

Role of omental milky spots in the local immune response

SIR,—Dr Koten and Professor den Otter's hypothesis (Nov 9, p 1189) concerning omental milky spots and Dr Shimotsoma and Dr Simpson-Morgan's (Dec 28, p 1596) subsequent correspondence require comment. First I would emphasise that this hypothesis was proposed at the 4th international symposium on the biology, immunology, and surgery of the greater omentum in May, 1991.¹ At this congress my colleagues and I introduced the term omentum-associated lymphoid tissue (OALT) for the milky spots,² which we published in two reports in 1991.^{3,4} Our data on milky spots in animals (distinct T-cell area, distinct B-cell area, specific macrophage subsets, specific reaction after immunisation) were the basis of these papers. Moreover, we have shown conclusively that precursor cells of the macrophage lineage can localise in and proliferate in the mouse milky spots,⁵ indicating that milky spots are a source of free peritoneal macrophages. We have lately identified, as did Shimotsoma and Simpson-Morgan, human milky spots. They contain mainly macrophages.⁶ Since, however, no T-cell or B-cell areas (apart from some isolated T and B cells) were found, we did not see any evidence for Koten and den Otter's hypothesis. Additionally, in man the introduction of the term OALT for milky spots is not supported by the data of Shimotsoma et al⁷ who reported that "the lymphocytes did not show any preferential location within the milky spots". We do, on the other hand, agree that human milky spots are important for the immunity of the peritoneal cavity, especially during inflammation. Milky spots then provide activated macrophages, which may play a key part against bacterial infection and tumour cell growth.

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1. Koten JW, den Otter W, der Kinderen D. The omentum—a remaining enigma. 4th international symposium on the biology, immunology and surgery of the greater omentum (Utrecht, Netherlands, May 30 to June 1, 1991): abstr 15.
2. Beelen RHJ, Hendrickx R, Eestermans IL, Wijffels JFAM. Milky spots may be considered as omentum-associated lymphoid tissue (OALT) and play a key role in the immunology of the omentum. 4th international symposium on the biology, immunology and surgery of the greater omentum (Utrecht, Netherlands, May 30 to June 1, 1991): abstr 14.
3. Beelen RHJ, Hendrickx RJBM, Eestermans IL, Wijffels JFAM. Milky spots can be considered as omentum-associated lymphoid tissue. In: Imhof B, ed. Lymphatic tissues and in-vivo immune responses. New York: M. Dekker, 1991: 519–24.
4. Beelen RHJ. The greater omentum: physiology and immunological concepts. *Neth J Surg* 1991; 43: 145–49.
5. Wijffels JFAM, Hendrickx RJBM, Steenbergen JJE, Eestermans IL, Beelen RHJ. Milky spots in the mouse omentum play an important role in the origin of peritoneal macrophages. *Res Immunol* (in press).
6. Krist LFG, Eestermans IL, Steenbergen JJE, Meyer S, Beelen RHJ. Cellular composition of the milky spots in the human greater omentum. *J Leukoc Biol* (in press).
7. Shimotsoma M, Takahashi T, Kawata M, Dux K. Cellular subsets of the milky spots in the human greater omentum. *Cell Tissue Res* 1991; 264: 599–601.

Therapeutic window for 5-HT reuptake inhibitors

SIR,—Fichtner et al¹ suggested a therapeutic window for fluoxetine to explain the induction of suicidal thoughts in patients treated with this antidepressant drug. They reported two cases of depressive relapse in patients receiving fluoxetine doses higher than that associated with the best antidepressant effect. We report a similar observation with fluvoxamine, another potent inhibitor of presynaptic serotonin reuptake.

A 32-year-old woman presented with DSM-III-R criteria for an obsessive-compulsive disorder without major depression. She had no suicidal thoughts and no history of suicide attempts and late luteal phase syndrome. She was started on fluvoxamine (200 mg per day) and two months later showed great improvement of obsessive-compulsive symptoms and an important but incomplete reduction in both somatic and psychic anxiety. The dose of fluvoxamine was then increased to 250 mg. One week later, the patient had severe symptoms of generalised anxiety with a score of 33 on the Hamilton anxiety scale,² panic attacks, and major suicidal tendencies, without change in obsessive-compulsive symptoms. Akathisia or depressive psychopathology did not develop. The dose of fluvoxamine was then reduced to 200 mg, with, a few days later, remission of anxiety

symptoms (Hamilton anxiety scale score 8), and a decrease in frequency and intensity of both panic attacks and suicidal thoughts. Ten days after the reduction of fluvoxamine dose to 200 mg, the treatment was discontinued with total disappearance of suicidal ideation after five days. However, the patient had progressively worsening anxiety symptoms, which led to the reintroduction of fluvoxamine (200 mg per day) three weeks later, with rapid remission.

This report describes the emergence of suicidal thoughts in a non-depressed patient treated with fluvoxamine for an obsessive-compulsive disorder. These suicidal tendencies without any concurrent akathisia or depressive psychopathology appeared at a dose higher than the optimum for effective control of obsessive-compulsive and anxious symptoms, suggesting a therapeutic window for fluvoxamine. Teicher et al³ previously reported similar induction of suicidal ideation with fluoxetine, also in doses well above the recommended 20 mg daily dose—ie, 40–80 mg (in 5 of 6 patients).³

This observation suggests that particular caution is needed in the escalation of dose, to prevent the possibility of suicidal thoughts.

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1. Fichtner CG, Jobe TH, Braum BG. Does fluoxetine have a therapeutic window? *Lancet* 1991; 338: 520–21.
2. Hamilton M. A rating scale for depression. *J Neurol Neurosurg Psychiatry* 1960; 23: 56–62.
3. Teicher MH, Glod C, Cole JO. Emergence of intense suicidal preoccupation during fluoxetine treatment. *Am J Psychiatry* 1990; 147: 207–10.

PTH(1–84) in hypercalcaemia of malignancy

SIR,—Dr Ratcliffe and colleagues (Jan 18, p 164) report the role of parathyroid-hormone-related protein (PTHrP) in the investigation of hypercalcaemia. They emphasise the importance of PTHrP in humoral hypercalcaemia of malignancy and the part that biochemical detection of this peptide will play in diagnosing the cause of hypercalcaemia. The diagnostic value of PTH (1–84), however, in the detection of a non-parathyroid cause for hypercalcaemia may be understated. In hypercalcaemia of malignancy most workers find that PTH(1–84) is above the limit of assay detection in less than 25% of cases.^{1–3} Those patients with detectable PTH(1–84) rarely have the high values seen in primary hyperparathyroidism. It seems from Ratcliffe and colleagues' figure that in patients with solid tumours (gpA) none had PTH(1–84) greater than the lowest value obtained in those patients with proven primary hyperparathyroidism (3.0 pmol/l). If the cut-off value of less than 3.0 pmol/l PTH is used in identifying patients with solid tumours associated with hypercalcaemia the sensitivity obtained will be much improved. PTH(1–84) values in hypercalcaemia of malignancy can be raised by calcium lowering therapy, and so it is important to obtain samples for measurement of PTH(1–84) early in a patient's admission.⁴ It would be interesting to know how in Ratcliffe and colleagues' study the serum calcium values altered in the second sample obtained in the 121 patients who remained hypercalcaemic and whether PTH(1–84) was measured on the admission or subsequent sample.

PTHrP assays will have an important part to play in the diagnosis and management of hypercalcaemia, but they are not freely available at present and will be costly when commercially available. Used wisely, PTH(1–84) assays can establish the diagnosis or exclude the incorrect diagnosis in most cases of hypercalcaemia.

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1. Nussbaum SR, Zahradnick RJ, Lavigne JR, et al. Highly sensitive two-site immunoradiometric assay of parathyrin and its clinical utility in evaluating patients with hypercalcaemia. *Clin Chem* 1987; 33: 1364–67.
2. Brown RC, Aston JP, Weeks I, Woodhead JS. Circulating intact parathyroid hormone measured by a two-site immunochemiluminometric assay. *J Clin Endocrinol Metab* 1987; 65: 407–14.
3. Logue FC, Perry B, Chapman RS, Milne I, James K, Beasall GH. A two-site immunoradiometric assay for PTH (1–84) using N and C terminal specific monoclonal antibodies. *Ann Clin Biochem* 1991; 28: 160–66.
4. Fraser WD, Logue FC, Gallacher SJ, et al. Direct and indirect assessment of the parathyroid hormone response to pamidronate therapy in Paget's disease of bone and hypercalcaemia of malignancy. *J Bone Min Res* 1991; 12: 113–21.