In vitro study of immunological events in human and experimental schistosomiasis: relationships between cytotoxic antibodies and circulating Schistosoma antigens*

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Summary. Complement-dependent cytotoxic antibodies were found in 54% of Schistosoma mansoni infected patients from Burundi and in 69 to 78% of Schistosoma mansoni infected Brazilian patients. The levels of cytotoxic Ab were not statistically different in sera from infected mothers and from their newborn children, suggesting a transfer through the placenta. A sandwich radioimmunoassay (SRIA) and the Radioimmunoprecipitation-PEG assay (RIPEGA) technique were used in order to detect respectively total schistosome circulating soluble antigens (CSA), and schistosome antigen '4' in sera from infected patients. An inverse relationship was found between the presence of cytotoxic Ab and both total CSA and antigen '4'. The cytotoxic Ab and total CSA levels were followed in five Erythrocebus patas monkeys for 30 weeks after Schistosoma mansoni infection. As in human schistosomiasis the presence of cytotoxic Ab was found to be inversely correlated with the presence of total CSA. The blocking role of Schistosoma mansoni antigens in a complexed form was suggested by the inhibitory effect of the ultracentrifugation pellet of infected human serum on the cytotoxic activity. Moreover, the CSA absorption of infected monkey serum by passage through an anti-CSA immunosorbsent significantly increased the cytotoxic activity. Possible mechanisms for the inhibitory role of circulating immune complexes on complement-dependent cytotoxic activity are discussed.

Keywords: Schistosoma mansoni, schistosomula, Erythrocebus patas monkeys

* A collaborative study performed in Brasil, Burundi, France and Upper-Volta.

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Introduction

The existence of complement-dependent cytotoxic antibodies for schistosomula in vitro, first reported in monkeys by Clegg & Smithers (1972), was also detected in various experimental models (Murrell & Clay 1972) and in human infections (Capron et al. 1973, 1974, Smith & Webbe 1974). In further studies (Capron et al. 1977) the IgG class and the specificity of this cytotoxic antibody in man were precisely indicated. A statistical correlation was found between the cytotoxic activity of the patient's sera and both the severity of the disease and delayed hypersensitivity to S. mansoni antigen. However in that work, no correlation was shown between the occurrence of circulating Schistosoma mansoni antigen in urine and the complement-dependent cytotoxic activity of the patient's sera. Until now, it has been difficult to correlate in vitro studies with protective immunity in vitro (Sher et al. 1974, Murrell, Dean & Stafford 1975) and therefore to understand the significance of this cytotoxic antibody.

Numerous authors have described the presence of specific circulating schistosome antigens (CSA) both in human schistosomiasis (Carlier et al. 1975, Bout et al. 1977, Santoro et al. 1977, Madwar & Voller 1977, Carlier, Bout & Capron 1978, Carlier et al. 1980b, 1980c) and in experimental infections (Berggren & Weller 1967, Gold, Rosen & Weller 1969, Nash, Prescott & Neva 1974, Deelder et al. 1976, Houba et al. 1976, Carlier et al. 1978, 1980a, 1980b). As in human cases, these CSA were only found in the highly concentrated biological fluids (Carlier et al. 1975, Santoro et al. 1977, Carlier et al. 1978), a sensitive technique using a solid phase sandwich radioimmunosassay (SRIA) was recently designed in order to detect very low levels of CSA (Carlier et al. 1980c). Moreover, the use of the radioimmunoprecipitation-PEG assay (RIPEGA) has allowed the demonstration and the quantification of a specific schistosome antigen called antigen '4' in human and experimental schistosomiasis (Santoro, Vandemeulebroucke & Capron 1978a, Santoro et al. 1978b, 1979).

In the present study, we have analysed the possible relationships between complement-dependent cytotoxic antibodies and CSA using the SRIA to measure total CSA levels and the RIPEGA to detect the specific antigen '4' in the serum. This work was performed both in human and in monkey schistosomiasis, the last model allowing a kinetic study of the two parameters, cytotoxic Ab and CSA.

Material and methods

PARASITES

The experiments performed in Lille, France, employed cercariae of the Puerto Rican strain of Schistosoma mansoni maintained as previously described (Capron
et al. 1974). *S. mansoni* schistosomula were prepared by the method of Clegg & Smithers (1972). The cercariae used in Bobo-Dioulasso, Haute-Volta, were obtained from a life-cycle originally established from a local field population of *Biomphalaria pfeifferi* infected with a local strain of *S. mansoni* and maintained in *Erythrocebus patas* monkeys.

**HUMAN SERA**

Two groups of patients were studied. The first was composed of African patients from Burundi. Twenty-six *S. mansoni*-infected mothers living in a schistosomiasis endemic area in Burundi and admitted to the maternity ward of the ‘Hospital Prince Regent Charles de Bujumbura’ were selected by the presence of *S. mansoni* eggs in stool examinations. Blood samples were obtained during delivery. The blood samples of their 26 new-born children were obtained from the umbilical cords. Twelve uninfected mothers from an area free of schistosomiasis and their newborn children composed the control groups. The blood was allowed to clot at room temperature, serum was separated, centrifuged and stored frozen at \(-20^\circ\mathrm{C}\).

The second group of patients was composed of 43 Brazilian patients with a mild form of chronic schistosomiasis. They were divided into two groups according to the faecal egg output: group I, 29 sera from infected patients eliminating less than 100 eggs/g stool; and group II, 14 sera from infected patients eliminating more than 100 eggs/g stool. Sera from these patients were stored frozen. Sera of 11 uninfected patients from an area free of schistosomiasis formed the control group.

**MONKEY SERA**

Five male or female monkeys (*Erythrocebus patas*) weighing 2 to 5 kg and maintained in Bobo-Dioulasso, Haute-Volta, were used. No sign of parasitic infection was found before experimentation. The monkeys were infected without anaesthesia through transabdominal exposure. A plastic tube was placed on the shaved skin of the abdomen and a suspension containing 1000 cercariae was then applied to the abdominal skin for 45 minutes. Animals were bled before and at 2 week-intervals after infection, and the sera were lyophilized in 2 ml aliquots. Four uninfected monkeys maintained in the same conditions were used as controls. The evaluation of *S. mansoni* eggs in the stools was performed according to the technique described by Ridley & Hawgood (1956).

**CYTOTOXICITY ASSAY**

The cytotoxicity assay was performed as previously described (Capron *et al.* 1974, 1977) with minor modifications. Experiments were carried out in sterile
plastic microplates with flat-bottomed wells (Nuclon, Denmark). Fifty schistosomes were added to each well and incubated in a total volume of 200 µl consisting of 50% heat-inactivated human or monkey serum, 20% fresh guinea-pig serum (source of complement), and 30% MEM medium. The microplates were incubated at 37°C for 4 days in 5% CO₂ humidified atmosphere and the percentage cytotoxicity was evaluated by microscopic examination. All sera were tested in triplicate and the given values represent means of triplicate tests (± s.e.m.). A percentage of cytotoxicity superior or equal to 30% was considered as significant (Capron et al. 1974).

DETECTION OF CIRCULATING SOLUBLE ANTIGENS (C.S.A.)

Two methods were used to detect *Schistosoma mansoni* CSA. Total CSA were quantified in human and monkey schistosomiasis using a solid phase sandwich radioimmunoassay (SRIA) as previously described (Carlier et al. 1980a) but with one modification: anti-CSA antibodies from infected patients were used instead of rabbit immunoglobulins. The results were expressed in percent as B-BO/B10-BO. B is the counts per min (cpm) of the studied sample, BO the background cpm using control sera and B10 the cpm obtained using 10 µg of *Schistosoma mansoni* soluble antigen prepared according to Capron et al. (1968). The given values represent means of triplicate assays.

The RIGEPA technique (Santoro et al. 1978b) using radioiodinated anti-antigen '4' antibodies, was performed to quantify the presence of circulating antigen '4'. Results were expressed as percentage ¹²⁵I-labelled anti-F4 antibodies precipitated as compared with the protein-bound radioactivity precipitable with 20% trichloracetic acid (Means of triplicate assays).

CYTOXICITY INHIBITION EXPERIMENTS

Two kinds of cytotoxicity inhibition experiments were performed. The first procedure used a serum from an infected patient (TOR) in which no detectable cytotoxic activity could be observed. This serum was ultracentrifuged (120 000 g at 4°C for 3 h). The upper two-thirds of the supernatant (just under the lipidic layer) and the pellet were recovered. The pellet was then resuspended to the initial volume in MEM. For the inhibition experiments, a positive cytotoxic human serum (DES) was incubated with the ultracentrifugation pellet of the negative cytotoxic serum (TOR) in the cytotoxicity assay. The concentrations used were 40% heat-inactivated positive immune serum, 20% pellet, 20% fresh guinea-pig serum and 20% medium containing schistosomula.

The second procedure used an immunoadsorbent column prepared with anti-CSA human immunoglobulins. Immunoglobulins from a *Schistosoma mansoni*-infected patient serum (215 mg) were obtained using ammonium sulphate precipitation and bound to CNBr-activated 4B Sepharose (Pharmacia, France).
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as previously described (Axen, Porath & Ernback 1967). A pool of infected monkey sera was passed through this immunoadsorbent column. Control monkey sera was similarly treated. Cytotoxic activities of the sera before and after CSA absorption were then investigated.

Results

CYTO TOXIC ANTIBODIES AND CIRCULATING SOLUBLE ANTIGENS IN HUMAN INFECTION

The complement-dependent cytotoxic activity for Schistosoma mansoni schistosomula was studied in sera from African patients (Table 1). Activity was detected in 54% of Schistosoma mansoni infected mothers and the mean percentage of cytotoxicity obtained in this group was not different from the mean percentage of cytotoxicity obtained in the sera from their newborn children. When sera from infected and uninfected mothers were compared, a statistically significant difference was observed ($P<0.001$), a similar result being obtained when sera of children born from infected or uninfected mothers were compared ($P<0.001$).

A significant cytotoxic activity ($\geq 30\%$) was demonstrated in a higher number of cases in the sera from infected Brazilian patients (68.9 to 78.5%) than in the group of African patients (42 to 54%) (Table 1). Nevertheless the mean percentage of cytotoxicity in the positive sera was not significantly different in these two populations. It can be seen in Table 1 that although the percentage of cytotoxicity

<p>| Table 1. Cytotoxic activity of sera from S. mansoni infected patients |
|---------------------------------|-----------------|-----------------|</p>
<table>
<thead>
<tr>
<th>Sera</th>
<th>Mean % Cytotoxicity (± s.e.m.)</th>
<th>Number of positive sera (%)</th>
<th>Mean % Cytotoxicity in the positive sera</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>AFRICAN PATIENTS</strong></td>
<td></td>
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</tr>
<tr>
<td>Infected mothers</td>
<td>36.2 ± 4.7*</td>
<td>14/26 (54%)</td>
<td>52.3 ± 5.9</td>
</tr>
<tr>
<td>Newborn children of infected mothers</td>
<td>32.1 ± 4.2*</td>
<td>11/26 (42%)</td>
<td>50.7 ± 5.9</td>
</tr>
<tr>
<td>Uninfected mothers</td>
<td>18.1 ± 1.7</td>
<td>0/12</td>
<td>0</td>
</tr>
<tr>
<td>Newborn children of uninfected mothers</td>
<td>14.1 ± 1.9</td>
<td>0/12</td>
<td>0</td>
</tr>
<tr>
<td><strong>BRAZILIAN PATIENTS</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group I</td>
<td>38.3 ± 3.3*</td>
<td>20/29 (68.9%)</td>
<td>45.8 ± 3.5</td>
</tr>
<tr>
<td>Group II</td>
<td>46.3 ± 3.5*</td>
<td>11/14 (78.5%)</td>
<td>51.1 ± 3.0</td>
</tr>
<tr>
<td>Controls</td>
<td>11.4 ± 2.3</td>
<td>0/11</td>
<td>0</td>
</tr>
</tbody>
</table>

* Significantly higher than with the uninfected controls ($P<0.001$).
in group I (patients eliminating less than 100 eggs of Schistosoma mansoni/g stool) (38.3%) was lower than in group II (46.3%), the difference was not statistically significant.

The results of the detection of total CSA by the SRIA technique applied to sera from infected patients were indicated in an earlier work (Carlier et al. 1980a). CSA was detected in 24 sera from the 26 infected mothers (mean level of this group: 40.57% ± 4.19, s.e.m.). Twenty-four out of their 26 newborn children had comparable CSA levels in umbilical cord sera (35.03% ± 3.95, s.e.m.) and a significant correlation was established between CSA levels of mothers and newborn children (r = 0.73; P < 0.001). When the results of the detection of total CSA were compared with the levels of complement-dependent cytotoxic antibody, an inverse correlation was observed (r = -0.39; P < 0.01; n = 52). A statistical study on the frequency of these two parameters by McNemar’s test confirmed that an inverse relation existed between the presence of total CSA and cytotoxic Ab (Table 2; P < 0.01; n = 52).

The results of the detection of specific Schistosoma mansoni antigen ‘4’ in Brazilian patients by the RIPEGA technique were reported in a previous work (Santoro et al. 1978b). An inverse relationship was also seen between the presence of circulating Schistosoma mansoni antigen ‘4’ and the complement-dependent cytotoxic antibody using McNemar’s test (Table 2; P < 0.05; n = 41).

### CYTOTOXIC ANTIBODIES AND CIRCULATING SOLUBLE ANTIGENS IN EXPERIMENTAL MONKEY INFECTION

In Erythrocebus patas monkey infection, a kinetic study of cytotoxic Ab and total CSA as detected by the SRIA was performed from day 0 to approximately 30

<table>
<thead>
<tr>
<th>Cytotoxic* Ab</th>
<th>Total CSA†</th>
<th>Antigen ‘4’‡</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0</td>
<td>&lt;12%</td>
</tr>
<tr>
<td>&lt;30%</td>
<td>2</td>
<td>29</td>
</tr>
<tr>
<td>≥30%</td>
<td>2</td>
<td>19</td>
</tr>
</tbody>
</table>

* Number of sera giving a percentage cytotoxicity <30% or ≥30%.
† Number of sera giving a percentage of B-BO/B10-BO (see material and methods) zero or positive.
‡ Number of sera giving a percentage of 125I-labelled anti-F₄ Ab precipitated ≤12% or >12%.

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Table 2. Relations between cytotoxic Ab, total CSA or antigen ‘4’.
weeks after the primary infection (Figure 1). The study of complement-dependent cytotoxic antibodies revealed the presence of a first peak of cytotoxic activity around 7 to 11 weeks after infection. A second peak of cytotoxic activity was observed around week 24 after infection. The percentage of cytotoxicity in the uninfected monkey sera was always lower than 30%.

Total schistosome CSA could be detected earlier than the cytotoxic antibody, usually around week 3 to 5 according to the level of infection. When the mean values of cytotoxic Ab and total CSA were compared, no parallelism was found between the evolution of these two parameters.

Moreover, it can be seen that, at the periods when no cytotoxic activity was detectable, the levels of CSA reached high values (at week 5 and 30). In contrast, low levels of CSA were present when the levels of cytotoxic Ab were very high at week 7, 11 and 18.

ROLE OF BLOCKING FACTORS ON CYTOTOXICITY

As there seemed to be an inverse relationship between cytotoxic Ab and CSA in schistosomiasis infections in humans and in monkeys, it was interesting to study the possible blocking role of schistosome CSA or CIC on the complement-dependent cytotoxic antibody. The first kind of cytotoxicity inhibition experiments showed the cytotoxic activity of the ultracentrifugation supernatant, to be significantly increased in comparison to that of the untreated total serum (TOR) \( (n=2; \ P<0.05) \) (Table 3). Conversely the cytotoxicity of the positive human serum (DES) was dramatically decreased after incubation with the ultracentrifugation pellet of the previous cytotoxic negative serum (TOR) \( (81\% \ inhibition; \ n=3; \ P<0.01) \) (Table 3).

The second kind of experiment performed only with monkey sera (because of the larger quantity available) also favoured the hypothesis of the blocking role of free or complexed schistosome CSA. Infected monkey sera, recovered at the periods when the cytotoxic activity was low and when the CSA were at the maximum level, were passed through the anti-CSA immunosorbent column. The complement-dependent cytotoxic activity of the infected monkey sera was signifi-
This Cytotoxic activity seemed to be complement dependent, since no activity of the absorbed sera was detected in the absence of complement. Moreover, control monkey serum treated in the same conditions showed not cytotoxic activity after passage through the immunosorbent.

Table 3. Blocking role of a factor present in the ultracentrifugation pellet of infected human serum

<table>
<thead>
<tr>
<th>Sera</th>
<th>% Cytotoxicity* (± s.e.m.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Human serum TOR</td>
<td></td>
</tr>
<tr>
<td>untreated</td>
<td>11.5±2.5</td>
</tr>
<tr>
<td>supernatant</td>
<td>58.5±11.5†</td>
</tr>
<tr>
<td>Human serum DES</td>
<td></td>
</tr>
<tr>
<td>untreated</td>
<td>39.3±0.4</td>
</tr>
<tr>
<td>incubated with pellet (TOR)</td>
<td>7.3±1.8‡</td>
</tr>
</tbody>
</table>

* Mean of triplicate experiments ± s.e.m.
† Significantly higher than with the untreated serum TOR (P<0.05).
‡ Significantly lower than with the untreated serum DES (P<0.01).

Table 4. Role of absorption of circulating antigens on the cytotoxic Ab in monkey infection

<table>
<thead>
<tr>
<th>Serum</th>
<th>% Cytotoxicity*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>With complement</td>
</tr>
<tr>
<td></td>
<td>Without complement</td>
</tr>
<tr>
<td>Infected monkey serum</td>
<td></td>
</tr>
<tr>
<td>untreated</td>
<td>15.3±2.0</td>
</tr>
<tr>
<td>absorbed</td>
<td>98.4±1.2†</td>
</tr>
<tr>
<td>Normal monkey serum</td>
<td></td>
</tr>
<tr>
<td>untreated</td>
<td>23.8±3.5</td>
</tr>
<tr>
<td>absorbed</td>
<td>21.3±3.4</td>
</tr>
<tr>
<td></td>
<td>1.2±0.4</td>
</tr>
<tr>
<td></td>
<td>4.3±2.3</td>
</tr>
</tbody>
</table>

* Mean of two experiments performed in triplicate (± s.e.m.).
† Significantly higher than with untreated serum (P<0.001).
Discussion

Little attention has been paid to the study of complement-dependent cytotoxic antibody in human schistosomiasis (Capron et al. 1973, 1974, 1977, Smith & Webbe 1974). Since, no convincing evidence of a protective effect against Schistosoma infection has been provided. The present studies were undertaken to investigate the possible relationships between the presence of this complement-dependent cytotoxic antibody and the levels of circulating Schistosoma antigens, as evaluated by a technique recently described (Carlier et al. 1980c).

This study has confirmed an earlier report (Capron 1974) showing a higher number of positive cytotoxic sera in Brazilian patients than in African patients. This difference may be explained by possible variations in the strain of *Schistosoma mansoni* from Africa and Brazil, or by differences in the intensity of infection. It should be noticed however that the percentage of cytotoxicity in the positive Brazilian sera was less than that obtained in our previous work (Capron et al. 1977) but in the present study, only patients with a mild form of schistosomiasis were selected. The comparison between the levels of cytotoxic Ab in sera from the infected mothers at the delivery and in the umbilical cords from their newborn children indicated the likely passage of cytotoxic Ab through the placenta. These results are in agreement with previous findings concerning the IgG nature of the complement-dependent cytotoxic Ab in man (Capron et al. 1977).

Detection of cytotoxic Ab and circulating soluble antigens (CSA) in the same human sera has revealed an inverse relationship between these two parameters. In fact, the presence of total CSA is associated in 94% of cases with the absence of cytotoxic Ab. It is also noteworthy that with a technique allowing the detection of specific *Schistosoma mansoni* antigen "4", that this antigenic fraction was absent in 83% of the sera giving a cytotoxic activity. These observations suggest that circulating *Schistosoma mansoni* antigens may have a blocking effect on the complement-dependent cytotoxic antibodies, particularly in a complexed form, since the ultracentrifugation pellet of infected human serum could decrease the cytotoxic activity. Moreover, these findings should be related to the detection of complexed *Schistosoma mansoni* antigen "4" in both human (Bout et al. 1977) and murine schistosomiasis (Santoro et al. 1979). In fact, this specific antigen appears to be one of the major complexed antigen present in schistosomiasis (Santoro et al. 1979).

The kinetic study of the presence of cytotoxic Ab in five *Schistosoma mansoni* infected patas monkeys revealed a very high level of cytotoxicity after 2–3-month infection. The presence of lethal antibody has already been reported by Clegg & Smithers (1972) in the rhesus monkey, but in this last model only a very low level of cytotoxicity was detected until the 4th month. Moreover, the maximum level of cytotoxic activity in all the infected rhesus monkeys was inferior to that obtained
in *Erythrocebus patas*. A possible reason for these differences may rely upon two facts: either the infective dose (1000 cercariae for *Erythrocebus patas* compared to 175 cercariae in the rhesus) or the different susceptibility of these two monkey strains. The rhesus monkey is an unusual host which is able to develop a solid resistance against a challenge infection (Smithers & Terry 1965) whereas the patas monkey seems to be a normal host, naturally infected with *Schistosoma mansoni* (Kuntz, Huang & Moore 1977) and one which does not seem to be protected against a challenge infection (Sellin *et al.* unpublished results).

The use of a sandwich radioimmunoassay (Carlier *et al.* 1980c) allowed a kinetic study of CSA in monkeys. When the evolution of cytotoxic antibodies and total CSA was compared, the same inverse relationship between these two parameters was observed as in the human sera. It was therefore interesting to study in this monkey infection the blocking effect of circulating antigens or immune complexes. Using an immunosorbent prepared with antibodies directed against CSA it was possible to show a very important increase of the cytotoxic activity in the antigen-absorbed serum.

The present studies support the hypothesis that blocking factors associated with complexed *Schistosoma mansoni* circulating antigens inhibit the cytotoxic activity of complement-dependent cytotoxic antibody in Primate infections. Three different mechanisms might be responsible for this inhibitory effect. Firstly, CSA could be complexed to the cytotoxic Ab. This seems unlikely, since ultracentrifugation and absorption experiments have shown that the cytotoxic Ab was still detected in the supernatant or in the absorbed serum when CSA was removed. Another mechanism could be the complexing of CSA to antibodies different from the cytotoxic antibodies, resulting in a blocking effect due to a competition for antigenic sites on the worm surface between the two antibodies or to a consumption of complement. This second possible mechanism also seems improbable, since in this case the antibodies present in the CIC should be in antibody excess which is rather unusual. The removal of complement by the immune complexes is unlikely as a large excess of complement is used for the cytotoxicity assay. A third possible mechanism has arisen from the recent work by Torpier, Capron & Ouaisi (1979) showing the presence of Fc receptors on the schistosomula surface. Immune complexes of antibody and circulating antigens could therefore bind to these Fc receptors by the Fc fragment of their immunoglobulin component and thus have a blocking role on the subsequent fixation of the lethal antibody (mainly by steric hindrance). Such possibilities are presently under investigation.

The existence of inhibiting immune complexes has already been proposed in other cell-mediated cytotoxicity mechanisms. Possible examples are the blocking activity associated with the serum of tumour-bearing individuals (Sjögren *et al.* 1971, Baldwin, Embleton & Robins 1973). The coexistence of specifically cytotoxic lymphocytes and blocking serum factors has also been detected in some conditions (Hellström & Hellström 1970). The antibody-dependent cell-mediated
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Cytotoxicity mechanisms can also be inhibited by immune complexes (MacLennan 1972). More recently, the inhibitory role of circulating immune complexes on the cytotoxicity of eosinophils against schistosomula has been reported in human and in rat schistosomiasis (Butterworth et al. 1977, Capron, Torpier & Capron 1979). These results, associated with other work on circulating immune complexes (Santoro et al. 1978a) allow us to point out the possible competition between antibody in a free or in a complexed form in the three cytotoxicity mechanisms identified in human, in monkey, in rat schistosomiasis and involving complement-dependent IgG (Capron et al. 1973, 1977, Clegg & Smithers 1972, Capron et al. 1974); IgE-dependent macrophages (Capron et al. 1975, Joseph et al. 1978); and IgG-dependent eosinophils (Butterworth et al. 1975, 1976, Capron et al. 1978).

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