

DISTRIBUTION OF THE ANTI-GAMMA GLOBULIN FACTORS IN THE SYNOVIAL MEMBRANE AND OTHER TISSUES IN VARIOUS DISEASES*

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It is well established that the synovial membrane represents one of the major sites of the formation of anti-gamma globulin factors (AGGF)[†] in rheumatoid arthritis (RA) (Mellors, Heimer, Corcos, and Korngold, 1959; McCormick, 1963).

During the examination of a number of synovial specimens obtained from cases of RA we were interested to observe the different patterns produced by the specific fluorescence due to AGGF.

This paper describes these findings and also the concentration of AGGF in other tissues, namely the bone marrow and the liver, in patients with diseases primarily involving these tissues, in all of whom circulating AGGF were present. It was our purpose to look for differences in the percentage of AGGF-containing cells in these tissues in relationship to the primary pathological process.

Material and Methods

Synovium.—Specimens of synovial membrane were obtained by needle biopsy of the knee from 43 patients with RA and eight with various other diseases—liver disorder (3), Waldenström's macroglobulinaemia (3), polyarteritis nodosa (1), macroglobulinaemia (1). All those with RA had had the disease for more than a year, and most of them for several years. Sterile saline (approximately 100 ml.) was injected into the synovial cavity through the suprapatellar pouch, until the joint became swollen and hard. If synovial effusion was present, the fluid was withdrawn before the saline was injected. The biopsy specimen was obtained by inserting the Polley-Bickel needle into the lateral aspect of the knee 1 to 2 cm. from the external corner of the patella, along its superior margin. When almost all the saline had been withdrawn, the cutting edge of the needle moved easily and as a rule several fragments of synovial tissue could be obtained.

Liver.—Eighteen liver specimens were obtained with a Menghini biopsy needle from eight cases of liver disease (cirrhosis (4), infective hepatitis (3), Banti syndrome (1), seven of RA, and three of Waldenström's macroglobulinaemia. The tissues were quick frozen at -70° C. and later examined for the presence of AGGF and other globulins.

Marrow.—Eleven bone marrow specimens were obtained by sternal puncture in three cases of macroglobulinaemia, five of RA, and three of liver disease (cirrhosis (2), infective hepatitis (1)). The smears were fixed with cold acetone and then stained with fluorescent conjugates.

Anti-gamma globulin activity was demonstrated by reaction with aggregated human gamma globulin and/or pooled normal rabbit gamma globulin, both conjugated with fluorescein or tetramethyl-rhodamine isothiocyanate (B.B.L.-Baltimore). The rabbit gamma globulin was prepared by precipitation with 4.1 M ammonium sulphate; then it was heat-aggregated (at 63° C. for 10 minutes) like the human gamma globulin.

Macroglobulin was demonstrated by reaction with a fluorescein-conjugated rabbit anti-human 19S antiserum as well as by the absence of specific fluorescence when the tissue sections were pre-treated with 2-mercaptoethanol. A strictly specific anti-IgG antiserum prepared in our laboratory was employed to detect the presence of 7S IgG immunoglobulin in some biopsy specimens. A Leitz Laborlux microscope was used with a Philips 150 mercury vapour light source. Details of the immunofluorescence staining methods have been described elsewhere (Bonomo, Tursi, and Minerva, 1966).

The AGGF-containing cells were estimated by taking the average in at least three medium-power ($\times 500$) microscopic fields; usually from ten to fifteen fields were counted for each slide. These criteria were used by Cohen, Ohta, Singer, and Popper (1960) and Bonomo and others (1966).

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[†]In this paper the terms anti-gamma globulin factors and rheumatoid factors are used interchangeably.

Results

Patterns of Fluorescence

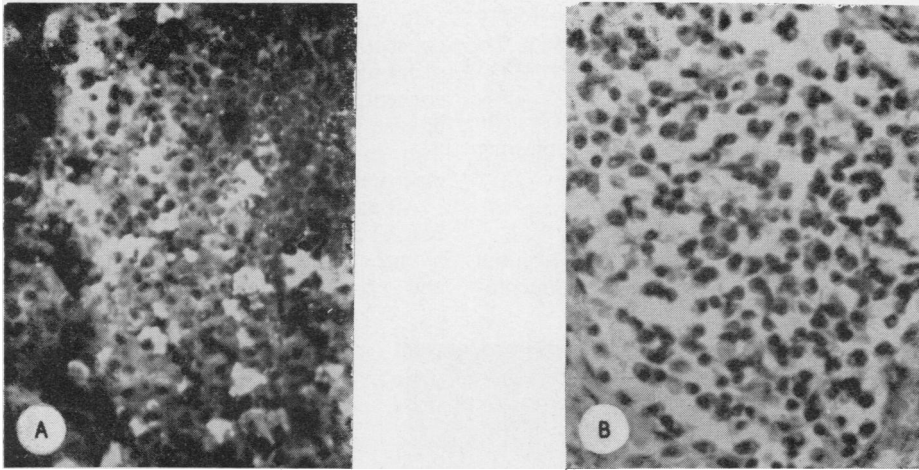
In the specimens of synovial membrane obtained from cases of RA, three patterns of fluorescence due to AGGF were observed: sparse, lymphoid, and vascular.

(1) Only sparse fluorescence was seen or aggregates of a variable number of AGGF-containing cells (mostly plasmocytes and lymphocytes) were scattered in the synovial tissue.

(2) The AGGF-containing cells produced a fluorescence with the aspect of lymphoid follicles (Fig. 1A). On staining with haematoxylin and eosin, the synovium appeared to be infiltrated with several such follicles (Fig. 1B).

Sometimes hypertrophic villi (Plate 1, overleaf) were seen to be rich in plasma cells containing AGGF.

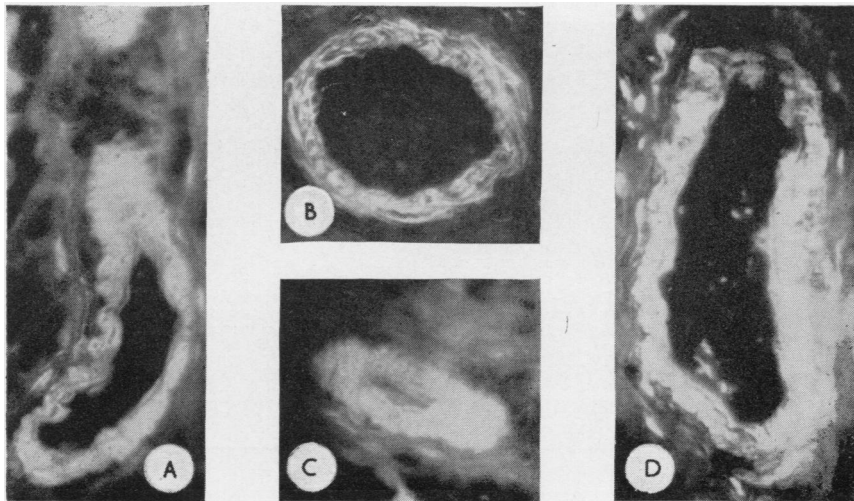
(3) A conspicuous amount of fluorescence due to the AGGF was seen in the vessel walls and in cells scattered around the vessels (Fig. 2 A, C, D).



(A) Lymphoid infiltrate with areas rich in cells containing rheumatoid factor that stain brightly. (Stained by fluorescein-conjugated aggregated human gamma globulin). $\times 250$.

(B) Adjacent section of same specimen stained by hematoxylin-eosin. It shows lymphoid infiltrate in the synovium rich with plasma cells and lymphoid cells. $\times 250$.

Fig. 1.—Synovial membrane; rheumatoid arthritis.



(A, C, D) Rheumatoid arthritis. Rheumatoid factor deposited in the vessel walls stains brightly with fluorescein conjugated aggregate. $\times 400$.

(B) Polyarteritis nodosa. Gamma globulin in the vessel walls stain brightly with fluorescein labelled anti-human gamma globulin antiserum. $\times 250$.

Fig. 2.—Synovial membrane.

A similar pattern of AGGF distribution has been described in two cases of "malignant" RA (Pernis, Ballabio, and Chiappino, 1963). In these specimens vasculitic alterations with perivascular infiltration of mono-nuclear cells were found when adjacent sections of the same biopsy specimen were stained with haematoxylin and eosin (Fig. 3).

In most cases with a vascular distribution of the AGGF there was no lymphoid infiltration and *vice versa*, so that these two patterns of synovial alteration seemed to be mutually exclusive.

In a few cases large non-cellular deposits were seen (Plate 2, opposite). Like the non-cellular deposits of immunoglobulins and complement described by Fish, Michael, Gewurz, and Good (1966), these may be due to destruction of phagocytic RA cells or plasma cells with release of the cytoplasmic content into the supporting tissue.

Disease Activity and Patterns of AGGF

The disease activity was graded from 0 to 3 on the basis of laboratory findings (erythrocyte sedimenta-

tion rate, haemoglobin, serum protein levels), radiological appearances (cartilage erosion, osteoporosis), and clinical data (muscle atrophy, grip strength, number of joints involved, analgesic tablets per day, functional capacity).

The relationship between the pattern of AGGF distribution and disease activity is shown in Table I; the disease was more severe and the titres of circulating AGGF tended to be higher in patients with a vascular pattern of AGGF distribution.

Concentration of AGGF in Different Tissues

In eleven cases it was possible to estimate this concentration in bone marrow, liver, and synovial membrane. The AGGF appeared to be mostly concentrated in the sites primarily involved by the disease process, the synovial membrane in RA, the liver in liver disease, and the bone marrow in macroglobulinaemia (Table II, see p. 125).

All patients with AGGF in the bone marrow also had circulating AGGF in the blood; this applied to cases of RA, liver cirrhosis, macroglobulinaemia, and chronic bronchitis. The AGGF-containing

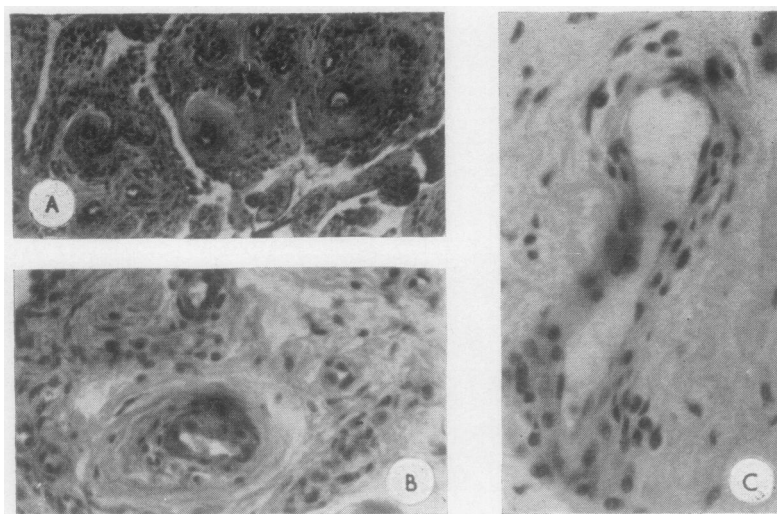
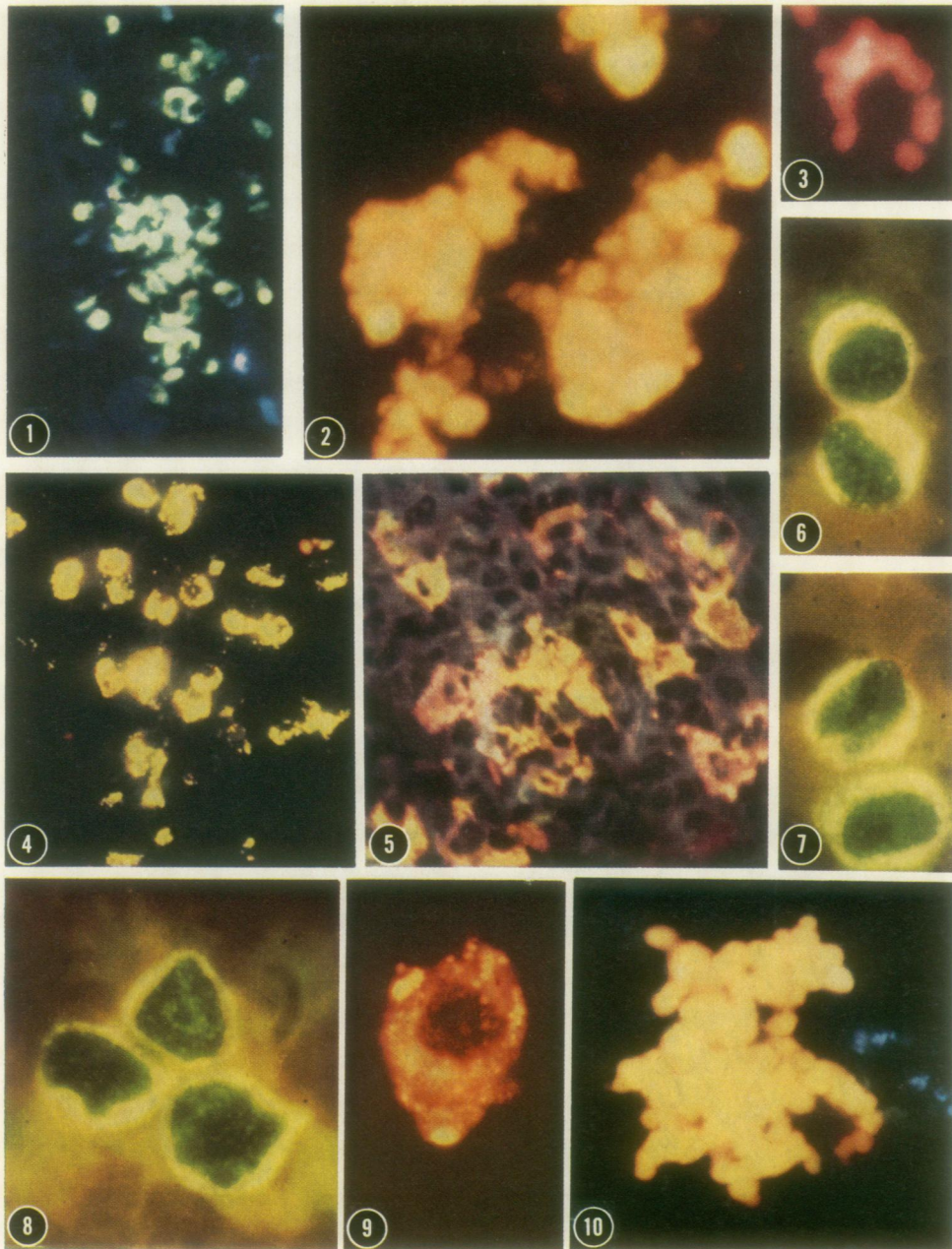


Fig. 3.—Synovial membrane. Rheumatoid arthritis. (A, B, C) Vasculitic alterations in cases with deposition of rheumatoid factor in the vessel walls (Hematoxylin eosin; A: $\times 40$; B: $\times 100$; C: $\times 250$).

TABLE I
PATTERNS OF ANTI-GAMMA GLOBULIN FACTOR DISTRIBUTION IN SYNOVIAL MEMBRANE
IN RHEUMATOID ARTHRITIS

Pattern	No. of Cases	Grade of Disease Activity			Hyland RA Test Titre (reciprocals)		
		1	2	3	Negative	20-160	320
Vascular	20	0	5	15	4	10	6
Lymphoid	12	1	9	2	2	8	2
Sparse	11	2	8	1	1	9	1



All sections stained by fluorescein labelled aggregated human gamma globulin followed by rhodamine-labelled rabbit gamma globulin. The fluorescence photomicrographs were taken on Kodachrome X daylight type 35 mm. film. Exposure times ranged from 1 to 3 minutes.

(1) Synovial membrane. Rheumatoid arthritis. A hypertrophic villum vertically oriented rich in plasma cells containing rheumatoid factor, mainly reacting with human gamma globulin (apple-green fluorescence). $\times 250$.

(2) Synovial membrane. Rheumatoid arthritis. Noncellular deposits of rheumatoid factor, mainly reacting with rabbit gamma globulin (yellow-orange fluorescence). $\times 950$.

(3) Liver. Rheumatoid arthritis. Plasma cell containing rheumatoid factor reacting with rabbit gamma globulin (orange-red fluorescence). $\times 1500$.

(4) Liver. Rheumatoid arthritis. Infiltrate of plasma cells and lymphocytoid cells containing rheumatoid factor reacting with both reactants (human and rabbit gamma globulin-yellow fluorescence). $\times 250$.

(5) Synovial membrane. Rheumatoid arthritis. Lymphoid infiltration with several plasma cells and lymphoid cells containing rheumatoid factor, mainly reacting with rabbit gamma globulin (yellow-orange fluorescence). $\times 400$.

(6) (7) (9) Synovial membrane. Rheumatoid arthritis. Lymphocytoid cells of lymphoid infiltrate containing rheumatoid factor reacting with both human and rabbit gamma globulin (6-7. yellow fluorescence $\times 1000$). Large plasma cell with Russell bodies mainly reacting with rabbit gamma globulin (9. orange-red fluorescence). $\times 1500$.

(8) Liver. Rheumatoid arthritis. Lymphocytoid cells reacting with both human and rabbit gamma globulin (yellow fluorescence). $\times 1000$.

(10) Liver. Liver cirrhosis. Large Russell-body plasma cell with eccentric unstained nucleus. Russell bodies contain rheumatoid factor reacting with both human and rabbit gamma globulin (yellow-orange fluorescence). $\times 2000$.

TABLE II
DISTRIBUTION OF ANTI-GAMMA GLOBULIN FACTORS IN VARIOUS TISSUES*

Case No.	Diagnosis	Liver	Synovial Membrane	Bone Marrow
1	Rheumatoid Arthritis	+	++	+
2	Rheumatoid Arthritis	+	++++	+
3	Rheumatoid Arthritis	++	++++	—
4	Rheumatoid Arthritis	++	++++	+
5	Rheumatoid Arthritis	+	++	+
6	Macroglobulinaemia	+	+	++++
7	Macroglobulinaemia	+	—	+++
8	Macroglobulinaemia	—	—	++++
9	Cirrhosis of Liver	+++	—	+
10	Cirrhosis of Liver	++	—	+
11	Infective Hepatitis	++++	—	+

*Estimated mean maximum anti-gamma globulin factor-containing cells in at least three high-power fields:
+ represents 2-3 cells
++ 4-6
+++ 7-9
++++ 10 or more

cells were particularly numerous in cases of macroglobulinaemia with high titres of circulating AGGF (Fig. 4).

The mean percentage of AGGF-containing cells in the bone marrow was as follows:

- Five cases of RA 2.60 per cent.
- Three cases of macroglobulinaemia 20 per cent.
- Three cases of liver disease 4.43 per cent.

AGGF were also demonstrated in the lymphocytoid cells present in the sputum of a patient with chronic bronchitis in agreement with previous findings (Bonomo and Tursi, 1963).

Results of Mixed Staining

Certain sections from liver and synovial membrane specimens were treated with both aggregated human gamma globulin and rabbit gamma globulin, conjugated with fluorescein isothiocyanate and tetramethylrhodamine isothiocyanate respectively.

It has been found that some cells form a factor which combines either with the fluorescent aggregate or the fluorescent immune complex, while some cells react with both (Mellors, 1963; McCormick, 1963).

Synovium.—Specimens of synovial membrane from RA cases contained cells reacting with both

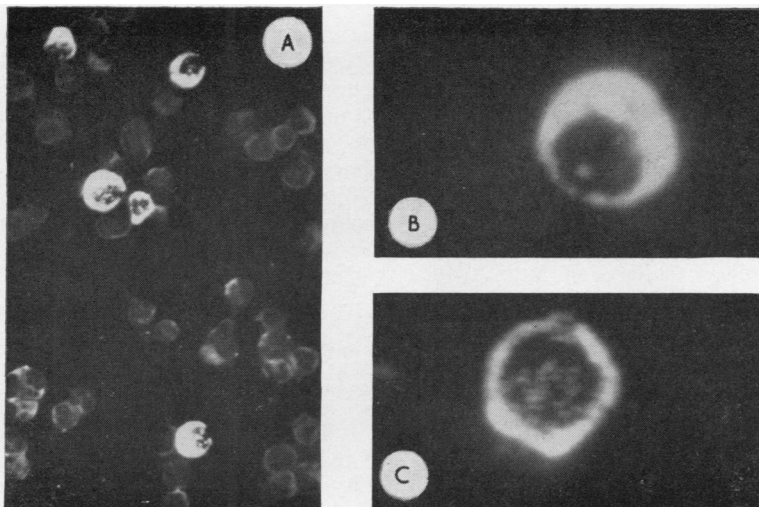


Fig. 4.—(A, B, C) Bone marrow. Waldenström macroglobulinemia. Plasma cells (B) and lymphoid cells (C) containing various amounts of antigamma globulin factor stain brightly with fluorescent aggregate (A: × 250; B, C: × 950).

reactants (Plate 6, 7) or mainly with rabbit gamma globulin (Plate 5, 9); cells reacting predominantly with human gamma globulin were less common (Plate 1).

Liver.—Specimens of liver tissue from cases of liver disease reacted mainly with human gamma globulin. Those from cases of RA reacted mainly with both reactants (Plate 4, 8) or with the rabbit gamma globulin (Plate 3). Reaction with rabbit gamma globulin was very rarely found in specimens from patients with liver disease (Plate 10).

The presence of AGGF in liver tissue sections cannot be ascribed to phagocytosis alone, although AGGF were found frequently (but not exclusively) in Kupffer-like cells. AGGF-containing cells were indeed more numerous in the liver in patients with liver disease (particularly infectious hepatitis) than in patients with RA, although the levels of circulating AGGF were much higher in the latter.

Fibrin in the Synovial Membrane

In three specimens of synovial membrane from cases of RA the presence of fibrin was investigated by an anti-human fibrin antiserum conjugated with fluorescein isothiocyanate (Sylvania Co., Milburn, N.J.), and the presence of RF was evaluated by aggregated and rhodamine-conjugated human F_{II}.

By this mixed procedure fibrin was found in the synovial lining. This agrees with previous findings (Kaplan, 1963), and much of the fibrin associated with RF showed a perivascular distribution.

Discussion

The existence of generalized immunological alterations not confined to the synovial membrane, lymph nodes, or spleen may be inferred in cases of RA from the distribution of the AGGF in various tissues and the behaviour of the immunologically competent cells (Bartfeld and Juliar, 1964; Malaguzzi-Valeri and Pipitone, 1965).

The distribution of AGGF in arthritic synovium conforms to the histological alterations in this tissue. A similar relationship has been observed in liver tissue (Bonomo and others, 1966). The presence of globulin is also related to the histopathological changes in arteritic lesions of the skin (Scott and Rowell, 1965) and synovium, as found in our case of polyarteritis nodosa (Fig. 2B).

Many recent findings (Dumonde and Glynn, 1962; Zvaifler and Pekin, 1963; Rodman, Williams, Bilka, and Müller-Eberhard, 1964; Fostiropoulos, Austen, and Bloch, 1965; Hollander, McCarty, Astorga, and Castro-Murillo, 1965; Astorga and Bollet, 1965; Ziff, 1965; Delbarre, Kahan, Amor,

and Krassinine, 1966; Norton and Ziff, 1966) favour the immunological interpretation of rheumatoid synovitis, as does the benign course of synovial involvement in subjects with immunological insufficiency who develop RA (Good, 1963).

In particular, gamma globulin with antibody function deposited at the affected sites may represent the stimulus to the formation of AGGF. Indeed 7S gamma globulin, which may be the source of aggregated gamma globulin, has been found in the early lesions of rheumatoid synovitis (Kaplan, 1963).

Likewise, 7S IgG immunoglobulin, although in much smaller amounts, has been detected in synovium showing vasculitic and lymphoid alterations in our long-standing cases of RA.

The vascular deposition of AGGF may be caused by the presence in vasculitic lesions of the cells that produce these factors. On the other hand, aliquots of rheumatoid macroglobulin, particularly in cases with a high titre of circulating AGGF, may adhere to the vessel walls because of the nature of the macroglobulin itself or because of a reaction with globulin fractions or immunoglobulin complexes adhering thereto.

The synovial deposition of fibrin as well as its association with rheumatoid factor in perivascular areas may be related to the pathogenesis of rheumatoid synovitis. Indeed, an experimental model of arthritis has been achieved by the immunological reaction to fibrin (Dumonde and Glynn, 1962).

Various effects of the AGGF, mostly protective in nature, have recently been described. A localizing effect of RF on denatured gamma globulin has been found which may prevent severe systemic reactions (Gough and Davis, 1966), phagocytosis of gamma-globulin aggregates, and possible removal of abnormal globulins (Parker and Schmid, 1962; Williamson and Ling, 1965), blocking complement-fixation (Zvaifler and Bloch, 1962; Gough and Davis, 1966) and complement-dependent phenomena (Schmid and Roitt, 1965).

Therefore, the distribution of RF in the synovium, and particularly its vascular deposition may be due to a protective mechanism limiting the spread of lesions of which the original cause is still unknown.

It has been suggested that the vascular deposition of RF may contribute to rheumatoid vasculitis (Epstein and Engleman, 1959; Scott, Hourihane, Doyle, Steiner, Laws, Dixon, and Bywaters, 1961), but although present on the surface of the vascular endothelium of lymph nodes obtained from seropositive rheumatoid patients, it was not found in

arteritic lesions of the digital vessels (Douglas, 1965).

Thrombosis and haemorrhage was produced in the vessels of the living rat mesentery by the intravenous injection of rheumatoid euglobulin preparations (Baum, Stastny, and Ziff, 1964).

The close association of the AGGF with histological lesions in various tissues suggests that they form part of the body's immune reaction to tissue damage.

These factors do not seem to be completely devoid of pathogenetic meaning. In fact they appear to be an obligatory requirement of rheumatoid synovitis (Hollander, Fudenberg, Rawson, Abelson, and Torralba, 1966); furthermore, the presence of conspicuous amounts of rheumatoid macroglobulin in the vasculitic lesions of the synovium still leaves unsolved the question of its possible involvement in their development.

Summary

In rheumatoid arthritis three patterns of distribution (sparse, lymphoid, and vascular) of anti-gamma

globulin factors detected by immunofluorescence were observed in biopsy specimens of the synovial membrane. Such patterns reflected the histological alterations in the synovium.

The concentration of AGGF was greatest at the main sites of the disease process, *i.e.* the synovium in arthritis, the liver in liver disease, and the bone marrow in macroglobulinaemia. AGGF were also found in cells in the sputum of patients with chronic bronchitis.

Circulating AGGF were found in the blood of all these patients.

Mixed staining procedures with specific fluorochromes showed, in the synovium and liver of cases of arthritis, cells containing factors active against both aggregated human gamma globulin and rabbit gamma globulin or predominantly against the latter.

In contrast, cells reactive with human gamma globulin were most frequent in the liver tissue and bone marrow of patients with liver disease and macroglobulinaemia respectively.

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La distribution des facteurs anti-gamma globuline dans la membrane synoviale et dans d'autres tissus au cours de différentes maladies**RÉSUMÉ**

Dans la polyarthrite rhumatoïde on a observé trois tableaux de distribution (clairsemé, lymphoïde et vasculaire) des facteurs anti-gamma globuline, détectés par immunofluorescence dans des prélèvements biopsiques de la membrane synoviale. De tels tableaux refléchissaient les altérations histologiques dans la synoviale.

La concentration des facteurs anti-gamma globuline était la plus forte aux lieux principaux du processus morbide, c'est à dire dans la synoviale en l'arthrite, le foie en la maladie hépatique et la moelle osseuse en la macroglobulinémie. On a trouvé aussi ces facteurs dans l'expectoration des malades atteints de bronchite chronique.

On a décelé aussi des facteurs AGG circulants dans le sang de tous ces malades.

Des procédés de coloration mixte avec des fluorochromes spécifiques ont démontré dans la synoviale et dans le foie des cas d'arthrite, des cellules contenant des facteurs actifs contre la gamma globuline humaine agrégée et la gamma globuline de lapin ou principalement contre cette dernière.

Par contre, les cellules qui réagissaient avec la gamma globuline humaine se trouvaient le plus souvent dans le tissu hépatique et la moelle osseuse des patients atteints de maladie hépatique et de macroglobulinémie respectivement.

La distribución de factores anti-gamma globulina en la membrana sinovial y en otros tejidos en diferentes enfermedades**SUMARIO**

En la poliartritis reumatoide se observaron tres cuadros de distribución (esparcida, linfoide y vascular) de factores anti-gamma globulina (AGGF), detectados por inmunofluorescencia en especímenes biopsicos de la sinovia. Tales cuadros reflejan alteraciones histológicas en la sinovia.

La concentración de los AGGF fué la mayor en sitios principales del proceso morboso, quiere decir en la sinovia en caso de artritis, en el hígado en caso de enfermedad hepática y en la médula ósea en caso de macroglobulinemia. Se encontraron también estos factores en la expectoración de enfermos con bronquitis crónica.

Se descubrieron también AGGF circulantes en la sangre de todos estos enfermos.

Procedimientos de coloración mixta con fluorocromos específicos demostraron en la sinovia y en el hígado de los casos de artritis células con factores activos contra la gamma globulina humana agregada y la gamma globulina de conejo o principalmente contra la última.

En cambio, células que reaccionan con la gamma globulina humana encontrábase con la mayor frecuencia en el tejido hepático y en la médula ósea de pacientes con enfermedad hepática o con macroglobulinemia respectivamente.