AEROMEDICAL REVIEWS

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30 p Review 2-63

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Advanced Course in Aviation Medicine 62-A

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BROOKS AIR FORCE BASE, TEXAS
February 1963

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INTRODUCTION

A series of recent experiments has implicated the central nervous system in the mechanisms producing hepatotoxicity. Knowledge of toxic substances is of increasing importance in missile and space operations. Furthermore, in the field of aerospace medicine, it is important to continuously extend understanding of the functions of the nervous system and the neurohormones. Accordingly, the concept of a peripheral toxic effect being mediated by the central nervous system is worth attention and is the theme of this review. Since many of the morphologic and biochemical changes induced by carbon tetrachloride (CCl_4) are well known, this compound serves as a convenient example in discussing the theme with respect to hepatotoxicity (28, 46, 47, 135, 169).

Small amounts of CCl_4 in man and other mammals produce centrilobular necrosis and diffuse fatty infiltration of the liver, regardless of the route of administration. In moderately severe cases of CCl_4 hepatotoxicity, histologic findings include: swelling, degeneration, and necrosis of the polygonal cells of the central zone of the liver lobule; congestion of the central lobular veins and tributary sinusoids; and swelling of the mid-zonal cells (1, 69, 96, 130). Biliary changes are not usually seen. Fatty vacuolization of the liver cells involves the whole liver diffusely. This fat is composed mainly of triglycerides (17, 144, 145).

Classically, it has long been taught that these pathologic changes are the result of a direct effect of the CCl_4 on the liver cells (136). To some investigators these histologic findings have suggested a specific sensitivity of the central cells to chemical

poisons. Others have invoked a special collateral circulation between sinuses in the periphery of the lobule. Most, however, believe that these changes are essentially the result of centrilobular hypoxia induced by blood stagnation, by diminished centrilobular circulation, or by the peripheral cells using the available oxygen (2, 3, 20, 28, 31, 32, 46, 59, 68, 69, 70, 80, 103, 109, 135, 174).

The diffuse fatty metamorphosis that frequently occurs with the centrilobular degeneration is not explained by local areas of hypoxia nor by local circulatory changes. Many observers have questioned why the periportal liver cells, being nearest the incoming blood, show the least effect when they are exposed to the greatest concentration of the toxin. Furthermore, substances that are extremely toxic for cells in general, such as allyl formate and *Proteus* endotoxin, do produce greatest cell damage in the periportal areas and least in the centrilobular areas (151). Fatty infiltration usually does not occur after the latter agents are administered.

The literature on acute liver damage contains reports of many different substances and widely differing situations that produce essentially the same pathologic changes in the liver as CCl_4 (2). The nonspecific nature of the changes is emphasized by listing some of the conditions and circumstances in which they are found in man as well as in laboratory animals. In humans, central lobular necrosis has been recorded in right heart failure, malaria and blackwater fever, Chiari's disease, hyperpyrexia, severe burns, thyrotoxicosis, various allergic reactions, anemias, shock, severe hemorrhage, and acute postoperative necrosis, after tanning operations, and in poisoning by a wide variety of other chemical agents including chloroform and carbon monoxide (2, 68, 109, 135). In animals, similar pathology has been reported after exposure to low concentrations of oxygen (37, 133). Anaphylactic shock readily produces hepatic vein constriction, which readily gives rise to liver engorgement, and with maximal degeneration around the central vein. Histamine, peptone, and digitalis all diminish the outflow of blood from the liver of dogs (109, 123). Acetylcholine causes hepatic sinusoidal constriction in mice; however, vagal stimulation is usually without effect (123). Both the infusion of adrenaline and stimulation of the sympathetic nervous system have been

reported to diminish the blood flow through the liver and to produce fatty infiltration (107, 108, 158). Large doses of adrenaline lead to hepatic engorgement, fatty infiltration, and centrilobular necrosis.

The appearance of essentially identical pathologic changes under diverse conditions indicates a common factor. Fatty infiltration accompanies centrilobular necrosis consistently in cases involving adrenergic stimulation and poisonings. It occurs sporadically with centrilobular necrosis of other etiology such as certain anemias, some hypoxic states, and direct vascular abnormalities (46).

The mid-zonal hepatic necrosis typified by beryllium poisoning or yellow fever hepatitis is relatively rare. The mechanism of its localization is not understood.

Hepatic steatosis occurs without significant necrosis in poisonings with a variety of agents including ethionine, hydrazine, ethanol, and certain rare earths (17, 42, 55, 90, 110, 167). It also is produced by a wide variety of dietary deficiencies (47, 117).

EXPERIMENTAL BACKGROUND

Experimental poisoning with CCl_4 has an ancient and varied history. It has been reviewed by Himsworth (80), Drill (46, 47), Popper and Schaffner (135, 136), and Stoner and Magee (169). Three general theories or lines of reasoning have been developed to account for the hepatotoxic action of CCl_4. The first of these theories is that CCl_4 directly affects the cytoplasm of the liver parenchymal cell. The specific intracellular loci considered have been the mitochondria, the endoplasmic reticulum, and the microsomes (which are a micro structure within the endoplasmic reticulum).

An early work supporting direct mitochondrial damage was that of Christie and Judah (34). They demonstrated a defect in the ability of liver homogenates of CCl_4-treated animals to oxidize fatty acids and most citric acid cycle intermediates. This was

corroborated by the work of Dianzani (38-41) and others (6, 142, 143). They postulated that CCl_4 physically attacks the mitochondrial membranes of the liver cell causing loss of the coenzyme, diphosphopyridine nucleotide (DPN) (92). This would disrupt oxidative metabolism and lead to cell death.

It has been shown that CCl_4 reaches its peak in the liver of the rat within 1 to 2 hours after oral administration and almost immediately after inhalation (144). The increase in liver triglycerides during these first few hours is roughly coincident in time with attainment of the peak CCl_4 concentration after oral administration (144, 145, 156). At this time, electron microscope data reveal essentially no changes in the mitochondria, although they do appear in the endoplasmic reticulum and microsomal structures (75, 126, 165). By 15 hours after CCl_4 administration, early centrilobular degeneration is seen; by 20 hours, centrilobular necrosis is extensive (19, 143, 149).

According to the data presented, mitochondrial function is unimpaired for at least the first four hours and probably longer (4, 5, 6, 27, 55, 56. 75, 88, 89, 145, 147, 162, 165). The time of earliest, definite mitochondrial enzymatic impairment is approximately ten to twenty hours (6, 27, 145, 162). This is after the time liver steatosis and centrilobular degeneration are shown by direct microscopic observation to be extensive.

Gallagher and his co-workers (63, 64) have shown a protective effect for DPN-sparing agents. They argue that these data support the theory of direct mitochondrial damage. Since survival of the whole animal was the end point, the protective agents could have exerted their effects o.. mechanisms remote to the liver.

It appears therefore, that the available data are overwhelmingly against the view that the liver mitochondria are the primary loci involved with CCl_4 hepatotoxicity. Furthermore, as an adjunct of our knowledge that certain electrolyte shifts can seriously impair enzyme functions, many of the experimental results implicating direct effects on mitochondrial enzyme systems may have been due to artifact (52, 136, 137, 138, 148, 162, 163, 171).

The functional integrity of mechanisms localized in the endoplasmic reticulum as a locus of direct CCl_4 damage has a great deal of excellent data supporting it. The electron microscope has provided direct observational evidence of changes in the rat liver endoplasmic reticulum as early as one hour after CCl_4 administration by stomach tube, and almost immediately after inhalation (7, 126).

Smuckler et al. (165), using radioactive tracers, have shown depression in fibrinogen and albumin synthesis very early in the course of CCl_4 toxicity. They correlate this with the observable endoplasmic reticulum changes, and with the data of Brachet (14), which indicate that protein synthesis occurs in or on the ribonucleoprotein particles within these structures of the liver cells. Smuckler et al. (165) postulate that the steatosis is a consequence of the lack of protein with which the triglycerides may be coupled and transported from the cell. Others have found that the CCl_4-poisoned liver cell has an impaired ability to excrete triglycerides *(vide infra)* at approximately the same time (155, 156). Whether these two observations are related is not known.

A recent series of experiments also implicating a direct effect on endoplasmic reticulum are those reported by Recknagel and his co-workers (104, 142-147, 155, 156). Their hypothesis is that the formation of triglycerides by the liver is not interfered with in the CCl_4-poisoned animal, but that the triglyceride secretory mechanism is destroyed (4, 61, 104, 143, 145, 155, 156). Thus, the triglycerides accumulate in the liver and are seen histologically as fatty infiltration. Other reports verify the fact that fatty acid oxidation and triglyceride synthesis are not impaired in the poisoned liver for at least the first several hours (4, 5, 28, 31). It has been shown that the normal liver is constantly secreting triglycerides into the plasma (57). A net loss of fatty acids from plasma occurs as it passes through the liver; the free fatty acids not utilized within the liver are returned to the plasma as triglycerides and components of lipoproteins (57, 58, 166).

Recknagel and Lombardi (145) state that as early as two hours after CCl_4 poisoning, certain enzyme systems in the microsome fractions are changed. This observation is supported by

the work of Neubert (125) and Isselbacher (89) and their associates. Schotz and Recknagel (156) correlate this with the rapid accumulation of triglycerides in the liver (34% increase in one hour and 195% within three hours) at a time when the toxin is maximally concentrated in the liver. This would thereby imply a serious derangement of hepatic lipid metabolism (155). Recknagel and Lombardi suggest an unspecified hepatic mechanism localized in the membranous component of the endoplasmic reticulum as the key locus for direct action by CCl_4, at least for the production of the fatty infiltration.

The problem of why the concomitant degeneration and necrosis are localized in the centrilobular area is not explained by damage to a component found in all liver cells. Furthermore, very careful analysis has shown that the increased amounts of liver triglycerides have the same percentage of linoleic acid as adipose tissue triglycerides and plasma triglycerides (62, 110). Since mammalian liver is unable to synthesize any appreciable amount of linoleic acid, it is apparent that the triglycerides that accumulate in the liver after poisoning come from the adipose tissue depots rather than being formed within the liver *de novo* (9, 17, 110).

There is considerable evidence that significantly increased levels of plasma free fatty acids occur after CCl_4 poisoning and, indeed, after almost any stress (11, 17, 33, 112). The mobilization of free fatty acids from adipose depots has been shown to be due largely to epinephrine and norepinephrine (13, 51, 52, 57, 71, 72, 76, 93, 150, 154, 178, 179). An intact adrenal and pituitary are prerequisite for adrenergic fat mobilization (71, 106, 107, 111, 131, 140, 160). The adrenal corticoids and certain other hormones appear to play a permissive role (105, 106, 111, 140, 160, 161). A wide variety of adrenergic blocking agents has been found to prevent fatty infiltration of the liver (110, 115). This protective effect could conceivably be due to unappreciated pharmacologic effects, but the evidence indicates that it prevents mobilization of the free fatty acids from the adipose depot (12, 58, 154).

Rossi and Zatti (153) concluded that CCl_4 has a direct effect on microsomal enzymes that oxidize fatty acids and synthesize

phospholipids and triglycerides. Their own data show, however, that this is after other enzymatic and micromorphologic changes have occurred, and after fat accumulation has already begun.

A second major theory suggests that permeability changes in the cell wall and subcellular interfaces such as the boundary membrane of the endoplasmic reticulum are the direct and immediate consequence of CCl_4 poisoning (100). These changes then lead to electrolyte shifts and accumulation or depletion of certain metabolites (44, 127).

Rees et al. (149) stress that the earliest accurately charted cellular events associated with centrilobular necrosis are: loss of intracellular potassium and magnesium, and intracellular accumulation of water, sodium, chloride, and calcium. All of these they term "permeability changes." The earliest ultra-microscopic change in the cell is the swelling and then the dissolution of the endoplasmic reticulum (8, 126, 162, 165). The experiments of Neubert and Maibauer (125), which showed a decline in certain microsomal enzymes in CCl_4-poisoned rat liver, complement these morphologic findings. Considering the relationship of the endoplasmic reticulum to electrolyte metabolism (127, 129), it is consistent with the hypothesis that the critical event is the effect on the permeability of the cell wall so that the cell is unable to maintain the normal gradients of electrolytes and water (127, 172, 174). Studies with the electron microscope indicate that at least part of the endoplasmic reticulum may be an invagination of the cell wall (129).

It has been shown that cellular excess of calcium or loss of potassium severely interferes with normal mitrochondrial functions and, in particular, causes oxidative phosphorylation to cease (67, 117, 118, 137, 163, 164). It can be inferred that disruption of electrolyte homeostasis within the cells can have serious consequences generally; the aforementioned is but one example (118, 137, 163, 164, 172). Other areas within the cell probably would be affected as severely as the mitochondria, although this possibility has not been thoroughly explored (128). It has been shown that the liver parenchymal cell is normally hypertonic in relation to plasma by a factor of at least 2 (127).

Hokin and Hokin (81-86, 148) have elucidated a mechanism for transferring such hydrophilic substances as sodium and certain proteins across lipid membranes by means of a phosphatide cycle located within the membrane. Their work on phosphatidic acid and phosphoinositide may become prototypes of universal transmembrane transport mechanisms. Since CCl_4 is a nonpolar solvent, its dissolving in cell membranes, that are largely lipid, could account for the permeability changes of these membranes, possibly by direct interference with a phosphatide cycle. The work of Hokin and Hokin has not been mentioned previously in this context, to the author's knowledge. It is mentioned here as a new and perhaps provocative idea for further research. Triglycerides are probably attached to protein, thereby becoming hydrophilic, prior to secretion from the hepatic cell. Their accumulation and the associated electrolyte shifts raise the question of the existence of a phosphatide cycle in the liver cell membrane and the endoplasmic reticulum membrane that CCl_4 may affect.

A great deal of the research concerning hepatotoxicity has been tied to studying the effects of agents that have been shown to be protective wholly or in part after experimental poisoning. These agents include certain sulfa drugs, chelating agents, DPN-sparing agents, Phenergan, reserpine, oxygen, and a large number of adrenergic blocking agents (23, 24, 70, 80, 100, 110, 117, 120, 149). Rees (149) points out that these agents do not necessarily detoxicate CCl_4, since in some cases, such as with Phenergan, fatty infiltration occurs as before, although centrilobular necrosis is prevented. During the Phenergan protection, the aforementioned electrolyte shifts do not occur (118, 149). This is thought to be corroborating evidence for the importance of electrolyte permeability effects (21, 127).

A third major theory is that proposed by Brody and his coworkers (18, 20, 28, 30, 31, 121). It is a unifying theory and is a very provocative and interesting concept. He has implicated the central nervous system in the mechanism of CCl_4-induced hepatotoxicity (31). The stress initiated by CCl_4 evokes a sympathetico-adrenal discharge, causing vasoconstriction and reduced intrahepatic blood flow (36, 74, 108). The reduced blood

flow decreases the available oxygen which is used by the more favorably situated peripheral cells. The centrilobular cells thereby become hypoxic and subsequently undergo degeneration and necrosis (121). Concomitantly, the sympathetic discharge causes mobilization of fat from the peripheral adipose depots (74, 106, 140). This fat is carried to the liver (and elsewhere) where it is taken up. Why it stays in the liver is not discussed by Brody. However, the triglyceride secretory defect discussed by Recknagel et al. (146) is consistent with Brody's hypothesis in this regard. Some of Brody's experimental findings have not been corroborated by others; nevertheless, the concept itself is of great importance and worthy of every consideration (115, 149, 157). In general support of Brody's theory, it has been noted that stimulation of the sympathetic nerves leading to the liver or injection of Adrenalin have been shown to induce marked hepatic vasoconstriction and reduction of hepatic blood flow. These are followed by cloudy swelling and centrilobular degeneration and sometimes necrosis (28, 108, 158).

CCl_4 has been shown to deplete the adrenal medulla of catechol amines, increase their plasma levels, and then their urinary excretion (19, 157). A similar sympathetic adrenal response has been found by others after administration of such other toxins as ethanol (17, 77, 94, 111, 131). They also found hypophysectomy, thoracic cordotomy, adrenalectomy, and adrenergic blocking agents to be protective (17, 19, 20, 23, 24, 95, 110, 111, 131, 140).

The exact mechanism or point of sympathetic stimulation by these toxins is not known; however, it is known that agents such as CCl_4 and ethanol are central nervous system depressants or anesthetics. They can be assumed to have this effect on different levels within the central nervous system progressively, beginning in the highest phylogenetic level or cortex. Von Euler and Folkow (54) have shown by electrical stimulation of the orbital cortex of the cat that this area normally inhibits the secretion from the adrenal medulla. The hydrocarbon acting on the cortex might depress such inhibition before interfering with adrenal-stimulating centers located in the hypothalamus, thereby bringing about a prolonged sympathetic stimulation (22, 60). Also in the probable

pathway are the hypophysis and spinal cord, since removal of the hypophysis or transaction of the thoracic spinal cord protects the liver (17, 20, 110, 111).

It is well known that sympathetic discharge is a prompt, potent stimulus for the release of free fatty acids from the peripheral fat depots (12, 13, 76, 140). The adrenal medullary hormones are very effective in fat mobilization (13, 71, 160). It has been shown during the mobilization of free fatty acids following administration of CCl_4 and other toxins that adrenal catechol amines are being depleted (17, 19).

Several reports have indicated that hyperlipemia, such as occurs after fat ingestion, reduces the tissue availability of oxygen (91, 98, 122, 170, 171). If this is the case, it is possible that the increased plasma lipids following CCl_4 poisoning might aggravate any local hypoxia that may occur in the liver. There is at least one experiment finding no such effects, after administration of a fat emulsion intravenously (25).

Experiments have shown that hypoxia can evoke cloudy swelling, centrilobular degeneration, and areas of fatty infiltration in the liver (7, 32, 37, 68, 69, 79, 102, 113, 116, 133). Goldschmidt et al. (70) in 1937 showed the protective action of oxygen against the centrilobular necrosis that occurred after chloroform anesthesia.

In further support of Brody's theory, several experiments have shown reduction of hepatic blood flow immediately following CCl_4 administration (2, 3, 69, 134, 158, 176). In one of these, Wakim and Mann (176) held a CCl_4-soaked swab to the rat's nose during direct microscopic observation of the transilluminated liver edge and saw immediate intrahepatic vasoconstriction as well as gross paling of the liver. When the swab was taken away promptly, the circulation returned. When the inhalation continued for a longer period (e.g., thirty minutes), the vasoconstriction was prolonged (e.g., two to three hours) and the picture of central lobular degeneration and fatty infiltration ensued, becoming maximal at twenty-four hours. After repeated inhalations, cirrhosis

of the liver was produced. However, Stoner (168) used a thermocouple embedded in the liver of nonanesthetized rats to measure thermal conductivity, and found that blood flow in the liver did not decrease after CCl_4 administration. These results are inconsistent with direct observations. Even though this method is quite sophisticated and apparently very reliable, the evidence acquired by repeated direct visual observation is practically irrefutable.

The inconsistent results reported by various investigators concerning the protection afforded by various adrenergic blocking agents may be explicable (23, 44). There were considerable variations in the dosages of the agents and the times of administration. Since these agents are potent vasodilators, differences in absorption of the toxin itself probably occurred, as well as differences in peak concentration and duration of high toxin concentrations at the target organ(s). The portals of entry of the toxin (stomach tube vs. inhalation vs. injection) have further complicated comparison since the time of arrival and peak concentrations of the toxin at the target organ would be different. It is conceivable that vasodilation could allow the toxin to be more abundant at the target organ than it would have been otherwise, thus accounting for instances of aggravating toxicity instead of affording protection (23, 44).

DISCUSSION AND CONCLUSIONS

After a survey of the literature, it is concluded that the probable course of events, at least theoretically, is as follows: carbon tetrachloride dissolves in the lipids of the cell wall of the liver cells and membranous endoplasmic reticulum. By so doing, it interferes with the active mechanism responsible for maintaining transmembrane gradients of water, electrolytes, and hydrophilic proteins. A prototype for this mechanism might be the phosphatidic acid and phosphoinositide cycles that have been found in other organs. The liver parenchymal cell is normally hypertonic; so, as the cell membrane is altered, plasma water enters the cell osmotically and causes it to swell.

The changes thus far are mild or minimal, as maybe inferred by the term "cloudy swelling." Simultaneous with these changes, however, the sympathetic nervous system is being stimulated by unknown mechanisms. The sympathetic nervous system and its neurohumoral agents promptly cause hepatic vasoconstriction, reducing hepatic blood flow, and concomitantly oxygenation. The more favorably situated periportal cells utilize most of the available oxygen, rendering the centrilobular cells hypoxic. The hypoxia is superimposed on the already impaired transport mechanism of the membranes, causing still further impairment. The oxygen lack itself interferes with energy metabolism. The net result is degeneration and necrosis of the centrilobular cells.

A concomitant result of sympathetico-adrenal stimulation is the large-scale mobilization of free fatty acids from the peripheral fat depots. The fatty acids are carried in the plasma to the liver (and other organs). The liver cell oxidizes and esterifies them normally to produce large quantities of triglycerides. The liver cell is unable to secrete the triglycerides adequately. This inability may be associated with inadequate amounts of intracellular protein with which the triglycerides are bound, may be due to the membrane secretory impairment for hydrophilic substances, or may be due to some other defect not yet discovered. The result is accumulation of triglycerides within the liver, the main component of the fatty infiltration.

SUMMARY

A literature survey of hydrocarbon-induced, experimental, acute hepatotoxicity was made. It was concluded that CCl_4, and probably other hydrocarbons, directly interfere with the selective permeability of the liver cell wall and membranous endoplasmic reticulum for electrolytes, water, and certain hydrophilic proteins. Concomitantly the toxin stimulates the sympathetic nervous system and the release of its hormones. These reduce hepatic blood flow, by vasoconstriction, thereby inducing centrilobular hypoxia, degeneration, and necrosis. These also cause massive mobilization of fats from the peripheral depots. These fats accumulate in the liver where their secretion, as triglycerides, is blocked by unknown mechanisms.

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