EPITHELIAL PROLIFERATION FOLLOWING THE INTRA-BRONCHIAL INSUFFLATION OF ACID.

By M. C. WINTERNITZ, M.D., G. H. SMITH, Ph.D., and F. P. McNAMARA, M.D.

(From the Brady Laboratory of Pathology and Bacteriology of the School of Medicine, Yale University, New Haven.)

Plates 8 to 11.

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Hydrochloric acid insufflation into the bronchi of rabbits causes necrosis of a degree which varies with the amount and the strength of the solution employed. With extensive damage large areas of the lung undergo fixation, and hemorrhagic infarcts may develop. A more superficial injury results in a sterile pneumonia, and the repair of the pulmonary damage begins quickly. Coincident with the formation of granulation tissue and organization of the exudate, there is a proliferation of alveolar and bronchiolar epithelium. Overproduction of the epithelium occurs with the formation of polypi in the bronchioles, and even extension of the epithelium into surrounding tissue. Although invasion of preexisting healthy tissue by the proliferating epithelium has not been observed, the ultimate results of the process have not been studied. At this time only the early changes will be presented.

Epithelial Changes after Influenzal Pneumonia.

Reference has been made elsewhere[1] to the resemblance of the lesions which follow the intrapulmonary application of acid to those associated with influenzal pneumonia, and here it may be pertinent to mention the unusual epithelial changes not infrequently seen after fatal influenzal pneumonia. Alveoli lined by large, actively dividing cells are numerous, and desquamated cells only are found in the lumina. Other portions of the lung present different stages of acute reaction,

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

or even of organization. The epithelium of the larger air passages —trachea, bronchi, and bronchioles—shows active regeneration. In the bronchioles especially the epithelium may not only grow over a granulating exudate in the lumen, but may invade the surrounding alveoli. It is difficult to differentiate such a cellular reaction from an invasive epithelial neoplasm. Similar reactions have been observed after the intrabronchial insufflation of hydrochloric acid.

Epithelial Changes after Intrabronchial Insufflation of Hydrochloric Acid.

The experimental procedure here was identical with that employed previously, and, therefore, need not be described in detail. Rabbits were insufflated with 5 cc. of 0.25 per cent hydrochloric acid.[2] The description of the lesions consequent to such a procedure follows.

Proliferation of the Alveolar Epithelium.—This is seen as early as 36 hours after insufflation; in 52 hours many alveoli have an entirely new layer of lining cells. As a rule, these alveoli contain but little exudate. Serum, occasional fibrin strands, or erythrocytes occur, but large, pale-staining, polyhedral cells are more frequent. The alveolar space is small, attributable in part to the size of the lining cells. These large cells with granular protoplasm and vesicular nuclei often show mitoses. Occasionally a syncytial-like mass of newly formed epithelial cells is found. The karyokinetic figures appear quite regularly. Multipolar division is not encountered. Where many alveoli within a local area have a new epithelial lining, the intense blue staining of the area attracts attention, even under low magnification.

Proliferation of the Bronchiolar Epithelium.—The bronchiolar epithelium affords the best opportunity to study the reparative process. The acid, it will be recalled, kills the epithelium, which then stains intensely with eosin as a red ribbon. For some time this material adheres to the basement membrane, and, by the addition of fibrin or other substance, it may become even more conspicuous than in earlier stages. Gradually, however, it separates from the basement membrane and, folded upon itself, lies in the lumen. If the necrosis has not extended below the basement membrane and a few of the cells have been spared, these quickly begin to divide, and at the end

[2] Before insufflation the animals were completely anesthetized.

of 36 hours a portion of the bronchiolar wall is lined by young cells. These cells are conspicuous because of their size, the homogeneity of their protoplasm, the variation in the density of the nuclei, and the frequency of mitotic figures. The dead epithelium is often separated from the basement membrane by the development of these young cells (Fig. 1).

The necrosing action of the acid may extend through the epithelial lining of the bronchioles into the surrounding tissue. When this occurs the young epithelium finds an obstacle to its regeneration along the basement membrane. Where normally there should be a single layer of cells, several are found in a sector of a tubule in which the basement membrane is intact. When these young cells reach the point where necrosis involves the deeper structures, their pathway is obstructed. Consequently, they pile up and penetrate the pulmonary parenchyma (Fig. 2). As it extends, the epithelium selects the walls of surrounding necrotic alveoli for scaffolding (Fig. 3).

The ability of this young epithelium to proliferate is extraordinary. Even when the basement membrane of a tubule is intact, it may be lined by several layers of cells within 52 hours. The dead epithelium which has been replaced is found in the lumina of the bronchioles, and there may provide a surface for the extension of the new epithelium. A picture results similar to that obtained in tissue cultures. The bronchiole, relined with an epithelial coat several times as thick as normal, shows a mass of young cells, in contact with the epithelium at one point, extending over the dead membrane within the lumen. Presumably the young epithelium feeds on the necrotic material and conditions not unlike those present in tissue cultures provide for the proliferation (Fig. 4).

This source of nutriment is merely temporary, of course, and the new epithelium would die if more favorable conditions were not provided. The invasion of fibroblasts and capillaries may supply such a deficiency (Fig. 5). In Fig. 5 the stroma has penetrated the basement membrane of the tubule to afford the necessary scaffolding and vascularization of the epithelium, and the result is a typical epithelial polyp in the bronchus. This followed within 8 days after the acid insufflation, and the epithelium of the bronchus, both on the basement membrane and in the polyp, shows continued evidence of proliferation.

Proliferation Following Damage of Large Areas of Tissue.—The most striking reparative processes are those encountered where relatively large areas of tissue have been killed by the insufflated acid. Here the architecture is still discernible. The absence of polymorphonuclear reaction is remarkable; aside from some coagulated material, the nature of which is indeterminate, the lumina of alveoli and bronchi remain free. Proliferation of the granulation tissue from the surrounding healthy lung rapidly changes these areas. The epithelium is very active and grows into the dead material along the walls of the bronchioles and alveoli. Attempts to form new alveoli are noted at the periphery of such a necrotic zone. These alveoli are usually small, lined by high epithelium, and separated from each other by fresh granulation tissue. The picture resembles that of a fetal lung.

In other places epithelial activity is less uniform. Irregular clefts and cavities, lined by rapidly dividing epithelium, are found in the newly formed stroma (Fig. 6). The picture may easily be confused with that of a malignant neoplasm.

The extent of the epithelial proliferation varies in different individuals. The results described above represent the most marked changes in a relatively large series of animals studied as late as 10 days after insufflation. In every instance the proliferation, even when extensive, was regular. Direct division of cells was not observed and the mitoses were normal without evidence of variation in the chromatin content of the daughter cells. Nuclear division without corresponding division of protoplasm has been found occasionally.

CONCLUSIONS.

The damage caused by the introduction of acid into the pulmonary parenchyma is repaired rapidly.

The depth of the necrosis determines which elements will participate in the repair. If epithelium alone is injured, epithelium alone takes part in the repair. When the damage involves the deeper tissue, organization by granulation competes with and impedes the development of the epithelium.

An overproduction of the epithelium occurs and may form bronchiolar polypi or extend into the peribronchial tissue.

EXPLANATION OF PLATES.

PLATE 8.

FIG. 1. 36 hours. The necrotic epithelium has separated from the basement membrane, and one sector of the bronchiole shows regenerating lining cells.

FIG. 2. 52 hours. Normal extension of the young epithelium is obstructed where the necrosing process involves the deeper tissues of the bronchiolar wall. Here the cells tend to invade the surrounding tissues.

PLATE 9.

FIG. 3. 5 days. Many layers of newly formed epithelium line the small bronchiole and at one point extend into the surrounding tissue. The alveoli also are lined by new epithelium. Mitotic figures are frequent.

PLATE 10.

FIG. 4. 52 hours. Where the necrotic material is in contact with the newly formed bronchiolar epithelium, it serves as a scaffolding upon which the young cells extend.

FIG. 5. 5 days. Vascular granulation tissue has invaded a mass of epithelium, as seen in Fig. 4, through the bronchiolar wall. The result is a typical polyp.

PLATE 11.

FIG. 6. 8 days. The newly formed alveoli to the left have the appearance of fetal tissue. On the right the necrotic lung is being invaded by granulation tissue and rapidly developing epithelium.

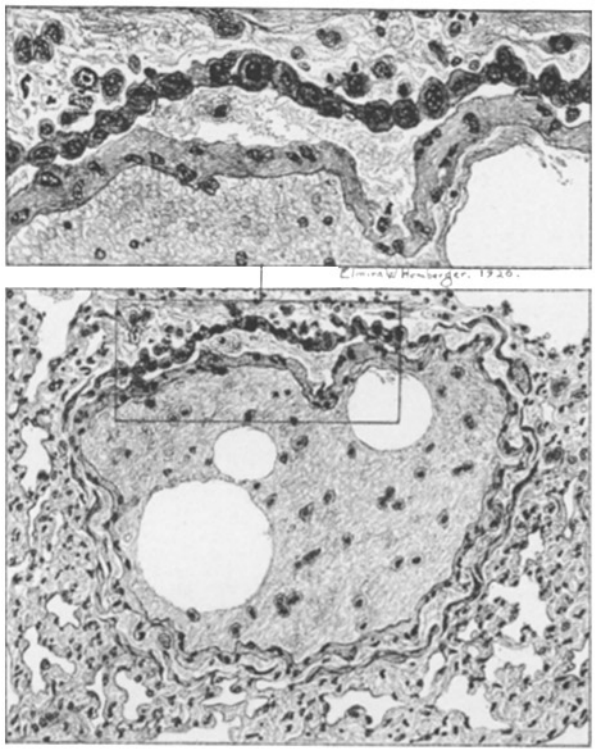

FIG. 1.

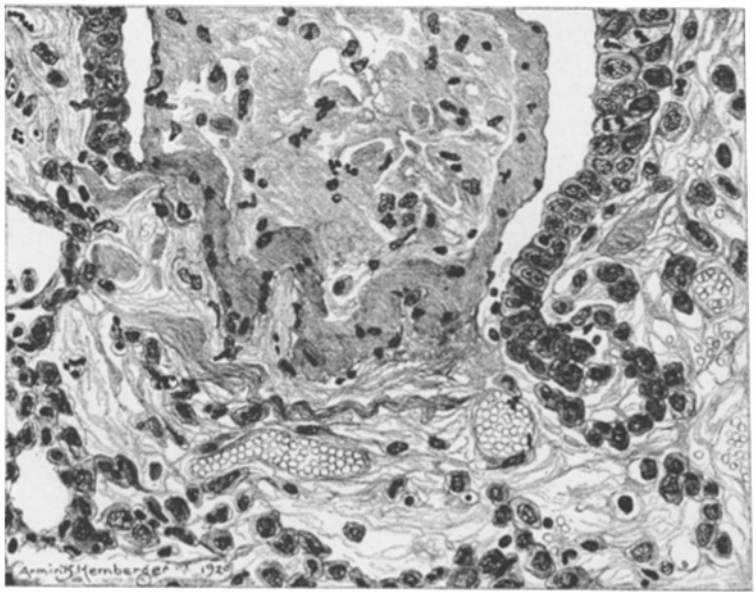

FIG. 2.

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

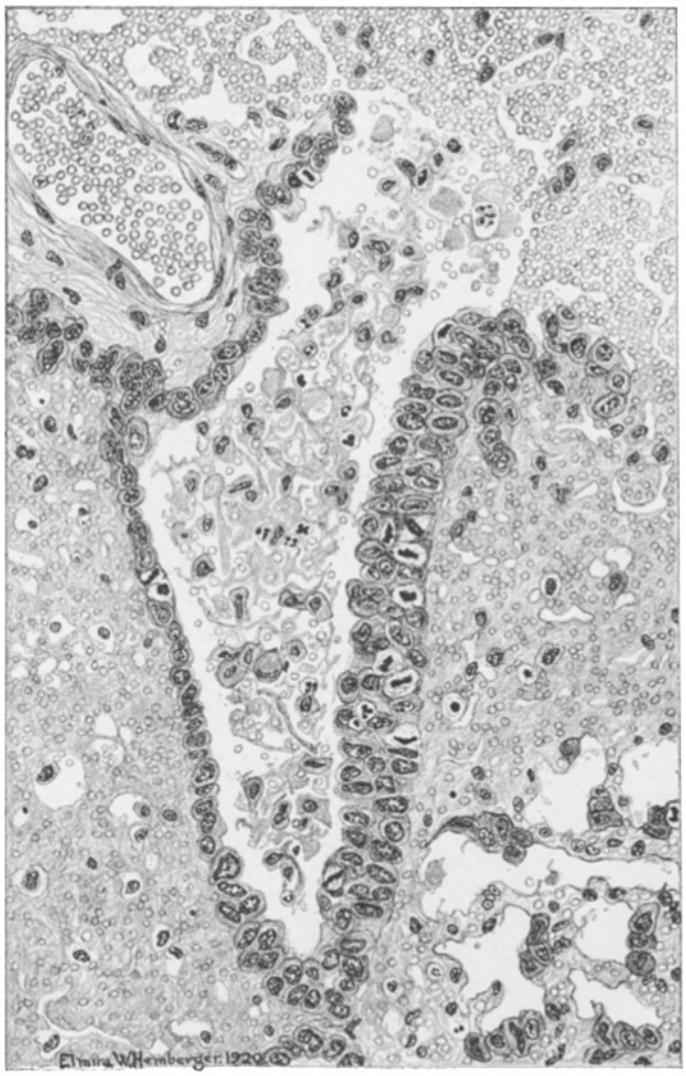

FIG. 3.

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

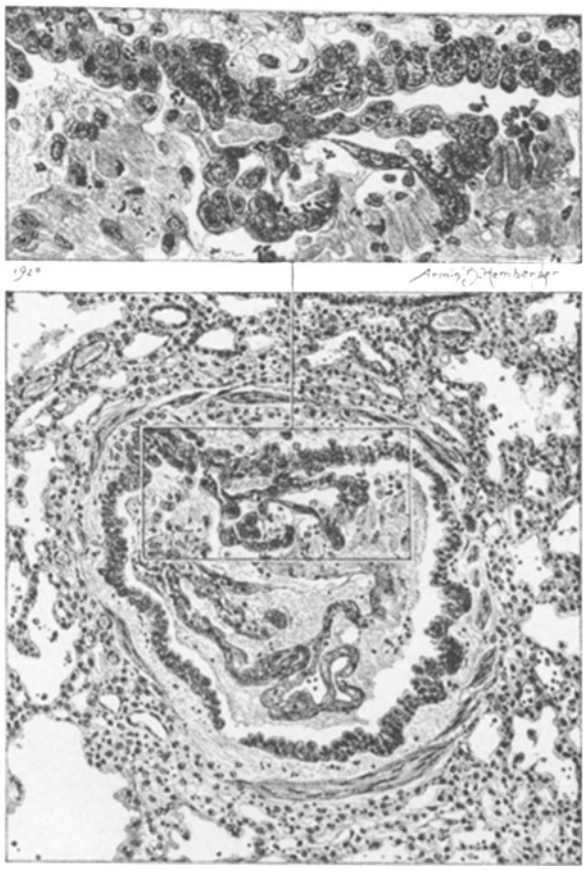

FIG. 4.

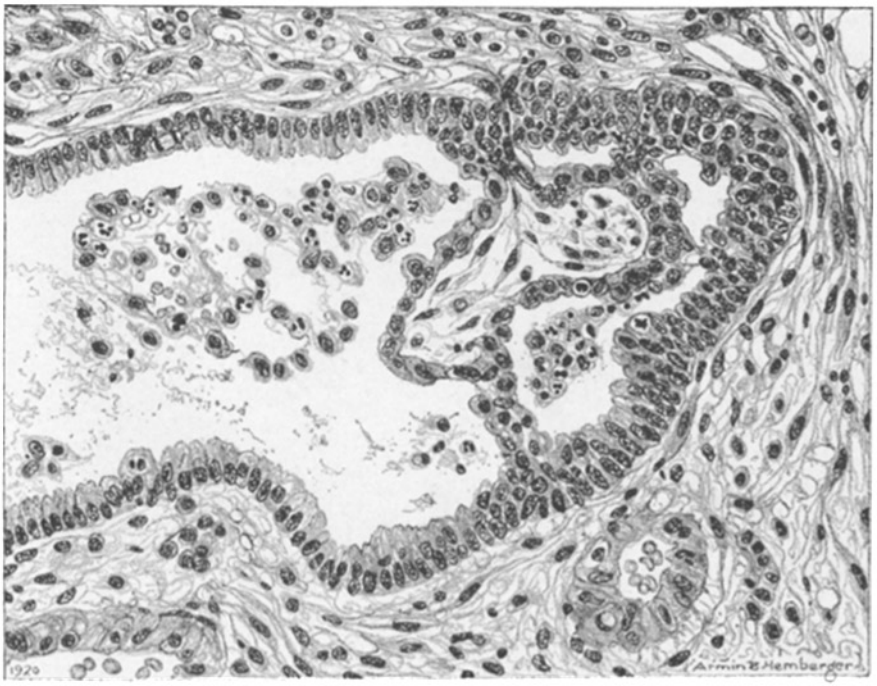

FIG. 5.

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

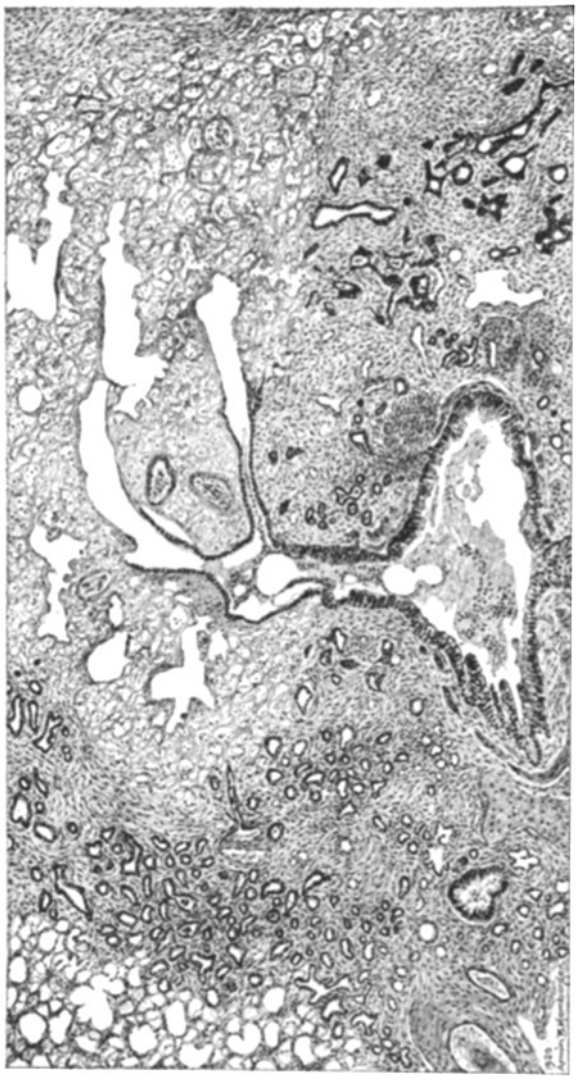

FIG. 6.

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