Diffuse and focal oxygen pneumonitis

A preliminary report on the threshold of pulmonary oxygen toxicity in man

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SYNOPSIS Utilizing hyaline membranes and proliferative pneumonitis as evidence of pulmonary oxygen toxicity, the lung changes in 21 patients (19 injured, two inhaled smoke) who died after oxygen therapy are correlated with the intensity and duration of oxygen administration. Diffuse pneumonitis inducing hypoxaemia was found in 10 (or 11) subjects, and in nine of them it was associated with the breathing of high concentrations of oxygen (60 to 100%) for at least two days. In at least eight subjects the pneumonitis contributed to death, and two others who survived for weeks had extensively fibrosed lungs. The breathing of 40% oxygen for a sufficient time seems to be a threshold for dangerous lung effects, since one patient developed a diffuse pneumonitis and another a partly-diffuse partly-focal pneumonitis while exposed to this concentration. Those respiring oxygen concentrations between 25 and 40% for days developed either subclinical focal lung lesions or had no relevant lung changes.

Serious lung disease can occur in patients breathing very high concentrations of oxygen at atmospheric pressure (Pratt, 1958, 1968; Cederberg, Hellsten, and Miörner, 1967; Nash, Blennerhassett, and Pontoppiden, 1967; Soloway, Castillo, and Martin, 1968; Moore, Lyons, Pierce, Morgan, Drinker, MacArthur, and Dammin, 1969; Burrows and Edwards, 1970) and this has been confirmed experimentally (Robinson, Harper, Thomas, and Kaplan, 1967; Nash, Bowen, and Langlinais, 1971). Radiological opacities develop in both lungs, airway resistance increases, and hypoxaemia, though often responsive for a time, returns and becomes refractory to inhalation of even pure oxygen. The lungs often become hepatized, and show *inter alia* widespread hyaline membranes and, with a longer survival, a proliferative pneumonitis involving alveolar epithelium and fibroblasts. The suggestion of intermittent positive-pressure ventilation ('respirator lung') as a cause of the lung disorder has been undermined by experiments in goats (Nash *et al*, 1971) and the conclusion cannot be escaped that pulmonary oxygen toxicity is the main, if not the entire, cause of the pneumonitis.

However, little is known of the threshold exposures to oxygen which can produce toxic lung effects.

Received for publication 27 September 1973.

This preliminary report is concerned with this aspect and with evidence of subclinical as well as clinical lung damage.

For histological assessment, definite criteria were needed and, in the clinical setting of the present cases, hyaline membranes and proliferative pneumonitis are regarded as diagnostic of oxygen damage. Other microscopic accompaniments like thickened, congested alveolar septa, lung oedema, and alveolar haemorrhage could not be used since they are often found after injury and burns. Of course, hyaline membranes and proliferative pneumonitis also occur in other conditions, but the other known or suspected causes like paraquat poisoning (Toner, Velters, Spilg, and Harland, 1970), busulphan toxicity, topical sulphamylon therapy, and viral hepatitis were not relevant. As controls, the lungs from many other injured and burned subjects were examined: hyaline membranes were not found in the absence of oxygen therapy, and proliferative foci were otherwise seen only in relation to the edges of infarcts, organizing pneumonia, and other local causes. The suggestion (Moore *et al*, 1969; Blaisdell, Lim, and Stallone, 1970) that pneumonitis associated with hyaline membranes can develop *de novo* in severely injured subjects as part of the obscure condition referred to as 'shock lung' has not been con-

firmed. Consequently, it seems reasonable to conclude that hyaline membranes, proliferative pneumonitis, or both in patients respired with added oxygen in the Birmingham Accident Hospital are indicative of pulmonary oxygen toxicity.

The Patients and Methods

The lung changes in 21 patients who died after oxygen therapy are correlated with the intensity and duration of oxygen administration (tables I and II), radiological changes, hypoxaemia, and other factors. The patients were admitted to the Major Injuries Unit or the Burns Unit, where observation, investigation, and treatment were carried out.

In 19 patients, the conditions responsible for the respiratory distress necessitating oxygen were the effects of chest injury (9 subjects), head injury (3), fat embolism (2), inhalation of smoke (2), and single cases of combined head and chest injury, head injury and fat embolism, and chest injury and fat embolism. In case 2, the cause of the distress which followed the fractures was obscure, and in case 9 fat embolism is not unlikely.

Initially in two patients, oxygen was administered by a mask or nasal spectacles, but intermittent positive-pressure ventilation was used in 20 of the 21 subjects utilizing either endotracheal intubation or tracheostomy (six patients) after a period of intubation. Either pressure-controlled (East Radcliffe or East Freeman) or flow-volume controlled mechanical ventilators (Cape, Smith-Clarke) were used. Case 11 was treated in an oxygen tent. The concentrations of oxygen in the inspired gas (FIO_2) were measured at intervals by an oxygen analyser in six subjects (cases 3, 4, 11, 15, 16, and 21) and these are shown in *italics* in tables I and II. Otherwise, the FIO_2 values were calculated from the oxygen flow rates and minute ventilation volumes serially recorded on the clinical ventilation charts. Arterial blood gas analyses utilized Radiometer equipment. Estimates were done in many cases when respiratory distress developed and PO_2 values below 50 mm Hg were found in most of them before the administration of oxygen. Serial analyses were performed during the course of ventilation, usually once or twice daily or more often when indicated.

Full necropsy examinations were carried out. In some cases the lungs were inflated through the trachea with neutral formol saline, which showed clearly the hepatization finely honeycombed with emphysema characteristic of this kind of pneumonitis. All tissues were fixed in formol-saline. One to three blocks from each lobe of both lungs were processed histologically in paraffin; and a battery of staining methods helped to evaluate hyaline

membranes, alveolar fibrin and thrombi, collagen, and reticulin. Frozen sections stained by oil red O were also prepared to demonstrate fat emboli.

Results

By clinicopathological correlation the cases can be divided into three main groups (tables I and II).

1 Those who developed a diffuse, well marked pneumonitis associated with worsening of hypoxaemia and causal or contributory to death (cases 1-8). Also included are two examples of prolonged oxygen administration (cases 9 and 10) and an unusual case of diffuse pneumonitis confined to one lobe (case 11).

2 Those with only focal distribution of pneumonitis without apparent clinical effects (cases 12 to 18).

3 Those without evidence of pneumonitis (cases 19-21).

Fig 1 Case 1: arterial PO_2 and other changes during ventilation with 80 to 100% oxygen.

Case No.	Sex, Age (yr)	Clinical State Requiring Oxygen Therapy	Interval Injury to Death	Oxygen Therapy			Oxygen Pneumonitis		
				Duration	Method	FIO ₂ (%)	Hyaline Membranes	Proliferation	Contributory to Death
1	M 12	Chest injury	2½ days	2 days	MV	80-100	+++	±	Yes
2	M 23	Respiratory distress 2 days after fractured pelvis	7 days	Last 4 days	MV	60-100	+++	+, ++	Yes
3	M 20	Chest injury	5½ days	5 days	MV	60-100	++	++	Yes
4	F 78	Smoke inhalation (conflagration)	7 days	6½ days	MV	40	+, ++	++	Yes
5	M 36	Chest injury	8½ days	8 days	Mask initially MV	75 last 5 days	+	+++	Yes
6	M 43	Chest injury	13 days	11 days	MV	80-100 last 7 days	±	+++	Yes
7	M 6	Chest injury	13 days	12 days	MV	90-100 last 8 days	+	+++	Yes
8	F 15	Fat embolism (fractured femur, tibia)	15 days	13 days	MV	80-100	++	+++	Yes
9	M 42	Respiratory distress 1½ days after fractured tibia, ankle, dislocated hip	47 days	Nasal day 2-8 MV after day 8 Day 8-16 Day 16-28 Day 28-44 Day 44-47		40-60 80-100 40-60 80-100	±	+++	Probably
10	M 49	Head injury and fat embolism (fr femur, tibia) ruptured diaphragm	15 weeks	Day 3-8 Day 8-25 Day 25- Last 8 days	MV	90 40-65 ? Air	0 Fibrous thickening of alveolar septa	+	Uncertain
11	F 50	Inhalation of smoke (75% burns)	8½ days	8 days	Tent	40	Left lower tube ++ Elsewhere Focal	++ or +	Uncertain

Table 1 Patients with diffuse oxygen pneumonitis

MV = mechanical ventilation; FIO₂ = percentage of oxygen in inspired gas
FIO₂ values in italics were estimated by direct oxygen analysis of the inspired gas.

Case No.	Sex Age (yr)	Clinical State Requiring Oxygen Therapy	Interval Injury to Death	Oxygen Therapy			Oxygen Pneumonitis		
				Duration	Method	FIO ₂ (%)	Hyaline Membranes	Proliferation	Contributory to Death
12	M 17	Head injury	12 hours	11½ hours	MV 10 hrs.	35-50	Slight, focal	0	No
13	M 21	Fat embolism (fractured tibiae, femurs)	3 days	2½ days	MV last day	95 O ₂ last day	Focal	0	Probably no
14	M 32	Chest injury	4 days	3½ days	MV	60-70	Focal	Focal	No
15	M 60	Head and chest injury	6½ days	6 days	MV	25-30	Focal	Focal	No
16	M 60	Chest injury, fat embolism (multiple rib fractures)	11 days	10 days	MV	28-36	Focal	Focal	No
17	F 80	Chest injury (also fractured pelvis, femur, both tibiae)	13 days	12 days Day 1-6 Day 9-13	MV	40 30	Focal	Focal	No
18	F 74	Chest injury	3/12	Intermittent 3/12	MV or mask		—	Focal, multiple tiny scars	Probably no
19	M 37	Head injury	13 days	Last 2 days	MV	35-70	None	None	—
20	F 6	Head injury, stopped breathing, onto ventilator	3½ days	36 hours	MV	100	None	None	—
21	M 77	Chest injury	15 days	14½ days	MV	For 13 days 26-32	None	None	—

Table II Patients with focal pneumonitis or no pneumonitis after oxygen therapy

MV = Mechanical ventilation.
FIO₂ values in italics were estimated by direct oxygen analysis of the inspired gas.

Fig 2

Fig 2 Lung showing hyaline membranes lining terminal airia (case 2). Haematoxylin and eosin (H & E). $\times 120$.

Fig 3

Fig 3 Active proliferative pneumonitis showing fibroepithelial invasion of numbers of alveolar sacs and thickened alveolar septa (case 6). H & E, $\times 48$

DIFFUSE PNEUMONITIS

Cases 1-8

Ventilation with added oxygen was continuous for periods of two to 13 days, and in seven subjects concentrations in excess of 60% oxygen were inspired during the whole or greater part of the period (table I). The concentrations were between 80 and 100% in four cases and were up to 100% for periods in six subjects. Bilateral diffuse radiological opacities were apparent by the third or fourth day and subsequently progressed. In five subjects ventilatory pressures had to be significantly raised (fig 1) necessitating a change of respirator in three cases. Though all patients probably benefited from oxygen for a time, initial relief of hypoxaemia was observed in only three subjects. Hypoxaemia developed again or worsened, and terminal or preterminal PO_2 values between 28 and 48 mm Hg were found in five cases (1, 2, 4, 6, and 7). Arterial PCO_2 was usually maintained within normal limits

by altering the minute volume, but in four cases a terminal hypercarbia accompanied the hypoxaemia. One or more episodes of cardiac arrest occurred in four subjects and three of them died in cardiac arrest. Figure 1 shows the course of events in case 1.

Histological changes were diffuse and extensive, involving all parts of both lungs. They can be divided into two overlapping stages, 'early exudative' and 'later proliferative' phases. Extensive and well marked eosinophilic hyaline membranes lining many terminal airia (fig 2) characterized cases 1 and 2 who died within a few days of oxygen ventilation. Evidence of early alveolar epithelial spreading and regeneration was also visible under some hyaline membranes. Other features included thickened, hyperaemic alveolar septa; proteinaceous alveolar oedema sometimes containing desquamated epithelial cells, fibrin, or haemorrhage; and interstitial oedema involving lobular septa and subpleural zones. Polymorphonuclear leucocytic infiltration was absent except in foci of concomitant pneumonia.

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Hyperplastic changes were pronounced in those surviving longer (cases 3 to 8) and involved epithelial, fibroblastic, and other interstitial elements. Hyaline membranes were often present, though generally less numerous. Hyperplasia of epithelial cells (pneumocytes) was manifest either as linear sheets of cubical cells migrating over alveolar surfaces as if attempting to reline them, or as solid masses of cells projecting into alveoli from thickened septa (fig 3) or both. It was not possible to decide which type of pneumocyte was involved. Some binucleate and occasional multinucleate giant forms or other bizarre cells were seen. This solidifying proliferating alveolitis was often associated with invading fibroblasts and collagen. Alveolar wall thickening often included a degree of collagenization and sometimes new tortuous capillaries could be distinguished. Proliferative activity also involved terminal bronchi, some showing dysplasia of epithelium to a multilayered form. Alveolar exudate became condensed to eosinophilic masses invaded and surrounded by mononucleated cells, either macrophages or proliferating pneumocytes or both.

Other lung findings consisted of acute bronchitis (five subjects) with small foci of bronchopneumonia in three of them; multiple micro-arterial or capillary microthrombi (7); small macroscopic thromboemboli (three cases, two had small infarcts). Major lung emboli and tiny septic emboli were also found in case 8. Pulmonary fat emboli were numerous in cases 1 and 3 and a few marrow emboli were seen in case 5.

One subject (case 4) developed hypoxaemic pneumonitis while breathing oxygen at only 40% concentration.

Case 4

A woman of 78 years was rescued from a smoke-filled, burning room, and half an hour later was admitted in respiratory distress and semiconscious. She was not burned. The distress rapidly increased and the arterial blood showed respiratory acidosis and hypoxaemia (PO_2 46 mm Hg). Much black (carbon) secretion was aspirated from the airway. Mechanical ventilation was instituted through an endotracheal tube, initially with 100% oxygen when the PO_2 rose to 95 mm Hg and she became fully conscious. The oxygen concentration was reduced two hours later to 60% (PO_2 160 mm Hg) and soon after to 40% when the PO_2 was 76 mm Hg (fig 4). Ventilation with 40% O_2 was continued. Radiological opacities appeared throughout both lungs by the third day (fig 5) and refractory hypoxaemia developed. The tracheal sputum grew *Klebsiella* and later also *Ps. pyocyanea*. On the sixth day, PO_2 was

Fig 4 Case 4: arterial PO_2 during respiration with 40% oxygen with development of refractory hypoxaemia.

only 48 mm Hg, and next day she died in cardiac arrest.

Necropsy showed a severe tracheobronchitis with purulent exudate. The lungs (together 1470 g) were indurated, showing firm, partly red, partly grey cut surfaces. Histology showed a major widespread non-infective pneumonitis, acute bronchitis associated with carbon, and a few arterial microthrombi. Hyaline membranes lined some alveolar ducts (fig 6) and proliferated alveolar epithelium often mixed with collagen-forming fibroblasts were widespread and prominent (fig 7). The appearances were similar to those observed after very high oxygen concentrations.

Cases 9 and 10

Mechanical ventilation with various air-oxygen mixtures had been continued for weeks, the concentrations ranging from 40 to 100% oxygen at different times.

In case 9, PO_2 fluctuated between 50 and 90 mm Hg, with a preterminal PO_2 of 152 mm Hg breathing 100% O_2 . He died with multiple complications including bacterial endocarditis, bronchopneumonia, lung abscesses, and myocardial infarction. The lungs

Fig 5

Fig 7

Fig 6

Fig 5 Case 4: chest radiograph on third day of respiring 40% oxygen showing bilateral granular and fluffy opacities in the lung fields.

Fig 6 Case 4: hyaline membrane pneumonitis. H & E, $\times 120$.

Fig 7 Case 4: proliferative fibroepithelial pneumonitis with focal collagen formation. Elastica & Van Gieson $\times 120$.

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showed widespread fibrosing proliferative pneumonitis, a few hyaline membranes (fig 8) and many alternating areas of emphysema and scarring. Alveolar septa were thickened by fibrosis and many alveoli seemed to be strangled. Recent alveolar epithelial proliferation was also seen.

Case 10, unconscious from a head injury, had been ventilated for about 14 weeks, most of the time with added oxygen. He died with respiratory infection. The lungs also showed widespread chronic fibrous thickening of many alveolar walls with small scars and areas of atelectasis. The appearances were consistent with fibrotic changes resulting from a pneumonitis.

Case 11

An unusual distribution of lesions developed during the administration in a tent of 40% oxygen for eight days. The left lower lobe was consolidated by a diffuse and active proliferative pneumonitis with many hyaline membranes. Elsewhere, however, only

scattered foci of pneumonitis and few hyaline membranes were visible. Purulent bronchiolitis and bronchopneumonia were prominent.

FOCAL PNEUMONITIS (TABLE II)

This group is characterized by scattered foci of hyaline membranes or proliferative lesions or both, ventilation with oxygen concentrations generally less than in those with diffuse pneumonitis, and death from complications unrelated to oxygen administration.

Only proliferative lesions not explainable by local causes are included, and as a consequence two other cases with focal lesions were excluded from the series. The density of lesions varied somewhat: often only one or two foci were seen per lung section and some sections showed neither hyaline membranes nor areas of proliferation.

Cases 12 and 13

This patient (case 12) was ventilated with 35 to 50%

Fig 8

Fig 8 Case 9: fibrosing pneumonitis with strangulation of alveoli newly lined by alveolar epithelium. Residual hyaline membrane also present. H & E, $\times 48$.

Fig 9

Fig 9 Case 13: focus with hyaline membranes lining terminal atria. Picromallory $\times 120$.

Fig 10

Fig 10 Case 15: focal proliferative pneumonitis showing hyperplastic alveolar epithelium relining denuded alveoli and invading condensed exudate within alveolar sacs. Phagocytic invasion also present. H & E, $\times 120$.

Fig 11

Fig 11 Case 17: focal proliferative pneumonitis with a residual hyaline membrane. H & E, $\times 120$.

oxygen for 10 hours before death from a head injury. A few scattered hyaline membranes were found in the lungs which also showed prominent congestion, much alveolar and some interstitial oedema.

Case 13 had clinical fat embolism, and was given 95% oxygen during his last day of life. Hyaline membranes were distributed focally in most but not all parts of the lungs (fig 9) but proliferative changes were not seen. Many fat emboli, a few marrow emboli and a focal necrotizing arteriolitis in a few vessels were also found. Though the hyaline membranes in cases 12 and 13 are believed to represent the effects of oxygen toxicity, it is uncertain whether they represent the beginning of a focal or diffuse pneumonitis since time may be needed for the full picture of the latter to develop.

Cases 14-17

Cases 14 to 17 showed foci with hyaline membranes and with proliferative pneumonitis, the latter consistent with oxygen therapy lasting three and a half

to 12 days. The individual lesions, though scattered and relatively small (generally 5 to 10 mm diameter), were histologically similar to those seen in the diffuse condition (figs 10 and 11). Elsewhere the lung tissue was often congested and oedematous; moderate numbers of fat emboli were found in case 15 and numerous emboli in case 16; and small foci or larger areas of bronchopneumonia were present in all cases. Condensed eosinophilic coagulum invaded by epithelial and phagocytic cells within groups of alveoli (fig 10) were also noted, often in areas containing hyaline membranes or proliferative changes. Case 14 had been respired with 60 to 70% oxygen for three and a half days, but significantly lower oxygen concentrations had been used in cases 15, 16, and 17, ranging between 25 and 40%. This is probably significant. Normal PO_2 values were maintained in case 15 during the administration of 25 to 30% oxygen. Moderate or intermittent hypoxaemia during ventilation in cases 14, 16, and 17 was

consistent with the nature of the injuries and complications.

Case 18

Case 18 received intermittent added oxygen by mask or ventilator over a period of three months. Small foci of active fibrosing pneumonitis (fig 12) and multiple tiny lung scars were present, the latter possibly representing healed foci of pneumonitis. She died with bronchopneumonia. The arterial PO_2 was 64 mm Hg three days before death.

Fig 12 Case 18: focal proliferative pneumonitis with interstitial fibrosis and sheets of spreading alveolar epithelium. H & E, $\times 120$.

CASES WITHOUT PNEUMONITIS (TABLE II)

Cases 19-21

Case 19 was mechanically ventilated during his last two days of life with oxygen concentrations ranging between 35 and 70%. PO_2 on the day of death was 160 mm Hg. Case 20 stopped breathing and was mechanically ventilated with 100% oxygen until she died 36 hours later; during oxygenation PO_2 was

110 mm Hg. Case 21 was mechanically ventilated for 14½ days with oxygen concentrations kept between 26 and 32% which were sufficient to prevent hypoxaemia.

Discussion

The history of oxygen poisoning dates back to Priestley and Lavoisier in the 18th century, and Bert in 1878 showed that exposure to hyperbaric pressures could be fatal. The pulmonary toxic effects were first described by Smith in 1899. Birds, mice, rats, and guinea pigs exposed to 0.7 to 0.8 atmosphere of oxygen died within a few days with extensively congested lungs which showed pneumonic-like changes, whereas exposure to 0.4 atmosphere of oxygen for a week was innocuous. The dangerous respiratory effects in various animals of concentrations above 0.7 atmosphere of oxygen have been confirmed by Binger, Faulkner, and Moore (1927), Ohlsson (1947), and others.

The earliest description of pulmonary hyaline membranes in experimental oxygen poisoning seems to be that by Clamann, Becker, Freyseng, and Liebegott (1940) and the diffuse exudative and proliferative changes found in monkeys (Robinson *et al*, 1967) and man are now well established. However, the development of focal lesions in patients respired with added oxygen is not well recognized. Reference to a focal or a widespread formation of hyaline membranes in patients respired with added oxygen was made by Cederberg and colleagues (1965). This is confirmed in the present study and extended to include proliferative changes. Cederberg *et al* were unable to establish a relationship between duration-intensity of exposure and the extent of hyaline membranes though they concluded that continuous administration of oxygen, in a concentration of more than 50% or of more than 40% for a prolonged period, involves the risk of pulmonary hyaline membrane formation.

In the present study, a focal distribution of lesions generally correlates with inspired oxygen concentrations less than or duration of exposure shorter than those associated with diffuse changes. Table III summarizes the relationships found in 19 subjects. Eight of the nine with diffuse lung changes had been breathing concentrations above 60 or 80% for at least two days. On the other hand, three of the six subjects with focal changes and one of the three without relevant lung effects had been respired with oxygen concentrations between 25 and 40% for six days or longer. Relatively limited exposure time (one and a half days and less than 24 hours respectively) may account for the absence of pneumonitic changes in case 20 and for only focal hyaline mem-

FIO ₂ (%)	Duration	Pneumonitis		
		Diffuse	Focal	None
80-100	< 1 day		Case 13	
	1½ days			Case 20
	2 days	Case 1		
	7 days	Case 6		
	8 days	Case 7		
	13 days	Case 8		
60-100	12 days & 3 days	Case 9		
	4 days	Case 2		
	5 days	Case 3		
	8 days	Case 5		
75	3½ days		Case 14	
60-70	2 days			Case 19
35-70	6½ days	Case 4		
40	8 days		Case 11	
35-50	10 hours		Case 12	
30-40	5 & 4 days		Case 17	
25-36	6 days		Case 15	
	10 days		Case 16	
	14½ days			Case 21

Table III *Relation between oxygen therapy and lung changes*

branes in case 13 despite breathing 100 and 95% oxygen, and may also account for the limited focal changes in case 12 given 35 to 50% oxygen for 10 hours.

The development of a diffuse hypoxaemic pneumonitis in case 4, and of a partly diffuse-partly focal disease in case 11 indicates that the breathing for days of only 40% oxygen may be dangerous. Both these subjects were admitted with an acute tracheobronchitis from the inhalation of smoke, and it may be argued that irritative changes had predisposed their lungs to oxygen toxicity. However, Ohlsson (1947) found that rabbits rendered hypoxaemic by pulmonary blast injury or by diphosgene were more tolerant to high oxygen concentrations (80-90%) than normal animals. The report by Cederberg *et al* includes two patients who developed widespread hyaline membranes after breathing oxygen concentrations no greater than 40 and 50% respectively for 13 and five days. The overall findings point to an inspired oxygen concentration

of the order of 40% at atmospheric pressure as a threshold of dangerous toxic effects, provided that exposure is sufficiently long. In case 14, bilateral radiological lung opacities had appeared on the third day which indicates that this may be long enough. Present findings are consistent with the apparent lack of ill effects in United States astronauts who are said to breathe pure oxygen at one-third of an atmosphere for prolonged periods, though they suggest that some of them may develop subclinical focal changes terminating in fine lung scars.

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