steigt, dass vorher nicht nachweisbare Zellen färbbar werden[6]. Dieses Verhalten ist eher erstaunlich, löst doch das Hypertensin im Nebennierenmark eine Steigerung der Sekretion der Katecholamine aus[7,8] wie Reserpin[9], das im Darm aber eine Verminderung des Serotoningehaltes[10,11] und der Argentaffinität und damit eine Reduktion der Zahl färbbarer argentaffiner Zellen bewirkt[12]. Die Ergebnisse dieser Untersuchung sind für die menschliche Pathologie von einer gewissen Bedeutung, da bei verschiedenen Nierenkrankheiten eine Vermehrung der argentaffinen Zellen des Verdauungstraktes nachgewiesen werden konnte[13,14].

Summary. The duodenum of guinea-pigs were dissected immediately after death and incubated for 10 min at 37 °C in a solution of Krebs-Ringer-Bicarbonate buffer, in which Hypertensin (CIBA) was added. The result was that the argentaffine cells were more numerous after the incubation period, as compared with the controls. The 2 controls were pieces placed into the solutions of Formalin and blank Krebs-Ringer-Bicarbonate buffer.

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An Electron Microscopic Study of Selective, Acute Degeneration of Sympathetic Nerve Terminals after Administration of 6-Hydroxydopamine

2,4,5-Trihydroxyphenylethylamine or 6-hydroxydopamine (6-HO-DA) has been reported to provoke efficient and extremely long-lasting noradrenaline (NA) depletion in various sympathetically innervated organs of different species[1–3]. The mechanism of this depletion, however, is not clear. Irreversible damage of NA storage sites[1,2] as well as stoichiometrical replacement of NA by 6-HO-DA, and/or its metabolites[3] have been postulated.

The successful electron microscopic localization of 5-hydroxydopamine (5-HO-DA)[4] which acts as a false sympathetic transmitter[5] encouraged the study of possible ultramorphological changes induced by its isomer 6-HO-DA.

Cats were given 4 injections of 20 mg/kg 6-HO-DA i.p. over a period of 48 h at 12 h intervals. Three days, 15 days, 3 and 4 months after the first injection small pieces of iris, vas deferens, spleen capsule and right heart auricle were removed, fixed in glutaraldehyde, post-fixed in osmium tetroxide and embedded for electron microscopy. The residual parts of the organs were homogenized and their NA content was determined according to the method described by Bertler et al.[6].

The animals tolerated the serial injections and after-effects without serious complications. After the first injection of 6-HO-DA they showed signs of more or less intensive peripheral sympathomimetic stimulation such as pupillary dilatation and hair erection on the back and tail.

In animals sacrificed 3 days after the first injection of 6-HO-DA the NA content of all organs studied was decreased to less than 10% of that of controls. At this time ultrathin sections of the spleen capsule, a tissue which contains only adrenergic nerves[7], revealed that virtually all autonomic nerve endings were in various stages of degeneration whereas the surrounding Schwann cells and smooth muscle cells appeared intact (Figure 1). Some of the nerve terminals occasionally contained still recognizable ultrastructural components such as dense core vesicles and mitochondria. In others the alterations had already attained such a degree that it was possible to recognize them only by their typical topographical localization between smooth muscle cells and/or the surrounding Schwann cells.

In the iris and vas deferens where adrenergic and cholinergic nerves often lie side by side[7,8], the changes were even more impressive since only the adrenergic terminals were degenerated, whereas the cholinergic ones, i.e. terminals with empty vesicles, appeared completely normal (Figures 2 and 3). Two weeks after the treatment the images of degenerated nerves had all disappeared. The tissue sections resembled the normal ones with the exception that virtually no adrenergic nerve terminals, i.e. terminals containing dense core vesicles, were present.

Thus it can be concluded that the noradrenaline depletion by 6-HO-DA results from an acute degeneration of the adrenergic nerve terminals. It is notable that all other structures including the cholinergic nerve terminals remained intact. It seems most plausible that 6-HO-DA is taken up selectively by the sympathetic nerves in a manner similar to NA, the physiological transmitter. It remains to be elucidated if 6-HO-DA is also stored in the vesicles. Once concentrated in the nerve terminals 6-HO-DA and/or its metabolites, which might possibly be formed, provoke their degeneration by a mechanism which remains obscure. 6-HO-DA is a strong reducing agent and in neutral aqueous solution it undergoes rapid oxidation. This property might partially be responsible for the degenerations observed in the nerve terminals.

The selective degeneration of the adrenergic nerves occurs only in the distal part of the neuron, and not in the perikaryon. Indeed, 3–4 months after treatment nerve terminals with dense core vesicles had regenerated in all

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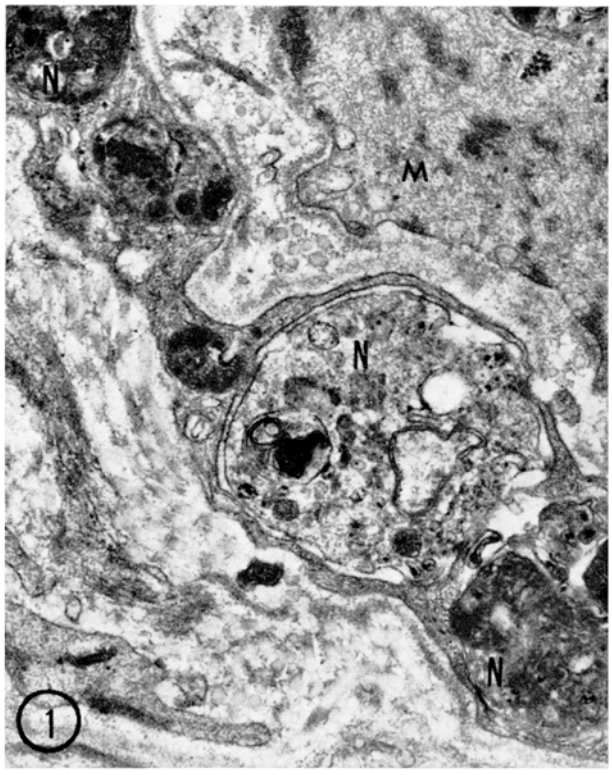

Fig. 1. Spleen capsule from a cat treated with 6-HO-DA. Autonomic nerve terminals (N) in various stages of degeneration. M: smooth muscle. × 35,000.

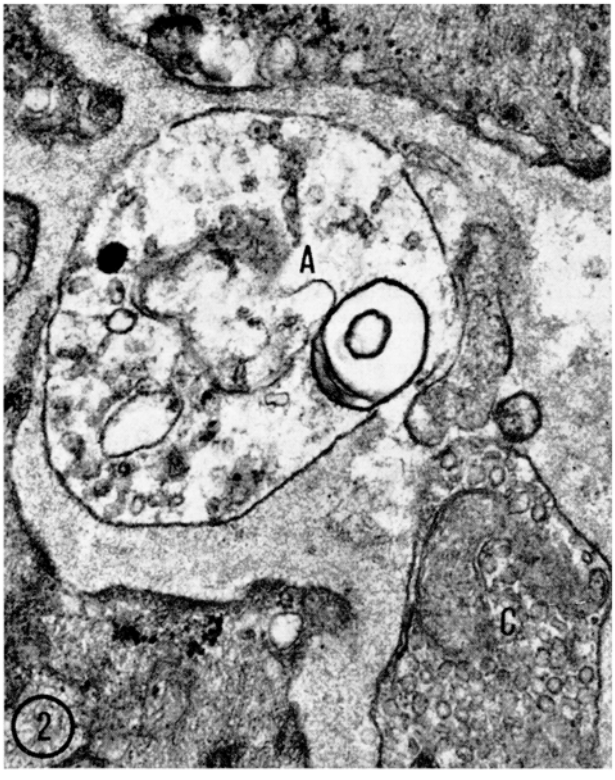

Fig. 2. Iris from the same animal as shown in Figure 1. A well preserved cholinergic nerve terminal (C) lies close to a degenerated adrenergic nerve terminal (A). × 50,000.

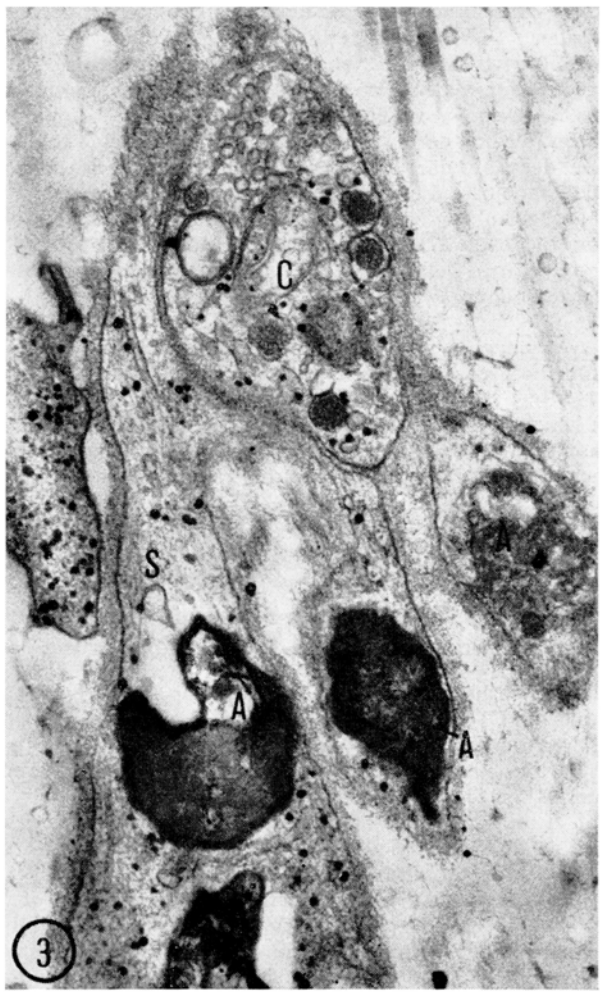

Fig. 3. Biopsy of the vas deferens taken from a cat 3 days after the first injection of 6-HO-DA. Degenerated adrenergic nerve terminals (A) lie close to a well preserved cholinergic nerve (C). S = Schwann cell. × 50,000.

the organs studied, i.e. iris, vas deferens, right heart auricle and spleen capsule. Concomitantly, the NA content determined in these organs had risen and approached again the values obtained from control animals. It was verified that degeneration had also occurred in the adrenergic nerve terminals of those animals sacrificed 3–4 months after the initial injection, by taking a biopsy of one of the vas deferens under aseptic conditions 3 days after the first injection of 6-HO-DA and examining it with the electron microscope (Figure 3).

In conclusion, 6-HO-DA acts in a completely different way from its isomer 5-HO-DA[4], producing a selective but reversible degeneration of adrenergic nerve terminals, and thus represents a new tool for chemical sympathectomy.

Résumé. Le traitement de chats par la 6-hydroxydopamine (6-HO-DA) provoque une dégénérescence sélective et réversible des terminaisons nerveuses adrénergiques postganglionaires. Les terminaisons nerveuses cholinergiques ne sont pas affectées par ce traitement.

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