of acini are seen, showing that it is the 'basket' or myo-epithelial cells which are specifically displayed (Fig. 3). The nucleated parts of these cells when seen from the flat have often a triangular shape from which long branching and tapering processes emanate. The length and width of these agree with the sectioned appearances of the alkaline phosphatase positive material around the acini. It is worth noting that the reaction does not give a homogeneous appearance to the cytoplasm, but rather a mottled one, very often combined with a fibrillar pattern (Figs. 2 and 3).

Similar, but much smaller and less extensively ramifying, alkaline phosphatase positive basket cells were also seen in the very short intercalated ducts which are present in these glands. The remaining portions of the duct system were alkaline phosphatase negative. Blood capillaries gave—as is usual with rat tissue—an irregular and erratic reaction. When alkaline phosphatase was visualized by the azo-dye method, the result was the same.

This almost specific localization of alkaline phosphatase in the myo-epithelial cells of the rat sub-maxillary gland links up satisfactorily with the findings of Dempsey, Bunting and Wislocki⁶, who demonstrated the presence of alkaline phosphatase in the myo-epithelial cells of the mammary gland of rat, and of Silver⁷, who showed that the same holds for the mammary gland of sheep and rabbit and the sheep's parotid, but it still remains to be seen whether it is a general property of myo-epithelium.

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Addendum.—Since this communication was submitted for publication, my attention has been directed to a letter by R. L. Holmes (*Nature*, 178, 311 (1956)).

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Antagonists of the Action of Reserpine on Smooth Muscle

WE have recently directed attention to the fact that citrate antagonizes reserpine inhibition of contractions induced in the guinea pig ileum by acetylcholine chloride, histamine acid phosphate, serotonin and barium chloride¹. A consideration of the general pharmacology of reserpine has led us to believe that this substance may have a general non-specific depressant effect upon contractile tissue^{1,2}.

Fig. 1. (A) All contractions produced by 0.25 $\mu\text{gm.}$ per ml. acetylcholine chloride. (B) All contractions produced by 0.20 $\mu\text{gm.}$ per ml. histamine. At R, 30 $\mu\text{gm.}$ per ml. reserpine added. At R + NaP, 30 $\mu\text{gm.}$ per ml. reserpine and 1 mgm. per ml. sodium pyruvate added. At R + KGA, 30 $\mu\text{gm.}$ per ml. reserpine and 1 mgm. per ml. α -keto-glutaric acid added.

Since reserpine non-selectively antagonizes contractions due to acetylcholine chloride, histamine acid phosphate, serotonin and barium chloride in the guinea pig ileum, it appears to be affecting underlying mechanisms connected with the production and utilization of the energy necessary for the drug-induced contractions rather than specific receptors. These mechanisms probably involve the breakdown and resynthesis of carbohydrate through the glycolytic and tricarboxylic acid cycles. It seemed worth while, therefore, investigating the influence of adding known intermediates of carbohydrate metabolism to the isolated guinea pig ileum immediately before addition of reserpine.

The ileum was stimulated by either acetylcholine chloride (0.2–1.0 $\mu\text{gm.}$ per ml.), histamine acid phosphate (0.1–1 $\mu\text{gm.}$ per ml.), serotonin (15–40 mgm. per ml.) or barium chloride (0.2 mgm. per ml.) at 3-min. intervals. Reserpine was added 1 min. before the spasmogen and the metabolite 5 sec. before reserpine. All metabolites were tested over the dose-range, 125 $\mu\text{gm.}$ –1 mgm. per ml. The following were ineffective as reserpine antagonists: glucose-1-phosphate, fructose-1,6-diphosphate, fructose-6-phosphate, pyruvate (Fig. 1), fumarate, succinate and adenosine triphosphate. The following were very active: citrate, *cis*-aconitate and α -keto-glutarate (Fig. 1). Malate and oxaloacetate had intermediate activity. Maleic acid (the *cis*-isomer of fumaric acid) at doses of 500 $\mu\text{gm.}$ or 1 mgm. per ml. was very active. Removal of calcium from the bath fluid by disodium dihydrogen versenate did not produce antagonism to reserpine.

The possibility of release of histamine or acetylcholine chloride by the metabolites was excluded by repeating the experiments using, where appropriate, Tyrode's solution containing either atropine sulphate (100 $\mu\text{gm.}$ per litre) or mepyramine maleate (200 $\mu\text{gm.}$ per litre).

Since the most active reserpine antagonists are intermediates of the tricarboxylic acid cycle, it seems not unlikely that this is a site of action of the alkaloid.

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