Schizophrenia and influenza

SIR,—Dr Crow and colleagues (July 13, p 116) boldly assert that "prenatal exposure to influenza and schizophrenia are unrelated". In their case-note follow-up study no significant association could be demonstrated between recall by mothers of influenza infection during their pregnancy and subsequent schizophrenia in the offspring who were in utero at the time of the 1957 influenza epidemic. Crow et al have fallen into the trap of assuming that for an influenza virus to have a role in triggering a process that might eventually lead to schizophrenia there would have to be full-blown influenza in the mother.

Several alternative mechanisms are possible. One is that mothers who mount a particularly effective immune response against the influenza virus and therefore have mild or subclinical infection might in some cases produce an anti-influenza immune response that crossreacts with brain antigens and therefore damages the developing fetus. Some years ago we investigated whether influenza virus could bind to particular receptors in the brain.[1] Unexpectedly, we found that rabbits which had been immunised with certain strains of influenza produced autoantibodies directed against a 37 kDa brain-specific protein whose identity has not yet been clarified. Of course this finding may or may not have relevance to neuropathology in man, but it seems unsafe to dismiss it out of hand.

Another possibility is that although the mother mounts an effective immune response and therefore does not succumb to clinical influenza the fetus does not escape so lightly. Congenital transplacental infection by rubella as a result of maternal infection, which is often subclinical,[2] provides a striking demonstration of this type of mechanism. Infection of fetuses with influenza could lead directly to brain damage. It is equally possible that such infection during maturation of the immune system can lead to alterations in the immune response repertoire, which makes autoimmune cross-reactions in response to subsequent influenza infections more probable.

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Aluminium, Alzheimer's disease, and drinking water

SIR,—We offer epidemiological evidence which, like that of Martyn et al,[1] may implicate aluminium in drinking water as an aetiological factor in Alzheimer's disease.

Summary records of all patients discharged from general hospitals in the Province of Ontario are retained by Statistics Canada, from whom we obtained data relating to 2344 patients aged 55 or over who, during 1986, had a diagnosis of Alzheimer's disease (ICD 9, 331.0) or presenile dementia (290.0). Repeat admissions of the same individual had been eliminated. We obtained corresponding data for 2232 patients with non-psychiatric diagnoses who could be successfully matched by age and sex to patients in the Alzheimer's group, subject to the condition that both members of each case/control pair should be residents of a locality for which reliable water quality data were available through the Water Quality Surveillance Programme of the Ontario Ministry of the Environment, including a measure of aluminium concentration in the finished water of the municipal supply system.

ALUMINIUM CONCENTRATIONS IN DRINKING WATER FOR PATIENTS WITH ALZHEIMER'S DISEASE AND MATCHED CONTROLS

Aluminium concentration (mg/l)	Alzheimer's disease	Matched controls	Case/control ratio	Estimated relative risk
<0·01	14	17	0·82	1·00
0·01–0·099	1261	1361	0·93	1·13
0·10–0·199	442	425	1·04	1·26
≥0·200	515	429	1·20	1·46

The table shows the distribution of the case and control members of these matched pairs, as well as the case/control ratios and the implied relative risk associated with aluminium concentrations from below 0·01 mg/l to above 0·200 mg/l. The relative risk estimates form an unbroken, rising sequence, as would be predicted on the hypothesis that exposure to aluminium in drinking water is a risk factor for Alzheimer's disease, and one which, on the null hypothesis, has a chance probability of only 1 in 24 (ie, less than 5%).

In a more detailed analysis we shall consider the extent to which the data confirm the findings of Martyn et al[1] and Flaten.[2]

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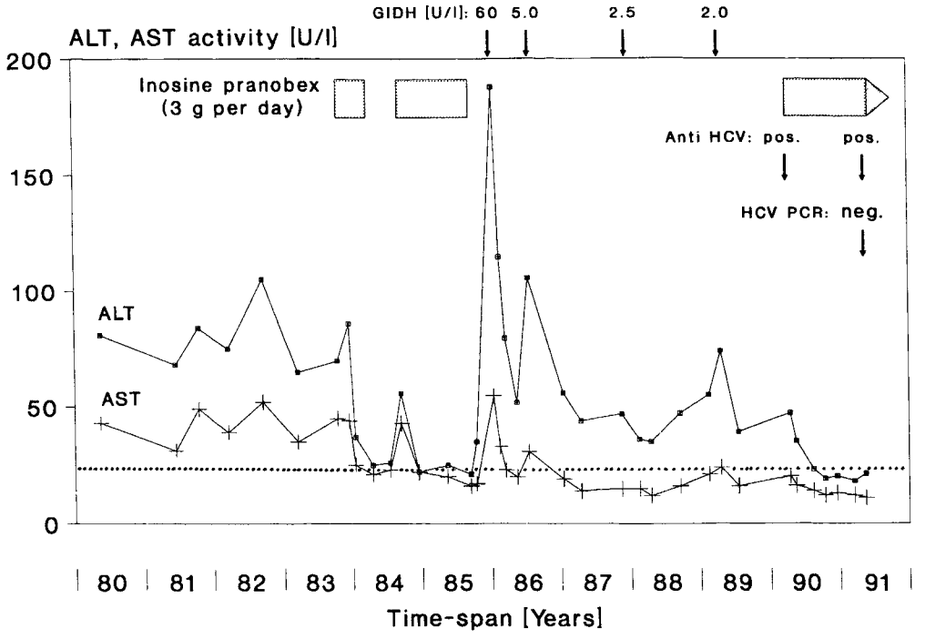
Treatment of chronic hepatitis C with inosine pranobex

SIR,—The report presented by Dr Reichard and colleagues (May 4, p 1058) on oral treatment of chronic hepatitis C with ribavirin encourages us to submit a case in which oral inosine pranobex was equally effective. Until now recombinant interferon alpha has been the only treatment available for chronic hepatitis C. Inosine pranobex enhances the cellular immune system by influencing interleukin-2 production and receptor expression and it has some direct antiviral activity also.[1,2] The drug has been introduced for herpes simplex.

A 38-year-old haemophilic patient (HIV antibody-negative) with chronic hepatitis C was given inosine pranobex for the first time in October, 1983, for prophylaxis against recurrent herpes labialis. During treatment with 3 g per day (body weight 68 kg) in three doses, alanine aminotransferase (ALT) activity fell sharply, being normal in February, 1984. 2 months after discontinuation of inosine pranobex, ALT activity rose but again it returned to normal when the drug was given for a second period (figure). Normal ALT lasted for 10 months until oral inosine pranobex was interrupted. In January, 1986, 3 months later, high ALT activity plus a steep rise in aspartate aminotransferase and glutamate dehydrogenase activity (peak 60 IU/l) was seen. These biochemical signs of liver-cell necrosis were interpreted as a rebound phenomenon after the withdrawal of inosine pranobex. Glutamate dehydrogenase activity returned to normal but ALT activity was persistently high, suggesting reactivation of chronic hepatitis C (figure).

When an enzyme immunoassay for antibodies against the hepatitis C virus (HCV) non-structural protein c-100 (Abbott) became available in April, 1990, the patient's serum was tested and found to be strongly positive. The specificity of this reaction was later confirmed by enzyme immunoassays (Abbott) for HCV non-structural protein 33c and the putative HCV core protein.[3] Inosine pranobex was then given again at a dose of 3 g daily and aminotransferase activities fell to normal (figure). The patient reported an improvement in physical comfort, and is less fatigued. The only side-effect was a slight increase in serum uric acid due to the metabolism of the inosine component of the drug.

We felt that the improvement was due to an inhibitory effect of the drug on the replication of the HCV RNA virus so we looked for HCV nucleic acid sequences in the patient's serum. About one year after the beginning of the last period of inosine pranobex a combination of reverse transcriptase activity and polymerase chain reaction was negative with HCV-specific primers, a test reported positive in the serum of 81% of HCV antibody-positive patients with chronic liver disease.[4]



Alanine (ALT) and aspartate (AST) aminotransferase activity during three periods of treatment with inosine pranobex.

Upper limit of reference interval for ALT activity shown by dotted line.

In a randomised placebo-controlled study in patients with HIV infection inosine pranobex prevented progression to AIDS as successfully as did zidovudine.[5] Thus, an in-vivo virus inhibitory effect of inosine pranobex has been demonstrated not only for DNA but also for RNA viruses.

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Anti-GOR to screen HCV-RNA-positive blood donors

SIR,—Even after the introduction of anti-c100 antibody testing in the screening of blood donors, the frequency of post-transfusion non-A, non-B hepatitis (PT-NANBH) in Japan remains well above zero—4·5% (12/265) (Dr Inaba and colleagues, June 1, p 1354), and 3·0% (35/1170) (joint study of the Japanese Red Cross PT-NANBH research group and PT-NANBH research group of the Japanese Ministry of Health and Welfare).

Yoshizawa et al[1] have suggested that anti-GOR antibody testing[2] is more effective than anti-c100 in the prevention of PT-NANBH. To evaluate the accuracy of anti-GOR, we examined 2277 blood donors for these antibodies (ELISA with spGOR2 peptide[2]), anti-c100 ('HCV Ab' ELISA, Ortho Diagnostics), and HCV-RNA by PCR (in some) with nested primers derived from the 5' non-coding region of the HCV genome.[3] 30 donors were positive for anti-GOR (1·3%), 23 (77%) of whom were positive for HCV-RNA, whereas 28 (1·2%) were positive for anti-c100, 18 (64%) of whom were HCV-RNA positive. Of 18 donors seropositive for anti-GOR alone, 11 (61%) were HCV-RNA positive, whereas only 6 (38%) of 16 donors seropositive for anti-c100 alone were HCV-RNA positive. All 12 donors seropositive for both anti-GOR and anti-c100 showed HCV-RNA positivity. Of 2231 donors who were seronegative for anti-GOR and anti-c100, 23 were randomly selected and tested for HCV-RNA, and were all negative.

11 HCV-RNA-positive donors missed by anti-c100 testing were detected by anti-GOR testing. Thus if 2249 (ie, 2277 minus 28) blood units serenegative for anti-c100 had been given by transfusion to 300 patients (average 7–8 units per patient), most probably 11 or more of the recipients would have acquired HCV infection. This figure (3·7%) is close to the frequency (3·0–4·5%) of PT-NANBH. Therefore, the frequency of PT-NANBH might fall drastically, to near zero, if donors were screened for anti-GOR as well as anti-c100.

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Timing of surgery for breast cancer and menstrual cycle

SIR,—Dr Badwe and colleagues (May 25, p 1261) show a 10-year survival of 54% for women operated on for breast cancer 3–12 days after their last menstrual period (LMP) and 84% survival for premenopausal women who underwent surgery at other times (n = 174).

It should be noted that investigation of a breast lump is often delayed until after the menstrual period in case the lesion is due to benign changes associated with cyclical hormonal fluctuations. If a breast mass does not change during or after menstruation, surgery may then be carried out. There could thus be a self selection for