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Oxygen Induced Pulmonary Hyaline Membranes (PHM) and Disseminated Intravascular Coagulation (DIC)

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Summary. Thirty-two rabbits were exposed to normobaric hyperoxia (100% oxygen at 1 ata) for 30 to 85 hours. A disseminated microthrombosis (DIC) representing a generalized intravascular activation of coagulation was first seen after 33 hours. The microthrombi were found mainly in the form of hyaline globules in the terminal vessels of the kidney, less often in other organs. The formation of pulmonary hyaline membranes (PHM) was observed only after oxygen exposure in excess of 54 hours. These findings support that the PHM following oxygen exposure in animal experiments, as PHM in the newborn and the adult, may be considered to be the expression and result of an intravascular coagulation activation.

A systematic search in newborns, children and adults for the pathogenesis of pulmonary hyaline membranes have turned up evidence that, parallel to disseminated microthrombosis, pulmonary hyaline membranes (PHM) may be considered the morphologic equivalent of a plasmatic hypercoagulability, meaning a generalized intravascular coagulation activation (Bleyl, 1971). The formation of intravascular circulating, soluable, intermediary products of the fibrinogen-fibrin transformation which is closely coupled to increased turnover of coagulation factors (consumption coagulopathy, Lasch *et al.*, 1971) apparently leads to both disseminated microthrombosis and, after extravasation into the alveoli, the formation of pulmonary hyaline membranes (Bleyl and Büsing, 1973).

The simultaneous occurence of intravascular microthrombi and pulmonary hyaline membranes has been demonstrated in various diseases: intrauterine asphyxia of the newborn (Bleyl and Büsing, 1970), cyanotic heart defects in the infant (Bleyl and Höpker, 1970), various forms of shock in the periphery (Bleyl *et al.*, 1971), gramnegativ sepsis, certain forms of inflammatory kidney diseases which lead to the socalled uremic pneumonitis (Bleyl and Werner, 1972), malignant tumors of different origin (Bleyl *et al.*, 1971), massive hemolysis with release of thromboplastic activity, i.e., fresh water aspiration, and finally hemolytic-uremic syndrome. In animal experiments it is possible to produce pulmonary hyaline membranes through prolonged thrombin infusion (Huber *et al.*, 1969; Büsing *et al.*, 1973).

Pulmonary hyaline membranes can also be seen in animal experiments after moderately long exposure to an oxygen atmosphere at atmospheric pressure (normobaric hyperoxia, Liebegott, 1941; Pichotka, 1941; Kühn and Pichotka, 1948, a.o., see Clark and Lambertsen, 1971). The following question then arise:

1. whether a generalized coagulation activity after toxic oxygen exposure could be detected, and if so,

2. which time correlation does this intravasal coagulation activity have to the formation of pulmonary hyaline membranes.

The present experiments will not include a description of the many diverse pulmonary changes which occur following toxic oxygen exposure as these have already been fully and completely discussed by other authors (Clamann, 1941; Kistler *et al.*, 1967; Kapanci *et al.*, 1969; Weibel, 1973 and others).

Material and Methods

The experiments were carried out on 42 bred rabbits with body weights between 2000 and 4000 g. The animals were individually kept in a chamber approximately 40 liters in size. Thirty-two animals were treated with 100% oxygen using a continuous stream and 10 controls were given compressed air under otherwise similar conditions. The chamber temperature was between 20° and 26°C, the humidity averaged 80% (60% to 100%) at a gas flow rate of 5 to 10 liters per minute. Feed and water were always available. The exposure time varied between 30 and 85 hours. Following the gas exposure, the animales were wasted by a blow to the neck in pentobarbital anesthesia. In order to avoid postmortal oxygen-induced resorption atelectasis, a few final respiratory excursions were allowed with atmospheric air (Pratt, 1965). The organs were fixed in 10% neutral formalin and 96% alcohol, bedded in paraffin and 4 μ sections stained with hematoxilin-eosin and PAS-reaction. The alcohol-fixed preparations were additionally treated with Ladewig trichromic stain. For the analysis of the specificness of the intra- and extravascular precipitating fibrinogen derivatives, expecially of fibrin mono- or oligomeres and fibrin polymeres, cryostat sections of the lungs and kidneys were examined employing immunfluorescent-optical techniques with fluorescein isothiocyanate tagged gamma globulin fraction of an anti-rabbit fibrinogen serum obtained from the goat (for details of this method, see Bleyl, 1969). In several cases the lungs were additionally treated using the p-dimethylaminobenzaldehyd-method of Adams (1957) for the detection of tryptophan, for it is known that fibrinogen derivatives have a relatively high tryptophan content as opposed to the other plasma proteins.

The evaluation of disseminated microthrombi included fibrin-rich as well as thrombocyte-rich and hyaline thrombi as long as they were PAS-positive and conformed to the criteria of Boyd (1967). Additionally, a disseminated microthrombosis would only be considered as such when microthrombi also occured outside the pulmonary flow tract. This appeared necessary to avoid false positive results caused by the intravenous barbiturate injection. All PAS-positive, homogeneous condensed or lumpy-fibrous deposits found in the alveoli and terminal bronchioles, whether partially or totally adherent to the walls, were considered pulmonary membranes.

Results

Localisation and Type of Microthrombi

Disseminated microthrombi could be detected with varying frequency in all organs. They were found in the pulmonary capillaries and venules in the form of thrombocyte-rich or hyaline, PAS-positive microthrombi (Figs. 1 and 2). Liver and adrenals were less frequently affected. The spleen presented only with sporadic fibrin-rich or hyaline globules in the sinusoides. Especially abundant the intravascular microthrombi were found in the arterioles, capillaries and venules of the kidney (Fig. 3). In extraordinary abundance, hyaline microthrombi—the so called "globules" of Hardaway (1966)—were found in the renal capillary flow tract. These microthrombi, some larger, some smaller than erythrocytes, demonstrated several light-colored inclusions of varying size upon staining with trichrome. These globules were PAS- and immunfluorescent-positive proving them to be fibrin derivatives. No microthrombi could be discovered in myocardium although

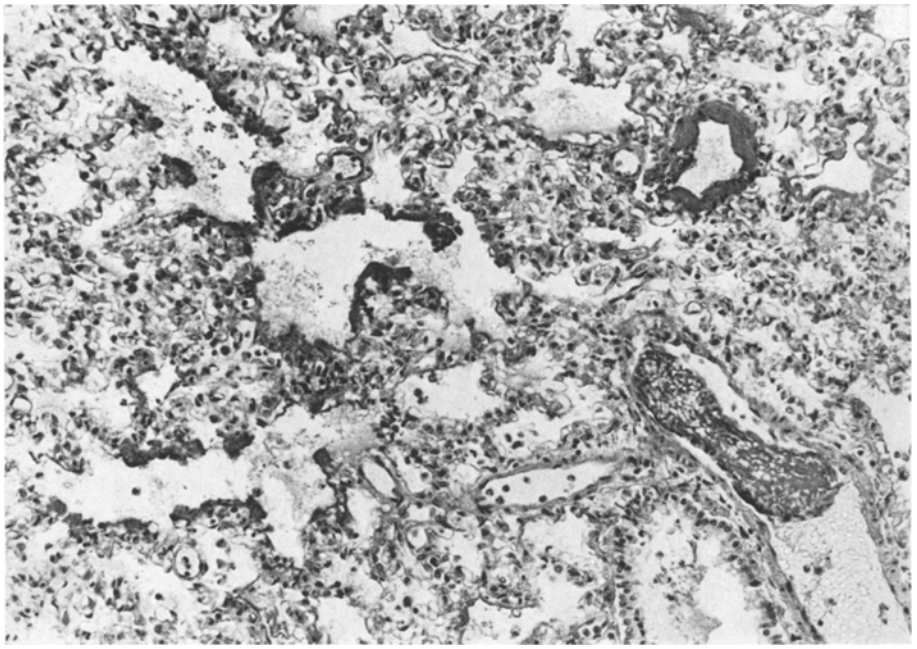

Fig. 1

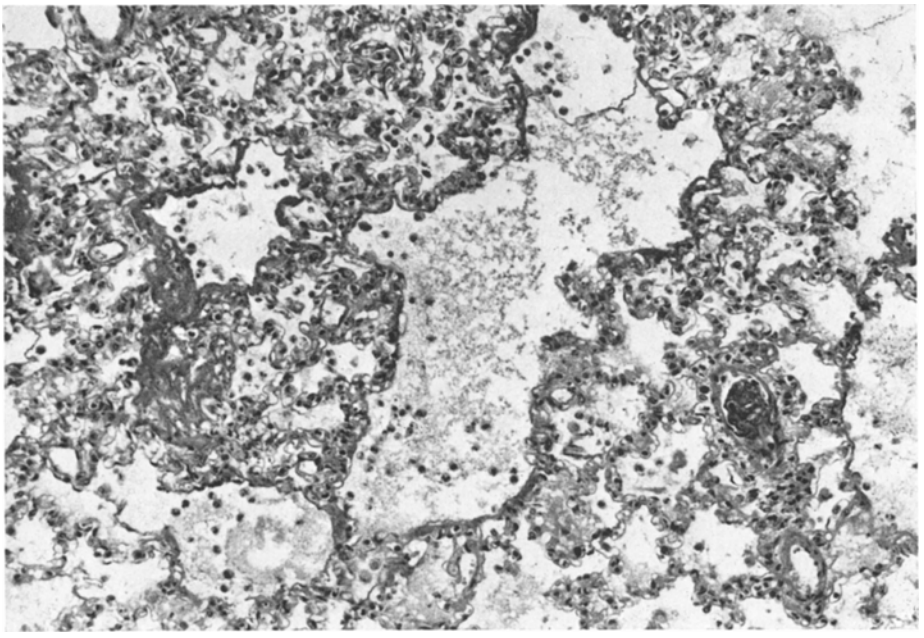

Fig. 2

Fig. 1 and 2. Rabbit lungs after normobaric hyperoxia of 70 hours. Simultaneous occurrence of fibrin-rich microthrombi and hyaline membranes. Formalin, paraffin, PAS reaction. Microphotogram × 160

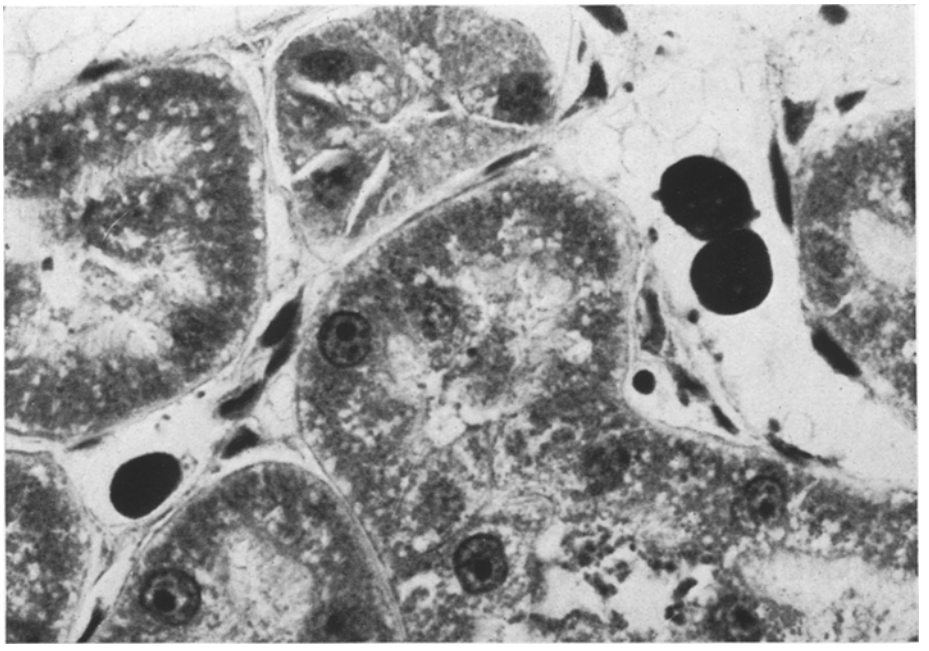

Fig. 3. Rabbit kidney after normobaric hyperoxia of 57 hours. Hyaline microthrombi (globules) in the terminal flow tract between the intracapillary erythrocytes, which are only shadows here. Alcohol, paraffin, Ladewig's trichrome. Microphotogram × 400

a few cases demonstrated parenchym necroses (Büsing *et al.*, 1973). In the controls not one case of microthrombi could be seen.

Manifestation of Microthrombi

The varying duration of gas exposure in the individual animals presented a time gradation of the individual experiments which allow no conclusions concerning the begin of coagulation activation but certainly about the moment of the manifestation of intravascular microthrombi. One animal already demonstrated intravascular microthrombi in histological sections after 33 hours of exposure (Fig. 4). With very few exceptions, animals with exposure times of 40 to 50 hours developed microthrombi, 55 to 70 hours of exposure caused microthrombi in all but one animal. Following exposure times in excess of 70 hours no microthrombi could be detected, however, the lungs of these animals did demonstrate hyaline membranes.

Localisation of the Pulmonary Hyaline Membranes

Distinct regional differences in the formation of the pulmonary hyaline membranes within the individual lung segments did not exist although the intensity appeared to vary. The membranes were present in the form of small bands or loose band-like conglomerations usually located on the internal surface of the

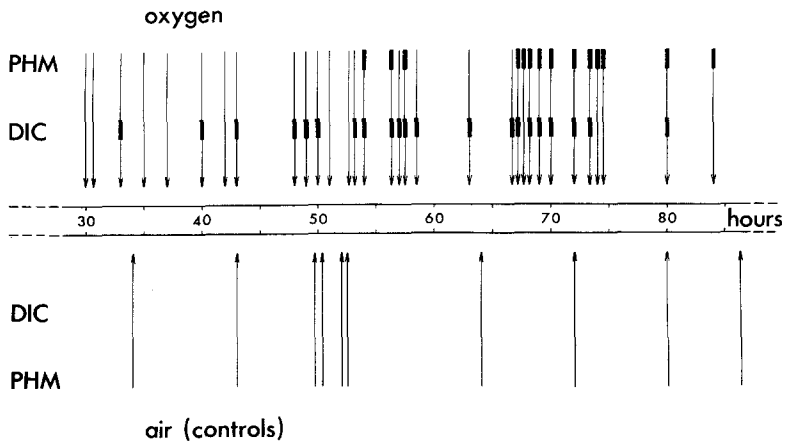

Fig. 4. Disseminated microthrombosis (DIC) and pulmonary hyaline membranes (*PHM*) as dependent upon exposure time. Above the oxygen exposed animals ($N = 32$), below the controls exposed to compressed air ($N = 10$). Each arrow marks one animal and the end point or duration of the exposure. The bar represents proof of DIC or PHM

terminal bronchioles, occassionally in the partially collapsed alveoli. Typical caplike extravascular fibrin precipitates were present on the interalveolar walls and near the immediate capillaries. Necrotic alveolar epithelium was not uncommonly included in the precipitate. Isolated intraalveolar extravasated erythrocytes or a varying degree of alveolar edema could also be seen (Figs. 1 and 2). Following oxygen exposure the animals with pulmonary hyaline membranes, as well as those that did not develop membranes due to early termination of the experiment, demonstrated characteristic pulmonary changes with interstitial, largely perivascular edema, broadened, cell-rich alveolar walls and marked dysatelectasis, i.e., an irregular and insufficient unfolding of the alveoli. After longer exposure times alveolar epithelium necrosis was usually present.

Manifestation of Pulmonary Hyaline Membranes

The differences in exposure time of the individual experiments allowed conclusions as to the beginning of the formation of pulmonary hyaline membranes. An exposure time of less then 50 hours caused no such membranes to be formed (Fig. 4), however, starting at 54 hours their formation could be observed. More than 65 hours in oxygen resulted in every animal demonstrating pulmonary hyaline membranes, whereby individual variation in the intensity of these membranes was not taken into account.

Frequency of PHM and DIC in the Experimental Material

The present experiments did not optimally lend themselves to answering the question of the frequency of disseminated microthrombi and pulmonary hyaline membranes following oxygen exposure. The time gradation required serveral experiments to be terminated early by wasting the animals at a point when micro-

Table 1. Number of experimental and control animals which demonstrated DIC or PHM after minimum exposure times of 40 to 55 hours, respectively

	Number of animals	Animals with microthrombi	Animals with hyaline membranes	Animals with hyaline membranes and microthrombi	Animals with hyaline membranes without microthrombi
Gas-exposure >40 h					
O_2	26	19/26	14/26	10/26	4/26
air	9	0/9	0/9	0/9	0/9
Gas-exposure >55 h					
O_2	17	13/17	13/17	9/17	4/17
air	4	0/4	0/4	0/4	0/4

thrombi or hyaline membranes had not yet formed due to insufficient exposure time (Fig. 4). Statistics concerning the frequency of microthrombi and hyaline membranes for the entire collective is therefore necessarily burdened with false negative values.

If only those animals are considered which were wasted after an oxygen exposure time excess of 40 hours, thereby eliminating a large number of animals all without microthrombi, due to minimal oxygen exposure, 19 of the remaining 26 animals demonstrated disseminated microthrombi, 14 had formed pulmonary hyaline membranes and 10 presented with both phenomena (Table 1). However, in this selected group are also animals included which received insufficient oxygen exposure to cause pulmonary membranes.

A reasonable frequency statistic appears to be obtained only when those animals with exposure times in excess of 55 hours are considered (Fig. 4). This means that 13 of 17 animals had microthrombi and 13 were found with hyaline membranes, 9 animals had both phenomena (Table 1). This is comparable to the statistics of Berfenstam *et al.* (1958) concerning the frequency of pulmonary hyaline membranes after normobaric longterm hyperoxia.

A statistical analysis of the correlation between microthrombi and pulmonary hyaline membranes is not possible due to the small remaining number of suitable animals in our study. A difference in the controls with respect to formation of disseminated microthrombi and pulmonary hyaline membranes following oxygen exposure can be recognized using the four-field test. The exact test of R.A. Fischer has shown a difference in the formation of hyaline membranes between two collectives of animals, one with less than 60 hours of oxygen exposure, the other with more (error probability less than 5%). The occurrence of microthrombi shows expectedly no significant difference when similarly examined.

Discussion

A generalized coagulation activation is coupled with an increased turnover of thrombocytes and coagulation factors leading to the formation of intravascular circulating fibrin monomeres which combine with fibrinogen or other fibrin monomeres to build soluable complexes. These intermediary products of the fibrinogen-fibrin transformation can be cleared

by the reticulo-histocyte system until the clearance function is overloaded (Bleyl *et al.*, 1969, 1971). Fibrin monomeres can also be reduced to soluable fibrin degradation products (FDP) by an activated humoral fibrinolysis. These degradation products cause antipolymerase activity (Latallo, 1962), i.e., they block further polymerisation of the intermediaries (Lipinski *et al.*, 1967; Marder and Shulman, 1969). Should the humoral fibrinolysis also become strained or not be able to keep pace with the intensity of the coagulation activation, the soluable complexes of the fibrinogen-fibrin transformation polymerize to high-polymer fibrin and, as intravascular microthrombi, are evidence for previous coagulation activation (Lasch, 1971).

Previous research on the morphological findings in oxygen exposed experimental animals have repeatedly reported on the intravascular fibrin thrombi in the pulmonary flow tract, but the microthrombi have been always attributed to local oxygen-induced injury to the lung (Kühn and Pichotka, 1948; Kloos *et al.*, 1957; Berfenstam *et al.*, 1958; Gould *et al.*, 1971, 1972). However, the present experiments show that the coagulation activation due to toxic oxygen exposure is not confined solely to the lungs. In the rabbit, oxygen exposure leads to a generalized intravascular coagulation activation with ensuing disseminated microthrombosis which not only affects the lungs but also other organs such as the liver, spleen and especially the kidneys.

In addition to fibrin-rich and thrombocyte-rich microthrombi, numerous spherical or club-shaped hyaline microthrombi, which were proven by fluorescent microscopy to be fibrinogen derivatives, were found in the kidneys and occassionally other organs following toxic oxygen exposure. These corresponds to the well-known globules or "Fibrinkügelchen" described by various researches (Apitz, 1942; Hardaway, 1966; Skjørten, 1968). In these globules fine elements can be electronoptically seen which have a periodicy of 200 Angström, characteristic for soluable fibrin intermediaries and insoluble fibrin polymeres (Skjørten, 1968). There is much to support that these hyaline microthrombi are intravascular precipitated coagulation products which possess a relatively proportion of fibrin degradation products in addition to fibrin monomeres and other plasma proteins. The hyaline microthrombi found after toxic oxygen exposure can be considered the morphological equivalent of intravascular coagulation activation with ensuing fibrinolysis activation.

Nair (1967) did a study on pulmonary healthy humans and found a reduced whole blood clotting time and a decrease in thrombocytes following short-term ventilation with pure oxygen. Under similiar conditions in humans and dogs, Winter *et al.* (1973) observed a thrombocyte consumption and a slightly increased turnover of fibrinogen. In addition to signs of coagulation activation, Phillips *et al.* (1969) found a reduction in blood plasminogen and plasmin inhibitors prior to the formation of pulmonary hyaline membranes after toxic oxygen application to guinea pigs. These findings can be readily attributed to the reactive consumption of fibrinolytic activity following prolonged coagulation activation. It is still open to debate whether this is the result of thrombocyte aggregation in the terminal pulmonary flow tract as has been observed by Nasseri *et al.* (1967) and Schulz (1973) after hyperbaric oxygenation and nomobaric hyperoxia, respectively, or, whether thrombocyte aggregation and coagulation activation are two independent phenomena.

The analysis of the time relationships between microthrombosis and pulmonary changes have shown that the formation of intravascular microthrombi as

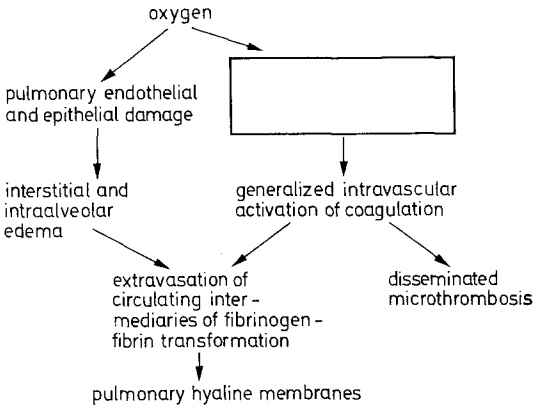

Fig. 5. Pathogenesis of pulmonary hyaline membranes after normobaric hyperoxia. The cause of intravascular coagulation activation remains open

evidence of coagulation activation precedes the pulmonary hyaline membranes by 10 to 15 hours. After 40 hours oxygen exposure several animals had microthrombi while hyaline membranes first appeared after 54 hours. After 67 hours, pulmonary hyaline membranes were regularly present.

The oxygen induced hyaline membranes fullfill a pathogenetic prerequesite which we found operative in previous investigations on the pathogenesis of pulmonary hyaline membranes in newborns and adults: apparently the presence of pulmonary hyaline membranes following toxic levels of oxygen is also preceded by a coagulation activation with formation of intravascular circulating intermediary products of the fibrinogen-fibrin transformation. After extravasation these intermediaries can precipitate in the alveoli as polymer fibrin and together with other plasmatic proteins and necrotic alveolar epithelium they form typical hyaline membranes. The intravascular circulating fibrin intermediaries undergo a more or less pronounced humoral fibrinolysis with formation of fibrin degradation products which polymerize intravasally with other fibrin monomeres and precipitate as typical hyaline microthrombi.

The time difference between the intravascular coagulation activation, recognized by the formation of fibrin-rich and hyaline microthrombi, and the formation of pulmonary hyaline membranes can be explained by the delay with which the coagulation independent, increased permeability of the pulmonary capillaries and alveolar walls appears after oxygen intoxication (exsudative phase of pulmonary injury following oxygen ventilation; Weibel, 1973). Electron microscopic examinations on apes and rats after 48 hours of normbaric hyperoxia reveal primarily only endothelium injury and interstitial edema. Alveolar wall injury with movement of fibrinogen derivatives out of the congested interstitium into the alveoli is delayed (Kistler *et al.*, 1967; Kapanci *et al.*, 1969). The present experiments lead to the conclusion that under the condition of hypercoagulability oxygen induced hyaline membranes can only then form after the capillaries and alveolar walls have been damaged by oxygen intoxication thereby permitting the extravasation of soluable fibrin derivatives (Fig. 5).

In four animals no microthrombi could be detected despite the presence of hyaline membranes. These were animals with relatively long exposure times. Since coagulation activation is regularly followed by an activation of fibrinolyis, we must assume here that either a secondary lysis of the thrombi or a primary inhibition of microthrombi formation by the antipolymerase activity of fibrin- or fibrinogen degradation products is responsibel (Mitchell, 1968). The one animal wasted after 67 hours was retrograde perfused through the aorta to fix the lungs for electron microscopy. Here a wash-out effect could be the cause.

From our experimental data the conclusion can be drawn that the oxygen induced pulmonary hyaline membranes in the rabbit have two pathogenetic prerequisites: the first component appears to be a generalized coagulation activation and is paralleled in the formation of pulmonary hyaline membranes in newborns with respiratory distress syndrome and in the shock lungs of adults. The second component is the extravasation of formed coagulation products made possible by the injury to the terminal pulmonary flow tract after hyperoxygenation (Fig. 5). The cause of the intravascular coagulation activation with respect to oxygen intoxication must remain open for the present. A conclusion as to the dangers of concentrated oxygen therapy in intensive care units for pulmonary failure cannot be drawn from the present discussion of the experiments carried out on pulmonary healthy animals.

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