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CHANGES IN THE MICROCIRCULATORY SYSTEM IN THE PAIN SYNDROME OF SPINAL ORIGIN

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Pathological pain leads to severe autonomic disturbances affecting the sympathico-adrenal system [1, 3-5, 8, 9]. Clinical and experimental studies have shown that in trigeminal neuralgia, facial pains of cervical genesis [3], reticulitis [1], and migraine [12] disturbances of the hemostasis system are observed. However, the state of the microcirculatory system has not been studied in central pain syndromes caused by the appearance of a generator of pathologically enhanced excitation (GPEE) in certain parts of the nociceptive system [8]. This paper is devoted to an explanation of this phenomenon.

EXPERIMENTAL METHOD

Experiments were carried out on 30 male Wistar rats weighing 200-250 g, divided into three groups (10 animals in each group): 1) control animals, 2) animals with a pain syndrome of spinal origin (PSSO), and 3) animals undergoing a mock operation.

A PSSO was induced in rats by the formation of a GPEE in the posterior horns of the lumbar division of the spinal cord by application of an agar wafer (1.5 × 3 × 6 mm) containing penicillin in a dose of 7.5 U/mm^3 [7]. Various substances which disturb inhibitory mechanisms in a neuron population or induce neuron depolarization are used nowadays to produce models of central pain syndromes based on the formation of a GPEE. The use of penicillin for this purpose is based on the fact that, as an antagonist of the inhibitory mediator GABA, it disturbs inhibition. Penicillin also acts directly on neuronal membranes by blocking chloride channels or reducing the transmembrane Cl^- gradient [10, 11].

Six components of PSSO (vocalization, general motor response, frequency of attacks, duration of attacks, local response, response to a stimulus) were evaluated on a 3-point

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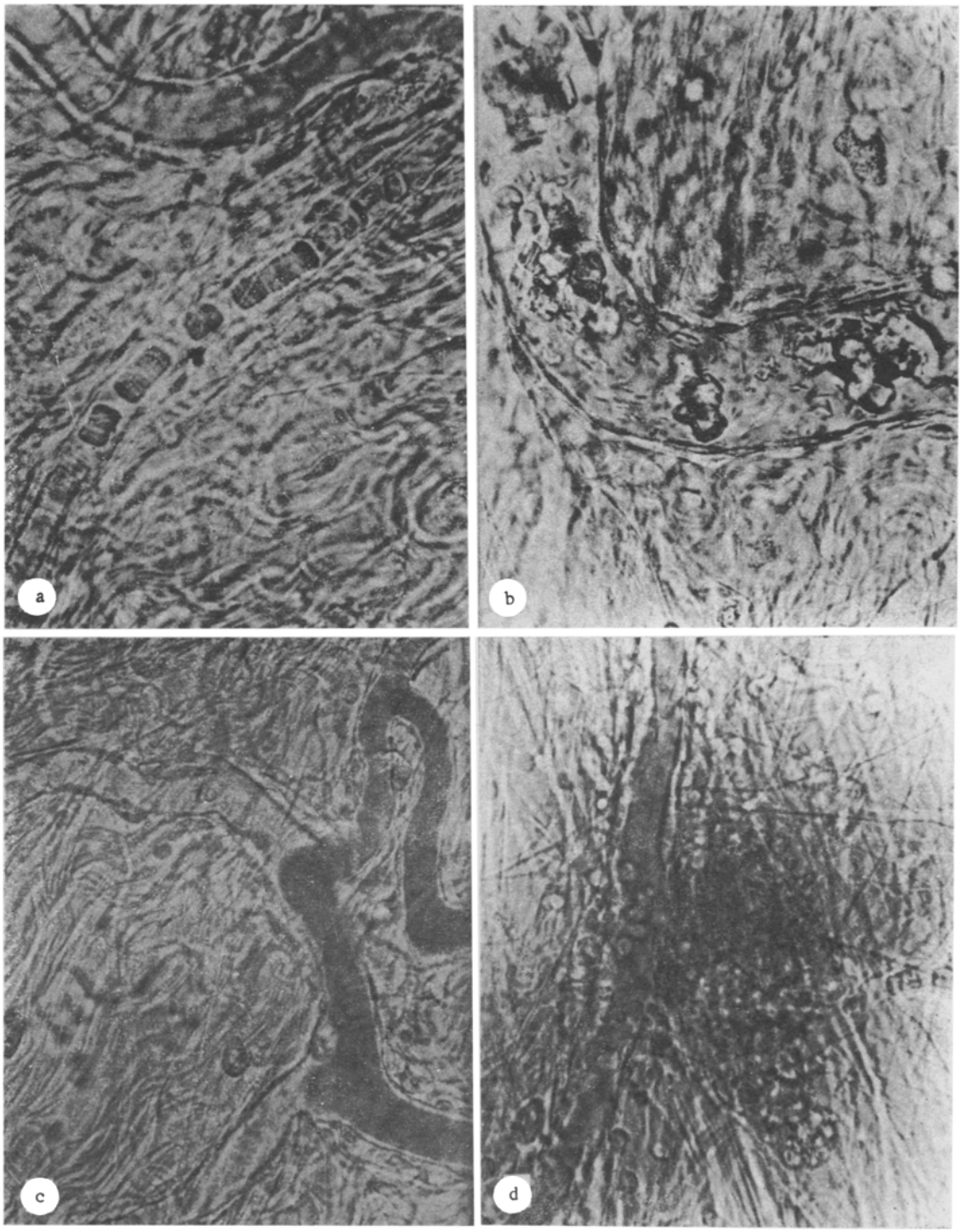
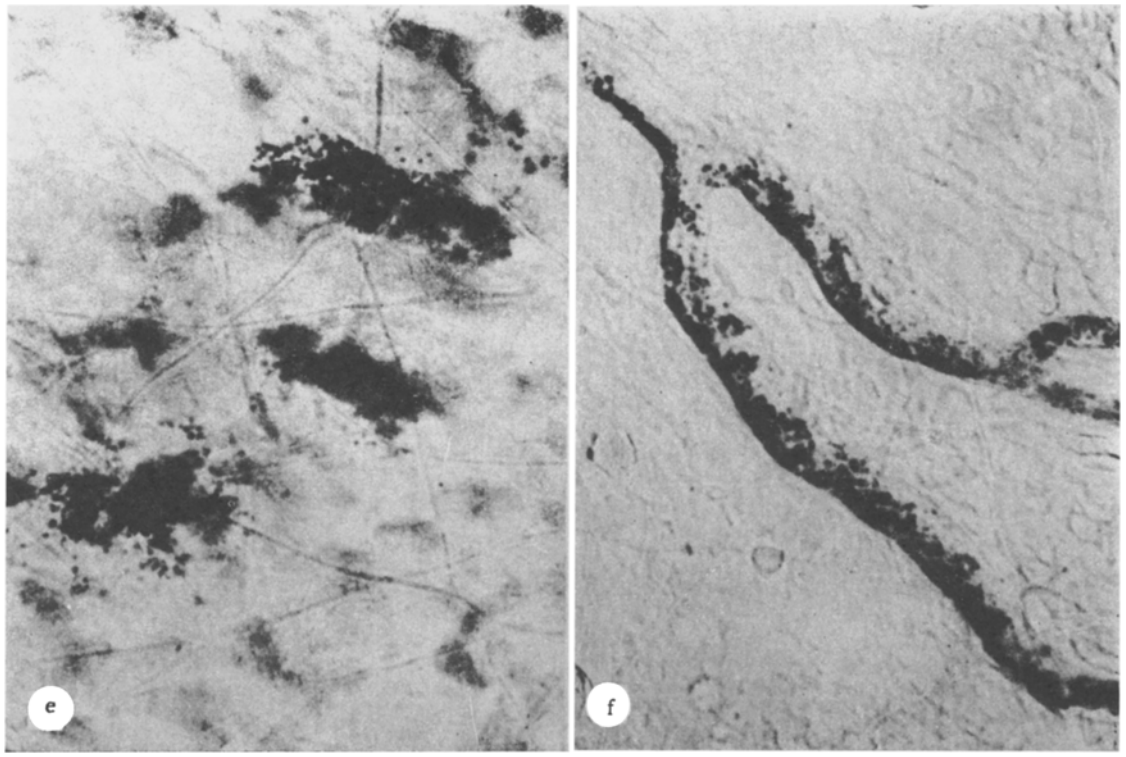


Fig. 1. Disturbances of the microcirculatory system in a PSSO. a) Aggregation of erythrocytes with "rouleaux" formation; b) aggregation of erythrocytes in a venule 60 μ in diameter; c) plasmatization of venule; d) extravasation of erythrocytes around the venule; e) preparation of mesentery: degranulation of mast cells; f) preparation of mesentery: deposition of colloidal carbon particles in wall of venule. a-d) Biomicroscopy of rat mesentery. 1890 ×; e) stained with toluidine blue, 225 ×; f) 180 ×. [Figure 1 continued on next page.]

scale. The state of the blood microcirculation was studied at the stage of maximal development of PSSO, namely 40-80 min after application of the agar wafer. The microcirculation in the mesentery of rats anesthetized with pentobarbital was studied under a biomicroscope with the aid of a system based on the "Docuval" microscope [2]. The morphological and functional state of the mast cells was assessed after fixation of an area of mesentery placed on the



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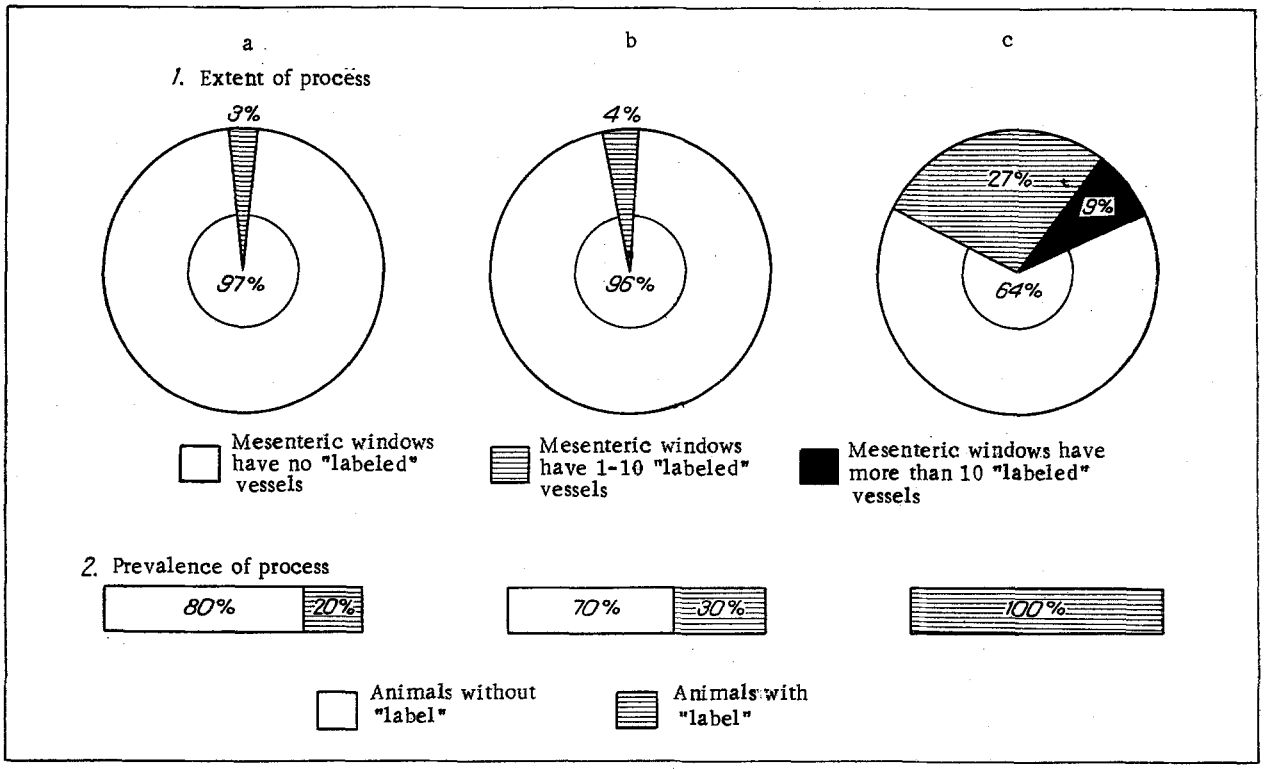

Fig. 2. Permeability of venules of mesenteric microcirculation of a rat with PSSO: a) control, b) mock operation, c) PSSO.

TABLE 1. Symptoms of Microcirculatory Disturbances in Rats with PSSO (n = 10)

Group of animals	Scale of microcirculatory disturbances (number of cases in % of total number of animals in series)							
	slowing of blood flow		aggregation of erythrocytes		"plasmatic" vessels	pavementing of leukocytes in venules	extravasation	stasis
	venules	arterioles	capillaries	venules				
1 (control)	20	0	0	10	0	40	0	0
2 (pain syndrome)	100*	10	70*	60*	80*	80*	20	80*
3 (mock operation)	20**	0	0**	10**	10**	40**	0	0**

Legend. *$p < 0.5$ Compared with group 1, **$p < 0.05$ compared with group 2.

light guide with alcohol and subsequent staining with 0.5% toluidine blue. Permeability of the venules of the mesentery was studied by the "labeled vessels" method [2].

EXPERIMENTAL RESULTS

In all the rats of group 2, after application of penicillin to the right half of the dorsal surface of the lumbar division of the spinal cord a PSSO developed with its characteristic features. The animals became restless 10-15 min after application. In the initial stage of the syndrome not all components of the PSSO were manifested to the same degree: in some rats the attack was accompanied by vocalization, in others by an intensive motor response in the form of licking and grooming the surface of the thigh, leg, and toes of the right hind limb. With the course of time the frequency and duration of the attacks increased, and between episodes many of the rats held their paw suspended in the flexed position. Usually the stage of maximal development of PSSO occurred after 20-30 min and it lasted 60-90 min after penicillin application, all parameters of the syndrome scoring 3 points. In the rats of group 3, no changes in nociceptive sensitivity were found after application of the agar wafer without penicillin.

The biomicroscopic study showed the presence of severe microcirculatory disturbances in the mesentery of rats with PSSO at the stage of its maximal development (Table 1). Slowing of the blood flow in venules 20-40 μ in diameter, in some cases slowing of the blood flow in arterioles 15-40 μ in diameter, aggregation of erythrocytes in the capillaries with "rouleaux" formation (Fig. 1a), the appearance of large aggregates of erythrocytes in the venules (Fig. 1b), and pavementing of leukocytes were observed. Much of the terminal vascular bed was excluded from the blood flow by plasmatization (Fig. 1c) and stasis. In 20% of the rats studied extravasation of erythrocytes was observed around the venules (Fig. 1d), evidence that the resistance of the walls of the venules was disturbed.

Comparison of the state of the microcirculation in animals of the three groups (Table 1) showed significant worsening in rats with a PSSO compared with animals undergoing the mock operation and with the control.

The mock operation and PSSO led to an increase in the number of contractions of lymphatic microvessels 150-200 μ in diameter compared with the control. For instance, in rats with PSSO the number was 7.3 ± 0.3 contractions/min, compared with 5.8 ± 0.3 in rats undergoing the mock operation and 3.0 ± 0.7 in the control rats ($p_{1-2} = 0.013$, $p_{1-3} < 0.001$, $p_{2-3} = 0.04$).

In the animals with a developed PSSO degranulation of the mast cells was increased up to 9.2 ± 0.9% (Fig. 1e), compared with 2.2 ± 0.2% both in rats undergoing the mock operation and in the control.

The increase in number of degranulated mast cells in rats with PSSO was combined with increased permeability of the venules for colloidal carbon particles (Fig. 1f; Fig. 2).

A similar pattern of microcirculatory disturbances, disturbances of vascular permeability, and increased secretory activity of the mast cells, was observed in the mesentery and other organs of animals of various species during severe emotional-painful stress [2]. Microcirculatory changes, expressed as growth dilatation of capillaries, enlargement of lymph nodes diapedetic bleeding, hemorrhages into the lumen of the bronchi, accumulation of leukocytes in the neighborhood of the venules, the formation of endothelial vesicles, separating into the capillary lumen, destruction of cytoplasmic membranes, and vesiculation and

fragmentation of erythrocytes have been found in the lung tissue of rats and mice when mechanisms of inhibition in the CNS were disturbed by the action of tetanus toxin [6].

The trigger mechanism of the microcirculatory disturbances mentioned above is evidently increased secretion of catecholamines, causing constriction of afferent arterioles, tissue ischemia, and a disturbance of local homeostasis.

It was shown previously [5] that catecholamine hypersecretion of this kind is observed in rats with PSSO caused by the creation of a GPEE in the posterior horns of the spinal cord by means of tetanus toxin. In the period of development of the PSSO, moreover, there was a marked increase in activity of the sympathicoadrenal system, manifested as an increase in catecholamine concentrations in heart tissues, the adrenalin concentration in the hypothalamic region and a comparatively small decrease in catecholamine concentrations in the adrenals. In the late stages of this severe pain syndrome, which caused death of the animals, there was a marked fall in levels of adrenalin, noradrenalin, and dopa in the heart and adrenals, evidence of exhaustion of the sympathicoadrenal systems at these stages of development of the process.

It can be tentatively suggested that microcirculatory changes discovered in association with an experimental PSSO are caused by activation of the catecholaminergic system in the period of maximal development of pathological pain.

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