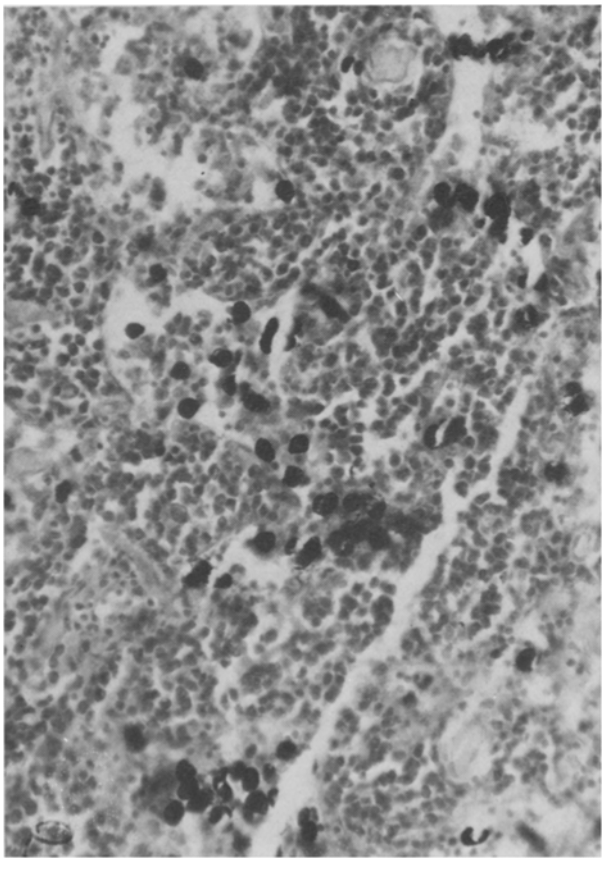
Intramuscular tumour challenge gave rise to a violent reaction in the thigh. The limb became warm and swelled to 2–3 × its original circumference. Histologically there was a massive infiltration of lymphoid cells, particularly of immunoblasts (Figure). This reaction lasted about 14 days.

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.

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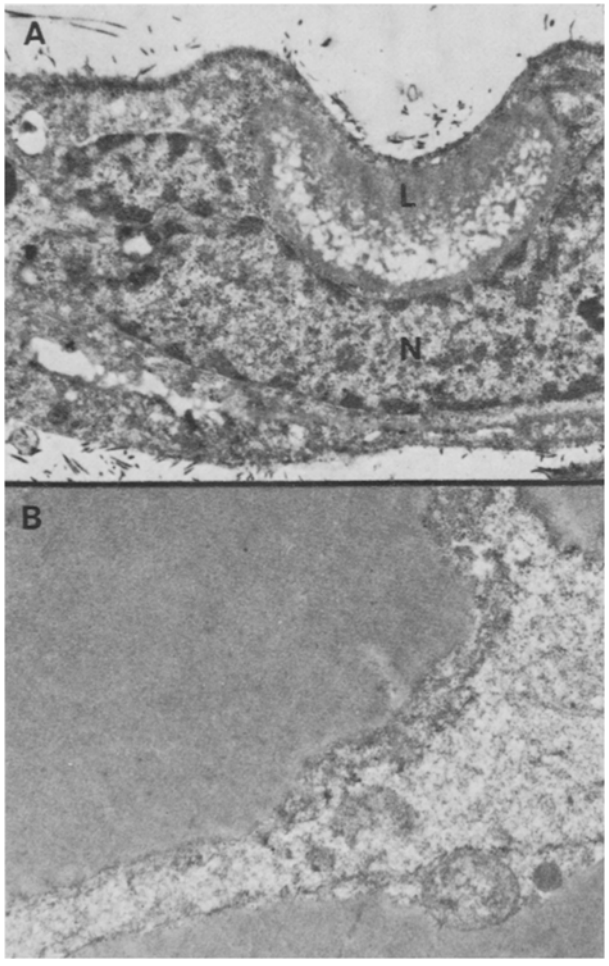
Differential Response of Bone Marrow and Extramedullary Adipose Cells to Starvation

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

the distal end of the tibial cavity (where the marrow is almost completely fat) was examined prior to and 1, 2, 5 and 10 days after the initiation of starvation. The tissues were fixed in situ in phosphate-buffered O_sO_4 (pH 7.4) for 10 min. Small blocks were then transferred to fresh fixative for 2 h, then dehydrated and embedded in Epon. Sections were made with a diamond knife, stained with uranyl acetate and lead citrate and studied in an electron microscope. Thicker sections were cut with a glass knife, stained with alkaline toluidine blue and studied by light microscopy.



Epididymal and marrow adipose tissue after 10 days starvation. A) Epididymal adipose cells show almost complete loss of lipid from their central fat globules. As a result, cell size shrinks. Only a small fat vacuole (L), displaying a 'fluffy' appearance, remains in the vicinity of the nucleus (N). B) In contrast, bone marrow adipose cells do not undergo lipid mobilization. Pinocytic vesicles and an extensive system of smooth endoplasmic reticulum do not appear in the cell. The central lipid vacuole is retained and maintains its homogeneous appearance (both figures ×17,500).

Results. The epididymal adipose tissue showed irregularities and projections at the surface of the cells as early as 1 day after the initiation of starvation. By day 2 many pinocytic vesicles had appeared in the peripheral rim of cytoplasm. After 5 days these findings were more extensive. In addition, the central fat globules had lost their homogeneity and displayed a 'fluffy' appearance suggesting fat mobilization. Cell size shrunk and the shrinkage could be measured by determining the distance between the cell membrane and the basal membrane as the latter does not conform to the diminished cell size. An extensive system of smooth endoplasmic reticulum and some dense bodies could be seen within the cytoplasm. By day 10, most of the cells had become spindle-shaped and now contained only small droplets of fat and some dense bodies (Figure A). In contrast to these findings, marrow adipose cells showed no discernible changes during the period of starvation and cell size remained unchanged. The central fat globules retained their homogeneity and the cytoplasm displayed no evidence to suggest fat mobilization (Figure B).

Discussion. The failure of marrow adipose tissue to mobilize fat in response to 10 days of starvation in the face of fat mobilization from extramedullary adipose tissue, may point to inherent differences in the metabolic response of these 2 tissues to short term starvation; on the other hand, the difference observed may be accounted for by the fact that medullary adipose tissue is contained within a rigid, non-expansile cavity, a situation that may somehow influence its response. Any change in the volume of a adipose cells within the bony cavity must be reciprocated by a corresponding change in the volume of the remaining elements (e.g. hemopoietic tissue). Marrow adipose cells do undergo degradation when hemopoietic tissue expands in response to experimental hemolysis[7]. It is possible that marrow adipose tissue is functionally distinct from its extramedullary counterpart; its primary function being the regulation of the intensity of hemopoiesis rather than the conservation of energy; its development and degradation being controlled by factors related to the regulation of hemopoiesis rather than by factors that relate to the nutritional status of the body[8].

Zusammenfassung. Nachweis, dass extramedulläres Fettgewebe im Hungerzustand mobilisiert wird während das Fettgewebe des Knochenmarks stationär bleibt, was die primäre Funktion des vom Energiestoffwechsel unabhängigen Knochenfettgewebes unterstützt.

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