Binder concluded that insulin is a microvascular vasoconstrictor.

Circulating insulin has general cardiovascular effects unrelated to its hypoglycaemic action, which have been attributed to hypovolaemia perhaps caused by stimulation of endothelial transport of plasma proteins[4] rather than to changes in vascular tone. Insulin, however, has a local vasodilator effect in the isolated rat tail, apparently due to antagonism of noradrenaline mediated vasoconstriction.[5] Any local vasoactivity of insulin in the intact human is hard to demonstrate as the standard clinical method of blood flow measurement, that of isotope washout,[6] is invalidated by high local insulin concentrations that could interfere with partition of the marker isotope between tissue and blood.[7] We applied photoelectric plethysmography, a non-invasive optical method, to measure changes in blood flow close to sites of subcutaneous injection of insulin.[8] In normal and stable diabetic patients subcutaneous injection of insulin produced variable increases in local blood flow lasting up to 60 minutes. Since control injections of insulin diluent did not have this effect this local hyperaemia appears to be due to intrinsic local vasodilator activity of insulin itself.[9]

More recently other workers have used laser doppler flowmetry, a technique similar to photoelectric plethysmography, to show that circulating insulin is a microvascular vasodilator.[10] The balance of evidence therefore seems to favour insulin having an intrinsic vasodilator and hyperaemic action. Through this action insulin could promote its own absorption; conversely, the apparent failure of insulin to exert this effect in certain patients with brittle diabetes[9] could impair absorption in these patients, some of whom seem to have a barrier to subcutaneous insulin absorption.

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SIR,—The results reported by Dr P G F Swift and others (26 March, p 1015) suggest that the change from insulins of conventional strengths to U100 insulin will not be associated with a significant change in insulin absorption rate. A simple mathematical model of subcutaneous insulin absorption supports this experimental finding.

If we assume for the moment that the subcutaneous insulin bolus is spherical then the amount of insulin available at the surface of this sphere would be proportional both to its surface area ($4\pi r^2$) and to the insulin concentration. Although U100 insulin is two and a half times more concentrated than conventional insulin of strength 40 U/ml, the surface area of a 100 U/ml bolus would be only 1·84 times smaller than that of a 40 U/ml bolus containing the same insulin dose. Under these conditions approximately 36% more insulin would be available for absorption at the surface of the spherical U100 bolus compared with that available from the 40 U/ml depot.

If, as is the case in vivo, the injected insulin conforms to tissue planes and adopts a flat "coin" shape of thickness t and radius r the U100 bolus would have a surface area that was a factor $((t+r^{100})/(\sqrt{2\cdot5}t+2\cdot5r^{100}))$ times that of the 40 U/ml dose, $r^{100}$ being the radius of the coin shaped U100 bolus. As t becomes small (or as the insulin disperses along the tissue plane) this relation approximates to 1/2·5 and therefore nullifies the two and a half times greater concentration of the U100 insulin.

From these simple calculations and assumptions it seems that the absorption of insulin from a subcutaneous site would be similar for a given insulin dose, irrespective of the concentration used.

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## Angiotensin converting enzyme and malignant histiocytosis

SIR,—We were interested by the report of Dr Boomsma and others (2 April, p 1106) of raised serum angiotensin converting enzyme activity in two patients with malignant histiocytosis. We have recently seen two infants initially thought to have histiocytic malignancy in whom monoblastic leukaemia was eventually diagnosed. Angiotensin converting enzyme activity was normal and lysozyme activity was raised in both these patients.

The first infant was a boy aged 4 months who presented with a skin nodule, hepatosplenomegaly, and testicular swelling; there were no circulating blast cells. A skin biopsy sample was said to show histiocytic malignancy. Subsequent examination of the bone marrow showed heavy infiltration with monoblasts, confirmed as such with cytochemistry and electron microscopy. His serum lysozyme activity was 32 mg/l (normal range 3·4-9·2 mg/l) and antiotensin converting enzyme activity was 42 U/ml (similar to age matched controls).

The second patient was a girl aged 6 weeks who presented solely with skin nodules, her peripheral blood count being normal. An initial skin biopsy examination suggested that the infiltrate was composed of malignant histiocytes, but marrow aspirate showed only 5% atypical mononuclear cells and was not considered diagnostic. Three weeks later, however, the marrow was heavily infiltrated with monoblasts, again confirmed by cytochemistry and electron microscopy. Her initial lysozyme activity was 96·5 mg/l, and serum angiotensin converting enzyme activity was 51 U/ml.

It has been suggested that angiotensin converting enzyme reflects maturation to the macrophage-histiocyte stage whereas lysozyme is a more non-specific marker of monocyte lineage,[1] and our two cases would support that view. It would be interesting to know the lysozyme activities of the patients described by Dr F Boomsma and others. Other cases of monocytic leukaemia with normal angiotensin converting enzyme activities have been described,[2] but the distinction between histiocytic malignancy and monoblastic leukaemia is usually easily made on more conventional grounds. This marker may be particularly useful in infants, in whom monoblastic leukaemia may present more commonly (or solely) with extramedullary features. The differentiation between monoblastic leukaemia and malignant histiocytosis will have some bearing on the future chemotherapy of these infants, and this enzyme may be a valuable addition in diagnosing this rare group of diseases.

We thank Miss P Kind, principal biochemist, Department of Clinical Chemistry, St Thomas's Hospital, for performing serum angiotensin converting enzyme assays.

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SIR,—Dr F Boomsma and others suggest that angiotensin converting enzyme could be used as a tumour marker in malignant histiocytosis (2 April, p 1106).

Another marker which has not been described in the published work seems worth mentioning. In 1964 I found that a patient with a firm diagnosis of histiocytic medullary reticulosis at the Hammersmith Hospital had a serum isocitrate dehydrogenase concentration of 336 IU/l (upper limit of normal range 3·8 IU/l). This was the highest concentration I had ever measured, so I have taken the opportunity of measuring serum isocitrate dehydrogenase concentration each time such a diagnosis is made.

The series now includes seven patients, and the lowest level recorded was 38 IU/l, with one at 110 IU/l, and all the others above 200 IU/l. Histiocytes are rich in this enzyme, and it is only in acute liver disease that the level rises to about 36 IU/l. As yet I am unaware of any other disease where this level is exceeded.

It seems, therefore, from a series of seven patients (supported by the excellent histology experience of Dr K Henry) that it is worthwhile measuring serum isocitrate dehydrogenase concentration in patients with this disease.

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## New drugs in respiratory disorders

SIR,—In his article on new drugs in respiratory disorders (19 March, p 955) Professor D C Flenley quotes the British Thoracic Association studies on short course chemotherapy in