PRODUCTION OF PULMONARY INFARCTS BY THE INSUFFLATION OF ACID.

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Plates 12 and 13.

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Infarcts of the lung, both in man and in experimental animals, result either from infected emboli in a normal organ or from bland emboli when cardiac decompensation or other disturbance has decreased the efficiency of the pulmonary circulation.[1] Such an explanation appeared adequate, since hitherto the infarcts so commonly found have been associated with the occlusion of a large supplying vessel with secondary extension of the thrombus into the smaller branches. A reverse of this process is shown in the experiments recorded below. The insufflation of acid into a normal lung leads to infarction, the primary process being a coagulative change in the capillary bed with secondary propagation of the clot into the larger vessels.

Extensive vascular injury in the pulmonary tissue occurs after the inhalation of irritating gases and also in influenzal pneumonia. Clinically, this is attested by the presence of blood in the sputum, and in both these conditions at autopsy hemorrhage into the lung is not infrequent. Following the inhalation of irritating gases, the pulmonary hemorrhages are often confined to the perivascular sheaths, but may involve the pleuræ, alveoli, and bronchi. These hemorrhages are rarely circumscribed in such a way as to be confounded with infarcts. In influenza the hemorrhage may be diffuse and not unlike that encountered after the inhalation of irritating gases; on the other hand, the red blood cell extravasation may be localized and definitely

[1] Karsner, H. T., and Ash, E. J., *J. Med. Research*, 1912–13, xxvii, 205.

circumscribed.[2] Indeed, the literature on the pathology of influenza refers to lesions, which, from their description, cannot be differentiated from infarcts. However, they have not been designated as infarcts, although the term "infarct-like areas" has been applied to them. Uncertainty with regard to this lesion is probably referable to the conception that bland infarcts occur only in a lung the circulation of which is impaired by cardiac decompensation or by compression of the pulmonary tissue by fluid or other substance foreign to the pleural cavity. A further difficulty in identifying these hemorrhagic consolidated areas as infarcts may have arisen through the fact that, although thrombi are frequent in the lung after pulmonary irritating gases and in influenzal pneumonia, a relation between them and infarcts has not been demonstrated. Many thrombi are unassociated with such foci, and on casual inspection at least, it is not always possible to demonstrate antemortem occlusion of the larger vessels leading to such infarct-like zones. Consequently, no explanation for the production of these infarct-like areas has been forthcoming, in spite of the fact that vascular lesions (thrombi) involving the smaller vessels in the alveolar walls and even the larger arterioles have been described by many observers.

In a previous communication[3] the results of intrapulmonary insufflation with an inorganic acid (hydrochloric) have been reported. Here it may be reiterated that the extent of the damage to the lung varies with the strength of the acid solution employed. When a 1 per cent solution of hydrochloric acid is insufflated into the lung of a rabbit,[4] the animal succumbs acutely, and during the few minutes it remains alive after the treatment, blood-stained fluid froths from the mouth. With weaker solutions the animals do not die acutely, and the destruction of the lung with subsequent inflammatory exudation is more outspoken.

[2] Winternitz, M. C., McNamara, F. P., and Wason, I. M., Pathology of influenza, New Haven, 1920.

[3] Winternitz, M. C., Smith, G. H., and McNamara, F. P., *J. Exp, Med.*, 1920, xxxii, 199.

[4] Before insufflation the animals were completely anesthetized.

Lesions in Animals That Survived Only 15 Minutes.

A few of the animals insufflated with 5 cc. of 0.25 per cent hydrochloric acid died within 15 minutes. In all of them the gross picture is identical and is illustrated in Fig. 1. The voluminous lungs are slightly congested throughout, but the most constant and marked changes occur in the lower lobes, usually the right. The increase in size is much more marked in the affected lobe than elsewhere. The lower third, and sometimes even half of the lobe, is garnet, and the color is accentuated by the glistening, smooth pleural surface through which it is seen. The discolored area of the lung is non-air-containing. On section, as on the surface, the line of demarcation is sharp and defines a wedge-shaped zone whose apex approaches the hilum (Fig. 2). Histologically, sections through such a consolidated area show a mass of well preserved erythrocytes filling the alveoli and even the bronchi. The alveolar and bronchiolar walls may still be made out; though shrunken, their cellular elements are intact and the nuclei stain (Fig. 3).

Lesions in Animals Killed at Varying Intervals after Insufflation of Acid.

Animals which survived the insufflation of acid in this concentration were killed at intervals up to 2 weeks after the operation, and examination of the lungs of such a series indicates clearly that there is a variation in the effects of the acid in animals of the same species. At times there are no areas of consolidation and discoloration like those described for the previous group, and the extent of such change varies from small foci to areas which involve the greater portion of a lower lobe. Especially in their lower half, these larger infarct-like areas often present a dull, even pale brown, surface. Above this zone, either sharply or gradually, the color becomes almost black. The surface markings are an index to the color change within the consolidated portion of the lung, and microscopic examination of the paler areas offers the most suggestive explanation of the etiology of the change. Sections from the dark, almost black portion of the consolidated lung are similar to those just described (Fig. 3). The alveoli are packed with disintegrating red blood cells, while the alveolar and bronchiolar walls are still well defined, and the cell nuclei retain

their affinity for hematoxylin. Evidence of organization and epithelial regeneration appears about the area of hemorrhagic extravasation, but discussion of this phenomenon will be deferred. The hemorrhage in the alveoli becomes less marked in sections from the paler areas. Here, the alveoli and bronchi contain a homogeneous, eosin-staining material; few red blood cells are included in the exudate. The most interesting changes occur in the alveolar and bronchiolar walls, which are swollen and often measure several times their normal width (Fig. 4). The nuclei do not stain with hematoxylin, and in the portions most affected no structure can be made out in the walls.

Striking infarct-like lesions have been produced in dogs also, by the insufflation of acid (20 cc. of 1 per cent hydrochloric acid). In this species the large size of the pulmonary vessels makes it easier to study those leading to the area of consolidation, and multiple sections frequently show them distended and occluded by a firm, red clot (Fig. 2). Histologically, in all animals, including rabbits and dogs, thrombosed vessels are found. The clot has the appearance of a propagated thrombus. It is devoid of the typical thrombotic architecture, and consists largely of red blood cells with leucocytes scattered more or less regularly among them. Occasional foci of platelets with radiating fibrin strands are present.

Explanation of Infarct-Like Areas.

The explanation for the unusual production of infarct-like areas after the insufflation of acid is not evident from the histological study of the more typical lesions. However, as has been said above, the microscopic picture of the paler brown peripheral zone that occurs when rabbits survive for several days, offers a clue toward the interpretation of the process. Here the swollen alveolar walls are necrotic (Fig. 4). The alveoli may contain serum and fibrin, but no cells—an unusual picture in the lung. The process resembles gangrene more than any other familiar lesion of this organ, and bears a strong resemblance to an anemic infarct in the spleen or kidney. The walls of the alveoli stain homogeneously with eosin; the architecture is obscured, but now and then either the lining cells or the vessel within the wall can be distinguished. Similar changes in the alveolar walls

have been described in influenza, and they also develop rapidly after the inhalation of irritating gases. It is impossible to distinguish the vessels, and frequently the blood and other constituents of the wall are so intimately fused that the individual elements can no longer be differentiated. The picture is not unlike that resulting from the application of carbolic acid to the gastric mucosa. In all probability the insufflated acid causes a fixation of the tissues with simultaneous inhibition of all cell activities. Consequently, the intermediary regressive processes dependent upon the loss of balance of the cellular ferments are lacking.

This picture results, as has been said, when the more concentrated acid is employed, and, therefore, may be considered to represent a maximal effect. Milder grades of damage also may result in thrombosis of the small vessels. If vessels in sufficient number are occluded, the resistance to the flow of fluid in the lung should be demonstrable by pulmonary arterial injection, and to test this point a series of experiments was devised.

It was found that a longer period of time than in normal subjects was required for a Berlin blue gelatin injection mass to appear on the venous side, even in animals that had succumbed within a few minutes after the insufflation of a 1 per cent solution of hydrochloric acid. The lung cannot be injected uniformly; and microscopically, in thick frozen sections, it is readily seen that many vessels are not permeated by the mass. When local, consolidated, red areas have developed, increased pressure, even after the dye has appeared on the venous side, does not result in injection of the consolidated zone. This zone contrasts sharply with the neighboring area, deeply stained by the dye in its vessels.

The injection method thus provides the means of determining the effects of the acid more minutely. The lung may appear uniformly blue, while, in fact, numerous, small areas, scattered through one or more lobes, contain none of the gelatin. On the other hand, a large area may be completely uninjected and sharply demarcated. Between these extremes there are many variations. Histological examination indicates that the acid coagulates the blood in the swollen vessels, and the phenomenon is actually demonstrated upon injection. By this method variations in the gross picture are explained through localization of the coagulative process.

Our immediate interest lies in the instances in which the action of the acid is confined to a local area. Where this occurs it is possible to show that large vessels leading to the sharply demarcated zone are distended with clot. However, these clots are not found in the animals that die within a few minutes; they are most marked after a period of several days.

From the above experiments we conclude that when concentrated acid reaches the alveolar walls, necrosis of the entire structure and thrombosis of the vessels follow. The resulting lesion depends on the extent of the necrosis and thrombosis. When a large number of vessels becomes occluded in a given area, the possibility of the propagation of the clot into the larger vessels is increased, and when this occurs, the lesion cannot be differentiated from an infarct.

Infarction in tissues with an extensive collateral circulation does not occur except under extraordinary circumstances. Therefore, one would hardly expect this process in the liver, and no really authoritative cases of infarction of the liver have been reported. Nevertheless, a liver lesion which can easily be confused with infarction has been observed recently in two cases in which the capsule of the organ was torn and the rent extended several centimeters into the parenchyma. Both individuals lived several days after they were injured. At autopsy, in each case, the hepatic tissue surrounding the clot at the point of rupture was the seat of a coagulative necrosis indistinguishable from the type of necrosis which occurs in infarcts of the spleen and kidney. When the liver was torn the smaller capillaries within the lobules were broken, and with the cessation of hemorrhage, clots formed at the mouths of these capillaries. These clots were propagated into the radicles of both the hepatic artery and portal vein, so that the extensive collateral circulation within the lobule, the safeguard against all but extraordinary conditions, was rendered ineffective. It would seem that this is a type of infarction that can result from the plugging of peripheral vessels with subsequent propagated clots into the larger supplying vascular bed. Unquestionably, this is the process by which infarcts are formed after insufflation with acid; and, in all probability, the infarct-like areas associated with influenza also result from similar damage to the intraalveolar capillaries or arterioles which undergo thrombosis.

CONCLUSIONS.

Intrabronchial insufflation of acid causes immediate necrosis of the walls of many alveoli. Thrombosis of the alveolar vessels is an associated phenomenon. When a large number of vessels becomes affected, a clot propagates rapidly into the larger supplying vessels. The resulting lesion is indistinguishable from a hemorrhagic infarct.

The infarct-like areas so frequently encountered in influenzal pneumonia, it is not unlikely, have their origin in a similar process.

Infarction depends not only upon thrombosis or embolism of the large vessels, but may be initiated by extensive damage to the capillary bed. By this process infarcts may form in organs which are normally protected by collateral circulation.

EXPLANATION OF PLATES.

PLATE 12.

FIG. 1. Infarct of the lung produced by the insufflation of 5 cc. of 0.25 per cent hydrochloric acid.

FIG. 2. Cross-section of an infarct of the lung. The larger supplying artery is occluded by a propagated clot.

PLATE 13.

FIG. 3. Histology of an infarcted area. The alveolar walls are thin and the alveoli are distended with erythrocytes.

FIG. 4. Section showing the maximal effect of acid on the lung tissue. The alveolar walls are necrotic and their vessels contain hyaline thrombi.

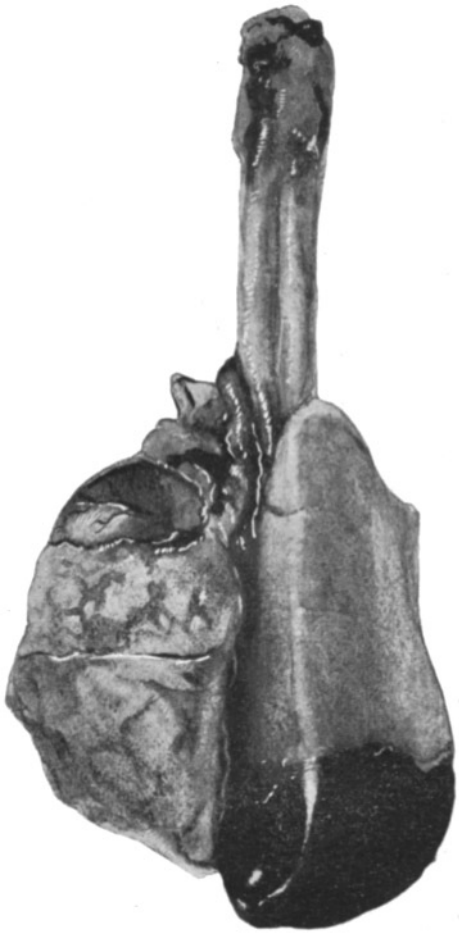

FIG. 1.

FIG. 2.

(Winternitz, Smith, and McNamara: Intrabronchial insufflation of acid.)

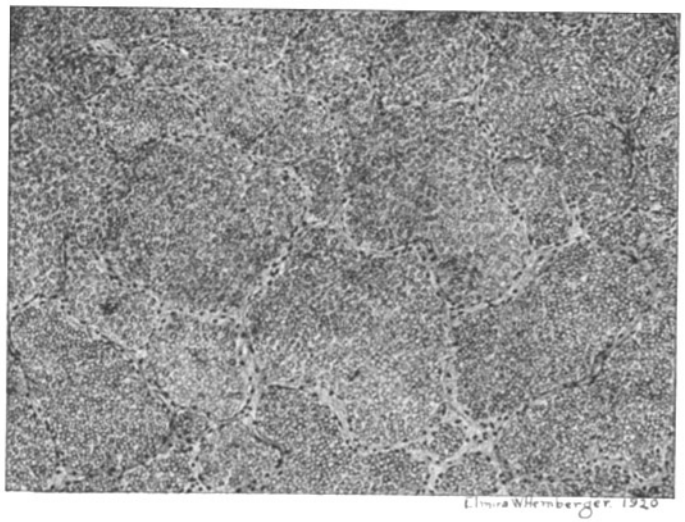

FIG. 3.

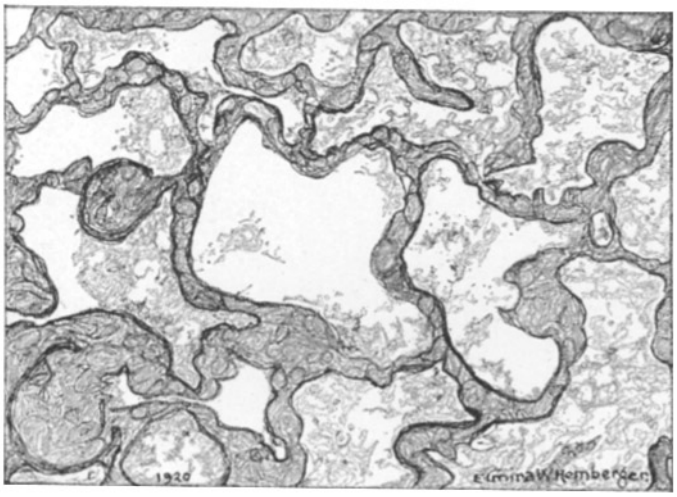

FIG. 4.

(Winternitz, Smith, and McNamara: Intrabronchial insufflation of acid.)