Alpha-chain disease and related small-intestinal lymphoma: a Memorandum*

Primary intestinal lymphomas are remarkably frequent in the Mediterranean region and South-West Asia. They are usually found in young persons from the lower socio-economic strata of the population. These conditions sometimes present a premalignant phase characterized by plasmacytic infiltration of the small intestine. It has been reported that early treatment of cases with antibiotics is followed by complete remission, suggesting that some environmental factors may be responsible for the disease. Some patients have an abnormal alpha-chain protein in their serum. This Memorandum reviews the present knowledge of the clinical, immunological, epidemiological, and therapeutic aspects of this condition.

Primary intestinal lymphomas are remarkably prevalent in the Mediterranean region and South-West Asia (*1*, *12*, *26*) and have a number of characteristic features. They are most frequent in young patients from underprivileged backgrounds who present with a malabsorption syndrome resulting from extensive and diffuse infiltration of the wall of the small intestine, predominantly by plasma cells. Clinical studies suggest evolution from a premalignant cellular infiltrate to frank neoplasia involving more primitive immunoblasts.

The frequency of primary intestinal lymphomas among populations exposed to conditions of poor hygiene (*35*) and evidence for complete remissions induced in early cases by oral antibiotic therapy (*30*), implicate environmental factors in the pathogenesis of this disorder. Since ingested microorganisms are a powerful proliferative stimulus to the secretory IgA system (*7*), the premalignant phase of the disease may represent an aberrant immune response by the secretory IgA system to sustained, topical, antigenic stimulation. The study of diffuse primary intestinal lymphomas therefore offers important opportunities for research into the pathogenesis of lymphoma in man. Uniquely, the association of a disordered immune response and the development of immunoblastic sarcoma, possibly from the same clone of cells, can be studied in a cell population that synthesizes a distinctive marker protein.

Over the last decade data have accumulated from isolated case studies in diverse regions and the time now seems opportune to initiate a new phase of research into this condition. As a first step, a co-ordinated international collaborative effort is essential to collate the data available and to establish standard nomenclatures, diagnostic criteria and therapeutic responses so as to lay the groundwork for systematic research into the etiopathogenesis and epidemiology of the disease. This Memorandum reviews the present knowledge about this disease. Since in the early stage it does not appear to be a truly malignant lymphoma, in this Memorandum the condition is termed " immunoproliferative small-intestinal disease " (IPSID).

CLINICAL FEATURES

The major clinical features of IPSID are remarkably uniform. They are (*4*, *8*, *22*, *24*, *37*): chronic diarrhoea, abdominal pain, abdominal distension, nausea and vomiting, marked weight loss.

Less common features include (*17*, *23*, *24*): oedema, tetany, low-grade fever (high temperatures are rare), melaena.

An occasional presentation is that of an acute

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abdomen due to obstruction, perforation, or intussusception of the small intesine (*1*, *3*, *10*).

The diarrhoea may have features of steatorrhoea or may be very watery and at times so copious as to require urgent fluid and electrolyte replacement. The severity of diarrhoea has on occasions led to hypokalaemic nephropathy with polyuria.

Population at risk

Although IPSID is seen mainly in the second and third decade, cases have been noted in all age groups. There are no clear sex differences. The disease affects populations of diverse ethnic and geographical origins (*34*). There is a predilection for certain ethnic groups in the same geographical region (*26*). The patients described have mostly been from the low socioeconomic strata (*33*).

Presenting signs

The common presenting signs include (*8*, *22*, *24*): emaciation, clubbing of fingers and toes, abdominal mass, abdominal tenderness, oedema. Occasionally tetany is found. Palpable peripheral nodes are a rare presenting sign.

It should be emphasized that hepatosplenomegaly is not a presenting feature of the disease.

Laboratory findings

Routine laboratory tests are not diagnostic. Abnormalities usually relate to malabsorption or loss of substances through the gastrointestinal tract. These include:

(*a*) malabsorption of fat, xylose, folate, and vitamin B_{12} with intrinsic factor. Fat, xylose, and vitamin B_{12} malabsorption are at least partially responsive to antibiotics;

(*b*) hypocalcaemia, hypomagnesaemia and hypokalaemia;

(*c*) hypocholesterolaemia;

(*d*) mild anaemia, usually hypochromic—eosinophilia and lymphopenia are not usually found;

(*e*) hypoalbuminaemia and protein-losing enteropathy;

(*f*) elevated alkaline phosphatase, often of intestinal origin (*8*, *24*, *27*);

(*g*) positive occult blood in stool may be found;

(*h*) a variety of parasites have been associated with the disease, *Giardia* being the most frequent;

(*i*) limited bacteriological studies of stools have not revealed any consistent pathogens: in several cases, bacterial overgrowth associated with bile–salt deconjugation in jejunal fluid and an antibiotic responsive ^{14}C-glycocholate breath test has been observed (J. C. Rambaud, unpublished results).

Radiological findings

Barium studies in IPSID patients frequently reveal an abnormal small-intestinal pattern, usually more marked in the upper small intestine (*2*, *4*, *10*, *26*). Findings include: (*a*) a characteristic coarse mucosal pattern with a pseudopolypoid appearance, (*b*) strictures and segmentation, and (*c*) impression by extrinsic nodes.

These findings are suggestive but are not diagnostic for this disease. Occasionally the appearances of osteoarthropathy are also noted (*10*). Absence of mediastinal adenopathy and radiological features of osteomalacia should be emphasized. Abdominal lymphoangiography may be abnormal but this investigation has limited value in the investigation of this disease.

Biopsy findings

Peroral mucosal biopsies at multiple sites have proved essential to the diagnosis and management of the disease. Plasmacytic infiltration may occasionally be noted in the colon, rectum, stomach, nasopharynx, bone marrow, or peripheral blood.

Laparotomy

Although laparotomy often reveals thickening of the small-intestinal wall, mesenteric lymph node enlargement, and a small spleen (*19*), absence of these findings on gross examination does not exclude the diagnosis.

Course of the disease

The course of the disease in the absence of therapy is progressive deterioration, usually culminating in frank malignancy with consequent obstruction, intussusception, or perforation of the small intestine (*1*). The course may be interrupted by periods of improvement. Death is usually due to either cachexia and infection or complications of localized tumour. Dissemination of the immunoblastic tumour outside the abdomen is a rare, late event of the disease (*1*, *3*).

The time lapse between initial symptoms and diagnosis ranges from one month to six years.

HISTOPATHOLOGY OF IMMUNOPROLIFERATIVE SMALL-INTESTINAL DISEASE (" MEDITERRANEAN TYPE ") (IPSID)

The histological features of this disorder are characteristic of the clinical syndrome of the so-called Mediterranean lymphoma with malabsorption, which is commonly associated with the presence in the serum of alpha-heavy-chain disease (αHCD) protein (*15*, *29*). The αHCD protein may occasionally be found in immunoblastic intestinal lymphomas not apparently associated with diffuse lympho-plasmacytic infiltration of the lamina propria of the mucosa.

The diffuse plasma-cell infiltration at the time of clinical presentation is usually massive, causing wide separation of the crypts of Lieberkühn and obliteration of the villous architecture, without, however, significant impairment of the integrity of the surface epithelium (*24*). In some instances, obliteration of the villi is not complete, and focal areas in which the villous architecture is preserved but in which the villous stroma is heavily infiltrated with plasma cells and/or lymphocytes may be evident (*3*).

Topographically, this form of the immunoproliferative disease usually begins in the upper small intestine (*22*), in contrast to the solitary lymphomas not associated with diffuse plasma-cell infiltration that have a predilection for the stomach, terminal ileum, and colorectal areas. The plasma-cell infiltration of IPSID is diffuse and extensive, frequently involving the entire length of the small intestine.

Histologically, the diffuse plasma-cell infiltrates, as well as the mixed lympho-plasmacytic infiltrates, are usually confined to the lamina propria of the mucosa and may lack conclusive cytological features of the neoplasia. Occasionally, they penetrate deeply into the submucosa and show cellular atypia consistent with plasmacytic sarcoma.

The morphology of the diffuse lympho-plasmacytic infiltrations is in keeping with the view that a premalignant stage of the disease may exist, a view that appears to be supported by regression of the clinicohistological and immunological abnormalities following oral antibiotic therapy (*30*).

In some cases, aggregates of lymphocytes containing large, scattered, atypical " immunoblastic " cells are present within the diffuse plasmacytic infiltration. The significance of these cells is not clear but they have usually been associated with, or may represent, neoplastic transformation.

The significance of mesenteric lymph node involvement by the same lympho-plasmacytic proliferation that is evident in the gut is not clear, since it may signify either a reaction pattern identical to that in the intestinal mucosa or actual dissemination of malignant cells to the mesenteric lymph nodes.

A histopathological classification [a] of this disorder is as follows:

(*a*) diffuse, dense, compact, and apparently benign lympho-proliferative mucosal infiltration,
  (i) pure plasmacytic
  (ii) mixed lympho-plasmacytic;

(*b*) as in (*a*), plus circumscribed " immunoblastic " sarcoma(s), in either the intestine and/or mesenteric lymph nodes;

(*c*) diffuse " immunoblastic " or plasmacytic sarcoma with or without demonstrable, apparently benign lympho-plasmacytic infiltration.

IMMUNOGLOBULIN ABNORMALITIES IN IPSID

A characteristic immunoglobulin abnormality is found in the majority of patients suffering from immunoproliferative small-intestinal disease (IPSID) whose intestinal biopsies show the characteristic diffuse lympho-plasmacytic infiltration, with or without the presence of an immunoblastic lymphoma. This abnormality is very rarely found in intestinal lymphomas not associated with IPSID.

The aberrant protein comprises a population of molecules consisting of incomplete heavy α-chains, devoid of light chains (*33*). The molecular weight of the monomeric polypeptide subunit varies between 29 000 and 34 000 (*11*). The length of these chains is thus greater than half but less than three-quarters of normal α_1 heavy chains. Antigenic analysis (*34*) and chemical studies (*35*) indicate that the entire Fc fragment is present in αHCD proteins, that their C-terminus is identical to that of normal α_1 chains and that the heavy-light peptide is missing. The hinge region has been shown by chemical methods to be present in all eight proteins so far studied. All attempts to raise specific antibodies to individuals αHCD proteins have failed, indicating the paucity of antigenic determinants in the N-terminal

[a] Explanatory notes: (*a*) (i) & (ii): atypical plasma cells or large lymphoid cells (" immunoblasts ") may be scattered within the lympho-plasmacytic infiltration. (*b*) & (*c*): Cells resembling Sternberg-Reed cells may be part of the tumour infiltrate.

A diffuse follicular lymphoid hyperplasia involving the intestinal mucosa, with or without a malignant lymphoma of the poorly differentiated lymphocytic type, may at times be encountered in patients with the clinical syndrome of Mediterranean lymphoma. This type, however, is not usually associated with αHCD.

portion of the fragment. In view of these results and of the molecular weight data, the missing portion of the chain is located in the Fd segment and involves both the V_H and C_1 regions.

The N-terminal sequences of several αHCD proteins are heterogeneous (*35*). Even for those proteins with a single N-terminal amino acid, marked heterogeneity became apparent after two steps in degradation. Attempts to obtain the N-terminal sequence on an automated sequencer were unsuccessful. The N-terminal residues are different from those found in any of the subgroups of the variable regions of normal heavy chains. The most likely explanation of this heterogeneity is that it is the consequence of intracellular proteolysis occurring after synthesis. The fact that the N-terminal residues found in the seven proteins studied were valine and/or isoleucine suggests that the postulated degradation may stop at this level for some reason, which could be enzyme specificity, steric hindrance, or the presence of a carbohydrate moiety. An analogy for intracellular proteolysis of an incomplete protein has been found in alkaline phosphatase of the amber and ochre mutants of *Escherichia coli* (*39*). Alternatively, post-synthetic cleavage may occur extracellularly. In one case of gamma heavy chain disease (γHCD) (where similar N-terminal heterogeneity may be found), the nascent abnormal chain in the cytoplasma and in the culture fluid during biosynthetic studies had a molecular weight of 36 000; by contrast the molecular weight of the serum γHCD protein was 28 000 (*5*).

The demonstration of a large internal deletion in a γHCD protein (*13*) led to the postulate that in αHCD there was a similar primary deletion followed and obscured by a secondary, limited intracellular proteolysis. This hypothesis has been supported to some extent by biosynthetic and structural studies. Cellular biosynthetic studies excluded the possibility of the synthesis of a normal α-chain with subsequent degradation to a smaller fragment after its release from the ribosomes (*5*). Comparison of the amino acid sequence of the hinge region of αHCD protein from patient Def with that of a normal IgA_1 showed that, after a short segment, thought to correspond to the variable region, protein Def displays a gap which comprises almost the whole Fd segment including the C_{H1} domain (*40*). Normal synthesis resumes at a valine residue in the hinge region just preceding a segment that contains a partially-duplicated fragment and the interheavy chain disulfide bonds. From there on the molecule is apparently normal with the exception of a substitution of threonine for serine in position 12. Protein Def is therefore possibly synthesized as an intracellularly deleted α_1 heavy chain. Similar conclusions were reached from the study of another αHCD protein (*41*). It is possible, however, that the N-terminal sequence is not a portion of the V region but rather a non-cleaved polypeptide. It is of interest that valine at position 9 of the hinge peptide, where the identity with a normal α_1 chain starts, could be the equivalent of glutamine at position 216 of γ-chains, the site where normal synthesis resumes in several γHCD proteins with internal deletions (*14*).

Thus the primary defect in αHCD proteins appears to be a deletion affecting the variable and first constant regions of the heavy chains, which are under independent control. Any genetic hypothesis about αHCD proteins should also take into account the fact that immunofluorescent and radioimmunoelectrophoretic studies of proteins synthesized *in vitro* have failed to detect any light-chain production in the cells which secrete αHCD proteins (*34*). This failure of light-chain synthesis has been confirmed by biosynthesis studies of nascent Ig subunits in such patients (*5*). Since light and heavy chains are under the control of unlinked genes, this peculiar situation raises a puzzling problem for the cellular geneticist. The possibility remains that the light chain is transcribed but not translated. Studies looking for the presence or absence of its messenger are warranted.

All 50 αHCD proteins examined to date belong to subclass 1 (*36*), an unexpected and unexplained finding since 30–40% of normal secretory IgA protein is subclass 2 (*16*). This finding, together with amino acid substitution in position 12 of Def, suggests that α HCD proteins may be monoclonal but this cannot be confirmed because the other essential criteria for monoclonality, i.e. light chain and homogeneity of V region leading to shared idiotypic specifity and antibody activity, cannot be tested.

Several αHCD proteins have been found to contain a J chain. The secretory piece binds to αHCD protein but the nature of the binding is unknown.

Whether αHCD proteins should be considered as " abnormal " is still an open question. Polypeptides analogous to the proteins of γHCD were recently reported to be present in very small amounts in normal plasma (*18*). However, if heavy-chain disease arises from proliferation of a clone of cells producing such polypeptides (which could be prone to neoplastic transformation) it is necessary to postulate a wide variety of cells carrying such deletions

in normal individuals since the site and length of the deletion appears to vary from one αHCD protein to another. It should be emphasized that deletions are not confined to HCD proteins and that various other types of heavy- and/or light-chain deletions have now been described in human (as well as murine) myeloma proteins.

The diagnosis of αHCD relies entirely upon laboratory studies including immunochemical analysis of the serum proteins and may be difficult in a routine laboratory. It can easily be missed on serum protein electrophoresis, and electrophoresis did not demontrate the pathological protein in half of the 80 sera studied in Paris. When detectable by electrophoresis, the αHCD protein shows as an abnormal broad band usually in the α2 or β region. The characteristic narrow band, suggestive of a monoclonal Ig abnormality, is absent. In most of the cases where the pathological protein was not detectable, serum electrophoresis showed only a decrease in serum albumin and a moderate to severe hypogammaglobulinaemia.

The diagnosis is usually suspected or established by immunoelectrophoretic analysis of the serum of these patients. In many cases the protein abnormality escaped detection by routine immunoelectrophoresis using polyvalent antiserum to human normal serum; analysis with monospecific antisera for IgA is therefore essential.

αHCD protein usually gives an abnormal precipitin line either extending from the α_1 globulins to the slow β_2 region or showing a faster electrophoretic mobility than normal IgA. However, in a few patients the αHCD protein had a slow electrophoretic mobility. The anomalous component does not of course precipitate with antisera to light chains. However, it should be emphasized that this lack of precipitation with anti-K and anti-λ antisera is not a sufficient criterion for the diagnosis of αHCD since many IgA myeloma proteins, even though they contain light chains (mainly λ chains) fail to precipitate with such antisera. Selected antisera to IgA which contain antibodies related to the conformational specificity of the Fab region and which precipitate only with α- and light-chains combined, were found to be very useful for the diagnosis of αHCD by immunoelectrophoresis or the Ouchterlony technique (*34*). Alternatively, the immunoselection plate method of Radl can be used (*8*). In all doubtful cases the pathological protein should be purified, reduced, and alkylated, and the lack of light chains should be demonstrated directly by starch or polyacrylamide gel electrophoresis or by gel filtration after dissociating the molecule.

The striking and unexpected electrophoretic heterogeneity of these presumably monoclonal αHCD proteins is certainly due in part to the heterogeneity of their N-terminal sequences as discussed above. It may also be related to two other features, the high carbohydrate content of most αHCD proteins (*35*) and their propensity for polymerization. Indeed, on ultracentrifugation αHCD proteins appear to consist of dimers with a 3-4S sedimentation constant and, in most instances, of larger polymers of various sizes (*34*).

The serum levels of normal IgA, IgG, and IgM are usually depressed. These decreases are not solely due to a protein-losing enteropathy, as shown by the disproportionate depression of serum immunoglobulin levels relative to the serum albumin concentration.

The diagnosis of αHCD is made more difficult by the very low concentration of pathological protein in the urine. In most patients, however, it could be detected in concentrated urine and had the same electrophoretic and immunochemical characteristics as that found in the serum. Bence-Jones proteinuria was never found. The pathological protein was also found in significant amounts in jejunal fluid, as expected from the involvement of the intestine, whereas the IgA in the parotid saliva of these patients was normal (*34*).

In order to establish the true incidence of αHCD in IPSID patients, it will be necessary to study systematically the immunoglobulin content of the intestinal fluid and to perform biosynthesis studies of intestinal biopsies on those patients without detectable αHCD protein in the serum.

Interesting exceptions to the usually characteristic protein findings have been reported. A small homogeneous IgG component has been found in addition to αHCD protein in serum in two patients. In sera from these patients who presented with the typical clinico-pathological features of the intestinal form of αHCD an entire IgA myeloma globulin was found and Bence-Jones protein was present in the urine in one of these patients. γHCD protein was demonstrated in the serum and in an intestinal biopsy from another patient with the typical clinico-pathological pattern of IPSID. The αHCD protein present in the serum of three patients apparently suffering from a respiratory form of αHCD was indistinguishable from that described above for the much commoner intestinal form (*38*).

OTHER IMMUNOLOGICAL STUDIES

Although IPSID may be considered the consequence of a basic underlying immunodeficiency, tests of immune competence in patients have received scant attention. No studies of immunoglobulin levels in jejunal fluid have been reported and no functional tests of the secretory immune system have been performed in these patients.

Leucopenia is not a feature of IPSID and limited testing of T-cell function using mitogenic responses to phytohaemagglutinin and skin testing has not revealed evidence of a gross defect in cell-mediated immunity. No antigen-specific tests of T-cell function have been made.

No studies of tumour-associated antigens have been made in IPSID patients.

CELL CULTURE—VIROLOGY

Attempts to establish a continuous line of αHCD-secreting cells in culture have failed. However, cells from the lympho-plasmacytic infiltrate can be cloned in short-term culture and usually remain viable for several weeks.

Limited serological studies for antibodies against Epstein Barr virus, cytomegalovirus and herpes simplex virus have not provided any significant findings.

BACTERIOLOGY AND PARASITOLOGY

In a survey of 60 case reports, bacteriological data from stool culture is available on only 5 patients. The only pathogen cultured was a *Salmonella* in one patient. In several patients, overgrowth of aerobes and anaerobes has been demonstrated in jejunal fluid. In most of these patients, steatorrhoea, vitamin B12 absorption (Schilling test) and the ^{14}C-glycocholate breath test improved markedly following a short course of tetracycline given orally (J. C. Rambaud, unpublished results). These findings suggest that a stagnant loop syndrome may contribute to the malabsorption in these patients. In two cases, however, no evidence for a stagnant loop syndrome was observed (*6*, *25*).

Parasitic infestation was found in 21 patients of the 60 studied (34%) (*31*). Giardiasis was the commonest infestation found (*31*) but many other parasites have been reported including *Entamoeba histolytica*, *Trichomonas hominias*, *Trichuris trichuria*, hookworm, coccidia, and *Ascaris lumbricoides*. Thus, no particular bacterial pathogen or parasite has been found in association with IPSID and, in many instances, no evidence of parasitic infestation was present at the time of diagnosis. These findings do not necessarily militate against a causal role for bacteria or parasites, specific or nonspecific. Infection or infestation may be present only during the early phase of αHCD, especially during early infancy, when the intestinal immune system is immature, and may not be manifest in identifiable form years later at the time of diagnosis. Unfortunately, the absence of Fab in αHCD protein (*33*) precludes its use for identifying putative antigenic stimuli.

EPIDEMIOLOGICAL AND FAMILY STUDIES

Epidemiological knowledge of this disorder is limited. What little is known comes from case information accumulated in a small number of clinical centres, notably in Algeria, France, Iran, Iraq, Israel, Lebanon, South Africa, Tunisia, and the United Kingdom.

General incidence

While certain regional patterns are suggested by the available clinical data, the general incidence of the disease is not clearly defined, either for the world as a whole or for any given country. Limited surveys by small-intestinal biopsy in the general population of South-West Asia leave unresolved the suggestion that a large reservoir of subclinical disease may exist.

Age

The disorder appears to affect primarily young adults 20–40 years of age, although occasional cases have been described in younger and older persons. This young age distribution contrasts sharply with the older pattern seen in other forms of small-intestinal lymphoma (the so-called " western type ").

Sex

Both sexes seem to be about equally affected. Again this stands in contrast to the usual picture of lymphomatous disease, in which male cases predominate.

Racial or ethnic incidence

Although at first the disease seemed primarily to affect Arab populations of the eastern and southern Mediterranean regions (hence the term " Mediterranean lymphoma "), there now appears to be a wide spectrum of racial or ethnic incidence, reflected in an emerging pattern of wide geographical distribution. Notably this includes non-Ashkenazi Jews

in Israel, but not Jews of European or American origin (*26*). In South Africa, Cape Coloureds and mulattoes are affected, although apparently not the more numerous Bantu population in that country (*23*).

Socioeconomic status

A striking and generally consistent feature of the disease is its occurrence in low socioeconomic strata of the population. Occasional cases, however, come from higher social levels.

Geographical distribution

While most cases are still recorded in South-West Asia and northern Africa, cases have now been described in many parts of the world including South Africa, Europe (especially along the Mediterranean coast), the Indian subcontinent, and South and Central America (*35*). While the disease appears to be extremely rare in Europe and North America, the report of an atypical intestinal case from Finland suggests that no region of the world is exempt (*32*). No tendencies for cases to be clustered discretely within particular regions of particular countries have been described.

Secular trends

It is not known whether the disease is increasing or declining in incidence in particular populations, except that, in Israel, the disease appears to be declining in frequency.

Familial incidence

While only limited family studies have been made, there appears to be no strong predilection for cases to cluster in families. Only one instance of disease in primary relatives has been described, two sibs in southern Iran. No obvious HLA patterns were suggested in a small series of patients from Iran; surveys of Ia antigens have not been carried out. No clear immunoglobulin abnormalities have been found in a limited number of sera from close relatives of patients surveyed in Israel (*28*). The observation that family members of an IPSID propositus have the intestinal isoenzyme of alkaline phosphatase in serum (*27*)—a feature of IPSID (see page 616) warrants further study.

Potential etiological factors

No formal epidemiological or joint epidemiological/laboratory studies (whether using the retrospective case-control or prospective cohort approach) have yet been conducted to assess the wide range of etiological factors that may contribute to this possibly multifactorial disease. What information exists comes from limited and anecdotal sources: inconclusive data regarding dietary habits in a few Lebanese cases and scattered bacterial cultures of intestinal flora. There has not been any definitive work concerning relationships with potentially oncogenic viruses, particularly the Epstein-Barr herpesvirus.

THERAPY

Reports of intensively studied IPSID patients are still uncommon and mainly concern those published as cases of αHCD. Although the natural history of this disorder is not fully known, provisional therapeutic guidelines may be obtained from the data available on two main groups of patients published in the literature.

Firstly, those patients whose intestinal mucosa showed a dense predominantly plasma-cell infiltration confined to the lamina propria; 16 patient are classified in this group.

Seven of these patients were treated with oral antibiotics—mainly tetracycline and ampicillin—alone. Four achieved complete clinical, histological, and immunological remission following 2–10 months of treatment (disappearance of αHCD protein from serum and intestinal juice, and normal plasma cells in the lamina propria of the gut as assessed by immunofluorescence studies) (*21*, *24*, *30*). In two patients this complete remission lasted 6 and 2 years, respectively, after the cessation of all treatment. The clinical condition of a fifth patient is much improved after 6 months' treatment, but the intestinal histology is unchanged and αHCD protein is still present in serum. In a sixth patient 2 years of continuous oral tetracycline therapy was required to achieve remission (disappearance of malabsorption and of αHCD protein from serum, and radiological changes in the small intestine) (B. Ramot, unpublished results). A seventh patient died from intercurrent infection during therapy for IPSID.

Six other patients of this group were treated by chemotherapy alone—melphalan, cyclophosphamide, chlorambucil, vincristine, and prednisone in various combinations, sequences, and dosages. Only one patient in this group achieved complete clinical, histological, and immunological remission after an

8-month course of chlorambucil, and this remission is still maintained 6 years after ceasing therapy. A second patient was almost completely asymptomatic, with no detectable αHCD protein in serum, 3 years after beginning intermittent treatment with cyclophosphamide and prednisone, preceded by an ineffective course of vincristine. A third patient showed no improvement after 6 months of similar treatment. Three patients had only a temporary improvement (with complete clinical remission in one case) and died after the development of an immunoblastic sarcoma.

Three patients received combined therapy with oral antibiotics and chemotherapy. One of these achieved complete clinical, histological, and immunological remission after 15 months of treatment with tetracycline, oleandomycin, and cyclophosphamide. This remission was maintained 12 months after all treatment ended. Subsequently, an ileal immunoblastoma developed in this patient (*20*). A second patient was clinically asymptomatic after 6 months of treatment with tetracycline and melphalan (histological and immunological status unknown) (*8*). One patient experienced complete clinical remission with incomplete histological and immunological improvement during a one-year treatment, but relapsed (after stopping therapy) and eventually developed an immunoblastic sarcoma (*9*).

The delay between the first symptoms and the beginning of treatment, and the initial clinical and histological status appeared to bear no relationship to whether or not the patients responded to therapy. However, it should be emphasized that the histology of the mesenteric lymph nodes was known in only 5 cases, and that information on the small-intestinal pathology was incomplete, in terms of length and depth of involvement, in all patients except one. Among the 6 patients who achieved complete remission, 5 had initial low concentrations of αHCD protein in serum, compared with 2 of 5 patients who did not respond to treatment.

The second group provides the results of therapy on 6 IPSID patients suffering from immunoblastoma. Complete sustained remission has apparently been achieved in 2 cases using deep X-ray therapy. Two patients with mesenteric lymph node "histiocytic sarcoma" coexisting with a pure plasmacytic infiltration of the gut, were treated with total abdominal irradiation of 30 gy (3000 rad) and sterioids (*23*). They achieved complete clinical and immunological (serum only) remission, lasting 2 and 1 years, respectively. However, the histology of the small intestine after treatment was unchanged in one case and was unavailable in the second case.

In 3 patients the immunoblastic cells were scattered within the small intestine and lymph node plasmacytic proliferation (*3*). Transient clinical improvement was obtained in these 3 patients with various types of chemotherapy. Complete clinical and histological remission was obtained in one case after two courses of the MOPP [a] regimen but thereafter clinical relapse was observed.

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[a] nitrogen mustard, vincristine (oncovin), procarbazine, and prednisone.

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