was presumably the cause of the increase in urine volume. It was accompanied by a smaller but at the higher dose still significant reduction in K^+ output and therefore suggests an inhibition of the output or effectiveness of mineralcorticoids. Mineralcorticoid levels might be expected to be higher in the diabetic rats due to a probable reduction in blood volume caused by persistent glycosurea and hyperkalaemia due to cellular damage (β-cell destruction caused by such low doses of streptozotocin is a slow process and would be expected to be continuing after 7 days[12]. High mineralcorticoid levels are indicated by the fact that the $Na^+:K^+$ ratio was much reduced in the control diabetic animals compared to the normal controls, mean urinary pH also being lower but not significantly so. After the larger chlorpropamide dose the $Na^+:K^+$ ratio was greatly increased. pH values were also significantly increased both effects further indicating either an inhibition of mineralcorticoid effectiveness or output by chlorpropamide.

Water diuresis following chronic chlorpropamide dosing showed significantly reduced water output. This is the opposite of the acute response and probably represents a compensatory effect occuring at a time when blood chlorpropamide levels were relatively low (last dose of chlorpropamide was given 18 h before the test).

The diuretic effect of glibenclamide in both normal and diabetic rats is in agreement with the clinical findings[9,3] and the hypothesis that this drug increases sodium and water delivery to the loop of Henlé by either increasing glomerular filtration rate or inhibiting sodium reabsorption in the proximal tubule[3]. As with chlorpropamide the situation was reversed after chronic dosing presumably for the same reason, i.e. a compensatory effect occurring during relatively low blood levels of the drug. Acute tolbutamide in contrast to the other two agents reduced urine volume. The reduction in K^+ excretion was significant ($p < 0.001$) at the higher dose and since Na^+ excretion was relatively unaffected the $Na^+:K^+$ excretion ratio was significantly raised suggesting as wtih chlorpropamide mineralcorticoid antagonisms. Such an effect however could be expected to increase urinary volume and if it does occur then it may not be the only mechanisms by which tolbutamide affects the pattern of water diuresis.

The question as to whether chlorpropamide and possibly tolbutamide reduce mineralcorticoid activity by reducing output or inhibiting their effectiveness on the kidney could be resolved only by determining mineralcorticoid excretion under the influence of the drugs. Increased levels of the hormones would be expected, due to a compensatory increase in secretion if the effect of chlorpropamide is at the level of the kidney.

Zusammenfassung. Es wurden die Wirkungen von Chlorpropamid, Glibenclamid und Tolbutamid auf die Nieren wasserbelasteter normaler und diabetischer Ratten untersucht.

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Alcohol-Induced Pulmonary Changes in Rats

A relationship between excessive chronic alcohol intake and lung disease has been suspected for many years. Severe and sometimes fatal episodes of pneumonia, pulmonary emphysema, pulmonary fibrosis, and/or bronchiectasis are frequently associated with chronic alcoholism. Burch and DePasquale[1] suspected that these changes are due, at least in part, to direct damage of lung tissue by alcohol, and suggested the existence of an alcoholic lung disease. Recently Banner[2] studied the pulmonary function in 30 alcoholic patients and found that diffusion impairment and mild obstruction are characteristics of chronic alcoholism. The purpose of the present paper is to describe the effects of prolonged alcohol consumption on the morphology of rat lungs.

Materials and methods. 12 Wistar strain male rats (body weight 130–150 g) were allowed to drink only white rum (40% alcohol) for 4 months. 6 animals from the same stock were kept as controls and given no alcohol. All animals were fed on a balanced commercial rat food ad libitum. The daily amount of white rum consumed during the experiment was 4.9 ml/100 g of body weight.

Tissue samples of the lungs were minced, fixed in cold 1.5% glutaraldehyde (in 0.1 *M* cacodylate buffer, pH 7.4, containing 3% sucrose) for 2 h, and postfixed in buffered 1% osmium tetroxide for 1 h. The tissue blocks were dehydrated with acetone and embedded in araldite[3]. Thick sections used for light microscopy were stained with toluidine blue; ultrathin sections cut on a Porter Blum microtome were stained with uranyl acetate and lead citrate. Electron micrographs were taken on a AEI-EM6B electron microscope.

Results. Minor signs of chronic murine pneumonia were seen in both control and experimental animals. This will not be considered further. The lungs of the animals after long-term administration of alcohol showed a proliferation of alveolar cells and thickening of alveolar walls (Figure 1). The alveolar cells were found in increased number and size both as lining cells and free within the alveolar spaces. The intraalveolar cells were large mononuclear macrophages of various sizes, which tended to be ovoid in shape, and had a foamy appearance due to numerous intracytoplasmic vacuoles. Their cytoplasm contained also dark small round inclusions in the toluidine blue-stained thick sections. These free cells were not evenly distributed throughout the whole pulmonary tissue, but groups of alveoli were heavily affected, while others were empty. Hyperplasia and hypertrophy of granular (type 2) pneumocytes with a vesicular cytoplasm could be also seen where the foam cells were present. Similar pathological changes could not be observed in the lungs of control animals.

With electron microscopy, the changes consisted of hyperplasia and hypertrophy of type 2 pneumocytes, intraalveolar accumulation of macrophages and alveolar wall thickening due to increase in collagen content

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(Figures 2, 3, and 4). The hyperlasia of granular pneumocytes was indicated by the location of these cells next to each other. They were marked enlarged and contained 1 or 2 nuclei (Figure 3). The electron density of the secretory vacuoles in type 2 pneumocytes was altered. Some vacuoles contained loosely packed concentric material, but the majority contained a moderately electron-opaque lipid material. The secretory vacuoles in control rats were smaller and their content lamellated and more osmiophilic. The macrophages were numerous and their cytoplasm was filled with fagocytized concentric secretions. They showed characteristic cytoplasmic processes and lacked microvilli, which were present in the granular pneumocytes (Figure 4). The intercellular spaces of the alveolar septa were moderately thickened by increased numbers of mature collagen fibres (Figure 2).

Discussion. Our experimental data indicate that prolonged consumption of white rum (40% alcohol) induces changes of the lungs in rats. Granular (type 2) pneumocytes became hyperplastic and hypertrophic, with enlarged and less osmiophilic secretory vacuoles. The pulmonary alveoli contained moderate numbers of large foamy cells. The structural features of these intraalveolar cells suggested that they correspond to alveolar macrophages filled with lipid material. It is generally accepted that the alveolar macrophages are derived from circulating precursors of bone marrow origin and developed by mitosis and maturation within the lung[4]. In our experiment, mild interstitial pulmonary fibrosis has been also observed.

Various changes similar to those seen in our studies have been reported in chronic pulmonary edema[5],

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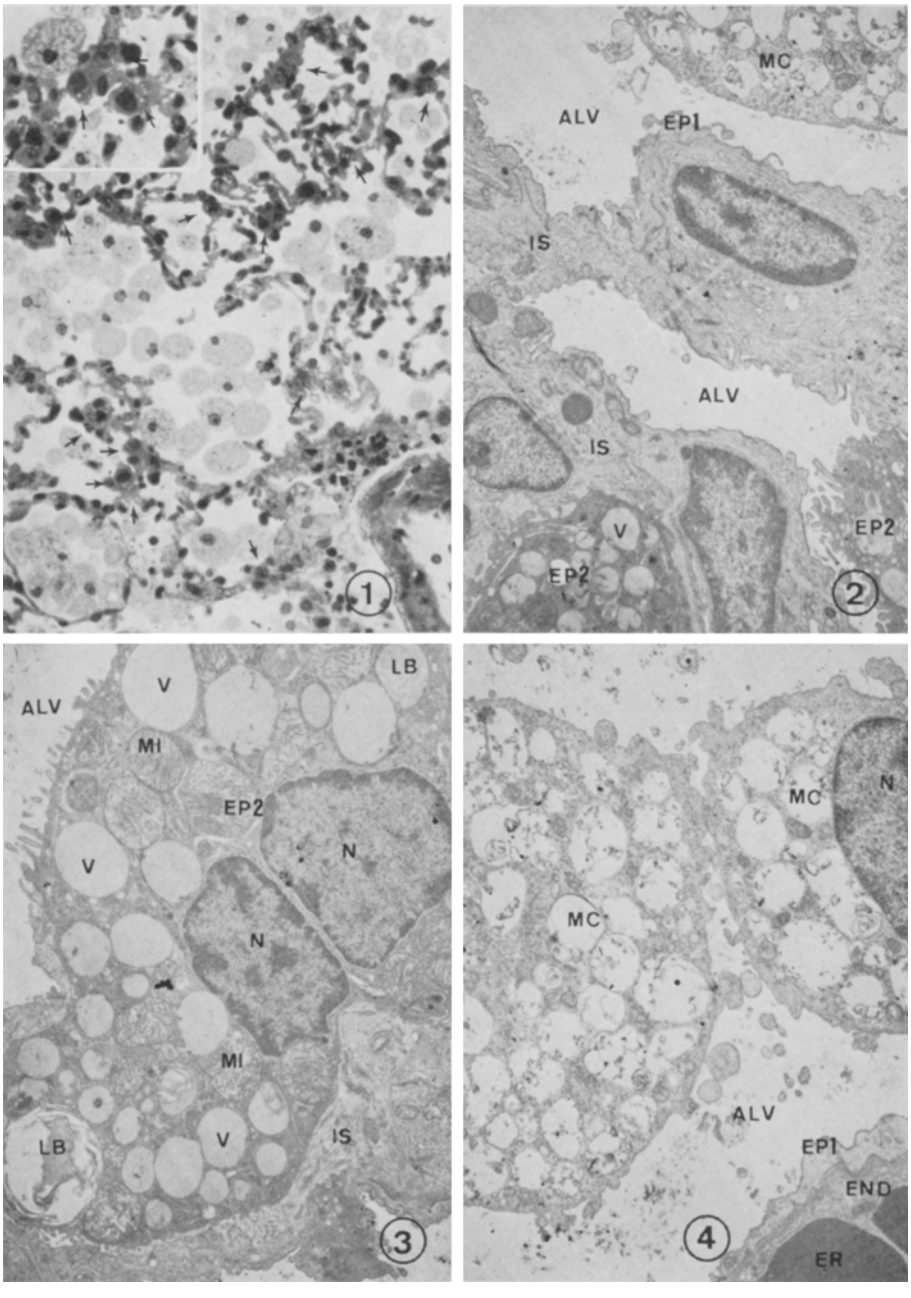

Fig. 1. Hyperplasia and hypertrophy of granular (type 2) pneumocytes (at the arrows), numerous intraalveolar macrophages and thickened alveolar septae in a lung from rat that drank only white rum (40% alcohol) for 4 months. Toluidine blue stain, 1 µm thick section. ×320. Inset, ×600.

Fig. 2. Portion of 2 alveoli from a test rat. Thickened alveolar septae. Portions of 2 granular pneumocytes and of a macrophage in alveolar space are seen. Electron micrograph (EM). Uranyl acetate and lead citrate (UA, LC). ×7500.

Fig. 3. Hypertrophic granular pneumocyte showing two nuclei from a test rat. The electron density of the secretory vacuoles is altered EM, UA, LC. ×7500.

Fig. 4. Portion of 2 macrophages from an alveolus of a test rat. The cytoplasm is filled with fagocytized secretions. EM. UA, LC. ×7500. ALV, alveolar space; IS, interstitial space; EP1, membranous (type 1) pneumocyte; EP2, granular (type 2) pneumocyte; MC, intraalveolar macrophage; V, secretory vacuole; LB, lamellated body; MI, mitochondria; N, nucleus; ER, erythrocyte; END, endothelium.

pneumonitis following chronic ganglionic blockade[6], oxygen toxicity[7,8], epinephrine-induced injury[9], desquamative interstitial pneumonia[10], pulmonary alveolar proteinosis[11], monocrotaline-induced pulmonary lesions[12], etc. Nevertheless the combination of features appears to be quite characteristic of a drug-induced disorder of lipid metabolism, as it can be seen in anorogenic drug-induced lipidosis[13–15].

Before a pathogenetic mechanism can be proposed for the lesions observed by us, some points have to be referred to: a) it has been found that rat lung tissue is capable of completely oxidizing alcohol and utilizing alcohol in the synthesis of fatty acids[16]; b) studies on the fate of alcohol in the organism have shown that alcohol metabolites in the form of total lipids and fatty acids accumulate in the lung[17]; c) alcohol has a lipolytic action by mobilizing the fat deposits of the body[18,19], probably due to its sympathomimetic properties[20–22]; d) it is well known that alcoholism is associated with hyperlipidemia[23–26]; and e) the lungs are an important route of excretion of lipids in rats[27,28].

According to these facts, it seems likely that alcohol-dependent metabolic derangements may well be the basic mechanism of the pulmonary pathological changes mentioned above. It is clear that further studies are needed before these observations can be fully understood, which may also contribute to the understanding of certain aspects of cellular function in the lung.

Zusammenfassung. Bei normaler Ernährung und täglichem Trinken von beliebigen Mengen 40%igem Zuckerrohrschnaps wurden bei weissen Laboratoriumsratten diverse anatomische und ultrastrukturelle Lungenveränderungen nachgewiesen: Hypertrophie und Hyperplasie der Pneumocyten vom Typ 2, Anhäufung intraalveolärer Makrophagen und Verdickung der Alveolarwände.

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Motion-Modulated Vestibular Neurons: Central versus Peripheral Effects of Cholinergic Blocking Agents

Studies in many laboratories have indicated the effectiveness of the belladonna alkaloids, scopolamine and atropine[1,2] and the antihistaminics, diphenhydramine and dimenhydrinate[3], in the prevention of motion sickness. Some recent studies have indicated that the effectiveness of these drugs in treating motion sickness is due to their anticholinergic action possibly mediated through a locus in the brainstem[4], rather than at the vestibular end organs.

However, several recent reports suggest that acetylcholine is the neurotransmitter at efferent nerve fibres innervating the hair cells of the inner ear. Both acetylcholine esterase and choline acetyltransferase have been localized at these efferent synapses and inhibitory post synaptic potentials recorded in hair cells can be blocked by D-tubocurarine[5]. The existence of an efferent component of the vestibular nerve mediated by acetylcholine indicates that the site of action of anticholinergic agents used clinically for the prevention of motion sickness may be peripheral rather than central.

The purpose of the work presented here was to assess the effectiveness of scopolamine methyl bromide and other quaternary compounds with muscarinic blocking activity in the vestibular nuclei and compare it with that of scopolamine hydrochloride. Because of the lack of access of quaternary ammonium compounds to the CNS, this comparison should distinguish between possible central or peripheral modes of action.

Materials and methods. 12 cats (3.5 to 4.5 kg) of either sex were anesthetized with halothane. Cannulae were inserted in the trachea, femoral vein and artery for adequate ventilation, i.v. injections and recording arterial blood pressure, respectively. After the animal's head was fixed in a stereotaxic apparatus, a midcollicular decerebration was performed. The lower brain stem was exposed by an occipital craniotomy and the cerebellum was left intact. Body temperature was maintained at 37 ± 1.0 °C.

A platinum-iridium microelectrode was advanced through the cerebellum and into the vestibular nucleus according to the stereotaxic coordinates of Berman[6].

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