Discussion. The foregoing results confirm that there is no white cell reaction in and around established tumour but that serum factors do not affect lymphoid cell cytotoxicity. However, such cytotoxicity is only effective when lymphoid cells and tumour target cells are brought into close contact as in the millipore experiment.

The concept of a non-specific 'lymphocyte migration paralyzing agent' produced by tumour would explain various phenomena observed in a tumour bearing host. As the tumour grows, there is increasing production of this agent and this would account for: the initial development[7] and subsequent loss[8] of concomitant immunity, the immunological stimulation, followed by immunological paralysis in the nodes draining the tumour[9,10], the evolution of generalized, non-specific allergy[11] and the inhibition of tumour by any (non specific) measure which promotes the infiltration of lymphocytes into tumour tissue[12,13]. All these are independent of serum factors viz. specific antibody.

Non-malignant homografts e.g. organ transplants equally induce humoral and cellular immunity – but fail to secrete paralyzing agent, hence the progressive monocytic infiltration which leads to the rejection of the graft[14].

As to the nature of the paralyzing agent produced by tumour, it is conceivable that it is an enzyme which inactivates prostaglandin. The prostaglandins are ubiquitous tissue hormones which participate in inflammatory[15] and allergic[16] reactions, promote the diapedesis[17] and migration[18] of leucocytes and enhance the cell mediated immune response[19].

The inactivation of prostaglandin by tumour would account for the (cell mediated) immunological unresponsiveness in the tumour bearing host[20].

Zusammenfassung. Experimenteller Nachweis, dass fortschreitendes Tumorwachstum nicht Serumfaktoren (Antikörpern) zuzuschreiben ist, sondern offenbar geschwulsteigenen Substanzen mit Lokomotionshemmung der Leukozyten.

RACHEL STEIN-WERBLOWSKY[21]

The Royal Veterinary College, London, N.W. 1 (England), 24 September 1973.

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[21] Present address: 15 Green Walk, London, N.W. 42AL, (England).

Skeletal Muscle and Tumour Metastasis

Muscle can undergo sarcomatous changes. It is an immunologically privileged tissue which can accept malignant and non-malignant homografts[1]. There are no mechanical factors to impair the haematogenous dissemination of tumour emboli into skeletal muscle[2].

It would therefore appear that neither the 'soil'[3] nor the 'haemodynamic'[4] hypotheses could offer an adequate explanation for the paucity of blood borne metastases in voluntary muscle. In the present communication a third hypothesis to account for this phenomenon, is put forward.

Materials and methods. Animals and tumours were used as in the previous communication.

Preparation and administration of tumour suspension. 1 volume of tumour was suspended in 2 volumes of saline and homogenized in a MSE homogenizer at 10,000 rpm for 90 sec. 4 groups of 10 rats received an infusion of 0.3 ml of tumour suspension: group A into the left femoral artery, group B into the left thigh muscles, groups C and D into subcutaneous and intradermal sites respectively.

Method of immunization. Amounts of 0.5 ml of tumour suspension were injected into the right flank. After 10–12 days, when the tumour had reached a diameter of approximately 15 mm, it was excised. The animal was challenged with 0.4 ml of intradermal tumour 3 weeks after extirpation of the immunizing growth. Animals which rejected the challenging tumour were considered to be immune and were used for the second part of these experiments.

Histological methods. Skin biopsies taken at various intervals after tumour challenge and muscle biopsies, taken at day 2, 7 and 10 after i.m. tumour inoculation into immunized and non-immunized animals, were fixed in formol saline and stained with methyl green-pyronin.

Results. Tumour took in 8 out of 10 animals of group A. This intraarterial infusion gave rise to a diffuse tumour growth in the whole lower limb. The i.m. inoculum, which took in all recipients, was confined to 1 muscle group only. Cutaneous grafts also took in all animals and grew into round, ulcerating nodes. Similar experiments, repeated with immune recipients resulted in tumour rejection in all instances. However, the rejection mechanism varied in each group.

Intradermal and s.c. tumour caused a localized induration of no more than 10 mm in diameter which subsided after 4–6 days. Histologically there was an accumulation of leucocytes, including immunoblasts, in the affected area. Intraarterial infusion did not cause palpable thickening though the limb appeared to be tender for several days after the infusion.

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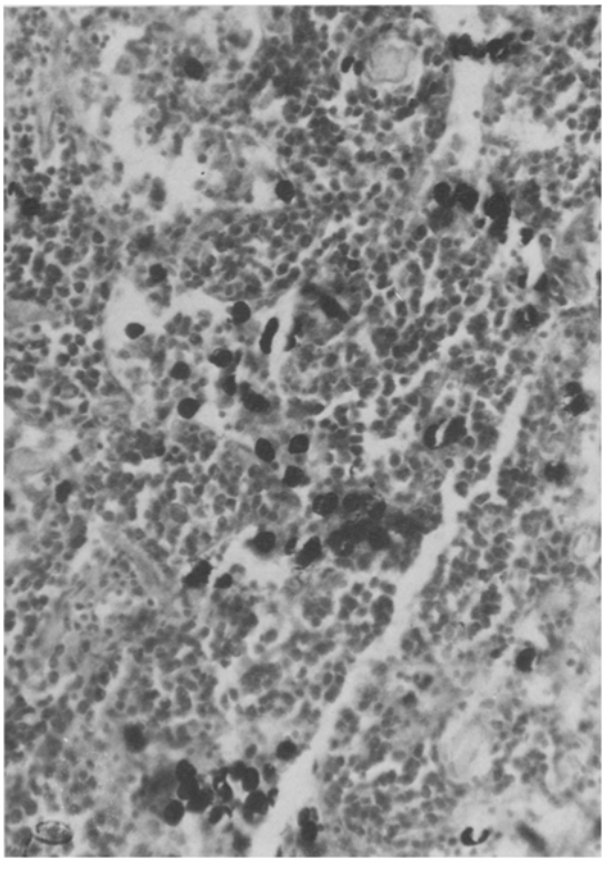
Intramuscular tumour challenge gave rise to a violent reaction in the thigh. The limb became warm and swelled to 2–3 × its original circumference. Histologically there was a massive infiltration of lymphoid cells, particularly of immunoblasts (Figure). This reaction lasted about 14 days.

Discussion. There is no correlation between the number of circulating tumour cells and the development of metastases[5]. Though the fate of the tumour cells which fail to implant is not known for certain, it is reasonable to assume that they are destroyed either in the vascular tree or in the tissues. In the latter instance, such destruction would occur as a result of a concomitant immune reaction manifesting itself in tissues capable of strong anamnestic reactions.



Leg muscle of immune rat, 2 days after tumour inoculation. The muscle is heavily infiltrated with lymphoid cells, particularly immunoblasts which stain dark red with pyronin and appear black on this photograph. Methyl green-pyronin. ×310.

As has been shown in the previous experiments – muscle produces a strong immune response. It is probable that tumour emboli are destroyed as soon as they extravasate from the muscle capillaries to elicit a (subclinical) hypersensitivity reaction.

Tissues which show little or no allergic response are frequently the site of secondary tumour spread e.g. bone or liver. Lung, which is capable of allergic reactions, can destroy large numbers of tumour cells since all haematogenous tumour emboli pass through this organ without necessarily setting up metastatic growth[5]. However, in the course of malignant disease, a point is reached where the capacity to mount an allergic response wanes (see previous communication) and when pulmonary tissue can no longer trap and inactivate large numbers of tumour cells.

Similar observations have been made with regard to other diseases. Metastatic tuberculosis can spread to bone e.g. spine but will not affect spinal muscle. Incidentally, this finding would also rule out circulatory factors to account for this selectivity. Syphilis involves practically all tissues except skeletal muscle. Viruses attack lung, liver, nervous tissue, skin, etc. but very rarely voluntary muscle though myalgia is a frequent accompaniment of viral disease.

It appears that there is an inverse relationship between the capacity of any one tissue to mount an allergic response and its readiness to accept tumour metastases. Muscle shows little primary homograft response but a very marked anamnestic reaction. This may account for its acceptance of a primary graft and for its effective rejection of secondary tumour.

Zusammenfassung. Die Ursache der Seltenheit hämatogener Tumormetastasen im Muskelgewebe wurde untersucht und festgestellt, dass weder «Bodenbeschaffenheit» noch «hämodynamische Faktoren» auf die Metastatisierung Einfluss haben, sondern dass lediglich die Fähigkeit des Muskelgewebes zu besonders intensiver allergischer Reaktion dafür verantwortlich ist.

RACHEL STEIN-WERBLOWSKY[6,7]

The Royal Veterinary College, London, N.W.1 (England), 24 September 1973.

[5] G. CRILE JR., W. ISBISTER and S. D. DEODHAR, Cancer *28*, 655 (1971).

[6] Present address: 15 Green Walk, London N.W.4 (England).

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Differential Response of Bone Marrow and Extramedullary Adipose Cells to Starvation

In man, as in some other mammalian species, much of the bony cavities are filled with adipose tissue (fatty marrow). Hemopoietic marrow (red marrow) also contains a variable number of fat cells[1]. Similarities in lipid chemical composition has led to the assumption that the fat contained within bone is a typical white adipose tissue such as that found in extramedullary sites[2,3]. This assumption may not be true. To test the hypothesis that the medullary adipose tissue may differ in its metabolic control from extramedullary white adipose tissue, an experiment was undertaken in rabbits to determine the structural changes in medullary and extramedullary adipose cells in response to starvation. The structural changes associated with lipid mobilization from extramedullary white adipose tissues are well recognized[4–6].

Materials and methods. New Zealand white rabbits (2.5–3 kg) were maintained in separate cages under normal laboratory conditions (ambient temperature 25 °C). Tap water was allowed ad libitum but all food was withheld. After 10 days starvation there was an average weight loss of 22%. The animals became irritable and hyperreactive. Tissue from the epididymal fat pad and