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RHEUMATOID FACTORS AND CIRCULATING IMMUNE COMPLEXES IN HYPERIMMUNIZED RABBITS

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Prolonged immunization of rabbits with bovine (BSA) and human (HSA) serum albumins resulted not only in the production of antigen specific IgG but also in the synthesis of rheumatoid factor (RF)-like autoanti-IgG antibodies in 9 out of 12 animals. RF activity was associated with 19S and 7S fractions of sera. The appearance, duration and disappearance of RF correlated with the presence and duration of circulating immune complexes (CIC). The immunization period was accompanied by fluctuations in RF activity and CIC level. This is probably due to the formation of secondary IC between RF and still existing CIC as was shown by analysis of CIC composition in vitro. The results suggest that RF response in the rabbit may be a composite response based on the contributions of both non-specific and specific effects of immune complexes. Hyperimmunized rabbits were shown to be a useful model for studying the circulation events concerning the relationship between rheumatoid factor and immune complexes.

Key words: Rheumatoid factor, immune complexes; hyperimmunization; rabbits

INTRODUCTION

Prolonged immunization of rabbits with bacterial or soluble antigens induces not only the formation of antigen specific antibodies but sharply stimulates the synthesis of auto-anti IgG antibodies closely mimicking human rheumatoid factor (Christian 1963, Herd 1973, Milošević-Jovčić and Nickolić 1976, Germuth et al. 1977). Hyperimmunization of rabbits also induces chronic polyarthritis having histopathological features that are considered to be characteristic of human rheumatoid arthritis (Aoki et al. 1972, 1985, Howson et al. 1986, Sumi et al. 1986, Klareskog 1989). In both rabbit and human arthritis, as well as in other inflammatory human and animal diseases associated with the presence of RF, this autoantibody in complexes with IgG was observed at the site of tissue lesions. This indicated that RF production might be related to the chronic inflammatory process (Aoki et al. 1972, Germuth and Rodrigues 1984, Ford and Kosatka 1982, Changlow et al. 1986).

However, RF has been detected, albeit in low titer, in the serum of healthy humans (Wernick et al. 1981, Welsh et al. 1983) and animals (van Snick and Masson 1980, Nemazee 1985). This indicated that the stimulus for RF production is not confined to a pathologic state and suggested that this autoantibody might have a physiological role. It was supposed that RF is produced in response to the presence of immune complexes (IC) (Jefferis 1980, Nemazee 1985, Devery and Hogben 1989; Roosnek and Lanzavecchia 1991). The traditional explanation is that IgG whose conformation has been altered by IC formation is a stimulus for RF production. By reacting with IgG in IC, RF increases the affinity of the IgG antibodies to their antigen and, due to the increase of the IC size, facilitates their clearance by the RES (Hogben and Devey 1986, Devey and Hogben 1989). That is probably why transient production of RF regularly accompanies secondary immune responses both in humans and in animals (Coulie and van Snick 1983, 1985).

The stage when an exuberant RF response, characteristic for the disease, begins is not known. This is, partially, due to the lack of information on the relatinship between RF and IC while they are in the circulation. Such data are, however, important for an insight into the effect of RF on circulating IC dynamics *in vivo* before they reach the sites of deposition.

In this work we studied the changes in the RF level depending on the appearance, duration and disappearance of IC in rabbitis immunized for a long period of time with bovine (BSA) and human (HSA) serum albumin. Hyperimmunized rabbits were shown to be a useful model for studying the circulation events concerning the relationship between RF and IC.

MATERIAL AND METHODS

Animals. A total of 12 male Chinchilla rabbits were immunized with BSA or HSA in two phases lasting 3 months each. After the first phase animals had a rest period of 7 months. For the first inoculation in each phase 20 mg of albumin-complete Frend's adjuvant mixture was administered subcutaneously into each animal. Further injections of 10 mg of the respective antigen were given at various time intervals (Sumi et al. 1985). Nonimmunized rabbits as well as those which received only complete Freund's adjuvant served as controls.

Blood was taken by ear vein puncture on days: 1., 3., 5., 8., 10., 13. and 15. after the first injection and on days 7., 15. and 30. after each later injection.

Antigen-specific antibodies (anti-albumin antibodies) were detected by double immunodiffusion in 1% agarose gel (Ouchterlony 1958).

Rheumatiod factor (RF) and its antiglobulin titers were determined by agglutination of latex particles coated with human IgG (Singer and Plotz 1956). Anti-antibody determination by this method is based on a cross-reaction, but since rabbit-globulin cross-react strongly it is considered unimportant.

Circulating immune complexes (CIC) were registered by direct PEG test (Živanović 1980). After precipitation of CIC with polyethyelene glycol-PEG (Mw

6000, 3% w/v) the level of IC was estimated semiquantitatively by reading the optical density (OD) of the redissolved PEG precipitate.

The reactivity of rabbit RF with autologous, homologous and heterologous IgG as well as with homologous IC prepared in vitro was studied in the agglutination inhibition system by estimating the inhibitory activity of native IgG, aggregated IgG and IC towards earch of the rabbits'RF (Milošević-Jovčić 1986).

In vitro immune complexes of BSA-rabbit anti-BSA and HSA-rabbit anti-HSA were prepared in 3x, 5x, 7x, 10x, 20x and 30x antigen excess after equivalence point determination and precipitation curve construction (Hudson and Hay 1980).

Human and rabbit IgGs were isolated by the Rivanol/ ammonium suophate procedure (Heide and Haupt 1964) and aggregated at 63^{0}C and 70^{0}C (Nikolić et al., 1983) respectively. Fractionation of rabbit sera was done by chromatography on DEAE Sephadex using a continuous gradient of phosphate buffer of different molarity (0.01 - 0.3M) at pH 7.0 (Michaelsen 1973).

RESULTS

1. Antialbumin antibodies (AAA), immune complexes (IC) and rheumatoid factor (RF)

Sera obtained from animals the day before primary immunization were all negative for precipitating AAA and RF, and IC values were in the range established for normal nonimmunized rabbits (OD below 0.400).

Circulating AAA appeared on day 5, 10 or 15 after the first injection of HSA or BSA (table 1).

Table 1. The appearance of antialbumin antibodies (AAA), immune complexes (IC) and rheumatoid factors (RF) in rabbit sera after immunization with BSA and HSA

Immunization		Days of appearance		
Rabt	Imunogen	AAA	IC	RF
1.	BSA	5.	10.	15.
2.	BSA	15.	13.	–
3.	BSA	5.	14.	15.
4.	BSA	15.	15.	18.
5.	BSA	15.	15.	18.
6.	BSA	15.	15.	18.
7.	BSA	15.	15.	18.
8.	BSA	18.	–	–
9.	HSA	5.	10.	15.
10.	HSA	5.	10.	15.
11.	HSA	15.	15.	18.
12.	HSA	10.	10.	–

IC in values exceeding those established for nonimmunized rabbits were registered 10 or 15 days after the first injection (table 1, figure 1).

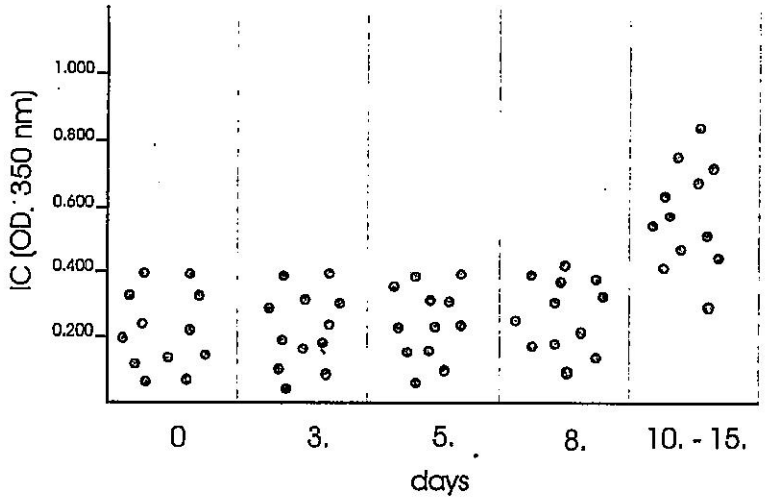

Figure 1. IC level in rabbit sera within the first 15 days after immunization.

RF was registered 15 or 18 days after the first injection in the majority of animals with titers which reached 1:40 to 1:256. Sera of 3 immunized rabbits were permanently seronegative till the end of immunization (table 1).

With the exception of one animal in which RF and IC were detected on the same day, the appearance of IC in the circulation preceded the appearance of RF by 3 to 5 days.

In control animals treated with Freund's adjuvant only, as well as in untreated animals (that were kept during the whole period of immunization under the same conditions as immunized rabbits) IC and RF were not registered.

2. The relationship between IC and RF during long term immunization of rabbits

In the first phase of immunization which lasted for 3 months a relationship between the level of circulating IC (CIC) and the activity of RF was observed in all rabbits: a high level of IC was followed by high titers of RF. However, an increase of CIC values observed about 10 days after each new dose of antigen was not always followed by an increase in RF titer. Moreover, the rise of IC level was sometimes followed by a decrease of RF titer (Fig. 2).

The second phase of prolonged immunization of the rabbits, which followed the first after a rest period of 7 months, was characterized by dynamic changes in CIC level similar to those observed in the first phase in that after each injection of antigen the CIC level increased and in the period between two antigen doses CIC level declined. The relationship between CIC and RF was, however, quite different from that observed in the first phase of immunization. RF was detected only once after the first injection in the second immunization phase. After all

succeeding injections rabbit sera remained seronegative regardless of the duration of IC.

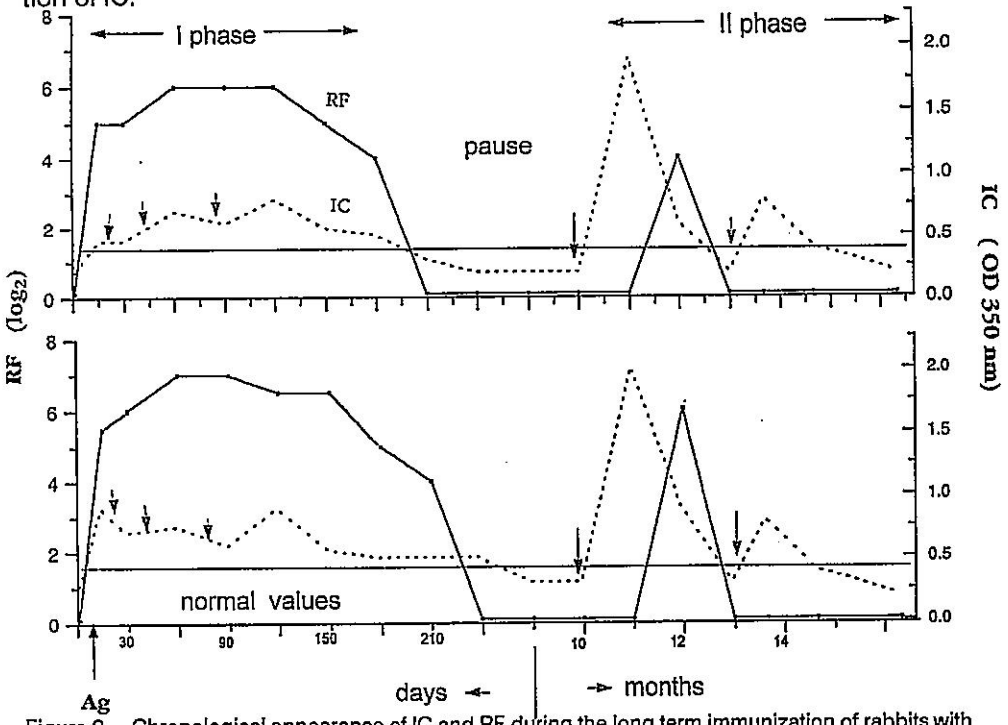

Figure 2 Chronological appearance of IC and RF during the long term immunization of rabbits with HSA (a) and BSA (b).

3. Rheumatoid factor (RF) as a constituent of secondary immune complexes (IC)

As fluctuations in IC level and RF activity observed during prolonged immunization of rabbits might be due to the appearance in the circulation of secondary IC formed between RF and albumin/anti-albumin IC, we analyzed a) anti-gammaglobulin activityof rabbit sera before and after precipitation of IC by PEG and b) the composition of IC.

3a) After removing IC by precipitation with PEG, the agglutinating activity of rabbit sera decreased. Mean values of RF titers for each period of immunization calculated for all rabbits were two to three times lower after precipitation of IC by PEG (table 2).

To check whether RF by itself was precipitable by PEG several human sera with high titers of RF but with a low optical density of PEG precipitates were used as controls. It was shown that after adding PEG to these sera the agglutinating activity of all of them was almost completely the same as it was before PEG precipitation.

Table 2. RF titers in rabbit sera before and after precipitation of IC by PEG

Immunization phase	RF titers in whole serum	RF titers in PEG supermatant
I	120	32
II	136	40
III	120	48
IV	100	44
V	60	26
VI	16	10
VII	8	0

3b) Serum samples obtained in different phases of immunization were fractionated by ion exchange chromatography. The same was done with IC previously extracted from these serum samples. All the samples were fractionated under the same elution conditions and the distribution of RF and anti-albumin antibodies was determined in all fractions obtained. The results showed that only in the initial phase of immunization, AAA and RF were in separated fractions. In all later phases of immunization AAA and RF were registered separately and together in the same fractions. After the separation of "RF negative" serum samples RF activity was registered in some of the obtained fractions. The appearance of "hidden RF" suggests that the agglutinating activity of RF was probably blocked by its reaction with primary immune complexes.

4. Isotype of rabbit rheumatoid factor (RF)

Gel filtration on Sephadex G-200 of a serum from rabbits immunized with BSA and HSA resulted in similar separation. Upon primary immunization anti-globulin activity was present in the 19S fraction (figure 3a) and in hyperimmunized rabbits this activity was registered in 19S and 7S fractions (fig. 3b, c).

5. The specificity of rabbitrheumatoid factor (RF)

Rabbit and other species IgG aggregated by heat inhibited the agglutinating activity of hyperimmune rabbit sera more intensively than the respective native IgG did (table 3). Ag/Ab complexes prepared in vitro between BSA or HSA and the corresponding anti-albumin antibodies synthesized by rabbits also expressed an inhibitory effect over the broad range of Ag/Ab ratio from three to thirty fold excess of antigen with the maximal inhibition of agglutination at 10 times antigen excess (fig. 4).

DISCUSSION

The present study describes the kinetics of the appearance of rheumatoid factor (RF) and provides new information on the relationship between this autoantibody and immune complexes (IC) in the circulation of rabbits during long term immunization with BSA and HSA.

Immunization led to the production of RF in 9 out of 12 animals. RF activity, as detected by the RF latex agglutination test, appeared 15-18 days from the beginning of immunization. In all RF positive sera circulating immune complexes

were registered in increased levels. CIC preceded the appearance of RF by 3-5 days. One of the most striking results was the appearance of both RF and CIC after the primary immunization.

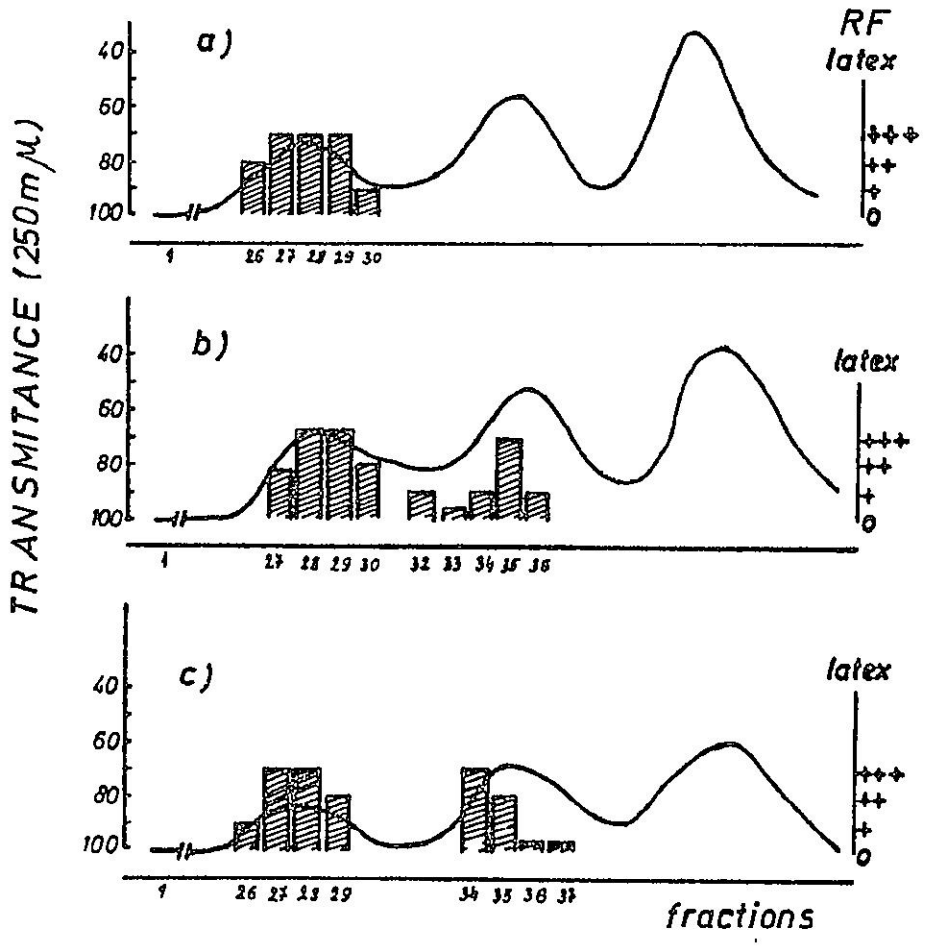

Figure 3. Gelfiltration of RF positive rabbit sera

Studies in mice have shown that the RF that appears after the first injection of antigen, is not formed in response to IC, but rather represents a part of polyclonal B cell activation (Popham and Dresser 1980). RF activity as a result of the specific immune response against IgG containing immune complexes can be developd only after multiple antigen administration, i. e. during the secondary immune response (Coulie and van Snick 1983, 1985, Nemazee and Sato 1983).

Table 3. Inhibitory activity of homologous (rabbit) and heterologous IgG towards RFs of hyperimmunized rabbits.

RF	IgG preparations					
	Human	Rabbit	Sheep	Bovine	Horse	Guinea pig
1	1:4	1:16	1:8	1:8	1:4	1:4
2	1:4	1:16	1:8	n.d.	1:4	1:4
3	1:8	1:8	1:8	1:2	1:4	1:4
4	1:4	1:8	1:8	1:4	1:4	1:2
5	1:4	1:8	1:8	–	1:4	1:4
6	1:2	1:8	1:4	1:8	n.d.	1:4

It was previously reported that immune complexes are capable of inducing rabbit lymphocyte proliferation (Soderberg and Coones 1978). It was also shown that IC may act as polyclonal B cell stimulators in vitro (Morgan and Wiegle 1983) as well as that primary immunization with preformed IC may result in RF production (Nemazee 1985). It is likely, therefore, that RF activity registered after the primary immunization of our rabbits was connected with IC that could have acted as polyclonal activators of rabbit B cells.

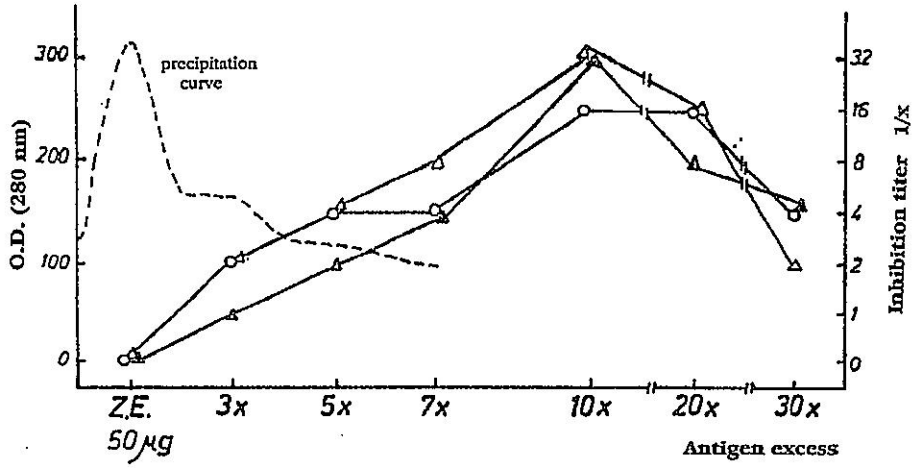

Figure 4. Inhibitory activity of BSA anti BSA and HSA anti-HSA IC prepared in vitro towards rabbit RFs

The next phases of prolonged immunization were characterized by the continuous production of RF. The presence of RF in the circulation correlated with the duration of IC. However, the increase of CIC values, which was registered after each new dose of antigen, was not always followed by an increase of the RF titer. This was particularly striking within the second round of immunization which followed the first after a rest period of 7 months; RF disappeared much earlier than IC did.

Decrease of RF activity or total seronegativity could be explained in several ways not mutually excluded. Most probably it was due to the saturation of RF by a high quantity of IC. Removing IC from rabbit sera by PEG with the simultaneous decrease of RF titer in each phase of immunization, as well as the appearance of "hidden" RF upon dissociation of IC point towards this. Coulie and van Snick (1983) showed in a mouse model that RF production induced by many proteins and measured in spleen cell cultures did not significantly increase circulating RF levels. Such a finding has been explained by the transient character of the RF response and by consumption of RF by IC formed after injection of antigen into immune animals. However, the possibility exists that some RF molecules were consumed by anti-idiotypic antibodies specific for variable domains of RF (Pasqually et al. 1984) as well as that RF changed its specificy during the hypeimmunization, thus becoming undetectable in a given test system. It was shown in rabbits that under hyperimmunization conditions the overall conformation of the Fc region within the population of IgG may be shifted towards a more disorganized state (Murray and Brown 1990). Structural differences may be associated with RF specificity. The appearance of latent subclass or allotype within the hyperimmunized rabbits is also possible (Davidson et al. 1986). It would be, therefore, interesting to see which subclass or allotype of rabbit IgG in IC is responsible for the autoantibody induction. However, the situation with the hyperimmunized rabbits seems complex, since at present it is not clear whether the RF production is due solely to the persistent immune complexes,or if other mechanisms are involved such that newly formed RF-IgG IC complexes take over the role of RF inducer in the late stage.

RF activity in hyperimmunized rabbits was associated both with the 19S and 7S fraction of sera. The appearance of 7S RF has been taken as evidence that RF production in later phases is connected with continuous autoantigenic stimulation rather than with polyclonal B cell activation (Levison 1989). It has been shown in mice that RF secreting B cells undergo clonal expansion with isotype switching comparable to the extent observed in conventional humoral response (Jacobsen et al. 1994). Although we have no direct evidence on the same clonal origin of 7S and 19S anti-IgG, their similar specificity towards autologous and homologous IgG aggregated by heat suggest that they most probably share idiotypy, the property which is indicative for the same origin of clones.

The results of our experiment confirm the statement (Stanley et al. 1987) that RF response may be a composite response based on contributions of non-specific effects of immune complexes through polyclonal activation and specific anti-IgG response with RF directed against epitopes on complexed IgG produced in the anti-antigen response.

The functional significance of rabbit RF has yet to be determined. Nevertheless, the dynamics of its appearance and disappearance during long term immunization as well as the relationship that exists between RF and IC suggest that this autoantibody most likely facilitates the clearance of IC formed during the immunization. However, decrease of RF titer might be due to the deposition in capillary walls, especially if it changed the charge during the immunization (Ford 1989.) Such RF could be capable of acting as an immunoadsorbent and binding,

in vivo, both endogenous and exogenous circulating immune complexes as well as aggregated IgG (Ford and Kosatka 1985). Further studies in our experimental model are necessary to clarify this aspect of RF production in hyperimmunized rabbits.

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N. Milošević-Jovčić, Lj. Tošić and N. Dovezenski: Rheumatoid factors and circulating immune complexes in hyperimmunized rabbits

REUMATOIDNI FAKTORI I RASTVORLJIVI IMUNOKOMPLEKSI KOD DUGOTRAJNO IMUNIZOVANIH KUNIĆA

NADEŽDA MILOŠEVIĆ-JOVČIĆ, LJUBINKA TOŠIĆ I N. DOVEZENSKI

SADRŽAJ

Reumatoidni faktor (RF) je auto-anti IgG antitelo koje se javlja kod ljudi i životinja pod različitim patološkim uslovima, a u neznatnoj količini i kao fiziološka komponenta normalnog imunog odgovora. Iako se pojava RF-a dovodi u vezu sa imunokompleksima (IC) koji dugotrajno perzistiraju u cirkulaciji, dinamički aspekti ovog odnosa nisu poznati. U ovom radu je ispitan odnos RF-a i IC kod kunića dugotrajno imunizovanih govedijum i ljudskim serumskim albuminima. Pokazalo se da je imunizacija kunića ovim antigenima praćena ne samo pojavom anti-albuminskih antitela već i reumatoidnih faktora. Od 12 životinja 9 je stvaralo ovu kategoriju autoantitela. RF aktivnost je registrovana u 19S i 7S frakcijama kunićevih seruma. Pojava, trajanje i iščezavanje RF-a koreliralo je sa prisustvom i trajanjem cirkulišućih imunokompleksa (CIC). U toku imunizacije zapažene su fluktuacije u nivou RF-a i IC što se može dovesti u vezu sa stvaranjem sekundarnih kompleksa između RF-a i već postojećih IC, a o čemu svedoče podaci dobijeni analizom sastava CIC in vitro. Rezultati ukazuju da bi pojava RF-a u toku dugotrajne imunizacije mogla da se dovede u vezu i sa nespecifičnim i sa specifičnim efektom imunokompleksa.