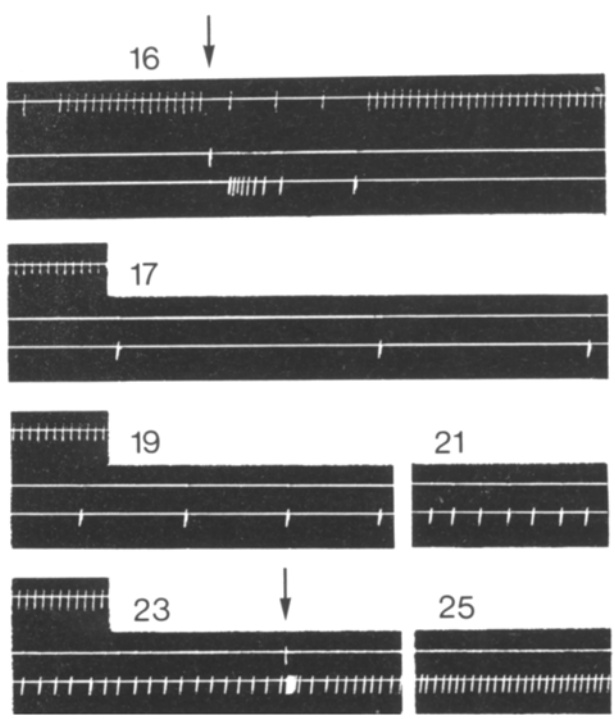
Effect of Bretylium on Degeneration Secretion of Saliva

Following section of postganglionic nerves there is a period during which transmitter is released from the endings of the degenerating nerves in amounts sufficient to cause 'degeneration activity' in the denervated organ. This phenomenon has been observed both after section of cholinergic and adrenergic nerves, and both in glands and smooth muscle[1]. A puzzling fact is that the appearance of e.g. 'degeneration contraction' of the rat's periorbital smooth muscle and 'degeneration vasoconstriction' in the rabbit's ear elicited by sympathetic ganglionectomy can be postponed by administration of bretylium[2,3]. It has so far not been possible to attribute with certainty this effect to any of the known pharmacological actions of the drug on adrenergic nerves[1,2]. It therefore seemed of interest to investigate whether a similar delaying effect of bretylium can be obtained after section of cholinergic nerves, and the effect on the submandibular 'degeneration secretion' of saliva following parasympathetic denervation was studied.

Methods. In 8 cats the chorda-lingual nerve was cut in ether anaesthesia. This parasympathetic decentralization of the submandibular gland causes a marked supersensitivity of the glandular cells, which renders the detection of secretory effects easier. After 3 weeks, when maximal supersensitivity has developed, a (partial) postganglionic parasympathetic denervation[4] was carried out, using a short-acting barbiturate (Baytinal Bayer, 20 mg/kg intracardially) as anaesthetic. 15–17 h later chloralose (60–80 mg/kg) was given i.v. after induction with ether. Tracheal cannula was inserted and both submandibular ducts were cannulated in the neck. Secretion was recorded as drops of saliva on a smoked drum, using an electromagnetic pen operated manually.



Effects of bretylium, 1 mg/kg (arrows) before and during 'degeneration secretion'. Records in each section, from below: drops of saliva, signal, time in min. The figures above each section denote the time (h) after the postganglionic denervation. No flow of saliva occurred until bretylium was first given; but afterwards there was a continuous flow at increasing rate.

Results. According to previous experience 'degeneration secretion' could, under the present conditions, be expected to start not much later than 18 h after the denervation[1]. In one of the 8 cats saliva was already flowing when the experiment started, 17 h after denervation. In the others no secretion occurred during an observation period of about $^1/_2$ h. Bretylium tosylate, 1 mg/kg, was then injected i.v. This invariably evoked a rapid flow of saliva; about 10–20 drops were produced by the gland of the operated side, sensitized by previous decentralization, and 3–10 drops by the contralateral gland. After this rapid flow, which lasted for 2–3 min, secretion did not cease completely on the operated side. It was very slow but gradually increased in rate in a way characteristic of 'degeneration secretion'. A typical example is shown in the Figure, which also demonstrates that the effect of bretylium, once the 'degeneration secretion' had started, was to cause a very rapid secretion during a few min and then a longlasting acceleration of the 'degeneration secretion'. This was the case with doses of bretylium of 1–5 mg/kg. Atropine, 0.5 mg/kg i.v., abolished not only the 'degeneration secretion' but the secretory effect of bretylium as well.

Discussion. The effects of bretylium described here resemble those of acetylcholine and methacholine; after an initial secretory effect these drugs are able to provoke 'degeneration secretion' when given shortly before this phenomenon is expected to start[5]. In previous experiments bretylium was found to stimulate the acetylcholine receptors of salivary gland cells of cats[6,7], and the present experiments hence suggest that the ability to provoke 'degeneration activity' following parasympathetic denervation is common to agents acting like acetylcholine. On the other hand, with the doses and with the time scale for bretylium injections used it has not been possible to demonstrate, after parasympathetic denervation, the delaying effect of bretylium discovered in certain organs after sympathectomy. The doses of bretylium used here are large enough to abolish the secretory effect of sympathetic stimulation in submandibular glands of cats[6]. The present observations are compatible with the view that the delaying effect of bretylium is dependent on the mechanisms for uptake and accumulation of bretylium possessed by adrenergic nerves[1].

Zusammenfassung. Die «Degenerationsaktivität», die in einigen Organen nach Sympathektomie auftritt, kann durch Bretylium verzögert werden. In Versuchen mit parasympatisch denervierten Speicheldrüsen konnte dieser Effekt des Bretyliums nicht nachgewiesen werden. Es zeigte sich, dass Bretylium hier einen eigenen sekretorischen Effekt hat und nebenbei eine latente «Degenerationssekretion» auslöst. In diesen Versuchen gleicht Bretylium Acetylcholin.

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