Mitochondria with signs of commencing myelinization were frequently seen 45 days after the operation (Fig. 1f). The lipid droplets formed aggregations and contained electron-translucent vacuoles (Fig. 1g). Changes in the blood vessels were less marked than earlier. Administration of glucose had no significant effect on the ultrastructure of the adrenal cortex of the experimental animals at the times studied.

In the modern view the mitochondria of the adrenal cortex play an active part in hormone synthesis [3]. Death of some of the mitochondria, and an increase in the number and vacuolation of the lipid droplets are morphological features reflecting lowered functional activity of the adrenocorticocytes of the zona fasciculata and zone reticularis of the adrenal cortex [2]. This suggests that after bilateral subdiaphragmatic vagotomy the secretory activity of the glandular cells of the zona fasciculata and zona reticularis of the adrenal cortex is inhibited.

The fact that the changes induced by vagotomy are similar in some of their manifestations with those observed by Demin [1] in the adrenal cortex after disturbance of its sympathetic innervation points to a nonspecific response to injury.

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INJURY TO PANETH'S CELLS IN RATS AFTER ADMINISTRATION OF DITHISONE AND 8-(ARENESULFONYLAMINO)QUINOLINES

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Injection of dithisone and 8-(arenesulfonylamino)quinolines into rats leads to selective injury to the zinc-rich Paneth's cells of the small intestine. The results confirm the possible role of zinc blocking in the development of cell degeneration.

KEY WORDS: *Paneth's cells; chelating agents; zinc.*

Administration of dithisone and 8-(arenesulfonylamino)quinolines causes selective damage to cells of the islets of Langerhans, which is explained by the high affinity of these chelating agents for zinc atoms contained in the insular tissue of the pancreas [1-4]. An analogous action of these agents on the Paneth's cells of the rat small intestine, which contain considerable amounts of zinc, may also be postulated.

The object of this investigation was to study the general mechanisms of the cytopathogenic action of chelating agents.

EXPERIMENTAL METHOD

Dithisone, 8-(p-toluenesulfonylamino)quinoline (8TSQ), and 8-(benzenesulfonylamino)-quinoline (8BSQ) were injected intraperitoneally and intravenously into 350 rats in doses of 10 to 100 mg/kg. Dithisone was injected as a 1% solution in 0.5% ammonia solution and

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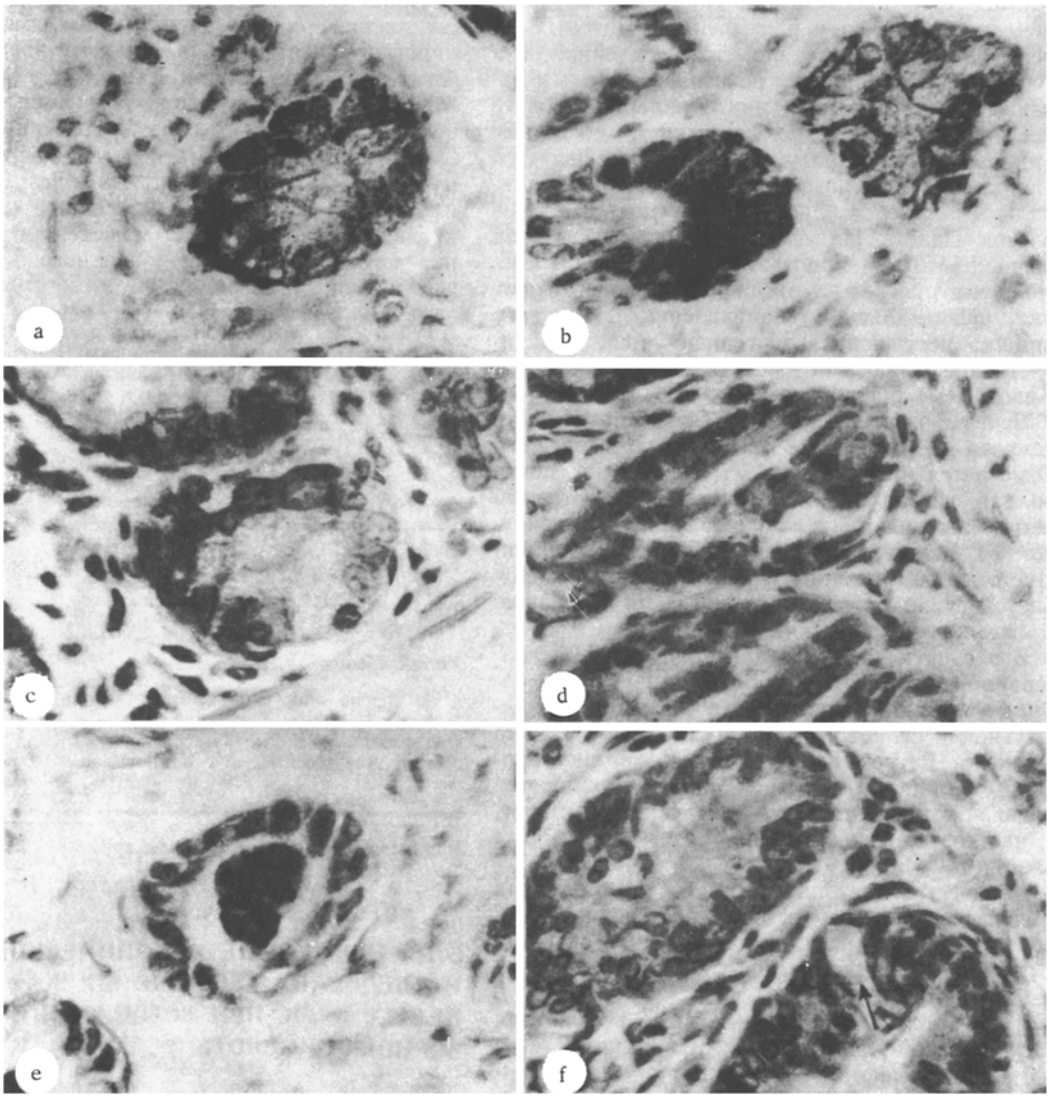

Fig. 1. State of the Paneth's cells in rats after receiving dithisone: a) basal part of crypts of intact rats, consisting chiefly of Paneth's cells (stained by Brachet's method); b) increase in pyroninophilia of individual Paneth's cells after injection of dithisone; c) terminal parts of crypts of intact rats consisting mainly of Paneth's cells, with specific granules visible in the cell cytoplasm (hematoxylin-eosin); d) desquamation of a conglomeration of Paneth's cells in an experimental rat, pycnosis of nuclei and degranulation of cytoplasm of cells (hematoxylin—eosin); e) marked pyroninophilia of cell debris in lumen of crypts of rat receiving dithisone; f) a single degranulated Paneth's cell is visible in basal part of crypts (arrow) of experimental rats (hematoxylin—eosin). 900×.

8TSQ and 8BSQ as a 0.5% solution in 0.1 N NaOH. The animals were killed 10 min, 2 and 8 h, and 1-15 days after injection of the compounds. Pieces of the ileum were fixed by Kopsch's method and in absolute alcohol. Paraffin sections 5 μ thick were stained with hematoxylin—eosin, with solutions of bromphenol blue in mercury chloride and water, and also by Brachet's and Feulgen's methods.

EXPERIMENTAL RESULTS

A decrease in the number of oxyphilic and protein granules in the Paneth's cells was observed 10 min after injection of dithisone. The size and shape of the granules, which are relatively constant in intact animals, varied considerably in the experimental animals. Some granules resembled fine dust, others large vesicles. In shape they were circular,

quadralateral, rod-shaped, and polygonal. An increase in the pyroninophilia of some Paneth's cells was observed, whereas their DNA content was substantially unchanged (Fig. 1a, b).

The destructive and degenerative changes in the Paneth's cells were more marked still 2 h after the injection. The content of the two types of granules was proportionately reduced. A few granules were usually grouped around the lumen of the crypts. Besides enlarged granules, some granules were scattered like dust. The pyroninophilia remained increased but the DNA content in general was unchanged, although there was an increase in the staining properties of some nuclei which were in a state of pycnosis. A characteristic feature of this stage was the desquamation of single or whole conglomerations of Paneth's cell into the lumen of the apical parts of the crypts. Empty spaces were seen at the site of the desquamated cells and the crypts appeared eroded and their lumen was dilated. The cell debris, moving toward the lumen of the intestine, gradually became homogenized, lost its oxyphilia, and stained strongly by Brachet's method (Fig. 1c, d).

The signs of necrosis of the Paneth's cells reached their maximum 8 h after injection of dithisone. Pycnosis, rhexis, and lysis of the nuclei were observed, with almost total degranulation of the cytoplasm. The cell debris could be seen in the lumen of the crypts (Fig. 1e), between the villi, and in the lumen of the intestine. The empty spaces formed at the site of the desquamated Paneth's cells disappeared as a result of the drawing together of adjacent intact cells.

In the subsequent stages the signs of cellular degeneration diminished. The debris was eliminated with the intestinal contents. The total content of oxyphilic and protein granules in the Paneth's cells was reduced. Some cells were completely degranulated (Fig. 1f). Signs of compensation appeared, as shown in particular by hypertrophy of the nuclei of some cells.

The number of Paneth's cells and their content of specific granules gradually increased but did not reach their initial level. Mitoses were frequently found in the basal parts of the crypts.

The mean number of Paneth's cells counted in the terminal part of each crypt of the intact control rats was 4.6. The number of these cells 24 h after intraperitoneal injection of dithisone (100 mg/kg) fell to 0.9, rising to 1.8 after 5 days. After intravenous injection of the same dose of the compound the changes were less marked: The number of cells was 1.4 after 24 h and 2.2 after 5 days. With a dose of 50 mg/kg of dithisone, lesions appeared only in some of the crypts, and by the end of the period of observation the crypts were almost completely restored. Injection of 20 mg/kg of dithisone caused only slight and reversible changes in the basal parts of the crypts. The effects of 8TSQ and 8BSQ were less severe than those of dithisone. After injection of all the chelating agents tested in a dose of 10 mg/kg no appreciable changes were found in the small intestine of the rats.

Injection of dithisone and compounds of the 8-(arenesulfonylamino)quinoline series into rats thus leads to selective damage of the zinc-rich Paneth's cells of the small intestine. The degree of degeneration depends on the complex-forming strength and the dose and mode of injection of the chelating agent. The results confirm the possible role of zinc blocking in the onset of the cellular degeneration. The method of blocking Paneth's cells described above may prove useful during the study of their functional role and the mechanisms of their regeneration.

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