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Glomerular monocyte infiltration in human nephropathies: Prevalence and correlation with clinical and morphological variables*

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Summary. Glomerular monocyte infiltration was evaluated by histochemical means (nonspecific esterase) and/or electron microscopy in 305 renal biopsies belonging to a wide variety of human renal diseases. Significant monocyte infiltration was never observed in a first group of nepropathies (minimal change disease, nephrotic syndrome with IgM deposits, focal segmental glomerulosclerosis, membranous GN, Berger's GN, healed GN, dense deposit disease, chronic non specific GN, benign familial haematuria, Alport's disease, renal amyloidosis, arteriosclerotic kidney, light chain GN). Conversely, it was present at varying frequency in a second group of nephropathies including: acute GN (58.3%), persistent GN (10%), membranoproliferative GN (25.2%), eryoglobulinaemic GN (82.6%), lupus GN (36%), extracapillary proliferative GN (50%) and Schoenlein-Henoch GN (40%).

The results indicate: 1) there is an evident association between monocyte infiltration and the subendothelial site of deposits; 2) the presence of monocytes is not affected by the size and extension of subendothelial deposits; 3) monocytes were more frequently observed when IgG, IgM and fibrinogen were present in the subendothelial deposits, Conversely, complement fractions do not seem to affect monocytic activity; 4) polymorphonuclear leukocyte exudation is less frequently found and mostly associated with monocyte infiltration; 5) in some GNs (persistent GN, cryoglobulinaemic GN and membranoproliferative GN), proteinuria was significantly higher in patients with than in those without monocyte infiltration, giving support to the hypothesis that in human beings as in experimental animals monocytes play a role in the pathogenesis of proteinuria.

Key words: Glomerulonephritis – Monocytes – Electron microscopy – Proteinuria

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Introduction

In recent years, intraglomerular monocytic infiltration has been extensively reported in various types of experimental GNs (for review see Schreiner et al. 1982 and Holdsworth 1983) and different roles for this cell type have been suggested (Fillit and Zabriskie 1982; McCluskey and Bhan 1982; Schreiner et al. 1982; Wagner et al. 1983). Increasing evidence has been achieved on their participation in several forms of human GNs (Shigematsu et al. 1973; Atkins et al. 1976, 1981; Monga et al. 1979, 1981; Jothy and Sawka 1981; Magil et al. 1981, 1982; Harry et al. 1982; Laohapand et al. 1983) and in the course of kidney rejection (Brentjens et al. 1979). The association of monocytic glomerular infiltration with the presence of subendothelial deposits has been suggested (Magil et al. 1981; Laohapand et al. 1983) and phagocytic activity of mononuclear cells on immune complexes in some types of GNs has been reported (Magil and Wadsworth 1981; Monga et al. 1976, 1979, 1981).

Some investigations have demonstrated that depletion of circulating monocytes, either by systemic irradiation (Schreiner et al. 1978) or antimacrophage serum (Holdsworth et al. 1981; Lavelle et al. 1981), largely prevents the glomerular lesions and proteinuria in experimental renal disease. In human pathology the relationship between monocytes and proteinuria has been investigated only occasionally (Jothy and Sawka 1981).

With the exception of the paper of Magil et al. (1981), there are no exhaustive studies dealing with the presence of monocytes in the glomeruli in a large series of human GNs. In the present study, 305 renal biopsies were examined for the presence of intraglomerular monocytes by means of non specific esterase staining reaction and/or by electron microscopy. Furthermore, some clinical and morphological variables were considered, in attempt to verify whether any correlation exists with the occurrence of monocytes in glomeruli.

Material and methods

Three hundred and five renal biopsies were selected from our files according to the following criteria: a) a definite diagnosis on the ground of morphological and clinical data; b) the availability of representative frozen sections and/or resin-embedded material.

The diagnoses were as follows; 24 minimal change diseases, 3 nephrotic syndromes with IgM mesangial deposits, 12 focal-segmental glomeruloscleroses, 34 membranous GNs, 24 acute GNs, 40 persistent GNs, 17 healed GNs with minor morphologic changes, 39 membranoproliferative GNs with subendothelial deposits, 5 dense deposit diseases, 8 Berger's GNs with IgA mesangial deposits, 5 Schoenlein-Henoch GNs, 13 nonspecific chronic GNs, 2 extracapillary GNs with and 4 without immunofluorescence linear deposits, 2 cases of benign familial haematuria, 3 cases of Alport's disease, 3 arteriosclerotic kidneys, 38 lupus GNs, 23 cryoglobulinaemic GNs, 3 renal amyloidoses, 3 light chain GNs.

All the cases were processed for light microscopy, 274 for electron microscopy and 225 for immunofluorescence according to the standard methods as previously reported (Monga et al. 1981).

Monocytes were searched for in 31 biopsies by non specific esterase staining alone, according to the method of Nachlas and Seligman (1949) modified by Pearse (1972) (Figs. 1, 3).

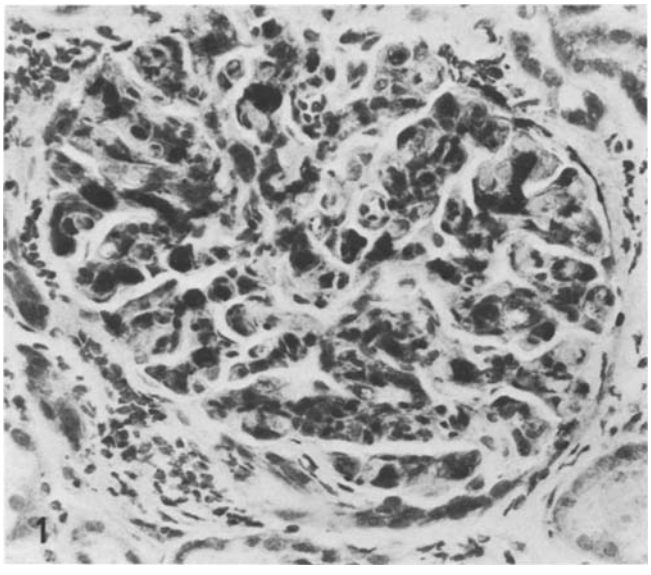

Fig. 1. Non specific esterase staining. Several monocytes (dark cells) are evident in the glomerulus. × 400

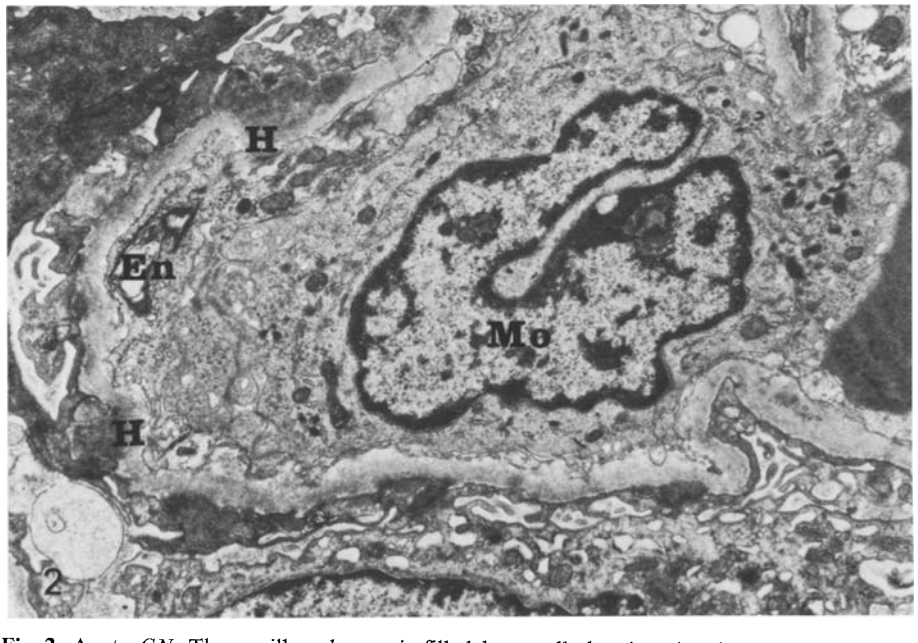

Fig. 2. Acute *GN*. The capillary lumen is filled by a cell showing the characteristic features of a monocyte (*Mo*): indented nucleus with chromatin clumping beneath the nuclear envelope, large cytoplasm with several lysosomes. *En:* endothelial cell. *H:* hump. × 8,500

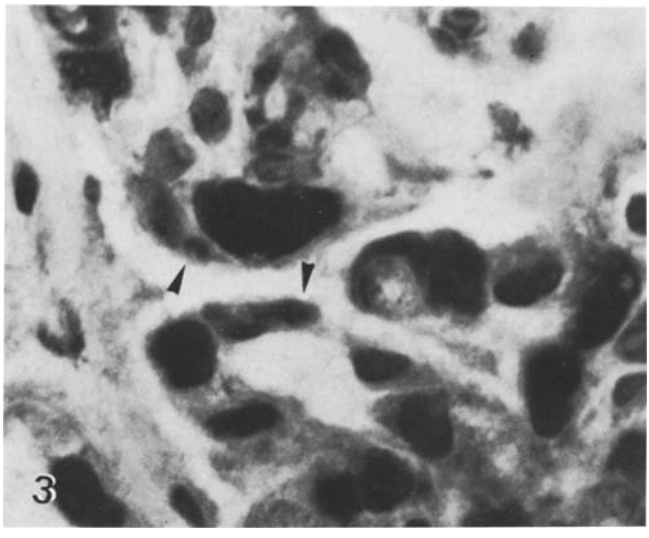

Fig. 3. Non specific esterase staining. Cryoglobulinaemic *GN*. Several clearly positive cells are recognizable. In addition, small round bodies or irregularly shaped objects which can be interpreted as monocytic cytoplasm are evident in capillary walls (*headarrows*). × 1,100

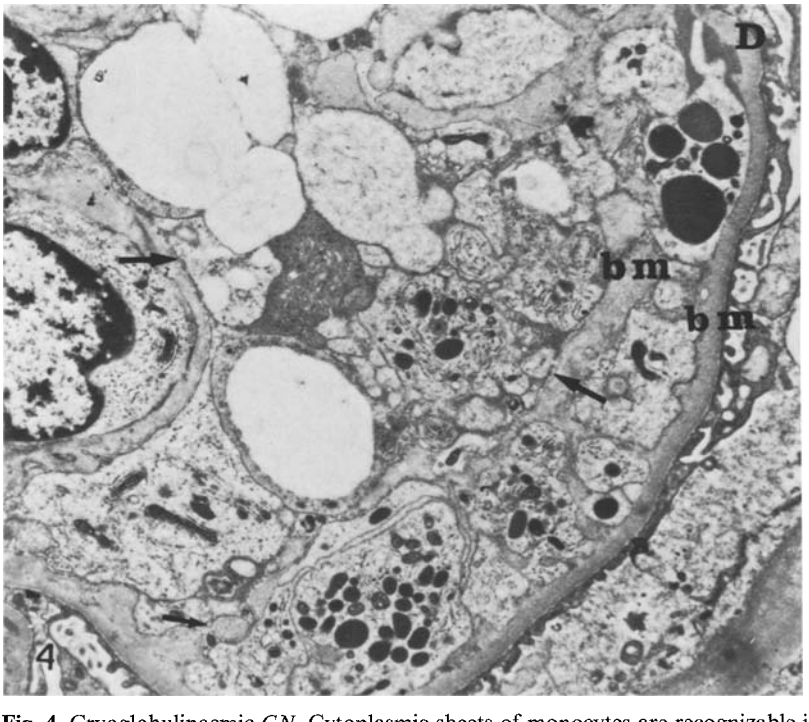

Fig. 4. Cryoglobulinaemic *GN*. Cytoplasmic sheets of monocytes are recognizable in the capillary wall between layers of basement membrane (*bm*), in contact with subendothelial deposits (*D*). Arrows point out the lamine fenestrata of the endothelium. × 5,100

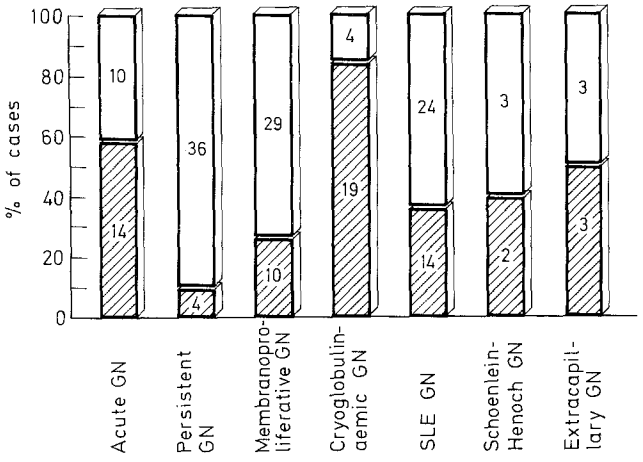

Fig. 5. Relative frequencies of the cases with (▨) or without (□) monocyte infiltration by nephropathies (175 cases)

In 20 cases both non specific esterase staining and electron microscopy were performed. Similar results achieved by two techniques confirmed the reliability of electron microscopy in detecting monocytes, which has been asserted by others (Morita et al. 1976; Hunsicker et al. 1979). By electron microscopy, monocytes were identified according to their nuclear shape, chromatin distribution, the type of cytoplasmic organelles as reported in several papers (Cawley and Hayhoe 1973; Nichols and Baiton 1975) (Figs. 2, 4).

Since electron microscopy allowed the examination of a rather small number of glomeruli (3 to 5 for each case) the presence of at least 3 monocytes per glomerulus was regarded as pathologically relevant.

In the same ultrastructurally-investigated glomeruli polymorphonuclear leukocytes were sought. Their presence was considered to be pathologically significant when at least 3 per glomerulus were found. In addition, the presence and site of electron dense deposits were evaluated. The size and extension of deposits were also considered and graded from − (negative finding) to + + + (presence of large and diffuse deposits).

Proteinuria (measured in gr $^0/_{00}$ by the Ponceau S method) on the days immediately before the biopsy was considered. For statistical evaluation the nonparametric Mann-Whitney (two tails) U test and χ^2 test were employed, assuming as the limit of significance $p < 0.05$.

Results

In relation to monocytic infiltration, nephropathies were subdived in two groups.

In the first group (130 cases), significant monocyte infiltration was never observed. This group included: minimal change disease, nephrotic syndrome with IgM deposits, focal-segmental glomerulosclerosis, membranous GN, Berger's GN, healed GN with minor morphological changes, dense deposit disease, chronic nonspecific GN, benign familial haematuria, Alport's disease, renal amyloidosis, arteriolosclerotic kidney and light chain GN.

In the second group, monocyte infiltration was detected in 66 out of 175 cases. This group included acute GN, persistent GN, membranoproliferative GN, cryoglobulinaemic GN, lupus GN, extracapillary proliferative

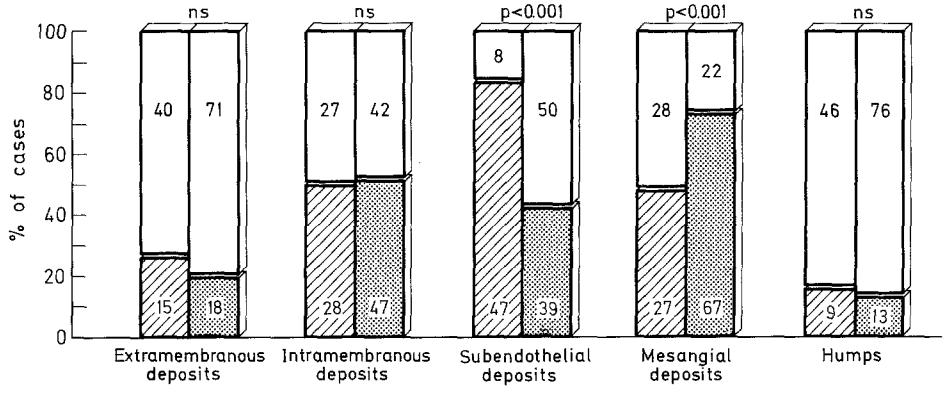

Fig. 6. Relative frequencies of deposits (in the second group of nephropathies), by site, in the cases with (▨) and in those without (▩) monocytes. Cases without deposits in white areas (□)

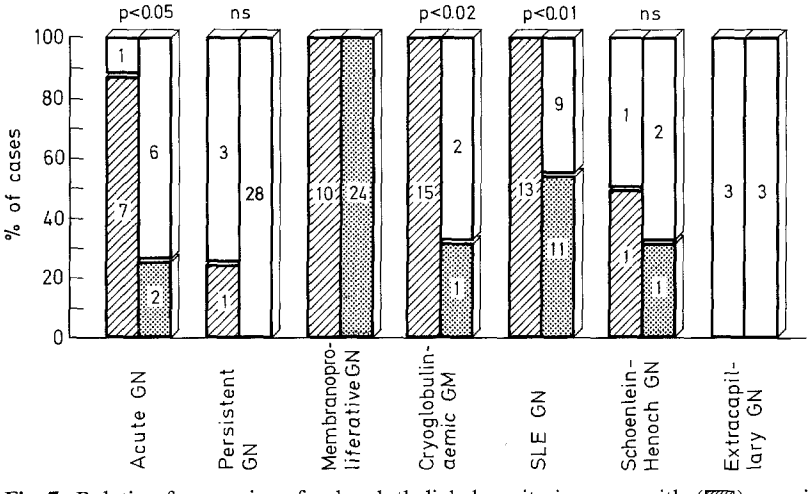

Fig. 7. Relative frequencies of subendothelial deposits in cases with (▨) or without (▩) monocytes by nephropathies. Cases without subendothelial deposits in white areas (□)

GN and Schoenlein-Henoch GN. Monocytes were mainly detected in the capillary lumina (Fig. 2), but in cryoglobulinaemic GN they could be found in the capillary wall as well. By the non specific esterase method, positive material was encountered in the latter site in the form of small round bodies or irregularly shaped objects (Fig. 3). Electron microscopy clearly showed cytoplasmic sheets between layers of basement membrane (Fig. 4) or between the latter and the endothelium. Because of the presence of numerous lysosomes and the absence of peripheral cytoplasmic microfilaments (characteristic of mesangial cells) they could be confidently considered as belonging to monocytes.

The various frequencies of monocyte infiltration in the single nephropathies are reported in Fig. 5. Both cases of extracapillary GN with linear

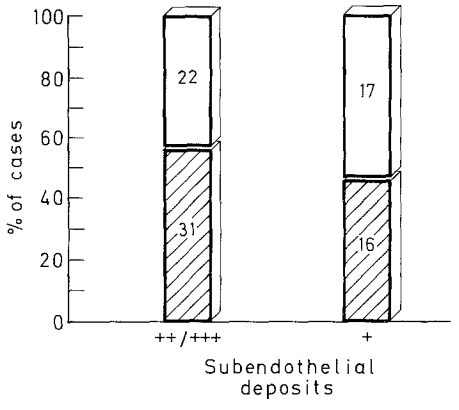

Fig. 8. Relative frequency of monocytic infiltration (▨) in the cases with large and evenly distributed (++/+++) or scarce (+) subendothelial deposits. Cases without monocytic infiltration in white areas (□)

immunofluorescence were positive for monocytes. As to the lupus GN, monocyte infiltration was variously distributed according to the histological pattern, being rather common in the diffuse proliferative form (9 out of 17 cases) and less frequent in the mesangial proliferative (2 out of 6 cases), focal proliferative (1 out of 8 cases) and membranous (1 out of 5 cases) forms. Monocytes were then detected in a case (out of 2) of lupus GN with severe intra-extra-capillary proliferation.

One hundred-forty-four biopsies of the second group were studied by electron microscopy. Irrespective of the diagnosis, a possible relationship between the site of electron dense deposits and the presence/absence of monocytes was considered (Fig. 6). Extra-membranous, intramembranous deposits and humps were found with similar frequency in the cases with or without monocytes, whereas mesangial deposits were more common in the cases without monocytes. Of note was that subendothelial deposits were detected in 47 out of 55 cases (85.4%) positive for monocytes. The differences in distribution of subendothelial deposits among the cases with or without monocytes was statistically significant by χ^2 test ($p < 0.001$).

When single nephropathies were separately considered (Fig. 7), the statistical significance was maintained for acute GN, cryoglobulinaemic GN and lupus GN ($p < 0.05$, 0.02 and 0.01 respectively), the subendothelial deposits being detected in 7 out of 8 (87.5%) acute GNs, 15 out of 15 (100%) cryoglobulinaemic GNs and 13 out of 13 (100%) lupus GNs positive for monocytes respectively. This kind of evaluation was obviously not feasible for membranoproliferative GN, where subendothelial deposits are constantly present.

If evaluated only among the 86 cases which displayed subendothelial deposits, monocyte infiltration was recorded in 47 (54.6%). As far as the single nephropathies are concerned (Fig. 7), it was found in 7 out of 9 cases (77.7%) of acute GN, in 15 out of 16 cases (93.8%) of cryoglobulinaemic GN and in 13 out of 24 cases (54.1%) of lupus GN. Monocytes were detected in 10 out of 34 cases (29.4%) of membranoproliferative GN.

In the 47 cases positive and in the 39 ones negative for monocytes,

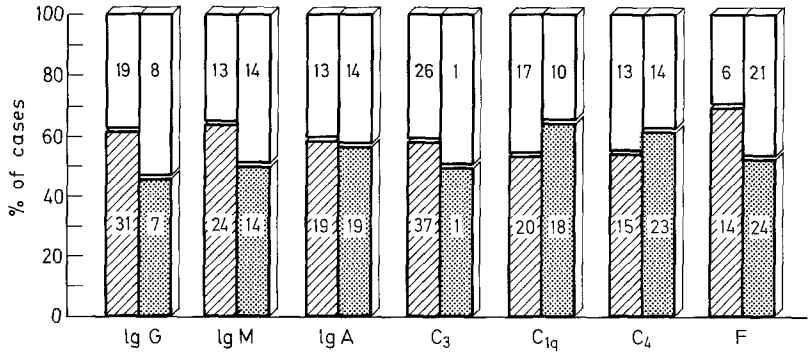

Fig. 9. Relative frequencies of monocytes in cases with (▨) or without (▩) the presence of different immunoglobulin classes, complement fractions and fibrinogen in the subendothelial deposits. Cases without monocytes in white areas (▭)

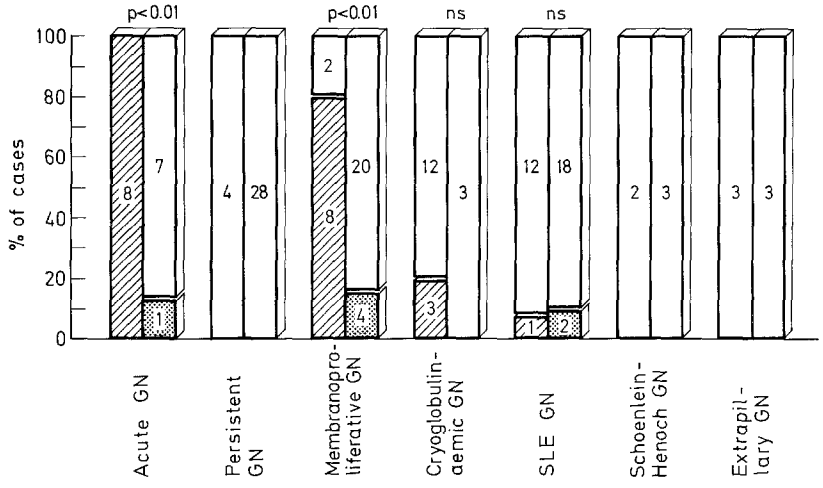

Fig. 10. Relative frequencies of polymorphonuclear leukocytes in cases with (▨) or without (▩) monocytes by nephropathy. Cases without polymorphonuclear leukocytes in white areas (▭). Evaluation of 144 cases

subendothelial deposits were large and evenly distributed in 31 and 22 and scarce in 16 and 17 respectively (Fig. 8). The reported figures were not statistically significant by the χ^2 test.

Sixty-five of the above considered 86 cases with subendothelial deposits were studied by immunofluorescence and the possible relationship between monocyte infiltration and the composition of immune deposits was evaluated (Fig. 9). Monocytes were found in 38 biopsies, being present in 14 out of 20 cases (70%) positive for fibrinogen, in 24 out of 37 cases (64.8%) positive for IgM and in 31 out of 50 cases (62%) positive for IgG. Lower percentages were detected for IgA, C3 and early complement fractions. As shown in Fig. 9, monocytes were also found with various percentages,

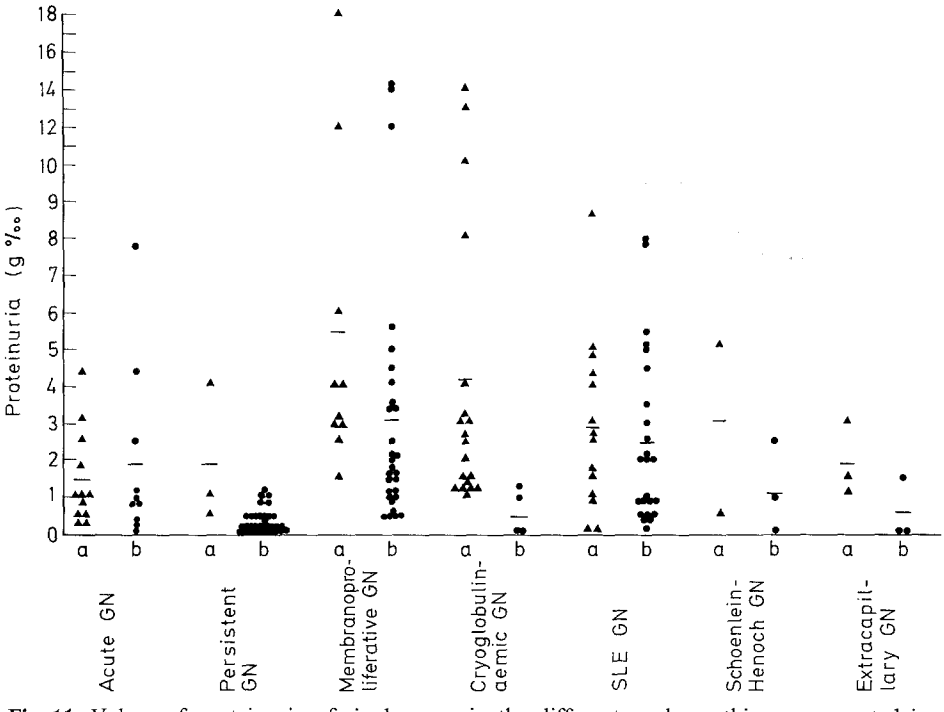

Fig. 11. Values of proteinuria of single cases in the different nephropathies are reported in the paired columns. In the columns *a* are grouped cases with monocytes, in columns *b* cases without monocytes. Standard deviation in the different nephropathies was as follows: Acute GN $a\pm1.27$, $b\pm2.42$. Persistent GN $a\pm0.89$, $b\pm0.32$. Membranoproliferative GN $a\pm5.77$, $b\pm3.63$. Cryoglobulinaemic GN $a\pm4.23$, $b\pm0.6$. Lupus GN $a\pm2.29$, $b\pm2.33$. Schoenlein-Henoch GN $a\pm2.96$, $b\pm1.2$. Extracapillary GN $a\pm0.94$, $b\pm0.81$. Horizontal lines indicate means values

in cases where single immunoglobulins, complement fractions and fibrinogen were absent.

C3 deposits were by far the most commonly found, being present in 63 out of 65 cases (97.7%). It must be noted that they were detected in 37 out of 38 cases (97.3%) and in 26 out of 27 cases (96.2%) with and without monocytes respectively.

Polymorphonuclear leukocyte infiltration was found in 27 out of the 144 cases of the second group investigated by electron microscopy. Association of polymorphonuclear leukocytes and monocytes was observed in 20 cases (74.1%), being variably frequent in the single nephropathies (Fig. 10). In acute GN, polymorphonuclear leukocytes were present in all the 8 cases with monocytes and only in one where the latter were lacking. In the membranoproliferative GN, granulocytes were observed in 8 out of 10 cases with monocytes and alone in other 4 cases. Granulocytes were detected in few cases of lupus GN (3 out of 33) and cryoglobulinaemic GN (3 out of 18), being associated with monocytes in a case only in the former and in all 3 in the latter. The differences of distribution of polymorphonuclear

leukocyte infiltration between the groups with or without monocytes were statistically significant by χ^2 test ($p<0.001$) when all the cases were considered together. When single nephropathies were separately considered, the statistical significance was maintained for acute GN ($p<0.01$) and membranoproliferative GN ($p<0.01$), but not for lupus GN and cryoglobulinaemic GN.

The values of proteinuria of single cases belonging to the second group of nephropathies are reported in Fig. 11. Irrespective of the diagnosis, the mean values of proteinuria were 3.5 $gr^0/_{00}$ (s.d. $\pm$3.7) in the cases with monocytes and 1.8 $gr^0/_{00}$ (s.d. $\pm$2.57) in those without monocytic infiltration. By the use of U test, a statistically significant difference between the values of proteinuria in the cases with or without monocytes was evident ($p<0.00003$). As far as the single nephropathies were concerned, U test showed statistically significant differences in persistent GN ($p<0.0108$), cryoglobulinaemic GN ($p=0.05$) and membranoproliferative GN ($P=$ 0.0174), but not in acute, Lupus, Schoenlein-Henoch and extracapillary GNs.

Discussion

In previous studies of our group (Monga et al. 1979 and 1981), glomerular monocytic infiltration was reported in some human acute and chronic GNs. The aim of this investigation was to assess the extent of monocytic infiltration in a wider variety of human renal diseases and to detect possible relationship with any pathological (type, site and composition of immune deposits, polymorphonuclear leukocyte infiltration) and clinical (presence and severity of proteinuria) features.

In the present study, monocytic infiltration was mainly evaluated by electron microscopy. Even though the usefulness of this technique with respect to the distinction of monocytes from activated endothelial and/or mesangial cells has been questioned (Magil and Wadsworth 1981), its reliability has been stressed (Morita et al. 1976; Hunsicker et al. 1979). Moreover, in our cases where both electron microscopy and non specific esterase staining were used, equally reliable results were achieved.

Monocyte infiltration was detected with different frequency in several forms of renal disease: acute GN, persistent GN, membranoproliferative GN, cryoglobulinaemic GN, lupus GN, Schoenlein-Henoch GN and extracapillary GN. In these nephropathies monocytes were found in 37% of our cases, a figure quite similar to that (43%) reported by Magil et al. (1981).

We detect monocytic infiltration mainly in the diffuse proliferative form of lupus GN and in cryoglobulinaemic GN (both characterized by the almost constant presence of subendothelial deposits) and in the cases of acute GN where subendothelial deposits were also found. At variance with what has been previously reported (Monga et al. 1979; Magil et al. 1981) monocyte infiltration has been shown to be present in membranoproliferative

GN as well, in agreement with some recent investigations (Atkins et al. 1981; Laohapand et al. 1983).

There is therefore some evidence that monocyte infiltration is connected with the presence of subendothelial deposits in human GNs. This statment is strongly supported by the lack of monocyte infiltration in GNs displaying immune complexes located in another site (such as membranous GN and Berger's GN). In addition, the few cases positive for monocytes characterized by a predominant site of deposit differing from subendothelial (e.g. mesangial and membranous forms of lupus GN) showed a scant, but definite presence of subendothelial deposits. Further, we found monocytes in some cases of Schoenlein-Henoch GN, which shares with Berger's GN several light microscopical, ultrastructural and immunohistochemical findings, but usually shows parietal involvement with subendothelial deposits.

Even though our own results and those of Magil et al. (1981) and of Laohapand et al. (1983) give strong evidence of the association between monocytes and subendothelial deposits, it is worth stressing that the latter may be present in the absence of monocyte infiltration. This occurrence is exceedingly rare in acute GN and cryoglobulinaemic GN, but rather frequent in lupus GN and even more common in membranoproliferative GN. It is difficult to explain the different behaviour in the various GNs, but it seems clear that monocyte influx is not affected by the size and extension of subendothelial deposits.

It could therefore be of interest to assess a possible role of the composition of deposits in causing glomerular monocytic influx. In a previous work (Monga et al. 1981), irrespective of the site of deposits, the association between monocyte infiltration and IgG was suggested in acute GN. In the present investigation, this association was confirmed, as far as the subendothelial deposits are concerned, in a large number of cases belonging to a wide variety of nephropathies. In addition, similar association was observed for IgM and fibrinogen. These findings could be easily explained by keeping in mind the attraction of monocytes by IgG immune complexes through their Fc receptor (Striker et al. 1979; Holdsworth 1983) and their phagocytic activity on IgM (Monga et al. 1979) and fibrin (Shigematsu 1970).

Magil et al. (1981) stressed that patients with monocytic activity invariably showed C3 localization within glomeruli and argued that this could be due to the chemotactic activity of C5 fraction. Likewise, C3 was detected in most of our patients with monocyte infiltration and subendothelial deposits, but the same immunofluorescence finding was found in a similar percentage of patients in which monocytes were lacking. Our data are in keeping with those of Holdsworth (1983) and give support to the suggestion of Unanue et al. (1981) that monocyte infiltration is complement-independent.

Unlike experimental GNs (Shigematsu 1970; Morita et al. 1976; Sano 1976; Schreiner et al. 1978; Holdsworth et al. 1980), an association or the sequential appearance of monocytes and polymorphonuclear leukocytes within glomeruli in human pathology have only occasionally been reported.

(Shigematsu et al. 1973; Harry et al. 1982). In our cases, polymorphonuclear leukocytes were less frequently found than monocytes, and, when present, they were mostly associated with the latter. Monocytes were frequently found alone, mainly in lupus and cryoglobulinaemic GNs.

It is known from experimental pathology that in some GNs polymorphonuclear leukocyte exudation takes place earlier than monocytic (Shigematusu 1970; Morita et al. 1976; Schreiner et al. 1978). It could therefore be argued that in our patients biopsies have been performed when polymorphonuclear leukocytes had disappeared, even though it cannot be excluded that, as in some experimental GNs (Sano 1976; Hunsicker et al. 1979; Holdsworth et al. 1980, 1983), they might not be important in some cases. However, Bhan et al. (1978, 1979) suggested that influx of monocytes could be due to an interaction between sentitized lymphocytes and antigens fixed in the glomeruli.

A statistically significant difference between the values of proteinuria in our patients with or without monocytic activity was evident. These findings are in agreement with the experimental data of Schreiner et al. (1978) and Holdsworth et al. (1981), showing the involvement of monocytes in the mechanisms of proteinuria. Neutral proteinases released by monocytes are known to degrade glomerular basement membrane "in vitro" (Davies et al. 1980). The relationship between the severity of proteinuria and the presence or absence of monocytes shows differences in the various nephropathies. Whereas monocytic infiltration seems to play a role in persistent GN, cryoglobulinaemic GN and membranoproliferative GN, this is not the case in acute, extracapillary, lupus and Schoenlein-Henoch GNs. Monocytes were never detected in some nephropathies with severe proteinuria, such as membranous GN or focal-segmental glomerulosclerosis. It is therefore obvious that proteinuria may be the result of several mechanisms (Glassock et al. 1981) other than enzyme release by monocytes, but the latter play a prominent role in several forms of human GNs.

In conclusions, some aspects on the role of monocytes in human GNs are worth stressing. Monocytes participate to the pathogenesis of only certain human GNs and can be present when immunological mechanisms are involved. Their infiltration has to be related to the presence either of antibasement membrane antibodies or of immune complexes. The latter are shown to play a prominent role when they are located in the subendothelial space. Some immunoglobulin classes (IgG and IgM) and fibrinogen, but not complement fractions seem to enhance monocyte infiltration. There is then some evidence that, at least in some nephropathies, mononuclear cells participate to the mechanism of proteinuria.

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