The level of noradrenaline in terminals and varicosities after the ligation performed in the sympathetic ground-plexus

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Summary. It is well-known that the ligation of nerve trunk induces an intensive accumulation of noradrenaline proximally to the ligation. A similar ligation, performed in the sympathetic ground-plexus, induces no changes in the segments of terminal fibres situated proximally.

It is well-known that noradrenaline, which is transported through axons from the pericaryon into the terminals, accumulates intensively above the ligation in the postganglionic sympathetic fibres of the nerve trunk[1–3]. The histochemical fluorescence method for visualization of noradrenaline identifies this accumulation as soon as 15 min after the ligation. Thick intensively fluorescent confluent formations appear in this area. Under normal conditions, on the other hand, no fluorescence appears in the sympathetic fibres situated in the trunks. In the sympathetic ground-plexus formed by the preterminal and terminal parts of the neuron, the noradrenaline level proves high enough to be visualized. The most intensive fluorescence appears in the varicosities, organells with a complicated mechanism stabilizing the level of the transmitter[4]. It is the level of noradrenaline after ligation in this area, that is the object of this report.

In 7 rabbits, 2 ligations were performed over the left side ankle-joint, one compressing the saphenous nerve, the other compressing the saphenous artery. Both compressions were performed with identical force. The saphenous artery was used because of its dense monoaminergic innervation distributed mainly within the adventitia as described by Doležel et al.[5] and Bevan and Purdy[6]. In order to preserve the blood flow in the proximal part of the artery for preventing trombosis and ischaemic lesions within the examined area, the arterial ligature was situated immediately under the collateral branch. The intact contralateral nerve and the artery were used as controls. After a ligation of 1–6 h, the nerves and arteries were excised, quenched in propan-butan mixture at the temperature of –170 °C, lyophylized for 7 days and condensed with formaldehyde gas at proper humidity according to Falck and Owman[7].

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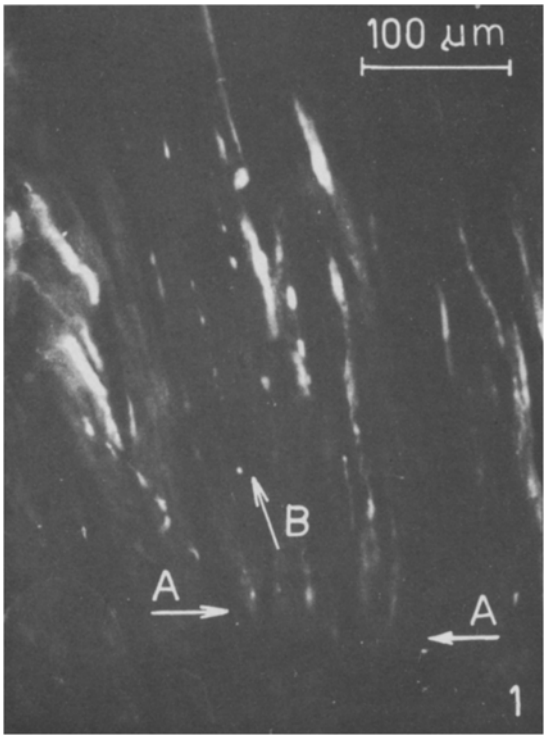

Fig. 1. Proximal part of the ligated saphenous nerve, longitudinal section, 4 h after the ligation. Note the noradrenergic swollen fibres above the ligation. *A* Ligature, *B* proximal direction.

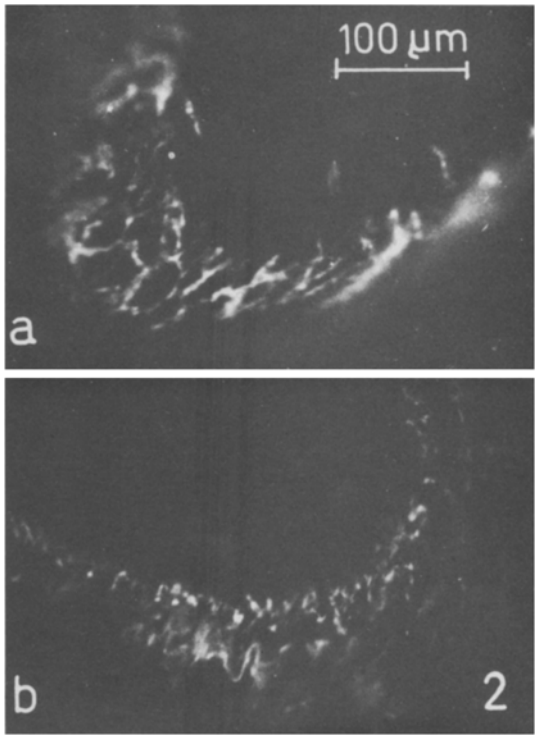

Fig. 2. Oblique section of the ligated saphenous arteries above the ligature. The appearence of the sympathetic ground-plexus the thickness of terminals, as well as the intensity of fluorescence, is identical in both arteries. *a* 1 h after the ligation, *b* 4 h after the ligation.

In accordance with the findings of Dahlström[2], the ligated proximal stump of the saphenous nerve revealed an accumulation of the noradrenaline transmitter accompanied by the thickening of the nerve fibres and by fluorescence (see figure 1), the intensity of which depended on the time of ligation. Besides weak background fluorescence, no accumulation of specific fluorescent material appeared in the contralateral normal saphenous nerve. The ligated arteries revealed the fluorescent sympathetic ground-plexus distributed in the deep adventitia between the elastic lamellae. Several fibres running between the muscle cells of the superficial media were found as well[5,6]. A normal shape and a normal degree of the intensity of fluorescence characterized the terminal ground-plexus, as visible in figure 2. No differences could be detected between the ligated and the normal contralateral artery.

In consequence, the mechanism of the varicosities performing the release, uptake, storage, synthesis and degradation of noradrenaline[4] reveals a system which stabilizes the intraneuronal level of noradrenaline. This stabilization is perfect and cannot even be destroyed by long-lasting ligation.

Vascular permeability in malignant disease

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Summary. Experimental demonstration that vessels draining large tumours are impermeable to cellular elements. Thus the pulmonary vessels of animals bearing large, primary (other than gastro-intestinal) cancers can become impermeable to tumour emboli. This imperviousness prevents the establishment of secondaries in the lung and promotes the transpulmonary passage of tumor cells. This phenomenon may account for the development of paradoxical metastases.

Tumour vessels have been shown to be permeable to humoral agents but impermeable to cellular elements. This selective permeability has been attributed to the presence of tumour-associated, macrophage-repellent alpha, 2, macroglobulin on the intima of tumour vessels[1]. The present study extends this observation and shows that, under certain conditions, vessels draining large tumours are equally impervious to cellular elements, including tumour cells.

Materials and methods. White Wistar outbred rats weighing 180 g were obtained from the Hebrew University Animal Breeding Station, Jerusalem. 2 tumour lines were used. The 1st was a spontaneous glioma obtained from the Weizman Institute of Science, Rehovoth; the 2nd was an induced prostatic tumour. Both were maintained by serial passage. Tumour suspensions were prepared by mincing 1 vol. for tumour in 1 vol. of saline and passing it through a metal sieve. Amounts of 0.5 ml of this suspension were injected i.m. or i.p. For i.v. administration, a standard suspension was allowed to stand for 10 min at room temperature for the large fragments to settle to the bottom of the tube. The supernatant was aspirated via a tuberculin needle and injected in amounts of 0.25 ml into the femoral vein.

Tumours were injected into the thigh muscles and the animal challenged 5 or 11 days later with i.v. or i.v. and i.p. tumour.

The alpha, 2, macroglobulin synthesis inhibitor chloramphenicol[2] (Synthomycetine Succinate Abic, Ramat Gan) was administered in doses of 100 mg by i.m. injection on the day of and on the day following i.p. tumour inoculation. Tissues for histological examination were fixed in formol saline and stained with haematoxylin eosin.

Results. The tumours infused into the femoral vein of animals with a 5-day thigh tumour, took and grew in the lung in the same way as in the controls. However, i.v. tumour challenge of animals carrying an 11-day thigh tumour yielded few, and if any, very small, lung tumours (table). At the same time, there was no impairment of i.p. tumour growth in the experimental group.

An 8-day i,p, tumour usually presented as a lump of no more than 1.0 g on the omentum with an occasional small nodule on the mesentery. In animals receiving chloramphenicol simultaneously with i.p. tumour, there was a special pattern of tumour growth. Tumour nodules, all of equal size, appeared along the path of mesenteric vasculature (figure 1). Histological examination of such a vessel showed margination and transmigration of numerous tumour cells across the vessel wall (figure 2).

Discussion. The absence of pulmonary deposits in animals with large thigh tumours cannot be attributed to a cell mediated immunodestruction of pulmonary tumour emboli, for the following reasons: Large tumours abrogate, rather than enhance, cellular immunity[3]. There is no

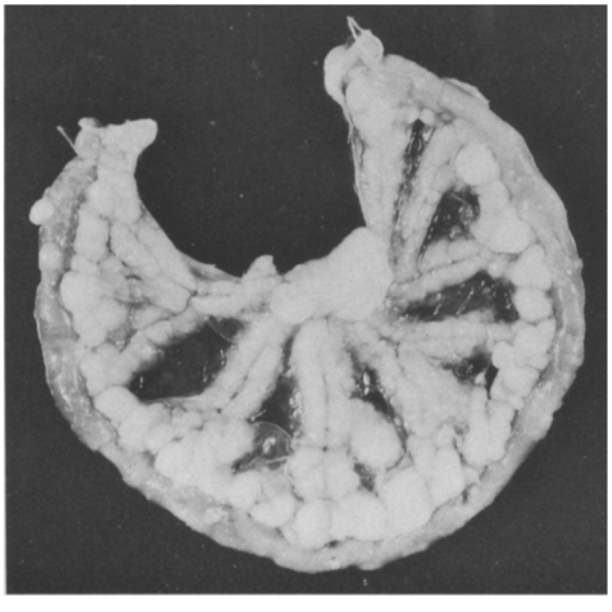

Fig. 1. Abdomen 8 days after i.p. inoculation of tumour suspension and i.m. administration of chloramphenicol. Tumour nodules of equal size distributed along mesenteric vascular channels.

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