PAPERS AND ORIGINALS

Comparison of combined and single-agent chemotherapy in non-Hodgkin's lymphoma of favourable histological type

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Summary and conclusions

Sixty-six untreated patients with advanced non-Hodgkin's lymphoma of favourable histological type were allocated alternately to initial treatment with cyclophosphamide, vincristine, and prednisolone or with chlorambucil. The complete remission rate was higher in the group receiving combination chemotherapy, but the overall response rate was the same for both groups. The mean duration of complete remission was the same as that of good partial remission, and was the same for both treatments. The duration of remission was influenced by histological type and extent of disease at presentation, but not age. Those who responded to the initial treatment (whether with complete or with good partial remission) survived significantly longer than did non-responders.

It is concluded that neither treatment is satisfactory and that new treatment programmes are needed for patients with a favourable prognosis, especially young patients with extensive disease.

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Introduction

Combination chemotherapy (with cyclophosphamide, vincristine, and prednisolone—CVP) has produced a significantly higher response rate in lymphosarcoma than cyclophosphamide alone.[1-3] We therefore carried out a study to confirm these results (using chlorambucil instead of cyclophosphamide as the single agent) and to relate duration of remission to the initial treatment and other variables in patients with stage III and stage IV non-Hodgkin's lymphoma of favourable histological type and presumed good prognosis.

Patients and methods

PATIENTS

Sixty-seven untreated patients with stage III and IV non-Hodgkin's lymphoma were included in the study between December 1972 and May 1976 (table I). One patient was withdrawn for social reasons, leaving 66 cases for evaluation. All patients were treated at St Bartholomew's Hospital and were followed up monthly after completing the treatment.

One of us (AGS) reviewed all histological sections and the diagnosis was made according to the Rappaport classification.[4] Whenever possible, imprint preparations of lymph node or other affected tissue were made and stained with a Romanowsky stain. All patients with nodular and diffuse well-differentiated lymphocytic (D-WDL) lymphoma were included. There were also 13 cases of diffuse lymphocytic lymphoma in which the cells were of intermediate differentiation. Since Rappaport would probably have diagnosed these as diffuse poorly differentiated lymphocytic (D-PDL) lymphomas, we have designated them "diffuse poorly differentiated lymphocytic, intermediate" (D-PDL(I)). These tumours correspond to the centrocytic lymphoma, small-cell variant, of the Kiel classification.[5] No patients with D-PDL lymphoma corresponding to the large-cell variant of centrocytic lymphoma (Kiel) were included. Patients were not excluded from the study if they had leukaemia—defined as either a persistent lymphocytosis in excess of 5×10^9/l (5000/mm^3) (associated with D-WDL) or the presence of abnormal peripheral blood lymphocytes identical to those in the lymph node (in patients with nodular lymphoma or D-PDL(I).

In each case the disease was staged according to the Ann Arbor classification used for Hodgkin's disease, with the following modifica-

TABLE I—*Numbers of patients with different types of lymphoma receiving the two regimens (numbers in parentheses denote patients with peripheral blood disease*)*

		Chlorambucil	CVP	Total
Sex ratio (M:F):		14:17	20:15	34:32
Age (y) Mean:		52	57	53
Range:		27-74	31-71	27-74
Stage III	N-PDL	3	3	6
	N-M		4	4
	D-PDL(I)			
	D-WDL			
Stage IV†	N-PDL	14 (6)	10 (7)	24 (13)
	N-M	4 (0)	3 (0)	7 (0)
	D-PDL(I)	5 (2)	8 (7)	13 (9)
	D-WDL	5 (5)	7 (7)	12 (12)
	Total ..	31 (13)	35 (21)	66 (34)

CVP = cyclophosphamide, vincristine, and prednisolone; N-PDL = nodular poorly differentiated lymphocytic; N-M = nodular mixed lymphocytic and histiocytic; D-PDL(I) = diffuse poorly differentiated lymphocytic, intermediate; D-WDL = well-differentiated lymphocytic.

*Diagnosed when definitely abnormal lymphoid cells were seen in a peripheral blood smear in N-PDL, D-PDL(I), and 2 of the cases of D-WDL irrespective of the lymphocyte counts, and in 10 cases of D-WDL with small-lymphocyte counts greater than 5×10^9/l (5000/mm³).

†Diagnosed by bone marrow aspiration and needle biopsy in 50 cases (22 N-PDL, 3 N-M, 13 N-PDL(I), and 12 D-WDL); open bone marrow biopsy in 2; wedge liver biopsy in 1; myelography in 1; cytology of pleural fluid in 1; and radiology, showing evidence of parenchymal lung disease, in 1.

tions: (1) Lymphangiography was not routinely performed in patients with clinical evidence of disease on both sides of the diaphragm. (2) Laparotomy was not routinely performed (it was carried out in only one case). (3) Liver biopsy was performed only in patients whose disease had not been classified as stage IV by other investigations (usually bone marrow biopsy).

Patients were allocated alternately to receive CVP or chlorambucil alone. The two groups were of different size because we also accepted in the study patients in whom lymphocytic malignancy was diagnosed on the basis of bone marrow biopsy but who did not have a lymph node biopsy; data on these patients have not, however, been included in the analysis and will be reported later.

TREATMENT

Single agent—Oral chlorambucil, 10 mg daily, was given continuously for six weeks. After a treatment-free interval of two weeks, three 15-day courses of chlorambucil, 10 mg daily, were given with 15-day intervals between the courses. All treatment was stopped after the third course.

Combination—Six cycles of CVP were given at 21-day intervals according to the National Cancer Institute regimen[3]—that is, oral cyclophosphamide, 400 mg/m² daily, for five days; intravenous vincristine, 1·4 mg/m² (maximum 2 mg), on the first day only; and prednisolone, 100 mg/m² daily, for five days.

Patients on chlorambucil were examined every 14 days, and those on CVP every 21 days. Doses were adjusted or treatment was postponed for one week if the total white cell count fell below 3×10^9/l (3000/mm³) or the platelet count below 100×10^9/l (100 000/mm³). Nine patients completely failed to respond to the initial treatment. Those originally treated with chlorambucil were then given CVP and vice versa.

No patients died as a result of drug effects. All had some degree of myelosuppression,[3] and everyone receiving CVP had alopecia.

No maintenance treatment was given to those who achieved remission. Relapse was treated only when it became symptomatic, unless there was histological evidence of conversion to a histological type with a poor prognosis. Most patients were treated on relapse with chlorambucil.

EVALUATION

We evaluated patients a month after the end of treatment and length of remission was calculated from this date. Duration of survival was calculated from the beginning of treatment. Responses were classified as:

Complete remission—Normal health with no clinical evidence of disease, confirmed by bone marrow aspiration and needle biopsy. Liver biopsy was not repeated in the only patient with liver-positive stage IV disease. Lymphangiography was performed in only five of the 17 cases of complete remission.

Good partial remission—Normal health associated with minimal residual disease (for example, no clinical evidence of disease but continuing focal bone marrow lesions).

Poor partial remission—Normal or reasonable health associated with more than half reduction of tumour mass.

Failure—Reasonable or poor health with less than 50% reduction of tumour mass.

Patients who achieved complete or good partial remission were considered responders and the others non-responders.

Relapse was diagnosed on the basis of clinical increase in palpable disease, and was confirmed whenever possible with repeat lymph node and bone marrow biopsies.

STATISTICS

Survival curves and graphic presentations were developed by standard life table formulae[6] and statistical significance was determined by the Wilcoxan tests modified to deal with life table data by Gehan.[7] The χ^2 method with Yates's correction was used to test significance in a 2×2 table.

Results

RESPONSE TO TREATMENT

The complete remission rate was significantly higher in the group treated with CVP than in that treated with chlorambucil ($P = 0{\cdot}05$); but the overall response rate (complete plus good partial remissions) was the same in both (table II). The response rate was significantly higher in patients with disease of nodular than of diffuse histological type ($P = 0{\cdot}05$) (table III). None of the other factors analysed (age, sex, stage, liver enlargement, splenic enlargement, bone marrow, or peripheral blood disease) influenced the response to treatment.

TABLE II—*Response of patients to chemotherapy*

Treatment	No of patients	CR	GPR	PPR	F	CR rate (%)	Response (CR + GPR) rate (%)
Chlorambucil	31	4	19	2	6	4/31 (13)	23/31 (74)
CVP	35	13	16	3	3	13/35 (37)	29/35 (83)
Total ..	66	17	35	5	9	17/66 (26)	52/66 (79)

CR = complete remission; GPR = good partial remission; PPR = poor partial remission; F = failure.

TABLE III—*Number of patients responding with complete or good partial remission in relation to treatment and histological type*

Histological type	Treatment		Total
	Chlorambucil	CVP	
N-DPL	13/17	13/13	26/30 (87%) } 36/41 (88%)*
N-M	4/4	6/7	10/11 (91%)
D-PDL(I) ..	3/5	6/8	9/13 (69%) } 16/25 (64%)*
D-WDL	3/5	4/7	7/12 (58%)
Total ..	23/31 (74%)	29/35 (83%)	52/66 (79%)

*$P = 0{\cdot}05$.

DURATION OF REMISSION

A good response (complete or good partial remission) was obtained in 52 cases. Thirty-two have relapsed so far. The others have continued in remission for seven to 41 months (median 13 months). The overall duration of remission is shown in fig 1. The most favourable histological subtype was nodular mixed lymphocytic and histiocytic lymphoma, patients with disease of this type having significantly longer remissions than those with nodular poorly differentiated lymphoma ($P = 0{\cdot}02$) or diffuse poorly differentiated lymphoma of intermediate type ($P = 0{\cdot}04$) (fig 2).

The length of remission was influenced neither by the initial treatment (fig 3) nor by whether there had been a complete or only a good partial remission (fig 4). All five patients who achieved only a poor partial remission had relapsed by 18 months. Clinical liver enlarge-

ment, clinical splenic enlargement, and bone marrow disease (diagnosed by bone marrow aspiration or needle biopsy) did not influence the length of remission significantly when analysed individually but the combination of all three did (P = 0·001) (fig 5). None of the other factors analysed (age, sex, or peripheral blood disease) influenced the length of remission.

SURVIVAL

Seventeen out of 66 patients have died and one took her life after a month in remission; the rest survived between 12 and 54 months from the start of treatment. The median survival of the whole group has not yet been reached. The only factor shown to influence survival is the response to treatment, responders (those with a complete or

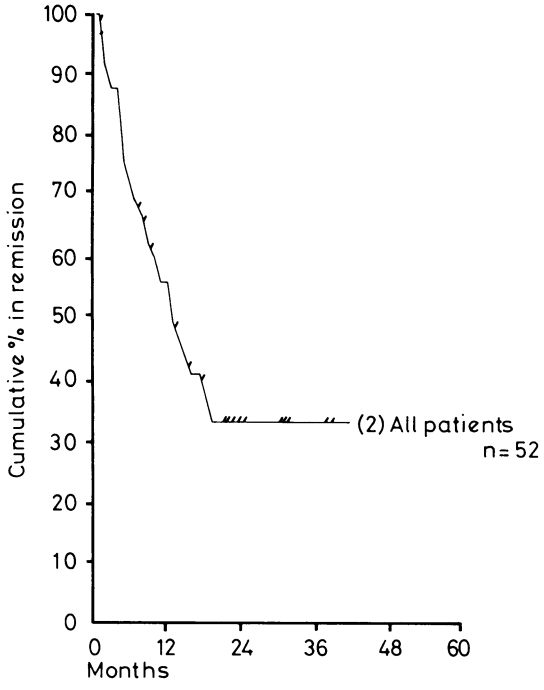

FIG 1—Duration of remission (complete or good partial). Each patient in remission is represented by a dash; patients shown in parentheses were in remission when curve stopped.

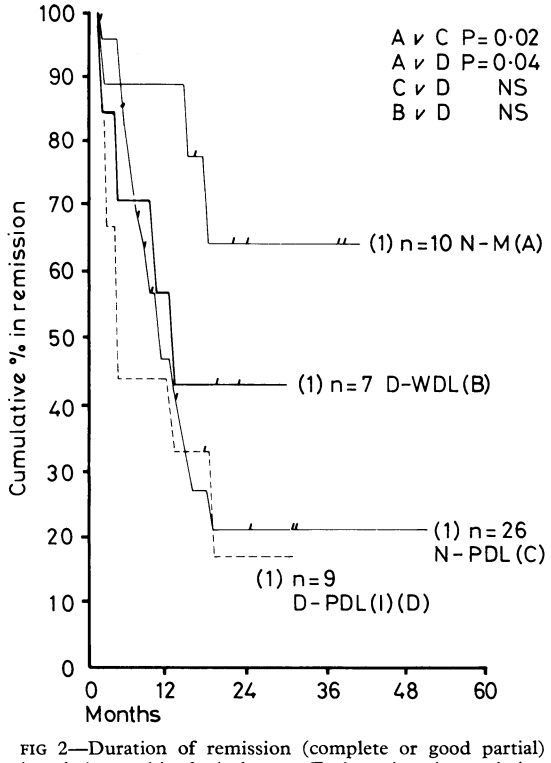

FIG 2—Duration of remission (complete or good partial) in relation to histological type. Each patient in remission is represented by a dash; patients shown in parentheses were in remission when curve stopped. N-M = nodular mixed; N-PDL = nodular poorly differentiated lymphocytic; D-PDL(I) = diffuse poorly differentiated, intermediate.

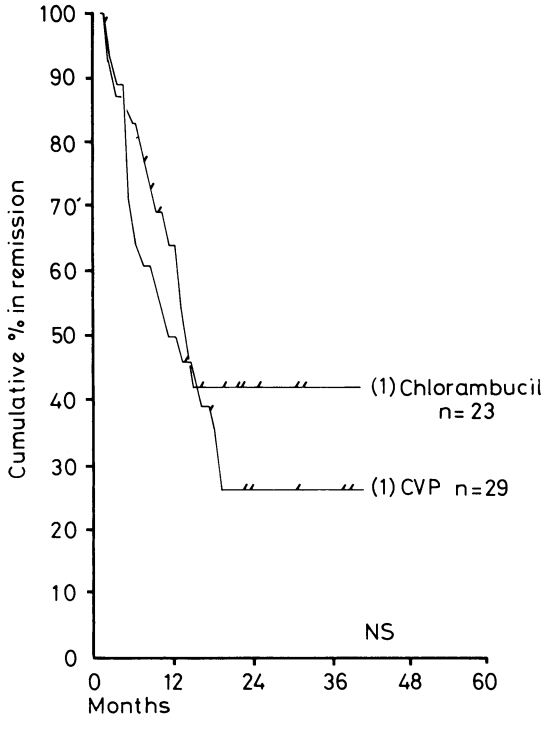

FIG 3—Duration of remission (complete or good partial) in relation to initial treatment. Each patient in remission is represented by a dash; patients shown in parentheses were in remission when curve stopped. CVP = cyclophosphamide, vincristine, and prednisolone.

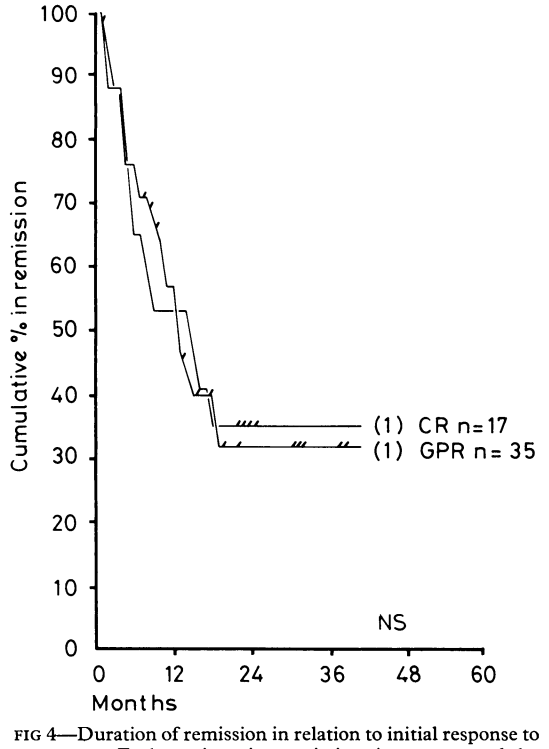

FIG 4—Duration of remission in relation to initial response to treatment. Each patient in remission is represented by a dash; patients shown in parentheses were in remission when curve stopped.

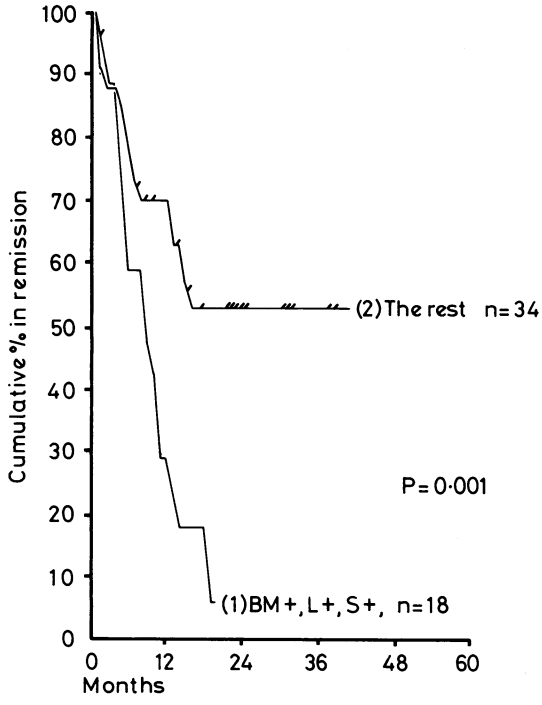

FIG 5—Duration of remission in relation to clinical hepatosplenomegaly and bone marrow disease. Each patient in remission is represented by a dash; patients shown in parentheses were in remission when curve stopped. BM+= bone marrow positive; L+=liver positive; S+=spleen positive.

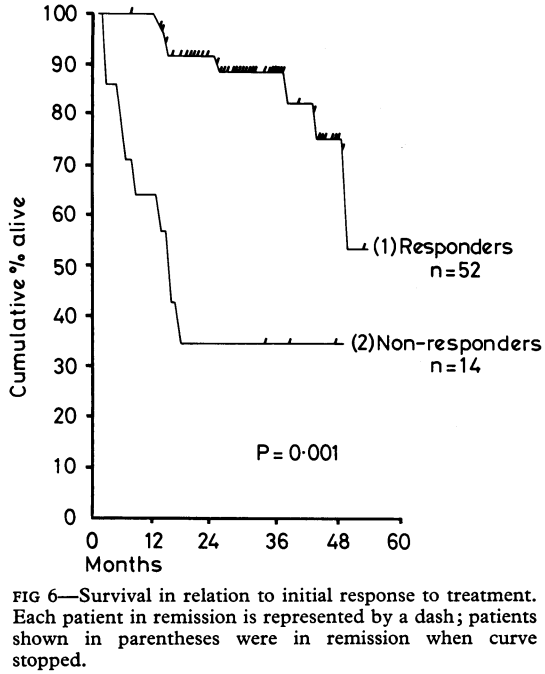

FIG 6—Survival in relation to initial response to treatment. Each patient in remission is represented by a dash; patients shown in parentheses were in remission when curve stopped.

good partial remission) having survived significantly longer than non-responders (P=0·001) (fig 6).

None of the other factors we analysed were shown to influence survival. The longest follow-up is only 54 months, however, and since the predicted median survival of such patients is around four years this is clearly only a preliminary analysis.

Discussion

We must conclude that neither of our regimens is satisfactory for advanced non-Hodgkin's lymphoma of presumed good prognosis. Neither resulted in a high proportion of complete remissions though significantly more were obtained with CVP. Even the complete remission rate achieved with CVP was lower than that reported by others using the same or similar drug combinations[8] or total-body irradiation.[9] This difference is probably due to the fact that we stopped treatment after six cycles regardless of whether there was a continuing reduction of measurable disease, whereas at most other centres it is continued as long as improvement continues or until there is complete remission.

Complete remissions tended to be short and were no longer than good partial remissions. This may reflect the difficulty of detecting minimum residual disease.

Survival, as in other series,[10–12] was significantly longer in patients who had made a good response to treatment than in non-responders.

In a study of similar design single-agent treatment gave the same results as CVP.[13] There were, however, more complete remissions, with a longer mean duration, probably because treatment was continued for longer.

Because our treatments gave the same results we could evaluate other prognostic factors. The histological subtype influenced both response rate and duration of remission. We confirmed that the response rate is higher for patients with nodular than with diffuse lymphoma, and that nodular mixed lymphoma is associated with longer remissions than nodular poorly differentiated lymphoma.[14] The latter finding, however, should be regarded as tentative in view of the difficulty of precise histological diagnosis. If confirmed, the association of extensive disease at presentation (as judged by clinically evident enlargement of liver and spleen and bone marrow disease) with short remission may lead to more intensive treatment of those patients with extensive disease.

No other prognostic factors emerged from the data. Age, sex, stage, and the presence of bone marrow or peripheral blood disease did not affect response rate or length of remission in either the whole group or any of the subgroups. In most[15,16] (though not all[17]) series increasing age has adversely influenced the prognosis. Like us, Bloomfield *et al*[18] found that bone marrow disease did not influence the prognosis adversely in patients with generalised disease; in lymphoma of unfavourable histological type on the other hand bone marrow disease is an adverse prognostic factor.[19] Patients with leukaemia have been excluded from most studies of non-Hodgkin's lymphoma even though peripheral blood disease occurs frequently[20] and a picture similar to that of chronic lymphatic leukaemia may be associated with nodular lymphoma.[21] Our results show that in general leukaemia (as defined in this study) does not influence the prognosis adversely.

The most important findings of this small study are that (*a*) neither treatment is satisfactory, though relatively long remissions have occurred in about one-third of the patients regardless of which treatment they had; (*b*) extensive disease is associated with short remissions; and (*c*) the length of remission is not related to the age of the patient.

Our results and those of others make it clear that new treatment programmes are needed for non-Hodgkin's lymphoma of "favourable" prognosis. Intensive chemotherapy in selected patients with nodular lymphoma has had encouraging preliminary results,[22,23] but a longer follow-up is required to confirm its value. Although treatment with a single drug may be appropriate for older patients, a more aggressive approach may benefit the younger ones, especially those with extensive disease.

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Coeliac disease and immunological disorders

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Summary and conclusions

Out of 314 patients with coeliac disease, 63 had associated disorders of known or suspected immunological cause (excluding aphthous stomatitis and dermatitis herpetiformis). Autoimmune diseases appeared to occur more often in patients with coeliac disease than in the normal population, 52 such diseases being found in 45 patients. Of individual disorders, diabetes mellitus, thyroid diseases, and ulcerative colitis seemed to be more common than expected. Atopy (asthma and eczema) occurred in 7% of the patients.

Most of these immunological disorders developed when the patients were on normal diet. A gluten-free diet and virtually normal jejunum did not prevent their development, and the diet had little ameliorating effect on their course apart from an occasional dramatic improvement in atopic patients.

Introduction

There have been many reports of patients with coeliac disease and a coexistent disorder of known or suspected immunological aetiology.[1-7] It has been suggested that such disorders are common as a result of either circulating immune complexes originating in the damaged small intestine[1] or the passage of antigens across the damaged intestine.[7] Furthermore, Scott and Losowsky[1] thought that some immunological disorders in patients with coeliac disease might improve with a gluten-free diet. No supporting evidence for the suggestion was obtained from either individual patients or relatively small series of patients with coeliac disease,[8] however, and the effect of a gluten-free diet on the progress of these associated conditions has not been reported.

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We describe the various immunological disorders found in a large series of patients with coeliac disease and examine the relation of a gluten-free diet to the time of presentation and course of the disorders.

Patients and methods

During 1958-77, 314 adults with coeliac disease confirmed by jejunal biopsy[11] were followed up in this unit under the care of one of us (WTC). Fifty-four patients with coeliac disease seen before 1958 were excluded because either jejunal biopsy had not been carried out or their notes were inadequate for analysis. Of the 314 patients, 177 were women and 137 men; 28 of the women and 35 of the men died during the study.

Information about diseases of possible autoimmune or atopic aetiology was verified with the patients when possible and by review of notes on patients who had died or were seen only yearly. Aphthous ulceration and dermatitis herpetiformis—disorders with possible immunological aetiology related to gluten—were not included because of their known association with coeliac disease.[9 10]

Results

IMMUNOLOGICAL DISEASE

We found 75 immunological disorders in 63 (20%) of the 314 patients (see table). Of the 177 women, 34 (19%) had 41 immunological diseases, and of the 137 men, 29 (21%) had 34 diseases. Four women and five men had two immunological disorders each, and one woman had four coexistent disorders. In patients with autoimmune disorders the mean age at diagnosis of coeliac disease was 46 years, and in those with atopy it was 39 years. The mean age at onset of the autoimmune disorders was 38 years, but that of the atopic disorders could not be established.

Autoimmune disorders

Altogether, 52 autoimmune disorders were seen in 45 patients (14%); 28 were seen in 23 of the women (13%), and 24 in 22 of the men (16%). The most common disorder was diabetes mellitus. Ten patients had insulin-dependent diabetes, and four (three women and one man) had maturity-onset diabetes controlled by diet and oral hypoglycaemic agents. Eleven patients had thyroid disorders: four had thyrotoxicosis, of whom three (two women, one man) had Graves's disease and one man had a toxic adenoma; and seven (four women, three men) had myxoedema, of whom two had histologically proved Hashimoto's thyroiditis, one with a coexistent reticulum cell sarcoma of the thyroid.