DARMSTOFF, A GUT-STIMULATING COMPOUND OCCURRING IN THE INTESTINAL WALL

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Dialysates of isolated surviving intestinal loops show gut-stimulating effects different from those caused by histamine, choline, or other substances known to occur in intestinal tissue. The effects are due to a substance called "Darmstoff" (4). In all species investigated it stimulates the movements and raises the tonus of smooth muscle organs, such as intestine, uterus or bladder. The duodenum of the rabbit and the uterus of the guinea pig appear to be the most sensitive organs, while Darmstoff exerts only a slight effect upon the ileum of the guinea pig. The stimulating action begins after some latency and increases gradually. It is not antagonized by atropine, antistine, cocaine, or ganglionic blocking agents. Darmstoff does not cause a contraction of the rectus abdominis of the frog. However, the effect of acetylcholine on this organ is potentiated by extracts containing Darmstoff. The isolated frog heart is only slightly and not uniformly affected. The blood pressure of the rabbit sometimes shows a slight fall. Whether this effect is due to Darmstoff itself is not known.

With respect to its chemical properties, Darmstoff is different from other substances similar in origin and action. It behaves like an acid; in paper-electrophoresis at pH 6 Darmstoff goes to the anode (7). The free acid is only slightly soluble in water, but quite soluble in organic solvents such as butanol, ether, acetone. It is less soluble in chloroform. In an alkaline aqueous medium it is readily soluble. The distribution coefficient between butanol and acidified water is higher than 6. Countercurrent distribution in this system was used for purification of crude aqueous extracts from intestinal tissue in order to get Darmstoff preparations entirely free from histamine and choline.

Earlier investigations seemed to indicate a relationship between Darmstoff and substance P (1, 2, 5). Darmstoff was thought to be responsible for the gut-stimulating activity of substance P. The powerful hypotensive effect of substance P, however, must be due to another compound, since Darmstoff fails to give this effect (2, 5). Recent investigations have clearly shown that Darmstoff and substance P are different compounds. They can be completely separated by countercurrent distribution between butanol and water at neutral or acidic pH (8). Substance P is basic in nature. It is hypotensive and gut-stimulating by itself. Darmstoff occurs only as a contamination of common preparations of substance P obtained by double precipitation with ammonium sulphate (8). It contributes to their gut stimulating activity, particularly when tested on the intestine of the rabbit or of the frog, but less so, or not at all, when tested on the ileum of the guinea pig.

By its acidic behavior and ready solubility in organic solvents Darmstoff can be distinguished from other biogenic compounds, except prostaglandin which is similar chemically as well as pharmacologically. Darmstoff is present

in the whole gastrointestinal tract. Skeletal muscle does not contain it in comparable amounts. The substance was not only found in dialysates, in boiled aqueous or alcoholic extracts of gut tissue, but also in dialysates of uninjured intestine *in situ*. Apparently Darmstoff is present in free form, i.e., in active form, in the living intestine in concentrations which, according to investigations in rabbits (6), exceed the threshold concentration 5 to 20 times. Thus, the gut is under permanent stimulation by Darmstoff, a fact which explains its atropine-resistant motility. Whether the changes in motor activity of the intestinal wall are due to changes in the release of Darmstoff, depending on the activity of Auerbach's plexus, is not as yet known. Vagal stimulation of the stomach of the frog leads to the liberation of a substance resembling Darmstoff (4), but it is not known as yet whether or not the atropine-resistant transmitter is identical with Darmstoff.

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