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*ISO*PROPYL*NOR*ADRENALINE INHALATION AND MUCOUS MEMBRANES

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Inhalation of aerosols is now widely used in the treatment of bronchial asthma. Numerous substances are employed, of which adrenaline and its related compounds are the most powerful spasmolytics. The relief afforded is so striking (though often temporary) that numerous preparations and nebulizers are bought by the public, very often without medical advice or supervision.

In these circumstances it appears important to know whether inhalation of these compounds may be harmful to the mucous membranes of the air passages. Galgiani *et al.* (1939) found that inhalation of 1 per cent adrenaline in rabbits and cats caused damage to the mucous membranes of trachea and bronchi. Their results are partly supported by earlier findings of Fox (1931), who sprayed the nasal membranes of rabbits with 1/1000 adrenaline and found a mucopurulent discharge.

Very recently *iso*propyl*nor*adrenaline* (aleudrine) has become available. This substance is easily absorbed from the mucous membranes of mouth, pharynx, and the other air passages, and its spasmolytic action appears to be very strong (Herxheimer, 1948) and more powerful than that of adrenaline (Konzett, 1940). Our paper does not deal with the therapeutic merits of *iso*propyl*nor*adrenaline, but as its widespread use can be anticipated it seemed of importance to investigate whether such damage as has been stated to occur after the use of adrenaline would be caused also by this substance.

METHOD

Twelve rabbits were used. They inhaled an aerosol which was produced by connecting one of the commercial glass inhalers to a compressed air cylinder. A steady pressure was maintained from this cylinder, which caused a fine aerosol cloud to flow continuously from the nozzle of the inhaler. Over this nozzle a closely fitting plastic mask was fixed which was pressed over the rabbit's head; the aerosol jet issuing from the nozzle was directed straight against mouth and nostrils of the rabbit and filled the mask, escaping at its upper end. Mouth and nose of the rabbit were thus completely and continuously surrounded by the aerosol. That it actually breathed the aerosol could be seen from the fact that the vapour escaped from the mask in the breathing rhythm of the animal. When the animal breathed out the cloud increased strongly, and decreased during inspiration.

The concentration of *iso*propyl*nor*adrenaline used by one of us (H. H.) for treatment of asthma is usually 1 per cent, if it is nebulized by pressing the rubber ball of a hand inhaler. If a mechanical device, like an air-pressure pump or compressed air cylinder, is used, as little as 0.25 per cent is effective, as much more inhalant is breathed than with a hand inhaler. For this reason we started our experiments with a 0.25 per cent solution, nebulized by compressed air, which was inhaled for 10 minutes every day. The twelve rabbits were divided into three groups of four. One group inhaled pure aleudrine, one group aleudrine to which 0.2 per cent sodium metabisulphite had been added as a stabilizer, and the third group inhaled physiological saline. In each group one drop of glycerine was added to 2–3 c.c. of the solution to delay evaporation and to make the aerosol easily visible.

All the rabbits were treated in this way for 30 days; then one rabbit of each group was killed by a blow on the head. The remainder continued as before for a further 5 days. Then another rabbit of each group was killed. The remaining rabbits were treated with 0.5 per cent aleudrine (or saline) for 22 days. Then a third rabbit of each group was killed. Only one rabbit of each group now remained. They were subjected for 16 days to 1 per cent aleudrine aerosol except the rabbit in the control (saline) group.

When the rabbits were killed, the trachea was quickly excised, opened longitudinally, put in a bath of Ringer-Locke at 39° C., and pinned without stretching on to a cork. A minute drop of india ink was then dropped on to the mucous membrane half an inch below the cricoid cartilage and its movement towards the larynx (due to the action of the cilia) was watched. The speed of the movement over 0.5 cm. was measured with a stop-

* This substance was called "*iso*propyladrenaline" by Konzett (1940), but since it does not contain the N-methyl group of adrenaline it should be called *iso*propyl*nor*adrenaline.—*Editors.*

watch. This method of estimating the action of the cilia described by Hill (1928) did not prove very reliable. Sometimes movement was very strong in one part of the trachea but not in another; sometimes it was so weak that the india ink travelled only 2 or 3 mm. In many cases, however, a speed of about 1 cm. per 50–70 sec. was seen, and there were no differences between the three groups. Weak movement was observed also in the control group.

Trachea and lungs were then fixed in 10 per cent formol-saline and prepared for histological examination, after embedding in paraffin wax. Sections were stained with Ehrlich's Acid Haematoxylin and Eosin, with Heidenhain's Iron Haematoxylin, and with Mayer's mucicarmine stain.

Results

The result of the experiments with ciliary movement has already been mentioned. All the rabbits showed steady gain in weight throughout the experimental period. Histological examination showed no difference between the three groups. The ciliated epithelium was normal. There was no destruction or metaplasia of ciliated epithelium in trachea or bronchi and no polymorphonuclear infiltration of epithelium or submucosa. The goblet cells, stained by mucicarmine, were found in approximately similar density in all three groups. As compared with three rabbits not exposed to the inhaler, mucous activity in the trachea of the experimental animals was slightly increased.

Discussion

There is a striking contrast between our negative results and the positive results of Galgiani *et al.* with adrenaline, applied twice daily by pressing a hand inhaler 10 times. They used therefore an amount of inhalant considerably smaller than that used in our experiments. During one period of inhalation (10 squeezes) they removed 8 mg. of fluid from the inhaler, whereas in our experiments of 10 minutes duration between 600 and 800 mg. were aerolized, the variations being caused by the slight difference in the syphon of the inhaler and of the pressure used. This does not mean, of course, that this amount has been inhaled by the animals. Only a small fraction of it can have been inhaled and still less absorbed.

Of Galgiani's animals (rabbits and cats) exposed to the vapour, 4 died prematurely after 6 to 34 days. Two of these showed inflammatory changes in the respiratory tract. Another animal died on the 117th day of pneumonia and empyema. Five remaining animals were killed after varying periods of time. Two of them showed loss of cilia and three showed mucopus in the bronchi without histological changes. Of the 4 control animals two showed mucopus in the bronchi and a third died with evidence of bronchopneumonia and bronchitis. It must therefore remain doubtful whether this result has sufficient weight to prove a harmful action of adrenaline or of the sodium bisulphite which Galgiani *et al.* used as stabilizer. In our experiments, sodium metabisulphite did not produce any changes.

Our experiments show that aleudrine in therapeutic concentrations is not harmful to the mucosa of rabbits. Whether adrenaline produces harmful results remains an open question.

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