approximately 8 hours. Flux rates of crystalline INH across intestinal mucosa tended to be higher than those for tabletted INH during the entire experiment, but were only significantly different ($p < 0.05$) after 10 hours.

Discussion

We recently demonstrated that a continuous flow-through mucosal perfusion system with intestinal mucosa showed promise as an *in vitro* method for determining the permeability of agents from the gastrointestinal tract for drug registration purposes.[4] However, simultaneously, we observed that intestinal mucosa used in the above system was not very permeable to molecules with weights (M_w) > 500 Da. We therefore suggested that other mucosae, e.g. vaginal mucosa, might have to be considered as substitutes if large M_w agents are to be compared for BA/BE. Akin to other hydrophilic compounds, INH (M_w = 137.14 Da) probably permeates the intestinal mucosa via intercellular routes, the mucosal membrane in conjunction with the epithelial tight junctions providing the rate-limiting barrier.[6]

Although there was a tendency for flux rates of crystalline INH to be higher than those of the tabletted form, these differences were only significantly different after 10 hours (Fig. 1). A possible explanation is that the presence of the soluble

exipients in the tablets may alter the permeability properties of INH across this barrier. However, it is clear that the intestinal mucosal barrier appears to discriminate between the diffusion rates of what is the same molecule with and without exipients. In conclusion, we have shown that intestinal mucosa has barrier properties which may be useful to assess BA/BE properties of therapeutically active compounds *in vitro.* Further studies using the above system are therefore indicated.

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Clinically silent renal tumour producing erythropoietin

To the Editor: Asymptomatic patients may be referred for a haematology opinion when the routine blood count reveals elevation in haemoglobin level, haematocrit or red cell count.[1] There is an all too cavalier approach to this abnormality, which is not only an independent risk factor for arterial or venous thromboembolic disease[2] but may signal unsuspected underlying cardiac or pulmonary pathology.[3] Infrequently these findings may draw attention to an otherwise silent myeloproliferative syndrome in the form of primary proliferative polycythaemia or polycythaemia rubra vera of old.[4] Occasionally, and of major clinical importance, is inappropriate erythropoietin production by tumours, including kidney tumours.[5]

A systematic approach to this problem is essential.[1] The first step is to distinguish spurious from absolute erythrocytosis by simultaneous determination of red cell mass and plasma volume[6] since the latter may be independently reduced in a number of situations, including cigarette smoking.[7] In the majority of cases the most common cause is found in the lungs with desaturation that enhances normal erythropoietin production via a renal sensing mechanism. Less frequently

encountered is right-to-left shunting at the level of the heart or the great vessels. Conversely, increases in neutrophil and platelet count signal autonomous haematopoiesis in chronic myeloproliferative syndromes. Less frequent, but of major importance, is the need to recognise individuals with ectopic production of erythropoietin; of these the classic example remains cerebellar haemangioblastoma.[1] More common causes are found in renal cell carcinoma,[5] uterine fibroids,[8] and haemangiomas of the liver[9] and lung.[10]

A case is reported here to illustrate the occurrence of symptomatic expansion of red cell mass as a reminder to search carefully for otherwise silent tumours in this clinical context.

A 54-year-old woman was referred by her primary care physician with a haemoglobin of 183 g/l, a packed cell volume of 55%, and normal platelet and white cell count. Her history dated back 6 weeks. While at a health farm she had had routine blood tests done primarily to define her endocrine status as a basis for postmenopausal hormone replacement therapy. Seventy-five per cent thyroidectomy had been carried out 3 years previously for a benign lesion. She was on 100 µg of

thyroid hormone replacement daily. The remainder of the physical examination was negative. The erythrocytosis was attributed to smoking but formal pulmonary testing showed no abnormality and functional studies were all within the normal range. In view of the family history of ischaemic heart disease, cardiological assessment was requested but no cause was found for her blood count abnormality, with the only additional feature being total cholesterol of 8.4 mmol/l. Whole blood viscosity was elevated and a series of venesections was undertaken while searching for possible sources of ectopic hormone production. Clinical reassessment failed to reveal any palpable liver, spleen, kidney, uterus or other masses. The computed tomography (CT) scan exposed a non-homogeneous and partially calcified exophytic mass in the lower part of the right kidney less than 3 cm in greatest diameter (Fig. 1). There was no evidence of perinephric or vascular invasion and the imaging features were compatible with renal cell carcinoma, which often exhibits variable parenchymal density with calcification in up to 31% of cases.[11] Resection and the postoperative course were uneventful. Histopathological examination revealed a stage T1 grade 1 renal cell carcinoma. Haematology returned to normal within 4 weeks.

There is a general underappreciation of the hazards linked to erythrocytosis.[1] When part of a myeloproliferative syndrome in the form of primary proliferative polycythaemia, the risk of premature vascular disease is increased by concurrent thrombocytosis, and there may also be a decrease in naturally occurring anticoagulants and acquired elevation in homocysteine levels. In most circumstances the causative lesion lies in the pulmonary or vascular systems. However, in the absence of demonstrable pathology it is important to search for benign or malignant lesions that may be producing erythropoietin. In the latter situation the risk is increased because there may be associated elevations in fibrinogen and factor VIII integral to the inflammatory process, reactive thrombocytosis,[12] activation of the clotting system through the tissue factor — VII — over-expression and acquired or secondary hyperhomocysteinaemia. These various inflammatory pathophysiological mechanisms may all occur together in neoplasia and are the basis for resection that simultaneously reduces erythropoietin drive on the marrow and corrects acquired risk factors for thromboembolic disease.

This point was recently illustrated in a case where a rare cerebellar hemangioblastoma was located and resection re-established physiological levels of haemoglobin.[1]

In conclusion, an example of erythrocytosis due to ectopic hormonal production by clinically silent renal tumour is described. Return of red cell mass to normal following resection is presumptive evidence of cause and effect. Although unusual, this association is clinically relevant and meticulous

Fig. 1. Renal cell carcinoma. CT scan with contrast at the level of the lower pole of the right kidney. Exophytic partially calcified tumour (arrowheads) projects laterally and lies posterior to the ascending colon (open arrow).

search for such causes is appropriate in patients with otherwise unexplained elevation in haemoglobin level or packed cell volume.

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