between exposed and control men, but the proportion of sperm with normal morphology, percentage of motile sperm, and rapidly motile sperm were all reduced in exposed men (table 2).

Our findings are similar to those in animals, in which in-utero exposure to similar toxic levels of these chemicals reduced daily sperm production and increased percentage of abnormal sperm.[1] Our findings of reduced hamster oocyte penetration by sperm of PCB/PCDF-exposed men is relevant to fertility. Whether fecundity is reduced in exposed men, and how these effects can be extrapolated to the general population exposed to background levels of PCBs, PCDFs, and dioxin-like chemicals, warrants further investigation.

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Lithium-induced increase in human brain grey matter

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Rodent studies have shown that lithium exerts neurotrophic or neuroprotective effects. We used three-dimensional magnetic resonance imaging and brain segmentation to study pharmacologically-induced increases in grey matter volume with chronic lithium use in patients with bipolar mood disorder. Grey-matter volume increased after 4 weeks of treatment. The increases in grey matter probably occurred because of neurotrophic effects.

Lithium has been used for the treatment of manic depressive illness (also referred to as bipolar mood disorder) for 50 years, but the mechanisms by which this cation exerts its long-term beneficial effects are not yet clear. Lithium has been shown to robustly upregulate concentrations of the cytoprotective protein bcl-2 in areas of rodent brains and in human neuronal cells.[1] In addition

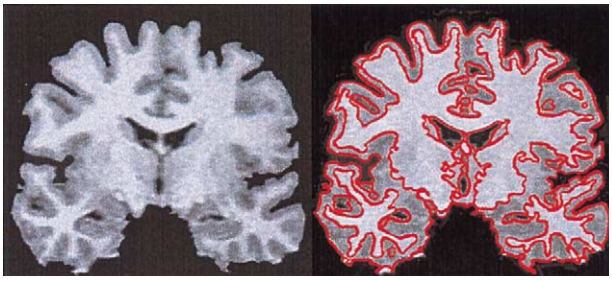

Figure 1: **Grey-matter segmentation**

to exerting major neuroprotective effects,[2] bcl-2 has neurotropic effects and improves the regeneration of central nervous system axons. Consistent with upregulation of bcl-2, lithium exerts various neurotropic and neuroprotective effects in vitro. We tested the hypothesis that chronic use of lithium exerts neurotrophic effects in the human brain in vivo. We postulated that lithium's neurotrophic effects would result in neuropil increase, manifesting as increases in grey-matter volume.

We used high-resolution three-dimensional magnetic resonance imaging and quantitative brain-tissue segmentation (figure 1) to investigate the effects of 4 weeks of treatment with lithium in patients with bipolar mood disorder (n=10, seven men, three women, mean age 33·0 years [SD 15·1]). All patients were classified as bipolar I (history of depression and mania) and were in depressed states at the time of the baseline scan. Patients remained hospitalised in the neuropsychiatric research unit throughout the study. The protocol was approved by our institutional review board and we obtained written informed consent from each patient. Magnetic resonance scans were done at baseline (medication-free, after a >2-week medication washout), and after 4 weeks of masked lithium treatment given at doses that produced therapeutic concentrations (about 0·8 meq/L).

Lithium significantly increased total grey-matter volume in eight out of ten patients. The mean change was about 3%, which represented roughly a 24 cm^3 increase in total brain grey-matter volume (figure 2). No significant changes or trends were seen in brain white-matter volume or in quantitative measures of regional cerebral water content (measured by magnetic resonance spectroscopy). The increases in grey-matter content probably occurred because of neurotrophic effects, rather than cell swelling, or changes in magnetic resonance imaging contrast associated with lithium treatment.

Indirect evidence has shown similar longitudinal effects of mood stabilisers on brain tissue volume. Volumetric brain-imaging studies and postmortem brain studies suggest that bipolar disorder is associated with cell loss or atrophy in several brain areas, especially the frontal cortex. Drevets and colleagues[3] have shown that a specific region in the frontal lobe grey-matter identified as the subgenual prefrontal cortex (region sg24) was significantly smaller (about 40%) in patients with bipolar disorder than in matched controls. In view of the effects of lithium and valproate on bcl-2 concentrations in the frontal cortex, the investigators reanalysed the imaging data. Patients treated with lithium or valproate had significantly higher subgenual prefrontal cortex volumes than non-treated patients, but volumes were not significantly different from controls.

We are doing subregional analysis of our brain imaging data to find out whether lithium exerts greater effects in discrete areas of the brain that have previously been associated with brain atrophy. Additional evidence

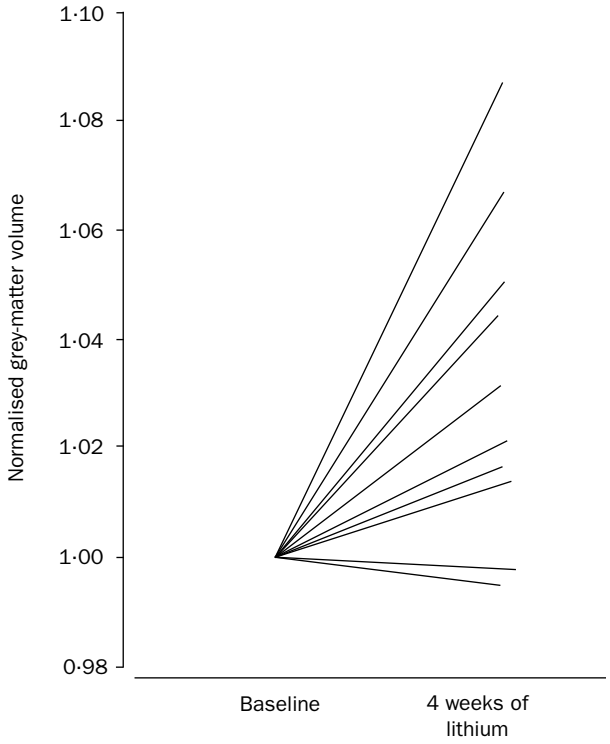

Figure 2: **Change in grey-matter volume for each patient**

for neurotropic effects of lithium in the human brain comes from a study that showed that N-acetyl-aspartate increases in grey matter with chronic use of lithium.[4] N-acetyl-aspartate is a putative marker of neuronal viability and function and this compound is believed to be localised mainly in the neurites rather than in the cell body. The lithium-induced increase in N-acetyl-aspartate might, therefore, be due to expansion of neuropil content, which would be consistent with the increase in grey matter we saw. Chronic use of lithium has been shown to increase neurogenesis in adult rodent brains, and studies by Eriksson and colleagues[5] have shown that neurogenesis occurs in adult human brains. Taken together, the increases in human grey matter, the increases in human-brain N-acetyl-aspartate concentrations, the increases in bcl-2 levels, the clear evidence for neurotrophic/neuroprotective effects, and the increased neurogenesis in rodent studies suggest that some of the long-term benefits of lithium may be mediated by neurotrophic effects. The potential use of lithium in other disorders requires additional investigation.

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Detection of rare malignant cells and their apoptotic fragments in cerebrospinal fluid

Bernd R Kranz

Routine cerebrospinal fluid cytology often fails to detect small numbers of malignant cells exfoliated from primary lymphomas of the central nervous system and metastatic carcinomas. Immunocytochemistry on poly-L-lysine-coated slides was optimised to permit unequivocal identification of a single carcinoma cell in 1 mL of cerebrospinal fluid, as well as carcinoma cell-derived apoptotic bodies that themselves contribute to enhanced diagnostic sensitivity.

In contrast to malignant leptomeningitis in systemic lymphomas and leukaemias,[1] primary central nervous system (CNS) lymphomas[2] and CNS metastases commonly exfoliate only tiny numbers of malignant cells into the cerebrospinal fluid. These cells are easily missed in routine cytology, which relies on morphological criteria alone and on assessment of small numbers of cells recovered in conventional cytospin preparations from paucicellular cerebrospinal fluid. This problem can be kept to a minimum by use of immunocytochemistry on cells attached electrostatically to poly-L-lysine-coated multispot slides. The optimum conditions to preserve morphological, cytochemical, and immunological details[3] and to keep cell loss to a minimum were defined. The latter task included single centrifugation to preconcentrate

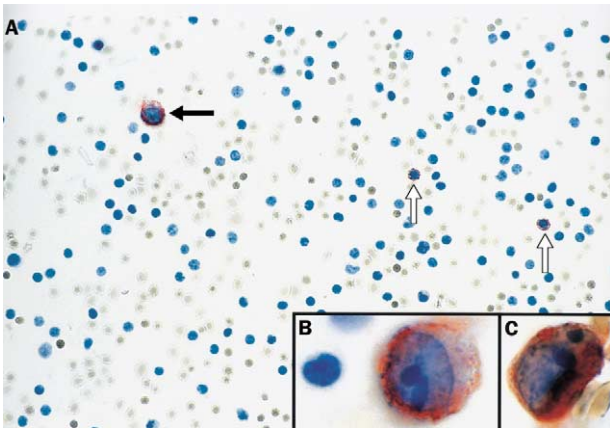

Figure 1: **Primary CNS lymphoma identified by immunocytochemistry alone**
Single B immunoblast stained positive for CD20 (solid arrow), intermingled with negative (T) lymphocytes, a few positive small B lymphocytes (open arrows), and contaminating erythrocytes, at low (A) and high (B) magnification. Positive cytoplasmic staining for immunoglobulin λ chains (C), but not κ chains, suggests that blast cells are monoclonal (antigens stained red with aminoethylcarbazole as chromogen in the immunoperoxidase reaction).