number of forming young muscle fibers, as is suggested, in particular, by a 2- to 3-fold decrease in the size of the reparative field noted in rats at the light-microscopic level [3].

The general conclusion from this study is that weightlessness prolongs the early regenerative process without substantially affecting the sequence of its phases. Presumably, the action of factors inhibiting this process will be eliminated subsequently in the course of restitution of the normal blood supply and trophic influences. Also, it should be borne in mind that the rate of regeneration is altered when the functional load is reduced.

Since, as indicated by this study (data not shown), the time course of atrophy and regeneration in the space-flight group has several features in common with that in control group 3 (the one in which the rats were suspended by the tail in the antiorthostatic position), the latter model may be used to study the further course of posttraumatic regeneration.

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Inhalation Injury in Burn Patients and Reparative Regeneration in Tracheobronchial Mucosa

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Until just recently flame burn was the most common cause of death in burn patients (90%). In 85% of cases concomitant injuries were typical such, as skin burns with inhalation traumas of the respiratory pathways. These patients died within 20 days following injury, about half of them succumbing within the first 8 days. During recent years inhalation injury as a separate entity has been the focus of in-depth investigation by a number of workers in different fields [3]. The major aspects attracting interest include pathological changes in the bronchopulmonary system resulting from exposure to chemical toxins contained in smoke coupled with extensive tracheobronchial injuries and marked impairment of the pulmonary microcirculation [3,4]. Polymorphonuclear leukocytes causing pulmonary disturbances are thought to play the main role in the mechanism involved in inhalation injury [5].

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The genesis of series injuries in the tracheobronchial mucosa as determined by *in vivo* fibrobronchoscopy somewhat precedes the development of massive edema, infiltration, pneumonia, and obstructive lesions, and this is why physiological changes become clinically manifest only when severe bronchopulmonary complications have set in [3,5]. The use of fibrobronchoscopy at the earliest possible stages renders the treatment of burn patients more effective. At this time priority is being given to studies which would provide the most accurate diagnostic and prognostic criteria for *in vivo* analysis of all pathological processes. The regenerative and hyperplastic compensatory processes occurring in inhalation injury with impaired respiratory function have not been studied in detail [2].

The aim of this study was to develop a new approach for comprehensive morphological analysis of the extent of injury and adaptive reorganization of the tracheobronchial mucosa in burn patients with inhalation injury by historadioautographic diagnostic fibrobronchoscopy.

MATERIALS AND METHODS

One hundred twenty-six fibrobronchoscopic biopsy specimens obtained from 15 patients at the Burn Center were studied. The average age of the patients was 37 (age range from 19 to 63); average area of third-degree (a, b) burns 56% (37-70%). The skin burns were in all cases complicated by smoke inhalation. From the time they were admitted, the patients were subjected to daily or (when indicated) sanative-curative fibrobronchoscopy and periodic (once a week) fibrobronchoscopy under local anesthesia. The biopsy specimen was taken as the flexible bronchoscope was passed down the tracheobronchial tract to the ostia bronchi lobares. The use of a fibroscope with fiber optics allowed direct visual monitoring of the tracheobronchial internal surface lesions in the course of treatment. The tracheobronchial lesions were assessed by the extent and severity of edema, multiple petechial hemorrhages, the presence of erosions and ulcerations, and the type of discharge and airway obstruction. The patients were divided into 3 groups according to the observed lesions. The first group included patients exhibiting by the 4th-5th day symptoms of focal purulent and necrotic as well as fibrinous tracheobronchitis, the second group included patients at 8 to 14 days with signs of focal seropurulent and fibrocatarrhal tracheobronchitis, and the third group included patients found to have focal serocatarrhal and catarrhal tracheobronchitis 17 to 24 days after the injury. This classification had to be validated by objective morphological criteria; for this purpose historadioautography of tracheobronchial biopsy specimens was performed for the above groups. A morphological method and light-microscopic radioautography were used. Fibrobronchoscopic specimens (small mucosa fragments from the affected area) were incubated in medium 199 with ^{3}H-thymidine in a dose of 10 μCi/ml for 1.5 hours at 37°C. The specimens were fixed in 10% neutral formalin, and the material was embedded in paraffin. Deparaffinized sections 4 μ thick were stained with hematoxylin and eosin either immediately or after covering with M-type photoemulsion (time of exposure about 10 days) to prepare radioautographic sections, which were stained with toluidine blue. In each group morphological changes of the mucosa were analyzed by estimating the mitotic and biosynthetic activity of the epithelial cells and underlying connective tissue according to the rate of incorporation of tritium-labeled DNA and RNA precursors by the cell nuclei. The proliferation rate and cell viability were assessed by calculating the nuclear labeling index (NLI, %) in the corresponding radioautographic preparations, and the level of mitosis was determined by calculating the mitotic index (MI, %). The number of cells analyzed varied from 200 to 1000.

RESULTS

In the first few days following injury (4 to 6 days) fibrobronchoscopic specimens showed polymorphic pathological changes in the partially intact epithelial layer. The morphological preparations exhibited destructive lesions of the epithelium with partial lysis of the basal membrane, signs of focal necrosis, and inhaled carbon particles (Fig. 1, *a, b*). The remaining epithelium consisted of 1 to 2 rows of monomorphic cells. The deep destructive lesions which had developed as a result of inhalation injury led to a marked impairment of the tracheobronchial epithelial drainage function, hypersecretion of the remaining goblet cells, and tissue edema. The mucosa lamina propria is represented by fragments of edematous connective tissue with moderate inflammatory cellular lymphoid infiltration (Fig. 1, *c*).

The lesions of the airway mucosa with focal destruction and necrosis were characteristic of the clinical picture of the first group of patients. These pathological processes were found to be predominant in the period up to 6 days after injury, promoting progressive airway obstruction by a thick secretion which resulted in hemodynamic disturbances, hypoxia, and various pathophysiological changes in the body

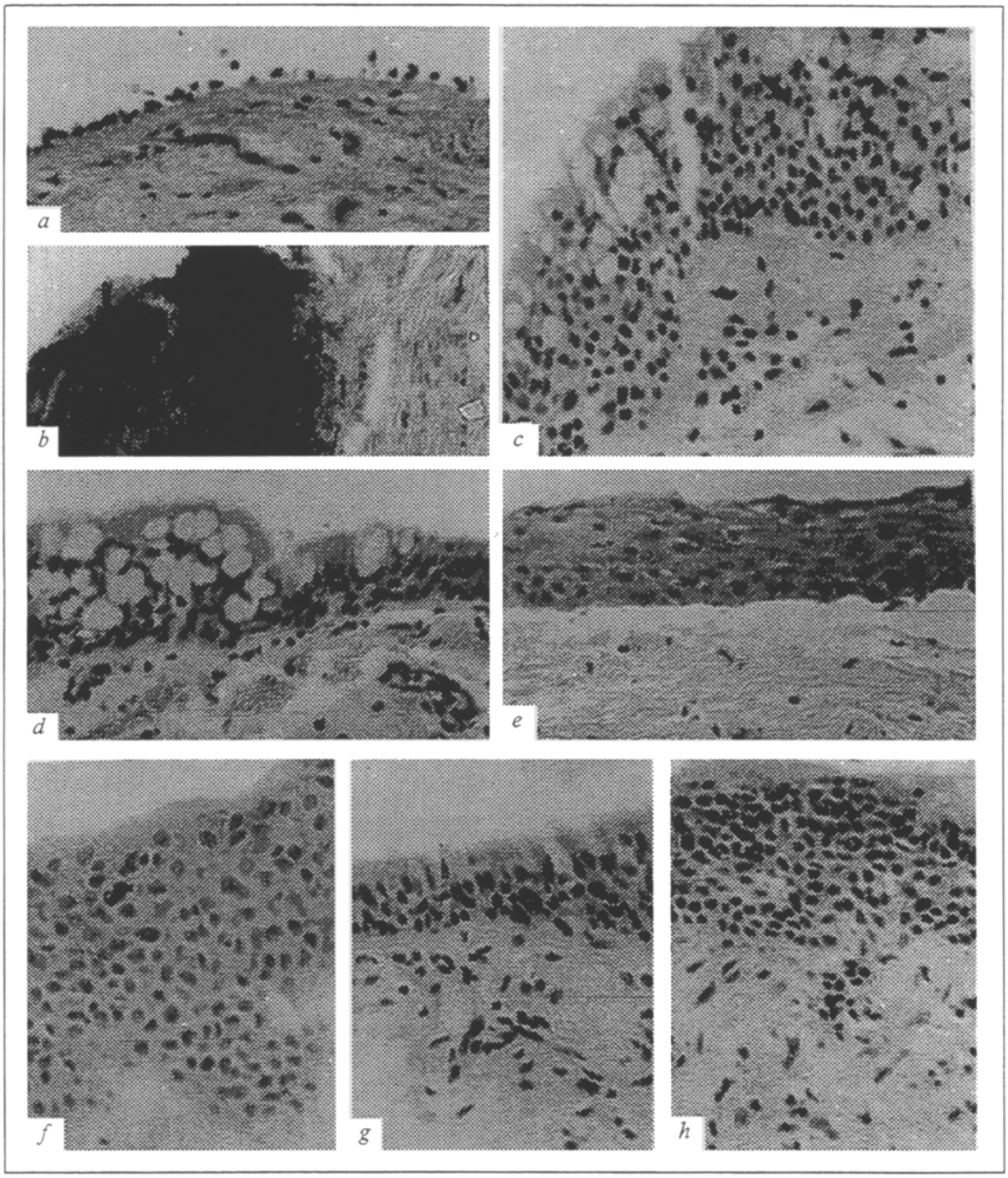

Fig.1. Pathogenesis of inhalation injury in burn patients and reparative regeneration in tracheobronchial mucosa. Histological study of fibrobronchoscopic biopsy material from airways burned at different times following inhalation injury. First group: *a*) local destruction of epithelium of main bronchus with exposure of basal membrane (squamous epithelium, edematous connective tissue with moderate lymphocytic infiltration; 5 days after injury), ×250: *b*) total destruction of epithelium of main bronchus with incorporation of smoke particles into connective tissue mucosa; *c*) hyperplasia and hypersecretion of preserved goblet cells (massive edema of connective tissue with lymphocytic and eosinophilic infiltration, 4 days after injury, ×250. Second group: *d*) areas of squamous stratified epithelium alternating with stratified epithelium with goblet cells (lymphocytes, neutrophils, and eosinophils) are seen in the edematous connective tissue submucosa, 8 days after injury; *e*) multistratified squamous epithelium (13 days after injury), ×250. Third group: *f*) multistratified squamous epithelium of main bronchus with areas of basal layer growing into connective tissue submucosa (17 days after injury); *g*) stratified epithelium with goblet cells near tracheal bifurcation (17th day); *h*) squamous stratified epithelium in main bronchus with solitary goblet cells alternating with areas of nondifferentiated epithelium made up of large monomorphic cells (edema and lymphocytic, leukocytic, and plasma cell infiltration of submucosa, 24 days after injury), ×250. Staining with hematoxylin and eosin

TABLE 1. Changes in Functional Activity of Mucosa Epitheliocytes in Area of Main Bronchi Affected within the First 24 Days Following Inhalation Injury

Group of patients							
first		second			third		
Synthesis of nucleic acids							
DNA MI_T, %	RNA MI_Y, %	DNA		RNA MI_Y, %	DNA		RNA MI_Y, %
		f, %	MI_T, %		MI_T, %	f, %	
2.0±0.5	72.0±8.0	26.5±2.0	16.7		36.0±4.0	20	
		21.5±1.5	8.8	90.0±5.0	18.0±0.2	4	93.0±5.0
		12.5±2.0	33.0		15.0±4.6	33	
		9.0±1.5	29.0	67.0±4.0	4.3±1.0 (norm)	43	
		2.5±0.5	12.5	82.0±5.0			

Note. f: frequency of MI values in the preparation of the given group.

typical for the obstructive syndrome. This syndrome could be controlled by using repeated fibrobronchoscopy.

On the eighth day the destructive changes in the tracheobronchial epithelium tended to give way to adaptive changes; at this stage epithelium repair was observed, the areas without epithelium becoming smaller and the areas of transitional epithelium expanding. The transitional epithelium contained one or two and up to five or more rows of cells including goblet cells (but more often without them), either scarcely stratified or forming foci of stratified squamous epithelium (Fig. 1, *d, e*). Epithelial repair occurred by mitosis of basal epitheliocytes, their mitotic index rising from 4.0 to 19.0%. Eight to 14 days after injury the inflammatory processes found in the lamina propria of the mucosa were, as before, moderate lymphocyte and leukocyte infiltration.

Adaptive morphological changes of the epithelium in the patients of the third group (17 to 24 days following injury) were most pronounced. Compensatory morphological changes predominated, leading to ciliated stratified epithelium repair not by hyperplasia of basal epitheliocytes alone but also by elements of differentiation, their mitotic index being 3 to 9%. The process was so active that in some areas infiltration of the newly formed epithelium deep into the subepithelial tissue was observed (Fig. 1, *f*). In the epithelial layer there appeared areas of stratified epithelium with goblet cells, nondifferentiated epithelium containing large monomorphic cells and multistratified squamous epithelium (Fig. 1, *g, h*). The connective-tissue submucosa was found to be edematous and infiltrated with lymphocytes, neutrophils, eosinophils, and plasma cells.

The morphological finding demonstrate that fibrobronchoscopy used at early stages after burn injuries is effective in reversing airway obstruction and promotes early active compensatory reactions, including DNA and RNA biosynthesis in the nuclear cells in reparative regeneration in the tracheobronchial mucosa.

The analysis of radioautographic preparations of the tracheobronchial mucosa revealed (Table 1) that in the first group only about half of the biopsy specimens contained epithelium, with weak incorporation of ^{3}H-thymidine: the labeled basal cells had an NLI of 2%, that is, below the physiological variation level, which in our case was 4.3% (as is consistent with data [1]). Most of these biopsy specimens showed a moderate incorporation of ^{3}H-uridine (NLI=72%). In the second group labeled basal epitheliocytes were observed in all the preparations, most of them (about 88%) showing higher ^{3}H-thymidine incorporation in comparison with the values found under normal conditions; for 25% of epitheliocytes the NLI was 5 times higher. For more than half of the labeled epitheliocytes the NLI rose to 90%. For about 40% of ^{3}H-labeled epitheliocytes this index was equal to its physiological value, whereas for the rest of them it varied within the range of 15 to 36%, the maximum value being observed for 20% of the epitheliocytes. The index of uridine-labeled nuclei increased to 93% on average. It should be noted that in the first and, especially, in the third group the cells of submucous connective tissue showed active ^{3}H-uridine incorporation along with ^{3}H-thymidine incorporation in the third group.

These data point to the development of vigorous regenerative and hyperplastic processes within 24 days following injury with gradual restoration of the lost epithelial fragments. Slow proliferation of the intact epithelium in the regenerative area with moderate epitheliocyte viability was observed together with necrotic lesions in the tracheobronchial mucosa. Later the activation of basal epitheliocyte mitosis was noted, with high proliferative activity of epitheliocytes, far above the physiological level. Active formation of transitional and multistratified squamous epithelium went along with a high rate of protein synthesis in both

epitheliocytes and connective tissue cells. Subsequently, the mitotic activity and proliferation of basal epitheliocytes dropped to the level typical for normal stratified epithelium; however, foci of proliferation were still seen, with maximal viability of epithelial cells and submucosa during the stimulation of proliferative processes.

Thus, the initial destructive processes observed in the tracheobronchial mucosa and functional depression of the intact cellular elements gave way on the 8th day to reparative processes developing in the affected area, which were characterized by activated division of basal epitheliocytes with a high functional activity of the new transitional epithelium. On the 17th day the process of morphological and functional changes in the tracheobronchial mucosa appears to go through a new stage: normal tracheobronchial epithelium is being formed. Although this process was rather intensive transitional epithelium with aggregates of epitheliocytes undergoing intensive mitosis persisted as long as 24 days following injury.

The pathogenetic characteristics of inhalation injury and restoration of the respiratory function observed for treatment with fibrobronchoscopy open up new arenues for further speeding up the organism's compensatory and adaptive reactions to maintain homeostasis, and make it possible to predict the outcome of bronchopulmonary complications in burn patients.

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Development of Chronic Renal Deficiency in Spontaneously Hypertensive Rats

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Experimental modeling of chronic renal deficiency (CRD) performed on animals with a subtotal nephrectomy [5] demonstrates the role of nonimmunogenic factors in CRD development. A comparative study of CRD formation in normotensive and spontaneously hypertensive rats (SHR) makes it possible to assess the significance of the systemic hemodynamics damage [4].

MATERIALS AND METHODS

A comparative analysis of the development of CRD was performed in a subtotal nephrectomy model in Wistar rats and Okamoto SHR which are a model

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