untreated illness were matched from the general practice computer by sex, height within 2 cm, age within 2 years (except that a woman born in 1916 had a control born in 1912, and a man aged 75, height 1.66 m was paired with a man aged 74 of height 1.70 m). The first presented match was used, therefore being random in regard to weight.

First, 19 patients who had taken lithium regularly with or without antidepressants or neuroleptics for 10–24.5 years (average 15.5 years), had a combined weight of 1507.3 kilos compared with 1500.6 kilos of the matched controls.

Second, the 42 patients on lithium had a mean BMI of 27.7 with the control's mean BMI being 27.5. With a BMI of 30 or over, 10 lithium patients were obese as were 11 controls.

Third, paired *t*-tests, applied to patients and their matched controls, show that for 17 patients taking lithium only, $t=1.56$, $P=0.14$, and for 25 patients taking additional neuroleptics or antidepressants, $t=-0.5$, $P=0.81$.

Thus in 400.5 lithium-patient years, with or without tricyclic antidepressants or neuroleptics, weight gain was not significant. The same conclusion was reached at Epsom's Affective Disorder Clinic where patients were weighed regularly for 5 years after commencing lithium (Coppen, 1994).

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Influenza and schizophrenia

SIR: Cannon *et al* (1996) traced a small cohort of women known to have developed a flu-like illness in pregnancy at the time of the 1957 influenza epidemic, compared them with matched controls with no history of influenza and failed to find any higher incidence of schizophrenia in the children of the former than of the latter (2 *v.* 2). On this basis they concluded that "our results do not support the hypothesis that individuals exposed to influenza in prenatal life are at increased risk of schizophrenia". As Woodgate & Curtis (1996) have already observed, this is indeed true, but neither do their results threaten the hypothesis, for their cohort was far too small.

Ecological studies of the 1957 epidemic of A2 influenza in Finland, England, Scotland, Denmark and Queensland all found a significantly increased incidence of schizophrenia in the offspring of women exposed to that epidemic during the second trimester of pregnancy, but only in that trimester. The hypothesis to be tested, therefore, is whether or not maternal influenza in the second trimester of pregnancy is subsequently associated with an increased incidence of schizophrenia in the child. Unfortunately, only 80 of Cannon *et al*'s 238 index mothers had had flu-like illnesses in the second trimester and to test the hypothesis they would have needed at least 2700.

Depending somewhat on the diagnostic criteria employed, the lifetime risk of schizophrenia is about 0.85%. For simplicity, let us assume a lifetime risk of 1%, and also ignore the fact that Cannon *et al*'s subjects were only 33 or 34 years old at the time of study, and therefore not yet out of the risk period for schizophrenia, and that all of the flu-like illnesses recorded may not have been influenza. Let us also assume that maternal influenza in the second trimester of pregnancy doubles the child's lifetime risk of schizophrenia (or, alternatively, that exposure during an unidentified three week period in that trimester increases the risk 8-fold). If Cannon *et al* had wished to leave only a 25% risk of failing to detect a doubling of the incidence of schizophrenia in their subjects' offspring (Type II error) and only a 5% chance of obtaining, by chance, a spurious doubling of that risk (Type I error) the sample size they would have needed can be calculated by solving the two equations:

$$\alpha=\sum_{r=r_0}^{r=t} \text{Bin}\ (r;\ t;\ P)$$

$$\beta=\sum_{r=0}^{r=r_0-1} \text{Bin}\ (r;\ t;\ P)$$

where α is the value of the Type I error, β the value of the Type II error and Bin $(r;\ t;\ P)$ the binomial probability of r events in a sample size t when the probability is P. It is important to appreciate, though, that t refers to the number of schizophrenic offspring rather than to the number of mothers (i.e. for Cannon *et al*, $t=4$). If there is no difference between the number of schizophrenic offspring produced by the index and control mothers, $P=P_0=\frac{1}{2}$. If, as we hypothesise, the number of schizophrenic offspring is twice as high for the index mothers as it is for their controls, $P=P_1=\frac{2}{3}$.

If α has a value (for a two-tailed test) of 0.025 the values of β for sample sizes from 10 to 100 are:

sample size (t)	10	20	30	40	50	60	70	80	90	100
β	98	85	71	60	51	44	29	25	16	14

Thus, even with 60 schizophrenic offspring, which on our assumptions would require an initial cohort of 2000 index and 2000 control mothers, there would still only be a 56% (100 – 44) chance of detecting a significant result. And to have at least a 75% (100 – 25) chance of detecting a doubling of the risk of having a schizophrenic child more than 80 schizophrenic offspring would be needed, which would require an initial cohort of at least 2700 index and 2700 control mothers.

It is apparent, therefore, that the size of the cohort studied by Cannon *et al* (n=80) was hopelessly inadequate. Similar criticisms apply to an earlier study of similar design by Crow & Done (1992). Even though they had 945 mothers with a history of a flu-like illness in the second trimester of pregnancy they only had 7 schizophrenic offspring.

Cannon *et al* are right to point out that ecological studies of the kind that we and others have performed cannot by themselves establish an aetiological role for maternal influenza, because it remains unknown which, or even what proportion of, pregnant women actually contracted influenza. They are quite wrong, though, to suppose that their negative findings, or those of Crow & Done, weaken that evidence.

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No evidence for association between *CNTF* null mutant allele and schizophrenia

SIR: Recently, Thome *et al* (1996) reported data suggesting a possible association between a null mutated allele of the ciliate neurotrophic factor (CNTF) gene and endogenous psychosis in Caucasian individuals. CNTF is thought to be important for the survival of motor neurons (Sendtner *et al*, 1992). Disruption of the *CNTF* gene in mice causes motor neuronopathy (Masu *et al*, 1993). The null mutation in the human *CNTF* gene producing a new splice acceptor site resulting in an aberrant protein has been found to be polymorphic in Japanese (Takahashi *et al*, 1994) and Caucasian (Thome *et al*, 1996) populations. Thome *et al* (1996) reported that the frequency of the mutant allele in psychiatric patients was significantly increased, compared with controls. We analysed the *CNTF* genotypes of 205 unrelated Japanese patients with schizophrenia, aged 25–65 years (mean 48.9), who met DSM–III–R criteria for schizophrenia, and of 184 age and gender-matched unrelated Japanese controls, aged 31–65 years (mean 50.1).

With our sample size, there was more than 0.98 chance of detecting an odds ratio of 2.28 at α=0.05, one-sided. In our subjects, the distribution of the single genotypes in controls *v.* schizophrenics was as follows. Normal: 65.6% *v.* 70.2%; heterozygote mutant: 29.2% *v.* 27.3%; homozygote mutant: 5.2% *v.* 2.4%. The mutant allele frequencies in the schizophrenics and the controls were 0.16 and 0.18, respectively (Odds ratio is 0.90, 95% CI 0.62–1.32). Thus, our subjects provided no evidence for an association between the *CNTF* null mutant allele and schizophrenia.

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Should the administration of ECT during clozapine therapy be contraindicated?

SIR: There are only a few reports (Masiar & Johns, 1991; Green *et al*, 1994) regarding the