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Inhibition of Gastric Secretion of Hydrochloric Acid *in vivo* by Carbonic Anhydrase Inhibition

THIS preliminary communication on the inhibition of acid secretion *in vivo* in dogs by one of a new group of potent carbonic anhydrase inhibitors is prompted by the recent report of Davies and Edelman¹, which has appeared since our work was completed. These workers have shown that several other known carbonic anhydrase inhibitors, which include protosil, *p*-toluenesulphonamide, *p*-sulphonamidobenzoate and thiophene-2-sulphonamide, can suppress the *in vitro* acid secretion of the isolated frog and toad gastric mucosa, although sulphanilamide was without effect.

We employed the hetero-cyclic sulphonamide 2-acetyl-amino-1,3,4-thiadiazole-5-sulphonamide, which is 440 times as potent as sulphanilamide for the 100 per cent inhibition of carbonic anhydrase *in vitro*². The single intravenous injection of this material in doses of 20-60 mgm./kilo inhibited 79-97 per cent (mean, 89 per cent) of the output of hydrochloric acid from Heidenhain pouches in three unanæsthetized dogs, stimulated by the subcutaneous injection of 0.025 mgm. of histamine base every 10 min. This inhibition, which occurred after a latent period of 20-80 min., persisted for at least 3-6 hr., and the secretory function appeared to be completely recovered in 24 hr.

It has been predicted by previous workers that any degree of carbonic anhydrase inhibition sufficient to interrupt the process of acid secretion by the parietal cell must lead to the speedy death of the animal by virtue of interference with carbon dioxide transport by the blood, yet no toxic reactions were observed in this dose-range.

When the dosage was extended to 120 mgm./kilo, one of these dogs expired in respiratory arrest, while the two other pouch dogs as well as two unoperated dogs tolerated this dose well. There was no increase in the degree of acid inhibition at this dose-level.

The details of these experiments will be published elsewhere.

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Nature of Reticulin

THE main obstacle to the characterization of reticulin has always been its close association with collagen. As a preliminary to an attempt to establish the nature of reticulin fibres, a histological survey of all likely tissues was carried out, and it was found that the mid-cortical connective tissues of the kidneys of children free from renal disease consist almost entirely of reticulin. The only collagen present in this situation occurs in the immediate neighbourhood of the larger blood vessels.

Reticulin was identified histologically as fine branching fibres which appear black when appropriately treated with any of the modifications of the Maresch-Bielschowsky silver-impregnation technique; take up the acid aniline dye in the Mallory connective tissue stain; show little or no fuchsinophilia in sections stained with van Gieson's picro-fuchsin; and appear red when subjected to the McManus periodic acid-Schiff's reagent procedure.

Collagen was identified in histological preparations as bundles of non-branching fibres which assume a yellow-brown colour in untuned Maresch-Bielschowsky type preparations; take up the acid aniline dye of Mallory's connective tissue stain; show well-marked fuchsinophilia when stained with van Gieson's picro-fuchsin; and give a negative reaction to the periodic acid-Schiff's reagent test.

By a process of careful dissection, followed by maceration of frozen sections of unfixed tissue in decinormal sodium hydroxide, reticulin was isolated and prepared for electron microscopy and X-ray diffraction study. Histological control was exercised throughout to ensure that the specimens consisted only of histologically acceptable reticulin and contained no collagen.

Other samples of reticulin, known to be contaminated with collagen to a greater or lesser extent, were prepared in the same way from human liver, lung, adrenal, spleen, lymph-nodes and myocardium for purposes of comparison. Reticulin has also been suggested as one of the components of the organic matter of teeth, and the present investigations indicate that it is probably present in dentine.

Reticulin from all sources produced essentially similar appearances. In electron micrographs of unshadowed specimens it appeared as very thin laminated membranes made up of a network of minute randomly arranged fibrils embedded in an apparently structureless membrane, the relative proportions of fibre and matrix varying in different specimens, even in material obtained from the same source.

In specimens shadowed with uranium the fibrils show a striated structure, the period of the striations being of the order of 650 Å. Occasional bundles of fibrils were seen which were sufficiently large to be visible in an optical microscope. These bundles were only seen in material from specimens known to contain collagen. No bundles of fibrils which would be visible with an optical microscope were found in the specimens from renal cortex. In specimens in which aggregation of the fibrils into bundles had occurred, the fibril diameters were usually 400-500 Å. In other specimens fibrils as small as 100 Å. in width were sometimes encountered. The supporting membranes appeared to vary in thickness. Areas photographed were usually in the range 50-150 Å. The illustrations (Figs. 1 and 2) are of an adrenal specimen ($\times 30,000$). Electron micrographs of specimens which had been boiled in water and then shadowed showed that