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BENIGN AND MALIGNANT PROLIFERATIVE RESPONSE[1]

Dermal Infiltration. Origin and Importance

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Abstract. Lymphoreticular infiltration (LRI) is the most common type of dermal infiltration. The LRI is made up of two main components: (i) a dermal skeleton, and (ii) the infiltration in a strict sense. (i) The dermal skeleton consists of the blood vessel involved, most probably a postcapillary venule, and activated fibroblasts (Fig. 3). The activated fibroblasts contain "paraplasmatic granules" in their processes (Fig. 4). Since the fibroblasts are in mutual contact by their ramifications (Fig. 3), they are reticulum cells by definition (Bessis). In our opinion they are the only local reticulum cells in the dermis. They are not stem cells, nor do they belong to the reticulo-endothelial system and they do not give rise to histiocytes. (ii) In the skeleton of LRI, other cells infiltrate, predominantly monocytes and lymphocytes. The LRI may specialize and contain various amounts of neutrophilic, basophilic, or eosinophilic leukocytes and plasma cells. If enough B-lymphocytes and plasmacells are involved, abnormal globulins may be produced (e.g. syphilis II). The lymphomas are considered to be malignant proliferative disorders of LRI-type. LRI is found in allergic spreading reactions mediated by stimulated lymphocytes. A similar spreading of lymphocytes is to be expected if the allergen sensitizes a lymphocyte with neoplastic information (e.g. tumor virus) (Fig. 6). The degree of dedifferentiation and the response of the organism to the dedifferentiated lymphocytes is the reason for the variety of lymphomas.

Key words: Lymphoma; Fibroblasts; Monocytes; Reticulum cells; Stimulated lymphocytes; Mucinosis

1. *Benign proliferative response*

The topic, dermal infiltration covers a wide field, but the discussion here, will be confined mainly to just one type of infiltration—the lymphoreticular (LRI).

Other names for LRI are lymphomonocytic, lymphohistiocytic, lymphadenoid, mononuclear, or merely round cell infiltration or reaction. It has also been called perivascular island reaction (17).

Reaction is a better term than infiltration, since the word reaction distinguishes between this phenomenon and malignant proliferative disorders, as well as indicating that the disorder involves not only cells of the infiltrate that invade the dermis, but also residents of the dermis itself (47).

LRI is the most common infiltration in skin. It is found in various conditions, e.g. allergic eczematous contact dermatitis, drug eruptions, infectious exanthemas (virus, bacterial, treponemal, fungal, epizoonoses), autoimmune phenomena (lupus erythematodes, lichen planus), defence reactions against tumours, and in transplantation.

An extreme variety of LRI is lymphocytoma, with the formation of reaction centres. Another variety is tuberculoid granuloma. Here, the parallel between immunological defence and infective agents is well known; in a tuberculoid granuloma, relatively few bacteria or fungi are to be found.

LRI is seen predominantly in the delayed type of allergy—according to Gell & Coombs, type IV allergy conveyed by T-lymphocytes. Animal experiments and observation of patients suggest that LRI may also be found in other allergic reactions, and even in the later stages of the Arthus phenomenon (17, 44, 45).

It must be stressed, however, that the different allergic reactions (types I–IV according to Gell & Coombs) do not occur only in isolation. On the contrary, two or more reactions are frequently combined, as has been shown in particular by the study of penicillin allergy (12).

In H & E sections the infiltrates seem to consist predominantly of two components: 1) Larger cells with large nuclei and large nucleoli. These cells hold together by the ramifications of cytoplasma (3, 9, 48, 54) and form a net, a reticulum. The word reticular in LRI is therefore used in a purely descriptive way. 2) Smaller lymphoid cells.

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Table I. *Cells in the dermis*

1. Residents
Nerve cells
Langerhans cells
Melanin-forming? cells
Muscle cells
Vascular cells
Mast cells
Fibrocytes
Histiocytes?
Reticulum cells??
2. Neighbours
Epithelial cells
Melanin-forming cells
Fat cells
3. Visitors and "migrant workers" ("Gastarbeiter")
Leukocytes (Eos. Pol. Bas)
Lymphocytes (B. T. O)
Plasma cells
Monocytes
4. Invaders
Tumour cells

In cryostat sections, which can be prepared with virtually no shrinkage, it can be seen that the two types of cells stick as close together as might be expected of macrophages and lymphocytes, according to the most recent discoveries in immunobiology (6, 13, 19, 20, 27, 28, 56).

However, this simple picture derived from routine sections is deceptive. Numerous other cells participate in LRI, but these, for example basophilic leukocytes (8), can be demonstrated only with special staining techniques or after special pretreatment. Therefore lymphoid cells which do not behave like T- or B-lymphocytes, are not necessarily O-lymphocytes.

Before considering the basic details, it would be as well to recapitulate which cells one may expect to find in the dermis (Table I).

Cells in the dermis

There are four main cell groups in the dermis (Table I). 1. The residents of the dermis—in other words, those cells which are born there and reside there permanently. A question mark can be set against some cells usually regarded as residents, since it is doubtful whether histiocytes and reticulum cells are natives of the dermis. Monocytes migrating through the dermis have apparently been mistaken for histiocytes. Fibroblasts phagocytize to a certain degree (22, 36, 41) and also reveal a high activity of hydrolytic enzymes and so apparently they too have been called histiocytes. Fibroblasts are generally recognized as another functional condition of fibrocytes.

2. Neighbours occasionally visit the dermis. Apart from tumours, the invasion of the dermis by epithelial cells is a rare phenomenon. It is to be seen for example in lichen planus (colloid bodies), but we have also found it in the skin of children with pheochromocytomas (23, 53).

3. Visitors and migrant workers are cells which visit the dermis in order to help the skin fulfil various vital functions.

4. Tumour cells.

Nervous elements

Neurohistology has been discredited by overevaluation of silver-stained fibres. With the electron microscope, however, nerve elements may be recognized more precisely. My colleagues Mahrle and Orfanos have found that Merkel cells, most probably nerve receptors, are present not only in the human epidermis and hair follicles, but also in the dermis. Degenerative changes (osmiophilic bodies) have been seen in cutaneous nerves damaged by drugs or tumours (42) (Fig. 1). In contrast to many other cells, the influence of nerve elements does not necessarily depend on their quantity. To neglect the rapid information that nerve elements give to and receive from the central nervous system, would be like acting in the age of electronics as if we were still living in the age of stage coaches.

Langerhans cells

Langerhans cells, for a long time neglected, are now considered to derive from mesenchyma and to have a special function as mediators of allergic reaction of the cellular type. But many questions concerning their function and origin remain unanswered (7). In the normal epidermis, lymphoid cells, probably lymphocytes and monocytes, are available to react with allergens.

Mast cells and basophilic leukocytes

Mast cells are located around the blood vessels from which infiltrates develop. Just a few of our findings in relation to mast cells in normal and pathological skin ought to be mentioned. By mere observation it is hard to determine if the number of mast cells in pathological skin is increased or diminished, as we learned when trying to count mast cells per mm^3. Apparently, they are not stainable

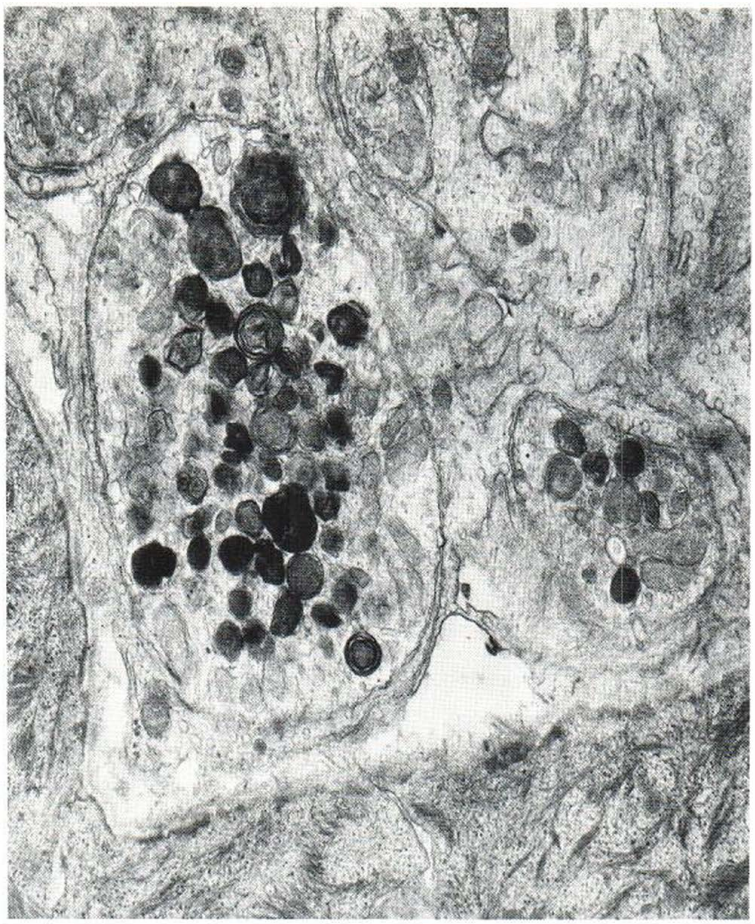

Fig. 1. Dystrophic axoplasma of a cutaneous nerve with osmiophilic lamellar bodies (Courtesy of Drs. Runne & Orfanos (42) ×21 000).

and are even absent under certain conditions—a phenomenon which remains to be studied (53). The increase in mast cells in the papillary body of psoriatic lesions and the very early decrease as a result of successful therapy with dithranol, is remarkable (43). Unpublished observations by Künzig and myself suggest that mast cells in the dermis may vary considerably in quality. For example, numerous mast cells surround basal cell epitheliomas, in whose stroma, more mast cells are sometimes present than in exanthematic lesions of urticaria pigmentosa, but the functional difference is obvious. Mast cell and leukocytes and especially eosinophilic leukocytes occasionally give a strongly positive dopa-reaction, which may lead to diagnostic errors (Fig. 2).

Eosinophilic leukocytes

The functional and diagnostic importance of eosinophilic leukocytes is not yet clear (3). Our own histological examinations of insect bites amongst a group of inpatients all bitten by the same gnats during the same period, revealed that, in contrast to general opinion, eosinophilic leukocytes are sometimes absent from insect bite granulomas. When neutrophilic leukocytes degenerate or are dried out, e.g. in the horny layer, their cytoplasma is stainable with eosin. Special techniques are necessary to distinguish such leukocytes from true eosinophils. Thus, whereas H & E sections give the impression that there are numerous eosinophils in pustular psoriasis or in mercury dermatitis, special staining techniques for eosinophils reveal that there are few or none.

Skeleton of LRI

The LRI possesses a skeleton of its own, consisting of residents of the dermis: (i) the vascular tree (venules) (27, 28, 44, 45, 54), (ii) reticulum fibres connecting the venules with the surrounding connec-

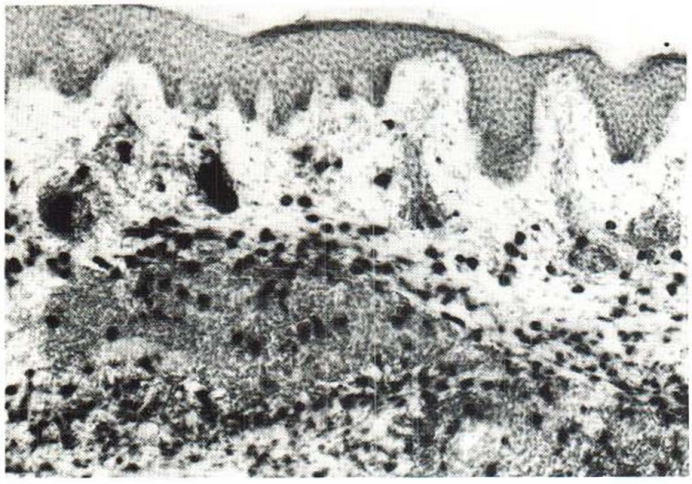

Fig. 2. Dopa-positive eosinophilic leukocyte around a venule in allergic granulomatosis (Churg & Strauss). ×95.

tive tissue of the dermis, and (iii) the fibrocytes coordinated with the venules.

Using microradiograms (X-rays of histological sections) and polarized light, we found that the collagenous bundles in the region of LRI were absent but had not usually been pushed aside (44, 45).

Blood vessels

LRI develops around small blood vessels and, according to our studies and the findings of other authors (27, 28, 44, 45, 47, 54), these are most probably venules. In lymph nodes the post-capillary blood vessels apparently have a special function in the circulation of lymphocytes. In contrast to the arterioles, reticulum fibres radiate from the venules to the dermis, so that the venules are much more closely linked to the collagenous tissues than the arterioles.

Reticulum fibres

Reticulum fibres are found in infiltrates of varying origin (e.g. syphilis II, leishmaniasis, tuberculoid infiltrates, hemangiomas and malignant proliferative disorders). Like many other authors, we therefore feel that reticulum fibres are of little diagnostic value in benign and malignant disorders, and in the determination of cells (48).

Fibrocytes and fibroblasts

Fibroblasts and fibrocytes are cells that are even more interesting than was thought in earlier days. Apparently they may contain contractile fibres (14, 34). Our histochemical studies have revealed that the fibroblasts in the dermis are coordinated with particular blood vessels, with a specific vascular "tree" (*Gefäßbaum*) (47, 49, 54). From this vascular tree, most probably a venule, fibrocytes are "activated" and morphologically they become fibroblasts (Fig. 3) (33, 49, 54). They reveal a higher enzyme activity (non-specific esterases, leucine aminopeptidases), their nuclei and their nucleoli are enlarged, and the cytoplasm is swollen and more basophilic.

This phenomenon is found in allergic reactions of the delayed type (Fig. 3). The activation may involve the fibrocytes in the entire dermis and in the collagenous septa of the subcutaneous layer of the area concerned. Connective tissue cells change their functional state more rapidly than other cells. Therefore classification of connective tissue cells by histochemical techniques is of relative value only.

Fibrocytes have long extensions which are easily seen in thick, unfixed, cryostat sections (Fig 3). When activated, these fibroblasts contain paraplasmatic granules in their extensions (46, 52). According to our histochemical findings the chemical composition of these paraplasmatic granules is variable (46). The granules are mostly basophilic, but they are sometimes metachromatic and/or stained with alcian blue or even with mucicarmine (Fig. 4) (46, 52). When numerous granules are present, they may appear like extracellular deposits of glycosaminoglycans in the dermis, especially since such deposits are sometimes present at the same time. The fibroblasts probably produce an abnormal mucous material in some mucinoses.

Paraplasmatic granules must be distinguished

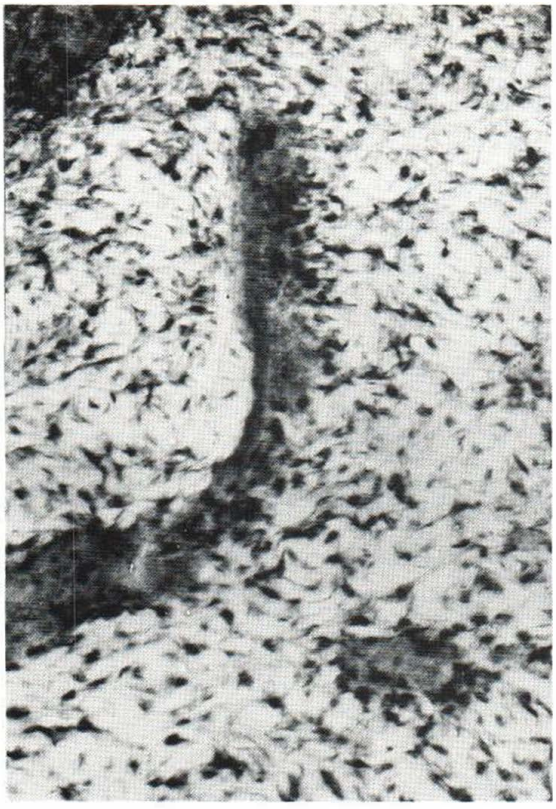

Fig. 3. Activated fibrocytes (fibroblasts) around a venule in allergic contact dermatitis caused by DNCB in a patient with malignant melanoma. The fibroblasts are in contact with each other by their extensions (non-specific esterases). ×90. Reproduced from (47).

from microorganisms, e.g. leishmanias and others, and also from remnants of nuclei, since leukoclasia is, at least to some degree, a common feature of LRI.

We have mentioned already that fibrocytes may phagocytize under certain conditions and to a certain degree. This fact has led to the assumption that certain macrophages (histiocytes) derive from fibrocytes. Tissue cultures, however, make it clear that the "professional" macrophages, in other words cells with a pronounced ability to phagocytize larger particles, have another origin (3, 25). The professional macrophages spread over surfaces, have a characteristic in their cell surface with particular movements, and they have special submicroscopical structures in the cytoplasm (41). All in all, this constitutes a precise description of a monocyte (3). Unfortunately, our conception of monocytes is derived from blood smears where they look large and flat owing to their special ability to spread over the slides (3). Monocytes are no larger than other blood cells; their surface is full of ruffles, as has been clearly demonstrated by an excellent picture taken by Bessis with a scanning microscope (3). Thus, they are able to surround particles and to bind antigens and prepare them for lymphocytic activity.

Reticular cells (Retikulum-Zellen)

"The reticular cell appears to be a myth in any serious discussion of connective tissue." ... "The term reticular cell seems to be confusing and possibly redundant and if used should be defined" (6, p. 3).

As Aschoff himself stressed, the reticulo-endothelial system is purely functional, and has now already shrunk to a monocytotic-phagocytotic system (3). When Aschoff first reported on the RES, Lubarsch (31) pointed out that phagocytosis is a relative and not a characteristic phenomenon of cells. Stimulated and damaged cells start to phagocytize. Some authors call immature cells reticular cells, from which some or even all types of blood cells and of connective tissue cells are supposed to derive (3, 6, 25, 26, 48, 50). In the bone marrow

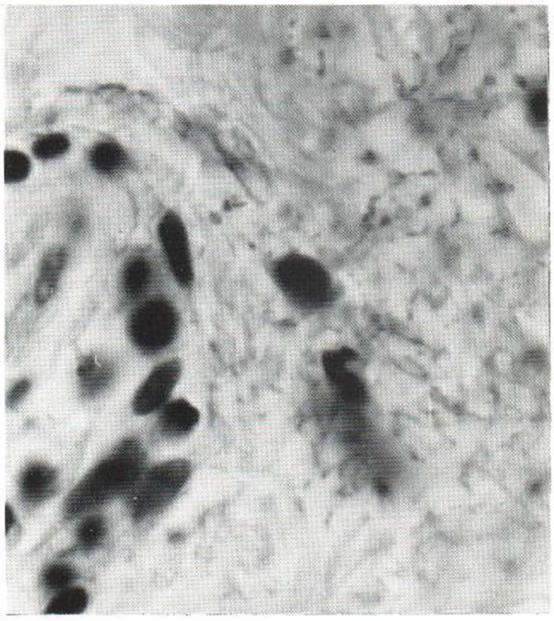

Fig. 4. Paraplasmatic granules in the extensions of fibroblasts. Plaque-like form of cutaneous mucinosis, mucicarmine. ×1000.

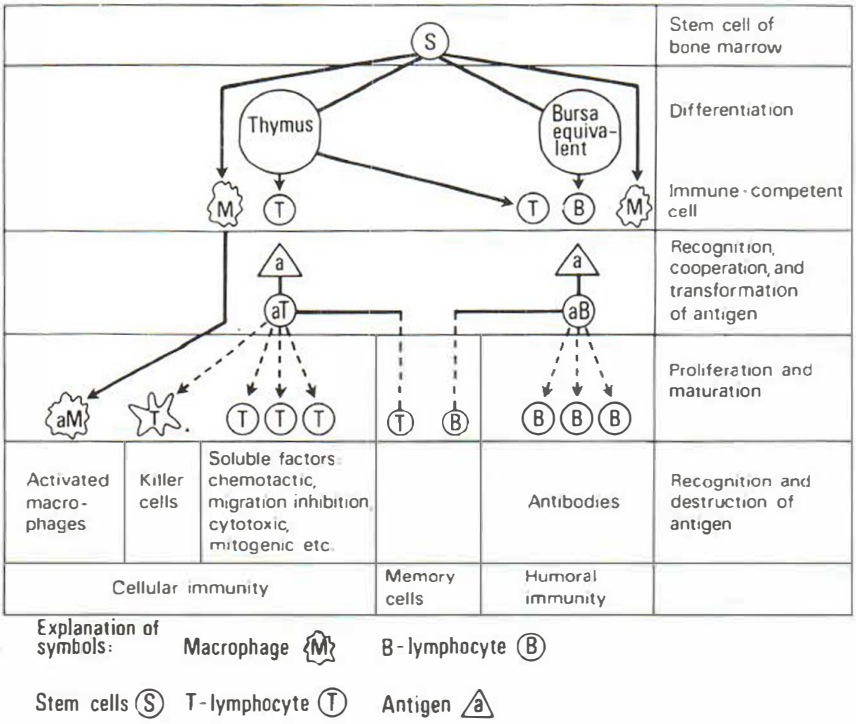

Fig. 5. Morphological basis of humoral and cellular immunity. (Courtesy of Prof. Wacker (56).)

such cells exist, but it is better to call them stem cells in order to avoid confusion (6). In the dermis the presence of such cells as residents has never been established.

For other authors the reticular cell is just a border or supporting cell (*Belegzelle oder Stützzelle*) which is supported by reticulum fibres (3, 6, 48). The fibrocytes are such cells in the dermis, but they are excluded from the RES (3).

Thus, the question is open as to where the macrophages originate. According to Maximow and his colleagues, some (though not all) lymphoid cells may become macrophages (25, 48). It is certain that some macrophages look like lymphoid cells, but it is also well known that monocytes have the ability to alter their appearance drastically. Under certain conditions they may look like small sausages and appear in cross sections like lymphocytes (48). The findings of several authors reveal that in granuloma the macrophages derive from cells not preexisting in the dermis but coming from blood stream, either from lymphocytes or monocytes (4, 25, 35, 41, 55).

Lymphocytic stimulation

The discovery of lymphocytic stimulation in vitro by Nowell, Hungerford, Donelly and Beck in 1959 was not only an important step in immunology but also opened new frontiers in histology (11, 30, 45).

Without doubt lymphocytic stimulation was seen and described much earlier by Maximow and his pupils, especially Lang, but since 1959 lymphocytic stimulation has been induced under controlled conditions. My colleague Orfanos, together with other workers at the Department of Internal Medicine in Cologne (38), examined stimulated lymphocytes with an electron microscope. They found signs of phagocytosis in stimulated lymphocytes, but no definite transformation to macrophages. Despite the authors' own caution, they were misquoted as actually having seen real transformation (28). Künzig and I then induced a series of histochemical reactions in stimulated lymphocytes, as previous accounts had been so controversial (11, 19, 30). In our experiments the stimulated lymphocytes behaved like lymphocytes and not as macrophages, and the activity of non-specific esterases remained very weak. On the other hand cells with a strong activity of non-specific esterases are found very early on in LRI (44, 45). The Rebuck-test (skin window test) reveals a predominance of macrophages, as all authors have described (16, 25). However, transitional forms between lymphocytes and macrophages are not to be seen (25).

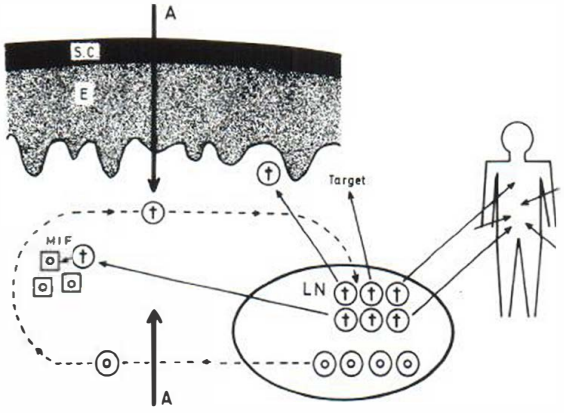

Fig. 6. Malignant proliferative response. An allergen (*A*) sensitizes a lymphocyte with neoplastic information (e.g. tumorvirus), the sensitized lymphocyte returns to the lymph node (*LN*) and gives rise to a clone of lymphocytes with the same malignant information which then spread to the skin. Here a neoplastic proliferation with and without benign granulomatous reaction develops. The neoplastic lymphocytes may produce migration-inhibition factors and leukotactic factors (M.I.F.) as normal stimulated lymphocytes. s.c.=stratum corneum, E=epidermis (reproduced from (47).)

Without going into detail here, there is an interaction between B- and T-lymphocytes and, in addition, between lymphocytes and monocytes (11, 13, 20, 56) (Fig. 5).

The stimulated lymphocytes produce leukotactic factors and inhibit the migration of monocytes, as well as other leukocytes (Fig. 5). It is easy to understand that this results in an accumulation of macrophages, and stimulated and non-stimulated lymphocytes, and so the early appearance of macrophages in lymphocytic stimulation at least does not exclude the possibility that the macrophages may be derived from monocytes. On the other hand, modern studies of lymphoblastomas suggest that morphological cells similar to histiocytic or reticular elements may derive from lymphocytes, for example in nodular lymphoma (29).

Demonstration of lymphocytic stimulation in the dermis is of practical interest. Through the absorption of ^{3}H-thymidine by stimulated lymphocytes, lymphocytes with and without stimulation may be distinguished from one another, thus in allergic eczematous dermatitis (24). Pullmann and I found numerous lymphoid cells labelled with ^{3}H-thymidine in the infiltrates of malignant melanomas, but not around other tumours (39, 40). Primary melanoma differed from metastasis. With the spread of metastasis, the number of labelled cells decreased. Practically all labelled cells were lymphoid, but 1.25% contained melanine granules (39).

II. *Malignant proliferative response*

There is no sharp border line between the morphology of benign and malignant proliferative disorders. Besides the clinical picture and course, it is principally the morphology of cells that helps us to distinguish between benign and malignant disorders (2, 15, 48, 50). In brief, the lymphomas seem to be the malignant variety of LRI. Solitary sarcomas of the skin are rare; primary multiple neoplastic lymphoreticular proliferations are common (15, 47, 48). The parallel between these spreading reactions and those of allergic spreading is obvious, as can be seen from allergic eczematous dermatitis and other allergic phenomena (mycids, drug eruption). Some spreading reactions mainly involve the epidermis and the upper dermis, and it has been assumed that the formation of spongiotic vesicles is caused by invading cells (18, 49, 54, 57). Other exanthemas are predominantly related to the deeper dermis. Fig. 6 explains our theory (47): The "lymphocyte on call" prowls through the dermis and also through the epidermis. It finds an allergen—or its allergen—and becomes sensitized. It returns to the lymph node and creates new generations of lymphocytes, which again spread to the dermis in order to find their targets. If the "lymphocyte on call" has taken on a neoplastic information, i.e. through a previous contact with a tumour virus (1), its behaviour may be fatal for the individual involved. The lymphocyte returns to the lymph node and gives rise to an abnormal generation of lymphocytes which spread all over the integument. According to the degree of abnormality, granulomas of varying malignity will develop, ranging from completely non-differentiated cells similar to stem cells without reticular fibres, to granulomas similar to LRI (5, 15, 48, 50). This is indeed the actual situation we find in lymphomas (2). In addition, depending on the antigenicity of tumour cells and the functional similarity to normal lymphocytes and also depending on the immunological situation of the organism, other cells will accumulate around the neoplastic lymphocytes (47, 48, 50). These may be T- or B-lymphocytes (51). Pathological B-lymphocytes produce patholog-

ical immune globulins which are not infrequently to be found in patients with lymphomas (21, 37).

Immunological characterization of lymphocytic and monocytic cells will answer many of these questions (10, 32), but unfortunately we ourselves have not yet been able to isolate enough undamaged cells from the lymphomas to obtain results.

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