesicles containing lipoprotein granules. Membranous whorls were also present in the 500 ppm groups.

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INTRODUCTION

Based upon feeding experiments using commercial mixtures of polychlorinated biphenyls (PCBs) (Kimbrough *et al.*, 1972; Litterst and Van Loon, 1972, 1974; Litterst *et al.*, 1972; Turner and Green, 1974; Kasza *et al.*, 1976) and chemically pure isomers of PCB with chlorine substitution at the 4 and 4' positions (Hansell and Ecobichon, 1974), a well-established series of events is seen in the rat liver. Proliferation of smooth endoplasmic reticulum (SER) (Kimbrough *et al.*, 1972; Hantell and Ecobichon, 1974; Kasza *et al.*, 1976) occurs with a concomitant rise in activity of enzymes of the microsomal mixed-function oxidative system (Litterst and Van Loon, 1972, 1974; Litterst *et al.*, 1972; Turner and Green, 1974) and an increase in microsomal protein (Litterst and Van Loon, 1972). These changes are frequently associated with hepatocytomegaly, increased liver weight, and increased liver-body weight ratios (Kimbrough *et al.*, 1972; Litterst and Van Loon, 1972; Kasza *et al.*, 1976). Despite the fact that a markedly fatty liver develops (Kimbrough *et al.*, 1972; Litterst *et al.*, 1972; Kasza *et al.*, 1976), no necrosis occurs with a one-month exposure at dietary levels of up to 500 ppm (Kasza *et al.*, 1976).

Another halogenated biphenyl compound that has received attention currently is polybrominated biphenyl (PBB) and, more specifically, the commercial mixture FireMaster® BP-6. Its importance has been emphasized by an accidental contamination of animal food, which led to a widespread poisoning of farm animals in Michigan (Jackson and Halbert, 1974). Lee *et al.* (1975a, 1975b) studied the morphologic alterations in rat liver brought about by oral intubation and short-term feeding exposure to octabromobiphenyl. The liver was enlarged, and the hepatocytes had hypertrophy, margination of basophilic cytoplasm, foamy cytoplasmic vacuolation, laminated cytoplasmic inclusions, and proliferation of SER. The effect of FireMaster BP-6® on hepatic drug metabolism was also studied (Dent *et al.*, 1976).

Although the contamination of the environment (Gustafson, 1970; Kolbye, 1972) and the morphologic alterations associated with PCB toxicity have been the subject of several investigations (Kimbrough *et al.*, 1972; Hansell and Ecobichon, 1975; Kasza *et al.*, 1976), limited morphologic study has been done on PBB (Lee *et al.*, 1975a, 1975b; Sleight and Sanger, 1976). The primary objective of the present study was to compare the relative hepatotoxicity of equivalent doses of PCB and PBB on liver morphology, using light and electron microscopy. The study described here is part of a larger study in which the biochemical and cytogenetic effects of feeding 5, 50, or 500 ppm of PCB or PBB for 2, 3, or 5 weeks were investigated (Garthoff *et al.*, 1977).

MATERIALS AND METHODS

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Animals

Four-week-old male Holtzman rats, divided into six groups consisting of seven rats each, were fed the following diets: 5, 50, or 500 ppm of either

PCB (Aroclor 1254) or PBB (FireMaster® BP-6). A seventh group of nine rats served as a common control. The PCB test material was obtained from lot number 370-71-698 and the PBB from lot number 1050-74-55, which are held by the Food and Drug Administration to serve as reference materials. The chemicals were ground into the commercial rat chow diet, using a large mortar and pestle. These concentrates were serially diluted to prepare the test diets; see Garthoff et al. (1977) for additional details.

The control group was kept in a different room to avoid any possible cross-contamination. The animals were housed individually in stainless steel cages with wiremesh bottoms. The daily lighting schedule was 12 hr of light followed by 12 hr of darkness. The rooms were kept at 72°F and 50% humidity. Feed and water were available *ad libitum*. The animals were fed with their dietary levels for 5 wk; control animals were fed the same food without test materials. After 5 wk, rats were sacrificed and, at the time of necropsy, whole body and liver weights for each animal were recorded to determine mean liver weights, mean body weights, and liver-body weight ratios.

All materials and excreta were incinerated to prevent environmental contamination.

Histopathology

Livers were collected from test animals and controls and were fixed in 10% buffered formalin. After fixation, the tissues were trimmed, dehydrated in a graded series of ethyl alcohol, infiltrated with xylol, and embedded in paraplast. Embedded tissues were cut in 5-6 μ m sections and stained with Mayer's hematoxylin and eosin (H & E) for histopathologic examination.

Histochemistry

Special stains of selected liver sections were made. Trichrome stain was used to detect fibrosis. Glycogen in hepatocytes was evaluated by periodic acid Schiff reaction. To demonstrate lipid, oil red O-stained frozen sections of the liver were prepared.

Electron Microscopy

Electron microscopic examination of livers was conducted on control animals and on animals exposed to 5, 50, or 500 ppm of PCB or PBB. Livers for electron microscopic examination were minced (1 mm³) in 3 percent glutaraldehyde in 0.1 M phosphate buffer (pH 7.4) and fixed for 2 hr. Following a single buffer rinse, tissues were postfixed in 2 percent buffered osmium tetroxide for 1 hr, dehydrated in graded ethyl alcohol solutions, embedded in Epon (Luft, 1961), and sectioned on a Sorvall MT-1 ultramicrotome. For correlation between light and electron microscopic observations, semithin sections (0.5-1 μ m) of Epon-embedded material were stained with toluidine blue (Trump et al., 1961) and viewed under a light microscope. Thin sections were stained with uranyl acetate (Watson, 1958) and lead citrate (Venable and Coggeshall, 1965) and viewed under a JEOLCO 2B electron microscope.

Six electron micrographs were recorded from each section at a primary magnification of 14,000X. Random sampling of fields was ensured by positioning the fluorescent viewing screen of the microscope into one specified corner of six consecutive squares of the supporting copper grid as previously described [Weibel *et al.*, 1969].

RESULTS

Weights

The mean body and liver weights, mean liver-body weight ratios (expressed as percentages), and statistically significant differences between groups are given in Table 1. The mean liver-body weight ratios of the 50 and 500 ppm groups were increased over the control with both PCB and PBB.

Histopathology

In PCB-treated rats the most prominent liver alteration was fatty degeneration, which was most marked in the 500 ppm group. This change manifested itself by intracytoplasmic vacuolation which occurred either as a large, rounded empty space that occupied almost the entire cytoplasm of the hepatocyte or as fine intracytoplasmic vacuoles that gave the cells a foamy appearance (Fig. 1). Mononuclear infiltration was present in a few foci. The most common location of these foci was adjacent to the fatty degenerative areas (Fig. 2). The locations of intracytoplasmic vacuolation in the hepatic lobules were in the midzonal regions (Fig. 3). Most of the involved cells were hypertrophic, and cellular pleomorphism could be observed. Several of the nuclei were pushed to a marginal position within the cells. In those cells which had cytoplasmic vacuoles, oil red-O stain demonstrated fat droplets. In livers of rats fed 50 ppm PCB, qualitatively similar changes were present, but the changes were less severe.

In the PBB-treated rats, fatty degeneration occurred in a similar location to that seen in the livers of rats treated with PCB. Most of the fat-containing vacuoles occurred as small droplets, giving a foamy appearance to the cytoplasm; there were large vacuoles too, but in smaller numbers than seen after PCB. In addition to the fatty changes in the PBB-treated rats, the most striking changes occurred in the pericentral zone. Here the cells became markedly hypertrophic with well-marked borders. The cytoplasm became rather homogeneous and stained lightly with eosin, giving a "ground-glass" appearance. The nuclei lost their central orientation, and several showed pyknosis. In a few cells there were no nuclei. These degenerating cells surrounded the central veins and, at the periphery of the lesions, there were multinucleated hepatocytes (Fig. 4). Bile duct hyperplasia was also observed. At the 50 ppm dose level, all these changes were present but to a lesser degree. There were no changes at 5 ppm and in the controls.

Lightly stained, eosinophilic, lamellar cytoplasmic inclusions were detected in both the PCB- and PBB-treated animals at the 500 ppm dose

TABLE 1. Effects of PCB and PBB on Mean Liver and Body Weights and Liver-Body Weight Ratios in Rats¹

Weights	Dietary Level (ppm)					
	0 ²	PCB			PBB	
		5	50	500	5	50
Liver, g	11.49±0.50	13.20±0.69 ³	15.82±1.78 ³	19.88±1.95 ³	12.72±0.72 ³	19.44±1.42 ³
Body, g	352.0±28.2	380.0±14.1	384.5±34.4	308.5±28.9	364.0±23.3	388.0±16.8
Liver-body, %	3.28±0.18	3.47±0.11	4.17±0.25 ³	6.44±0.18 ³	3.50±0.10	5.02±0.52 ³

¹Values are means ± SD for n = 9 (controls) or 7 (treated groups).²Used as control value for all treated groups.³Significantly different from control, p<0.05.

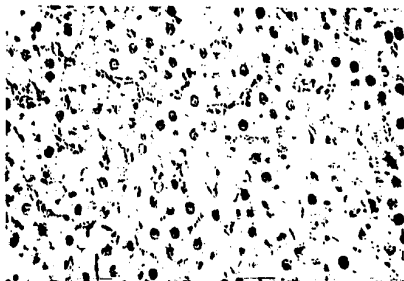


FIGURE 1. Fatty vacuolation of the liver of a rat treated with 500 ppm PCB for 5 wk. Several of the intracytoplasmic vacuoles have a "foamy" appearance. H & E stain, 250X.

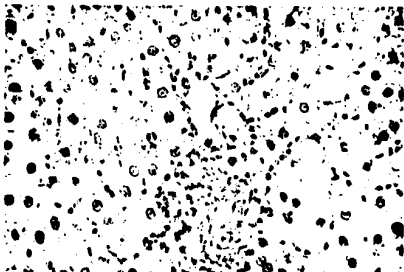


FIGURE 2. Mononuclear infiltration present adjacent to the fatty degenerative area in the liver of a rat treated with 500 ppm PCB for 5 wk. H & E stain, 250X.

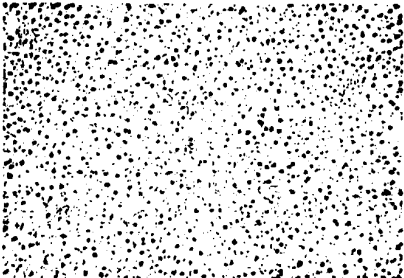


FIGURE 3. Intracytoplasmic vacuolation with a predominantly midzonal arrangement in the liver of a rat treated with 500 ppm PCB for 5 wk. H & E stain, 100X.

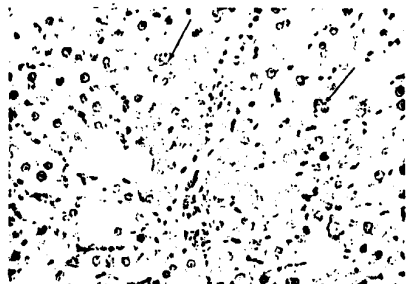


FIGURE 4. Markedly hypertrophic and degenerating hepatocytes with a "ground-glass" appearance surrounding the central vein in a rat treated with 500 ppm PBB for 5 wk. There are multinucleated giant cells (arrows). H & E stain, 250X.

level (Fig. 5). The number of inclusions was greater in the livers of PBB-treated rats. At the 50 ppm dose level, inclusions were present only in the PBB-treated group. Inclusions in the affected areas did not show specific zonal distribution. Hypertrophied cells were seen to contain several inclusions. Generally, the inclusions were spherical, varying in size from a few microns to such large dimensions that they occupied almost the entire cytoplasmic space. Several inclusions were surrounded by a narrow halo, and the ring-like inclusions surrounded empty spaces in the centers. High magnification of some inclusions revealed a laminated structure. Inclusions were seen in both the slightly and markedly affected cells. Several inclusions were detected in cells where fatty changes were not seen by light microscopy.

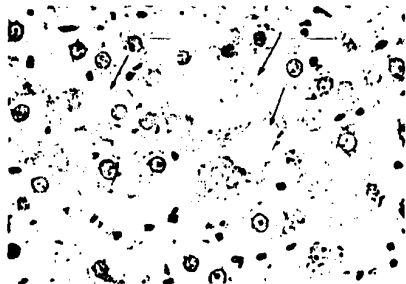


FIGURE 5. Several intracytoplasmic inclusions are present (arrows) in a rat treated with 500 ppm PBB for 5 wk. A few nuclei show pyknosis. H & E stain, 400X.

Histochemistry

The special stains to detect fibrous proliferation and an increase of glycogen did not react specifically. The oil red-O stain demonstrated an increase of lipids in the cytoplasm of hepatocytes in both the PCB- and PBB-treated rats at the 50 and 500 ppm levels, with the greater increase at the 500 ppm level. At 5 ppm and in controls there was no lipid increase.

Electron Microscopy

Toluidine blue-stained semithin sections of control and treated rat liver confirmed the findings previously noted in paraffin sections. In the treated groups markedly hypertrophied hepatocytes were seen, which contained large areas of cytoplasm free of dark-staining granules (mitochondria and lysosomes). By electron microscopy, these areas were sites of SER proliferation and decreased numbers of mitochondria and lysosomes.

A survey micrograph of a typical control hepatocyte is shown in Fig. 6. Control hepatocytes contained abundant stacks of rough endoplasmic reticulum (RER) in parallel arrays. At the periphery of RER stacks, variable amounts of SER were encountered. Mitochondria were numerous, were randomly positioned within cytoplasm, and revealed typical cristae and matrix granules. The Golgi apparatus was encountered in most



FIGURE 6. Portion of two hepatocytes of control rat. Golgi apparatus (GA) shows distended cisternae. Note parallel stacks of RER. 16,000X.

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micrographs and often contained granules (250-800 Å in diameter) of lipoprotein (Jones *et al.*, 1967; Glaumann *et al.*, 1975); these granules were particularly obvious in condensing vesicles (Fig. 7).

All aspects of the ultrastructure of control hepatocytes conformed to previous descriptions of normal liver (Bruni and Porter, 1965).

The major ultrastructural findings in control and treated livers are given in Table 2. Both normal-appearing mitochondria and branching, cup-shaped forms (Fig. 8) were seen in animals fed 5 ppm PCB or PBB. The RER was arranged in parallel stacks as seen in controls. The SER of the cytoplasm of this group showed a slight increase over that of controls. SER was found both at the periphery of the cells and near the nuclei. A moderately increased number of intracytoplasmic lipid droplets was seen after 5 ppm exposure to PCB or PBB in comparison with controls.

Cytoplasmic lipid usually appeared as round droplets of low electron density. These often appeared to be impinging upon adjacent membranes, producing a "pseudomembranous" arrangement. This was described previously in livers of PCB-treated rats (Kasza *et al.*, 1976). Other lipids appeared within membranes of the endoplasmic reticulum (Fig. 9), referred to as liposomes (Lombardy and Oler, 1967). Still other lipids were seen as lipoprotein particles within Golgi condensing vesicles. The number of Golgi condensing vesicles containing these particles was increased after exposure to 5 ppm PCB or PBB. Exposure to 50 ppm PCB or PBB was associated with a marked proliferation of SER. RER appeared as meandering tracks.

In addition, the number of mitochondrial profiles appeared to be decreased in both groups. The number of cytoplasmic lipid droplets was

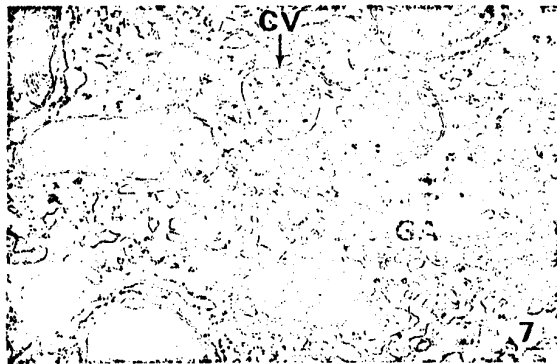


FIGURE 7. Portion of hepatocyte from control rat showing Golgi apparatus with adjacent Golgi condensing vesicles (CV) containing lipoprotein particles. 56,000X

TABLE 2. Major Ultrastructural Findings in Control and PCB- and PBB-Treated Rat Livers¹

Group	Mitochondria	Endoplasmic reticulum		No. of lipid droplets	No. of liposomes	No. of Golgi condensing vesicles containing lipoprotein particles	No. of membrane whorls
		Smooth	Rough				
Control	Orthodox configuration	>1/3 field in 2 of 96 fields	In parallel stacks	20	2	146	0
PCB, 5 ppm	Occasional branched and cup-shaped profiles	>1/3 field in 5 of 96 fields	In parallel stacks	31	36	236	0
PBB, 3 ppm	Occasional branched and cup-shaped profiles	>1/3 field in 7 of 96 fields	In parallel stacks	45	73	244	0
PCB, 50 ppm	Increased number of branched and cup-shaped profiles	>1/3 field in 42 of 96 fields	Meandering tracks	48	51	101	0
PBB, 50 ppm	Increased number of branched and cup-shaped profiles	>1/3 field in 48 of 96 fields	Meandering tracks	198	50	80	11
PCB, 500 ppm	Decreased number of profiles	>1/3 field in 39 of 96 fields	Meandering tracks	177	957	73	5
PBB, 500 ppm	Decreased number of profiles	>1/3 field in 64 of 96 fields	Meandering tracks	126	523	105	11

¹Findings are based upon examination of 6 micrographs (14,000 × original magnification) per block, 4 blocks per animal, and 4 animals per group. Only hepatocyte cytoplasm was studied. Total micrographs per group = 96.



FIGURE 8. Portion of hepatocyte cytoplasm from rat exposed to 5 ppm PBB for 5 wk. Note indented surface of mitochondrion forming "cup-shaped" profile with lipid droplet in concavity. 35,000X

increased over the 5 ppm groups. PBB-treated animals showed more lipid droplets than the PCB-treated animals. The number of liposomes in PCB-treated animals was greater after 50 ppm than after 5 ppm exposure; the reverse was true for the PBB-treated animals. However, the number of liposomes produced was the same for both 5 ppm PCB and PBB. Membrane whorls were encountered in the 50 ppm PBB-exposed animals but not in the 50 ppm PCB-exposed group; a total of 11 were seen in 3 different animals. These membrane whorls (Fig. 10) appeared to arise from smooth-surfaced endoplasmic reticulum and were always seen in areas of marked SER proliferation. The number of Golgi condensing vesicles containing lipoprotein particles was markedly increased in both groups at the 5 ppm exposure level. However, after 50 ppm, the number of these structures was less than that of controls.

Animals exposed to 500 ppm of PCB or PBB revealed a reduction in the number of mitochondria per field, marked SER proliferation (Fig. 11), disarray of RER, and lipid accumulation. The number of cytoplasmic lipid droplets in 500 ppm PCB-treated rats was higher than that seen after 50 ppm. Fewer lipid droplets were seen after 500 ppm PBB than at 50 ppm, but the number was greater than in the controls and lower dose exposure groups. The number of liposomes concomitant with a decrease in the number of Golgi condensing vesicles containing lipoprotein granules was markedly increased in both groups. In addition, exposed animals frequently contained Golgi condensing vesicles with flattened cisternae (Fig. 10). Membrane whorls were encountered in livers of rats exposed to both PCB and PBB at the 500 ppm concentration.

DISCUSSION AND CONCLUSIONS

The effects of PCB and PBB on the livers of 9-week-old male Holtzman rats were compared. The primary lesion produced by PCB was fatty

PM, 500 ppm	Decreased number of profiles	>1/3 field in 44 of 50 fields	Membrane whorls	126	523	105	11
Findings are based upon examination of 6 micrographs (14,000 X original magnification) per block, 4 blocks per animal, and 4 animals per group. Only hepatocyte cytoplasm was studied. Total micrographs per group = 96.							

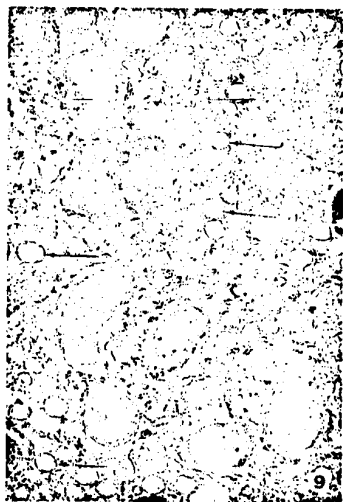


FIGURE 9. Hepatocyte cytoplasm from rat exposed to 50 ppm PCB for 5 wk. Note lipid of characteristic low electron density within membranes of smooth-surfaced endoplasmic reticulum. 44,000X.

degeneration, multilobular and occurring in the mid- and pericentral zones of the lobules. A limited number of cytoplasmic inclusions was detected, but only at the 500 ppm dose levels. Cellular hypertrophy accompanied the fatty degeneration in the involved areas. The fatty degeneration was less intensive than we saw in Osborne-Mendel rats fed PCB at the same dose levels (Kasza *et al.*, 1976). Also, lamellar inclusions were not seen in that strain of rats, which might indicate strain differences in reaction to PCB. In the PBB-treated rats the fatty degeneration also occurred in the mid- and pericentral zones of the liver lobules. Lamellar cytoplasmic inclusions were numerous at the 500 ppm dose level, and a few were detected at the 50 ppm dose level. The intracytoplasmic inclusion bodies detected by light microscopy corresponded to the concentric laminated membranes of SER found by electron microscopy (Figs. 5 and 10). The most striking difference between the PCB- and PBB-treated rats was the presence of hypertrophic cells around the central veins in the PBB-exposed rats. The enlarged hepatocytes had ground-glass appearing cytoplasm. These cells surrounded the central veins at the depth of one to three cell thicknesses. Most of the inclusions occurred adjacent to these areas on the peripheries.



FIGURE 10. Portion of two hepatocytes from rat exposed to 50 ppm PBB for 5 wk. Smooth-surfaced endoplasmic reticulum has proliferated and fills cytoplasm. Golgi apparatus (GA) shows flattened cisternae. $\times 21,000\times$.

Electron micrographs from control and PCB- and PBB-treated animals revealed qualitative similarities in ultrastructural alteration. Both compounds caused proliferation of SER, which was particularly pronounced in the 50 and 500 ppm groups. In addition, liver weights and liver-body weight ratios increased upon exposure to either compound at all concentrations studied (Table 1). Increased lipid within hepatocytes followed exposure to both compounds; furthermore, the sites of lipid accumulation (i.e., as free fat droplets in the cytoplasm and as membrane-bounded liposomes) were identical. PCB and PBB caused an increase in cell size, with affected hepatocytes showing rounded margins with extensive areas of cytoplasm free of mitochondria and lysosomes. These findings confirm previous morphologic reports on PCB (Nishizumi, 1970; Kimbrough *et al.*, 1972; Norback *et al.*, 1972; Koller and Zinkl, 1973; Kasza *et al.*, 1976) and PBB (Lee *et al.*, 1975a, 1975b; Corbett *et al.*, 1975; Sleight and Sanger, 1976). Although enzyme activity in the hepatic mixed-function oxidative system was not measured in the present study, it has been shown that proliferation of SER by halogenated biphenyls is associated with a rise in enzyme activity (Litterst *et al.*, 1972; Dent *et al.*, 1976; Sleight and Sanger, 1976).

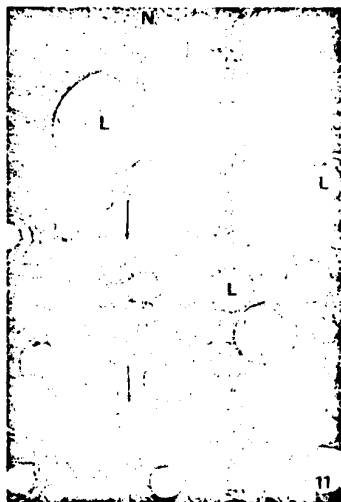


FIGURE 11. Portion of hepatocyte from rat exposed to 500 ppm PBB for 5 wk. Nucleus (N) is at top of field. Cytoplasm contains parallel membranes in whorl arrangement. 21,000X.

Quantitative differences were seen in relation to liver weight. Values for PBB-treated animals were higher at each exposure level (Table 1). In addition, membrane whorls or laminated cytoplasmic inclusions occurred after exposure to 50 ppm PBB but not 50 ppm PCB. At 500 ppm, membrane whorls were seen in the hepatocyte cytoplasm of both PCB- and PBB-treated animals, but the number of whorls was higher with the latter compound. Although the significance of the membrane whorls has not been established, they arise from endoplasmic reticulum (Smuckler and Arcasoy, 1969) after exposure to various compounds, including phenobarbital (Burger and Herdson, 1966), toxic fat (Norback and Allen, 1969), DDT (Ortega, 1966), ethionine (Steiner *et al.*, 1964), and inhibitors of protein synthesis (Hwang *et al.*, 1974). Since membrane whorls form during normal and regenerating processes, including embryonic formation of egg membrane during vitellogenesis (Sweeney *et al.*, 1970) and regenerating liver (Becker and Lane, 1965), those whorl-like membrane structures may be indicative of a normal stage in membrane formation and/or repair (Hwang *et al.*, 1974). Hutterer *et al.* (1969) described the hypertrophic hypoductive SER as the transition between adaptation and degeneration or injury. Since membrane whorls represent hypertrophic SER, the question of the functional ability of these membranes following polyhalogenated

biphenyl exposure is important. In this regard, Sleight and Sanger (1976) demonstrated enhanced activity of hepatic mixed-function oxidative enzymes concomitant with membrane whorl formation.

Based upon our observation of 96 randomly selected fields of identically magnified hepatocyte cytoplasm, the number of Golgi condensing vesicles containing lipoprotein particles appeared to increase in both PCB- and PBB-treated animals after exposure to 5 ppm of the compounds (Table 2). A decrease occurred after exposure to 50 and 500 ppm, and, in these animals, the Golgi cisternae appeared to be flattened (Fig. 10). Concomitantly, in the 500 ppm animals, the number of liposomes increased 20-fold in the PCB-treated rats and 10-fold in the PBB-treated rats. Litterst *et al.* (1972) found increases in hepatic triglyceride in PCB-exposed rats. In the rat liver, the primary pathway for utilization of hepatic triglyceride is secretion into the circulation in the form of lipoproteins (Jones *et al.*, 1967; Stein and Stein, 1967; Glaumann *et al.*, 1975). This process appears to involve synthesis of protein, triglyceride, and other lipid moieties, conjugation of lipid and protein, intracellular transport via the endoplasmic reticulum and Golgi apparatus, intracellular migration under the influence of microtubules (Orci *et al.*, 1973), and secretion into the extracellular space. Our data indicate that a blockade in the transport of lipid occurs upon exposure to PCB and/or PBB (Kasza *et al.*, 1976 and this paper). Furthermore, the blockade occurs at the Golgi apparatus or between the endoplasmic reticulum and the Golgi apparatus. In addition, Mehlman and associates (1974) found that exposure to PCB decreased the availability of free fatty acids for hepatic mitochondrial oxidation. Such decreased utilization would be expected to lead to fatty liver (Cederbaum *et al.*, 1975). Additional work on the effect of halogenated biphenyls upon the rate of synthesis and turnover of microsomal and cytoplasmic lipids is needed to further characterize the fatty liver.

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