Sir: As a practising psychiatrist and psychoanalyst, I welcomed Hinshelwood's (1999) editorial which highlights the problem we face in helping difficult patients. Although I agree with his description of the defensive use of 'scientific psychiatry' in these areas, I am concerned he has fallen into the trap that he wished to avoid, namely, an overtly simple split between objective science and subjectivity.

The problem, I think, is to equate positivist scientific research with a scientific approach that could simply be called 'the search for truth' and which is central to all clinical work. What I think is missing from Hinshelwood's argument is the centrality of the problem that we all have of inquiry into the truth. This is as important in psychotherapy as it is in empirical science. Whether we are carrying out a research project looking into epidemiology, or assessing a patient in order to decide about diagnosis and treatment, or listening to a patient in a psychotherapy session in order to decide what would be the most helpful comment to make, we are involved in a process of inquiry that involves gathering information and making judgements. I think we have considerable resistance to this process in terms of learning the truth and making critical judgements.

Learning the truth not only makes us face what may be unpleasant and potentially painful but also makes us face our limitations in terms of our knowledge and what we can do to help our patients.

Making judgements involves taking authority and is often confused with being judgemental. I believe that an overly subjective approach that eschews inquiry, as much as an overly objective scientific approach, are both ways of avoiding this and are equally dangerous. I am sceptical that often objective empirical research, which now dominates psychiatry, is not actually about discovering the truth, but is a means of confirming convictions of what is already believed to be the truth. I think Hinshelwood is right to point out how this approach is often used to avoid the disturbance of our patients but he has not stressed the emotional difficulties faced in truth-seeking research nor the dangers of over-subjectivity.

Hinshelwood, R. D. (1999) The difficult patient. The role of 'scientific psychiatry' in understanding patients with chronic schizophrenia or severe personality disorder. *British Journal of Psychiatry*, **174**, 187–190.

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Lipids and schizophrenia

Sir: I was pleased to see the potential importance of lipid metabolism in schizophrenia recognised by an editorial (Walker *et al*, 1999). It is unfortunate, however, that the review of the literature is highly selective and omits many recent findings, possibly because of the delay between first submission and publication. The main omissions are first, there is now substantial evidence for two abnormalities in phospholipid metabolism in schizophrenia (Horrobin, 1998, 1999). One is an increased rate of breakdown of phospholipids. The other is a reduced rate of incorporation of highly unsaturated fatty acids (HUFAs) into phospholipids.

Second, a phospholipase A_2 (PLA_2) and specifically a calcium-independent PLA_2, is a strong candidate for the protein involved in increased phospholipid breakdown (Ross *et al*, 1997). One of the fatty acid coenzyme A ligases (FACLs), and specifically FACL-4, is a strong candidate for the defect in incorporating HUFAs into phospholipids (Piccini *et al*, 1998). The FACL enzymes rapidly remove free HUFAs from the cytoplasm. When they are defective, increased free HUFA levels lead to excess HUFA oxidation.

Third, the simultaneous presence of a PLA_2 and an FACL abnormality will have important consequences because these are two key enzymes involved in the signal transduction processes following activation of various receptors, including D_2 and 5-HT_2 receptors. Activation of those receptors leads to a change in G-protein configuration and PLA_2 activation. PLA_2 activation leads to the formation of two highly active signal transduction molecules, a lysophospholipid and a free HUFA. This activation process must be rapidly terminated. This is achieved by the formation of HUFA–coenzyme A under the influence of FACL, and the re-formation of a stable phospholipid by linking the HUFA back to the lysophospholipid. The simultaneous presence of a PLA_2 and an FACL abnormality will lead to defective incorporation of HUFAs into cell signalling compartments and increased oxidation of HUFAs.

Fourth, an overactivity of PLA_2 would explain why D_2 and 5-HT_2 blockers are particularly effective in schizophrenia, even though in unmedicated patients abnormalities in dopamine or serotonin metabolism or abnormalities in their receptors have been hard to find or replicate. Since D_2 and 5-HT_2 receptor occupation provide part of the drive to PLA_2 activation (Vial & Piomelli, 1995), blockade of these receptors will decrease PLA_2 activity but not normalise it if the abnormality is actually at the signal transduction level. This may help to explain why the average effect sizes of both old and new neuroleptics are always less than 30%.

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Walker, N. P., Fox, H. C. & Walley, L. J. (1999) Lipids and schizophrenia. *British Journal of Psychiatry*, **174**, 101–104.

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Sir: The recent editorial on lipid system abnormalities in schizophrenia in the *Journal* reflects the tremendous progress that is taking place on the biological frontiers in schizophrenia research (Walker *et al*, 1999), with the possibility that dietary regulation of polyunsaturated fatty acids (PUFAs) and the introduction of the so-called 'nutripharms' may herald a new chapter in the prevention of schizophrenia. However, there is evidence that the lipid dysfunction might not be specific to schizophrenia and may be present in other psychiatric disorders, notably depression.

Smith (1991) was the first person to hypothesise that an abnormal fatty acid composition may be related to the immune inflammatory pathophysiology of major depression. In another study, Finkel *et al* (1996) found that paroxetine, a selective serotonin reuptake inhibitor, acts by inhibiting the synthesis of nitric oxide, a free-radical believed to damage lipids and nucleic acids responsible for schizophrenia. This raises the intriguing possibility that