

Cell receptor studies on seven cases of diffuse histiocytic malignant lymphoma (reticulum cell sarcoma)

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SYNOPSIS Expression of B and T lymphocyte receptors has been studied in seven cases of reticulum cell sarcoma. In one case, surface receptors and tests of phagocytic function demonstrated the histiocytic origin of the neoplastic cells. In four cases, tumour cells expressed both B and T lymphocyte markers (two cases) or showed a normal pattern of expression of B and T lymphocyte markers. In the other two cases, lymphocyte receptors were not detected, and there was no evidence of phagocytic function: this class of receptor-silent tumours is of uncertain pathogenesis. The significance of these observations is discussed.

In man the different classes of lymphocyte are morphologically indistinguishable by light microscopy, but can be detected by tests which show differences in the reactivity of the cell surface. B lymphocytes carry stainable surface immunoglobulin (Fröland, Natvig, and Berdal, 1971) and express receptors for complement and the Fc portion of the immunoglobulin molecule (Shevach, Jaffe, and Green, 1973). T lymphocytes lack stainable surface immunoglobulin but show the ability to bind washed sheep red cells (Fröland, 1972) under experimental conditions. There is also evidence to show that T lymphocytes carry surface antigens which are not present on B lymphocytes but which they share with brain (Brown and Greaves, 1974). By exploiting these differences in surface reactivity, or antigenicity, B and T lymphocytes can readily be identified and quantitated in human peripheral blood (Brown and Greaves, 1974; Habeshaw and Young, 1975).

There have recently been attempts to identify neoplastic cells of B and T derivation in neoplasms of the lymphoid and haematopoietic systems (Smith, Barker, Clein, and Collins, 1973; Shevach *et al* 1973; Edelson, Kirkpatrick, Shevach, Schein, Smith, Green, and Lutzner, 1974; Jaffe, Shevach, Frank, Berard, and Green, 1974). In chronic lymphocytic leukaemias most of the examples so far studied have shown the neoplastic cells to be B cell

in type (Pincus, Bianco, and Nussenzweig, 1972; Piessens, Schur, Moloney, and Churchill, 1973; Mellstedt and Petterson, 1974). These cells express generally a single heavy chain component indicating a clonal origin (Silberman and Schrek, 1974). In some cases the neoplastic cells lack receptors for complement (EAC) (Shevach *et al*, 1973) or carry HTLA (human thymic lymphocyte antigen), a T cell marker (Edelson *et al*, 1974). In other leukaemias, a prolymphocytic leukaemia (Dewar, Habeshaw, Young, Stuart, Parker, and Wilson, 1974) and a variant of chronic lymphocytic leukaemia (Shevach *et al*, 1973) cells bearing both B and T lymphocyte markers have been described.

In solid tumours of lymph node, lymphocyte receptors of both B and T type have been described. In a lymph node secondary associated with thymic lymphoid tumour the cells were of T lymphocyte derivation (Smith *et al*, 1973). In nodular lymphocytic lymphoma, the tumour cells were of B derivation, corresponding to the follicular cells of the normal germinal centre (Jaffe *et al*, 1974).

Cellular infiltrates in skin associated with mycosis fungoides, Sezary cell leukaemia, and lymphosarcoma have also been studied (Edelson *et al*, 1974). In all cases the infiltrating cells show the characteristics of T lymphocytes.

Macrophages, which may be confused with lymphoid cells, can also be identified in cellular infiltrates, for example, in grafts during rejection and in malignant leukaemic reticuloendotheliosis. This

technique makes use of the IgG-sensitized red cells which adhere to macrophages in frozen sections of the appropriate tissue (Shevach *et al.*, 1973). This technique can be used to identify complement (EAC) or immunoglobulin (EA) receptors in tissue, but it is not suitable for the localization of the sheep receptor (E) expressed by T cells (Shevach *et al.*, 1973; Jaffe *et al.*, 1974).

There is no firm conviction as to the derivation of the less well differentiated lymphoreticular neoplasms classified as reticulum cell sarcoma. Gall (1958) proposed that within this group of tumours was a group characterized by the resemblance of tumour cells to histiocytes (macrophages), an entity which he termed 'histiocytic malignant lymphoma' (see review by Stuart, 1974). Lukes (1968) suggested that the neoplastic cells were of lymphoid origin from their morphological resemblance to follicular centre cells. If either of these opinions is correct, a study of the surface receptors of tumour cells from reticulum cell sarcoma might show conclusively their origin either as T or B lymphoid, or as histiocytic, thus allowing conclusions to be drawn as to the pathogenesis of individual tumours.

In this study an attempt has been made to identify the neoplastic cell population of reticulum cell sarcoma as being either of T or B lymphoid origin as proposed by Lukes, or as being truly histiocytic, ie, macrophage-like, as proposed by Gall (1958).

Materials and Methods

CONTROL LYMPH NODES

Control lymph nodes comprise two groups, the first consisting of nine nodes from groin, axillary, cervical, or abdominal groups removed from patients with non-neoplastic conditions. These were classified on the basis of site of origin and light microscopic appearance. The second group consisted of five nodes removed from patients with systemic neoplasia (carcinoma or Hodgkin's disease) which were not microscopically involved by the tumour. These were classified according to site and diagnosis of the primary condition. All nodes were obtained as fresh surgical specimens within minutes of their removal.

NEOPLASTIC LYMPH NODES

These were received as fresh surgical specimens, and were immediately received into Hanks BSS or medium 199 and chilled in ice. The diagnosis of histiocytic lymphoma (reticulum cell sarcoma) was made by frozen section and subsequently confirmed by paraffin section and electron microscopy. The source was inguinal (case 4) cervical (cases 1, 3, 7), and axillary (cases 2, 5). An enlarged spleen, almost

totally replaced by tumour, was the source of cells in case 6.

PREPARATION OF LYMPH NODE CELL SUSPENSIONS

The lymph node was sliced into small fragments and immediately transferred to Hepes buffered medium 199, containing 10 units heparin/ml. The fragments were further teased under the medium and cells washed out by gentle pipetting. Cells were filtered through stainless steel gauze, washed twice in medium 199, and the concentration was adjusted to 3×10^6 /ml. Samples were smeared and stained with Giemsa, and viability was assessed by trypan blue dye exclusion.

PREPARATION OF SPLEEN CELL SUSPENSION (CASE 6)

Albumin gradients were used to concentrate neoplastic cells from the crude spleen suspension. Discontinuous gradients of bovine serum albumin were set up at 2, 4, 8, 12, 17, 22, 28, and 35% from stock bovine serum albumin (Armour) diluted with medium 199. Each layer was 4 ml in volume, and the gradients were loaded with 5 ml of cell suspension containing 100×10^6 cells. Sedimentation was allowed to continue for two hours at room temperature under gravity. All cell suspensions were tested for viability and smears were made at each fractionation step to ensure that suspensions were representative. Fraction 6 (22% albumin) contained 60% large abnormal cells, and was used in the receptor studies.

PREPARATION OF RED CELLS AND ROSETTES

Washed sheep red cells (E), sheep red cells sensitized with IgG antibody (EAlG), and sheep red cells sensitized with IgM antibody and complement (EAC) were used in the rosette tests.

E rosettes

E rosettes were prepared by centrifuging washed sheep erythrocytes, together with lymph node cells in a ratio of 40:1, at $80 \times g$ for five minutes. Incubation was continued for two hours at 4°C, and lymph node cells binding three or more erythrocytes were counted.

IgG rosettes

IgG rosettes for detecting Fc receptors were prepared by sensitizing sheep cells with purified anti-sheep RBC IgG for one hour at 37°C. Sensitized cells were washed once in phosphate-buffered saline and screened for microscopic agglutination. Rosette formation was assessed as for E rosettes.

EAC rosettes

Sheep red cells were sensitized with rabbit anti-sheep RBC IgM for one hour at 37°C, and then reacted with either guinea-pig or human complement, using a two-stage sensitization procedure. The exclusion of sheep cell determinants was shown by rosetting with IgM-coated sheep cells alone. Sheep cells sensitized with complement were incubated with lymph node cells in a ratio of 40:1 at 37°C for 10 minutes, followed by two hours at 4°C. Quantitation of rosettes was as for E rosettes.

IMMUNOFLUORESCENCE

Detection of immunoglobulin-bearing cells was performed using a sensitive 'sandwich' technique. The morphology of immunofluorescent cells was assessed by dark ground and phase-contrast microscopy.

PHAGOCYTTIC CELLS

Phagocytic cells were assessed functionally by their ability to ingest neutral red.

The techniques employed here have been described in detail elsewhere (see Habeshaw and Young, 1975).

Results

MICROSCOPY

Microscopy of our seven cases shows that all of them conform to the usual view that reticulum cell sarcomata are composed of large cells with moderate amounts of cytoplasm and large vesicular nuclei which frequently contain nucleoli (fig 1). Electron microscopy of five tumours confirmed that certain features were common to all although differences in the degree of cytoplasmic differentiation were noted. As a rule the cytoplasm contained large numbers of ribosomes with quite variable amounts of rough-

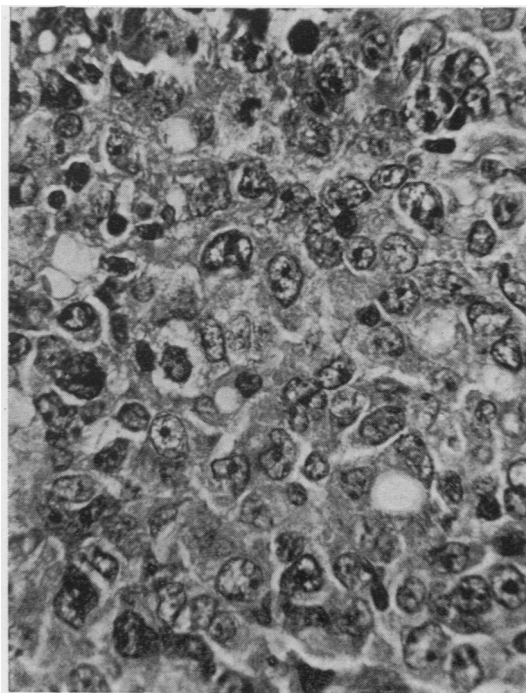


Fig 1 Representative light microscopic appearance of reticulum cell sarcoma. *H & E* × 600.

surfaced endoplasmic reticulum. Also mitochondria were abundant. All cases showed prominent nucleoli and the nuclei often contained deep clefts or had a lobulated appearance (fig 2). The neoplastic cells did not form fibres to any conspicuous degree and when dendritic cells were found they were interpreted as part of a population of normal residual cells. Ingestion of dead cells by macrophages was noted but there was no indication of overt phagocytosis by

Patients	Diagnosis	Site	E (%)	EAIgG (%)	EAC (%)	NR (%)	Fluorescence (%)	Viability (%)
1	Reactive sinus hyperplasia	Coeliac	55	18	40	27	32	65
2	Normal	Groin	42	70	46	1.0	—	80
3	Reactive	Axilla	41	8	—	—	22	82
4	Follicular reactivity	Mesentery	38	13	52	27	35	80
5	Sarcoid reaction	Cervical	41	24	31	—	40	76
6	Sinus hyperplasia	Mesentery	49	45	—	—	22	93
7	Reactive	Groin	51	7	9	11	13	84
8	Reactive	Groin	32	11	24	10	53	86
9	Reactive	Groin	30	16	20	12	27	50
10 ¹	Carcinoma	Neck	42	18	15	18	32	68
11	HDLP ²	Mesentery	56	—	—	—	29	66
12	HDLP	Groin	31	29	49	1	27	55
13	HDLP	Groin	24	12	—	—	37	87
14	HDNS ²	Mesentery	37	27	16	11	33	78

Table I Control lymph nodes (non-neoplastic, reactive, or normal on histological examination)

¹Additional nodes from patients nos 10-14 with carcinoma or Hodgkin's disease were normal or reactive on histological examination.

²HDLP = Hodgkin's disease lymphocyte predominance; ³HDNS = Hodgkin's disease nodular sclerosis.

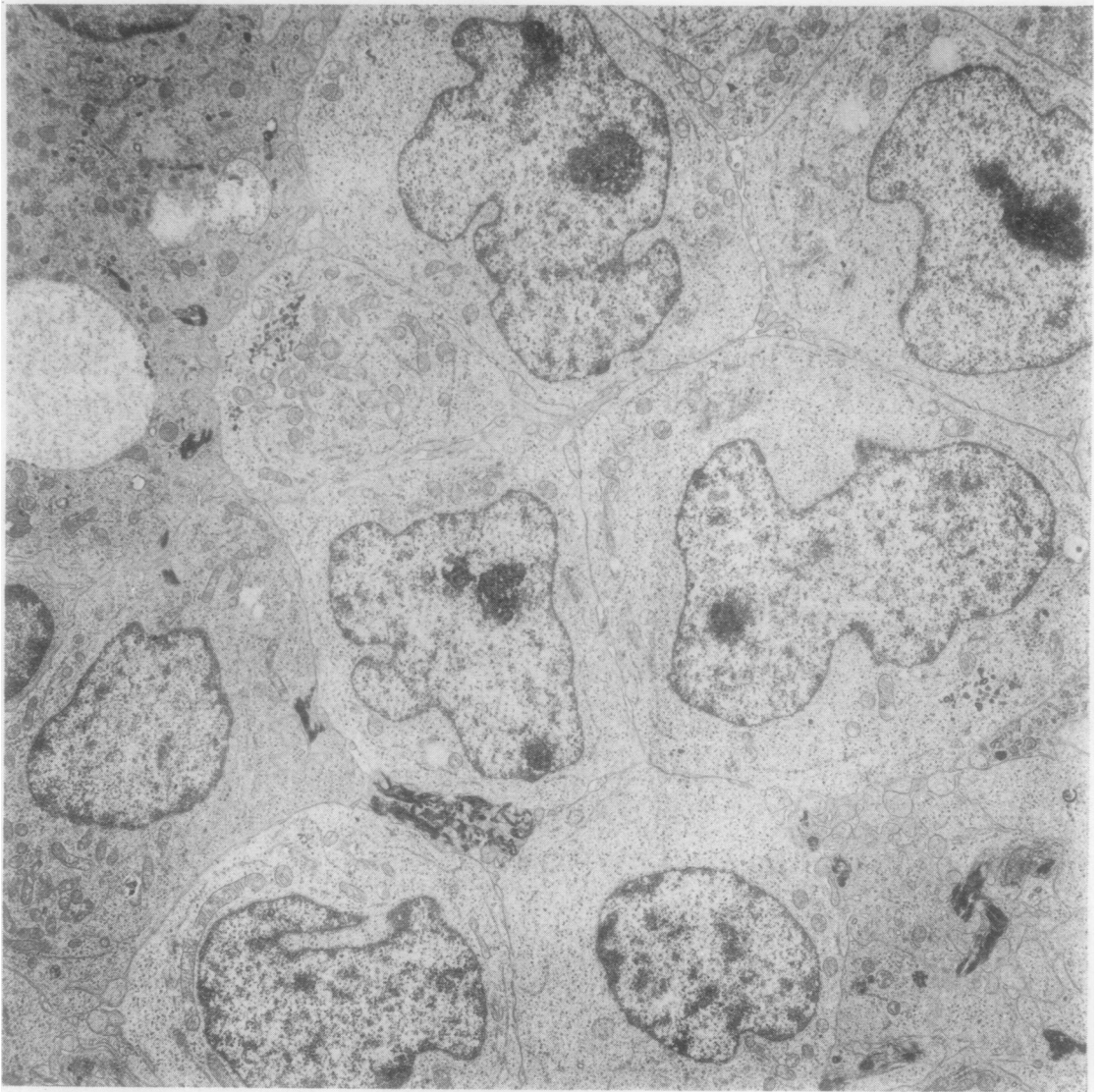


Fig 2 *Representative electron microscopic appearance of reticulum cell sarcoma.* $\times 3750$.

tumour cells. The degree of cytoplasmic differentiation varied between different tumours and between cells of the same tumour.

RECEPTOR STUDIES

The receptor pattern of lymphocytes from both groups of control lymph nodes indicates quite wide variability dependent upon the site of origin, viability, and reactive status of the node (table I). In general the proportion of T lymphocytes is lower and of B lymphocytes higher than in peripheral blood. The macrophages are more numerous than in

peripheral blood, although stromal macrophages are probably not represented in our preparations. The following ranges of cell receptors were obtained: E rosettes (T cells) 30-55%, EAIGG rosettes 7-70%, neutral red phagocytes 1.0%-27%, EAC receptors 9-52%, and immunofluorescent cells (B cells) 13-53%. In general the addition of totals of cells expressing receptors for sheep cells, cells showing stainable immunoglobulin, and the functional phagocytes ingesting neutral red gave a total equal to the percentage of viable lymph node cells.

The values for receptors in the neoplastic nodes

was at least as variable as in normal nodes (table II). In two cases (3 and 1) the receptor patterns were indistinguishable from those of normal nodes. In these cases, neoplastic cells expressed either B

Case No.	E Rosettes (%)	EAIgG (%)	Neutral Red Cells (%)	EAC (%)	Fluorescent Cells (%)	Viability (%)
K1	67	28	—	—	20	—
R2	15	—	60	12	26	63
S3	37	9	1	—	39	76
L4	49	40	12	30	—	69
B5	72	43	22	68	32	85
O7	30	6	4	7	6	85

Table II Receptor pattern of reticulum cell sarcomas in lymph node

lymphocyte or T lymphocyte receptors. The phagocytic population was low in case 3, suggesting that these were normal lymph node macrophages and not of neoplastic derivation. In the first case (K1) the majority of cells carried T cell markers, but viability and phagocytosis were not assessed and it did not prove possible to distinguish morphologically the neoplastic cells from reactive lymph node lymphocytes.

In case R2 the proportion of T cells was low, as was the total of cells expressing EAC receptors. The percentage of neoplastic cells ingesting neutral red was significantly greater than in control lymph nodes, and these accounted for the bulk of the viable cells. Overnight culture of these cells resulted in a glass-adherent population of large cells with convoluted nuclei. Some of these ingested red cells coated with IgG when incubated with them for two hours at 37°C (fig 3). Many of the cultured cells were indistinguishable from normal lymph node macrophages, others had large basophilic nuclei, and a few were binucleate. Phagocytosis of cell debris was widespread in the culture preparation. The predominance of phagocytically active cells in the original cell suspension, and the presence of morphologically bizarre phagocytic cells expressing receptors for IgG, lead us to conclude that in this case the tumour cells were of histiocytic, not lymphoid, derivation. Of the population expressing immunoglobulin determinants by fluorescence a minor population only showed the confluent ring or cap staining associated with B lymphocytes, a point reflected by the low level of cells expressing complement receptors—also a marker of B lymphocytes. In case S3 the receptor pattern is within normal limits.

In case L4, the percentage figures for E, EAIgG,

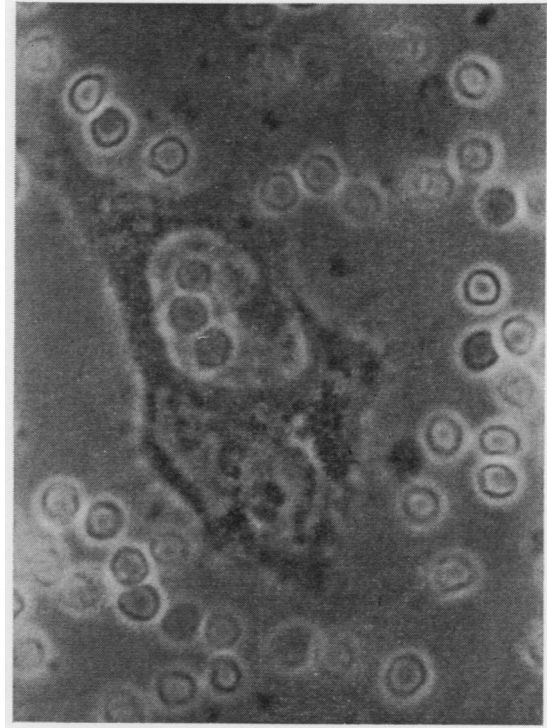


Fig 3 Very large cell in overnight culture of lymph node cells (case 2) which showed IgG receptors. Note phagocytic vacuole containing erythrocytes. Phase contrast $\times 700$.

EAC, and fluorescent cells also do not differ significantly from normal values. However, in this case the total of class-specific receptors expressed exceeds the total of viable cells and leads to the conclusion that at least one population of cells must express receptors not generally expressed by cells of that class. This is reflected in the totals for cells expressing T lymphocyte receptors (E) and receptors for EAIgG, which are normally expressed by a proportion of B lymphocytes and macrophages and not by T cells. Phase-contrast examination revealed rosette formation (by large neoplastic cells) with sheep red cells (E), immunoglobulin (EAIgG), and complement (EAC)-coated red cells, supporting the concept of 'receptor overlap' (figs 4, 5, 6).

In case B5, this overlap of receptors is confirmed, especially in relation to the T cell marker E, and the B cell receptor for EAC, whose combined total is 126% in a population where only 85% of cells were viable. Phase-contrast examination showed that in addition a minority of tumour cells failed to rosette with any of the particles (figs 7 and 8).

Cases R6 and O7 show the presence of a large

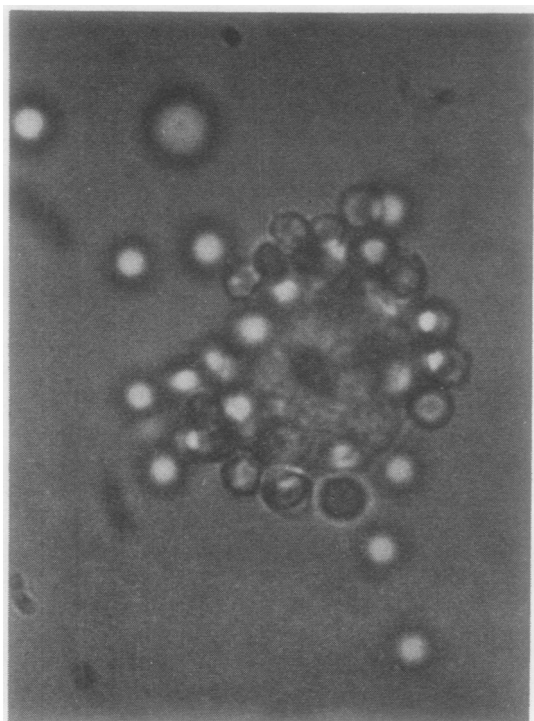


Fig 4

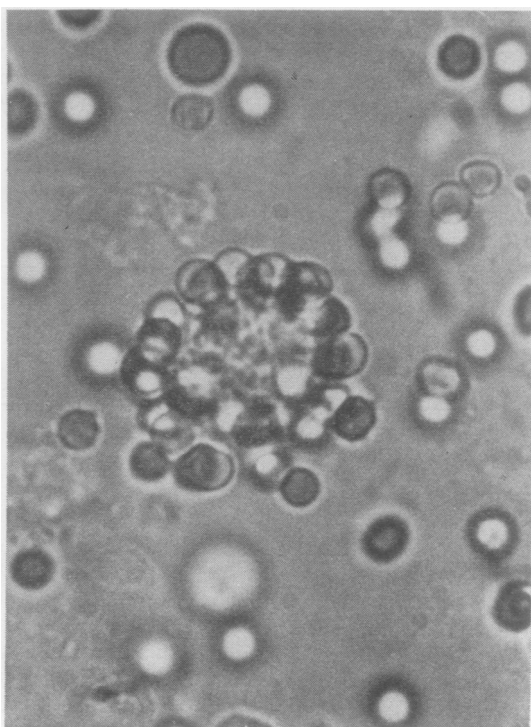


Fig 5

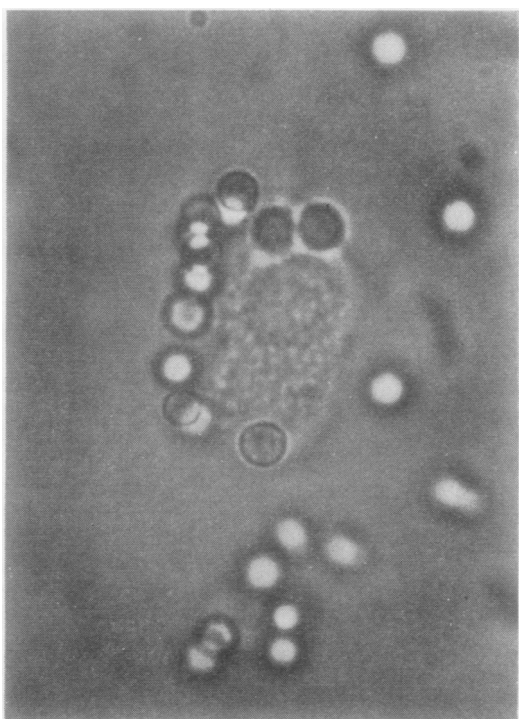


Fig 6

Fig 4 Tumour cell from case 4 showing rosetting with sheep erythrocytes. Phase contrast $\times 700$.

Fig 5 Large EAIgG rosette from case 4. Phase contrast $\times 700$.

Fig 6 Tumour cell from case 4, showing adherence of EAC-coated red cells. Phase contrast $\times 700$.

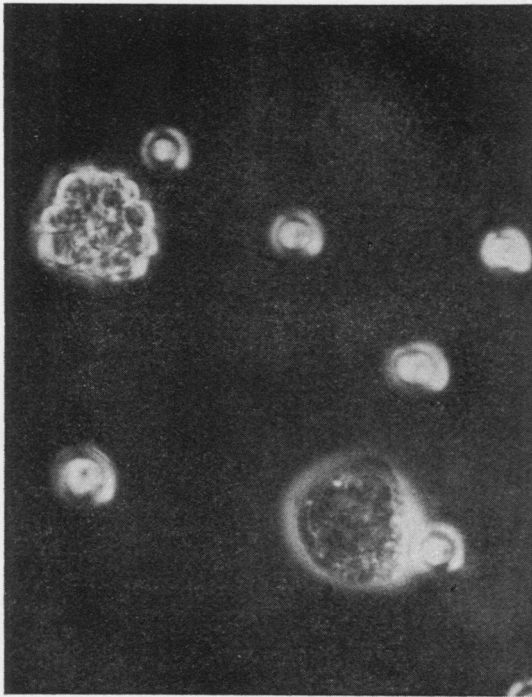


Fig 7 EAC rosette and large solitary cell from case 5. Dark ground illumination $\times 400$.

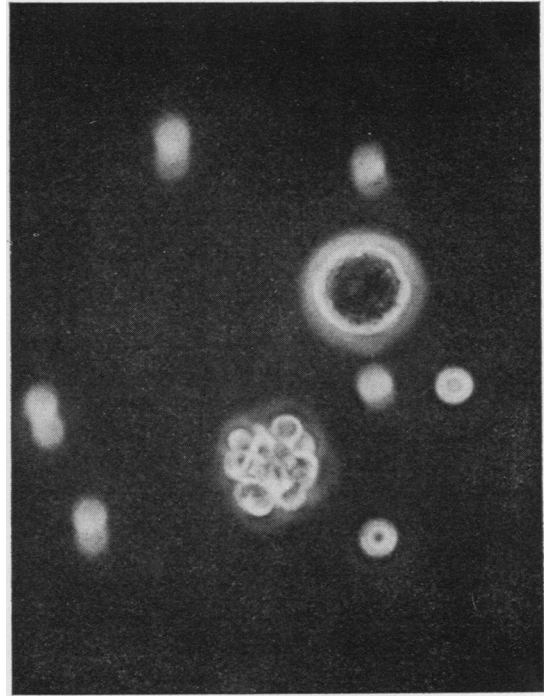


Fig 8 E rosette and large tumour cell from case 5. Dark ground illumination $\times 400$.

receptor silent population. Cells forming rosettes from the spleen preparation in case 6 can be accounted for by the contaminating lymphocytes and macrophages in the cell population (table III).

Receptors as Percentage		Differential Count as Percentage	
E	5	Tumour cells	60
EAlG	18	Small mononuclear cells	23
EAC	18	Polymorphonuclear leucocytes	7

Table III Receptor studies on albumin gradient fraction of spleen cell suspension from case R6

In case 7, phase-contrast microscopy showed that readily identifiable viable tumour cells comprised over 60% of the cell population studied. The great majority of these cells failed to rosette with any of the test particles or to ingest neutral red, although some weak EAlG and E rosettes were formed by tumour cells. A feature of interest in this case was the tendency of the tumour cells to show weak diffuse surface fluorescence with polyvalent antisera. This staining was not of the type associated with B lymphocytes, the staining being very weak and show-

ing no tendency to localize in caps or patches on the cell surface.

Discussion

This study of surface characteristics of malignant cells isolated from lymph nodes was facilitated by the choice of reticulum sarcoma where the cells are large and distinctive; furthermore in all our cases the entire node was replaced by tumour tissue obliterating the underlying architecture. Thus the receptor studies reflected the surface constitution of a predominantly tumour cell population. Nevertheless it may be difficult to distinguish between reactive lymphoid cells and neoplastic lymphocytes when the cells are in suspension and reference to histological sections is necessary to identify the nature of tissue taken for experiments.

In one case (2) we are confident in asserting a histiocytic origin for the neoplastic cells, since these were phagocytically active both in the original suspension and in tissue culture, and expressed receptors for EAlG in culture. In addition, these cells lacked receptors for both E and EAC (T and B lymphocyte markers).

In two cases (4 and 5) overlap of receptors was noted. Since examining these nodes we have developed techniques which allow simultaneous detection of T and B cell receptors, and an additional case of polymorphous leukaemia has been described in which this phenomenon occurred (Dewar *et al*, 1974). Other authors have also noted the expression of receptors for IgG (Yoshida and Andersson, 1972) by T lymphocytes undergoing transformation, by cells derived from chronic lymphocytic leukaemia (Shevach *et al*, 1973), and by circulating cells in an uncharacterized lymphoproliferative disorder (Sandilands, Gray, Cooney, Browning, Grant, Andersson, Dagg, and Lucie, 1974). A small population of normal peripheral blood lymphocytes bearing both B and T cell markers has also been described (Dickler, Adkinson, and Terry, 1974). There are therefore two possible conclusions to be drawn from cases 4 and 5; either the neoplastic population is derived from a subclass of lymphoid cells bearing both B and T markers, or the population is derived from T lymphocytes which have acquired B cell markers during neoplastic transformation (or vice versa). In both cases the origin of the neoplastic cells is lymphoid rather than histiocytic.

In cases 6 and 7, the tumour cells were receptor silent, and therefore not classifiable as either lymphoid or histiocytic in origin. In case 6, and one other receptor silent lymphoma we have studied, progression of the disease was rapid and both patients died within six to nine months of diagnosis. This might suggest that receptor silence is an ominous prognostic sign in lymphoreticular neoplasia. It could be due to loss of receptor characteristics by dedifferentiation of the neoplastic cell, or suggest an origin from a receptor silent class of cell possibly of stromal origin (reticulum cell or reticular macrophage). The presence of small, but detectable amounts of immunoglobulin on the tumour cells in case 7 do not necessarily imply a B cell origin. Weak, diffuse fluorescence of this kind can be observed in carcinoma cells from secondarily involved lymph nodes, and may represent the presence of circulating anti-tumour-cell antibodies. It is worth mentioning that in our experience carcinoma, or malignant melanoma, cells from involved nodes are also receptor silent. In our two receptor-silent cases the mode of presentation, the histological appearances, and the subsequent clinical behaviour exclude the possibility of metastatic carcinoma or malignant melanoma.

Receptor studies are expensive in time and it is pertinent to ask what contribution they can make to the understanding of lymphoid neoplasms. The contribution of such studies to pathology and medicine has already been assessed (Wybran and Fudenberg,

1974). In the field of lymphoid neoplasia, the present study has confirmed the views of Lukes and of Gall in proposing lymphoid and histiocytic origins respectively for this group of neoplasms. The overall picture is far from clear; in particular no explanation for the neoplasms with normal ratios of B and T cell markers is satisfied by the current dogma of clonal origin from a single class of neoplastic lymphocyte. Two possibilities are perhaps worthy of further examination: first that the neoplastic state requires the participation of both B and T lymphocytes, as do the normal phenomena of antibody secretion and germinal centre formation. As an alternative, perhaps a fixed neoplastic population sequesters from the circulation a reactive lymphoid population which proliferates in concert in the environment of the node. It is hoped that further investigations of the solid tumours of lymph nodes will cast more light on a difficult subject.

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