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sarcoidosis, and moderate hepatomegaly: aminotransferase levels had been normal or slightly raised between 1975 and 1978. In 1984 this patient died of coronary artery disease and necropsy revealed severe postnecrotic cirrhosis and chronic active hepatitis.[1] The other five patients with raised aminotransferase levels after exposure to the suspect immunoglobulin are still symptomless but continue to have fluctuating abnormal alanine aminotransferase (ALT) values (44–382, 69–660, 150–348, 42–67, and 43–421 U/l during the past year) while receiving monthly infusions of another intravenous immunoglobulin preparation.

Of the nine exposed patients who were unaffected at first, two have shown a slow, steady increase in ALT (35–66 and 53–126 U/l) but all nine have no symptoms.

The aminotransferase pattern is consistent with NANBH, but it is difficult to make this diagnosis in an immunodeficient patient given exogenous antibodies. We have recently tested frozen samples from six patients with raised aminotransferases for IgM antibodies to hepatitis B, cytomegalovirus, and Epstein-Barr virus. None were found; however, the patients' serum IgM levels were generally low and their ability to make IgM antibody is defective, making it difficult to interpret these serological tests. Liver biopsy in symptomless patients is not justified.

The two suspect lots of IVIG were produced from a single batch of fraction II paste in a pilot plant rather than a production facility. Lots produced subsequently by the same manufacturing procedure in the more controlled environment of a production facility have been given to at least six hundred patients worldwide, including twenty-three with primary immunodeficiency diseases without any reports of increased aminotransferase levels.

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LIVER DISEASE IN HAEMOPHILIA

SIR,—Progressive liver disease in patients with haemophilia[1–3] is assumed to result from replacement therapy with coagulation factor concentrates. Like Hay et al,[1] we think that progressive liver disease is an understated problem. Hay et al found by biopsy, progressive liver disease in 38% of patients with haemophilia (chronic active hepatitis 26%, cirrhosis 12%). These figures are close to ours. Between 1972 and 1985 we did 52 biopsies on 45 patients and found signs of subsided hepatitis in 24%, chronic persistent hepatitis in 27%, and progressive liver disease in 29% (16% chronic active hepatitis, 13% cirrhosis). The multicentre study by Aledort et al,[4] to which we contributed biopsy material, came to a similar conclusion about the frequency of cirrhosis.

Age may play a part[2] but in adults the development of liver disease seems to depend more on the state of the individual patient than on age. We found no correlation between age and liver status, the median ages being 31 for subsided hepatitis, 25 for chronic persistent hepatitis, 25 for chronic active hepatitis, and 33 for cirrhosis. 42 of our biopsies were done blind and the frequency of cirrhosis might have been even higher if biopsy material had been obtained from affected parts of the liver.[5,6] Unlike Hay et al, who used persistently raised transaminase levels as a criterion for biopsies, we studied all patients who needed surgery (in most cases orthopaedic) and who consented to biopsy, which explains why we found cirrhosis less often than Hay et al did. We found that transaminase levels rose with the severity of histological findings (see table). However, in the individual case, transaminase levels provided only a poor clue, and we agree with Hay et al that there is no relation between degree of abnormality in aminotransferase levels and the severity of the underlying liver disease.

150 patients receive regular treatment in our centre and extrapolating from the 13% frequency of liver cirrhosis found by biopsy in 45 patients we would expect there to be 19 cases of liver cirrhosis among these 150 haemophiliacs. 11 have been diagnosed (9 with clear clinical symptoms such as oesophageal varices, bleeding form oesophageal varices, or ascites and histologically so there are probably other cases of cirrhosis without specfic clinical symptoms among our patients with haemophilia. When liver cirrhosis was clinically diagnosed in our patients the median age was 43. Epple et al[7] found that in non-haemophiliacs in the region of Germany that includes Heidelberg the median age of patients at the time of diagnosis of cirrhosis was 56. 5 of our 11 haemophiliacs with liver cirrhosis have died from hepatic failure (1 with liver cancer at necropsy) and G. Landbeck tells us that in 97 haemophiliacs who died between January, 1978, and October 1985, in West Germany liver disease was the direct cause of death.[7]

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TREADMILL TESTS FOR ANXIOUS OR DEPRESSED PATIENTS

SIR,—It is as important to identify cardiovascular disease in anxious and depressed patients as it is in other groups—indeed anxious patients may be especially at risk.[1] Dr Channer and colleagues (Oct 12, p 820) argue that diagnostic exercise testing is "superfluous in anxious and depressed patients with atypical chest pain". Their data do not support such a strong conclusion.

Although their discriminant analysis found that anxious and depressed patients with atypical chest pain had a high probability of a negative treadmill test, this finding was based on only 4 patients—the 4 (out of 87) who had anxiety/depression and atypical chest pain. A positive test in any of these 4 patients would have rendered the discriminant analysis insignificant, yet the exercise tests were done in such a way that the depressed patients walked for a significantly shorter time and were thus less likely to have an ischaemic endpoint response. The results would have been meaningful only if the anxious and depressed patients had reached

CORRELATION BETWEEN HISTOLOGICAL DIAGNOSES AND LIVER FUNCTION TESTS

No of patients	No of tests per patient	Histological diagnosis*	GOT (U/L)	GPT (U/L)	GGT (U/L)	Bilirubin (mg/dl)
9	10	SH	24 (8– 38)	45 (9– 97)	27 (7– 78)	0·6 (0·3–0·9)
10	12	CPH	28 (17– 54)	75 (34–229)	49 (15– 92)	0·9 (0·4–2·3)
9	12	CAH	49 (15–102)	94 (26–252)	75 (17–246)	0·7 (0·3–1·2)

Mean values and ranges of liver function tests. Observation period two years.
*SH = subsided hepatitis; CPH = chronic persistent hepatitis; CAH = chronic active hepatitis.

Lancet 1985; ii: 1187

The recent spread of slim disease (AIDS) not only from Tanzania (as suggested by Serwadda et al) but also from Rwanda to southern Uganda and Kampala must be considered.

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LIVER DISEASE IN HAEMOPHILIA

SIR,—Professor Mannucci and Dr Colombo (Oct 5, p 774) contrast our report[1] of a high incidence of severe and sometimes progressive liver disease in a group of 34 haemophiliacs with their study of 10 patients.[2] They speculate that age (mean 32 years in our series, 12 years in theirs), and possibly also delta infection, might account for some of the differences between our findings.

Age may be a factor. The relation between age and histological diagnosis in our patients was examined by analysis of variance, and there was a significant difference between the mean ages of patients with chronic persistent hepatitis (CPH), chronic active hepatitis (CAH), and cirrhosis (25, 35, and 48 years respectively; $p<0{\cdot}01$). Older patients may, in some cases, merely have had longer for the natural history of their liver disease to unfold. On the other hand, since most of our 34 patients of all ages probably contracted hepatitis in 1973–76, a variation in host-response to viral infection with age may also be important.

A crucial difference in patient selection also underlies the differences between our results since all our patients had persistently abnormal transaminases at the time of biopsy. In contrast, 8 of the 10 patients described by Mannucci et al[2] had normal or intermittently abnormal transaminases at the time of their first follow-up biopsy. We believe that haemophiliacs with persistently abnormal liver biochemistry may be affected more frequently by progressive and severe liver disease than the rest. When discussing our results, we therefore related the number with severe liver disease, not to the 34 on whom biopsies were done, but to the 79 patients from whom they had been selected. We were thus able to derive a frequency for cirrhosis of at least 11·5%, for example. Physical signs and liver tests on the remaining patients not investigated by biopsy suggest that cirrhosis awaits histological confirmation in a further 5 or 6 patients. The frequency of cirrhosis may thus be more than 15%, a figure in close accord with that from a retrospective study of 155 unselected liver biopsy and necropsy specimens collected worldwide by Aledort et al.[3] Even this study may underestimate the incidence of cirrhosis in haemophilia since many of the liver biopsies reviewed dated from the mid-1970s or even earlier. The incidence of acute hepatitis in haemophilia increased rapidly in 1973–75, with the introduction of concentrates, and the time scale for the development of liver disease dated from then for most patients. Cirrhosis may take many years to develop and so many patients with biopsy evidence of CPH or CAH in the 1970s will now have progressed to cirrhosis.[1] Non-haemophiliacs followed up after post-transfusional non-A, non-B hepatitis (NANB) are similarly affected, cirrhosis arising in 15–25% of individuals.[4–6]

In contrast with the experience in the Italian population, neither delta infection nor hepatitis B is a major problem among our patients, since only 2 are HBsAg-positive. The delta antigen has been detected in 6 of our 34 liver biopsy specimens and this has not been associated with progressive disease. In our population, NANB hepatitis is the predominant cause of haemophilic liver disease, and this gives rise to serious and sometimes progressive liver disease in a substantial minority of patients.

Mannucci and Colombo cite several reports, all dating from 1976, stating that liver disease was an insignificant cause of death in haemophiliacs. A decade later this statement warrants re-examination.

We thank Prof M. Rizzetto for testing our specimens for the delta antigen.

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COMMON ACTIVATED HELPER-T-CELL ORIGIN FOR LYMPHOMATOID PAPULOSIS, MYCOSIS FUNGOIDES, AND SOME TYPES OF HODGKIN'S DISEASE

SIR,—Dr Kadin should be congratulated for his attractive hypothesis linking the above diseases (Oct 9, p 864); indeed, other research groups are developing broadly similar concepts using the same monoclonal antibodies. Kadin's hypothesis can already be substantially expanded using published data, which in part support his proposals.

MacKie[1] has suggested that the initial event in mycosis fungoides (MF) is retrovirus infection of epidermal Langerhans' cells. C-type virus-like particles have been identified in the skin and lymph nodes of such patients,[2,3] and HTLV has been isolated from a case of the closely related Sézary syndrome,[4] while the HTLV p19 antigen has been identified in skin and lymph nodes of a case of MF.[5]

Although HTLV I and II contain oncogenes and are associated with T cell proliferation, HTLV-III contains no oncogenes and is purely T cell cytotoxic. It is, therefore, reasonable to modify Kadin's hypothesis by suggesting that in some instances retrovirus-induced T cell immune paresis could permit secondary DNA virus infection (such as Epstein-Barr and cytomegalovirus) with resulting cellular proliferation and malignancy. Intensive research into the possible presence of new HTLV subtypes in this group of diseases is urgently required.

The similarities between Hodgkin's disease (HD) and MF are well illustrated by a histological classification of MF proposed by Goos and Christopher.[6] MF is regarded as showing four subtypes with poikilodermatous, mixed cellularity, lymphocyte predominance, and lymphocyte depleted features. The latter aggressive subtype displays numerous large atypical cells with binucleate forms resembling Reed-Sternberg (RS) cells[7] and morphological distinction from HD is difficult. The differential diagnosis is further complicated by the expression of the HD-associated antigen Ki-1 in MF.[8] The monoclonal antibody Leu-M1 (Becton Dickinson) also reacts with RS cells[9] and we have demonstrated positive staining in some of the RS-type cells of MF (unpublished). The expression of such antigens in advanced forms of MF supports the view that the disease dedifferentiates during evolution from its usual banal origin. However, these findings imply that the diagnostic accuracy of saying one disease changes into another is limited and fraught with problems.

Both MF and lymphomatoid papulosis are characterised by close association between lymphoid and antigen presenting (Langerhans') cells, but Kadin does not incorporate this area into his hypothesis. Although classically MF has been regarded as a primary cutaneous disorder, there is now reasonable evidence that it