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Lung disease with chronic obstruction in opium smokers in Singapore

Clinical, electrocardiographic, radiological, functional, and pathological features

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Fifty-four opium smokers with chronic obstructive lung disease were studied for two-and-a-half years. Forty-eight patients had a cough for at least two years before the onset of inappropriate exertional dyspnoea. Fine, bubbling adventitious sounds suggesting small airway disease were heard on auscultation over the middle and lower lobes in 38 patients.

The prevalence of inflammatory lung disease and chronic respiratory failure in this series is suggested as the main cause for the frequent finding of right ventricular hypertrophy and congestive heart failure.

Physiological studies revealed moderate to severe airways obstruction with gross over-inflation and, in 32 patients, an additional restrictive defect probably due to peribronchiolar fibrosis.

Radiological evidence of chronic bronchitis and bronchiolitis was observed in 45 patients, 'pure' chronic bronchiolitis in six patients, and 'widespread' emphysema in 25 patients respectively. Necropsy examinations in nine patients, however, showed destructive emphysema of variable severity in all. Chronic bronchiolitis often associated with striking bronchiolectasis was present in six cases. More severe bronchiolar rather than bronchial inflammation was noted.

The heavy opium smokers had characteristic nodular shadows on chest radiography, sometimes associated with a striking reticular pattern not seen in 'pure' cigarette smokers. This was due to gross pigmented dust (presumably carbon) deposition in relation to blood vessels, lymphatics, and bronchioles, and also within the alveoli.

It is speculated that the initial lesion is an acquired bronchiolitis. Opium smoking induces an irritative bronchopathy favouring repeated attacks of acute bronchiolitis and eventually resulting in obliterative bronchiolitis, peribronchiolar fibrosis, chronic bronchitis, and destructive emphysema.

Opium smoking has been a problem in Asia for many years. Although the psychological and medical aspects and its control have received much attention (Medical Research Council, 1920; League of Nations, 1930–32 and 1937; Leong, 1959), little interest has been shown in the effects on the respiratory system. Gaide and Neuberger (1938) noted the frequency of dyspnoea and productive cough in opium smokers, and likened the condition to a form of pneumoconiosis, while Pham-Ngoc-Thach (1939) studied the course of pulmonary tuberculosis in opium smokers, noting its slow progression and tendency to fibrosis.

Khoo, Toh, and Leong (1960) briefly reported radiological abnormalities suggestive of pneumoconiosis in elderly Chinese who were chronic opium smokers.

Mazaud, Castera, Migeon, André, and Luong (1963), studying a group of 50 opium smokers in Saigon, found respiratory disorders of varying severity in 22 cases, and concluded that opium smoking led to a chronic irritative bronchopathy later complicated by fibrosis and emphysema.

Since there has been no comprehensive study of the clinical, radiological, functional, and pathological features of the lungs in opium smokers, the present study was begun in 1966. In reporting

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its results we seek to delineate the salient features of chronic airways obstruction.

CLINICAL MATERIAL

A special clinic was set up in 1966 for the study of chronic opium smokers attending the Department of Medicine, University of Singapore. The following criteria for selection were used:

1. a history of at least five years of continuous opium smoking;
2. a forced expiratory volume in one second (FEV_1) less than 60% of the forced vital capacity (FVC), after inhalation of isoprenaline aerosol;
3. no known 'specific' aetiology for the pulmonary disability, e.g., occupational pneumoconiosis, advanced pulmonary tuberculosis, sarcoidosis;
4. willingness of the patient to co-operate in providing clinical information and returning for subsequent follow-up examinations;
5. no other known serious illness at the time of initial examination (patients with coronary artery disease, rheumatic heart disease, neoplasia or a diastolic blood pressure over 100 mmHg were excluded);
6. an opportunity to evaluate the patient during a stable phase of the disease.

Between November 1966 and September 1968, 65 chronic opium smokers were seen. Fifty-four Chinese patients (50 males and 4 females) fulfilled all the criteria. Eleven patients were excluded from the study; four had only minor airways obstruction, three had advanced pulmonary tuberculosis, two subsequently did not attend regularly, one had diffuse interstitial pulmonary fibrosis, and the last had an associated congenital heart lesion.

METHODS

In addition to routine clinical history-taking a standardized questionnaire was employed, based on the Medical Research Council's Questionnaire on Respiratory Symptoms (1960). Most questions required only yes/no answers. This was done to ensure a standardized and comparable analysis especially with respect to cough, phlegm, breathlessness and/or wheezing and oedema. Reference was also made to the relation, if any, of nasal catarrh, previous chest illness, and cigarette and opium smoking to the illness. No occupational or environmental exposure to dust or other inhalants was noted.

PHYSICAL EXAMINATION All patients were examined by one of the authors (J. L. D. C.) using a standardized technique. The physical signs were recorded independently of the assessment of lung function. Doubtful findings were recorded as absent.

ELECTROCARDIOGRAPHY A standard 12-lead electrocardiogram plus V4R was taken in all instances and repeated at three-monthly intervals. Right ventricular hypertrophy (RVH) was assessed according to the criteria of Goodwin and Abdin (1959).

RADIOGRAPHY Posterior-anterior and left lateral chest radiographs were taken at the time of enrolment and, when possible, at six-monthly intervals thereafter. The radiographs were read separately by two of the authors (H. K. B. and J. L. D. C.) without prior knowledge of the clinical findings. The criteria of Simon (1964) were used for the diagnosis of 'widespread' and 'possible' emphysema. Chronic inflammatory changes were recorded when abnormalities termed 'patchy clouding', 'honey-comb' shadowing or 'extensive pleural reaction' were present (Simon and Galbraith, 1953; Simon, 1962).

BRONCHOGRAPHY This was carried out in those patients considered fit to undergo the procedure because earlier work had shown that disease at bronchiolar level in chronic obstructive lung disease could be demonstrated using oily propyliodone[1] (Da Costa, 1969a). A standard posturing technique was adopted following instillation of propyliodone into the bronchial tree by percutaneous puncture of the cricothyroid membrane.

Chronic bronchitis was suggested when changes, e.g., irregularity in bronchial calibre, dilated mucous gland ducts in the segmental bronchi, peripheral bronchial occlusions with tapering irregular or 'squared' endings ('broken bough' appearance), were noted. Chronic bronchiolitis and bronchiolectasis were diagnosed when irregularity and dilatation were noted in the very small terminal branches of the bronchial tree, e.g., the 'spikes' and 'peripheral pooling' of Simon (1962).

PULMONARY FUNCTION TESTS These were performed with the patients seated at rest. Gas volumes are expressed at body temperature and pressure saturated with water vapour (B.T.P.S.).

(a) *Ventilatory tests* FEV_1 and FVC were measured in triplicate (the highest value being accepted) using a 9-litre Godart closed-circuit spirometer, and then repeated after inhalation of 500 μg isoprenaline. The FEV_1 was also expressed as a percentage of the FVC (FEV_1/FVC %).

(b) *Total lung capactiy (TLC) and subdivisions* The functional residual capacity (FRC) was measured in duplicate using the closed-circuit helium dilution technique (Meneely and Kaltreider, 1949). Equilibration time had to be prolonged to as long as 20 minutes in some patients. An agreement of 200 ml or less was required of two successive determinations. Predicted normal values for (*a*) and (*b*) were 'extrapolated' by combining normal data from this laboratory with those of Needham, Rogan, and McDonald (1954), Kory, Callahan, Boren, and Syner (1961), and Boren, Kory, and Syner (1966).

(c) *Arterial blood gas studies* Femoral arterial blood samples were obtained in a heparin-lubricated syringe with patients recumbent breathing room air. Arterial oxygen saturation (Sao_2) was determined using an A.O. oximeter (model 10800, American Optical Co.). The arterial blood pH was measured

[1]Dionosil Oily, Glaxo Laboratories Ltd., U.K.

immediately with an electrode (model PHM 27, Radiometer, Copenhagen) and the arterial blood carbon dioxide tension (P_{aCO_2}) was derived from pH determinations at two standard carbon dioxide tensions and the Siggaard-Andersen curve nomogram (Siggaard-Andersen, 1962).

OTHER STUDIES These included:

Haematological studies

(a) Haemoglobin and haematocrit estimations in all patients;

(b) Blood volume studies in patients suspected of having polycythaemia, using the Evans Blue method (Crooke and Morris, 1942). These patients had a dusky, plethoric appearance, a haemoglobin content of more than 15·9 g/100 ml, and a haematocrit greater than 55%.

Sputum examination

(a) Whenever possible the volume and purulence of 24-hour sputum specimens were recorded.

(b) Routine sputum cultures (×3) for *Mycobacterium tuberculosis* and smears (×6) for acid-fast bacilli in all cases.

PATHOLOGICAL STUDIES. Necropsy examinations were performed on 9 of the 18 patients who died during the two-and-a-half-year period of observation. The lungs and heart of each were subjected to a standardized pathological examination.

On opening the thoracic cavity, the thoracic organs were studied *in situ*. After freeing all pleural adhesions, the upper respiratory tract, trachea, bronchi, lungs, and heart were removed in one block. On dissection of the heart, the left ventricle with the septum and the free wall of the right ventricle were weighed separately; the ratio of the weight of the left ventricle and septum to the weight of the free wall of the right ventricle $\frac{LV+S}{RVW}$ was calculated (Fulton, Hutchinson, and Jones, 1952; Fulton, 1953). RVH was then graded arbitrarily as follows:

No RVH	LV+S/RVW greater than 2·0
Mild RVH	LV+S/RVW=1·8−2·0
Moderate RVH	LV+S/RVW=1·5−1·7
Severe RVH	LV+S/RVW less than 1·5

The lungs were fixed by intrathoracic instillation of aqueous formalin under pressure, according to the methods of Heard (1960). After fixation, the external aspects of the organs were examined for abnormalities such as pattern and degree of pigmentation and emphysematous bullae.

From one lung in each case, 2 cm thick slices were cut, extending from the hilum laterally to the periphery. With the aid of a dissecting microscope the cut surfaces were examined under water after barium sulphate impregnation (Heard, 1960). Other slices not impregnated with barium sulphate were used to prepare large lung sections mounted on paper, according to the method of Gough and Wentworth (1949).

From the same lung, tissue was taken from the main bronchus and from all lobes for histological examination. Routine paraffin sections, 7 μ thick, were stained with haematoxylin and eosin, Verhoeff-van Gieson, and mucicarmine.

From the other lung in each case, resin casts of the bronchopulmonary tree were made, according to the method of Tompsett (1952).

Emphysema was classified as centrilobular, panacinar, irregular (severe emphysema not otherwise classifiable), and bullous (where emphysematous bullae more than 1 cm in diameter were present). The severity of emphysema in each case was assessed by examination of the cut lung slices as well as paper-mounted large lung sections. Emphysema was graded as mild, moderate, and severe (CIBA Guest Symposium, 1959).

The amount of pigmented dust deposition (presumably carbon), as judged by naked-eye examination of the external and cut surfaces of the lungs as well as by histological examination, was graded arbitrarily as mild, moderate, considerable, and very considerable.

The presence or absence of chronic bronchitis was assessed by histological examination of the main bronchi for evidence of hypertrophy of the mucous glands, according to the criteria of Reid (1960).

Chronic bronchiolitis was diagnosed when there was widespread inflammatory thickening of the walls of the bronchioles, with mononuclear cellular infiltration with or without bronchiolar dilatation.

RESULTS

PATIENT CHARACTERISTICS The mean age, height, and weight for the group is shown in Table I.

TABLE I

AGES, HEIGHTS, AND WEIGHTS OF OPIUM SMOKERS

	Males	Females
No. of patients	50	4
Mean age (yr)	61	56
Standard deviation	±6	±7
Range (yr)	48–77	48–65
Mean height (in)	63	58
Standard deviation	±2	±4
Range (in)	57–67	53–61
Mean weight (lb)	85	67
Standard deviation	±14	±12
Range (lb)	55–119	55–81

OPIUM AND CIGARETTE SMOKING HISTORY All the patients smoked cigarettes as well as opium. Thirty-three patients (61%) were classified as either medium or heavy smokers, smoking an average of one packet (approximately 0·75g) prepared opium plus 15 cigarettes per day or more (Table II), while six patients (11%) were heavy smokers, smoking an average of more than two packets prepared opium plus more than 25 cigarettes a day.

TABLE II

SMOKING HISTORY BY AVERAGE DAILY CONSUMPTION OF OPIUM AND CIGARETTES

	Opium (packets)			
	Light (1/day)	Medium (1–2/day)	Heavy (> 2/day)	Total No.
Cigarettes				
Light (< 15/day) ..	4	6	3	13
Medium (15–25/day) ..	5	15	7	27
Heavy (> 25/day) ..	3	5	6	14
Total No. ..	12	26	16	

The mean age of onset and mean duration of opium smoking were 29·9 years and 25 years respectively, while for cigarette smoking it was 23·8 years and 35·9 years respectively. The opium smokers started smoking cigarettes in their early twenties and then took to opium smoking in their late twenties.

SYMPTOMATOLOGY There were no asymptomatic patients in this series. Dyspnoea on exertion was present in 52 patients (96%). Thirty-eight patients (70%) were severely dyspnoeic (Table III), while only two patients were not dyspnoeic even after severe exertion.

TABLE III

DISTRIBUTION OF SEVERITY OF DYSPNOEA IN SERIES

MRC Grade of Dyspnoea	No. of Patients	%
1	2	4
2	5	9
3	9	17
4	18	34
5	20	36
Total	54	100

Only 4 of the 54 patients in this group denied having a cough. Forty-seven patients had a productive cough on most days, for at least three months each year for two consecutive years, 22 of these having a productive cough for more than 10 years.

Five patients had a history of recurrent transient attacks of breathlessness relieved either spontaneously or by bronchodilator therapy. In three of these, the attacks had originated during childhood long before the onset of persistent dyspnoea (Table IV).

Data concerning other clinical features are summarized in Table IV.

TABLE IV

OTHER CLINICAL FEATURES IN OPIUM SMOKERS

	No. of Patients	%
Recurrent respiratory infections ..	37	69
Weight loss	34	63
Dependent ankle oedema	23	43
Wheezing	22	41
Haemoptysis	10	18
Nasal catarrh	8	15
Childhood 'asthma'	3	5

PHYSICAL EXAMINATION The main findings on physical examination are shown in Table V. The fine, moist, bubbling adventitious sounds heard mainly over the middle and lower lobes, both during inspiration and expiration, were strongly suggestive of disease in small airways. The mean blood pressure was 120 systolic (±16, 90–160) and 70 diastolic (±10, 40–90) mmHg.

TABLE V

FINDINGS ON PHYSICAL EXAMINATION IN OPIUM SMOKERS

Physical Signs	No. of Patients	%
'Over-inflation'[1]	52	96
Moist adventitious sounds	38	70
Central cyanosis	31	57
Wheezes	26	48
Congestive cardiac failure	23	42
Clubbing	4	7

[1]e.g., increased antero-posterior diameter of the chest, diminished chest expansion, generalized hyperresonance with loss of liver and cardiac dullness, and decreased vocal fremitus.

ELECTROCARDIOGRAPHIC FINDINGS The mean frontal plane P axis (AP) was +86° (±8, +45 to +90°), 80% of the patients having an AP of +90°. The mean frontal plane QRS axis (AQRS) was +79° (±26, −150° to +140°) and 41% had an AQRS of +90°. P pulmonale of Winternitz (1935) was present in 24 cases (44%). It was noted to be transient in seven cases and appeared to be related to episodes of acute respiratory failure.

The lead I sign (Fowler *et al.*, 1965), i.e., isoelectric P wave, QRS less than 1·5 mm, and T wave less than 0·5 mm, was present in 39 cases (72%), while 'rotation' of the transitional complex beyond V4 occurred in 37 cases (69%). ST-segment and T-wave changes in leads II, III, VF, and/or the right-sided anterior chest leads were detected in 20 cases, being transient and apparently related to episodes of acute respiratory failure in six cases.

Almost three-quarters of the patients (74%) did not show definite electrocardiographic evidence of RVH (grades 0–1), while about one-sixth (17%) showed varying degrees of RVH (grades 2–4). It

[1]±S.D. range

was not possible to classify the remainder who had a complete or incomplete right bundle-branch block pattern.

Arrhythmias were commonly detected in the older and more ill patients with respiratory failure (Table VI).

TABLE VI

ARRHYTHMIAS IN OPIUM SMOKERS

Type	No. of Patients
Premature beats	10
Ventricular	6
Atrial	5
Nodal	1
Paroxysmal supraventricular tachycardia	4
Multifocal atrial	3
Junctional	1
Junctional rhythm	1
Atrial fibrillation	1
Sinus arrest	1
Sinus bradycardia with first-degree heart block	1

RADIOLOGICAL FINDINGS According to the criteria of Simon (1964), 'widespread' emphysema was present in 25 cases and avascular radiolucent areas with or without a definite hairline shadow (bullae) were seen in 13 cases (24%). Evidence of chronic inflammatory lung disease (CID) was found much more frequently, being present in 45 cases (83%).

On radiological grouping the most frequent

TABLE VII

ANALYSIS OF RADIOLOGICAL FEATURES OF CHRONIC INFLAMMATORY DISEASE IN OPIUM SMOKERS

Radiological Features of CID	No. of Patients	%
Linear shadowing	34	63
'Honeycomb' shadowing	26	48
Extensive pleural reaction	23	43
Ill-defined coarse or fine nodulation	15	28
Patchy clouding	14	26
Generalized reticular pattern	4	7

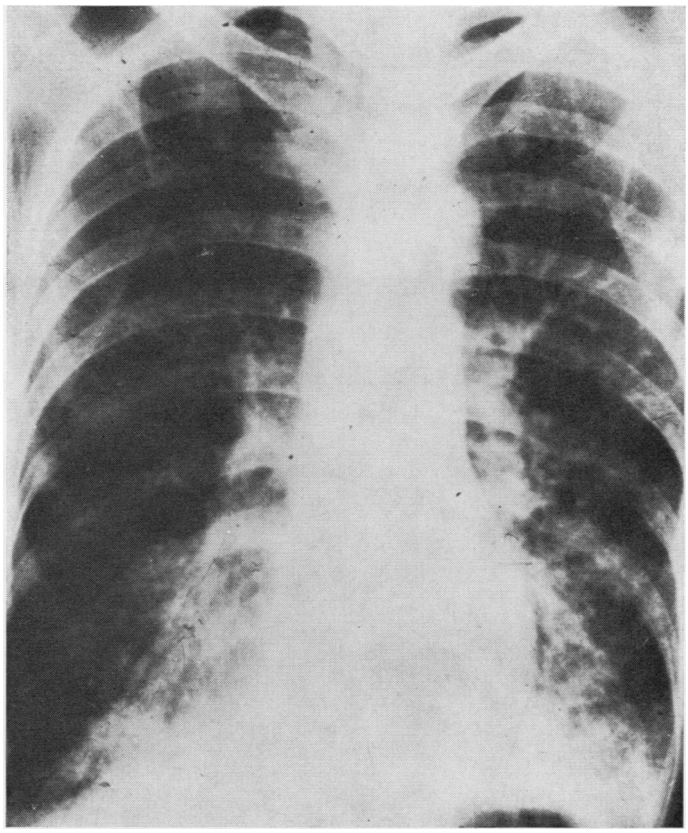
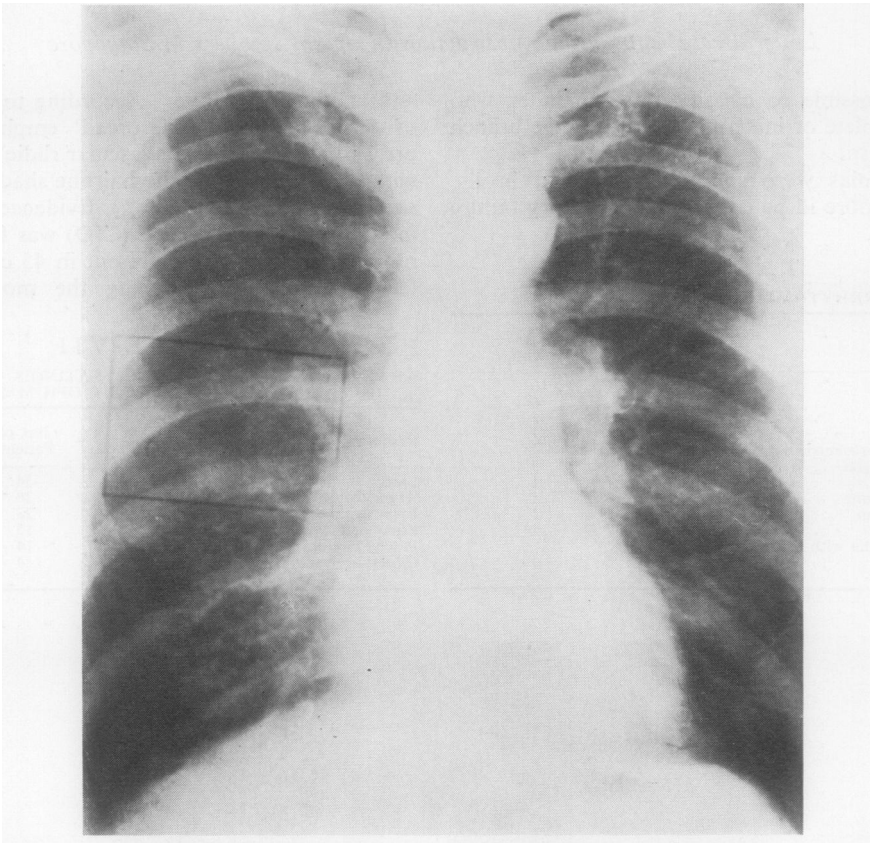
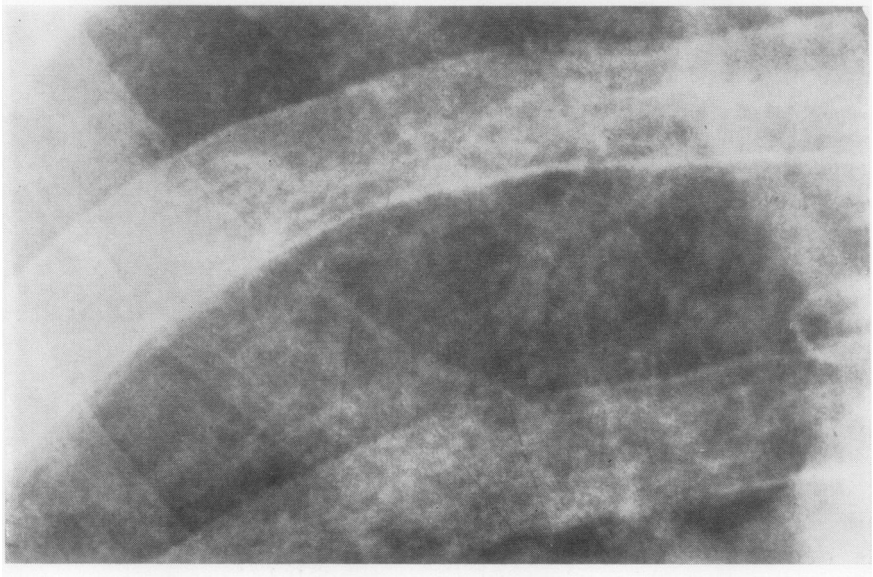


FIG. 1. *Chest radiograph (postero-anterior view) showing patchy clouding with honeycomb shadowing in both lower zones during an episode of acute on chronic bronchiolitis.*



(a)



(b)

FIG. 2. (*a*) *Chest radiograph* (*postero-anterior view*) *showing diffuse ill-defined nodulation in both lung fields, especially in demarcated area in right mid-zone, typical of excessive opium smoking.* (*b*) *Enlargement of demarcation area in Fig.* 2*a showing the appearance of the nodulation.*

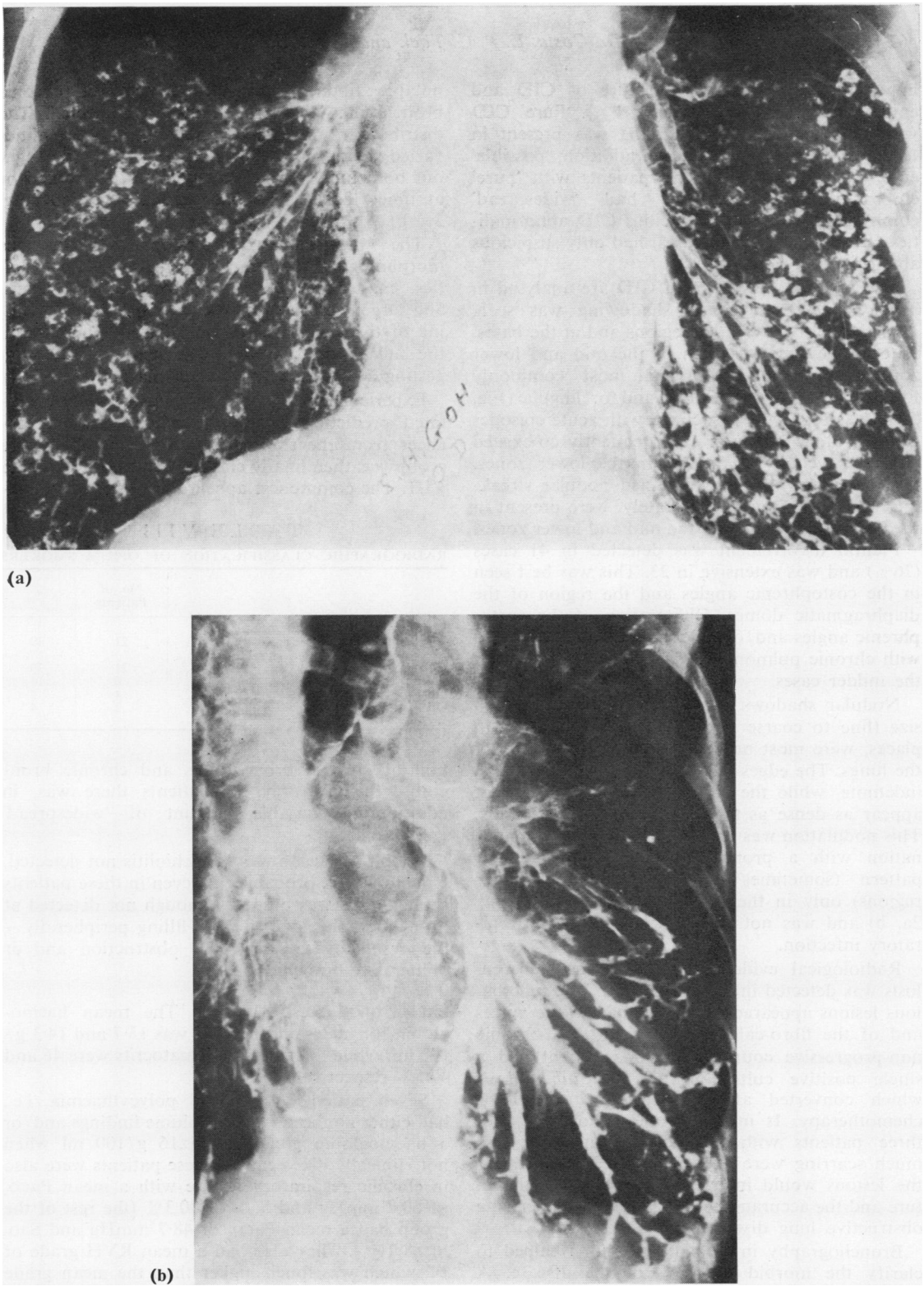


FIG. 3. (*a*) ***Bronchogram*** (*postero-anterior view*) *showing diffuse evenly distributed bronchiolectasis in both lungs. The main bronchi were remarkably well preserved and classical bronchitic features were absent.* (*b*) ***Bronchogram*** (*oblique view of left side*) *showing gross bronchitic changes with scattered peripheral bronchiolectasis. Note that the peripheral filling extends in some places right up to the lateral chest wall, implying loss of peripheral lung tissue.*

appearance was a 'mixed' picture of CID and emphysema, seen in 22 cases (41%). 'Pure' CID without evidence of emphysema was present in 13 cases, while 10 cases had, in addition, 'possible' emphysema. There were no patients with 'pure' emphysema though three had 'widespread' emphysema with only suspicious CID abnormalities. The remainder (six cases) had only suspicious abnormalities.

The findings suggestive of CID are analysed in Table VII. 'Honeycomb' shadowing was seen, especially in the perihilar regions and at the bases. Patchy clouding was seen in the mid and lower zones, often bilaterally and most commonly localized to the middle lobe and/or lingula (Fig. 1). It was especially associated with acute episodes of respiratory infection and frequently co-existed with honeycomb shadowing in the lower zones. Linear shadowing and ill-defined nodular streaking, in combination or separately, were present in the peripheral regions of the mid and lower zones.

Pleural involvement was detected in 41 cases (76%) and was extensive in 23. This was best seen in the costophrenic angles and the region of the diaphragmatic domes. Obliteration of the costophrenic angles and/or apical thickening associated with chronic pulmonary tuberculosis were seen in the milder cases.

Nodular shadows, often ill-defined, varying in size (fine to coarse nodulation) and confluent in places, were most numerous in the upper half of the lungs. The edges of the shadows were soft and indefinite, while the shadows themselves did not appear as dense as the opacities seen in silicosis. This nodulation was found separately or in combination with a prominent background reticular pattern (sometimes radiating from the hilar regions) only in the heavy opium smokers (Fig. 2a, b) and was not related to episodes of respiratory infection.

Radiological evidence of pulmonary tuberculosis was detected in 32 cases (59%). The tuberculous lesions appeared to be confined to the apices and of the fibro-calcified variety with a chronic non-progressive course. Only one patient had a single positive culture for *Myco. tuberculosis* which converted after specific antituberculosis chemotherapy. It must be noted, however, that three patients with advanced tuberculosis and much scarring were excluded from this study as the lesions would interfere with the clinical picture and the accurate assessment of the underlying obstructive lung disease.

Bronchography in 37 patients (69%) helped to clarify the morbid anatomy of the disease. A notable finding was the amount of chronic bronchiolitis and bronchiolectasis detected. The distribution of the bronchiolar abnormalities varied, being diffuse and evenly spread throughout both lungs, sometimes patchily distributed or at times localized to one particular region (Fig. 3a, b).

The bronchiolectatic lesions had various morphological appearances, e.g., berry-like opacities, smaller translucent single or clustered lesions, and larger confluent or loculated pools. Also, filling of the peripheral bronchial tree almost up to the lateral chest wall was common (Fig. 3b), suggesting a loss of lung parenchyma peripherally.

Experience gained from bronchography facilitated prediction of the bronchographic appearances from the standard chest radiographs. The group was then finally classified as shown in Table VIII. The commonest appearance was a combination of chronic bronchiolitis and chronic bronchitis. In half of these patients there was, in addition, a variable amount of 'widespread' emphysema.

TABLE VIII

RADIOGRAPHIC CLASSIFICATION OF OPIUM SMOKERS

	No. of Patients	%
Chronic bronchiolitis+chronic bronchitis (CB)+'widespread' emphysema (E)	21	39
Chronic bronchiolitis+CB	21	39
'Pure' chronic bronchiolitis	6	11
CB+E	4	7
CB+localized bronchiectasis	2	4

In only six cases was bronchiolitis not detected. It is, however, probable that even in these patients bronchiolitis was present although not detected at bronchography, due to poor filling peripherally—the result of mucous plug obstruction and/or obliterative bronchiolitis.

HAEMATOLOGICAL FINDINGS The mean haemoglobin for males and females was 13·7 and 14·3 g/100 ml, while their mean haematocrits were 46 and 47·5% respectively.

Seven patients (13%) had polycythaemia, i.e., had either abnormal blood volume findings and/or a haemoglobin greater than 16 g/100 ml when not clinically dehydrated. These patients were also in chronic respiratory failure with a mean $Paco_2$ of 60·7 mmHg and Sao_2 of 80·3% (the rest of the group had a mean $Paco_2$ of 48·7 mmHg and Sao_2 of 88·7 %). They also had a mean RVH grade of 2·2 which was much higher than the mean grade

of 0·7 for the rest of the group, though the numbers involved were too small for statistical evaluation.

PULMONARY FUNCTION STUDIES The mean values for the static lung volumes (expressed as per cent of predicted) are shown in Table IX. Only 4% of the total group had a residual volume (RV) within the normal range, while almost three-quarters (71%) had values more than 150% of predicted. The FRC followed a similar trend with 82% having values greater than 120% of predicted, more than half of these being greater than 150%. The mean TLC was within the normal range in 60% of the group; only one patient had a TLC less than 80% and two had a TLC more than 150% of predicted. The RV/TLC ratio was 50% or more above normal values in three-quarters of the group.

Blood gas analyses revealed chronic respiratory failure in 26 of the 54 patients studied. Thirty-five patients had an Sao_2 less than 94%, with a range of 58 to 99%. Thirty-one patients had $PaCO_2$ values greater than 47 mmHg, with a range of 33 to 82 mmHg.

PATHOLOGICAL FINDINGS The findings are summarized in Table X. Fibrous pleural adhesions were invariably present and often dense, occasionally forming a fibrous sheath over the lung(s) (Fig. 4). Pigmented dust deposition was gross in all but one case (Figs 4 and 5). Characteristically, the dust deposition was concentrated in the regions of the dilated and destroyed air spaces. Microscopically, the pigment (presumably carbon) showed a distinctive distribution. It was generally found within macrophages situated around small blood vessels (Fig. 6), in relation to lymphatics, around bronchioles, and less prominently in thickened interalveolar septa (Fig. 7) and lying free within the alveoli. In severe cases, pigment occurred as dense clumps lying in connective tissue. It was noteworthy that only mild fibrosis was present even in areas where pigment was heavily deposited.

Correlation of the pathological and radiographic findings showed that the ill-defined fine to coarse nodulation and the reticular pattern noted in the chest radiographs of the heavy opium smokers were mainly due to dust deposition in the lung parenchyma. Mild thickening of the interalveolar septa, though present, was not impressive.

Destructive emphysema was present in all nine cases, usually of moderate severity. Centrilobular emphysema was usually present and was moderate to severe in six cases. There was no appreciable panacinar emphysema in three cases, while in the others it was only mild or moderate. In two instances there was irregular emphysema. Bullae were seen in five cases. They were usually situated in the apices or the free margins of the lungs. Chronic bronchitis of mild or moderate severity

TABLE IX

LUNG FUNCTION DATA IN OPIUM SMOKERS[1]

	Males		Females	
	No. of Observations	Mean ± S.D. (range)	No. of Observations	Mean ± S.D. (range)
Ventilatory tests:	50		4	
FVC, after isoprenaline, % predicted		66 ± 15 (36–97)		64 ± 20 (39–83)
FEV_1, after isoprenaline, % predicted		40 ± 14 (11–77)		37 ± 17 (20–59)
% obtained FVC (FEV_1/FVC %)		41 ± 9 (21–57)		47 ± 12 (33–57)
Static lung volumes	45		3	
VC, % predicted		67 ± 12 (36–95)		59 ± 18 (37–80)
FRC, % predicted		153 ± 37 (90–268)		166 ± 13 (129–183)
TLC, % predicted		112 ± 22 (64–171)		101 ± 9 (91–109)
RV, % predicted		198 ± 65 (100–392)		166 ± 39 (133–209)
RV/TLC %		61 ± 10 (34–82)		66 ± 6 (62–72)
Arterial blood gas studies:				
SaO_2, %	48	89 ± 7 (67–99)	4	78 ± 19 (58–96)
$PaCO_2$, mmHg	50	50 ± 9 (33–82)	4	54 ± 12 (42–69)
pH	48	7·36 ± 0·04 (7·27–7·48)	4	7·36 ± 0·03 (7·32–7·39)

[1]Full details of lung function data may be obtained from J. L. D. C.

TABLE X

PATHOLOGICAL FEATURES IN OPIUM SMOKERS AT NECROPSY

Case	Pleural Adhesions		Pigmented Dust Deposition	Emphysema				Chronic Inflammatory Lung Disease			Pulmonary Tuberculosis	Heart $\left(\frac{LV+S}{RVW}\right)^4$
	Right	Left		Centrilobular	Panacinar	Irregular	Bullous	Chronic Bronchitis[3]	Chronic Bronchiolitis	Bronchiolectasis		
9	+ +	+ +	Considerable	+ +	+ +	+ +	+ +	+	+	–	–	1·0
29	+	+	,,	+ +	+	+ + +	+ +	–	+	+ +	–	2·1
38	+	+	,,	±	+ +	–	+ +	–	+ +	+ +	–	1·3
46	+ + +	+ + +	+ +	+ +	–	–	–	–	+ +	+ + +	RUL	1·4
52[1]	+		+ +	+ +	±	–	–	±	–	–	–	1·7
65	+ + +	+ + +	+ +	+	–	–	–	–	+	+	–	2·0
76	+ + +	+ + +	+	±	±	–	+ +	+ +	–	–	RUL	2·2
79	+	+	Considerable	+ +	–	–	+ +	+ +	+ +	+ +	–	1·2
90[2]	+	+ + +	Very considerable	+ + +	+	–	–	–	–	–	–	2·5

– not observed
± doubtful
+ mild
+ + moderate
+ + + severe
+ + + + very severe
R or L right or left lung
RUL right upper lobe

[1] A bronchogenic carcinoma of left lung was present at necropsy; findings refer to right lung only.
[2] A small carcinoma of larynx was present at necropsy.
[3] Mild bronchiectasis could not be excluded.
[4] $\left(\frac{LV+S}{RVW}\right) = \frac{\text{wt. of left ventricle and septum}}{\text{wt. of free wall of right ventricle}}$ and normally lies between 2·3 and 3·3 (Fulton *et al.*, 1952).

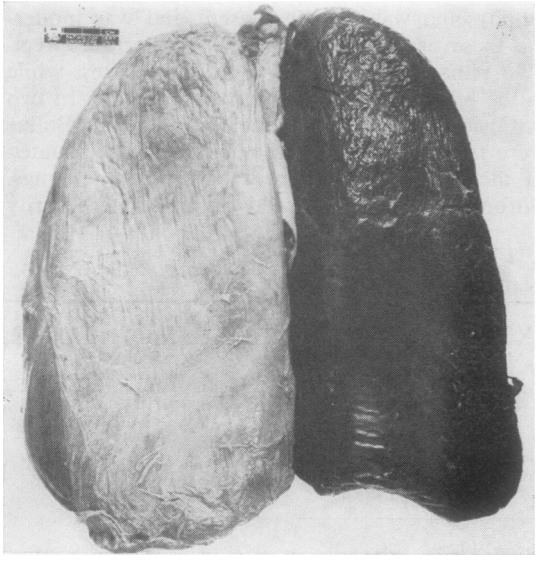


FIG. 4. *External appearances of the lungs. The right ung is encased in fibrous adhesions. The left lung shows very severe pigmentation (presumably due to carbon).*

was found in four cases. Chronic bronchiolitis was present in six cases. In five of these, moderate to severe bronchiolectasis was evident in some regions. These findings demonstrated the importance of chronic inflammation, especially of the bronchioles, in opium smokers with chronic obstructive lung disease.

Two patients had upper lobe fibrocaseous tuberculosis. In these instances, the lobes involved were avoided for study of the other features.

Histological evidence of pulmonary arteriolosclerosis was present in five patients, and this correlated well with a low $\frac{LV+}{RVW}$ ratio. It was noteworthy that gross and microscopic examination of the lungs did not reveal any pulmonary thromboemboli.

PROGNOSIS One-third of the group died during the two-and-a-half-year study. A further 17% were lost to follow-up. Polycythaemia, increasing weight loss, moderate to severe electrocardiographic evidence of RVH, decreasing FVC, severe airways obstruction, and persistent hypercapnia and hypoxaemia were apparently the major factors having an adverse influence on the prognosis.

DISCUSSION

The average age of this group of Chinese patients resembled that of European patients with chronic obstructive lung disease reported by Burrows, Niden, Barclay, and Kasik (1965) and Fletcher, Jones, Burrows, and Niden (1964). They had, however, a lower mean body weight with a greater incidence of weight loss and lower mean socioeconomic grouping. In addition to the severity of chronic obstructive lung disease itself, the shorter stature and larger number of patients over the age of 60 in this series, other factors could have had a bearing on the weight loss and body weight of this group of patients. Lack of appetite in opium

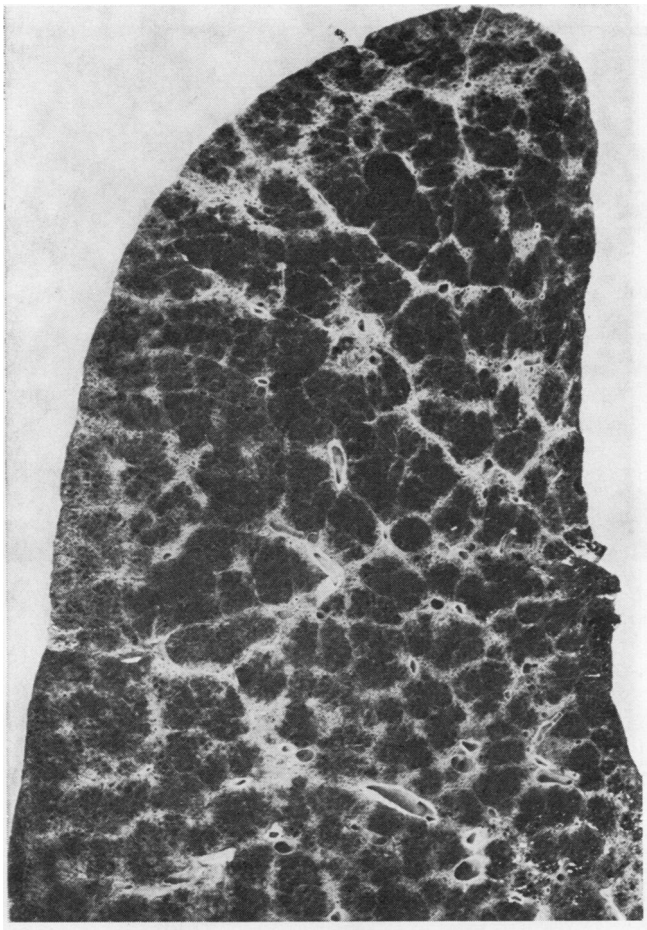


FIG. 5. *Cut surface of lung showing severe centrilobular emphysema and heavy pigmentation in the emphysematous regions. (Barium sulphate impregnated lung slice,* × 1/2).

smokers is well known. This, combined with poverty resulting from the need to use most of their resources to buy opium and the progressive decline down the social ladder, could result in under-nutrition.

Although dyspnoea was usually the chief and most distressing complaint, especially later in the course of the disease, a productive cough was present at least two years before the onset of dyspnoea in almost three-quarters of the group. This, together with the frequent presence of characteristic fine inspiratory and expiratory moist sounds over the middle and lower zones, suggested that chronic inflammatory bronchiolar disease was the important lesion in these patients.

Definite electrocardiographic evidence of RVH in 17% of the patients studied is in agreement with the findings of Mazaud *et al.* (1963) in opium smokers in Saigon. In this connexion it may be noted that marked clockwise 'rotation' of the transitional complex with rightward shift of the mean frontal plane P axis were shown by previous clinico-pathological studies to be more sensitive indices of early RVH than changes in the QRS axis (Toh and Da Costa, 1968). It is therefore likely that more than 17% of the present series had some degree of RVH. Table XI shows that the prediction of the severity of RVH by the electrocardiographic method of Goodwin and Abdin (1959) was successful except in those cases

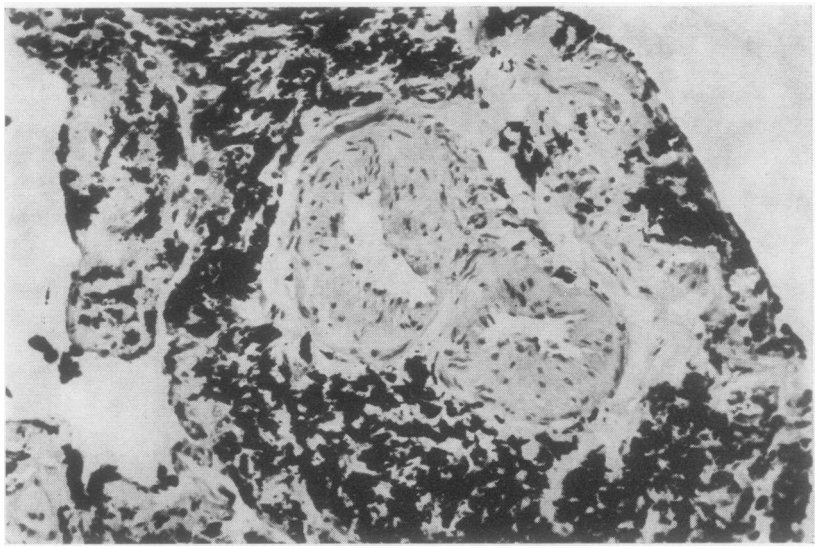


FIG. 6. *Microscopic section of lung showing the perivascular distribution of carbon pigment with thickening of the pulmonary arterioles.* (*H. and E.*, × 125).

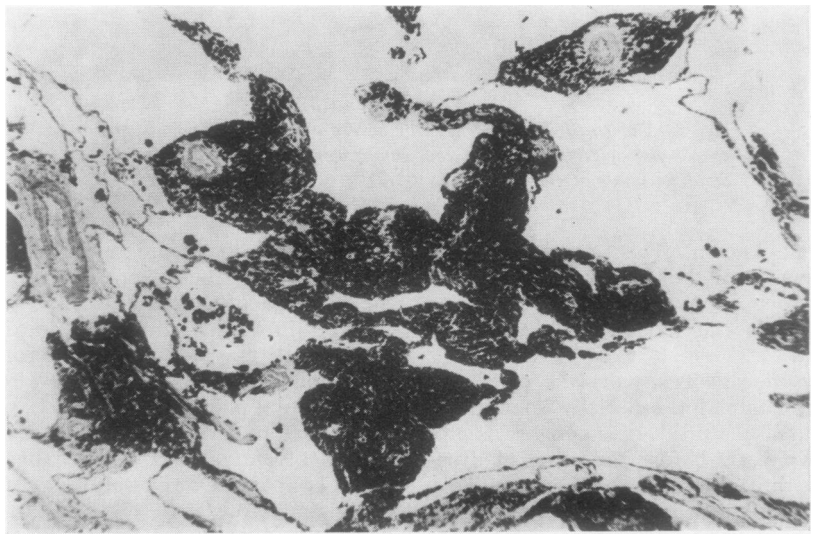


FIG. 7. *Microscopic section of lung showing irregular thickening of the alveolar septa, densely impregnated in these areas with carbon pigment* (*H. and E.*, × 38).

TABLE XI

PATHOLOGICAL, ELECTROCARDIOGRAPHIC, AND RADIOGRAPHIC FINDINGS IN OPIUM SMOKERS AT NECROPSY

Case	Radiographic Features			Electrocardiographic RVH Grading	Pathological Features						
	'Widespread' Emphysema	Chronic Inflammatory Lung Disease			Degree of RVH[1]	Emphysema				Chronic Inflammatory Lung Disease[2]	
		Chronic Bronchitis	Chronic Bronchiolitis			Centrilobular	Panacinar	Irregular	Bullous	Chronic Bronchiolitis	Chronic Bronchitis
9	±	+	++	1	Severe	++	++	++	++	+	+
29	+	++	+++	1	Nil	++	+	+++	++	+	−
38	+	+	++	3	Severe	±	++	−	++	++	−
46	±	+	++	3	Severe	++	−	−	−	++	−
52	+++	−	±	1	Moderate	++	±	−	−	−	±
65	+	++	+++	1	Mild	+	±	−	−	+	−
76	+	++	++	0	Nil	±	−	−	++	−	++
79	±	++	++	2	Severe	++	−	−	++	++	++
90	±	+	++	1	Nil	+++	+	−	−	−	−

− not observed
± doubtful
\+ mild
++ moderate
+++ severe

[1]The degree of RVH was arbitrarily graded as follows:

Nil, or no RVH, when $\frac{LV+S}{RVW}$ greater than 2·0

Mild, $\frac{LV+S}{RVW}$ = 1·8 to 2·0

Moderate, $\frac{LV+S}{RVW}$ = 1·5 to 1·7

Severe, $\frac{LV+S}{RVW}$ less than 1·5

[2]Mild bronchiectasis could not be excluded.

with predominant emphysema, where the electrocardiographic grading underestimated the degree of RVH seen at necropsy. However, Burrows *et al.* (1965), in a comprehensive study of chronic obstructive lung disease, found definite RVH in only 7% of their group of mostly cigarette smokers. This variance may possibly be explained by the prevalence of inflammatory lung disease and blood gas abnormalities in this series.

Cardiac arrhythmias were seen in 25% of the patients in this series. The commonest arrhythmia was the ventricular ectopic beat. However, as more than 40% of the patients were taking digitalis for heart failure, it was difficult to evaluate this finding. Corazza and Pastor (1958) also noticed that nearly one-third of their patients with chronic cor pulmonale had cardiac arrhythmias—usually premature ectopic beats or supraventricular tachycardia. On the other hand, Mazaud *et al.* (1963) and Burrows *et al.* (1965) did not mention the presence of arrhythmias, and Mitchell and Filley (1964) noted only 'various arrhythmias' in their series of 150 patients with chronic obstructive lung disease (mainly cigarette smokers). Fowler *et al.* (1965) observed transient atrial arrhythmias in 5 of their 15 patients with emphysema and cor pulmonale. The other common arrhythmia noted was a multifocal atrial tachycardia. This disturbance of rhythm, previously described by Katz and Pick (1956) and Abrams and Eaddy (1965), was shown by Shine, Kastor, and Yurchak (1968) to be especially prevalent in severely ill patients suffering from acute or chronic pulmonary disease with cor pulmonale. This increased irritability of the atria has been ascribed to a number of factors occurring either alone or in combination in the presence of chronic pulmonary disease—dilatation with stretching of the atrial walls (Scherf, Scharf, and Goklen, 1949), hypoxia (Prinzmetal *et al.*, 1952), hypercapnia (Corazza and Pastor, 1958), and respiratory acidosis (Dripps, Eckenhoff, and Vandam, 1957).

Radiographic studies showed that a mixed picture of chronic inflammatory disease and 'widespread' emphysema was the commonest finding (chronic inflammatory bronchiolar disease being the predominant lesion) in these opium smokers. However, necropsy in nine patients showed that mild to moderate panacinar and centrilobular emphysema were not detected by the radiological methods used in this study for assessing emphysema (Table XI). This was expected as Reid and Millard (1964) reported similar findings.

Chronic inflammatory lung disease produced two types of fibrous reaction—parenchymal and pleural. Parenchymal fibrosis consisted mainly of peribronchiolar fibrosis with variable (usually mild) alveolar septal thickening. Initially, an attack of acute bronchiolitis with peribronchiolar inflammation could result in small areas of peribronchiolar consolidation-collapse. Coalescence of these areas produces a picture of 'honeycomb' shadowing or patchy clouding on the chest radiograph (Fig. 1). Partial or sometimes complete resolution might occur in mild cases with adequate medical treatment. However, in susceptible subjects, especially those with a catarrhal diathesis—the 'host factor' of Orie *et al.* (1961), recurrent

attacks of acute bronchiolitis, especially in poorly drained regions like the right middle lobe, lingula or basal segments of the lower lobes, could give rise to retention of mucopurulent secretions with increasing atelectasis and fibrosis, producing the linear shadowing and/or nodular streaking extending peripherally in the mid and lower zones of the chest radiographs.

Extensive pleural fibrosis was found in almost half of the opium smokers in this series, confirming the high incidence of pleural reaction noted in Mazaud's series. Simon and Galbraith (1953), however, in a study of chronic bronchitis in the United Kingdom, noted 'abnormal pleural shadows' in only 6% of their cigarette-smoking patients. The explanation for this high incidence of pleural fibrosis in the opium smokers in this study is obscure, since there was no past history of pleurisy, empyema or pleural effusion in any of the patients. It is possible that subpleural dust accumulation in the lymphatics by obstructing drainage was of importance in the pathogenesis of the pleural fibrosis.

In addition to this fibrosis, the heavy opium smokers developed distinctive radiological changes not seen in 'pure' cigarette smokers either in Singapore (Da Costa, 1969b), England (Simon and Galbraith, 1953) or the U.S.A. (Weiss, 1969)—ill-defined nodular shadows with or without a background reticular pattern. The severity of these changes varied in different smokers, depending on the amount and the duration of opium smoking. These shadows resembled those described by Gärtner and Brauss (1951) in the pneumoconiosis of soot workers. Khoo *et al.* (1960), in a preliminary report describing an 'unidentified type of pneumoconiosis' in Singapore, noted a similar coarse reticular pattern with linear peripheral shadowing in the lower zones in certain elderly Chinese subjects, many of whom were found to be chronic opium smokers. Mazaud *et al.* (1963), in a study of opium smokers in Saigon, noted that 'pulmonary fibrosis' was the commonest radiological abnormality. They observed two main patterns—'frayed' opacities of varying sizes scattered throughout both lung fields and a reticulated pattern with lines of 'fibrosis' radiating from the hilar regions. Pathological studies in this series have shown that both the reticular pattern and the ill-defined nodulation noted in the chest radiographs of the heavy opium smokers were mainly caused by the heavy dust (carbon) in the lung parenchyma and that interalveolar fibrosis, if present, was not of major importance. Although pigmented dust deposition in some of the heavy opium smokers was gross, its distribution did not differ from that seen in 'pure' cigarette smokers.

Gaide and Neuberger (1938) commented on the frequent association of tuberculosis in opium addicts. Pham-Ngoc-Thach (1939), studying tuberculosis in opium smokers in Saigon, noted both the apparent susceptibility of opium smokers to tuberculosis and the chronicity of the illness. Tuberculosis, although often present in this series of opium smokers, was usually quiescent, of the fibrocalcified type, and frequently affected the apices. Before it can be accepted that there is an increased prevalence of pulmonary tuberculosis in opium smokers or that, if present, pulmonary tuberculosis often runs a slow chronic course with much fibrosis, further more detailed population studies are required.

Bronchography played a significant part in clarifying the nature of the disease. Mild cases showed a localized, patchy or diffuse, evenly distributed chronic bronchiolitis with little or no chronic bronchitis. Severe cases were complicated by chronic bronchitic changes of varying severity with advancing pulmonary and pleural fibrosis and destructive emphysema. The cases with advanced bronchitic changes also had localized cylindrical or fusiform bronchiectasis in the more proximal bronchi. The importance of chronic inflammatory disease, the dominant feature in these opium smokers, was demonstrated by the absence of 'pure' widespread emphysema and the predominance of 'tussive' patients in this series.

The radiological and pathological features make it possible to speculate on the pathogenesis of chronic obstructive lung disease in these opium (and cigarette) smokers. As patchy or diffuse chronic bronchiolitis has been noted even in the absence of opium and/or cigarette smoking (Da Costa, 1969b), it is postulated that the initial lesion is usually an acquired bronchiolitis following a viral or bacterial infection. Chronic opium- and cigarette smoking superimposes an irritative bronchopathy (opium, in addition, probably paralyses ciliary movement and inhibits the cough reflex and bronchial peristalsis), which sets up a vicious cycle favouring recurrent episodes of acute bacterial bronchiolitis in the already damaged bronchioli, especially in poorly drained regions of the lung. This eventually results in obliterative bronchiolitis, peribronchiolar atelectasis and fibrosis, and destructive emphysema. Such lesions have been described by McLean (1959) and recently emphasized by Bignon *et al.* (1969). Inflammation from this bronchiolar focus of infection also extends proximally and is associated with an

ever increasing degree of chronic bronchitis eventually complicated by fusiform bronchiectatic changes in the more proximal bronchi.

Excessive chronic opium smoking introduces an added element of heavy pigmented dust deposition (Da Costa and Tock, 1969) due presumably to the inhalation of carbon particles and possibly other irritants in the opium smoke. This pigmentation was much greater than that observed in 'pure' heavy cigarette smokers either in Singapore, England (Reid, 1967) or the U.S.A. (Mitchell, Vincent and Filley, 1964).

Auerbach, Stout, Hammond and Garfinkel (1963) have shown that rupture and focal or diffuse fibrosis of alveolar septa and thickening of arteriolar walls, though part of the ageing process, occur much more commonly in cigarette smokers and are related to both the duration and dosage of cigarette smoking. Boren (1964) and Weiss (1965) have shown in animal experiments that carbon can adsorb large amounts of irritant gases and, acting as a carrier, can produce toxic effects. Weiss (1969) has postulated that this may be the mechanism whereby focal damage occurs in the lungs with resultant pulmonary fibrosis. However, in spite of the deposition of large amounts of pigmented dust in the lung parenchyma of the opium smokers in this study, interalveolar fibrosis was insignificant. The fibrosis which was found was related to chronic bronchial and bronchiolar inflammation.

The morbid anatomy of the obstructive lung disease in these opium and cigarette smokers thus differs in certain respects from that described in cigarette smoking chronic bronchitis studied by Simon and Galbraith (1953) and Reid (1955; 1956) where bronchitic changes (with mucous gland hyperplasia) were the predominant feature early in the course of the disease and bronchiolitis, when observed, was scanty and irregularly distributed, becoming more prominent only as the disease progressed (Reid, 1956).

It was of interest that pulmonary thromboembolism was not found in this series, either clinically or at necropsy. Both Mitchell *et al.* (1968) and Bignon *et al.* (1969) have reported an increased prevalence of pulmonary thromboemboli in their series of patients with chronic obstructive lung disease. However, it has been noted that pulmonary thromboembolism is rare among Chinese in Singapore (Ransome and Tock, unpublished observations). This racial tendency to a lower prevalence of pulmonary thromboembolism could be the main reason for the absence of this complication in this series.

In common with other studies of chronic obstructive lung disease (Baldwin, Cournand and Richards, 1949; Burrows, Niden, Fletcher and Jones, 1964), a wide range of physiological abnormalities was found in this series. Airways obstruction varied in severity and gave rise to marked over-inflation. However, it was significant that the TLC was relatively normal in most cases and this was probably due to a restrictive defect—the result of inflammatory lung disease (especially peribronchiolar fibrosis). This pattern of functional disturbance in chronic obstructive bronchitis has also been observed by Palmer and Diament (1970).

A high prevalence of chronic respiratory failure (associated with chronic inflammatory lung disease) was noted in this series. As both hypoxaemia and hypercapnia have been shown greatly to influence pulmonary artery pressure and vascular resistance (Fishman, 1961; Enson *et al.*, 1964; Barer, 1966), and heart failure has been observed to correlate better with hypoxaemia and hypercapnia than with the ventilatory defect (Platts, Hammond and Stuart-Harris, 1960), this was probably the main reason for the increased prevalence of heart failure and RVH in this series.

The prognosis of opium smokers with symptomatic chronic obstructive lung disease is poor; in this series one-third of the patients were dead after two and a half years. This is in agreement with other previously reported series of mainly cigarette smokers with chronic obstructive lung disease (Renzetti, McClement and Litt, 1966; Oswald, Medvei and Waller, 1967; Burrows and Earle, 1969). In this study the major factors found to have an adverse influence on the prognosis were severe airways obstruction, persistent hypercapnia, severe RVH, heart failure, polycythaemia, and progressive weight loss. Similar findings were noted in cigarette smokers with chronic obstructive lung disease by Boushy, Adhikari, Sakamoto and Lewis (1964), and Burrows and Earle (1969).

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