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Vascular hepatotoxicity related to heroin addiction

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Summary. The hepatotoxic effect of heroin has been demonstrated in liver biopsies by morphometric analysis of four groups of patients: twenty-one drug abusers (DA) at the time of the biopsy, eighteen patients who had stopped drug consumption for at least six months (ex-DA), twelve patients with post-transfusional chronic active hepatitis (PTCAH), and eleven controls (CONTROL). Semiquantitative assessment showed the extent of sinusoidal dilatation and the inflammatory and fibrotic reaction in the terminal hepatic vein (THV). Thickening and cellularity of the venular wall and the volume density of sinusoidal lumen (Vsl) in the Zone I and III of the hepatic acinus, were also evaluated. The morphometric analysis used computerized measurements. In DA, the sinusoidal dilatation (100% of cases), the sinusoidal and THV inflammation (81% and 67.7%, respectively), localized mainly in the centrilobular zone, were more pronounced than in ex-DA, in patients with PTCAH and in CONTROL (significantly different $P<0.0001$). Conversely, the fibrotic reaction (perisinusoidal fibrosis – 44.4% and perivenular fibrosis – 61.1%) was more frequent in ex-DA. The THV inflammation in DA was replaced by a fibrotic matrix deposit in the THV wall (wall surface/internal surface $=2.72\pm0.37$ in ex-DA; 1.38 ± 0.32 in DA; 0.87 ± 0.14 in PTCAH and 0.45 ± 0.03 in CONTROL – significantly different $P<0.001$), associated with a perisinusoidal fibrosis, after drug withdrawal. Moreover, there was significantly decreased venular wall cellularity in ex-DA (wall surface/mesenchymal cells $=949\pm158$ in ex-DA; 622 ± 40 in DA; 619 ± 61 in PTCAH; 547 ± 23 in CONTROL – $P<0.001$). Semiquantitative and morphometric data suggest that these vascular lesions and their reversibility may be due to the direct hepatotoxic effects of heroin.

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Introduction

The association of liver function test abnormalities and drug abuse is well documented and mainly related to viral hepatitis: indeed much emphasis has been placed on the role of the needle and syringe exchange in the transmission of hepatitis B or C (Alter and Michael 1968; Litt et al. 1972; Marks and Chapple 1967). Previous studies have implicated viral hepatitis (Levine and Payne 1960; Potter et al. 1960) or alcoholic hepatic disease (Stimmel 1972) as the predominant cause of hepatic damage in heroin dependency. Different degrees of hepatocellular necrosis, portal inflammation by mononuclear cells, often associated with fibrosis and bile duct changes have been reported (Cooper et al. 1975; Edland 1972). However, some workers have thought that the role of viruses is sufficient to explain the genesis of the liver dysfunction in addicts. Other possibilities have been entertained, such as the direct toxic effect of the drug (Kloss et al. 1984). In fact, cocaine toxicity has been demonstrated by reports of renal infarction (Perino et al. 1987), intestinal infarction (Nalbandian et al. 1985), myocardial infarction, arrythmia and ischaemia (Coleman et al. 1982), pulmonary emphysema and congestion (Cherubin et al. 1972), cerebral infarction (Schwartz and Cohen 1984) and death (Mittleman and Wetli 1984). In the liver, this toxic effect has also been established and documented in animal models (Ellington and Rosen 1987; Shuster et al. 1977) and a few cases of fulminant hepatonecrosis in humans, have been described (Edland 1972; Perino et al. 1987). For some authors, chronic parenteral or non parenteral heroin consumption may be associated with frequent and severe elevation of trans-

aminase values (Cooper et al. 1975; Marks et al. 1967). Moreover, focal inflammatory lobular infiltrate, Kupffer cells hyperplasia, increased lipofuscin in hepatocytes, portal inflammation and eosinophilic bodies indicating cellular necrosis were found by Sarin et al. (1987) in liver biopsies from heroin smokers.

Heroin (diacetylmorphine) is a synthetic morphine derivative, which is hydrolytically deacetylated to 6-acetyl-morphine, in human, and excreted in urine (Edland 1972). The bioactivation of the drug is carried out by a cholinesterase and probably other enzymes in the blood and produces reactive metabolites, which are responsible for the toxic liver lesions. The metabolic conversion to monoacetylmorphine also occurs spontaneously in solution and has been demonstrated after exposure to blood and tissue homogenates of liver, kidney and brain. The direct clearance of heroin is less than 1% of the administred dose (Sawynok 1986). The liver has the greatest ability to produce monoacetylmorphine, which is transformed into morphine 3-glucuronide, concentrated in the bile and excreted by the kidneys. Liver injury increases as free morphine is conjugated and excreted in the urine (Edland 1972).

As perivenular, sinusoidal and perisinusoidal areas are known to be the preferential targets of numerous heptotoxic substances, out attention in this communication is focused onto the sinusoidal and terminal hepatic vein (THV) alterations in biopsies from drug abusers, by means of histological and morphometric investigations, in an attempt to define better the role of heroin on liver injury.

Material and methods

The study was conducted on thirty nine heroin intravenous drug abusers (mean age 26 ± 7 years) who had elevated transaminase values. Eighteen patients had stopped drug consumption for at least six months (ex-DA) and twenty-one were drug abusing at the time of the biopsy (DA). Their biopsies were compared to those of twelve patients with post-transfusional chronic active hepatitis (PTCAH) without cirrhosis (mean age 35 ± 5 years) who had denied previous drugs abuse. Eleven other patients, whose biopsies were performed during cholecystectomy, and whose liver function test and liver histology were normal, comprised the control group. All patients were HBs-Ag and were also anti-HIV negatives. For addicts hepatitis C status was unknown.

All specimens were fixed in Bouin's fluid and embedded in paraffin. Sections at 4 μm were stained with haematoxylin-eosin, Gordon and Sweet's method, Masson's trichrome and picro-sirius red for collagen. The semiquantitative evaluation was carried out to determine the extent of the: (*i*) sinusoidal dilatation, THV and sinusoidal inflammation, graded on a scale of 0 to 2+ (0=none, 1+=minimal and 2+=extensive and/or severe), (*ii*) THV wall thickening, graded according to Caulet et al. (1989), modified from

Table 1. Number of THV measured for morphometric study of wall cellularity and wall thickening

	Biopsy cases	THV number	Transversely sectioned THV
CONTROL	11	99	34
DA	21	144	54
ex-DA	18	32	10
PTCAH	12	64	26

THV transversely sectioned selected by IDmin/IDmax > 0.67

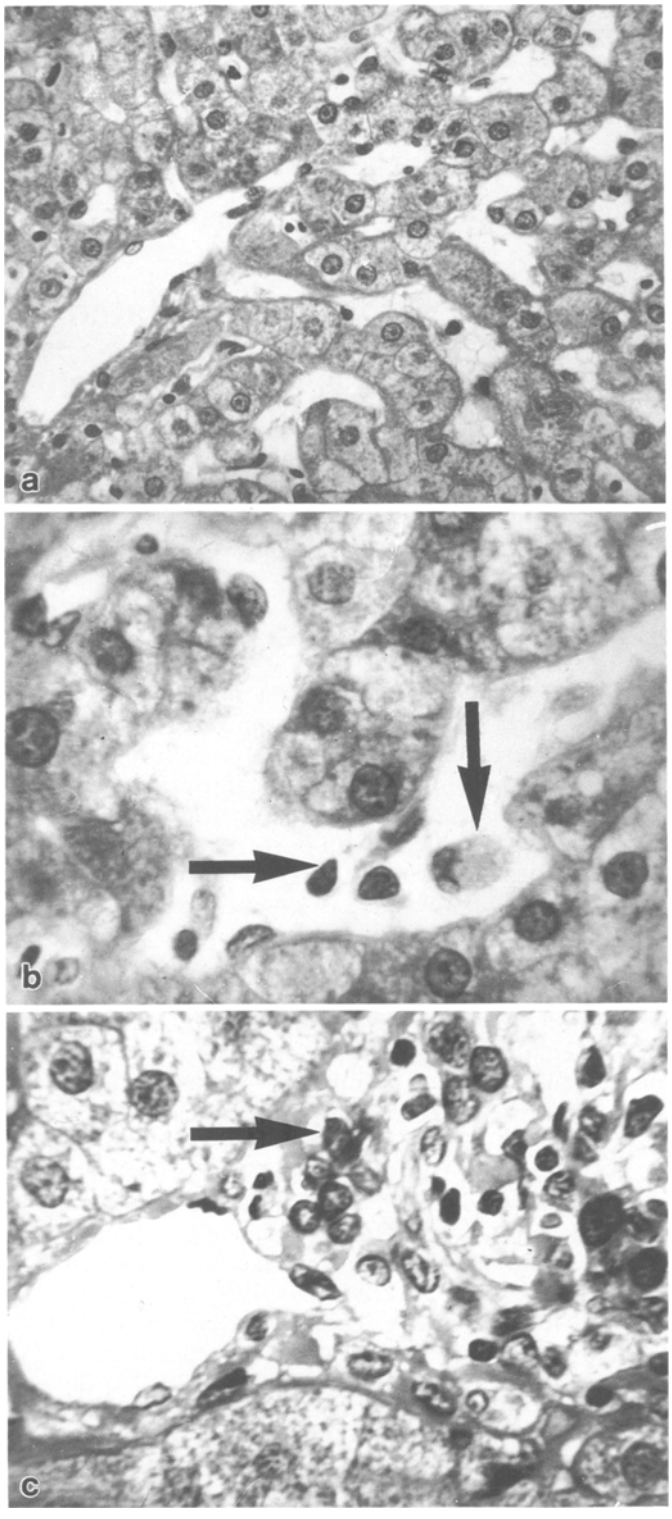

Fig. 1a–c. Vascular centrilobular histological lesions in heroin users. **a** Sinusoidal dilatation. Masson's trichrome; **b** Polymorphonuclear and lymphomonocytes (arrows) in the sinusoidal lumen. Masson's trichrome; **c** Patch inflammation (arrow) in THV wall. Masson's trichrome. **a** ×384; **b, c** ×960

Orrego et al. (1979), of 0 to 3+ (0=normal THV wall, 1+=thin irregular rim of fibrosis, 2+=moderate regular or irregular rim of fibrosis, 3+=thick surrounding fibrosis), (*iii*) perisinusoidal fibrosis, was graded on a scale of 0 to 3+ (0=none, 1+=minimal, 2+=moderate and 3+=extensive and/or severe).

Morphometric measurement were performed using a semiautomatic image analysis system (Leitz-Dialux microscope, Varioscan V16 camera, Leitz ASM 68 K computer with black and white monitor, digitizing table and Hewlett-Packard Thinkjet printer). Leitz ASM 68 K Measures Graphic and Statistics program were used.

Terminal hepatic veins (THV) were analysed on Masson's trichrome and picro-sirius red stained slides. Microscopic images of vein sections were projected onto the monitor linked to a digitizing table using ×25 or ×40 objective lens. The external perimeter and the functional internal border lumen were traced with an electronic pen and the measurements were stored and evaluated by the computer. The following variables were automatically obtained: internal surface (IS), external surface (ES), external diameter (ED), internal perimeter (IP), maximal (IDmax) and minimal (IDmin) diameters.

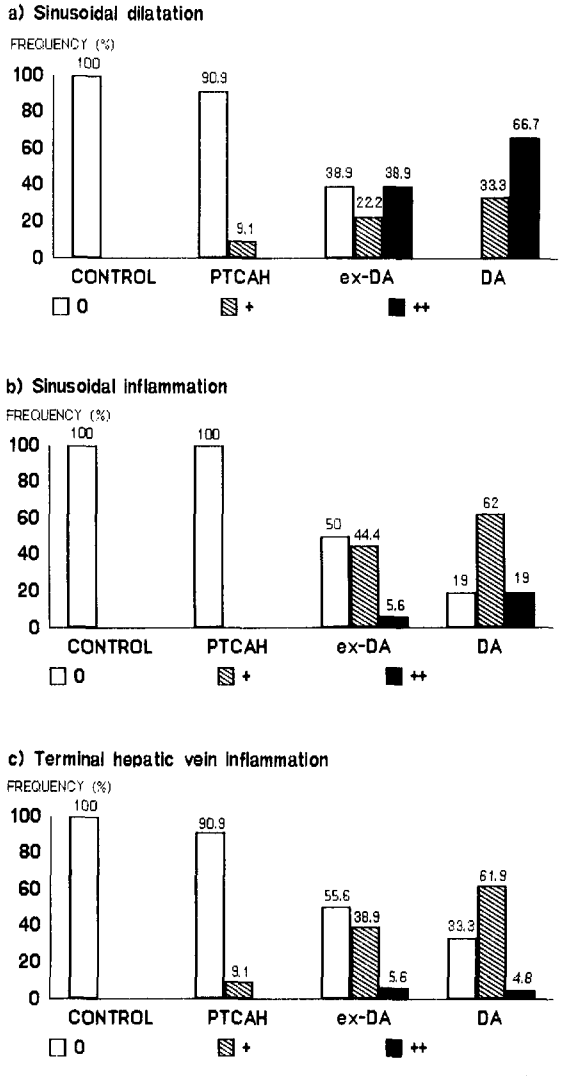

Fig. 2a–c. Frequency distribution of vascular lesions by semiquantitative assessment in CONTROL, PTCAH, ex-DA and DA patients. Graded on scale of 0 to 2+ as 0=none, 1+=minimal and 2+=extensive and/or severe. Tested by cross-tabulation and expressed by their Kendall's Tau C (τ). **a** Sinusoidal dilatation. $\tau=0.69$, $P<0.0001$. **b** Sinusoidal inflammation. $\tau=0.57$, $P<0.0001$. **c** THV inflammation. $\tau=0.43$, $P<0.0001$

Two hundred and forty THV were analysed and compared with previous morphometric analysis of the THV in eleven surgical biopsies (Porto et al. 1989). THV were selected by IDmax up to 150 μm and transverse sections were accepted when the ratio IDmin/IDmax was greater to 0.67 as shown in Table 1.

The wall surface was calculated by the difference between external and internal surface (WS=ES−IS). The thickness of the venular wall was evaluated by the ratio WS/IS (wall surface/internal surface). Mesenchymal and inflammatory (mononuclear and polymorphonuclear) cells were counted in the THV wall on haematoxylin-eosin and Masson's trichrome stained slides. The cellularity of the THV wall was assessed by studying the ratio of wall surface/mesenchymal cells – WS/Mc (Porto et al. 1989). The extent of venular inflammation was also estimated by the ratio inflammatory cell/mesenchymal cell number and scored as follow: Ic/Mc=none=0, 1+=1.00<Ic/Mc, 2+=1.00<Ic/Mc<2.00 and 3+=Ic/Mc>2.00.

The study of the volume density of the sinusoidal lumen (Vsl) was performed on paraffin sections after Gordon and Sweet's silver reticulin impregnation according to Lemoine et al. (1982). Stained slides were examined through a Laborlux D and Varioscan V 16 camera. A graticule with 35 intersection points was superimposed onto the monitor (12.5×17.5 cm) on which projected images of liver lobules represented 0.45 mm^2 field of the tissue section, using ×100 objective lens. The volume density of sinusoidal lumen in each biopsy was estimated by the ratio Ps/Pt. The sum of the intersection points of graticule inside the sinusoidal lumen corresponded to Ps; Pt represented the total of fields of a specific zone multiplied by 35 (Bioulac-Sage et al. 1984). The lobular variations of sinusoidal volume were evaluated in distinct series of counts from the centrilobular and from periportal areas. Point-counting was performed in the hepatic acinus including 4 to 6 hepatocytes

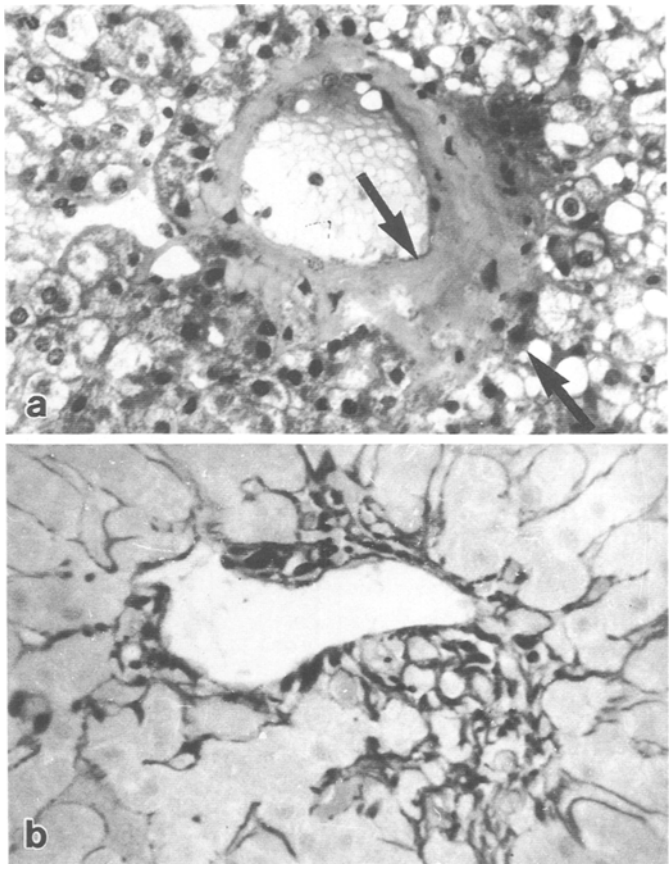

Fig. 3a, b. Fibrosis of perivenular area in ex-heroin users. **a** Fibrotic thickening of THV wall (arrows). Masson's trichrome. **b** Perisinusoidal and pericellular fibrosis. Picro-sirius red. **a, b** ×384

surrounding the THV (Zone I) and the portal tracts (Zone III). In each biopsy, 2 to 7 microscopic fields were studied for the mentioned zones.

Statistical analysis was performed with SPSS. Relationships between semiquantitative variables (dilatation, inflammation and fibrotic reactions) were tested by cross-tabulation and expressed by their Kendall's Tau C (τ). THV morphometric variables were tested after logarithmic transformation. Comparison of THV variables and volume density of the sinusoidal lumen in each patients group were tested with univaried analysis, and the groups were accepted as significantly different, at the 0.05 level, by the Scheffe procedure. Values are expressed as mean $\pm$ standard error of mean (SEM).

Results

Microscopic observations showed that sinusoidal dilatation was predominantly distributed in the centrolobular areas. It was associated with a vascular inflammatory cell reaction, characterized by the presence of polymorphonuclear and mononuclear cells in the sinusoidal lumen and in the THV wall (Fig. 1). Vascular dilatation and inflammation were constant features in DA (Fig. 2). Moreover, matrix thickening of the perisinusoidal space and of the venular wall were detected. These fibrotic findings were principally scored in minimal or moderate grades. THV and centrolibular perisinusoidal fibrosis were more pronounced in ex-DA, as shown in Figs. 3 and 4.

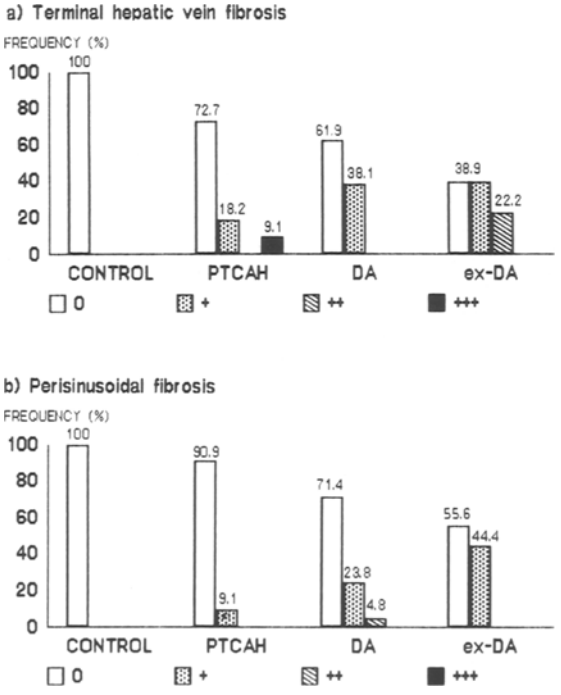

Fig. 4a, b. Frequency distribution of fibrosis assessed by semiquantitative analysis in all groups of patients studied. Tested by cross-tabulation and expressed by their Kendall's Tau C (τ). **a** THV thickening is graded on scale of 0 to 3+: 0=normal THV wall, 1+=thin irregular rim of fibrosis, 2+=moderate regular or irregular rim of fibrosis, 3+=thick surrounding of fibrosis. $\tau=0.32$, $P<0.001$. **b** Perisinusoidal fibrosis is graded on scale of 0 to 3+: 0=none, 1+=minimal, 2+=moderate; 3+=extensive and/or severe. $\tau=0.27$, $P<0.01$.

Table 1 shows the total number of THV studied morphometrically and accepted as transversely sectioned in each group of patients. The comparison of the ratio wall surface/internal surface in the four series showed that in the DA and ex-DA groups the results were respectively 3 to 6 times greater than those of the CONTROL group and from 1.5 to 3 times greater than those of the PTCAH (Fig. 5). The differences were significant between DA versus CONTROL, ex-DA versus DA and ex-DA versus PTCAH patients.

The measurements of venular wall cellularity by the ratio WS/Mc showed no significant difference between

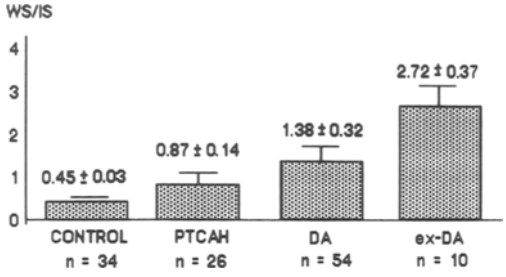

Fig. 5. Comparison of the THV wall thickening assessed by WS/IS (wall surface/internal surface) of transversely sectioned THV from biopsies of CONTROL, PTCAH, DA and ex-DA patients. Tested by univariate analysis, significantly different $P<0.001$, ex-DA patients had THV significantly different from all others groups (Scheffe procedure at 0.05 level).

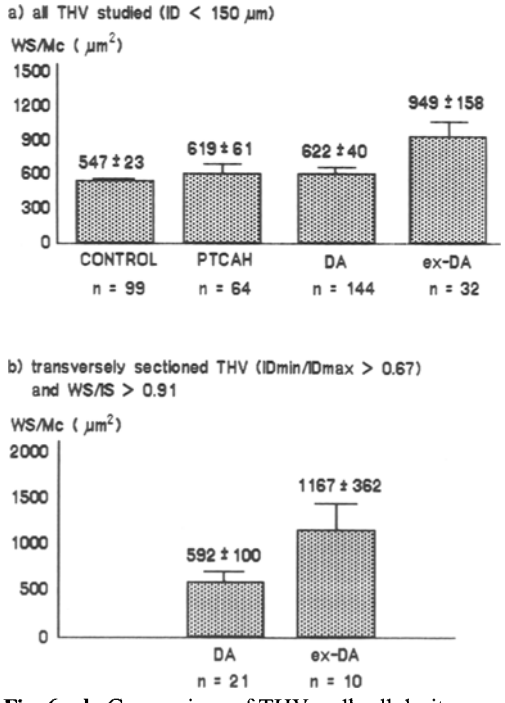

Fig. 6a, b. Comparison of THV wall cellularity assessed by WS/Mc (wall surface/mesenchymal cells) of all measured THV from biopsies of CONTROL, PTCAH, DA and ex-DA patients. Tested by one univaried analysis, significantly different $P<0.001$; ex-DA patients had THV with fewer mesenchymal wall cells than in all other groups (Scheffe procedure at 0.05 level). **a** Histogram of WS/Mc for the veins with ID<150 µm. **b** Wall cellularity of transversely sectioned THV (IDmax/IDmin>0.67 and WS/IS>0.91).

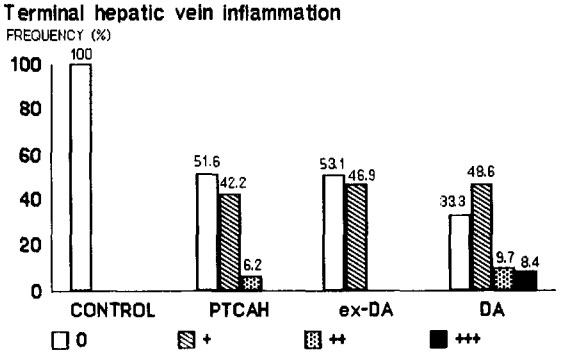

Fig. 7. Frequency of THV inflammation assessed by Ic/Mc (inflammatory cells/mesenchymal cells) counting in the wall from CONTROL, PTCAH, ex-DA and DA patients. Graded on scale of 0 = none, 1+ = 1.00 < Ic/Mc, 2+ = 1.00 ≤ Ic/Mc < 2.00 and 3+ = Ic/Mc ≥ 2.00. Tests by cross-tabulation and expressed by their Kendall's Tau C ($\tau = 0.40$; $P < 0.0001$).

Table 2. Analysed surface of parenchyma and sinusoidal lumen in the groups of patients studied (point-counting method, with a 100x objective – corresponding to 0.45 mm² field – with 35 points graticule).

	Control	DA	ex-DA	PTCAH
Zone I				
n	53	55	18	250
Parenchyma				
mean	11.7	8.2	7.8	9.3
range	20.8–2.3	14.9–1.8	11.6–2.3	14.0–2.3
total	129	123	39	113
Sinusoidal lumen				
mean	0.8	1.3	0.6	0.7
range	1.5–0.1	3.1–0.2	0.8–0.1	1.1–0.2
total	9	19	3	9
Zone III				
n	54	68	27	266
Parenchyma				
mean	10.8	9.8	6.9	10.0
range	20.3–5.4	21.2–5.4	12.2–2.3	17.2–3.6
total	119	147	49	120
Sinusoidal lumen				
mean	0.8	2.7	0.7	0.8
range	2.1–0.4	4.2–1.3	1.2–0.2	1.2–0.4
total	10	40	5	9

Values expressed in $\mu m^2 \times 10000$; *n* = number of analysed fields

DA and control veins. In contrast, the cellularity of the fibrotic THV wall was significantly decreased in ex-DA compared with the other groups. The study performed on transversely sectioned veins presenting WS/IS > 0.91 confirmed the decrease of mesenchymal cell number in the ex-DA (Fig. 6).

The study of venular inflammation showed that the thickened wall, in the majority of the DA, was determined by mural inflammatory infiltration mainly composed by polymorphonuclear cells. In contrast, ex-DA

Table 3. Volume density of sinusoidal lumen

	Zone I	Zone III
CONTROL	7.0 ± 0.4	8.0 ± 0.7
DA	15.4 ± 0.6*	28.4 ± 1.4*
ex-DA	7.3 ± 1.0	9.7 ± 0.4
PTCAH	7.7 ± 0.3	8.1 ± 0.3

Values expressed in % (Mean ± SEM); * – significantly different from all zone I and zone III from the other series, $P < 0.001$, modified *t*-Student test, anova $F_1^6 = 9.64$, non-homogeneous series $P < 0.01$

THV exhibited few inflammatory cells in their fibrotic walls. The frequency of THV with inflammatory infiltration is presented in Fig. 7.

Table 2 presents the measurements of hepatic parenchyma surface and sinusoidal lumen area in the zone I and III of hepatic acini. The Vsl was significantly increased in the hepatic lobules of DA, particularly in the zone III, $t = 13.15$, modified Student test, $p < 0.001$. There were significant differences of the Vsl values when DA were compared to ex-DA, PTCAH and CONTROL patients (Table 3).

Discussion

The recent increase in drug consumption in our society has become a major preoccupation (Organisation Mondiale de la Santé 1987). Intravenous heroin is known to be the most common means of addiction. The present investigation has established morphological changes in liver related to drug abuse. Biopsies from a control group and patients with post-transfusional chronic active hepatitis were compared with those from heroin abusers to define drug induced liver modifications. To exclude the involvement of viruses in the genesis of these hepatic lesions, we checked that all patients were HBs-Ag and anti-HIV negative. Our morphological study showed that most of liver changes affected the vascular lobular system (THV and perisinusoidal space), mainly in the centrilobular area. Cellular necrosis, steatosis or cholestasis were never seen. Semiquantitative and morphometric analysis stressed that inflammatory and fibrotic thickening of THV were more extensive in DA and also confirmed that, in the same group, the Vsl was more pronounced in the zone III. The thickening of the THV wall expressed by the ratio WS/IS which is very pronounded in ex-DA, seems to be related to a fibrotic process and to a decrease of mesenchymal cell number, as in the cicatricial reparative process. All these morphological findings suggest a possible toxic effect in the genesis of the vascular lobular lesions.

Very few reports on heroin induced liver vascular injury are to be found in medical literature. Among the somatic effects of drug abuse, hepatic lesions appear to be a widespread medical complication but little attention has been paid to liver changes due to the drug itself. It is probable that pure heroin and its contaminants may play a role in the genesis of liver disease (Litt et al. 1972).

The development of the necrotizing angiitis related to methamphetamine injection, alone or associated with heroin or d-lysergic acid diethyl-amide, has been suggested (Citron et al. 1970), although the multiplicity of injected substances as probable contaminants did not allow Citron et al. to establish, the exact role of heroin in the aetiopathogenesis of liver vascular lesions. Furthermore, Sarin et al. (1987) related Kupffer cell hyperplasia, the presence of lipofuscin pigment in hepatocytes, portal and lobular inflammation and occasional fatty changes in varying proportions to heroin in heroin smokers. These patients had no history of parenteral drug abuse, no serological evidence of viral injury, no history of alcohol consumption and showed no malnutrition. Their hepatic lesions appeared to be due to the direct toxic effect of the drug.

Sinusoidal dilatation and peliosis hepatis are of unknown origin and have been described in chronic liver disease, such as tuberculosis or linked to iatrogenic hepatopathy. They are also related to oral contraceptives, chenodiol, anabolic steroids, medroxyprogesterone acetate, vinyl chloride, arsenic, thorium dioxide, azathioprine and corticosteroids (Bagheri and Boyer 1974; Taxy 1978; Zafrani et al. 1983). A recent report (Scoazec et al. 1988) showed a relationship between sinusoidal dilatation and HIV infection. In our series all patients were HIV negative, indicating that this vascular alteration could be a direct consequence of drug toxicity. Furthermore, in four of the eight AIDS patients, studied by Scoazec et al. (1988), the liver injury related to HIV, could also be associated with drug toxicity. In another report, sinusoidal changes were associated with the systemic vascular proliferation in AIDS patients, but drug status were not detailed (Czapar et al. 1986).

Clinical and morphological findings suggest that liver damage by drugs may be the result of direct toxic effects or be the consequence of an hypersensitivity process, which emphasizes the role of cell mediated immune reactions (Kunze et al. 1985). It has been shown that codein and its metabolites have induced an increase in enzymatic activity, mediating a leakage of enzymes from the hepatocytes (Ellington and Rosen 1987; Kloss et al. 1984). Comparable effects have been seen with induced hepatic damage by dihydralazine, propranolol, carbamazepine, aromatic retinoid and azathioprine (Davion et al. 1984; Kunze et al. 1985; Thune and Mork 1980; Watanabe et al. 1979). In addition, veno-occlusive disease, perisinusoidal fibrosis and hepatoportal sclerosis have been demonstrated in patients exposed to arsenic, vitamin A, cupric sulphate, thorium dioxide and azathioprine (Zafrani et al. 1983).

Finally, in addition to the indirect heroin induced liver lesions, our quantitative morphological data suggests that the microvascular alterations, mainly in the centrilobular zone of DA, like other drug induced liver injuries, may also be due to the direct hepatotoxic effects related to heroin. The disappearance of these vascular lesions in the majority of the subjects that had stopped drug consumption, suggested the potential for reversibility of this drug induced vascular toxicity. In addition, fibrosis after drug withdrawal of the THV wall and the Disse space suggests a process resembling scar formation.

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