Increased circulating water-soluble vitamin levels have been noted during the acute phase of human viral hepatitis, and this has also been reported in rats with CCl₄-induced hepatic necrosis. Low hepatic vitamin concentrations in the rats were followed by low levels later in the illness. Although patients with DCLD of alcoholic aetiology tended to have lower circulating levels of vitamins than those with non-alcoholic DCLD, the prevalence of abnormally low concentrations did not differ. Decreased dietary nutrient intake and alcohol appeared to be less important determinants of biochemical vitamin deficiency than the presence of liver disease per se. Finally, urinary excretion of these vitamins or their major metabolites in patients with severe liver disease correlated poorly with circulating levels of vitamins.


PATIENTS AND METHODS

The 34 patients with FHF included 22 with hepatic necrosis due to paracetamol overdose, 10 with acute viral hepatitis and 2 with halothane-associated hepatitis. The mean interval (± SEM) between the first symptoms of hepatitis and the time of study was 7.7 ± 1.7 days, and as far as could be ascertained, dietary intake before the onset of hepatitis had been adequate in all patients.

Liver Interventions: Supportive therapy for hepatic failure, including neomycin, lactulose and, in some cases, fresh frozen plasma to correct coagulation deficiencies, had been given to all patients. Energy intake comprised intravenous infusions of 10% dextrose only and no amino acid or lipid preparation was used.

Thirty-three patients with DCLD were studied. The aetiology was as follows: active chronic hepatitis with cirrhosis (4), primary biliary cirrhosis (3), secondary biliary cirrhosis (1), haemochromatosis (1), crypogenic cirrhosis (1) and schistosomiasis (1). Four patients had subacute hepatic necrosis and had been ill for 4 - 6 months, and 18 had cirrhosis attributable to alcohol. Nine of the latter group admitted to a daily alcohol consumption of at least half a bottle of spirits, or the equivalent, within the 2 weeks of the study (classified as recent heavy drinking), while 4 had been drinking one-third to one-half of a bottle (recent moderate drinking). The remaining 5 claimed complete abstinence from alcohol for...
RESULTS

A strikingly high prevalence (75%) of B-hypervitaminæmia was found (Fig. 1) in patients with FHF during the first week of the illness. This was followed by low plasma PLP levels during the third week of the illness in 40% of patients. The other vitamins did not follow this pattern. Elevated blood niacin (25%) occurred at any stage during the course of the illness, as did subnormal thiamine (54%), niacin (38%) and ascorbic acid (12%). Hypovitaminæmia of one or more vitamins was found in 71% of FHF patients.

In DCLD (Fig. 1) the emphasis was on hypovitaminæmia (88%), with B (87%) most prominent, followed by thiamine (65%), ascorbic acid (39%) and niacin (16%). Hypervitaminæmia was uncommon, with the exception of a 29% incidence of high blood niacin concentration. Vitamin levels in DCLD did not correlate with the clinical state, aetiology and duration of illness, or dietary history.

Patients with alcoholic cirrhosis had significantly lower mean red cell transketolase, plasma pyridoxal phosphate and plasma and urine ascorbic acid than normal controls (Table I), while only plasma pyridoxal phosphate in the non-alcoholic group was significantly lower than in controls. However, with the exception of red cell transketolase, no significant difference could be demonstrated in a direct comparison between alcoholic and non-alcoholic cirrhotic patients. In fact, plasma pyridoxal phosphate and urinary 4-pyridoxic acid excretion tended to be lower in the non-alcoholic group, although not significantly so. The overall prevalence of hypovitaminæmia (Table II) was very similar in the 2 groups, and no significant

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**TABLE I. COMPARISON OF INITIAL CIRCULATING VITAMIN CONCENTRATIONS (MEAN ± 1 SEM) IN NORMAL CONTROLS AND IN PATIENTS WITH ALCOHOLIC AND NON-ALCOHOLIC DCLD**

<table>
<thead>
<tr>
<th>Vitamin</th>
<th>Normal controls</th>
<th>Alcoholic DCLD</th>
<th>Non-alcoholic DCLD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thiamine</td>
<td>41.9 ± 1.7 (N = 12)</td>
<td>27.0 ± 2.9* (N = 17)</td>
<td>35.9 ± 2.7** (N = 14)</td>
</tr>
<tr>
<td>RBC transketolase (U/l)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TPP effect (%)</td>
<td>10.7 ± 2.2 (N = 12)</td>
<td>21.0 ± 5.4 (N = 17)</td>
<td>14.6 ± 3.8 (N = 14)</td>
</tr>
<tr>
<td>Vitamin B₆</td>
<td>11.7 ± 1.0 (N = 19)</td>
<td>3.5 ± 0.6* (N = 17)</td>
<td>2.5 ± 0.5* (N = 14)</td>
</tr>
<tr>
<td>Plasma pyridoxal phosphate (ng/ml)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vitamin C</td>
<td>0.91 ± 0.12 (N = 19)</td>
<td>0.60 ± 0.10* (N = 13)</td>
<td>0.81 ± 0.54 (N = 14)</td>
</tr>
<tr>
<td>Plasma ascorbic acid (mg/100 ml)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Leucocyte ascorbic acid (µg/10 WBC)</td>
<td>36.1 ± 5.2 (N = 7)</td>
<td>36.0 ± 10.5 (N = 6)</td>
<td>29.8 ± 5.6 (N = 8)</td>
</tr>
<tr>
<td>Niacin</td>
<td>0.89 ± 0.07 (N = 12)</td>
<td>1.18 ± 0.18 (N = 17)</td>
<td>1.10 ± 0.11 (N = 14)</td>
</tr>
<tr>
<td>Blood niacin (mg/100 ml)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Versus normal controls (P<0.0005).
** Versus alcoholic DCLD (P<0.0025).
difference in the hypovitaminaemia of individual vitamins could be demonstrated by the $\chi^2$ test.

Urinary excretion of vitamins or their major metabolites was not significantly different in patients with FHF or DCLD (combined, alcoholic or non-alcoholic) compared with normal controls. The exception was that mean ($\pm$ 1 SEM) urinary ascorbic acid excretion in FHF patients was significantly lower than that of normal controls (12.0 $\pm$ 3.0 mg/24 h and 30.3 $\pm$ 3.9 mg/24 h respectively; $P<0.0025$). There was no correlation between circulating concentrations of individual vitamins and their urinary excretion products and even very high circulating levels of PLP in FHF were not reflected in the urinary 4-pyridoxic acid excretion.

**DISCUSSION**

The present finding of a 71% overall prevalence of low vitamin levels in FHF has not been previously described. With regard to vitamin B$_6$, it has been suggested that an initial release of PLP$^{35}$ may result in depletion of hepatic vitamin B$_6$ and subsequent low circulating concentrations of the vitamin. Hepatic release of niacin or increased synthesis from the endogenous tryptophan load$^{36}$ may have contributed to the finding of elevated blood niacin concentrations in a number of FHF patients. However, the importance of hepatic release of vitamins other than B$_6$ in producing a deficiency state is uncertain. Dietary factors are unlikely to be of major consequence, since the mean interval between the first symptoms and the time of study was only 7.7 $\pm$ 1.7 days, and as far as could be ascertained, dietary intake before the onset of the illness had been adequate.

The high prevalence (88%) of biochemical vitamin deficiency in chronic severe liver disease is clearly shown in this study. Many factors could contribute to this, but the lack of correlation with dietary intake and the similar incidence in alcoholic and non-alcoholic patients run contrary to previously held views that dietary factors or the direct effects of alcohol$^{15,16}$ were of paramount importance.$^{15}$ Rather, it would seem that severe liver disease itself in some way determines vitamin deficiency. Many vitamins (e.g. B$_1$ and B$_6$) need to be activated in the liver: increased requirements, increased degradation$^{15}$ or excretion$^{15}$ may be important. The interplay of these factors may also explain the lack of correlation between urinary vitamin excretion and circulating concentrations. In addition, hepatic necrosis may result in elevated circulating vitamin concentrations even in the presence of depleted total body stores. Thus, while measurement of plasma PLP is a valid index of vitamin B$_6$ nutrition in patients without liver disease,$^{21,22}$ it may give misleadingly high readings in patients with extensive hepatocellular necrosis. Minor degrees of necrosis, as in chronic active hepatitis, were not found to cause elevated plasma PLP values in the present study.

It has been suggested that transketolase apo-enzyme synthesis in the liver may be depressed in severe hepatocellular disease, leading to low erythrocyte transketolase activity even in the presence of normal thiamine levels.$^{23}$ On the other hand, we have previously shown that, upon supplementation with thiamine, red cell transketolase activity can be restored to normal even in the presence of severe impairment of liver function.$^{24}$ We therefore accepted both a low red cell transketolase activity and a high TPP effect as indicators of thiamine deficiency.$^{25}$

The high prevalence of deficiency of thiamine, niacin and vitamin B$_6$ in DCLD reported here is at variance with the figure of 10% obtained by Morgan et al.$^{26}$ for B-complex vitamins, perhaps because of a greater severity of liver disease in the present study. However, there is good agreement on ascorbic acid deficiency (31% in the present study, 35% in the study of Morgan et al.$^{26}$).

The vitamin deficiencies present in patients with severe liver disease may be of considerable importance. Vitamins are co-factors for many enzymic reactions. For these reasons, and because of the high prevalence of deficiency encountered in this study, the supplementation of all patients suffering from severe liver disease with water-soluble vitamins is indicated. The advent of new methods of treating hepatic encephalopathy with tailored amino acid infusions$^{27}$ will also require appropriate and effective vitamin co-factors to encourage optimal utilization. Recommendations as to dosage and formulation of such supplementation must await further study, since documented gross disturbances of the metabolism of certain vitamins$^{21,22}$ may render the use of conventional preparations largely ineffective.

The assistance of Drs N. Krasner and B. McConnell is gratefully acknowledged. Dr J. E. Rossouw was supported by a grant from the South African Medical Research Council.

**REFERENCES**

Hodgkin’s Disease – a ‘B’ Neoplasm?

W. G. STAPLES, A. E. VISSER

SUMMARY

Lymph node tissue from 2 patients with Hodgkin’s disease was studied by light microscopy using the immunoperoxidase technique with a panel of monospecific antisera. Hodgkin’s mononuclear and Reed-Sternberg cells were shown to exhibit features characteristic of B cells. The possibility that Hodgkin’s disease is a B-cell neoplasm is discussed.


Early observers found that in a large percentage of patients with Hodgkin’s disease the tuberculosis reaction was negative, even in those who had active tuberculosis. Later it was shown that this immunological defect was due to a lack of responsiveness to antigens evoking a cell-mediated, delayed-type immunological reaction. Humoral immunity was intact, but lymphocyte transformation by phytohaemagglutinin was impaired. This suggested that Hodgkin’s disease affected the function of T lymphocytes. In keeping with this concept is the fact that the earliest sites of Hodgkin’s disease in lymph nodes are in the paracortical areas and in the spleen in the peri-arterial lymphoid sheaths, both being thymus-dependent areas. Work by Peckham and Cooper and later by Dorfman et al. suggested that Reed-Sternberg cells originated from transformed lymphocytes. In 1974 Taylor, using the immunoperoxidase method, demonstrated that some of the Reed-Sternberg cells contained intracytoplasmic immunoglobulin. In a study of the lacunar cells of nodular sclerosing Hodgkin’s disease, Anagnostou et al. demonstrated intracytoplasmic immunoglobulin in Hodgkin’s mononuclear cells, Reed-Sternberg cells and the lacunar variants. With the antisera to heavy chains used, only the gamma component was detectable intracytoplasmically, of similar distribution and intensity of staining. On the basis of these findings they suggested that both the lacunar cells and Reed-Sternberg cells originated from abnormal transformed B lymphocytes (immunoblasts). This is at