In light of recent evidence from several laboratories, two hypotheses have evolved concerning the possible function of the Type I cells of the carotid and aortic bodies. One of these hypotheses, proposed by OSBORNE and BUTLER[11], states that the Type I cell is the chemosensor. They propose that afferent nerve fibers are spontaneously active, but under normal conditions the frequency of their discharge is tonically supressed by transmitter release from the Type I cell. However, during hypoxia, this inhibition by the glomus cell is reduced by afferent fibers synapsing on the Type I cell, thereby decreasing its secretion and permitting an increased discharge frequency of the afferent fibers. The other hypothesis, proposed by MCDONALD and MITCHELL[10], states that the Type I cells are not the actual receptors. The Type I cell, according to this hypothesis, has a function similar to an interneuron-like cell which secrets an amine, probably dopamine, that modulates sensory nerve endings. The afferent nerve endings are thought to be the chemoreceptors while the Type I cells, through reciprocal synapses, modulate afferent endings forming an inhibitory feedback loop. Indeed, the Type I cells of the aortic and carotid bodies have many morphological characteristics in common with interneuron-like cells[12,13].

In addition to the known chemoreceptor function of the aortic and carotid bodies, these glomera may also be endocrine organs. Striking morphological and cytochemical similarities exist between the Type I cells and polypeptide hormone-producing cells of the APUD (amine precursor uptake and decarboxylase) series of endocrine cells[4,14,15]. Ultimately, the Type I cell may be shown to possess multiple functions. The heterogeneous distribution of vesicle profile diameters observed in this study may indicate the storage of different biogenic amines, different secretion or maturation states within the glomus and/or a multiplicity of physiologic functions for the Type I cells, perhaps as chemoreceptors and endocrine cells.

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The permeability of tumour vessels

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Summary. Experimental proof that tumour vessels are permeable to humoral agents but impermeable to cellular elements viz. leucocytes. The cause of this impermeability is believed to be the deposition of immunosuppressive alpha globulin on the walls of tumour vessels. This concept is of relevance in organ transplantation and cancer immunotherapy.

Vascular damage and lymphocytic infiltration are the events which lead to the rejection of organ allografts[1]. These reactions do not occur in tumour transplants. Tumour vessels are host's and therefore immunologically inert[2]. Lymphocytic infiltration in and around tumour is scant[3,4].

Autologuous lymphocytes kill tumour target cells in vitro but generally fail to invade and to kill such tumours in vivo[5]. A tumour-bearing animal can mount a foreign body reaction in its normal but not in its tumorous tissue[6]. – It would appear, therefore, that lymphocytes are unable to traverse the wall of tumour vessels. – The purpose of the present investigation is to study the properties of tumour vessels with special reference to their cellular permeability.

Materials and methods. White Wistar outbred rats, young females of 160–180 g and female weanlings of 80–100 g, were obtained from the Hebrew University Animal Breeding Station, Jerusalem. – The tumour, originally a spontaneus glioma obtained from the Weiz-

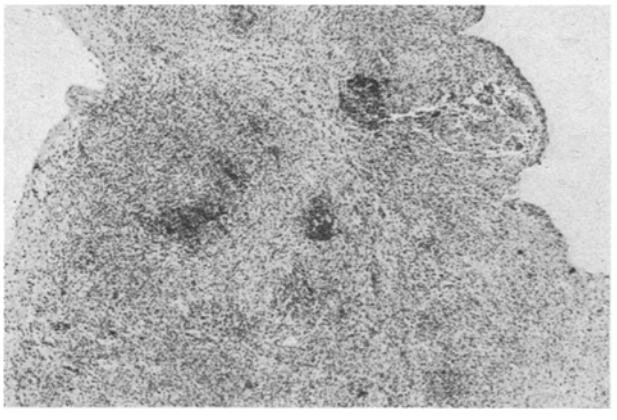

Fig. 1. Ovary 10 days after s.c. implantation. Dense lymphocytic infiltration and loss of structure. HE × 60.

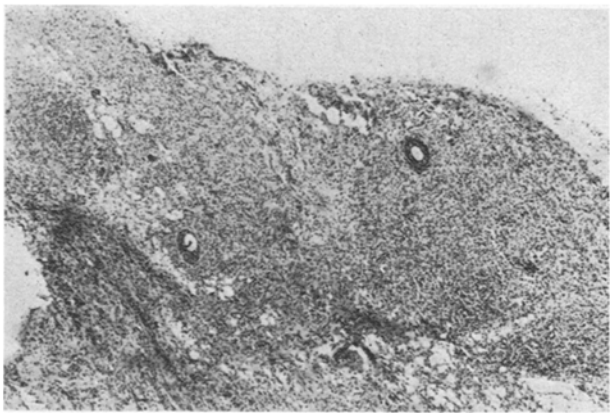

Fig. 3. Autologous ovary of ovarian graft recipient (Figures 1 and 2). Immature ovary. HE × 60.

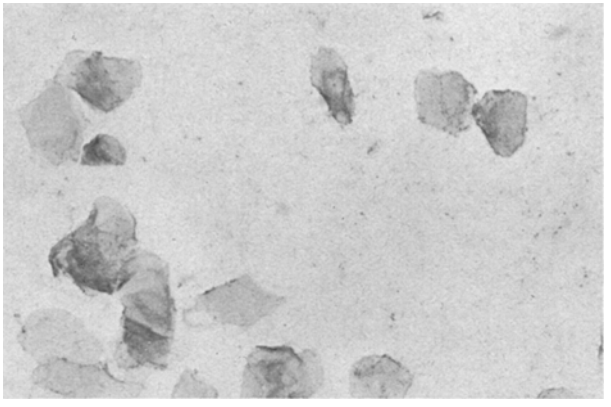

Fig. 4. Vaginal smear of weanling female rat with immature ovary, 10 days after s.c. and i.t. ovarian grafts (Figures 1–3). Estrus smear. Papanicolaou stain × 350.

man Institute of Science, Rehovoth, was maintained by serial passage. Tumour suspensions were prepared by mincing 1 volume of tumour with 1 volume of saline. Amounts of 0.3 ml of this suspension were injected subcutaneously (s.c.) into weanling rats. Average survival was between 2 and 3 weeks.

Ovaries were removed from young adult females and grafted under the skin or into a 7–10-day-old tumour of a weanling rat. These ovaries were removed 6–12 days after grafting and either regrafted s.c. into a second set of weanling rats or prepared for histological examination. The latter ovaries were fixed in formol saline and stained with haematoxylin eosin. Vaginal smears were prepared by Papanicolaou's method.

Results. Of 10 s.c. ovaries, 1 was intact after 4 days, 9 had become necrotic within 6–10 days after grafting (Figure 1). Eleven of 20 intratumoral (i.t.) grafts could not be retrieved as the centre of the tumour had become cystic or caseous. 9 ovaries were removed from the centre of solid tumours. These appeared to be morphologically and functionally intact 6–12 days after i.t. implantation. Histologically the ovaries presented a perfectly normal architecture. The blood vessels were filled with red and white blood corpuscles, but there was no margination of leucocytes, no endothelial damage, no diapedesis and no white cell infiltration in and around the i.t. graft. The graft was not invaded by tumour cells nor was there haematogenous dissemination of tumour within the graft (Figure 2).

3 animals received simultaneous s.c. and i.t. ovarian grafts from the same donor. The i.t. grafts were retained but the s.c. implants were rejected (Figures 1 and 2). The functional integrity of the ovaries was evidenced by the appearance of typical estrus smears in weanlings whose own ovaries were still immature (Figures 3 and 4). Ovaries which had survived for 10 days in an i.t. site were rejected when grafted under the skin of a secondary host.

Discussion. The foregoing results show that lymphoid cells destroy s.c. allografts within 6–10 days. They are, however, unable to line, damage or transmigrate a tumour vessel and so to attack a similar allograft at an i.t. site of the same recipient. Hormones produced by i.t. grafts are absorbed and exert their effect on the secondary sexual organs of the host. It is concluded that tumour vessels are permeable to humoral agents i.e. hormones, but impermeable to cells, viz. leucocytes. We wish to put forward the following hypothesis to account for this phenomenon:

Tumour produces an immunosuppressive alpha globulin[7]. This peptide has a negative chemotactic effect on leucocytes[8] and paralyses the migration of macro-

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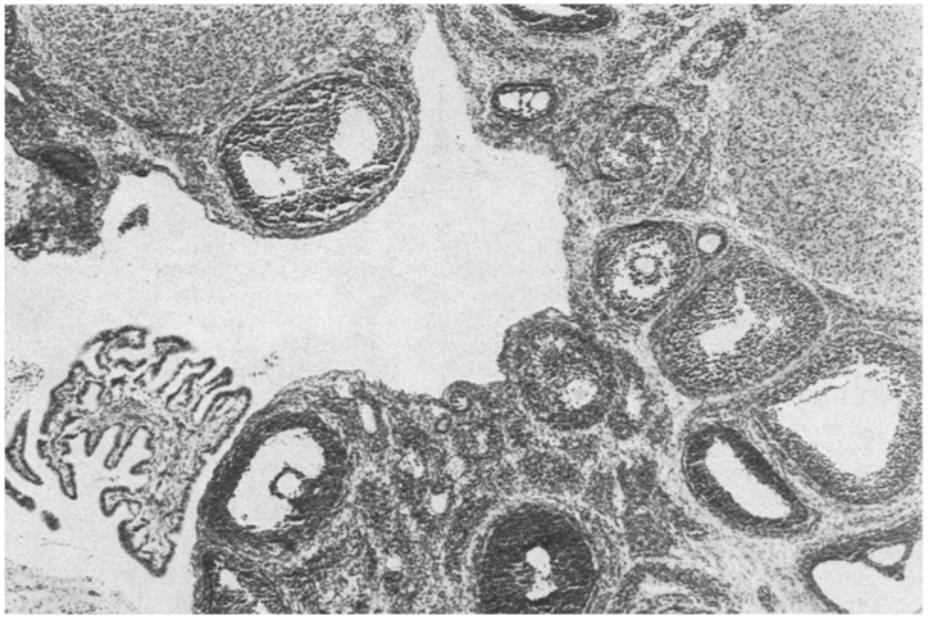

Fig. 2. Ovary 10 days after it implantation. Same recipient as for ovary in Figure 1. Normal architecture. HE × 60.

phages[9]. It is related to the smooth muscle antibody which appears in malignant disease[10]. The immunosuppressive globulin produced by tumour is absorbed via the tumour capillaries into the tumour vasculature. It binds to the smooth muscle fibres in its path, i.e. to the muscle fibres of the post-capillary venules. Thus tumour vessels, or graft vessels that have formed anastomoses with tumour vasculature, become coated with 'macrophage repellent' globulin. The presence of this peptide in the vessel wall effectively blocks diapedesis.

In the case of widespread tumour, there are large amounts of alpha globulin in the circulation[11]. These bind to vessel walls other than tumour walls. Serum globulins also coat circulating monocytes and abrogate their cytotoxicity[12].

Hence the non-specific generalized anergy in patients with advanced cancer[13]. Hence also the reversal of such anergy after extirpation of tumour[14], after washing of leucocytes[15] or after infusion of streptokinase[16] – an enzyme which specifically cleaves alpha globulin[17].

Re-implantation of an i.t. ovary into a non-malignant environment restores its vulnerability to immune attack as the alpha globulin required to coat the vessel wall is no longer available. This concept suggests a new approach to problems of organ transplantation or cancer immunotherapy.

Organ transplantation: Perfusion of the donor organ with immunosuppressive macroglobulin before and after grafting[18].

Cancer immunotherapy: Removal of alphaglobulin from the vessel wall and from the blood stream by the following means: a) Eradication of the source of macroglobulin, i.e. extirpation of accessible tumour[11]; b) Prevention of neoformation of this peptide by specific inhibitors[19] and c) Digestion of globulins already formed[16].

It is perhaps only then that conventional immunotherapy can become fully effective.

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Ultrastructural study of vanadocytes in Ascidia malaca[1]

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Summary. The ultrastructural aspects of vanadocytes, found in the circulating blood of Ascidia malaca, were studied in formaline-fixed material. The results indicate that the diverse morphological aspects of 'vanadophores' reported here, are probably concerned with different metabolic stages of vanadine.

In the blood of tunicates, vanadium is found in certain particularly acidic cells, called vanadocytes[2]. Fine structural study of such cells in Ciona intestinalis revealed the presence of certain cytoplasmic areas with special electron absorbance faculty[3]. This type of absorbance, observed also in Phallusia mammillata, is found in both osmium-fixed and formalin-fixed material[4]. On the basis of such observations, it was suggested that this particular type of electron absorbance in some cytoplasmic areas is due to the accumulation of vanadium. These areas have been termed 'Vanadophores'. In the present work Ascidia malaca vanadocytes were subjected to an ultrastructural study to obtain a better understanding of certain morphofunctional aspects of the 'vanadium-filled' cytoplasmic areas.

The blood of Ascidia malaca, collected through a puncture in the heart, was centrifuged at 800 × g for 10 min. The sediment, containing cells, was fixed in 10% neutral formaline prepared in filtered sea water. This type of fixation was preferred to that in OsO_4, since this is reduced in the cells containing hemovanadine (trivalent vanadium) rendering the vanadophores highly electron-dense. Osmium-fixed material is, furthermore, not suitable, because OsO_4 increases the consistency of vanadophores and thus hinders in the penetration of resin. The blood cell pellets, obtained as above and fixed in neutral formaline, were dehydrated and included in Epon according to the method of Luft[5]. Sections, obtained on L.K.B. Ultrotome III, were stained with lead citrate and uranil acetate and then studied at the electron microscope Philips EM 200.

The vanadocytes of Ascidia malaca (4–6 μm in diameter), stained as above, contain highly electron dense cytoplasmic inclusions of 1.5 μm, around the nucleus (figure 1). Similar electron dense cytoplasmic areas can be observed also in unstained sections, although less intense than those of stained preparations (figure 2). On the basis of these observations the electron-dense cytoplasmic areas in the blood cells of Ascidia malaca can be con-

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