EFFECT OF INTRABRONCHIAL INSUFFLATION OF ACID.

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The resemblance between the lesions of influenzal pneumonia[1] and those produced by the inhalation of pulmonary irritating gases[2] suggested a series of experiments which might assist in the interpretation of the characteristic influenzal lesions. Many of the war gases, particularly those which act as pulmonary irritants, contain free chlorine or liberate it when they are decomposed. The weight of evidence[3] also indicates that the lesions which these gases produce depend in part upon the halogen radical, and that variations in the lesions correspond with variations in the halogen concentration as well as with the portion of the respiratory tract attacked. Moreover, it is conceded that the decomposition of these gases is associated with the formation of hydrochloric acid. The experiments now reported show that intrabronchial insufflation of hydrochloric acid solutions causes similar lesions, and these are also identical with the lesions disclosed in the examination of the respiratory organs of individuals who die of influenza.

EXPERIMENTAL.

At first isotonic saline solution with hydrochloric acid added to a strength of 1 per cent was used. By intrabronchial insufflation 5 cc. of this solution were forced into the pulmonary alveoli of rabbits previously anesthetized completely. Immediately a blood-stained,

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

[2] Winternitz, M. C., et al., Collected studies on the pathology of war gas poisoning, New Haven, 1920.

[3] Lillie, R. S., Clowes, G. H. A., and Chambers, R., *J. Pharmacol. and Exp. Therap.*, 1919, xiv, 75.

frothy fluid appeared at the mouth and nostrils, and as the catheter was removed convulsions developed. Death followed within 3 to 5 minutes.

At autopsy the very voluminous lungs filled the pleural cavities and covered the cardiac area. Occasionally the most affected lobe was collapsed, the remainder being voluminous. The glistening pink or pinkish gray pleural surfaces were tense and frequently showed hemorrhages which varied in size and shape. While all the pulmonary tissue was increased in volume, usually the most marked increase was localized on one side, even in a single lobe made conspicuous by the pleural hemorrhages. On section the lungs poured forth a large quantity of straw-colored or blood-stained fluid. After the fluid was washed away hemorrhages similar to those noted upon the surface were found within the pulmonary tissue. Frequently the peribronchial and perivascular sheaths were prominent—translucent, watery, gray, and thickened. The trachea and the larger bronchi contained blood-stained fluid, and hemorrhage into the mucosa was common. Histologically, as might be expected, there was little change. Death occurred too quickly to permit anatomical manifestation of the disturbance in the balance of cell function. There were a thick, colloid-like precipitate within the alveoli and edema of the interstitial, periarteriolar, peribronchial, and perivascular structures. There were also hemorrhages which involved both the pleural interstices, the perivascular and peribronchial tissues, and, in some instances, the alveoli. Edema followed insufflation of the hydrochloric acid solution much more quickly than it follows the inhalation of chlorine; otherwise the pathological changes were identical.

The acute cause of death after the insufflation of hydrochloric acid may not be explained by the factor of acidity alone, because the same quantity of acid may be given rabbits intravenously with impunity. Consequently, death must be ascribed to some local effect. From the fact that other acids, for example, carbolic acid, produce thrombi when directly applied to tissues, it seemed possible that coagulation of the blood within the alveolar capillaries followed the acid insufflation, and such a local coagulative action was shown to take place. The process will be described in detail in a subsequent paper.[4]

[4] Winternitz, M. C., Smith, G. H., and McNamara, F. P., *J. Exp. Med.*, 1920, xxxii, 211.

In subsequent experiments in which the concentration of acid was reduced to 0.25 per cent, sudden death was rarely observed; the majority of the animals came out of the anesthesia and later showed no untoward symptoms, unless pulmonary infection had occurred. Similar results followed the use of acids as dilute as 0.1 per cent. The gross and microscopic pictures found, even in animals of the same species, varied greatly, and it would not be useful to differentiate the effects of the two more dilute solutions mentioned. In general, the lesions caused by the weaker acids are less extensive and the likelihood of acute death is minimal.

With concentrations of acid as divergent as 1 per cent and 0.25 per cent variations in the effects are quantitative rather than qualitative. In a few instances death occurred shortly after the insufflation of the 0.25 per cent acid, possibly because of individual susceptibility. In such circumstances it is difficult to recognize any difference in the effects of a stronger and a weaker acid solution. However, when insufflated animals are killed after a period of only 15 minutes, it is found that the 1 per cent solution has excited the greater accumulation of fluid in the bronchi and trachea, and the fluid is more intensely stained with blood. In both instances the degree of edema is much the same. The hemorrhages, so prominent on the pleural surfaces and in the perivascular sheaths after the insufflation of a strong acid solution, are much less marked after the administration of a more dilute one. The picture described below is that secured with the less concentrated acid.

Animals killed at intervals after acid insufflation show a progressive localization of the changes within the lung. The less severely damaged areas lose their congested, edematous condition and assume a pale pink, delicate appearance. The more involved areas, because of their volume, their consolidation, and the dulling of their serous surfaces, contrast sharply with the less injured tissue. Within 48 hours the consolidated areas, red at first, become paler, even quite gray. They are usually wedge-shaped, most frequently involve the right lower lobe, and may extend from its lower border to the hilum. Occasionally the right lower lobe alone is involved. Frequently the process extends from the right lower to the left lower and the right middle lobes. Generally the line of demarcation between the dark red consolidated zone and the neighboring zone is not clear either with regard to consistency

or color. Upon section through such a consolidated area all structure is obliterated by the dark red color, but as the hilum is approached the architecture may become more distinct. Here alveoli distended with fluid can be seen and an occasional small hemorrhage. Later the fluid exudate becomes granular and small plugs protrude above the cut surface. At this stage the lung is less uniformly pigmented; gray patches interspersed with brownish ones and small, dark brown foci may occur.

How early this reaction takes place is difficult to determine histologically. Serum, we know, appears in the alveoli almost immediately after the insufflation, and is associated with an intense vascular congestion. In local areas also hemorrhage into the interstitial tissue and the alveoli may be prominent. The subsequent exudative changes within the lung vary with the extent and the intensity of the initial damage. Within 48 hours there appear in the lung wedge-shaped areas which show a sterile fixation of the involved tissue now devoid of nuclei. With a less marked degree of damage the alveolar walls presenting nucleated cells are distinguishable, and their lumina are filled chiefly with erythrocytes. The extreme changes will be presented in detail in a subsequent communication.[4]

The inflammatory reaction associated with milder grades of injury deserves emphasis. Within 8 hours after the damage the epithelium of the bronchioles and of the atria becomes converted into a red, ribbon-like strand devoid of nuclei. This, often thicker than the original epithelium, is raised like a blister from its basement membrane by a serofibrinous exudate in which polymorphonuclear leucocytes are found occasionally. The dilated atria and the alveolar ducts, lined with red, are conspicuous. In small areas the thickened alveolar walls show no cell nuclei. Atelectasis is not present and the degree of dilatation of the alveoli varies. The alveoli are filled with an exudate rich in serum and fibrin which contains desquamated alveolar cells. Later to this exudate are added polymorphonuclear cells which earlier were more conspicuous not only in the alveolar walls, but also in the sheaths of the bronchi and vessels. Red blood cells are also found, and, in fact, all grades of exudate occur, from those composed entirely of closely packed erythrocytes to those in which these cells are scanty or absent altogether.

The dilatation of the alveolar ducts and the hyalinosis of the bronchiolar epithelium after acid insufflation are especially noteworthy. These phenomena were characteristic both of the lesions subsequent to influenzal pneumonia and of those after exposure to corrosive gases. The terminal bronchioles are converted into conspicuous, irregular sacs, which may compress the adjacent alveoli. The marked hyalinosis, it is clear, originates from an acute necrosis of the epithelium. Nuclei can often be seen at the base of the ribbon, and in the earlier stages cell demarcation is evident. Later, when nuclei and cell boundaries disappear this membrane grows by accretion with the addition of fibrin or other material, so that ultimately it becomes thick and tends to occlude the distended bronchioles and ducts.

SUMMARY.

Acid administered to rabbits by intrabronchial insufflation causes an immediate and extreme damage of the lung tissue. Within certain limits the degree and extent of the injury vary according to the concentration of the acid. With the greater concentrations death occurs promptly, almost immediately, and the lethal process has associated with it a decreased permeability of the pulmonary vessels. The latter fact has been confirmed by postmortem arterial injections. With weaker solutions the results, grossly and histologically, resemble those noted after influenzal pneumonia and gas poisoning. Thus, there is destruction of the epithelium of the bronchioles, the alveolar ducts, and the alveoli. The extent of the damage to the alveolar walls varies. Exudation occurs into the alveolar, interstitial, perivascular, and peribronchial tissues. Primarily this exudate is serous, but a rapid deposition of fibrin occurs, and later polymorphonuclear leucocytes and erythrocytes accumulate. In different animals, or in different portions of the same lung, there may be consolidations of different types, serofibrinous, hemorrhagic, or purulent, with or without destruction of the alveolar walls. Subsequent changes relate to the organization of the exudate, necrosis, proliferation of the epithelium in the alveoli and bronchi, and, finally, to the regeneration of the pulmonary parenchyma.

Experiments now in progress indicate that similar changes can be induced by various acids, both inorganic and organic. Experiments also show that similar changes are produced in other species of animals but that species differ in their resistance according to the acid and the concentration in which it is employed.

CONCLUSIONS.

Intrabronchial insufflation of weak solutions of hydrochloric acid, from 0.1 to 0.25 per cent, in rabbits causes an inflammatory process which resembles that encountered in influenza and after the inhalation of toxic gases. There are intense edema and congestion of the lung with hemorrhage, dilatation of the alveolar ducts and bronchioles, hyaline necrosis of the epithelium of these structures, and lobular, pseudolobular, and even lobar types of consolidation, which are more frequently serofibrinous but may be hemorrhagic or even purulent.