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Estrogen-induced hepatic toxicity and hepatic cancer: differences between two closely related hamster species

Coe JE, Ishak KG, Ross MJ. Hepatic toxicity of estrogen in hamsters. Liver 1998: 18: 343–351. © Munksgaard, 1998

Abstract: *Aims/Background:* Estrogen is known to affect hepatobiliary function; however, it is unusual for high serum levels of estrogen to actually result in clinically detectable hyperbilirubinemia. Women affected by cholestatic jaundice during pregnancy share this genetic susceptibility with two Cricetulus hamsters, the Armenian hamster (*Cricetulus migratorius*) and the Chinese hamster (*Cricetulus griseus*). Nevertheless, the pathophysiologic process responsible for this estrogen induced icterus may be different in women and hamsters. The present study compares various facets of estrogen-induced icterus in these two closely related hamsters. *Methods:* Hamsters were injected with various estrogens and the acute and chronic effects on liver were monitored by measuring changes in serum constituents and by observing changes in hepatic structure as seen grossly and by light and electron microscopy. *Results:* In previous studies, hepatic tumors developed in most Armenian hamsters after chronic estrogen treatment, but in the present study, the livers of Chinese hamsters were remarkably free of neoplastic change under similar conditions. Also, when compared with the responses in the Armenian hamsters, signs of hepatic destruction and regeneration were less prevalent in estrogen-treated Chinese hamsters, and they were less susceptible to the effects of estrogen (because larger doses of estrogen were required to produce icterus and the bilirubin levels were lower and of shorter duration). In contrast to the findings in Armenian hamsters, bile canaliculi were severely affected in livers of estrogen-treated Chinese hamsters, and hepatic microvesicular steatosis, indicative of an unusual lipodystrophy caused by estrogen, was prominent. An additional lesion peculiar to the Chinese hamster was striking sinusoidal dilatation, which may be analogous to the oral contraceptive-induced sinusoidal dilatation in humans. *Conclusions:* Although these two hamster species are genetically similar, the genes activated by the estrogen receptor show remarkable heterogeneity when their respective livers are examined. Comparisons within these species may provide information about the specific gene activation responsible for particular pathologic events.

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Estrogens are remarkably toxic to the liver of the Armenian hamster (*Cricetulus migratorius*). Within days after estrogen administration, they become profoundly icteric, and their livers show histologic evidence of degenerative and regenerative changes (1). With chronic estrogen treatment, evidence of the acute toxicity, such as icterus, diminishes but neoplastic changes occur in the liver so that foci, adenomas, and finally hepatocellular carcinomas are detected in livers of virtually all treated animals (2, 3). A wide variety of estrogens, natural (B-estradiol, Zeranol) and synthetic (ethinyl estradiol, diethylstilbestrol), are effective, and the acute and chronic effects can be inhibited by the concomitant administration of tamoxifen (3, 4). Both findings suggest that the hepatic effects are mediated by estrogen receptor (ER). Comparable examples of estrogen-induced hepatotoxicity/hepatocarcinogenicity are rare, although certain genetically susceptible women do become icteric during pregnancy

when high serum estrogen levels are present (5–7). Also, chronic treatment of humans with estrogen has been associated with the occurrence of liver tumors (8, 9). In other experimental animals, such as the rat, estrogens promote or enhance the hepatocarcinogenic effect of a known carcinogen, but by themselves they are poor initiators of neoplastic change (10).

The mechanism by which estrogen produces these unusual effects in the liver of the Armenian hamster is unknown. In the present report we studied the effect of estrogen when administered to the Chinese hamster (*Cricetulus griseus*). This hamster, classified in the same genus, is a close relative of the Armenian hamster. Although the administration of estrogen did induce a hyperbilirubinemia in both species, neoplastic change was not found in the Chinese hamster. Also, chronic estrogen treatment caused quite different histopathologic changes in the liver that were unique for the Chinese hamster. Comparative studies between these two *Cricetulus* species, or their hybrids, may provide insight into the genetic mechanism(s) responsible for estrogen-initiated hepatocarcinogenicity in the Armenian hamster.

Material and methods

Hamsters and drugs

Chinese hamsters and Armenian hamsters were obtained from Rocky Mountain Laboratories animal production unit. They were housed in a room illuminated by fluorescent lights with a 16/8 hour light/dark cycle and had free access to feed and water. Diethylstilbestrol (DES) pellets (15 mg Pelestrol, Franklin Laboratories, Denver, CO, USA) and Zeranol (RAL) pellets (12 mg, RALGRO, Pitman-Moore, Terra Haute, IN, USA) were surgically implanted subcutaneously (SC) in hamsters under metophane (Pitman-Moore) anesthesia. These pellets release estrogen for about 3 months. In previous experiments (1), we used a 12 mg DES pellet (Pfizer), which produced more hyperbilirubinemia and mortality than the Pelestrol pellet used in this study. Tamoxifen (TAM), a gift from Stuart Pharmaceuticals (Wilmington, DE, USA), was suspended in propylene glycol and 0.1 ml (5 mg) was injected SC. Five milligrams of a synthetic progestagen, medroxyprogesterone acetate (MPA) (Upjohn Co., Kalamazoo, MI, USA) were injected using a 50 mg/ml suspension in propylene glycol or a 100 mg/ml suspension formulated by Upjohn (Depo-Provera®). Similar results were obtained with both preparations. RU 486, a gift from Roussel Uclaf, Romainville, France, was put in a sealed 25 mm Silastic tube (0.058 inches ID, from Dow Corning, Midland, MI, USA) and surgically implanted s.c. in hamsters under metophane anesthesia.

Experimental design

Three-month-old male and female Chinese and Armenian hamsters in groups of five were inoculated on day 0 with 15 mg DES pellets or with 12 mg RAL pellets (from 1–3). Blood samples (0.1 ml) were obtained on day 0 and thereafter at weekly intervals from the retro-orbital plexus of anesthetized hamsters. Serum bilirubin was determined as before (4). Urine output of medroxyprogesterone (MPA)-treated Chinese hamsters was measured on a 24 h schedule, as done previously (11). At necropsy, hamsters were examined for gross pathologic changes and slices of liver were fixed in 10% buffered formalin. Cryostat sections were stained with oil red-O. After routine processing, paraffin sections (6 μm thick) were stained with hematoxylin and eosin and examined microscopically, as previously described (1). For transmisson electron microscopy, pieces of the liver (1 mm or less in thickness) were fixed in 2% gluteraldehyde and then embedded in Spurr's epoxy resin. Thick sections (1 μm), several blocks from each liver, were stained with toluidine blue and examined by light microscopy; following which thin sections were cut from some of the blocks. The thin sections (60–80 nm) were mounted on copper grids, post-stained with 1% aqueous uranyl acetate and Reynold's lead citrate stain, and examined in a Zeiss 109 electron microscope.

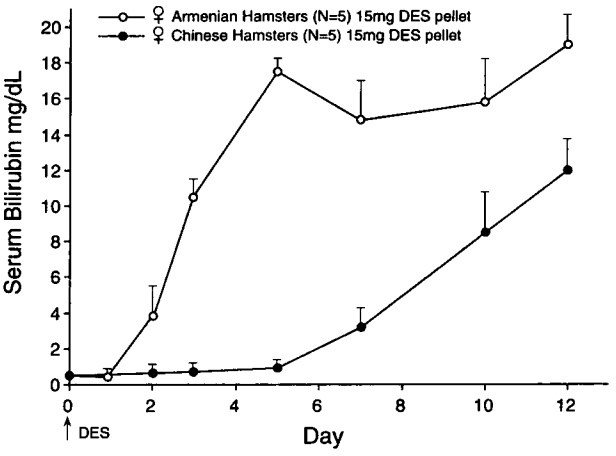

Fig. 1. Effect of DES on serum bilirubin in female Armenian hamsters ($n=5$) and Chinese ($n=5$) hamsters. Fifteen mg pellet of DES was implanted subcutaneously on day 0, and all Armenian hamsters (–○–) were icteric within 48 h, whereas 7 days were required before similar bilirubin levels were detected in Chinese hamsters (–●–). Bilirubin levels were higher in Armenian hamsters and lasted longer (not shown). Vertical bar = ±1 SEM.

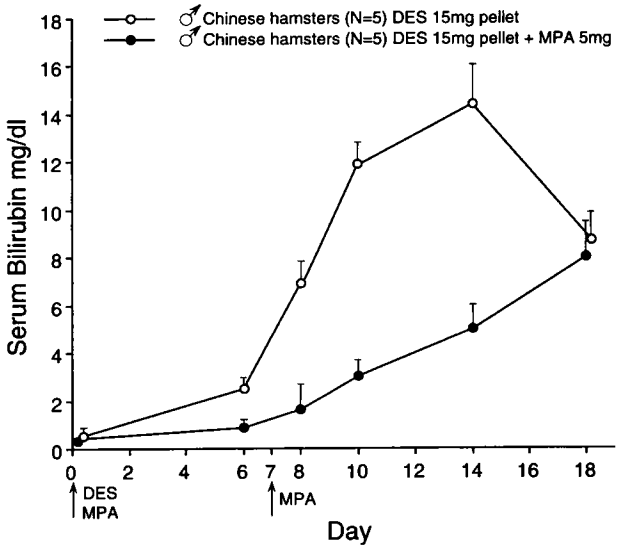

Fig. 2. Effect of MPA on DES-induced icterus in female Chinese hamsters. The group ($n=5$) injected only with DES on day 0 (-O-) developed higher bilirubin levels than the group which received DES+MPA injections (5 mg day 0, day 7) (-●-).

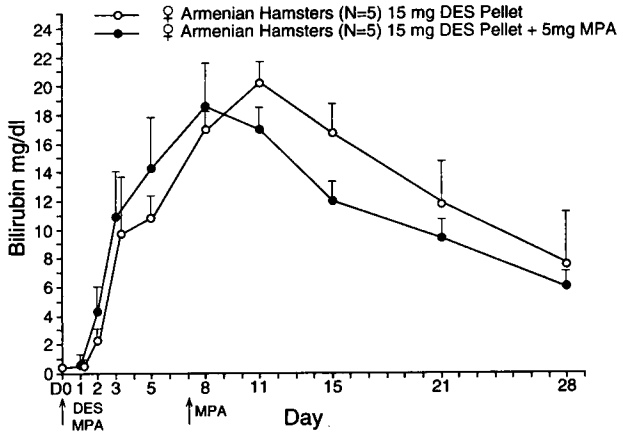

Fig. 3. Effect of MPA on DES-induced icterus in female Armenian hamsters (each group=5). Combination of DES+MPA (-●-) resulted in similar hyperbilirubinemia as DES alone (-O-).

The animal experiments were performed according to the National Institute of Health Guide for the Care and Use of Laboratory Animals.

Results

Acute effects of estrogen in hamsters

Estrogen-induced hyperbilirubinemia is common to both the Armenian and the Chinese hamster, but the kinetics are different in the two species. Figure 1 compares the increase of serum bilirubin in females of both species after administration of a 15 mg DES pellet (Pelestrol) on day 0. All Armenian hamsters became icteric within 48 h of treatment, whereas 7 days were required before the onset of icterus in the Chinese hamsters. Also, the serum levels of bilirubin were greater and tended to last longer (not shown) in the Armenian hamster than in the Chinese hamster. Chinese hamsters were also given Ralgro (RAL) pellets containing 36 mg of Zeranol, an estrogen dose that produces consistent hyperbilirubinemia in Armenian hamsters (3). In four separate experiments with Chinese hamsters, however, detectable serum icterus (serum bilirubin greater than 2 mg%) was found in only 7 of 24 females and 7 of 25 males. The average bilirubin level in the icteric animals was only 5 mg%, much less than the average bilirubin levels of 14 mg% found in 100% of Armenian hamsters.

Effect of MPA on DES-induced icterus

The acute hepatotoxic effects of estrogen are abrogated when Armenian and Chinese hamsters are given concomitant injections of Tamoxifen (3, 4), suggesting that these effects are mediated by estrogen receptor (ER). Progesterone can also counteract estrogen-induced changes in fat metabolism (12) and can diminish ER responsiveness in uterine tissue (13, 14). When Chinese hamsters were given both MPA and DES, the hepatoxicity induced by DES, as measured by serum bilirubin, was delayed and diminished (Fig. 2). This suggested that hepatotoxicity was mediated by ER and that MPA effectively inhibited its hepatic activity. On the other hand, in Armenian hamsters, MPA had no effect on the bilirubinemia induced by DES (Fig. 3).

We have previously shown that a similar sequence of MPA injections will induce an acute dia-

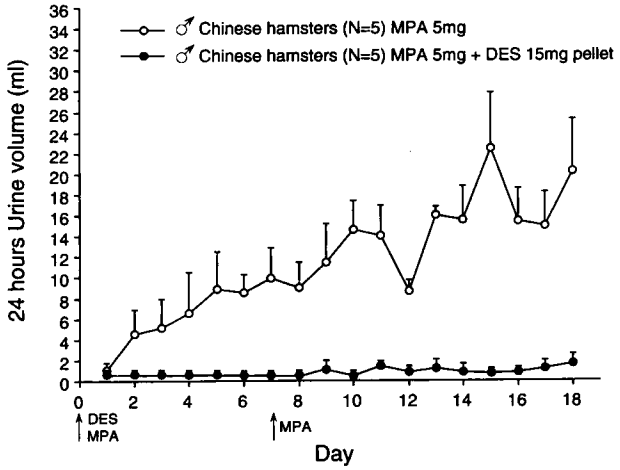

Fig. 4. Effect of DES on MPA-induced polyuria in Chinese hamsters. The group ($n=5$) receiving MPA (5 mg day 0, day 7) (-O-) developed marked polyuria whereas concomitant DES (-●-) abrogated MPA- induced diabetes insipidus.

Table 1. Incidence of hepatic tumors in Chinese and Armenian hamsters after estrogen treatment

Hamster	Estrogen	Day dose	Necropsy	Gross tumors*	
				Females	Males
Chinese	DES pellet	Day 0, 15 mg; Day 80, 6 mg	Day 270	0/7	0/5
Chinese	DES pellet	Day 0, 15 mg; Day 121, 6 mg; Day 301, 15 mg	Day 363	0/3	0/11
Chinese	DES pellet	Day 0, 6 mg	Day 205	0/2	
Chinese	RAL pellet	Day 0, 36 mg	Day 127–134, Day 251	0/13	0/7, 0/2
Chinese	RAL pellet	Day 0, 36 mg; Day 104, 36 mg	Day 161–205	1/5	0/2
Armenian	RAL pellet	Day 0, 36 mg	Day 142	3/6	1/3
Armenian	RAL pellet	Day 0, 36 mg; Day 94, 36 mg	Day 202	6/7	7/9

* Number of animals with hepatocellular adenoma or carcinoma/number of animals examined.

betes insipidus syndrome in the Chinese but not in the Armenian hamster (11). Therefore, the polyuria induced by MPA could be responsible for the diminished hyperbilirubinemia from DES in Chinese hamsters treated with MPA+DES. Yet, when the urine output of Chinese hamsters given both DES and MPA was measured, we found that the DES injection had effectively abrogated the polyuric response to MPA (Fig. 4). This was a paradoxical result considering the usual stimulatory effect of estrogen on the expression of progesterone receptor (PR) (15). To further evaluate the involvement of PR in the diabetes insipidus induced by MPA, a PR blocking agent, RU 486, was injected concomitantly with MPA. In one experiment with five Chinese hamsters, RU 486 had no effect on the MPA-induced polyuria, for the polyuric response was similar to that of a control group given only MPA (not shown). The results of this experiment are not conclusive, however, because the PR of the Chinese hamster may be similar to that of the Syrian hamster, which is refractory to RU 486 inhibition (16, 17).

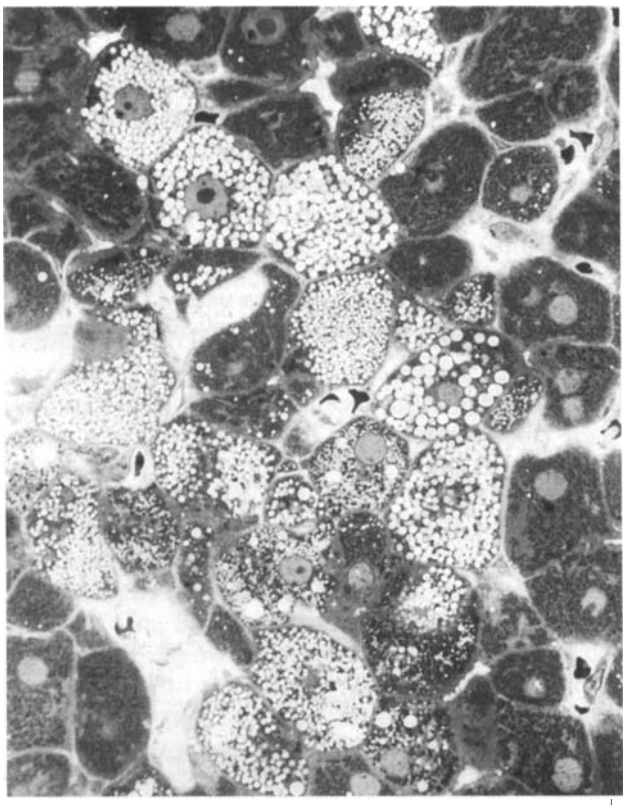

Fig. 5. Microvesicular steatosis of liver cells. (Epon-embedded section, 1 μm thick, toluidine blue stain, ×600).

Effects of long-term estrogen treatment

Chronic exposure to exogenous estrogens is associated with the occurrence of hepatic tumors in virtually all Armenian hamsters (3). This hepatic carcinogenesis did not occur in Chinese hamsters. Table 1 shows results of a number of experiments in which DES or RAL was administered to Chinese hamsters over a prolonged interval. Gross examination of the liver at necropsy revealed a striking absence of hepatic tumors when compared with their common occurrence in the Armenian hamster, because only one tumor was seen in one hamster.

The livers of 10 Chinese hamsters treated with DES for 12 months were examined microscopically.

Light microscopy findings

The changes affected liver cells, canaliculi, sinusoids, terminal hepatic venules and sublobular veins, and reticuloendothelial cells. Portal areas and their contents (bile ducts, arteries, veins) were unaffected. Stellate cells (perisinusoidal lipocytes, Ito cells) were uniformly hypertrophied, but this change was also observed in the control animals.

All livers showed patchy (non-zonal) enlargement of liver cells with microvesicular steatosis (Fig. 5). The change was considered moderate in four animals (#4, 6, 7, and 8) and marked in the remainder (#1, 2, 3, 5, 9 and 10). In all cases, the

presence of neutral lipid in the vacuoles was confirmed in frozen sections stained with oil red-O. Other changes affecting liver cells included moderate to marked anisonucleosis, scattered apoptotic bodies, occasional clusters of cells with Mallory bodies, scattered mitotic figures, and glycogenated nuclei in zone 1. No bile pigment was present in the cytoplasm.

In all animals, canaliculi were variably dilated with pseudogland formation (Fig. 6). Many canaliculi were surrounded by clusters of foamy xanthomatous cells (Fig. 7). The xanthomatous foci appeared to be unrelated to the canaliculi in some instances. Some dilated canaliculi had assumed 'giant' proportions with loss of the lining and shedding of surrounding xanthomatous cells and other debris into the lumen. (Fig. 6).

Moderate to marked sinusoidal dilatation was observed in all the livers (Fig. 8). The change was not zonal. In all livers the dilatation in some areas was striking, with dilatation of sinusoids, break up of the liver plates, and formation of pelioid cavities (Fig. 8). In most instances the endothelial lining was intact, but occasionally the sinusoids appeared bereft of endothelium. Often, there was sludging

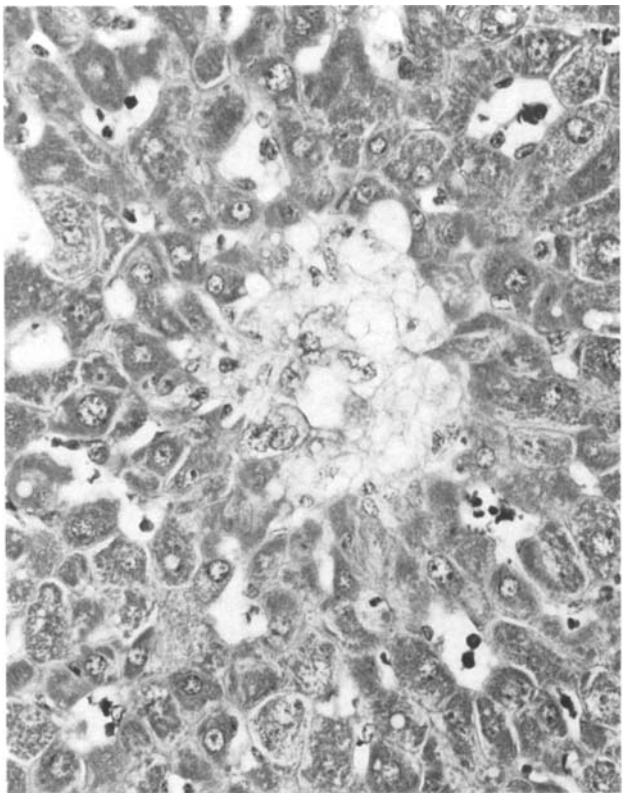

Fig. 7. A cluster of pseudoxanthomatous cells surrounds a moderately dilated canaliculus (H & E, ×400).

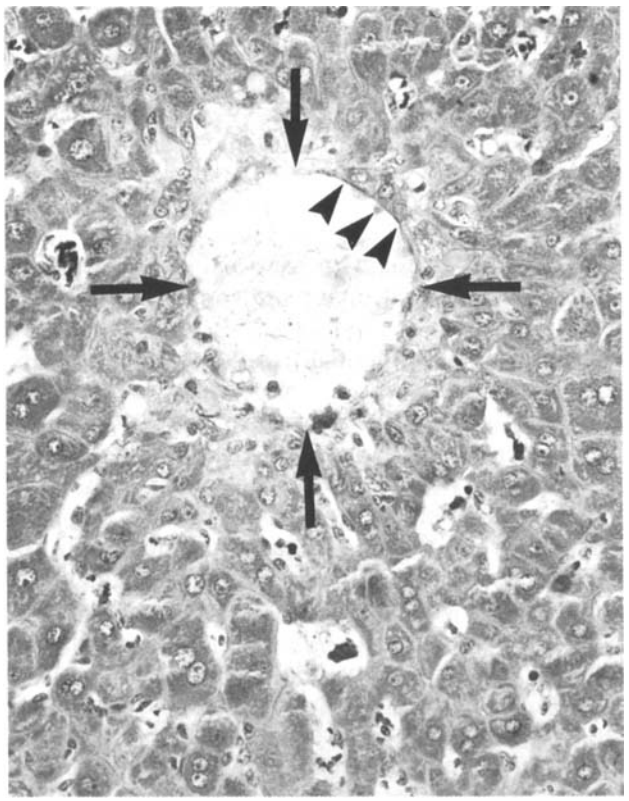

Fig. 6. Markedly dilated canaliculus. The lining membrane has been destroyed except for the segment indicated by the arrow heads. The ectatic canaliculus is indicated by four arrows. Note dilation of sinusoids in the surrounding parenchyma (H & E, ×300).

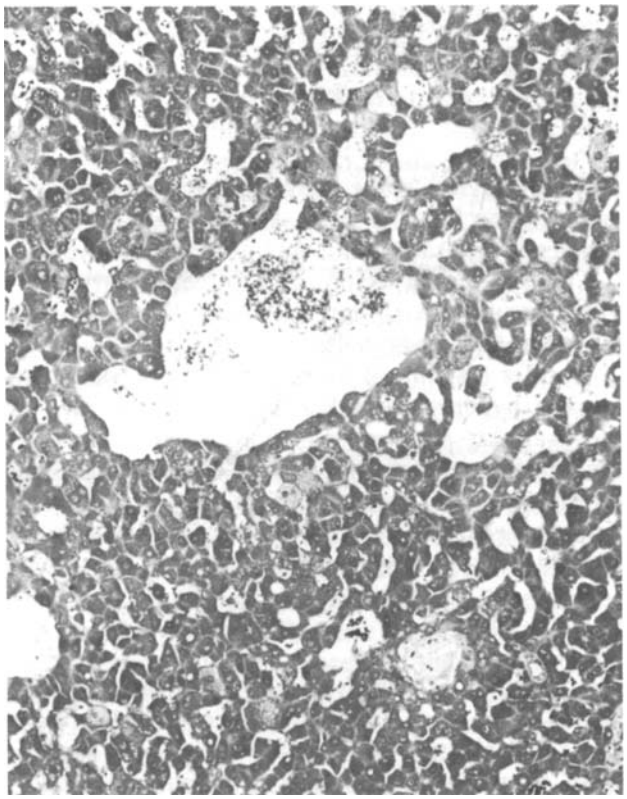

Fig. 8. Dilated sinusoids are scattered irregularly; the largest is pelioid and contains aggregated red cells (H & E, × 120).

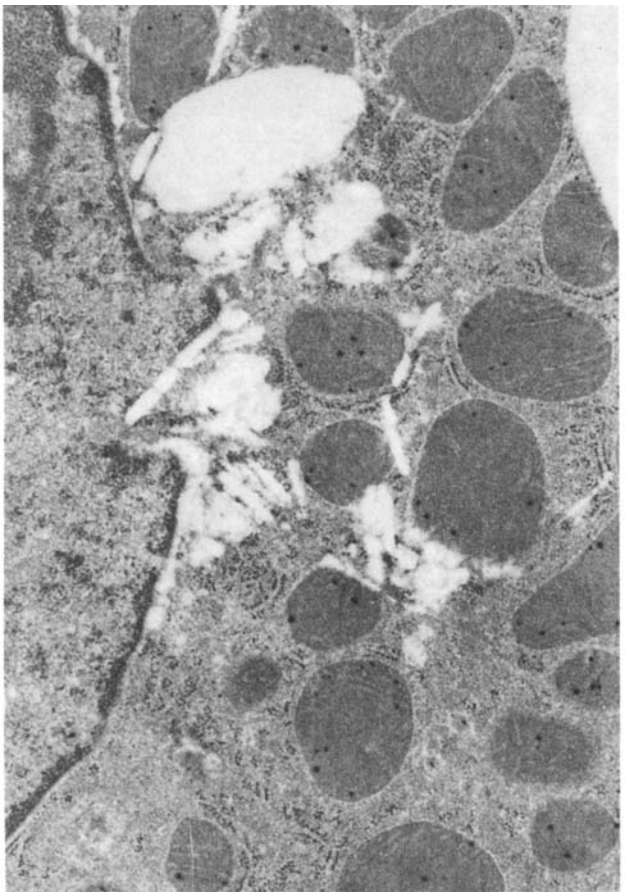

Fig. 9. Cluster of cholesterol crystals are lying free in the cytoplasm adjacent to the nucleus of an hepatocyte (electron micrograph, original magnification ×37,700).

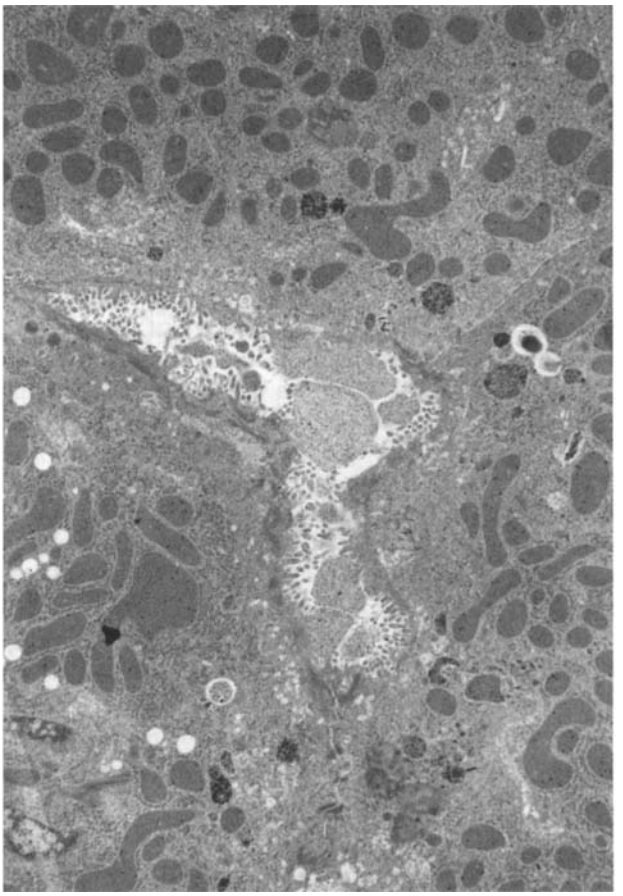

Fig. 10. Markedly swollen microvilli, some detached, are present in a dilated canaliculus with a thickened ectoplasm (electron micrograph, original magnification ×11,600).

of erythrocytes; some cells were fragmented and enmeshed in fibrin (Fig. 8). Extramedullary hematopoiesis, generally mild, was noted in all livers.

The sublobular veins, and sometimes the terminal venules, in all animals showed subendothelial prolapse of liver cells.

Kupffer cells in all livers exhibited moderate to marked hypertrophy. Most contained a brown or tan granular pigment, which was also present in the Kupffer cells of the controls. Many of the xanthomatous cells described above were derived from Kupffer cells. Lastly, Kupffer cells in all the livers showed variable erythrophagocytosis.

Ultrastructural findings

The presence of microvesicular steatosis was confirmed in all cases. In addition, scattered liver cells contained clusters of cholesterol crystals (Fig. 9); these were either perinuclear or pericanalicular. Organelles in liver cells showed only minor changes, such as variation in the size of mitochondria with an increase in matrical dense granules and focal proliferation of the rough endoplasmic reticulum.

The most prominent ultrastuctural changes involved canaliculi, which showed variable dilatation and swelling and shedding of microvilli (Fig. 10). The lumen was either empty or contained amorphous debris (including detached microvilli). Most dilated canaliculi showed thickening of the pericanalicular ectoplasm. Cisterns of the Golgi apparatus were often dilated. No dense pigment resembling bile was seen in canaliculi or in the cytoplasm of liver cells.

Sinusoids were often dilated and contained intact or fragmented erythrocytes and other circulating blood cells. Most Kupffer cells were hypertrophied and contained a finely granular, electron dense pigment in lysosomes consistent with lipofuscin. Some also contained phagocytosed erythrocytes, as well as occasional lipid globules or cholesterol crystals. Endothelial cells showed no noteworthy changes.

Table 2. Effect of estrogen on the livers of two species of hamster

	Armenian	Chinese
All estrogens, DES, EE, Zeranol	+++	+
Inhibition by TAM	+++	+++
Susceptibility	+++	+
Rapidity	+++	+
MPA inhibition	0	+
Hepatocyte transformation	+++	0
Lipid changes	+	+++
Histologic changes		
Mitotic figures	+++	+
Mallory bodies	+++	+
Canalicular changes	+	+++
Sinusoidal dilatation	+	+++
Microvesicular steatosis	0	+++
Neoplastic change	+++	0

0=absent; +=mild or minimal; ++=moderate; +++=marked.

Discussion

The domesticated strains now available of the Armenian hamster (*Cricetulus migratorius*) and the Chinese hamster (*Cricetulus griseus*) originated from wild hamsters captured near Yerevaw, Armenia in 1963 and Peking, China in 1948, respectively (18). Although not as well known as the Syrian or Golden hamster (*Mesocricetus auratus*), the Chinese hamster was actually used as an experimental animal for many years before the Syrian hamster became available. Indeed, the difficulty in obtaining the Chinese hamster for laboratory experiments prompted the capture and domestication of the Syrian hamster in 1930 (19). The unusual longevity of the Chinese hamster has been useful in toxicology research, and its few large chromosomes ($2n=22$) have been convenient for cytogenetic studies (20). The Armenian hamster and the Chinese hamster share not only the same chromosome number but also many anatomical features. Their serum proteins show many common features; especially noteworthy are the common antigens present on their various immunoglobulin classes (unpublished). We are not aware of a successful hybrid derived from these two *Cricetulus* species.

In both hamsters the response to the injection of estrogen is similar and unusual: both become jaundiced because of hepatobiliary dysfunction. Estrogen is known to alter hepatocyte physiology and impair hepatobiliary function in a number of experimental models (21–23). But, an estrogen-induced dysfunction severe enough to cause hyperbilirubinemia is unusual, except in these two genetically susceptible hamsters and in certain genetically susceptible women who develop cholestatic jaundice during pregnancy or have an idiosyncratic reaction to estrogenic compounds. The pathophysiology responsible for the jaundice may be different in the human and the hamster. For example, the bile plugs commonly found in cholestatic jaundice during pregnancy were not observed in the hamsters. For that matter, there are marked differences in pathophysiology between the two hamster species, suggesting different mechanisms responsible for the jaundice induced by estrogen. Table 2 compares the effect of estrogen injection on the liver of the Armenian hamster and Chinese hamster. In both, the estrogen receptor is the presumed mediator because a variety of estrogens with different structures can be used and their effect is blocked by concomitant injections of tamoxifen. The Armenian hamster is definitely more susceptible and responds more rapidly to estrogen administration than does the Chinese hamster. Even with massive doses of a potent estrogen, like DES, clinical icterus requires weeks to appear in the Chinese hamster versus days in the Armenian hamster. The more effective inhibition by MPA in the Chinese hamster when compared with that in the Armenian hamster could reflect these differences in estrogen responsiveness of the two species. Even so, the complete absence of any evidence of tumor formation in the Chinese hamster after 1 year of treatment with DES was unexpected, because neoplastic change was detected in the Armenian hamster after only 60 days of exposure to estrogen (2). Also, Zeranol, a weak estrogen, was carcinogenic in the Armenian hamster even when used in minimal amounts, that is, in a dose too small to induce detectable hyperbilirubinemia (3). Mallory bodies appeared early and were abundant in livers of estrogen-treated Armenian hamsters (1, 3), whereas they were rare in similarly treated Chinese hamsters.

Hepatic destruction with attendant regeneration appears more prevalent in estrogen-treated Armenian hamsters than in similarly treated Chinese hamsters, and this difference is reflected in the numerous mitotic figures in the livers of the Armenian hamsters (3). The hepatic regeneration may be a critical feature necessary for hepatic transformation in the Armenian hamster, as most models of hepatic carcinogenesis rely on hepatic destruction or ablation to promote maximal proliferation of hepatocytes, especially those genetically endowed for selective survival. Because hepatic destruction/regeneration was less apparent in the Chinese hamsters, successful neoplastic transformation after estrogen treatment may require a concomitant partial hepatectomy or some other means of stimulating hepatocyte growth. In contrast to what occurs in the Armenian hamster, the major hepatic pathology in the Chinese hamster was centered on the

canalicular damage, an alteration of fat metabolism, and striking sinusoidal dilatation. It is not known if these phenomena are related to each other. Other than the absence of bile accumulation, the canalicular changes are not unlike those seen in human cholestasis of intra- or extrahepatic causation. We are not aware of any published studies on the effect of estrogen on fat metabolism in the Chinese hamster. In the Syrian hamster, though, estrogen deprivation (castration) of females results in a rise of serum triglyceride and total cholesterol concentration to approach levels found in the serum of normal males (24). Similarly, in some experimental animals, estrogen injection depresses triglyceride levels (12), whereas in women, estrogen administration (replacement) typically results in higher serum HDL and triglycerides (25). Estrogen has a dramatic effect on fat metabolism in the Chinese hamster; its serum becomes grossly lipemic after DES treatment along with a modest elevation of cholesterol (1) and a marked elevation of triglycerides (unpublished observations). We believe this effect readily explains the hepatic steatosis and the accumulation of cholesterol noted in these animals microscopically. The mechanism for the profound hyperlipidemia induced by estrogen in the Chinese hamster is unknown. This response was not observed in the closely related Armenian hamster, and we do not know of another animal model showing such hepatic lipodystrophy after estrogen treatment.

The dramatic sinusoidal dilatation in the Chinese hamster lacks the zonality (zones 1 and 2) of the sinusoidal dilatation reported in women on long term oral contraceptives (26–28), rarely in pregnancy (29), and in rats given ethinyl estradiol (30). The pathogenesis of the lesion is unclear. An ultrastructural study of the liver of women with sinusoidal dilatation induced by oral contraceptives has shown preservation of sinusoids with striking perisinusoidal fibrosis (31). Also noted was the enhanced activity of sinusoidal endothelial cells and stellate cells. In the present study, the sinusoidal changes (sludging of and damage to erythrocytes and the erythrophagocytosis) are probably attributable to the sluggish circulation resulting from the dilatation. Endothelial and stellate cell changes and perisinusoidal fibrosis were not observed. In the estrogen-induced sinusoidal changes in the rat, the dilatation in zone 1 was accompanied by sustained constriction of sinusoids in zone 3, the hepatic acinar outlet (30). Another vascular lesion observed in this study, prolapse of liver cells into the wall of hepatic veins, was similar to that noted in our previous study of the Armenian hamster (1).

The ER has been highly conserved during evolution and functions at the molecular level as a regulator of gene transcription. It is hormonally activated by binding to an appropriate ligand. This results in conformational changes in its structure that permit the receptor to bind to the estrogen response element located 5′ (upstream) to the estrogen responsive genes and then modulate expression of that particular gene. It is apparent that the effect of ER on transcription is quite different in the liver of these two closely related hamsters, as they demonstrate a fascinating array of estrogen-induced pathophysiologic changes, including a common hepatobiliary dysfunction, an extraordinary hepatocarcinogenesis specific to the Armenian hamster, and profound lipodystrophy-canalicular aberration and sinusoidal lesions peculiar to the Chinese hamster. Comparative studies in these two species of hamster may reveal the gene activation responsible for these particular events.

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