In the population studied, including cases presenting with meconium ileus, the prevalence rate at birth was 1 in 4600, which does not deviate significantly from 1 in 3600. Our suggestion that neonatal screening leads to undertreatment is a logical sequel to Wilcken and Chalmers' equalisation of morbidity with days spent in hospital. There is no indication that there is a lower threshold for hospital treatment in the Netherlands than elsewhere, and in retrospect we could not find any evidence that hospital treatment was started without sufficient grounds. Generalisation of the Australian experience would be premature, especially in the presence of climatic differences and possible genetic heterogeneity. Possibly a superior way of home-based management for CF has been developed, but the advantages of screening as such are at the least dubious.

Dodge claims that the gains in an economic sense justify neonatal screening. Even if a gain of 75 hospital-days was the result of neonatal screening, the break-even cost for neonatal screening of every child born would be about 3% (75/2500) of the cost of one day spent in hospital. Screening at a price as low as this will be hard to achieve.

We can confirm that sweat-testing, even in the first 2 weeks after delivery, has a reasonable chance of success; we obtained more than 50 mg in 25 out of 46 healthy babies. The sweat test should be done as soon as there is the slightest suspicion of CF. In this way almost all cases can be detected early and at a much lower cost than that of mass screening.

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LIVER DYSFUNCTION CAUSED BY TIAPROFENIC ACID

SIR,—Tiaprofenic acid is a non-steroidal anti-inflammatory drug (NSAID) with few reports of adverse reactions. The following case demonstrates a clear relation between this drug and disturbance of liver function.

A 56-year-old woman had had polyarthropathy for about 6 years with episodic pain affecting knee, ankles, shoulders, and hands, mainly around the wrists. A firm diagnosis had not been made despite full rheumatological investigation, and she was maintained on intermittent NSAIDs. In May, 1985, her symptoms worsened. There were no abnormal joint signs and she was started on tiaprofenic acid 300 mg twice daily. She was on no other medication. 3–4 weeks later she reported a marked improvement in her symptoms. After a further 4 weeks on tiaprofenic acid, however, she reported anorexia and extreme lethargy.

Examination again revealed no abnormality and blood analysis showed a normal blood count and urea and electrolytes with an erythrocyte sedimentation rate of 10 mm/h. The alkaline phosphatase was 397 IU (normal 80–280), alanine transaminase 197 IU (normal 0–35), γ-glutamyltranspeptidase 100 IU (normal 7–35); the serum bilirubin remained normal throughout.

Tiaprofenic acid was discontinued and further investigations did not reveal antimitochondrial antibody and antinuclear factor was not detectable. The patient declined a liver scan.

Within 3 weeks the liver function tests had returned to normal but the joint symptoms recurred and tiaprofenic acid 300 mg twice daily was re-started and she again reported an improvement. During the following 3 weeks, however, the lethargy recurred and liver function tests again became abnormal (AP 463, ALT 168, GGT 185 IU, bilirubin normal). Treatment was discontinued and the liver function tests returned to normal over the next 4 weeks. Liver biopsy was not done.

The patient was a moderate drinker and pre-treatment liver function tests 2 years previously had been normal. There was a clear temporal relation with tiaprofenic acid treatment and this recurred on rechallenge; the abnormalities rapidly returned to normal on cessation of drug treatment. It is most unlikely therefore that there could be any explanation other than drug-related toxicity. I have found no other reports of hepatic problems with tiaprofenic acid although there have been two reports of abnormal hepatic function and two of hepatitis reported to the Committee on Safety of Medicines.

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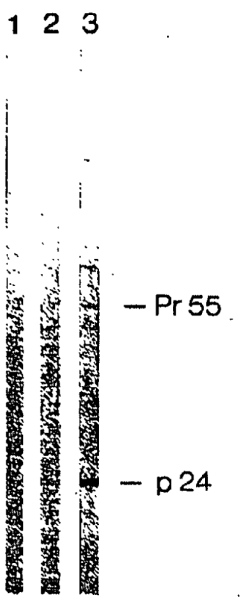
SEROCONVERSION TO HTLV-III IN HAEMOPHILIAC GIVEN HEAT-TREATED FACTOR VIII CONCENTRATE

SIR,—Commercial factor VIII concentrates (FVIII) are now heat-treated to reduce the risk of transmission of HTLV-III. Several reports have recorded the absence of antibodies to HTLV-III in patients after regular treatment with heat-treated FVIII concentrate.[1–3] However, Dr White and his colleagues (March 1, p 611) have described HTLV-III seroconversion in a haemophilia patient given heat-treated FVIII.

Since 1983, when commercial heat-treated FVIII preparations became available in the Netherlands, thirty-five seronegative haemophilia patients receiving these products have been included in a prospective follow-up study focusing on HTLV-III seroconversion. Two seroconversions have occurred among recipients of heat-treated intermediate purity FVIII concentrate. However, one of these patients also received non-heated products and was not analysed further. The other patient received exclusively the heat-treated FVIII concentrate.



Immunoblot analysis with purified HTLV-III as antigen.

Sera collected in June, 1983 (1); October, 1984 (2); and January, 1985 (3). Major *gag* gene product p24 and its precursor Pr55 are indicated.

A 27-year-old HTLV-III antibody negative man with severe haemophilia A (FVIII:C below 1%) who, since 1983, had been on heat-treated FVIII home treatment and prophylaxis presented in January, 1985, with fatigue and slight fever. He had an unexplained lymphadenopathy of at least 3 months' duration. He had no history of other recent illness, drug abuse, homosexuality, or recent visits to Africa or the Caribbean. Multifocal lymphatic enlargements and splenomegaly were observed. Confirmation of the use, exclusively, of heat-treated FVIII of US origin in the year preceding the start of the lymphadenopathy was available.

Routine laboratory investigations showed no abnormalities, and antibodies to cytomegalovirus and Epstein-Barr virus remained negative. Serological testing by direct binding assay detected antibody to HTLV-III, which was confirmed by immunoblotting (figure). Two earlier sera (spring and autumn, 1984) were antibody negative. The anti-HTLV-III titre was 226. During the ensuing months the symptoms slowly subsided and the lymph nodes disappeared. However, the HTLV-III antibody titre rose to

7140. Viral cultures from the patient's plasma set up in December, 1985 (Dr F. Barré-Sinoussi Institut Pasteur, Paris) have not so far revealed viral growth.

Thus, seroconversion to anti-HTLV-III positivity occurred in a patient using exclusively heat-treated intermediate and high purity FVIII concentrate of American origin. According to the manufacturers, one of the donors whose plasma was included in one of the transfused batches which was of intermediate purity, has developed AIDS. All other possible routes of infection were excluded.

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INCREASED PREVALENCE OF HTLV-III ANTIBODY AMONG DRUG ADDICTS FROM ITALIAN PROVINCE WITH US MILITARY BASE

SIR,—Although the incidence of AIDS in Italy is low the prevalence of HTLV-III antibody positivity among drug addicts is among the highest in Europe, ranging between 29% and 76%.[1,2] Drug addicts in large cities seem to be infected more often than those in small towns.[3]

To assess the pattern of spread of HTLV-III we tested 268 parenteral drug addicts, aged 17–36, living in Pordenone or Udine, two neighbouring provinces in north-east Italy close to the borders with Yugoslavia and Austria. 227 were voluntarily attending an outpatient drug abuse treatment programme, 41 were seen in local prisons. 15 females were prostitutes, and 8 males were bisexual. The drug addicts were clinically examined and HTLV-III antibodies were tested for in the same laboratory by ELISA (Abbott) with confirmation by western blot; only 1 of the 72 ELISA positive sera was negative by western blot.

HTLV-III seropositivity was eight times more frequent in drug addicts from Pordenone than in those from Udine. In Udine province none of the female drug addicts and none of those who had not travelled out of their region in the previous three years turned out to be infected. A similar, though slightly weaker, association was observed between living in Pordenone province and having a clinical diagnosis of lymphadenopathy syndrome before knowledge of the serological result (relative risk: 4·81, 95% confidence interval 2·51–9·22).

It is unlikely that a difference as strong as this could be due to chance or to selection. The drug addicts from Pordenone and Udine were very similar and the excess of HTLV-III positive individuals from Pordenone was not restricted to any particular subgroup. Adjustment[4] for the two factors significantly associated with the probability of being HTLV-III positive—ie, sexual behaviour and travelling in the previous three years—if anything, increased the relative risk (adjusted RR = 13·78). Selective referral of symptomatic cases to drug abuse services in Pordenone cannot explain these results since the relative risk was high in symptomless addicts too (RR = 6·96).

Economically and geographically Pordenone and Udine are very similar, with populations of about 300 000, similarly distributed in small towns and rural areas. A very large, but comparable, number of Italian soldiers operate in these areas, but Pordenone province also has one of the biggest US military bases in Western Europe (Aviano base, with about 2000 soldiers and 2000 dependents).

The frequency of HTLV-III seropositivity among US soldiers is unknown, reported percentages ranging between 0·29[5] and 5%.[6] We know of no data on the prevalence of infection or drug addiction

HTLV-III ANTIBODY IN 268 DRUG ADDICTS* BY PROVINCE AND OTHER CHARACTERISTICS

Characteristic	Proportion anti-HTLV-III positive		RR† (95% confidence interval)
	Pordenone	Udine	
Age (yr)			
⩽23	23/27	2/40	17·04 (4·82–60·16)
24–27	22/19	9/45	5·79 (2·33–14·36)
⩾28	12/17	3/49	11·53 (3·41–39·01)
Sex			
M	37/49	14/98	5·29 (2·70–10·35)
F	20/14	0/36	
Sexual behaviour‡			
Heterosexual	47/58	14/126	7·29 (3·90–13·65)
Bisexual/prostitute	10/5	0/8	
Visiting place			
Drug abuse service	50/55	8/114	12·95 (6·36–26–39)
Prison	7/8	6/20	2·92 (0·75–11·35)
Travelling‡			
Region only	11/26	0/32	
Italy	15/10	5/38	11·40 (3·65–35·59)
Out of Italy	26/16	9/63	11·38 (4·78–27·09)
Year of start of drug abuse			
⩽1976	10/12	6/35	4·86 (1·51–15·60)
1977–79	14/13	4/53	14·27 (4·65–43·76)
⩾1980	30/33	3/40	12·12 (4·01–36·68)
Lymphadenopathy syndrome‡			
Yes	32/6	6/7	6·22 (1·64–23·56)
No	25/57	8/127	6·96 (3·19–15·19)
Total	57/63	14/134	8·66 (4·73–15·84)§

*Some missing values.
†Udine as reference category.
‡Factor significantly associated with HTLV-III ($\chi^2_1 > 3·84$ or $\chi^2_3 > 5·99$; $p < 0·05$)
§RR adjusted for sexual behaviour and travelling = 13·78 (6·95–27·33).

at the Aviano base, but the presence of this base seems the only possible explanation for the striking prevalence of HTLV-III infection in Pordenone compared with Udine. Since in Pordenone only prostitutes who were also drug abusers showed high levels of HTLV-III antibodies,[7] syringe sharing, admitted by all drug abusers included in our survey, may be the most important route for HTLV-III transmission in this province.

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MECHANISM OF PARACETAMOL TOXICITY

SIR,—A *Lancet* editorial[1] on the possible use of cytochrome P_{450} inhibitors in the treatment of overdoses with paracetamol (acetaminophen) and subsequent letters indicate that it is time to reconsider the theory(s) on the mechanism of hepatocellular damage in paracetamol poisoning. Your editorial states that the covalent binding theory[2] explains the toxicity. In contrast, Dr Tee and