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Distribution of macrophages in rheumatoid synovial membrane and its association with basic activity

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Summary. Rheumatoid arthritis (RA) is an inflammatory disease of the synovial membrane, which results in the destruction of joints by inflammatory pannus. The synovial membrane shows proliferation and cellular infiltrates on microscopy with signs of chronic and acute inflammation. Macrophages are thought to play a central role in the pathogenesis of RA. We examined synovial membrane specimens of 21 RA patients using morphological, immunohistological and enzyme histochemical methods for number and distribution of macrophages. We were able to identify $41.5 \pm 8.8\%$ of lining cells as macrophages, depending on the method used. In abundant diffuse lymphocellular infiltrates, $23.4 \pm 11.1\%$ of mononuclear cells were macrophages. In addition, most cells in the region of tumorlike proliferation and a stromal population of fibroblastlike cells were detected by macrophage markers. Although cell number in synovial membrane increases drastically, we did not find correlations between the relative amount of macrophages in these regions and basic activity. Basic activity includes proliferative reaction as well as lymphoplasmacellular and mononuclear infiltration – both signs of an immunopathological process. In contrast, using enzymes or activation markers, there was a clear correlation. We consider that a constant high percentage of macrophages in RA synovial membrane is present regardless of any actual inflammatory process.

Key words: Rheumatoid arthritis – Immunohistochemistry – Enzyme histochemistry – Histopathology – Chronic synovitis – Macrophages

Introduction

In rheumatoid arthritis (RA), joints are deteriorated by a chronic inflammation of synovial membrane caused and perpetuated by immunopathological processes [1]. Initial vasculitis [2, 3] is followed by the exsudation of cells and mediators, edema, cellular infiltration, hyperplasia of the lining cell layer, and finally formation of pannus, subsequently causing further joint damage [4]. In some cases, the synovial membrane is infiltrated by numerous lymphatic cells and macrophages similar to lymphatic organ, where cellular and humoral immunopathological processes take place [5]. Fibrosis, hyperplasia of synovial lining cells, abundant diffuse infiltrates and lymphoid follicles, the presence of germinal centers, and high numbers of plasma cells were all interpreted as signs of chronic inflammation [6], in other words of basic activity [7]. Our special interest was to investigate cells of the monocyte-macrophage line in synovial membrane in relation to microscopic signs of chronic inflammation. For the detection of macrophages we compared immunohistochemistry using eight monoclonal antibodies (mAb) and the enzymatic determination of two esterases, alpha naphthyl acetate esterase (ANAE) and non-specific esterase (NSE). We examined which cells in selected topographic regions of synovial membranes (lining cells, stroma, "tumor-like proliferation" [4], other regions) are detectable as macrophages using the different markers.

Materials and methods

Patient material. We examined synovial membranes removed for therapeutic synovialectomy (from 12 knee joints, 3 carpal joints, 2 elbows, 1 hip, 1 shoulder and 2 phalangeal joints) from 21 patients with RA (age 46.3 ± 8 years; mean ± 2 SD) of the Department of Orthopedics at Leipzig University. All patients fulfilled the revised criteria for RA of the American Rheumatism Association [8]. All patients were being treated with nonsteroidal anti-inflammatory drugs (NSAIDs) in addition to second-line drugs such as steroids, methotrexate, penicillamine, gold or chloroquine. Immediately after surgical excision synovial membranes samples were examined for macroscopic signs of inflammation such as edema, hyperemia, and the presence of fibrin deposits. Regions macroscopically showing a high degree of local inflammation were prepared, rapidly frozen in *n*-butanol (Merck, Darmstadt, Germany) and stored at $-20\,^{\circ}C$ until cryosectioning was performed. Sections of 8 μm thickness were cut with a Cryo-Cut (American Optical Corporation).

Histomorphological examination. Sections of synovial membrane were stained with hematoxylin/eosin, Giemsa and van Gieson stain-

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Table 1. Characteristics of monoclonal antibodies used (mAb)[a]

mAb	Clone	Source	Ma	Gr	IDC	DRC	References
BL-M/G-3	CD11c	Department of Biology, Leipzig University	Yes	Yes	No	No	
Ki-M1	CD11c	Behringwerke AG, Marburg, FRG	Yes	No	Yes	No	[9], [32]
Ki-M2		Behringwerke AG, Marburg, FRG	Yes	No	Yes	No	[33]
Ki-M4		Behringwerke AG, Marburg, FRG	No	No	No	Yes	[33], [34]
Ki-M5		Behringwerke AG, Marburg, FRG	Yes	Yes	No	No	[9]
Ki-M6	CD68	Behringwerke AG, Marburg, FRG	Yes	No	No	No	[9]
Ki-M7	CD68	Behringwerke AG, Marburg, FRG	Yes	No	No	No	[9]
Ki-M8		Behringwerke AG, Marburg, FRG	Yes	No	No	No	[9]

[a] Some of the antibodies used have not yet been taken up in the CD system

ing. Fibrosis, hyperplasia of synovial lining cells, abundant diffuse infiltrates and lymphoid follicles, the presence of germinal centers, and high numbers of plasma cells were interpreted as signs of chronic inflammation [6, 7]. Histological parameters were quantified and scored according to a system described previously [7]: 0 represented a very weak intensity/very rare cell count; 1 a weak intensity/rare cell count; 2 a strong intensity/frequent cell count and 3 a very strong intensity/very frequent cell count. The scores were then used to provide indices of the degree of chronic synovitis. The regional distribution of all cell populations taken into account varied considerably, therefore a minimum of 30 fields was examined twice by two observers working independently.

Immuno- and enzyme histochemistry. Following 5-min fixation in acetone (Merck) (excepting slides for Ki-M4 detection, since this marker is destroyed by acetone [9]), and after inactivating endogenous peroxidase by methanol (Merck) containing acetic acid (Merck) for 10 min, the specimens were incubated with 100 µl of monoclonal antibodies (Table 1) for 22 h at 4 °C. Specimens were washed three times in phosphate – buffered saline, pH 7.3 (PBS). mAb detection was performed using the peroxidase anti-peroxidase (PAP) reaction. Slides were incubated with a 1/10 dilution of goat anti-mouse immunoglobulin (BL-ZAM, Department of Biology, Leipzig University) for 30 min at room temperature, and subsequently washed three times, with a monoclonal mouse anti-peroxidase antibody (BL-POD, Department of Biology, Leipzig University). Horseradish peroxidase (Hyland Corporation, USA) was added for half an hour, and 3,3′diaminobenzidine (DAB, Sigma) was used as a substrate. Counterstaining was performed with hematoxylin (Merck Darmstadt, Germany), and slides were mounted after dehydration.

Furthermore, we tested for alpha naphthyl acetate esterase (ANAE) and non-specific esterase (NSE) according to Lojda [11]. For ANAE detection, after fixation for 22 h at 4 °C in sucrose-formalin (pH 6.8), slides were incubated first in Holt's solution and then in a mixture of pararosaniline with sodium nitrite in PBS and alpha naphthylacetate in acetone (pH 5.0, 150 min) at room temperature. Slides were washed in water, fixed in 10% formalin, counterstained with hematoxylin and mounted. For NSE detection, specimens were incubated for 5 min at room temperature in a medium containing 10 mg alpha naphthylacetate sodium in 0.25 ml acetone, 0.1 m PBS (pH 7.4), 8 drops of 4% pararosaniline and 4 drops of 4% sodium nitrate. Slides were washed in water, counterstained with hematoxylin and mounted.

In examination of immuno- and enzyme histochemistry we quantified the number of stained synovial lining cells, giant cells, macrophages, fibrocytes/fibroblasts, polymorphonuclear neutrophils (PMN), lymphocytes, germinal centers, and cells of the mantle zone. Positive staining of lining cells and abundant diffuse infiltrates was determined in relation to a total cell count of 200 mononuclear cells regardless of the intensity of reaction.

Statistical analysis. Spearman's rank correlation was used to analyze correlations between the number of detected cells and the degree of chronic inflammation.

Results

In histomorphological examination we interpreted fibrosis, hyperplasia of synovial lining cells, abundant diffuse infiltrates and lymphoid follicles, the presence of germinal centers, and high numbers of plasma cells as signs of chronic inflammation [6, 7]. Histological parameters were quantified and scored to provide indices of the degree of chronic synovitis, which was found to be low in four cases, medium in ten, and high in five.

Using mAbs and enzymes, we identified $23.4 \pm 11.1\%$ cells in abundant diffuse infiltrates and $41.5 \pm 8.8\%$ cells in lining cell layer as macrophages. The frequency of positive findings using mAbs and enzymes as markers is shown in Table 2.

With Ki-M1, $20.5 \pm 10.4\%$ of mononuclear cells in infiltrates and $42.2 \pm 8\%$ of lining cells was stained. In two samples, cells of the region of tumorlike proliferation (Fig. 1), as well as a population of fibroblastlike cells were detected. Ki-M1 also detects interdigitating dendritic cells (IDC) which, however, could not be clearly distinguished from macrophages in our samples.

Ki-M2 binded to $41.3 \pm 8.5\%$ of lining cells and to $20.6 \pm 8.3\%$ of cells in abundant infiltrates. The staining pattern was comparable to Ki-M1.

Ki-M4 is a marker of follicular dendritic reticular cells (FDR) and was detected in the lymphoid follicles (Fig. 2), but not in the lining cell layer, and only once in 6% of cells in abundant infiltrates.

Using Ki-M5, we detected $42.4 \pm 8\%$ of lining cells and $25.3 \pm 10.1\%$ of mononuclear cells in infiltrates (Fig. 3). PMNs, cells of the mantle zone of follicles, a population of fibroblastlike cells, and in one sample cells in the region of tumorlike proliferation were stained.

Ki-M6 stained $49 \pm 8\%$ of lining cells (Fig. 4) and $25.2 \pm 9.8\%$ of cells in abundant infiltrates. Cells of the mantle zone of follicles, a population of fibroblastlike cells, and cells in the region of tumorlike proliferation were also detected.

Ki-M7 was shown to bind to $50.3 \pm 7.8\%$ of lining cells and to $29.1 \pm 9.8\%$ of cells in diffuse infiltrates, in addition to cells of the mantle zone of follicles, a population of fibroblastlike cells, and cells in the region of tumorlike proliferation.

Using Ki-M8, $45.9 \pm 11.8\%$ of lining cells and $25.3 \pm 11.8\%$ of cells in abundant infiltrates, cells of the

Table 2. Frequency of positive findings without considering the number or intensity of stained cells

	Detected in *n* cases	Ki-M1	Ki-M2	Ki-M4	Ki-M5	Ki-M6	Ki-M7	Mi-M8	M/G3	NSE	ANAE
Synoviocytes	21	21	21	–	21	21	21	21	21	21	21
Macrophages	21	21	21	–	21	21	21	21	21	21	21
"Fibrocytes"	21	7	4	–	4	17	21	14	2	–	–
PMNs	21	–	–	–	21	–	–	–	21	–	21
Lymphocytes	21	–	–	–	–	–	–	–	–	–	21
Cells in abundant diffuse infiltrates	20	20	20	1	20	20	20	20	20	20	20
Follicles	19	10	6	18	6	12	11	9	8	19	19
Endothelial cells	21	2	–	1	1	3	1	–	–	15	16
Germinal center cells	9	1	2	–	–	2	–	–	1	–	1
Cells of the mantle zone	19	4	10	–	10	10	13	14	4	6	7
Zone of mesenchymoid transformation	5	2	2	–	1	3	3	–	–	–	–

"Fibrocytes": a population of cells like fibrocytes, but stained by macrophage markers

mantle zone of follicles, as well as fibroblastlike cells (Fig. 5) were stained.

BL-M/G3 binded to $44.6 \pm 7.3\%$ of lining cells and to $22.6 \pm 7.3\%$ of cells in diffuse infiltrates, as well as to cells of the mantle zone of follicles, a population of fibroblastlike cells, and to PMNs.

ANAE was detected in some lymphocytes, PMNs, $33.3 \pm 14.2\%$ of lining cells, and $18.7 \pm 6.7\%$ of cells in diffuse infiltrates. NSE was shown to be detectable in $19.8 \pm 6.1\%$ of lining cells and $23 \pm 9.2\%$ of cells in abundant infiltrates.

In lymphoid follicles, all mAbs bound to single cells. At germinal centers, we observed staining with Ki-M1, Ki-M2, Ki-M6, BL-M/G3 and ANAE. In vascular endothelium, we found positive reactions to all markers except Ki-M2, Ki-M8, and BL-M/G3. Results from lining cell layer and abundant infiltrates are taken together in Fig. 6.

A significant correlation (using Spearman's rank correlation) between histological signs of chronic inflammation and the frequency of detected cells by macrophage markers was found only for Ki-M5 ($P > 0.02$) and ANAE ($P > 0.02$).

Discussion

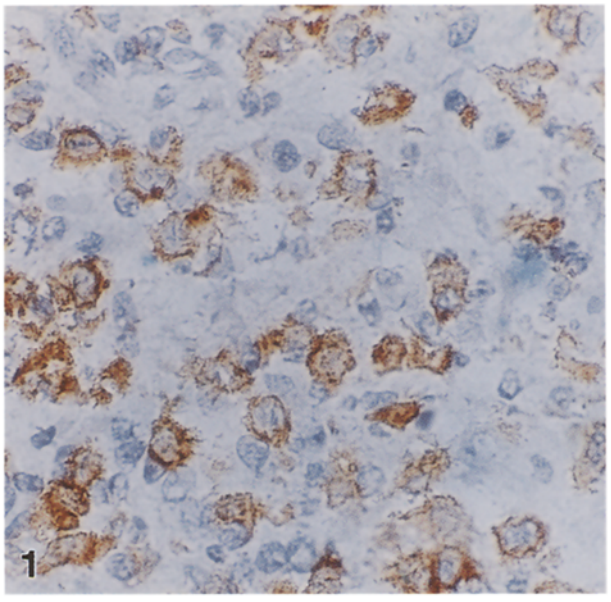
In RA, analysis of cells and cell cooperation in synovial membrane (SM) and pannus is the main focus of research. It is known that there is a close relationship between RA pathogenesis and chronic local immunopathological inflammatory processes. In synovitis we find signs of acute exudative and of chronic infiltrative-proliferative inflammation. These findings were assimilated by Geiler and Stiehl [7] to define both an actual activity and a basic activity. Basic activity includes proliferative reaction, lymphoplasmacellular and mononuclear infiltration, both of which are signs of an immunopathological process. In disease progression, the amount of rheumatoid factors, immunoglobulins, and complement factors in SM increases [1, 11]. Starting in the first few weeks of the disease, immunocompetent cells invade the synovial membrane, proliferative, and migrate. Invading cells become organized [1].

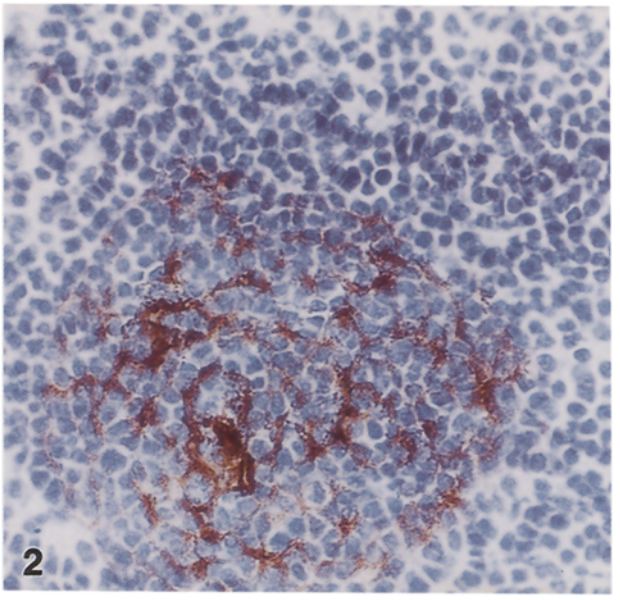
It is thought that macrophages play a central role in the pathogenesis of RA [12–14]. It is almost impossible to detect all macrophages using histological staining. We therefore used mAb and enzymes to detect these cells. A problem in using these markers is the presence of identical epitopes in different cell types. For instance, Ki-M5 and BL-M/G3 detect PMNs as well. Consequently, we used a whole macrophage panel. Expression of epitopes and activity of intracellular enzymes can be coupled to cell activity.

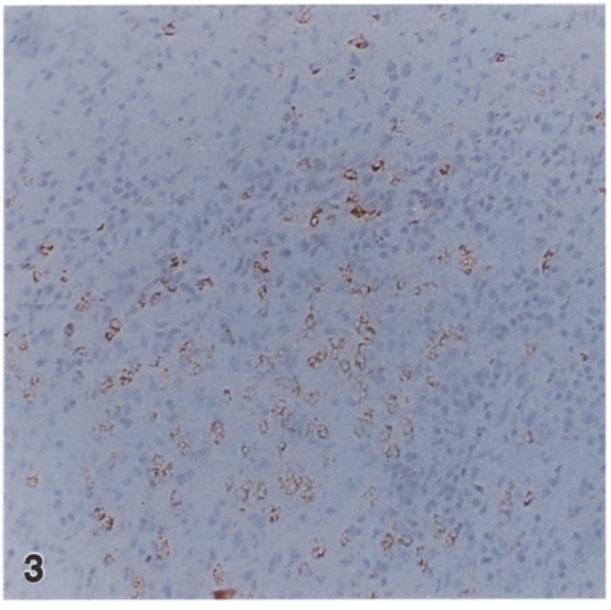
Macrophages are detectable in all regions of rheumatoid SM, especially in the peri- and interfollicular area, in the lining cell layer, in the sublining layer, perivascular, and in abundant diffuse infiltrates [15, 16]. Whereas follicles contain more follicular dendritic reticular cells (FDR), macrophages make up about 50% of cells in abundant infiltrates [17]. Our findings, by contrast, identified $23.4 \pm 11.1\%$ to be macrophages. This difference could be due to the use of different methods to detect macrophages.

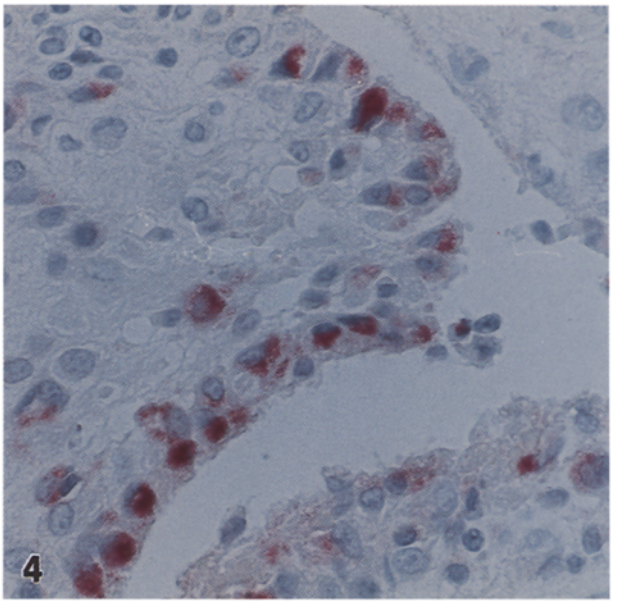
A typical finding in RA is a hyperplastic lining cell layer, which contains different types of synoviocytes and giant cells [18]. With mAbs, surface receptor analysis (IgFc, C3b, C3d, C1q), and using enzymes, A-synoviocytes can be detected as mononuclear phagocytes [19, 20]. We found $41.5 \pm 8.8\%$ of lining cells to be macrophages.

The number of cells we found to be macrophages is not an absolute number, but a percentage of total cell count of selected regions without consideration of cell density. Our results show a high count of macrophages using all markers with the exception of Ki-M4 (which is not a macrophage marker) and NSE. Although Ki-M1









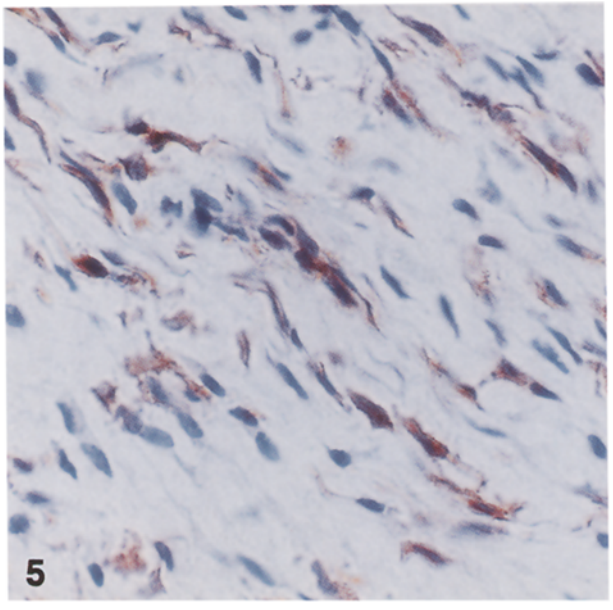


Fig. 1. Detection of cells in the region of tumorlike proliferation and additionally of a population of fibroblastlike cells using Ki-M1 (CD11c). No. S/3151, × 422

Fig. 2. Follicular dendritic reticular cells (*FDR*) inside synovial membrane lymphoid follicles. Ki-M4, no. S/3152, × 422

Fig. 3. Macrophages in abundant lymphocytoid infiltrations of the synovial membrane. Ki-M5. No. S/3120, × 264

Fig. 4. Staining of synovial membrane lining cells using Ki-M6 (CD68). No. S/3120, × 500

Fig. 5. Detection of fibroblastlike cells using mAb Ki-M8. No. S/3275, × 422

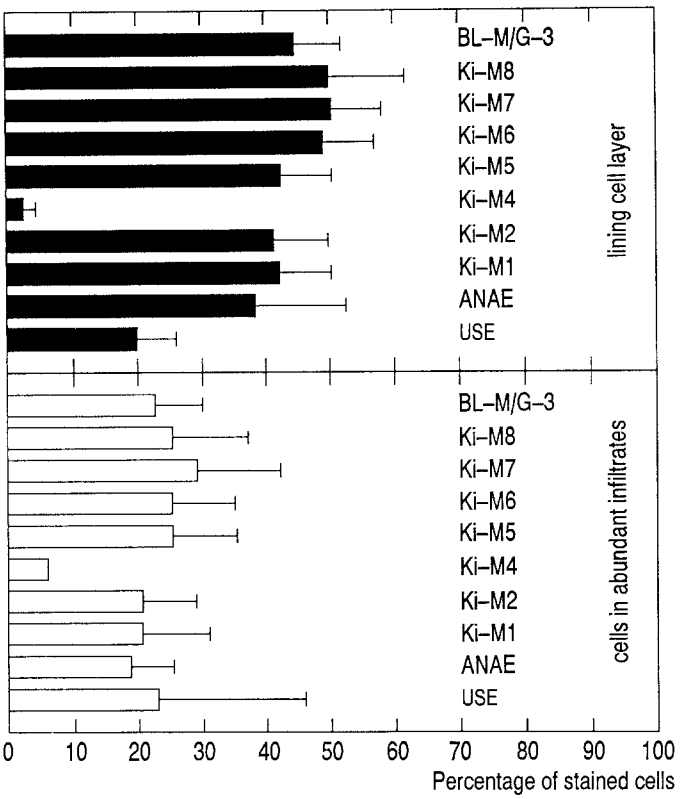


Fig. 6. Percentage and standard deviation of cells in the SM lining cell layer and in the abundant infiltrations detected by markers

and Ki-M2 also detect interdigitating cells and Ki-M5 and BL-M/G3 react with PMNs, the number of detected cells is similar to the other markers. This was also facilitated by the low actual activity of our samples.

In a population of fibroblastlike cells, we found macrophage markers in addition. The characteristics of these cells are not clear. There could be related to stellate or reticular cells, described in RA synovial membrane [21–24]. These contribute to joint destruction via a collagenase secretion and antigen presentation. We found macrophage markers in a comparable population. In contrast to Wilkinson et al. [25], who examined fibroblastlike cells in lining cell layer for uridine diphosphoglucose dehydrogenase (UDPDG) activity as a marker of fibroblastlike or type B synovial intimal cells and detected CD68 + UDPG + cells in RA, we found CD68 + fibroblastlike cells in the diffuse stroma of the synovial membrane. Interestingly, double-positive NSE + CD68 + cells as reported in [25] were not observed by us. These results underline the problem in detecting fibroblasts by their shape, findings which mean that it is possible that fibroblasts should be checked for verification and not just be classified by their morphological appearance [26, 27].

The region of tumorlike proliferation [4] is closely connected to the theory of viral or oncogeneic mechanisms in RA. We found here a positive staining with Ki-M1, Ki-M2, Ki-M5, Ki-M6 and Ki-M7. These findings support an affiliation of these cells with the macrophage-monocyte system.

Our results confirm a dense infiltration of the synovial membrane with cells of the macrophage-monocyte system in close morphological and functional relation to lymphoplasmacellular infiltration.

We were especially interested in the relationship between the macrophage content of the synovial membrane and basic activity. Basic activity is interpreted to correspond with local immunological activity [7, 28, 29]. Although the total amount of all inflammatory cell populations in synovial membrane increases with the duration of the disease and basic activity, the percent of the content of macrophages in selected sections stays constant. Only by using Ki-M5 and esterases as functional markers can a correlation between the percent of macrophage and basic activity be observed. According to these findings, Claus [30] and Riedel [31] have shown a correlation between basic activity and the number of macrophages containing lysozyme or acid phosphatase.

We conclude that in RA a constant ratio between macrophages and other cells is responsible for perpetuating the inflammation. Dependent on basic activity, the number of activated macrophages increases, indicated by the enhanced content of enzymes or by the expression of activation markers.

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