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Postmortem findings of pulmonary lesions of older datum in intravenous drug addicts

A forensic-pathologic study

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Summary. At post-mortem examination the lungs of 30 intravenous narcotic addicts were compared to two groups of 30 age- and sex-matched controls with no history of narcotic abuse. A distinctly uneven distribution of pulmonary pathology among the two groups was found, with various non-acute, non-granulomatous lesions dominating in the addict group. Microscopically, the typical pattern consisted of focally thickened, fibrotic and hypercellular alveolar septa, accumulation of haemosiderin-laden macrophages in alveolar walls as well as in the lumina of alveoli and respiratory passages, and vascular lesions with full-thickness fibrosis of arterial walls. An attempt at quantitative scoring of the changes indicated that the extent of pulmonary pathology increases with the addict's age or duration of narcotic abuse and with the degree of social deterioration. The same changes could also be demonstrated in some control cases with a history of salicylate or alcohol abuse, or with known heart/lung disease.

The addict group also exhibited myocardial alterations in 28 of 30 cases. Typical findings were myofibrillar degeneration and fatty infiltration.

In 15 of 30 addicts morphological and toxicological examination did not yield a definitive cause of death. However, the present demonstration of cardiopulmonary pathology suggests that narcotic addicts may be prone to acute circulatory and/or respiratory derangement even if no overdose of drugs is taken.

Key words: Lung – Heart – Drug addiction – Narcotics – Adverse drug reaction

Pulmonary oedema is a well-recognized consequence of heroin intake and is usually successfully treated with opiate antidotes and oxygen (Steinberg

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and Karliner 1968; Duberstein and Kaufman 1971; Frand et al. 1972). Oedema may develop acutely following intravenous drug administration and may essentially contribute to the addict's death. Its pathogenesis is still incompletely understood but previous studies have shown that patients with pulmonary oedema associated with heroin intake tend to suffer a more serious impairment of ventilatory function when compared with patients with pulmonary oedema secondary to myocardial infarction (Karliner et al. 1969).

In a preliminary report we described pulmonary lesions of longer duration than those seen in acute oedema, observed at postmortem in addicts with a past history of chronic multiple drug abuse (Rajs et al. 1980). The lesions comprised a focal thickening of the alveolar septa, accumulation of haemosiderin-laden macrophages as well as vascular lesions; different from the granulatomatous lesions reported by several investigators (Lewman 1972; Siegel 1972), associated with talc present as an adulterant in drug preparations.

The aim of the present study was to obtain a qualitative and quantitative post-mortem evaluation of the pulmonary lesions of older datum not associated with talc granulomata in drug addicts.

Table 1. Microscopic criteria for scoring of chronic pulmonary alterations in intravenous drug addicts

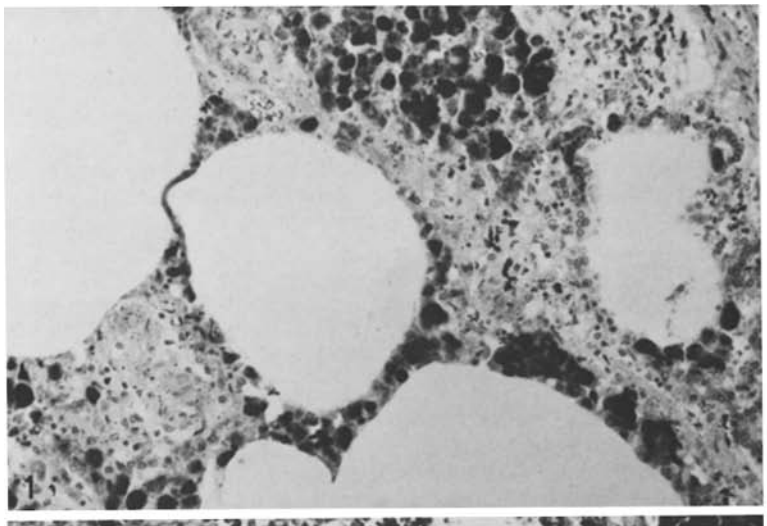
	Qualitative score
1+	Haemosiderin-laden macrophages in alveoli and/or intracellular or free haemosiderin in interstices
2+	Infiltration of alveolar septa with mononuclear leukocytes and macrophages, and fibrotic thickening of septa
	Quantitative score
+1	Single scattered haemosiderin-laden macrophages or cell debris in 1 or more sections
+2	Focal clusters of alveolar macorphages in 1 section
+3	Focal lesions as in +2 in 2 or more sections
+4	Confluent areas of lesions as in +2 in 2 or more sections

The total score represented a composite of the qualitative and quantitative evaluation of the lesions. The maximal score per case was 6.

Fig. 1. Lung section from a multiple drug addict showing oedematous thickening of alveolar septa containing numerous haemosiderin-laden macrophages (darkly stained). Perl's blue stain ×154

Fig. 2. Lung section from a multiple drug addict showing numerous haemosiderin-laden macrophages in a bronchial lumen. Perl's blue stain ×79

Fig. 3. Bronchial smear from the same case as in Fig. 2 showing numerous haemosiderin-laden macrophages. Perl's blue stain ×1032



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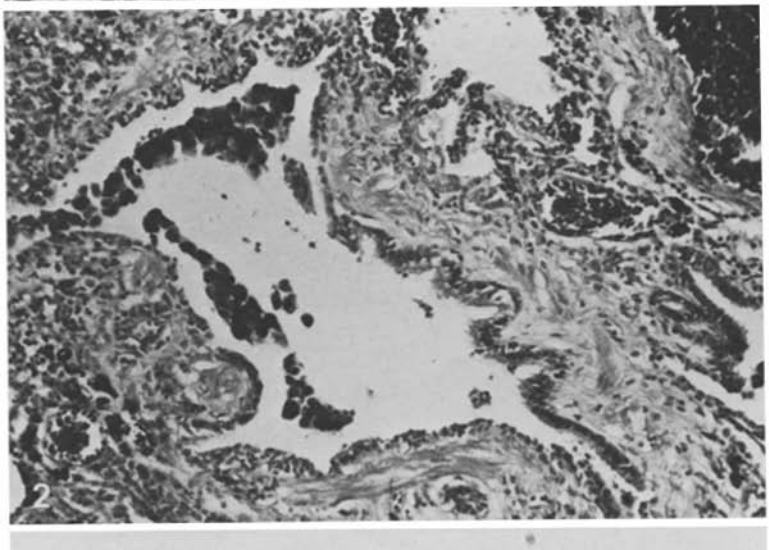

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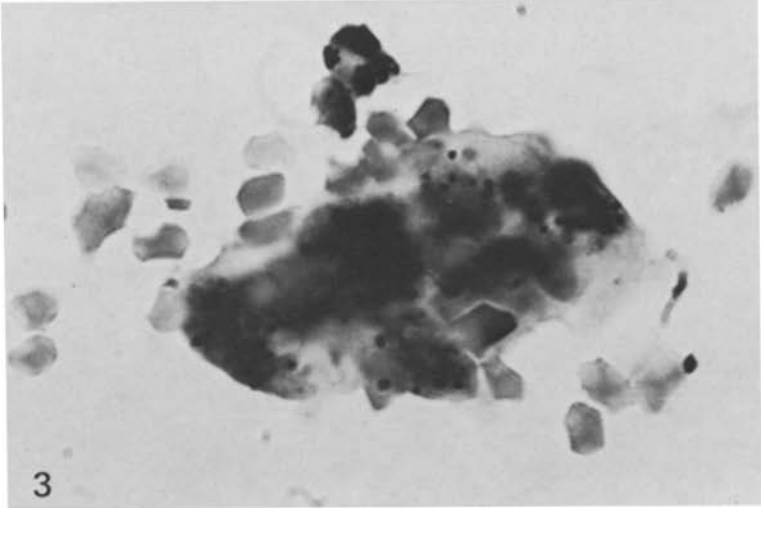

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Patients and methods

The study is based upon 30 consecutive medicolegal postmortems of persons of both sexes aged 20–49 years, mean 27 years, with a known history of intravenous addiction of opiates, most often heroin, and/or amphetamine. Twenty addicts had died under circumstances suggesting sudden death or a short survival time and continuous coma after intravenous drug injection. In ten cases the addicts were dead from violent action or from intercurrent diseases not directly associated with drug abuse.

Two age- and sex-matched groups of 30 consecutive autopsy cases dead from various diseases and injuries (Group I) or sequels of chronic alcohol and/or tablet abuse (Group II) was included in the study. In the controls no exposure to opiates nor central stimulants was known.

Samples were taken for routine histological examination and for chemical analysis of ethanol, hypnotics, tranquillizers, opiates and central stimulants. The chemical analyses were performed at the National Laboratory of Forensic Chemistry, Linköping, Sweden. Lung tissue sections were taken from all lobes, both from central and subpleural areas, and were routinely stained with Mallory's PTAH, Weigert's resorcin fuchsin elastic stain and Perl's blue stain (Armed Forces Institute of Pathology 1969) in addition to hematoxylin and eosin. In cases where excessive amounts of haemosiderin-laden macrophages were found in the lungs, Perl's blue stain was also applied on sections from the spleen, liver and pancreas. Myocardial tissue sections were treated as previously described (Rajs and Falconer 1979).

The chronic pulmonary alterations were classified qualitatively and quantitatively according to Table 1.

Results

All the drug addicts examined had a history of mixed drug abuse of many years' duration, often starting with cannabis and alcohol. In all cases where a history of single drug abuse – like heroin or amphetamine – was initially reported, deeper penetration of the past history or toxicological analysis clearly demonstrated multiple drug use. The narcotic addiction was always combined with a regular abuse of tranquillizers or sedatives, most often also with alcohol.

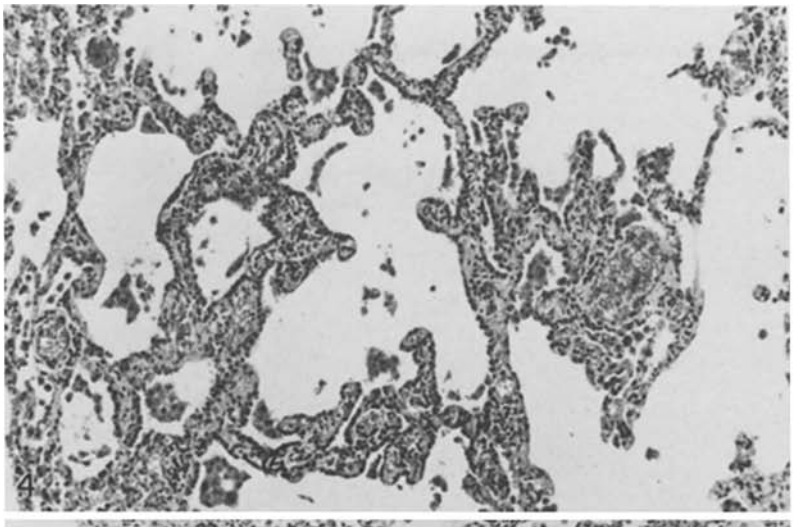
Hepatitis was known to have occurred in the majority of addicts. Cardiac hypertrophy and congestive heart failure had been clinically diagnosed in two patients and was interpreted as a consequence of amphetamine-induced pulmonary hypertension. Four patients had been complaining of dyspnoea but in no case had chronic respiratory insufficiency been clinically recorded.

Common post-mortem findings in the sudden death group were fluid blood and heavily congested organs, particularly the lungs, which regularly weighed 2–3 times more than normal (mean 1610 g). Moderate splenomegaly (weight 250–450 g) was present in 15 cases.

Fig. 4. Lung section from a multiple drug addict showing area with thickened alveolar walls. Hematoxylin and eosin ×97

Fig. 5. Lung section from a multiple drug addict showing thickening of arterial walls with increased cellularity, particularly in the adventitia. Some alveolar walls are also thickened. Hematoxylin and eosin ×61

Fig. 6. Lung section from a multiple drug addict showing thickened arterial wall with accumulation of mononuclear cells, mostly in the adventitia. Hematoxylin and eosin ×97



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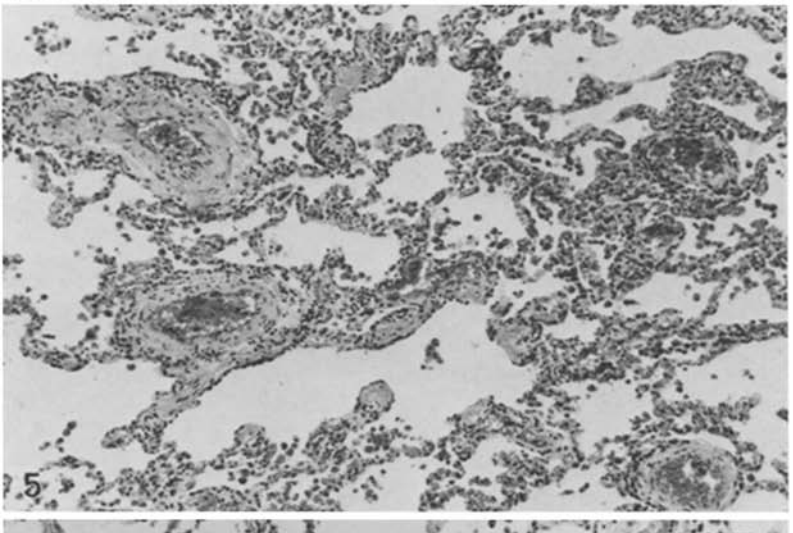

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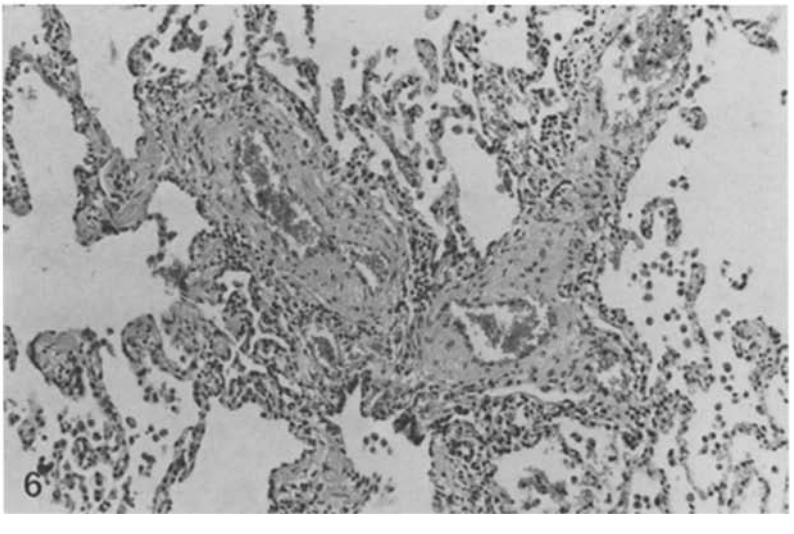

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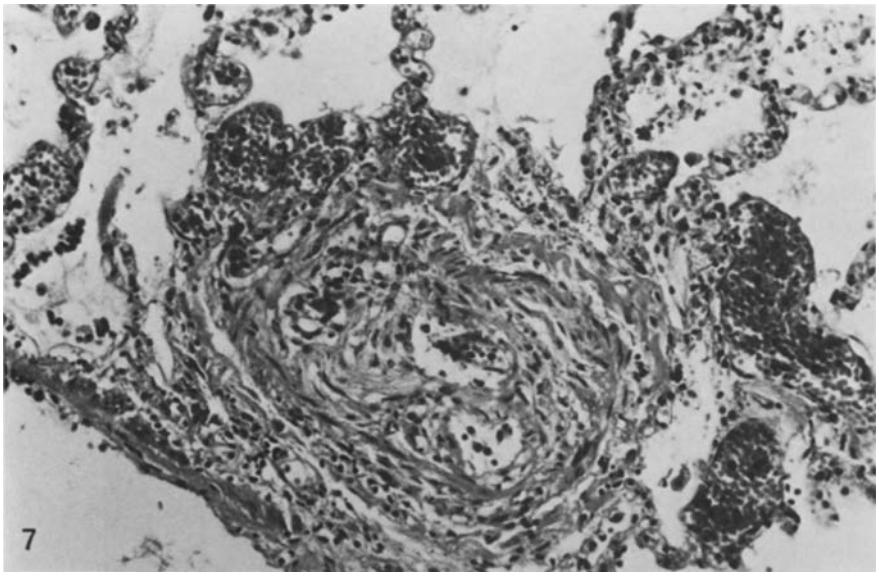

Fig. 7. Lung section from a multiple drug addict showing obliterated and recanalized arterial lumen. Hematoxylin and eosin × 58

In all 20 addicts who had died immediately after drug administration the microscopic examination of lung tissue revealed vascular congestion and recent focal haemorrhages. Focal exudation of protein-rich oedema fluid was seen in 14 of these 20 addicts; five of which also exhibited intravascular coagulation.

A characteristic observation was the presence of single scattered or numerous haemosiderin-laden macrophages in the interstices and the alveoli, focally or in confluent areas (Fig. 1). Such macrophages were seen in 25 cases and further in cases with lung lesion score >4 also in the bronchi (Fig. 2). In these cases haemosiderin-laden macrophages could be demonstrated in a bronchial smear taken at autopsy (Fig. 3). Fibrous thickening of alveolar septa was seen in six cases (Fig. 4). Talc granulomata were found in only two of 30 cases.

Another sign of pulmonary alteration of longer duration was vascular changes in minor branches of pulmonary arteries; in 12 cases thickening and fibrosis of the entire arterial wall was noted along with the appearance of mononuclear leukocytes and some haemosiderin-laden macrophages, mainly in the adventitia (Figs. 5 and 6). In two instances obliteration and recanalization of the minor branches of the pulmonary arteries was noted (Fig. 7). Even these lesions exhibited a scattered focal distribution. Fibrinoid necroses were not seen.

The comparison of the pulmonary lesion score distribution between drug addicts and controls is shown in Fig. 8. Among 30 addicts 26 exhibited such lesions as compared to 10 of 30 controls in control group I and 17

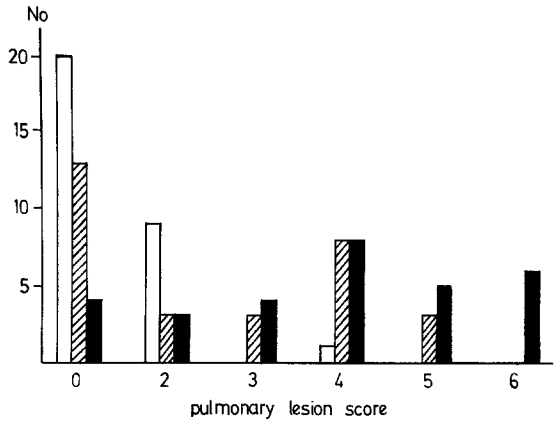

Fig. 8. Comparison of pulmonary lesion score distribution between drug addicts and control groups I and II. *Open column*: Control group I (non-abusers)
Shaded column: Control group II (abusers of alcohol/tablets)
Black column: Drug addicts

Table 2. Addicts with pulmonary lesion score less than 2

$N=7$	No
"Well-adjusted"	2
Endocarditis, sepsis	1
Ex-addict	2
<3 years abuse	1
No information	1

of 30 in control group II. A trend towards more severe pulmonary alterations – i e a higher lesion score – seemed to exist with increasing age in addicts – or with longer history of addition – whereas in persons with a shorter history of drug abuse and in those socially well adjusted, the pulmonary lesion score was lower (Table 2). On the other hand, a closer penetration of the past history of the controls in group I with a lesion score >2 disclosed the following conditions: epilepsy, bronchial asthma, periarteritis and congestive heart failure. Only in four cases was a possible underlying cause not stated. Figure 9 represents vascular lesions found in controls.

Macroscopically visible cardiac alterations were found in only four of 30 intravenous drug addicts (three cases of hypertrophy, one case of septic endocarditis of the aortic valve). Myofibrillar degeneration in terms of contraction bands, myocytic necrosis, stromal condensation and fibrous scars, however, was found to be the prevailing lesion at histological examination in 15 cases. In a total of five cases stromal condensation and scarring were suggesting healed episodes of myofibrillar degeneration, whereas in seven cases a pronounced fatty infiltration was indicative of alcoholic cardiomyopathy. The prevailing cardiac lesions seen in drug addicts are presented in Table 3.

The presence of opiates and/or central stimulants in samples taken at autopsy was demonstrated by chemical analysis in 26 of the 30 addicts.

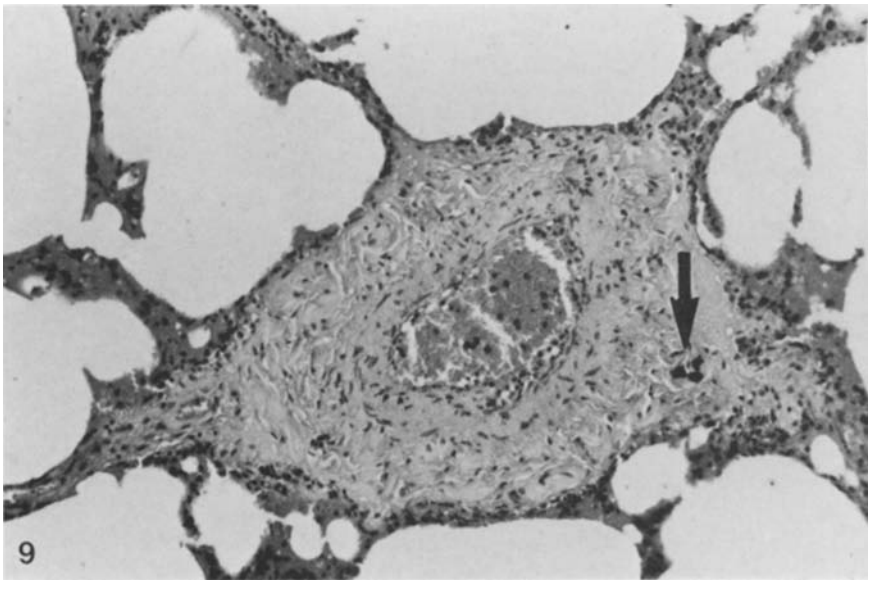

Fig. 9. Lung section from a 37 year old man who had been abusing salicylates (5–10 g per day) during several years. The arterial wall is thickened and shows increased cellularity. The arrow points at a lump consisting of debris positively stainable with Perl's blue stain. Hematoxylin and eosin ×36

Table 3. Prevailing cardiac lesions in 30 drug addicts

Type of lesion	*N*
Myofibrillar degeneration	15[a]
Residual after myofibrillar degeneration	5
Fatty infiltration	7
Acute septic endocarditis	1

[a] Three with hypertrophy

In seven cases such concentrations of morphine were found in blood that an acute overdose could be suspected, i.e. more than 30 μg per 100 ml whole blood (Monforte 1977). Apart from these seven cases plus eight addicts who died of external violence or intercurrent disease the cause of death could not be definitely stated in 15 of the 30 addicts.

Discussion

The intravenous drug addicts included in this study were all mixed drug abusers, which makes the cases in this series non-comparable to experimental animal models.

The reason for addicts developing a mixed pattern of abuse is not known, but it may be due to the energetic efforts of the police to suppress the

distribution of narcotic drugs and consequently to difficulties in maintaining a constant access to desired drugs (H. Heuman, personal communication).

The present study demonstrates that pulmonary and cardiac lesions of long duration are present in intravenous drug addicts. The pulmonary lesions also occur in controls, thus they are not specific for addiction to narcotics; just over-represented in the addict group.

Although the haemosiderin-laden macrophages morphologically appear to be identical to "heart failure cells", their focal distribution indicates a different origin. One possible explanation of the non-granulomatous pulmonary lesions is that they constitute the sequel to previous episodes of heroin-induced "narcotic lungs" (Siegel 1972), with congestion, oedema and haemorrhages clinically manifested as respiratory insufficiency triggered by intravenous injection of drug. Hypoxia may be one of the factors leading to lung congestion after heroin intake in cases where the amount of drug injected or inhaled is not larger than that usually taken (Duberstein and Kaufman 1972; Frand 1972). Furthermore, the oedema fluid is rich in protein, suggesting a more specific mechanism such as the well-known histamine-releasing effects of opiates (Katz et al. 1972). The vascular changes in the lungs (cf. Figs. 5 and 6) correlate with the effects for described amphetamine on blood vessels (Haft 1974). The angiothrombotic vascular lesions with recanalization of lumina (cf. Fig. 7) were previously reported to be an effect of intravenous injection of solutions prepared from drugs intended for oral consumption, containing insoluble microcrystals giving rise to foreign body embolization and granulomatosis (Tomashefski and Hirsch 1980).

Similar findings in controls who had been abusing tablets, particularly salicylates – or suffered from congestive heart failure or bronchial asthma – indicate that the pulmonary alterations have a complex and multifactorial aetiology. Recent minute focal haemorrhages in different organs, including lungs, were previously associated with the anticoagulant effect of salicylic acid (Krasoff and Bernstein 1947) or with a defect in pulmonary vascular permeability (Benowitz et al. 1979). Moreover salicylic acid is known to induce non-cardiogenic pulmonary oedema (Benowitz et al. 1979) or respiratory distress syndrome (Andersen and Refstad 1978), a condition whose pathoanatomic basis seems to be incompletely elucidated. Thus, besides the above-mentioned possible causative factors for pulmonary lesions in intravenous drug addicts, adverse reaction to drugs might be the common causative factor even if no opiates or central stimulants are taken.

Whether these lesions are of a chronic active character or merely denote sequelae after episodes of narcotic lungs, is still incompletely known. We feel that the presence of haemosiderin-laden macrophages and the concomitant cellular thickening of alveolar septa are of a transient character, while the fibrous thickening and the vascular changes are more persistent. The presence of blood and blood products appears to initiate a fibrogenic response in pulmonary haemosiderosis and haemosiderin deposition is also supposed to contribute or cause slowly progressive interstitial fibrosis in the lungs of patients suffering from mitral stenosis and chronic left ventricu-

lar failure (Murray 1974). The presence of haemosiderin-laden macrophages in the bronchial lumina further suggests a possibility for screening of drug addicts for signs of chronic cardiopulmonary impairment by means of sputum cytology.

It is our opinion that neither the pulmonary changes as described nor the chronic cardiac lesions are receiving appropriate attention (Rajs and Falconer 1979). In particular the myofibrillar degeneration of the heart as defined by Reichenbach and Benditt (1970) is little studied. The lesions described may predispose to sudden death.

References

Andersen R and Refstad S (1978) Adult respiratory distress syndrome precipitated by massive salicylate poisoning. Inten Care Med 4:211–213

Armed Forces Institute of Pathology (1969) Manual of histological and special staining technique. 2nd ed. McGraw-Hill Book Co., Inc, New York

Benowitz NL, Rosenberg I and Becker CE (1979) Cardiopulmonary catastrophies in drug overdosed patients. Med Clin North Am 63:267–296

Duberstein JL and Kaufman DM (1971) A clinical study of an epidemic of heroin intoxication and heroin-induced pulmonary edema. Am J Med 51:704–714

Frand UI, Shim CS and Williams MH (1972) Heroin-induced pulmonary edema. Ann Intern Med 77:29–35

Haft JI (1974) Cardiovascular injury induced by sympathetic catecholamines. Progr Cardiovasc Dis 17:73–86

Karliner JS, Steinberg AD and Williams MH (1969) Lung function after pulmonary edema associated with heroin overdose. Arch Intern Med 124:350–353

Katz S, Aberman A, Frand UI, Stein JM and Fulo M (1972) Heroin pulmonary edema. Evidence for increased pulmonary vascular permeability. Am Rev Respir Dis 106:472–474

Krasnoff SO and Bernstein M (1947) Acetylsalicylic acid poisoning. JAMA 135:712–714

Lewman LV (1972) Fatal pulmonary hypertension from intravenous injection of methylphenidate (Ritalin) tablets. Hum Pathol 3:67–70

Monforte JR (1977) Some observations concerning blood morphine concentrations in narcotic addicts. J Forens Sci 22:718–724

Murray JF (1974) Diffuse infiltrative diseases of the lung in Harrison's Principles of Internal Medicine, Seventh Edition, McGraw Hill Book Company, pp 1291–1298

Rajs J and Falconer B (1979) Cardiac lesions in intravenous drug addicts. Forens Sci Int 13:193–209

Rajs J, Högberg J, Härm T, Ormstad K, Edlund PO and Dahlström B (1980) The cause of sudden death in connection with intravenous administration of heroin. A preliminary forensic-pathologic and toxicologic study. Proceedings of The First Scandinavian Conference of Forensic Science. Linköping June 11–13. pp 59–63

Reichenbach DD and Benditt EP (1970) Catecholamines and cardiomyopathy: The pathogenesis and potential importance of myofibrillar degeneration. Hum Pathol 1:125–150

Siegel H (1972) Human pulmonary pathology associated with narcotic and other addictive drugs. Hum Pathol 3:55–66

Steinberg AD and Karliner JS (1968) The clinical spectrum of heroin pulmonary edema. Arch Intern Med 122:122–127

Tomashefski JF and Hirsch CS (1980) The pulmonary vascular lesions of intravenous drug abuse. Hum Pathol 11:133–145

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