## DIAGNOSIS OF EPIDEMIC AND SPORADIC INTERSTITIAL NEPHRITIS DUE TO HANTAAN-LIKE VIRUS IN BELGIUM

SIR,—Earlier in this week's *Lancet* (p 1445) we describe the identification of Hantaan-related virus as the cause of three cases of interstitial nephritis in a laboratory rat associated outbreak in an institution in Belgium. Before identification of the agent, we were struck by the similar presentation of these cases, which in 1979 we ascribed to a viral infection of unknown origin.[1] Recently, we have recognised three sporadic cases with no apparent link to the institutional outbreak or to each other. We summarise here the new cases, showing similarity between them and the institutional cases, although somewhat different variants of Hantaan virus could be involved.[2] The features common to all cases are sufficiently typical (see accompanying letter) to indicate when virological proof of infection should be sought, even in countries where haemorrhagic fever with renal syndrome (HFRS) has not been previously recognised, as in Belgium.

Three men aged 22–51 were admitted to hospital in January, June, 1983, for acute renal failure. The clinical presentation and evolution was virtually identical with that observed in the three institutional cases. After an influenza-like syndrome lasting 4–10 days with temperatures as high as 40·5C, all six patients had intense bilateral or right-sided loin pain followed by transient oliguria. On admission two patients had a urinary output below 200 ml per day. Transient intense proteinuria and microhaematuria was noted. Peak serum creatinine ranged from 3·9 to 10 mg/dl within 7–13 days of the onset of fever. Haemodialysis was done in only one patient. Renal biopsy (two cases) revealed a patchy interstitial infiltrate with acute tubular lesions.[1] Serum creatinine returned to normal 2–6 weeks after the episode.

FLUORESCENT ANTIBODIES AGAINST HANTAAN VIRUS IN SERA OF THREE BELGIAN PATIENTS SUSPECTED OF HFRS (SPORADIC CASES)

| Patient | Date | FA antibody titre to Hantaan virus (and overnight titre)* | |
|---|---|---|---|
| A | Jan 24, 1983 | 64 | (ND) |
| | Feb 15 | 128 | (512) |
| | April 25 | 512 | (2048) |
| B | June 10, 1983 | 128 | (256) |
| | Aug 8 | 1024 | (2048) |
| | Sept 28 | 2048 | (ND) |
| C | June 10, 1983 | 64 | (256) |
| | July 11 | 256 | (512) |

*Titres as reciprocal of highest serum dilution giving specific fluorescence. Titre was result of 30 min incubation of sera at room temperature, followed by washing three times and incubation of sheep-anti-human IgG FITC conjugate, 30 min at room temperature. Titres as mean of three independent experiments. Titres were also obtained after overnight incubation of sera at 4°C, followed by washing three times and 1 h incubation at 37°C with conjugate.

In the three sporadic cases viral antibody titres ranging from 64 to 128 were obtained on the 9th or 10th day after the onset of fever (table). For two patients, a significant rise (8 fold) in antibody titre was observed within 2 and 3 months (table). These titres were all significantly higher than those found among blood donors. The clinical picture and the benign outcome are virtually identical with those reported by Lähdevirta[2] in patients with epidemic nephropathy, an entity now known to be due to a Hantaan virus.[3,4] The source of the virus in the sporadic cases is not known. It could be *Clethrionomys glareolus*,[5] or another rodent living in Belgium; no patient had been out of Belgium for at least 2 months before they became ill.

Although it would have been desirable to show titre changes in all cases, the presence of Hantaan antibody and the clinical and laboratory features are sufficient to establish a diagnosis of HFRS beyond reasonable doubt. This should also apply to other countries where Hantaan infection is rare in the general population,[6] and may not have been previously recognised. Serological evidence of HFRS should be sought in all acute renal failure cases developing within a context of fever, bilateral loin pain, and transient intense proteinuria and haematuria.

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## SEROEPIDEMIOLOGY OF HANTAAN-RELATED VIRUS INFECTIONS IN BELGIAN POPULATIONS

SIR,—We have detected antibodies to Hantaan virus, the prototype agent of haemorrhagic fever with renal syndrome (HFRS), in sera of Belgians unrelated to the institutional outbreak described in this week's *Lancet* (p 1445). We used an indirect immunofluorescence antibody assay (IFA)[1] modified[2] mainly by the use of Hantaan-infected E6 cells inactivated by gamma irradiation, and stored at −80°C in growth medium containing 10% dimethyl sulphoxide. The sensitivity of this assay was similar to that of the IFA method used in the study of the outbreak. Sera were screened at a dilution of 1-in-16, and all sera were also examined on uninfected E6 cells as a check for specificity.

We found antibody in 21 (2·2%) of 950 blood donors in the Antwerp area; in 4 (0·7%) of 596 chronic haemodialysis patients in northern Belgium; and in 26 (3·8%) of 682 sera submitted from all over Belgium to exclude leptospirosis. In Antwerp, none of 37 laboratory personnel at the Institute of Tropical Medicine had antibody; 1 of 13 zoology laboratory personnel in frequent contact with wild rodents had antibody; and 2 of 161 children in hospital for various diseases had antibody. All these "positive" titres were in the range of 16 to 64; as in other studies the specificity of sporadic low IFA titres for HFRS infection is presumptive.

With blood donors as a reference group, leptospirosis suspects had a significantly higher antibody prevalence (relative risk 1·72; 95% unilateral confidence interval[3] 1·08–2·76) and chronic dialysis patients had a significantly lower antibody prevalence (RR 0·30; 95% confidence interval 0·13–0·70). No leptospirosis suspect with Hantaan antibody had leptospiral antibody, and the data suggest that some HFRS infections superficially mimic leptospirosis. There is no straightforward explanation for the low prevalence of Hantaan antibody in chronic dialysis patients, though this finding does suggest that HFRS rarely, and perhaps never, leads to severe permanent renal insufficiency.

Additional evidence for recent circulation of a virus related to HFRS in Belgium was obtained by the study of three sporadic cases, with high fluorescent antibody titres against Hantaan virus (see accompanying letter). The fluorescent antibody titre against different HFRS antigens was determined in one of these patients (table I, patient A).

Convalescent phase sera from patients with HFRS in Korea and the Far Eastern USSR reacted equally well by indirect immuno-

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