EVIDENCE FOR EXISTENCE OF AT LEAST TWO TYPES OF FACTOR-VIII-ASSOCIATED NON-B TRANSFUSION HEPATITIS

SIR,—After the introduction of a brand of commercial freeze-dried factor-VIII concentrate in the U.K. in 1974 we observed a cluster of cases of both non-B hepatitis and hepatitis B due to this product.[1] The attack-rate was 17%. Now six brands are in use—N.H.S. factor VIII prepared from volunteer donations in the U.K., and five commercial brands (one of European origin and four manufactured in the U.S.A.).

Moseley et al.[2] suggested the existence of two types of non-A, non-B hepatitis based on observations of multiple attacks of hepatitis in drug addicts. Further evidence for an infective agent as a cause of non-A, non-B hepatitis has come from inoculation experiments in chimpanzees.[3,4]

We have examined reports of clinically overt factor-VIII-associated hepatitis made by hæmophilia centre directors as part of a collaborative survey in the U.K. between 1972 and 1977[1,5,6] to see if the observations of Moseley et al. could be supported by evidence of multiple attacks of hepatitis in hæmophiliacs. We identified 19 patients with two or three well-documented attacks of hepatitis (table I). Brand L[1,7] was the first U.S. commercial brand to be available in the U.K. Brand M is of European origin. 18 patients had two attacks of hepatitis; 16 had hepatitis B and non-B. 2 other patients who were anti-HB_s positive had two attacks of non-B hepatitis—associated in the first patient, with brand L and, a year later, brand M, and, in the second patient, with the N.H.S. product in 1973 and brand L in 1974. 1 patient had three attacks of hepatitis; non-B, then B due to brand L, followed by non-B associated with brand M a year later. There was no consistent order in the successive attacks of hepatitis in different patients, supporting the view that the illnesses were due to distinct infective agents. Batches of concentrate are implicated as the likely cause of successive attacks of hepatitis because only one product (e.g., N.H.S. factor VIII) had been transfused for six months before the onset of hepatitis and no other blood product had been transfused during this period (3 cases), or because of the association with a batch of concentrate known to be implicated in other cases of hepatitis B or non-B transfusion hepatitis, often related to a change in the brand of factor VIII (16 cases).

TABLE I—FACTOR-VIII-ASSOCIATED HEPATITIS 1972-77

First attack		Second attack		
Product	Hepatitis	Product	Hepatitis	No.
L	Non-B	L	B	13*
N.H.S.	B	L	Non-B	1
L	B	N.H.S.	Non-B	1
N.H.S.	Non-B	N.H.S.	B	1
L	Non-B	M	Non-B	1
N.H.S.	†Non-B	L	Non-B	1
L	Non-B	L	B	1†

* 10 icteric, 3 asymptomatic hepatitis B.
† Patient had a third attack (brand M, non-B).

Sera from 6 patients with more than one attack of hepatitis have been tested for antibody to hepatitis A virus (HAAb) by solid-phase radioimmunoassay (Abbott). 4 of these, who had non-B hepatitis followed by hepatitis B, were HAAb negative in specimens taken after their non-B hepatitis. A fifth patient was positive for HAAb before the onset of non-B hepatitis, and also contracted hepatitis B as his second attack. The sixth patient had his first attack of non-B hepatitis in June, 1973, associated with N.H.S. factor VIII, and a second attack associated with brand L in 1974. He seroconverted for HAAb between his two attacks of non-B hepatitis. Presumably he had had a symptomless hepatitis A.

TABLE II—NON-B HEPATITIS IN PATIENTS TRANSFUSED WITH ONE OR MORE BATCHES OF BRAND L

Batch	No. receiving batch alone or followed by different batches	Cases of non-B hepatitis (%)	No. receiving each batch after transfusion with different batch	Cases of non-B hepatitis
P	30	0	0	0
R	38	2	17	0
Q	56	6 *(11)*	30	1
S	74	10 *(14)*	43	0
T	68	12 *(18)*	50	1
U	37	9 *(24)*	38	0
V	34	4 *(12)*	46	0
W	22	3 *(14)*	55	0
X	22	2	65	1
Y	12	1	17	0
Z1	25	2	61	0
Z2	29	1	92	0
Total	417*	52 *(12·5)*	497†	3

* Excluding batch P. † Excluding batches P and R.

Evidence that 52 of the first 55 cases of non-B hepatitis associated with brand L observed in the U.K.[1] were due to an infective agent of the same serotype is given in table II. (The 52 cases had incubation periods of 8–67 days. A mean of 29 days was obtained from 35 of these cases where only one batch of brand L, was received before the onset of hepatitis.) Those of the other 3 cases were greater than 80 days, which is 3 S.D. above the mean of 29 days. Since these 3 cases of hepatitis received more than one batch of brand L during the incubation period, they can be thought of as instances where transfusion of more than one batch was necessary before hepatitis developed. It is unlikely that other causes, such as a coincidental attack of hepatitis A, could account for these cases. Hepatitis A has lately been excluded by serological tests in 2 of these 3 patients.

Table II further analyses the data on the cases of hepatitis associated with different batches of brand L when first used in British hæmophilia centres in 1974–76. Columns 2 and 3 give the number of patients treated with each batch of brand L and the associated cases of hepatitis which occurred after the first transfusion. These are expressed as the number of patient exposures (column 2) and the associated number of cases of hepatitis (column 3). Columns 4 and 5 give similar information for the second or subsequent batches of brand L each patient received.

In 417 patient-exposures associated with first transfusions, 52 cases of hepatitis occurred in eleven batches (excluding batch P with no cases). Second or subsequent transfusions of brand L produced 3 cases of hepatitis after 497 patient-exposures involving ten batches (excluding batches P and R). This gives a rate of 4.72 cases of hepatitis associated with 37.9 patient-exposures per batch used for first transfusions and a rate of 0.3 cases of hepatitis associated with 49.7 patient-exposures per batch for second or subsequent transfusions. Therefore, first transfusions resulted in 1 case of hepatitis for every 8 patient-exposures per batch used whereas second or

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subsequent transfusions of brand L produced 1 case of hepatitis for every 166 patient-exposures per batch. A patient was thus 20 times less likely to contract overt hepatitis if he had previously received a transfusion of brand L known to have been associated with other cases of overt non-B hepatitis. This may be due to subclinical infection acquired after a previous transfusion and is consistent with the view that all cases of brand-L-associated, non-B hepatitis occurring after first transfusions of brand L were due to an infective agent of the same serotype. All the brand-L-associated non-B hepatitis cases in patients who experienced multiple attacks of hepatitis occurred after the first transfusion of brand L that these patients received.

These observations suggest that the non-B hepatitis associated with brand L manufactured in the U.S.A.[1] may be of a single type, different from the non-B hepatitis associated with brand M and N.H.S. factor VIII in use in the U.K. in 1974–76. The incubation periods of the N.H.S. factor VIII and brand M associated non-B hepatitis ranged from 10 to 119 days (mean 51 days). The differences between the means of the incubation periods observed are not statistically significant. This emphasises the need for further work to establish the epidemiology of transfusion hepatitis and to attempt to isolate the infective agents involved.

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URINE MICROSCOPY

SIR,—Dr Kesson and colleagues (Oct. 14, p. 809) in their paper on urine microscopy regard less than 10 white blood-cells (W.B.C.) per high-power field (H.P.F.) as normal, and, not surprisingly, they found that many abnormal urines were not detected by the H.P.F. method. However, 10 W.B.C. per H.P.F. should be regarded as a very high number. I have studied the relation between the number of W.B.C. per H.P.F. in the sediment of 10 ml of urine and the number of W.B.C./μl in uncentrifuged urine, taking ⩽10 W.B.C./μl as normal. All urines containing 5 or more cells per H.P.F. contained >10 W.B.C./μl (table), a limit five times as high as Kesson's. The table shows that no more than 1 W.B.C. per H.P.F. should be regarded as normal, if 10 W.B.C./μl is regarded as upper limit of normal. This limit is close to Gadeholt's ⩽13 cells/μl, a number based on extensive studies.[1] The diameter of the visual field varies with different microscopes, but no standard microscope has a visual field so broad as to justify <10 W.B.C. per H.P.F. as normal. However, I agree with Kesson et al. that W.B.C.s should be counted in a counting chamber.

SENSITIVITY OF H.P.F. METHOD OF URINE MICROSCOPY

W.B.C./H.P.F.	No. tested	No. with >10 W.B.C./μl
0	70	5 (*8%*)
1	22	8 (*36%*)
2	17	9 (*52%*)
3	11	8 (*72%*)
4	9	7 (*77%*)
5	56	56 (*100%*)

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DISSEMINATED ATYPICAL MYCOBACTERIAL INFECTION IN HAIRY-CELL LEUKÆMIA

SIR,—Atypical mycobacteria are not widely recognised as opportunistic pathogens.[1,2] These acid-fast bacilli, though capable of occasionally producing tuberculosis-like disease, have a low pathogenicity.[3] Moreover, disseminated atypical mycobacterial infection is rare, even in compromised hosts. We report here two cases of disseminated atypical mycobacteriosis in patients with hairy-cell leukæmia, itself a very uncommon lymphoproliferative disease.[4]

Case 1—A 28-year-old male was well until 4 weeks before admission (July, 1976) when he noted progressive fatigue and night sweats. On admission, his temperature was 39·5°C. The liver measured 20 cm on percussion, and the spleen tip was palpated at the left iliac crest. The white-blood-cell count (W.B.C.) was 1300/μl, platelets 30 000/μl, and hæmatocrit 38%. The peripheral smear showed 27% typical hairy cells with characteristic tartrate-resistant acid-phosphatase activity and prominent cytoplasmic projections.[5] The bone-marrow showed the typical morphology of hairy-cell leukæmia.[6] A chest X-ray showed enlargement of the left hilum. The patient's hospital course was marked by daily fever spikes of 39–41°C. Repeated attempts to culture pathogens from blood, sputum, and urine were unsuccessful, and the patient did not respond to broad-spectrum antibiotics (carbenicillin, a cephalosporin, gentamicin). A 5 tuberculin units P.P.D. skin test showed no induration. Fever persisted, and on the 21st hospital day, open lung biopsy was done. A left hilar lymph-node contained granulomas and many acid-fast bacilli. Isoniazid, ethambutol, and rifampin were started, but the patient's clinical condition did not improve. The patient became progressively hypoxæmic and hypotensive, and he died on the 42nd hospital day. Cultures of the biopsy specimen and of post-mortem lung tissue grew *Mycobacterium kansasii*. Granulomas containing acid-fast bacilli were found in the liver, lymph-nodes, and lung.

Case 2.—A 57-year-old male farmer was in his usual state of good health until one month before admission, when intermittent fever, shaking chills, and weight loss developed. He was evaluated at another hospital where the chest X-ray was reported to show fluffy interstitial infiltrates bilaterally. A histoplasmin skin test was negative. When a 3-week trial of prednisone, 10 mg daily, failed to produce a clinical response, the patient was transferred to our hospital, where evaluation of his peripheral blood smear showed 8% characteristic hairy cells. Bone-marrow biopsy and the presence of tartrate-resistant acid phosphatase in the hairy cells confirmed the diagnosis of hairy-cell leukæmia. After an unsuccessful trial with broad-spectrum antibiotics, a therapeutic splenectomy[4] was done, and an intraoperative liver biopsy specimen showed invasion by hairy cells. Postoperatively, the patient's clinical state improved strikingly and the lung infiltrates cleared. After 1 month in the hospital, the patient was discharged, only to return a week later because his temperature was 39°C. Biopsy of an enlarged left supraclavicular lymph-node showed non-caseating granulomata and acid-fast bacilli and grew *M. intracellulare* (Battey bacillus), which proved resistant to isoniazid 1·0 μg/ml, ethambutol 5·0 μg/ml, rifampin 5·0 μg/ml, kanamycin 6·0 μg/ml, streptomycin 10·0 μg/ml, and *p*-aminosalicylic acid 10 μg/ml, and sensitive to ethionamide 5 μg/ml. The patient was placed empirically on a six-drug regimen[7] consisting of isoniazid 600 mg/day, ethambutol 25 mg/kg daily, rifampin 600 mg/day, ethionamide 500 mg twice a day, pyrizinamide 1500 mg

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