ALIMENTARY TRACT AND PANCREAS

Primary immunodeficiency presenting with gastrointestinal disease in the tropics

I. N. ROSS* AND V. I. MATHAN

The Wellcome Research Unit, Christian Medical College and Hospital, Vellore, Tamilnadu, India

Accepted for publication 8 August 1987

Abstract Thirteen patients with hypogammaglobulinaemia were detected in a group of 1300 patients with chronic diarrhoea and malabsorption. Panhypogammaglobulinaemia was present in ten, selective IgA deficiency in two and in one deficiency of IgA and IgM. Functional antibodies were decreased but still detectable. Nodular lymphoid hyperplasia was present in jejunal mucosal biopsies in five and plasma cells were reduced or undetectable in eight. Epithelial lymphocytes were increased. There were only mild abnormalities in in vitro lymphocyte function. While the prevalence of *Giardia lamblia* was high in the immunodeficient subjects, the prevalence of other gastrointestinal parasites, pathogenic bacteria, or rotavirus, was not high. The pathogenesis of malabsorption in these patients was not clear. Overall morbidity in these immunodeficient patients was similar to that in reports from temperate countries, in spite of their living in an environment with a high prevalence of pathogens.

Key words: gastrointestinal immunity, malabsorption syndrome, primary immunodeficiency.

INTRODUCTION

Common variable immunodeficiency (CVID) is associated with gastrointestinal symptoms in 20–90% of patients described from temperate countries.1-3 Diarrhoea and *Giardia lamblia* infestation is often found in patients with CVID, while in thymus-derived lymphocyte

*Present address: Department of Medicine, School of Medical Sciences, University Sains Malaysia, Minden, Penang, Malaysia.
Correspondence: Professor V. I. Mathan, Wellcome Research Unit, C.M.C. Hospital, Vellore 632 004, India.
(T cell) deficiency states diarrhoea due to bacterial pathogens is frequent. Gluten-sensitive enteropathy or inflammatory bowel disease is present in approximately 5% of individuals with serum IgA deficiency. In tropical countries these immunodeficiency syndromes have been relatively infrequent. It has been suggested that this is due to a higher prevalence of infections, resulting in an increased morbidity and mortality in immunodeficient individuals, who may succumb before seeking medical help. This paper describes the clinical and immunological findings in 13 patients with primary immunodeficiency who were detected in southern India over a 10 year period during a detailed investigation of 1300 patients presenting with chronic diarrhoea due, in the majority, to a malabsorption syndrome.

METHODS

All patients were admitted to a metabolic ward and investigated in detail as described elsewhere. In particular the absorption of D-xyllose, fat and Vitamin B12 were tested. Per oral jejunal mucosal biopsies were graded as showing mild, moderate or severe changes; the presence of nodular lymphoid hyperplasia was noted and intra-epithelial lymphocytes (IEL) counted. Several samples of faeces and jejunal luminal fluid were examined in each patient for parasites and bacteria. An augmented histamine test (AHT) was performed in six patients.

Immunological studies

Patients with CVID were identified by routine cellulose acetate serum electrophoresis. Patients with IgA deficiency alone were identified by screening a random sample of 541 patients. Serum immunoglobulin deficiency was defined as concentrations either undetectable or less than the 95% tolerance interval for a healthy south Indian control population.

Serum samples were stored at −20°C until tested. Serum concentrations of IgA, IgD, IgG and IgM were measured by single radial immunodiffusion (SRID) using the globulin fraction of heavy chain monospecific antiserum (Seward Laboratories, London, England). Serum IgE was determined using Phadebas kits (Pharmacia Diagnostics AB, Uppsala, Sweden). Unstimulated saliva was collected, centrifuged and stored at −20°C. Jejunal luminal fluid was collected by small bowel intubation, centrifuged and stored at −20°C after the addition of 500 iu of Aprotinin (Trasyrol, Bayer, West Germany) per ml. Stored secretions were thawed at room temperature and IgA, IgG, IgM, secretory IgA (SIgA) and secretory component estimated by immunodiffusion in agar (antisecretory IgA, Seward Laboratories, antisecretory component, Behringwerke AG, Marburg, West Germany).

The ability to produce functional antibody was tested by measuring E. coli agglutinins in serum by haemagglutination and rotavirus antibodies in serum and jejunal luminal fluid (concentrated 10-fold by ultrafiltration), by a microscale enzyme-linked immunoabsorbent assay (ELISA) with horse radish peroxidase as the marker enzyme. The immunoglobulin classes (IgA, IgG and IgM) of plasma cells present in the small intestinal biopsies of four patients were determined by an indirect immunofluorescent technique using 4 μm alcohol-fixed paraffin-mounted sections and class specific rabbit antihuman antiserum followed by fluorescein conjugated goat antirabbit antiserum (Miles Laboratory Limited, Slough, England).

In vitro lymphocyte studies were performed on three patients. Lymphocytes were obtained from defibrinated blood after separation by centrifugation on a Ficoll-Hypaque density gradient. Peripheral blood B lymphocytes were identified and quantitated by surface immunoglobulin staining, using direct immunofluorescence and class specific (IgA, IgG, IgM) fluorescein labelled sheep
Immunodeficiency in the tropics

antiserum (Wellcome Laboratories, Beckenham, England). Quantitation of T cells was performed by rosetting with sheep erythrocytes and lymphocyte transformation performed using a microtiter method. Lymphocytes were stimulated in triplicate with phytohaemagglutinin-A (PHA), (DIFCO Laboratories, Detroit, Mich) at a final concentration of 100 µg/ml, purified protein derivative of tuberculin (PPD-298) at a concentration of 10 µg/ml (Central Veterinary Laboratory, Weybridge, England) BCG at 5 X 10^6/ml, a Mycobacterium leprae preparation at 5 X 10^5/ml and Dharmendra antigen (from M. leprae) at 100 µg/ml. Delayed type hypersensitivity in skin was tested with PPD 1:1000 intradermally in five patients.

Statistical analysis was performed using Student's t test and Chi-squared test with Yate's correction. Data were compared, where appropriate, with data from normal South Indian controls and other patients with gastrointestinal complaints but normal concentration of immunoglobulins.

RESULTS

Ten patients with hypogammaglobulinaemia were detected in 1300 consecutive patients admitted with diarrhoea for longer than 2 weeks; a prevalence of 0.8%. Three further patients with serum IgA deficiency were detected in 541 subjects whose stored serum samples were chosen at random from the above 1300 admissions, a prevalence of 0.6%.

Clinical studies

Twelve patients were male and 1 female (GN). All patients presented with a history of chronic or intermittent diarrhoea, varying in duration from 3 to 22 years, geometric mean duration 3.4 years (Table 1). This duration was significantly longer than that seen in 100 immunocompetent patients with chronic diarrhoea (usually tropical sprue) (geometric mean duration 6 months, range 2 weeks to 6 years, P < 0.001). Four patients also suffered from recurrent respiratory tract infections. Only two patients (GN and CH) complained of blood and mucus in the stool. However, sigmoidoscopy observed in 11 patients showed a hyperaemic, oedematous and friable mucosa without ulceration in two patients (LN, MA), ulceration in a further two patients (CH, SW) and ulcerated sessile polyps in one (GN). Large intestinal bacterial or parasitic infections were not demonstrated in these five patients.

A mild anaemia (Hb < 9 g/dl) was present in nine patients, two with megaloblastic bone marrow aspirates. Six patients had low serum concentrations of iron and folate and, in one patient, of Vitamin B12.

Giardia lamblia infection was found in six of 12 patients with hypogammaglobulinaemia at their first admission (Table 1). This was significantly higher than the prevalence seen in other individuals, with chronic diarrhoea (13:100) (P < 0.005). The prevalence of other parasites or bacterial pathogens was not increased. Ten patients had xylose malabsorption, seven borderline or frank Vitamin B12 malabsorption and 11 steatorrhoea. Gastric acid production measured by maximum acid output (MAO) was less than 5.8 mmol/h, in four of six patients in whom the test was performed, in two of these individuals there was virtual achlorhydria. The mean serum albumin concentration of the 13 patients was 36.1 ± 7.5 g/l. Although this was significantly lower than the mean in healthy controls (44.2 ± 2.5 g/l, n = 40, P < 0.01), it was significantly higher than the albumin concentration in patients with tropical sprue (30.3 ± 6.0 g/l, n = 30, P < 0.01).

Nodular lymphoid hyperplasia (NLH) was present in five patients (Table 2). Plasma cells were markedly decreased in all patients except patient MA and two patients with IgA deficiency in whom there was an increase. IEL in the immunodeficient patients was significantly increased (geometric mean count 47 IEL per 100 epithelial cell nuclei; 2s.d. range 21–206, n = 10; south Indian
<table>
<thead>
<tr>
<th>Patients</th>
<th>At onset of diarrhoea</th>
<th>At presentation</th>
<th>Follow-up (years)</th>
<th>Jejunal luminal fluid</th>
<th>Faeces</th>
<th>5 g D-xylene excretion (%)</th>
<th>Vitamin B&lt;sub&gt;12&lt;/sub&gt; absorption (dose/lt)</th>
<th>Fecal fat (g/24 h)</th>
<th>AHT total MAO (mmol/l per h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypogammaglobulinaemia</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MR 6</td>
<td>21</td>
<td>9</td>
<td>GL, SS, HW</td>
<td>GL, SS, HW</td>
<td>29</td>
<td>0.13</td>
<td>24</td>
<td>0.28</td>
<td></td>
</tr>
<tr>
<td>VG 12</td>
<td>28</td>
<td>9</td>
<td>GL</td>
<td>GL</td>
<td>29</td>
<td>0.36</td>
<td>5.5</td>
<td>ND</td>
<td></td>
</tr>
<tr>
<td>LN 26</td>
<td>29</td>
<td>NF</td>
<td>GL</td>
<td>GL</td>
<td>17</td>
<td>0.15</td>
<td>14</td>
<td>ND</td>
<td></td>
</tr>
<tr>
<td>BL 15</td>
<td>18</td>
<td>6 (died)</td>
<td>GL</td>
<td>GL Salmonellia</td>
<td>9</td>
<td>0.1</td>
<td>31</td>
<td>7.7</td>
<td></td>
</tr>
<tr>
<td>MA 48</td>
<td>49</td>
<td>5 (died)</td>
<td>GL Salmonellia</td>
<td>GL Salmonellia</td>
<td>6</td>
<td>0.6</td>
<td>17</td>
<td>ND</td>
<td></td>
</tr>
<tr>
<td>DY 10</td>
<td>13</td>
<td>NF</td>
<td>GL Salmonellia</td>
<td>GL Salmonellia</td>
<td>15</td>
<td>0.14</td>
<td>11</td>
<td>ND</td>
<td></td>
</tr>
<tr>
<td>JY 34</td>
<td>35</td>
<td>0 (died)</td>
<td>GL Salmonellia</td>
<td>GL Salmonellia</td>
<td>7</td>
<td>0.2</td>
<td>18</td>
<td>ND</td>
<td></td>
</tr>
<tr>
<td>SH 16</td>
<td>20</td>
<td>NF</td>
<td>GL Salmonellia</td>
<td>GL Salmonellia</td>
<td>21</td>
<td>0.44</td>
<td>9</td>
<td>1.5</td>
<td></td>
</tr>
<tr>
<td>AK 14</td>
<td>20</td>
<td>5</td>
<td>GL Salmonellia</td>
<td>GL Salmonellia</td>
<td>19</td>
<td>0.5</td>
<td>5</td>
<td>ND</td>
<td></td>
</tr>
<tr>
<td>CH 20</td>
<td>21</td>
<td>6 (died)</td>
<td>GL Salmonellia</td>
<td>GL Salmonellia</td>
<td>15</td>
<td>0.32</td>
<td>13</td>
<td>9.3</td>
<td></td>
</tr>
<tr>
<td>SW 15</td>
<td>35</td>
<td>1</td>
<td>GL Salmonellia</td>
<td>GL Salmonellia</td>
<td>19</td>
<td>0.2</td>
<td>18</td>
<td>0.4</td>
<td></td>
</tr>
<tr>
<td>IgA deficiency</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PB 15-75</td>
<td>16</td>
<td>2</td>
<td>GL Salmonellia</td>
<td>GL Salmonellia</td>
<td>19</td>
<td>0.17</td>
<td>ND</td>
<td>4.2</td>
<td></td>
</tr>
<tr>
<td>GN 8</td>
<td>11</td>
<td>6</td>
<td>GL Salmonellia</td>
<td>GL Salmonellia</td>
<td>19</td>
<td>1.3</td>
<td>3</td>
<td>ND</td>
<td></td>
</tr>
</tbody>
</table>

*The prevalence of Giardia lamblia in the immunodeficient patients on initial presentation was 6:12. Represents data obtained, in some cases, from several admissions.

GL = *Giardia lamblia* cysts or trophozoites; SS = Strongyloides stercoralis ova; HW = hookworm ova; RW = roundworm; EH = Entamoeba histolytica cysts; - = no organisms detected; ND = not done; NF = no follow-up.
healthy controls: geometric mean count 30, 2sd. range 15–57, n = 15; P < 0.01).

**Immunological studies**

Serum IgA concentrations were not detectable (<0.003 g/l) in eight patients and less than the 95% tolerance interval in the other five patients (Table 3). Serum IgD was undetectable (<0.003 g/l) in eight patients, but this frequency of undetectable IgD did not differ from that seen in healthy controls. The geometric mean serum IgE concentration for the immunodeficient group (112 U/ml, 2sd. range 2–3528) was significantly lower than that seen in healthy south Indian controls (658 U/ml, 2sd. range 25–17 584, n = 27; P < 0.005). The IgE concentrations appear particularly inappropriately low when the group mean of the nine patients with intestinal parasites (86 U/ml, 2sd. range 2–3208) is compared with the group mean of similarly infected immunocompetent patients (1058 U/ml, 2sd. range 106–10 500, n = 23; P < 0.001). Serum IgG concentrations were less than the 95% tolerance interval in 10 patients; one patient had elevated IgG. Serum IgM was undetectable (<0.01 g/l) in three patients, and less than the 95% tolerance level in eight. One patient (CH) was found to have normal immunoglobulin concentrations on initial presentation with diarrhoea. However, over the next 6 years he developed first selective serum IgA deficiency, then finally severe panhypogammaglobulinaemia.

Salivary and jejunal luminal fluid immunoglobulins, tested in five patients, were absent in three patients with CVID. A fourth patient (MR) with CVID had IgM in his jejunal fluid. The serum IgA deficient patient, PB, had readily detectable IgA in both saliva and jejunal luminal fluid. Secretory IgA was absent in all but patient PB, but the secretory component was present in all secretions examined.

**Functional antibodies**

The majority of patients had reduced serum titres of *E. coli* antibody (<1:32) of the IgM class (Table 3). Serum rotavirus antibody titres were also low in the majority of patients (<1:256). Jejunal luminal fluid rotavirus antibody, present in 11 of 13 immunocompetent subjects, was undetectable in three.

| Table 2 | Summary of small intestinal biopsy findings in 11 immunodeficient patients |
|---------|-------------------------------|-------------------------------|-----------------|----------------|-----------------|
| Patients | Crypt: villus ratio            | Plasma cells                  | Plasma cell Ig Class | NLH  | IEL counts* | Histological grading |
|----------|-------------------------------|-------------------------------|-----------------|----------------|-----------------|
| Hypogammaglobulinaemia |     | Decreased                    | O               | None           | 34              | Moderate        |
| MR       | 1 : 2                         | Decreased                    | O               | None           | 34              | Moderate        |
| LN       | 1 : 1.5                       | Markedly decreased           | O               | None           | 34              | Moderate        |
| Jv       | 2 : 1                         | Markedly decreased           | O               | None           | 34              | Moderate        |
| BL       | 1 : 1                         | Decreased                    | IgM only        | None           | 34              | Moderate        |
| VG       | 1 : 1                         | Absent                       | None            | 34              | Moderate        |
| DY       | 1 : 1                         | Increased                    | None            | 34              | Moderate        |
| MA       | 1 : 1                         | Decreased                    | None            | 34              | Moderate        |
| SH       | 1 : 3                         | Markedly decreased           | None            | 34              | Moderate        |
| SW       | 1 : 4                         | Markedly decreased           | None            | 34              | Moderate        |
| IgA Deficiency |     | Increased                    | IgA, IgG, IgM   | None           | 34              | Moderate        |
| CH       | 3 : 1                         | Increased                    | IgA, IgG, IgM   | None           | 34              | Moderate        |
| PB       | 1 : 1                         | Increased                    | IgA, IgG, IgM   | None           | 34              | Moderate        |

*Expressed as the number of IEL per 100 epithelial cell nuclei; normal south Indian geometric mean 30, 2sd. range 15–57 (n = 15).

Subsequently developed panhypogammaglobulinaemia.

O indicates no immunoglobulin-containing cells detected.

- Indicates assessment not possible.
Table 3 Serum concentrations of immunoglobulins, E. coli and rotavirus antibody titres in a normal control group and in immunodeficient patients

<table>
<thead>
<tr>
<th></th>
<th>IgA (g/l)</th>
<th>IgD (g/l)</th>
<th>IgE (U/ml)</th>
<th>IgG (g/l)</th>
<th>IgM (g/l)</th>
<th>E. coli Ab titre</th>
<th>Rotavirus Ab titre</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal south Indian controls</td>
<td>2.57 (1.00-6.59)</td>
<td>0.01 (0-0.25)</td>
<td>968 (14-31.056)</td>
<td>12.38 (6.29-23.27)</td>
<td>1.07 (0.49-2.32)</td>
<td>&gt;1:32</td>
<td>&gt;1:256</td>
</tr>
<tr>
<td>n = 57</td>
<td>n = 27</td>
<td>n = 52</td>
<td>n = 56</td>
<td>n = 28</td>
<td>n = 100</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Hypogammaglobulinaemia

<table>
<thead>
<tr>
<th></th>
<th>IgA (g/l)</th>
<th>IgD (g/l)</th>
<th>IgE (U/ml)</th>
<th>IgG (g/l)</th>
<th>IgM (g/l)</th>
<th>E. coli Ab titre</th>
<th>Rotavirus Ab titre</th>
</tr>
</thead>
<tbody>
<tr>
<td>MR</td>
<td>0</td>
<td>0</td>
<td>170</td>
<td>4.95</td>
<td>0.27</td>
<td>1:64</td>
<td>1:64</td>
</tr>
<tr>
<td>VG</td>
<td>0.32</td>
<td>0</td>
<td>5000</td>
<td>4.66</td>
<td>0.14</td>
<td>1:8</td>
<td>1:64</td>
</tr>
<tr>
<td>BL</td>
<td>0.32</td>
<td>0</td>
<td>20</td>
<td>1.45</td>
<td>0.35</td>
<td>1:8</td>
<td>1:64</td>
</tr>
<tr>
<td>LN</td>
<td>0.24</td>
<td>0.02</td>
<td>30</td>
<td>3.60</td>
<td>0</td>
<td>1:8</td>
<td>1:16</td>
</tr>
<tr>
<td>MA</td>
<td>0.24</td>
<td>0.02</td>
<td>200</td>
<td>4.77</td>
<td>0.43</td>
<td>1:32</td>
<td>1:256</td>
</tr>
<tr>
<td>DY</td>
<td>0</td>
<td>0</td>
<td>40</td>
<td>5.36</td>
<td>0.08</td>
<td>1:8</td>
<td>1:8</td>
</tr>
<tr>
<td>JF</td>
<td>0.32</td>
<td>0</td>
<td>3500</td>
<td>0.85</td>
<td>0.04</td>
<td>1:8</td>
<td>1:4</td>
</tr>
<tr>
<td>SH</td>
<td>0.11</td>
<td>0.03</td>
<td>10</td>
<td>3.06</td>
<td>0.07</td>
<td>1:8</td>
<td>1:8</td>
</tr>
<tr>
<td>AK</td>
<td>0</td>
<td>0</td>
<td>30</td>
<td>1.26</td>
<td>0</td>
<td>1:8</td>
<td>1:8</td>
</tr>
<tr>
<td>CH</td>
<td>0.02</td>
<td>0.75</td>
<td>600</td>
<td>0.43</td>
<td>0</td>
<td>1:8</td>
<td>1:52</td>
</tr>
<tr>
<td>SW</td>
<td>0</td>
<td>0.75</td>
<td>140</td>
<td>24.80</td>
<td>0.23</td>
<td>1:16</td>
<td>1:256</td>
</tr>
</tbody>
</table>

IgA deficiency

<table>
<thead>
<tr>
<th></th>
<th>IgA (g/l)</th>
<th>IgD (g/l)</th>
<th>IgE (U/ml)</th>
<th>IgG (g/l)</th>
<th>IgM (g/l)</th>
<th>E. coli Ab titre</th>
<th>Rotavirus Ab titre</th>
</tr>
</thead>
<tbody>
<tr>
<td>PB</td>
<td>0</td>
<td>0.10</td>
<td>520</td>
<td>6.31</td>
<td>0.53</td>
<td>1:16</td>
<td>1:128</td>
</tr>
<tr>
<td>GN</td>
<td>0.36</td>
<td>0</td>
<td>20</td>
<td>6.59</td>
<td>0.77</td>
<td>1:128</td>
<td>1:2048</td>
</tr>
</tbody>
</table>

Normal control values are expressed as geometric mean and 95% tolerance interval. 0 indicates undetectable by SRID (i.e. for IgA 0.003 g/l, IgD 0.003 g/l and IgM 0.01 g/l).

immunodeficient patients (MR, VG, PB) tested.

**Immunofluorescence on jejunal biopsies**

Two patients (MR, BL) with CVID had no immunoglobulin containing cells in the lamina propria (Table 2). In patient BL a section of NLH tissue was also found to be negative for such cells. Patient VG with CVID had apparently normal numbers of IgM containing cells, but none containing IgA or IgG.

**Peripheral blood lymphocytes**

The geometric mean lymphocyte count of the immunodeficient patients, 2.02 × 10^9/l (2s.d. range 0.9–4.29) did not differ significantly from the healthy control mean of 2.68 × 10^9/l (2s.d. range 1.52–4.72, n = 30). Only one of the three patients tested had reduced T cell counts. Lymphocyte transformation showed only slightly abnormal results, with a dissociation between a positive in vitro lymphocyte response to PPD, but a negative skin reaction in two patients.

**DISCUSSION**

Several features found in these patients indicate that they have a primary defect of immunoglobulin synthesis: peripheral blood lymphopenia is a major feature of intestinal lymphangiectasia, yet their mean lymphocyte count did not differ from healthy controls; hypoalbuminaemia is also a feature of protein-losing enteropathy, yet their mean serum albumin was significantly higher than that seen in patients with tropical sprue, who not only have normal or increased immunoglobulins, but also protein-losing enteropathy, serum IgE deficiency is not a feature of protein-losing enteropathy, yet seven pa-
Immunodeficiency in the tropics

513

tients had IgE concentrations less than 10% of the normal south Indian mean; there was no evidence of intestinal lymphangectasia in repeated small intestinal biopsies, but there was evidence of NLH, a lesion almost confined to primary B cell deficiency syndromes.21

Documentation of primary immunodeficiency in tropical countries has been infrequent and the prevalence among the general population is unknown. It has been suggested that individuals so affected would have an increased morbidity and mortality due to the high prevalence of infectious agents in these areas.2 Out of 600 immunoglobulin estimations over 6 years at this hospital in patients without primary gastrointestinal complaints, serum IgA deficiency (<0.3 g/l) was found in five children and three adults with recurrent infections. One in 200 children was found to have serum IgA deficiency, and diarrhoea was present in five of nine patients with CVID in northern India.22,23 Amongst 166 patients described as having tropical sprue, three had IgA deficiency and two probable CVID.19,24

These findings suggest that diarrhoea and malabsorption are a common form of presentation of immunodeficient patients in the tropics.

The most notable clinical feature that singled out the immunodeficient patients from immunocompetent patients was the chronicity of diarrhoea. Although two subjects died from respiratory tract infections, chronic respiratory tract infection — a common form of presentation in temperate zone patients — was not a consistent feature in the Indian patients. The malabsorption in these patients suggests that the diarrhoea was due to small intestinal disease. The high prevalence of Giardia in patients with CVID (50%) may be due to a combination of factors predisposing to this infection which may include hypochlorhydria.25 Giardia can produce mucosal damage and diarrhoea by several mechanisms including a self-damaging T cell immune response as shown in mice.26 Since in several of the present group of patients malabsorption and diarrhoea continued or recurred in the absence of G. lamblia (Fig. 1), a feature noted in other studies,17 other factors

Figure 1 Flow chart of clinical status of patient MA over a 94 month period, showing the variable relationship of parasitic infection to malabsorption. HWO — hookworm ova, GL — Giardia lamblia cysts or trophozoites, SS — Strongyloides stercoralis.
are also likely to be involved in the patho-
genesis of the small bowel lesion. Over a cumulative follow-up period of 51 years on
these 13 patients other intestinal parasites,
such as hook worm, Strongyloides stercoralis,
round worm, pin worm and Entamoeba histolytica,
were not found as significant infesta-
tions although their prevalence in the
community is high. Gastrointestinal infection
by recognized pathogenic bacteria was also
not a striking feature. Even in one patient
(BL), who was repeatedly hospitalized with
life-threatening episodes of watery diarrhoea
(faecal volume >4 l in 24 h) which required
fluid replacement and broad spectrum anti-
biotic therapy, recognized enteric pathogens
were not found, and there was no bacterial
overgrowth in the small intestine. Presumably
the causative agents of tropical sprue1 could
affect immunodeficient individuals and is
another possible factor in producing the small
intestinal lesion.

None of the patients have received
gamma globulin replacement, yet in spite of
this only three are known to have died from
infection. The majority of patients have been
managed by symptomatic treatment of infec-
tions as they occur.

The immunological findings in the Indian
patients were characteristically hetero-
geous, the only unifying feature being a
low or undetectable serum IgA. In two
patients tested here a dichotomy existed
between the presence of immunoglobulin
bearing peripheral blood lymphocytes and the
undetectability of the corresponding serum
immunoglobulin. A further dichotomy
existed between three patients with CVID
who had similar immunoglobulin deficiency
patterns, but variation in the class of immuno-
globulin-containing plasma cells detectable in
their small intestine. The latter may result
from a sampling error, as Matuchansky et al.
found a heterogeneous distribution of immu-
noglobulin-containing plasma cells. This
sampling error may also account for the
occasional presence of secretory immuno-
globulins in patients with apparently absent
lamina propria plasma cells.

In spite of markedly reduced immuno-
globulin concentrations in the patients with
CVID, what little antibody activity remained
appeared to be qualitatively normal and
belonged to the IgM class. Physiologically it
is believed that B lymphocytes undergo a
sequential maturation from IgM/IgD synthe-
sizing cells. In CVID there would seem to be
a failure of the normal switch from IgM to
other immunoglobulin classes.

In three patients tested here mild T cell
defects were demonstrable, as has been re-
ported in about one-third of patients with
CVID.25 There was no generalized T cell
abnormality, while the increased IEL found
particularly in Giardia infestation and the
absence of significant infestation by hel-
minths suggest an active T cell response.

The evolution of the immunodeficiency in
one patient (CH) offers additional evidence
that some forms of IgA deficiency and CVID
are part of the same spectrum of B lympho-
cyte disease. This patient developed first a
selective IgA deficiency and finally a severe
panhypogammaglobulinaemia over a 6 year
period. A similar evolution has been de-
scribed in a Caucasian female with Crohn’s
disease.1 Further the enzyme purine
5’-nucleotidase is deficient in lymphocytes
from both individuals with IgA deficiency
and CVID.26

The patients reported here demonstrate
that B lymphocyte disorders associated with
selective IgA deficiency or CVID are not
incompatible with prolonged survival in
tropical developing countries with a high
prevalence of infectious diseases. These dis-
orders manifest primarily as gastrointestinal
illnesses associated with malabsorption.
Immunodeficiency syndromes have to be
considered in the differential diagnosis of all
patients with chronic diarrhoea and mal-
absorption in this environment.
ACKNOWLEDGMENTS

The Wellcome Research Unit is supported by The Wellcome Trust, London, UK. I.N.R. was the recipient of a Wellcome Senior Fellowship.

REFERENCES


