Correspondence

EDITED BY LOUISE HOWARD

Contents ➢ Comprehensiveness of systematic review – update ➢ PACT to the future ➢ Drug treatment of resistant depression ➢ Cholesterol, depression and suicide ➢ Motor responses to transcranial magnetic stimulation in schizophrenia ➢ Clozapine-induced thrombocytosis ➢ Paternal age and schizophrenia in dizygotic twins

Clive Adams searched Medline between 1986 and June 1996 (inclusive) – the same period covered by the original investigation. A simple MRI search identified 142 studies in total. Employing Boolean logic and adding a refined schizophrenia search term (by using ‘and’) found 27 studies. Refining the MRI search term resulted in the location of 196 studies. Out of interest, EMBASE, a more comprehensive database covering 67% of 506 indexed psychiatry journals (v. 47% in Medline), was searched similarly and identified 289 potentially relevant studies. PsyCIT, covering 73% of indexed psychiatry journals, was not searched. Stephen Lawrie examined every identified citation for volumetric MRI studies in patients with DSM-III-R (American Psychiatric Association, 1987) schizophrenia and healthy controls, giving raw data that could generate case-control differences (expressed as a percentage) for relevant brain regions.

Five studies that should have been included in the original review were identified (see Table). One of these, Lim et al (1995), should have been identified in the simple Medline search, and all should have been identified in the hand search of journals. Indeed, Lawrie & Abukmeil were aware of two of the studies but mistakenly excluded them for not giving relevant raw data (Woods & Yurgelen-Todd, 1991) or for being published outside the time frame (Cowell et al, 1996). It should be noted, however, that two of the studies (Delisi et al, 1992; Cowell et al, 1996) simply gave information on more subjects than in earlier papers which were included in the review, and another two included the data in subsequent papers.

Incorporating the figures from the Table into the calculations of median percentage

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<tbody>
<tr>
<td>Methods</td>
<td>Medline refined MRI</td>
<td>Medline refined MRI &amp; EMBASE</td>
<td>Medline refined MRI &amp; EMBASE</td>
<td>Medline simple MRI &amp; EMBASE</td>
<td>Medline refined MRI &amp; EMBASE</td>
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<td>Subjects</td>
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<td>sk, 5, man</td>
<td>con, 5, sa</td>
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<td>Cranium</td>
<td>14m/3f patients 14m/5f controls age-matched</td>
<td>25 patients 33 controls both genders</td>
<td>11 patients 13 controls both genders</td>
<td>19m patients 18m controls age-matched</td>
<td>54m/3f/7 patients 62m/52f controls</td>
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<tr>
<td>Whole brain</td>
<td>L – 3.5% R – 4.5%</td>
<td>L – 4% m, – 3.5% f; R – 4% m, – 3.5% f</td>
<td>T – 10%</td>
<td>T – 10%</td>
<td>T – 10%</td>
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<tr>
<td>Cortical grey</td>
<td>L – 9% R – 9.5%*</td>
<td>T + 0.5%</td>
<td>T + 0.5%</td>
<td>T + 15% (Third +21%)</td>
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<tr>
<td>Cortical CSF</td>
<td>L +22% R +16%*</td>
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<td>T +6.5%</td>
<td>T +15% (Third +21%)</td>
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<td>Lateral ventricles</td>
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<td>L +16%* R +6.5%</td>
<td>T +6.5%</td>
<td>T +15% (Third +21%)</td>
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<tr>
<td>Prefrontal lobe</td>
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<td>L – 3% m, – 2% f; R – 3.5% m, – 3% f</td>
<td>L – 1% R – 4%</td>
<td>L – 5% m*, – 3% f; R – 4% m, – 2% f</td>
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<td>L – 5% m*, – 3% f; R – 4% m, – 2% f</td>
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<tr>
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<td>L – 10% R – 8.5%</td>
<td>L – 1% R – 4%</td>
<td>L – 5% m*, – 3% f; R – 4% m, – 2% f</td>
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<td>L +5.5% R 0.0</td>
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<td>Temporal white</td>
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<td>Temporal CSF</td>
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<td>Amygdala</td>
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<td>L – 11% R +0.5%</td>
<td>L – 4% R – 3%</td>
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<tr>
<td>Hippocampus</td>
<td>L – 4% R – 3%</td>
<td>L – 4% R – 3%</td>
<td>L – 4% R – 3%</td>
<td>L – 4% R – 3%</td>
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* reported as statistically significant difference in original paper; con, contiguous; sk, skipping; slices of ‘x’ mm thickness; sa, semi-automated; a, automated; man, manual; m, male; f, female; T, total; L, left; R, right; CSF, cerebrospinal fluid.
differences between patients with schizophrenia and controls generally has little effect for most brain regions—probably as a consequence of the small amount of additional data gleaned for any particular region in specific subject groups. The only region in a subject group to have more than one additional datum was the left and right temporal lobes in both genders combined. The result for this region was also changed by more than any other cortical region, from −6% and −9.5% (left and right) to −3.5% and −7%. Similarly sized but opposite effects were found for the prefrontal lobes, rendering the revised median differences more compatible with those of the temporal lobes (−5.5% and −4%, respectively). The largest overall change was for the right lateral ventricle volume in both genders, the median difference being reduced from 36% to 23% in patients with schizophrenia. The pre-specified region of maximal interest (left amygdalo-hippocampus) was not altered—the only relevant data (Waldo et al., 1994) reporting these structures separately. One previous study had reported data this way, giving a new median estimate (between the two studies) of −11.5% and −9% (left and right) for the amygdala, and −6 and −4% for the hippocampus.

The grey/white segmentation data in Woods & Yurgelun-Todd (1991), that only had two relevant previous studies, were the only data that actually altered the findings. Whereas prefrontal and temporal white matter was bilaterally increased before (Lawrie & Abukmeil, 1998), such volume increases are only evident in the left temporal lobe after incorporating the new data and the other three regions are actually reduced in line with overall and grey matter reductions. However, the inclusion of one further study—in an updated review (Lawrie, 1999)—re-instates the previous finding. Overall, therefore, the main conclusions of the review—that patients with schizophrenia have small reductions in whole brain volumes as well as greater reductions in medial temporal lobe structures—remain unaltered.

What has this exercise taught us? First, systematic reviewers can fail to include relevant articles through oversight, despite doing appropriate searches. Second, full reporting of comprehensive searches is desirable—as a general rule and because unidentified articles where there are few published papers are disproportionately important. Finally, readers with good memories will remember that we staked a bottle of Glenndronach malt whisky on the outcome of our efforts.

As there were exactly five additional articles identified (rather than more or fewer) we have declared an honourable draw.


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**PACT to the future**

The PRISAM papers (Becker et al., 1998) and subsequent editorial (Marshall et al., 1999) on assertive community treatment (ACT) highlight the quest by mental health professionals to provide appropriate and effective services to vulnerable individuals with severe mental illness. The design, implementation and model fidelity of ACT have been a widely researched aspect of community mental health care (Mueser et al., 1998).

Interestingly, the studies and editorials animatedly examine research carried out between 1992 and 1994, the inception and teething stage of the Nunhead psychiatric assertive community care team (PACT). Crucially, this period was characterised by staff and client recruitment, site relocation, and resource allocation while imbuing the tenets of ACT. Designers of ACT fidelity measures (McGrew et al., 1994) sound a note of caution that “implementation and fidelity are developmental” and this “natural temporal evolution in service” if not accounted for in research, can be a potential source of unexplained error.

The Nunhead PACT team has shown considerable development over the 1990s derived from tailoring a service to suit its own unique client population. Community mental health services are not identical as they cover unique geographical and socio-economic areas, with diverse ethnic, demographic and psychopathological characteristics. However, numerous studies of ACT facilities (mainly outside the UK) stress that model fidelity is fundamental to effective ACT service provision (Teague et al., 1998).

We present here an updated description of the Nunhead PACT team. The multi-cultural client population (53% male, 45% female), with a mean age of 46 years, has a predominant diagnosis of schizophrenia (80%) and the remainder affective psychoses. With a mean duration of illness of 17 years, characterised by multiple hospitalisations, admissions are currently one-sixth pre-ACT intervention levels.

The team comprises staff with diverse backgrounds namely psychiatrists, clinical psychologist, psychiatric nurses, social workers, a community forensic psychiatric nurse, an occupational therapist and support workers, with a staff (keyworker) : client ratio of 1 : 12. Furthermore, regular input from a benefits/welfare adviser, chaplain and community pharmacist has proven beneficial to clients and their carers. Dual diagnosis/substance misuse expertise is also being developed. The mean core staff duration in the team is 4.5 years. Patient input through client-led weekly community meetings and newsletters has been found to be invaluable. A variety of work rehabilitation activities (e.g. computer skills, tool workshop, photography and college courses) are being taken up by clients. Multi-sectoral collaboration with voluntary and statutory housing befriending, and ethnic and religious agencies has also facilitated engaging clients in the community. With its current resource and near total programme fidelity, it is likely that the service is actually more
advanced than many other ACT services? What intervals and outcome measures reliably assess ACT interventions? In our opinion, two years is a relatively short period to adequately engage, treat and initiate significant rehabilitation of a person with severe mental illness. We owe it to our clients to enhance their quality of life by sustaining the merits of PACT into the 21st century. Prospective longitudinal research may still identify elements crucial to advancing lessons of the past to the future.


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Drug treatment for resistant depression

On the basis of a four-week study carried out in 122 patients suffering from treatment-resistant depression, Poirier & Boyer (1999) claimed that “venlafaxine showed some evidence of superiority to paroxetine in this difficult-to-treat population”. Careful analysis of their results, however, suggests that evidence supporting this assertion can be improved.

First, it should be noted that the design of the study was inherently biased in favour of venlafaxine since, in both treatment groups, two-thirds of included patients had proved to be “resistant” to a selective serotonin reuptake inhibitor (SSRI). In spite of this, no significant differences were observed between venlafaxine and paroxetine for the primary efficacy variable (defined as the change in total Hamilton Depression Rating Scale (HAM-D) score between day 0 and day 28) in either the observed case analysis (−11.1 and −10.2 respectively; P=0.55) or the last-observation-carried-forward (LOCF) analysis (P=0.70, intention-to-treat).

Furthermore, there was no significant difference between the two treatments with respect to the response rates (>50% decrease from baseline in HAM-D score and a Clinical Global Impression (CGI) improvement score of 1 or 2) following the more robust LOCF analysis, although for the observed case analysis the difference just achieved significance (P=0.044).

Second, CGI severity and improvement scores improved over time following both treatments. Although there was no significant difference between the two groups, the trend was clearly in favour of paroxetine.

Finally, it should be noted that the dose titration for paroxetine was very rapid (30 mg as early as on Day 5) and neither optimal nor consistent with the manufacturer’s recommendations. This rapid titration could have contributed to the high incidence of adverse events found in the paroxetine-treated group (63% of patients treated with paroxetine compared with 69% of those given venlafaxine). In addition, it appears that the comparison was not performed at equivalent doses for both antidepressants; the mean daily dose of venlafaxine was 269 mg/day (i.e. 44 mg/day more than the maximal daily dose recommended by the manufacturer in ambulatory patients) v. 36.3 mg for paroxetine, which is not the maximal dose for this agent.

To sum up, the authors emphasis on a fairly marginal significance emerging from a subsidiary analysis of a secondary efficacy parameter seems disproportionate.


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Author’s reply: We do not consider that our study was “inherently biased in favour of venlafaxine” for three main reasons:

(a) The proportion of two-thirds of patients included in each group who were previously resistant to treatment with an SSRI is a realistic picture of what is observed in everyday practice, since the prescription of an SSRI is now the predominant one in any type of depression.

(b) Two-thirds of the patients included in the venlafaxine (a serotonin and noradrenaline reuptake inhibitor) group were previously resistant to tricyclic antidepressant drugs, which also act on noradrenaline and serotonin. The bias in favour of venlafaxine is in the same proportion as the bias in favour of paroxetine.

(c) There is no clear evidence that a patient resistant to an SSRI must not be switched to another SSRI. Not all SSRIs are the same, and the consistent pharmacological differences between these drugs authorise our point of view for such a switch.

What is more, Dr Daniels’ opinion, that when a patient is resistant to an SSRI subsequent treatment with paroxetine (another SSRI) should be avoided, is likely to be incorrect as in our study, a significant number of patients previously resistant to an SSRI afterwards responded to treatment with paroxetine.

The fact that no significant differences were observed between venlafaxine and paroxetine with respect to the mean HAM-D change, both in the observed-case and in the LOCF analyses, was fully recognised in our report. The main differences we reported between the two drugs was in remission rate – an important criterion for prediction of future outcome.

Finally, regarding the dosages of the drugs used, at the time the study protocol was designed, paroxetine dosage (including dose titration) was not very clear in terms of regulatory recommendations (in France at least) and it was not possible to recommend a dosage of paroxetine as high as 40 mg/day. This can be seen as too low now, in the light of subsequent research on the dose-response relationship for paroxetine.

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Cholesterol, depression and suicide

In a recent study low serum total cholesterol was associated with an increased risk of suicide (Partonen et al, 1999). However, the study population was a special subgroup, since the subjects were older male smokers. In addition, the final trial participants were very selected, since the target population included approximately 283 000 subjects, but
only 2933 were recruited (ATBC Cancer Prevention Study Group, 1994).

Continuing our previous research (Vartiainen et al., 1994) and analysing random population samples of Finnish subjects, we prospectively monitored mortality of 18,344 men (aged 25–64 years) through the National Death Register for a mean of 14.6 years. There were 91 suicides among 7649 smokers and 33 suicides among 10,695 non-smokers. In order to replicate the findings of Partonen et al., we classified cholesterol into the same three categories. Using the Cox model the relative risks were adjusted for identical variables except for carbohydrate intake. Among smokers the unadjusted risks (with 95% CIs) of suicide increased from 1.00 to 1.48 (0.63–3.47), and to 1.80 (0.75–4.31) with increasing cholesterol level. The relative hazards changed clearly after adjustment for covariates (1.00, 1.38, 1.62, respectively), but remained non-significant. In the report by Partonen et al., the relative risks did not change at all after adjustment for covariates, which we find surprising. We found no association between cholesterol and suicide in non-smokers.

Inconsistent findings between these two large longitudinal studies may have resulted from several confounding effects. First, 75% of the participants in the ATBC study were treated with alpha-tocopherol alone, beta-carotene alone, or both. It is possible, theoretically, that these antioxidants possess some unknown central nervous system effects. Second, the method of suicide may influence the cholesterol-suicide association. Our own findings implicate that very high serum total cholesterol is associated with the increased risk of violent, but not with non-violent suicide (Tanskanel et al., 2000). Third, it has been suggested that cholesterol is only a surrogate marker of changes in dietary polyunsaturated fatty acids, which have been linked to depression (Hibbeln & Salem, 1995) – one of the strongest risk factors for suicide. Probably various other factors also confound this controversial relationship.

We read with interest the excellent large-scale prospective study reported by Partonen et al. (1999). They found that low serum total cholesterol appears to be associated with low mood and suicide. However, others have reported conflicting results (McCallum et al., 1994). Weidner et al. (1992) found that patients on a cholesterol-lowering diet were associated with reductions in depression if they were instructed to increase fish consumption. This implies that differences in the composition of polyunsaturated fatty acids (PUFAs) might explain the conflicting finding. The PUFAs are classified into two main groups: omega-3 (or n-3) of which the parent essential fatty acid is alpha-linolenic acid (C18:3n-3), and n-6, of which the parent essential acid is linoleic acid (C18:2n-6). Maes et al. (1999) found that major depression is associated with: significantly decreased total n-3 fatty acids; increased monounsaturated fatty acids and C22:5n3 proportions and increased C20:4n6/C20:5n3 and C22:5n6/C22:6n3 ratios; lower C22:4n6, C20:5n3 and C22:5n3 fractions in phospholipids; lower C18:3n3, C20:5n3 and total n3 fatty acids, and higher C20:4n6/C20:5n3 and n6n3 ratios in cholesteryl esters; and lower serum concentrations of phospholipids and cholesteryl esters. These findings are consistent and have shown well-established positive correlation between depression and coronary artery disease. Many studies have documented evidence of hypothalamic–pituitary–adrenocortical axis hyperactivity within medication-free patients with major depression, including hypercortisolaemia (Raadsheer et al., 1994). Hypercortisol-aeim can induce hypercholesterolaemia, hypertriglyceridaemia and hypertension. These are well known to be predisposing factors of cardiovascular disease. If low serum cholesterol concentrations were linked to increased depression, it would be difficult to interpret the correlation between depression and coronary artery disease. The relationship between cholesterol and depression may not be specific enough.


Authors’ reply: We analysed data from the ATBC Cancer Prevention Study, which was a primary prevention trial to test whether alpha-tocopherol and beta-carotene supplements would reduce the incidence of lung and other cancers (ATBC Cancer Prevention Study Group, 1994). Smokers were recruited from the total population of elderly men and assessed for eligibility. A previous diagnosis of cancer, current severe angina with exertion, chronic renal insufficiency, cirrhosis of the liver, alcohol dependence, or a disorder limiting participation in the long-term trial were grounds for exclusion.

We concluded that low serum total cholesterol appeared to be associated with low mood. We also found that low serum total cholesterol predicted, after adjusting for risk factors, the occurrence of conditions indicative of poor outcome, such as hospitalisation owing to major depressive disorder and death from suicide. Findings were similar for violent deaths exclusive of suicide. Trial supplementation had no effect.


on the main outcome measures, as we reported in the original paper, nor did the antioxidant supplementation modify the effect of serum total cholesterol on suicide.

Tanskanen et al (above) report in their letter that the risk of suicide was increased with higher serum total cholesterol levels in random samples of Finnish smokers. We do not have any obvious explanation for these conflicting findings, but study populations were rather dissimilar. Their subjects (aged 25–64 years) were mainly from eastern Finland, whereas our subjects (aged 50–69 years) were from south-western Finland. The results of other cohort studies investigating the association of serum total cholesterol levels with death from suicide have been inconsistent, since there has been no association or the association has been inverse in previous studies. Tanskanen et al, as well as Su et al (above), raise the possibility of dietary fatty acids affecting the occurrence of depressive disorder, which in turn is one of the strongest risk factors for suicide. Our aim is to analyse, in subsequent studies, the relationships between various dietary factors (fats, carbohydrates, and amino acids), depressed mood and suicide risk.


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J. Virtamo National Public Health Institute, Department of Nutrition, Helsinki, Finland
J. Lonnqvist National Public Health Institute, Department of Mental Health and Alcohol Research, Helsinki, Finland

**Motor responses to transcranial magnetic stimulation in schizophrenia**

We read with interest the paper by Borojerdi et al (1999). Our group found a shorter latency for motor evoked potentials (MEPs) to transcranial magnetic stimulation (TMS) in unmedicated people with schizophrenia of, on average, 2 ms compared with age- and gender-matched normal subjects (Puri et al, 1996). In contrast, Borojerdi et al (1999) reported no such latency difference (in their group of medicated patients) and speculated that the presence of antipsychotic medication may have confounded their results. Indeed, our group has previously reported the effects of such medication on the latency and form of the inhibitory silent periods to TMS (Davey et al, 1997), which is known to occur as a result of activating superficial intracortical inhibitory interneurons, possibly GABAergic (Davey et al, 1994). Borojerdi et al (1999) found a longer latency of transcallosal inhibition to TMS in a group of medicated patients with schizophrenia but did not include a group of drug-naive patients. It is clearly important to be able to differentiate between pathophysiological mechanisms resulting from schizophrenia and the actions of antipsychotic medication on the cortico-spinal system.


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**Clozapine-induced thrombocytosis**

Clozapine is known to cause blood dyscrasias, typically neutropenia and agranulocytosis. A raised platelet count, with clozapine as the sole implicated agent, had been reported to the Committee on Safety of Medicines in three cases. This is the first to be published.

A middle-aged male with ICD schizophrenia failed to respond to neuroleptic medication (haloperidol 25 mg/day, chlorpromazine 500 mg/day), or olanzapine at a dose of 20 mg/day for six weeks. He was therefore started on clozapine. He continued to receive droperidol 20 mg/day and zopiclone 7.5 mg nocte.

Fifteen days after commencing clozapine he complained of nausea. His clozapine was increased the next day by 25 mg to 300 mg/day. He complained of arthralgia and became hypotensive (b.p. 90/60 mmHg). Clozapine was stopped and the symptoms subsided over 36 hours. Clozapine was then restarted at a dose of 100 mg twice daily. He re-developed hypotension, arthralgia, malaise and sweating after one dose. He was apyrexic. Five days after the onset of nausea, the platelet count was 454×10⁹/l (normal range: 150–450×10⁹/l), the erythrocyte sedimentation rate (ESR) 70 mm/h and the C-reactive protein 103. Eight days later the ESR had fallen to <5 mm/h but the platelet count had risen to 774×10⁹/l. Five days later the platelet count had fallen to 393×10⁹/l and subsequently returned to normal.

Muller et al (1991) reported fever 7–15 days after commencing clozapine in 12 patients with non-specific inflammatory parameters, including a raised white cell count, ESR and C-reactive protein. They did not comment on platelet changes. This case has similar symptoms but without pyrexia. The rapid re-emergence of symptoms on re-challenge suggests an immune response to the drug, and both thrombocytosis and thrombocytopenia are recognised features of such a reaction.


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**Paternal age and schizophrenia in dizygotic twins**

Crow (1999) reported that dizygotic twinning increases with parental age as does the incidence of schizophrenia. Our study of 574 patients with schizophrenia showed that the incidence of schizophrenia increases with paternal age (Raschka, 1998). Scientific publications reported increased incidence of at least 12 illnesses with increased paternal age. The rate of mutations in spermatogenesis increases with age (Penrose, 1955; Vogel & Motulsky, 1979; Raschka, 1995; Sankaranarayanan, 1998). Other age-related changes are also known.
to occur in spermatogenesis. The study of the effect of paternal age could yield useful information regarding the reported greater occurrence of schizophrenia in dizygotic twins.


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One hundred years ago

The employment of the insane

The Lancet of 28th October refers to work done at the Wernersville State Asylum, Pennsylvania, where chronic patients considered fit to labour are received from the other State institutions. The results of five years' experience of agricultural labour are given as follows:—(a) Of the patients 6 per cent. can perform work equal to paid labour, 30 per cent. can perform labour equal to one half of paid labour, and 50 per cent. are equal to one fourth of the value of paid labour. The balance of 14 per cent. are non-working, and this includes those who are ill or are found on trial not to be able to work. (b) The estimated value of the gross amount of work done during the current year, on a basis of 400 men, is $29,000. The estimated cost of food per head is 20 cents per diem, or $1.40 per week. (c) The health and welfare of the patients are medically attended to, and the medical reports regarding the health and mortality are found to be entirely satisfactory. Indoor work, e.g. brush-making, is now being introduced as an extension of the original industrial scheme, and it is believed that this also can be pursued with profit. These results are representative of our experience in asylums of this country where an adequate area of agricultural ground has been secured. It is somewhat surprising that the Lancet should go on to recommend that the example of Wernersville should be followed by other institutions in Britain and America. Old-established asylums such as Wakenfield and Utica are veritable hives of industry; it is years since machinery was introduced in the shoemaking department at the former, and the old men were encouraged to make and repair stockings; while the useful trades at Utica are representative of the greatest possible variety, and would be still more efficient but for the interference of trades unions. Of course every asylum ought to have a farm proportionate to its size. It is late in the day to advocate that primitive measure.

REFERENCE

Journal of Mental Science, January 1900, XLVI, 208.

Research by Henry Rolin, Emeritus Consultant Psychiatrist, Horton Hospital, Epsom, Surrey

Corrigenda

Acute manic symptomatology during repetitive transcranial magnetic stimulation in a patient with bipolar depression, BJP, 175, 491. The authorship of this letter was reported incorrectly. The authors are: M. Garcia-Toro, A. González, M. Romera (Complex Hospitalar GESMA, c/Jesus no. 40, 07003 Palma de Mallorca, Spain) and A. Pascual-Leone (Laboratory for Magnetic Brain Stimulation, Beth Israel Deaconess Medical Center and Harvard Medical School, Department of Neurology, 330 Brookline Avenue, Boston, MA 02215, USA).

Medial prefrontal glutamate and dreaming, BJP 175, 288–289. The name and affiliation of the fourth author were omitted from the manuscript in error. R. S. Menon (Laboratory for Functional Magnetic Resonance Research, John P. Robar Research Institute, Box 5015, 100 Perth Drive, London, Ontario, Canada N6A 5K8) was a scientific advisor to the study team and helped collect the spectroscopic data reported.

Polydactyly and functional psychosis, BJP, 175, 291–292. The author of this letter is M. S. Bhatia (not M. S. Shatia as originally reported).