Cytotoxicity of human and baboon mononuclear phagocytes against schistosomula *in vitro:* induction by immune complexes containing IgE and *Schistosoma mansoni* antigens

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SUMMARY

Normal human blood monocytes, pre-incubated at 37°C with sera from patients infected with *Schistosoma mansoni,* strongly adhered to *S. mansoni* schistosomula *in vitro,* whereas no significant adherence was induced by sera from uninfected individuals. Comparable adherence occurred with normal baboon blood monocytes or peritoneal macrophages when these cells were incubated with sera from *S. mansoni*-infected baboons. Adherence of macrophages to schistosomula was associated with damage to the larvae, as estimated by a ^{51}Cr release technique. Neither adherence nor cytotoxicity was induced by pre-incubation of the schistosomula, instead of the monocytes, with immune serum. The relevant factor in immune serum was heat-labile, but was not a complement component. Absorption and ultracentrifugation experiments showed that immune complexes, containing *S. mansoni*-specific IgE antibody and soluble parasite antigens, produced monocyte or macrophage adherence and cytotoxicity. Similar observations have been reported previously in the rat model. Since the production of large amounts of IgE is a predominant feature of schistosome infections in man and experimental animals, it is possible that this new mode of mononuclear phagocyte activation could act as an immune effector mechanism against *S. mansoni.*

INTRODUCTION

Susceptible hosts of *Schistosoma mansoni* develop, to a varying extent, a resistance to reinfection attributable to acquired immunity. In man, in whom adult worms may survive for more than 25 years, a decrease in the parasite population is observed with time, even in patients exposed to reinfection in endemic areas (Smithers & Terry, 1969). In some animals, primary infection is followed by a state of resistance to reinfection, which seems to be complete in the Rhesus monkey (Smithers & Terry, 1965), temporary in the rat (Maddison *et al.,* 1970) and only partial in the mouse (Hunter *et al.,* 1962).

This acquired resistance is mainly directed against immature worms, shortly after their penetration into the skin of the infected host. In recent years, several immune mechanisms have been reported to kill *S. mansoni* larvae *in vitro.* One such mechanism involves a cell-independent, complement-dependent cytotoxic IgG antibody (Clegg & Smithers, 1972; Capron *et al.,* 1974). It seems likely, however, that cooperation between antibody and a non-sensitized effector cell could also represent an efficient mechanism in acquired resistance. Recent experiments have provided some evidence for the interaction of IgG antibodies with various cells, including neutrophils in the rat and guinea-pig (Dean, Wistar & Murrell, 1974); eosinophils in man (Butterworth *et al.,* 1975), the baboon (Butterworth *et al.,* 1976), the rat

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(Capron *et al.*, 1978) and the mouse (Mahmoud, Warren & Peters, 1975); and macrophages in the rat (Perez & Smithers, 1977).

More recently, it has been reported that specific IgE antibody, which is produced in large amounts during schistosome infections, appears to activate normal rat macrophages, leading to the killing of schistosomula *in vitro* (Capron *et al.*, 1975). When adherent peritoneal exudate cells from uninfected Fischer rats were incubated with serum from syngeneic rats which were immune to reinfection, subsequent addition of *S. mansoni* schistosomula was followed by the adherence of peritoneal cells to the schistosomula. Adherent cells were identified as macrophages, while the serum factor inducing macrophage activation, adherence and cytotoxicity was shown to be composed of immune complexes between *S. mansoni*-specific IgE and circulating parasite antigens (Capron *et al.*, 1976, 1977).

The present paper extends the observation of mononuclear phagocyte activation and cytotoxicity induced by IgE immune complexes to human and baboon monocytes and to baboon peritoneal macrophages. Sera from infected patients and baboons were able to induce adherence and cytotoxicity of normal monocytes and macrophages against *S. mansoni* larvae. As in rats, the serum factor involved was heat-labile, complement-independent and contained IgE antibody.

MATERIALS AND METHODS

Animals. Male Kenyan baboons (*Papio anubis*) were caught locally, weighing 4–5 kg. Heavy natural infection with *S. mansoni* was excluded by a series of eight stool examinations for schistosome eggs. Infection and bleeding were carried out according to the method described by Sturrock, Butterworth & Houba (1976).

Parasite. A Kenyan strain of *Schistosoma mansoni* was recovered from naturally infected *Biomphalaria pfeifferi*, and was maintained by passage in uninfected mice and snails which had been bred in the laboratory. Schistosomula were prepared by the method of Clegg & Smithers (1972) and labelled according to the technique previously described (Butterworth *et al.*, 1976).

Sera. Except when otherwise stated, non-inactivated sera from patients with stools containing *S. mansoni* eggs, and sera from experimentally infected baboons, bled at various times after infection, were used for cell activation. Normal sera and sera from patients with filariasis, fascioliasis, hydatidosis, trichinosis and amebiasis were used as controls for the specificity of monocyte cytotoxicity.

Cell cultures. For baboon and human monocytes, 15 ml of heparinized blood were diluted with 15 ml Eagle's minimum essential medium (MEM) containing 20 mM HEPES, 100iu penicillin/ml, 100 μg streptomycin/ml and 120 ng fungizone/ml (GIBCO, Grand Island, NY). The diluted blood was layered on to a mixture of 7% Ficoll (Pharmacia, Uppsala, Sweden) and 10% sodium metrizoate (Nyegaard, Oslo, Norway). Centrifugation was carried out at 4°C for 30 min at 300 g. The interface, consisting mainly of monocytes and lymphocytes, was washed twice in 40 ml MEM. The pellet was resuspended in MEM containing either 15% heat-inactivated foetal calf serum for baboon monocytes, or 20% heat-inactivated autologous serum for human monocytes, to a final dilution of 2.5×10^6 monocytes per ml. The cell suspension was seeded into flat-bottomed microplates (Nunclon, Roskild, Denmark), 0.2 ml per well, and cultured at 37°C in humidified airtight plastic boxes. After 3 hr, non-adhering cells were removed by energetic washing of each well, and the adherent population was then incubated overnight in the same medium.

For baboon peritoneal macrophages, a FG·10 Ryle's tube (Pharma–Plast, Sydney, Australia) was introduced, through a 1 cm abdominal incision, in the peritoneal cavity of a normal baboon, sedated with 1 mg/kg Sernylan (Parke–Davis, Detroit, Michigan). From 200 to 300 ml heparinized (50 u/ml) Hanks's balanced salt solution (GIBCO, Grand Island, NY) were injected through the Ryle's tube. By gentle massage and slight compression, the washing medium was withdrawn through the tube into a flask previously cooled in an ice-water bath. The yield was generally 60–75% of the injected medium. The cell suspension was centrifuged at 800 g for 5 min at 4°C. The pellet was resuspended in 15 ml MEM and layered on to a Ficoll–Metrizoate mixture as described above for blood monocytes. The final macrophage-rich pellet was resuspended in MEM with 15% inactivated foetal calf serum and cultured as indicated for monocytes.

Cell activation and cytotoxicity. Overnight cultures of macrophages or monocytes were washed and incubated with MEM containing 20% of the serum to be tested for activation and immune adherence. After incubation for 5 to 7 hr, approximately fifty ^{51}Cr-labelled schistosomula were added to each well. These preparations were then cultured overnight. Each diluted serum preparation was also tested, without cells, for direct toxicity towards schistosomula. Immune adherence and cytotoxicity were measured according to the procedure previously described (Joseph, Dessaint & Capron, 1977). Briefly, macrophage adherence and schistosomula mortality were estimated by microscopical examination, and the release of chromium from labelled larvae was evaluated. For this purpose, half of each supernatant was collected, the other half being taken out with the pellet. Both supernatant and pellet were counted in a Packard gamma counter and the cytotoxic activity of mononuclear phagocytes in each well was expressed as the percentage of total chromium released from the larvae into the supernatant. All assays were done in quadruplicate and analysed by Student's *t*-test.

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Immunosorbents. An IgG fraction of goat anti-human IgE, specific for the ε-chain, was coupled to Cyanogen bromide-activated Sepharose 4B (Pharmacia, Uppsala, Sweden) according to Axen, Porath & Ernback (1967). Anti-human IgG immunosorbent was also tested as a control. Sera were absorbed on the columns for 1 hr, then washed through with physiological saline and used at the appropriate dilution without further treatment.

Ultracentrifugation. Sera from *S. mansoni*-infected patients were submitted to 120,000 *g* centrifugation at 4°C for 3 hr. Just under the 0·2 ml lipidic layer, the upper two-thirds of the supernatant were collected and the lower third discarded. The pellet was then resuspended to the initial volume either in normal homologous serum, or in heat-inactivated (1 hr 56°C) foetal calf serum.

Anticomplement sera. Anti-human complement rabbit immune sera (Behring Werke A.G., W. Germany) were used. Anti-C3/C3c, anti-C4 and anti-C3-activator were dialysed against MEM overnight at 4°C, and were tested by direct addition to macrophage cultures, at a final dilution of 5% in MEM containing either 15% *S. mansoni*-infected baboon or human serum, or 15% inactivated foetal calf serum for controls, for their ability to inhibit the induction and expression of macrophage cytotoxicity.

RESULTS

Baboon macrophage and monocyte activation

After a 5 hr pre-incubation of normal baboon peritoneal macrophages in the serum of experimentally infected animals, the addition of *S. mansoni* larvae led to a high level of macrophage adherence to schistosomula between 3 and 20 hr, with some larvae being completely coated with cells (Fig. 2). The same result was obtained with blood monocytes, pre-incubated in these immune sera. No such adherence occurred after pre-incubation of either cell type in normal baboon serum. The percentages of schistosomula bearing ten to fifteen cells and of completely coated schistosomula are given in Table 1,

TABLE 1. Immune adherence and cytotoxicity against chromium-labelled *S. mansoni* schistosomula induced in normal baboon blood monocytes by different baboon sera*

| | Chromium release (%) | | Dead schistosomula (%) | Schistosomula(%) | | Total % of schistosomula with adherent cells |
	With monocytes	Without monocytes		With 10 to 15 adherent cells	Completely coated	
Normal serum	37·5 ± 4·9	34·5 ± 0·8	1 ± 0·8	15 ± 2·6	0	15 ± 2·6
One year immune serum†	53·5 ± 6·7‡	34·0 ± 2·9	54 ± 1·8	47 ± 3·5	47 ± 3·5	94 ± 2·8
Heated immune serum	28·9 ± 2·8	22·0 ± 2·3	1 ± 0·7	18 ± 2·0	0	18 ± 2·0

* Means of quadruplicates ± s.d.
† Baboon infected 1 year before with 3 × 500 cercariae at monthly intervals.
‡ Significantly higher than normal serum ($P < 0.025$).

showing that complete coating was only observed when monocytes were incubated with immune serum. The total percentage of schistosomula with adherent cells was six times greater with immune than with normal serum. The cytotoxicity of activated monocytes against larvae, expressed as dead schistosomula on the basis of light microscopy, or as chromium release from labelled schistosomula, was also significantly greater with sera from infected animals than with control sera. The activating factor of immune serum was heat-labile, since both cytotoxicity and cell adherence fell to the normal serum level when monocytes were incubated with heated immune serum (3 hr at 56°C). The decreased cytotoxicity observed in preparations containing heated immune serum without cells may be attributable to the presence of complement-dependent IgG antibodies in such sera. These have been demonstrated in samples from infected patients (Capron *et al.*, 1974). The finding that non-inactivated normal serum, without monocytes, induces more release than heated immune serum (34·5% *vs* 22·0%) is probably due to the fact that schistosomula can fix and activate complement directly by the alternative pathway (Sher, 1976).

Sera from animals infected approximately one year previously with 1000 cercariae in a single infection,

or with 500 cercariae in three successive infections at monthly intervals, gave higher levels of immune adherence and of cytotoxicity than sera from baboons infected for shorter periods.

Pre-incubation of schistosomula with immune serum failed to induce immune adherence and cytotoxicity of unincubated macrophages: the chromium release was always below 25%. This percentage represents the spontaneous release from larvae after an overnight culture in MEM containing 20% foetal calf serum. Since the activating factor was heat-labile, it was possible that complement might act in this process. Table 2 provides some indication that the heat-labile factor was not one of the complement

TABLE 2. Failure of anti-complement sera to inhibit immune serum mediated activation of baboon peritoneal macrophages against *S. mansoni* larvae*

| | Dead schistosomula (%) | Schistosomula (%) | | Total % of somula with adherent cells |
		With 10 to 15 adherent cells	Completely coated	
Normal serum	13·4 ± 6·4	10·9 ± 0·3	0	10·9 ± 0·3
Immune serum	41·9 ± 2·9	20·0 ± 12·8	57·1 ± 12·3	77·1 ± 0·5
Immune serum† + anti-C4	56·0 ± 6·0	51·0 ± 1·3	38·0 ± 0·7	89·0 ± 2·1
Immune serum† + anti-C3	71·9 ± 5·2	48·9 ± 5·9	34·4 ± 3·4	83·3 ± 2·5
Immune serum† + anti-properdin	51·9 ± 9·0	46·7 ± 8·8	12·0 ± 2·4	58·7 ± 6·4
Anti-C4†	15·0 ± 4·5	0	0	0
Anti-C3†	17·4 ± 9·7	2·0 ± 2·8	0	2·0 ± 2·8
Anti-properdin†	20·4 ± 11·8	0	0	0

* Means of quadruplicates ± s.d.

† Dialysed anti-complement sera were tested by direct addition to macrophage cultures at a final 5% dilution in 15% immune or foetal calf serum.

components. The mortality and cell adherence produced by macrophages and immune serum were not significantly decreased by simultaneous incubation with anti-C4, anti-C3 or anti-properdin (C3 activator) sera. At the concentration used (5%), anti-complement sera only produced a slight decrease in the number of completely coated schistosomula, and no decrease in the total percentage of larvae with adherent cells.

Human monocyte activation

Using human monocytes, forty-one different sera from *S. mansoni* infected patients were tested for their ability to mediate monocyte cytotoxicity to schistosomula. With a few exceptions, these sera showed a marked capacity to activate monocytes, leading to a level of chromium release from schistosomula similar to that observed with immune baboon serum (Fig. 1). Coated schistosomula had the same appearance as those incubated with baboon cells (Fig. 3), but the total percentage of schistosomula with adhering human monocytes was lower than that obtained with baboon monocytes or macrophages. None of the nineteen sera from patients with other parasitic infections and none of the thirteen normal sera induced a significant level of monocyte adherence or cytotoxicity.

The adherent blood leucocytes had been cultured for 20 hr at the time of activation with immune serum and for more than 24 hr by the time that schistosomula were added. This procedure, and the extensive cell washing, enriched blood monocytes to more than 95%, as judged by Giemsa staining. Ultrastructural studies of cells adhering to schistosomula confirmed that monocytes were closely involved in this effector mechanism (Fig. 4).

The most impressive feature of the early events which occurred when larvae were mixed with human monocytes activated with immune serum, was the chemotactic migration of monocytes towards their target, an effect visible by 1 hr after the beginning of the incubation (Fig. 5). Monocytes incubated with
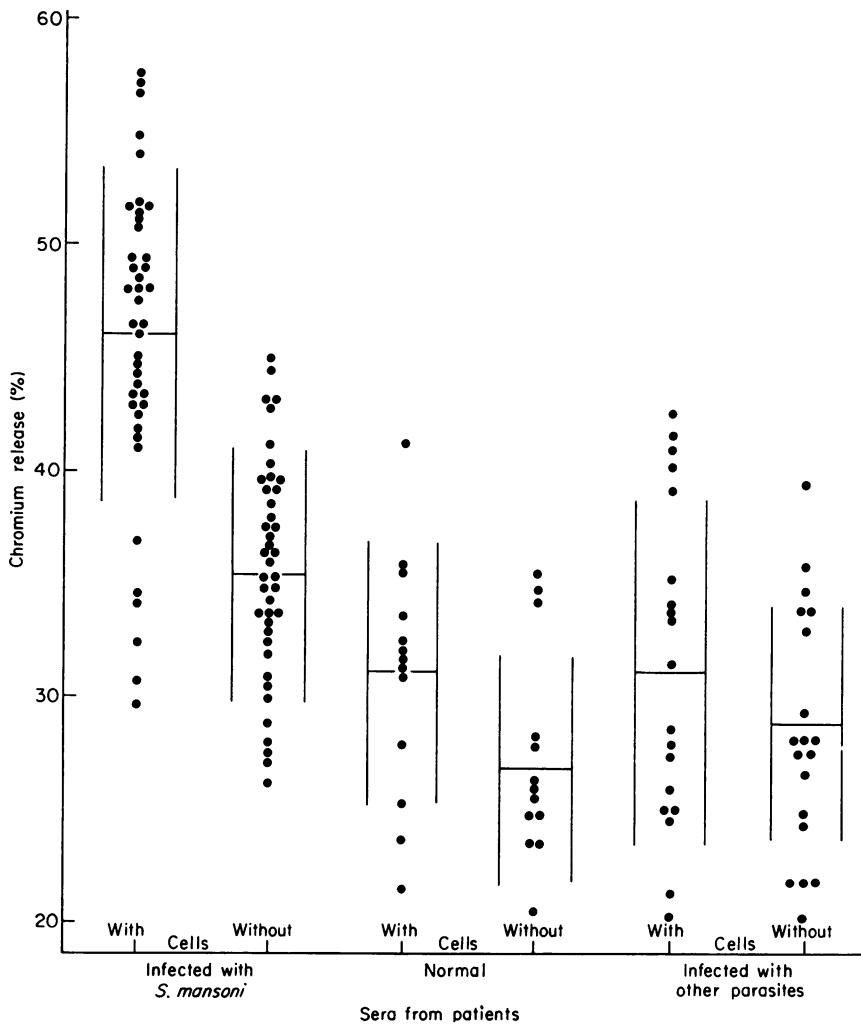
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FIG. 1. Cytotoxicity of human monocytes against *Schistosoma mansoni* schistosomula, induced by sera from patients with various infections. The chromium release observed with cells activated in sera from patients with schistosomiasis is significantly different from the release in the same medium without cells ($P = 1.5 \times 10^{-6}$). The nineteen non-*Schistosoma* infections were filariasis, trichinosis, fascioliasis, hydatidosis and amebiasis.

normal serum did not show this active process and were spread at random on the plastic dish, even in the area of the target schistosomulum.

Human monocytes were also sensitive to activation by immune baboon serum and incubation in such sera led to significant percentages of completely coated schistosomula. Chromium release, however, was lower than with monocytes incubated with immune human serum ($43.0\% \pm 5.7$).

The humoral factor involved in activation and cytotoxicity

The heat-lability of the activating humoral factor for macrophages and monocytes, which was also shown to be complement independent in earlier experiments, suggested that IgE was involved in the immune adherence and cytotoxic process. To test this assumption, IgE-absorption of human immune serum by goat anti-human IgE was carried out. Immune adherence and cytotoxicity fell to control levels with IgE-depleted human serum, while the capacity to activate cells was not significantly depressed by the passage of immune serum through an anti-human IgG immunosorbent (Table 3). Although
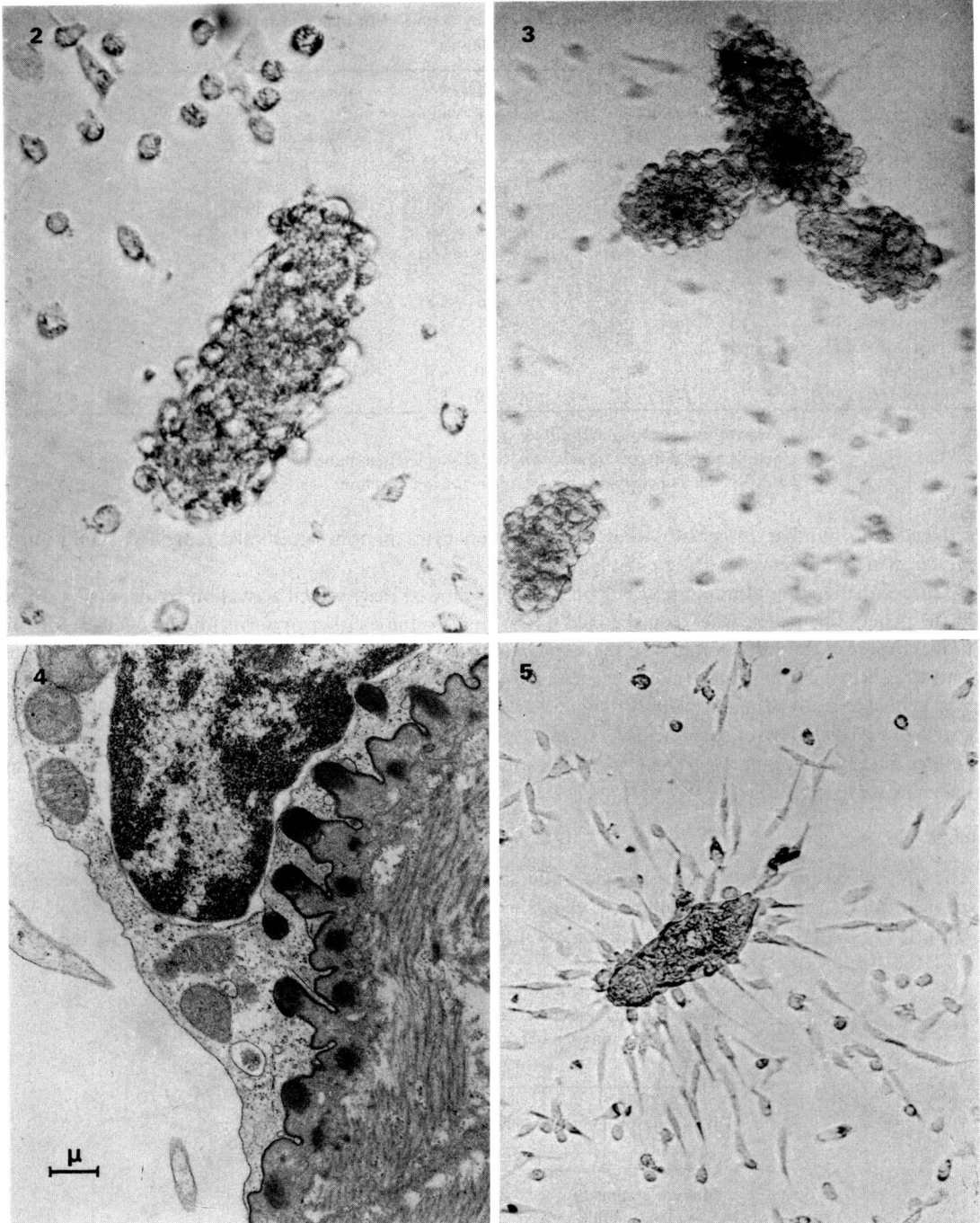
FIG. 2. *Schistosoma mansoni*-schistosomulum completely coated with normal baboon peritoneal macrophages pre-incubated for 6 hr in immune baboon serum. This appearance develops between 6 to 12 hr after mixing activated macrophages with parasite larvae, but the picture shown here was taken after a 16-hr (overnight) incubation.

FIG. 3. *Schistosoma mansoni*–schistosomula coated with normal human monocytes activated for 6 hr by serum from an infected patient.

FIG. 4. Electron micrograph of a human monocyte activated with immune serum, adhering to a schistosomulum, 2 hr after the interaction of targets with effector cells. This particular picture of close contact between effector cell and target does not show the typical azurophil particles which are characteristic of human blood monocytes, but these were visible in the majority of cells.

FIG. 5. Typical migration of activated human monocytes towards a schistosomulum, 1 hr after the beginning of incubation.

TABLE 3. Adherence, death and chromium release induced by serum-incubated human monocytes against *S. mansoni*-schistosomula*

	Schistosomula with adherent cells (%)	Dead schistosomula (%)	Chromium release (%)	
			With monocytes	Without monocytes
Normal serum	18·0 ± 5·2	21·7 ± 4·7	36·1 ± 5·7	36·4 ± 2·0
Immune serum	75·3 ± 5·5†	65·1 ± 6·0†	53·0 ± 3·6†	37·4 ± 5·9
IgE-depleted immune serum	14·0 ± 4·6	23·3 ± 3·0	37·0 ± 9·1	34·8 ± 5·8
IgG-depleted immune serum	70·3 ± 4·5†	56·3 ± 12·1†	50·0 ± 4·9†	34·0 ± 3·8
Ultracentrifugation pellet‡				
Unheated	52·7 ± 6·6†	42·6 ± 5·8†	51·0 ± 8·7†	36·0 ± 6·0
Heated (56°C 3hr)	14·4 ± 2·7	10·1 ± 2·1	35·4 ± 4·4	27·4 ± 2·3
Ultracentrifugation supernatant				
Unheated	25·3 ± 4·9	27·0 ± 6·0	42·0 ± 3·3	38·5 ± 8·0
Heated (56°C 3hr)	17·0 ± 2·7	20·0 ± 5·4	31·1 ± 4·8	23·4 ± 3·3

* Mean of two sera in quadruplicate ± s.d.

† Significantly different from normal or IgE-depleted immune serum ($P < 0·001$).

‡ Resuspended in normal human serum to the initial volume.

reduced, the number of schistosomula bearing monocytes in this latter case remained significantly higher than that observed with IgE-depleted serum.

Ultracentrifugation of immune serum at 120,000 *g* showed that the cell activation factor was localized in the pellet. The pellet, when resuspended to the initial volume either in normal homologous serum or in inactivated foetal calf serum, gave the same cytotoxicity as untreated immune serum. The monocyte activating factor in the resuspended pellet was heat-labile, as in whole serum, since heating at 56°C for 3 hr abolished both adherence and cytotoxicity. Both unheated and heated supernatants failed to induce a significant level of cytotoxicity (Table 3). Absorption of immune human serum with soluble *S. mansoni* antigen in amounts ranging from 1 to 10 mg/ml progressively decreased monocyte cytotoxicity to an insignificant level (Table 4).

DISCUSSION

The present results demonstrate that incubation *in vitro* of normal human monocytes in sera from *S, mansoni*-infected individuals is followed, as in the previously described rat model (Capron *et al.*, 1975. 1976, 1977; Joseph *et al.*, 1977), by cell activation. This process of cell activation is revealed by the rapid

TABLE 4. Effect of absorption of immune human serum by increasing amounts of a saline extract of adult *S. mansoni* worms on human monocyte cytotoxicity against labelled schistosomula*

Serum for monocyte incubation	% chromium release
Untreated immune serum	51·0 ± 5·6
Immune serum absorbed with	
S. mansoni soluble antigen†	
1 mg/ml serum	48·0 ± 4·4
2 mg/ml serum	42·0 ± 3·1
4 mg/ml serum	37·4 ± 2·4
10 mg/ml serum	35·5 ± 3·9
Normal serum	31·4 ± 2·7

* Mean of quadruplicates ± s.d.

† 1 hr incubation with antigen followed by 30 min centrifugation at 8000 *g*.

adherence of activated monocytes to schistosomula. Similar observations were made when normal baboon monocytes or peritoneal macrophages were incubated in immune baboon sera. Ultrastructural observations have shown that, as in the rat model, the adhering population consisted exclusively of mononuclear phagocytic cells. The lack of phagocyte adherence with larvae pre-incubated in immune serum rules out an opsonization mechanism of the target.

This adherence step is followed by a cytotoxic event which is manifest as a highly significant increase in chromium release when compared to the controls. A good correlation was observed between chromium release and microscopical estimates of the death of schistosomula. In most cases, significant differences were observed between immune sera alone and immune sera with monocytes, indicating an active role of the monocyte in cytotoxicity.

Absorption experiments, using anti-IgE and anti-IgG columns, showed that IgE molecules were involved in monocyte adherence and cytotoxicity. This finding confirms our previous observations in the rat, and thereby extends the interest of this new mechanism of macrophage activation to human schistosomiasis.

The various experiments reported in the present paper show a very close similarity with the results obtained when rat macrophages were used (Capron *et al.*, 1977; Joseph *et al.*, 1977). The possibility that IgE-immune complexes may be involved is also supported by preliminary observations that human monocyte activation can be induced when ultracentrifuged pellets of immune serum are isolated and resuspended in normal serum. It should also be stressed that the use of peroxidase-labelled anti-human IgE has, as in the rat macrophages, allowed the demonstration of IgE binding on to the monocyte surface. The different parameters and specificity of monocyte IgE receptors will be discussed elsewhere.

From these results, it may be considered possible that in human schistosomiasis the IgE-monocyte system might represent an effector mechanism of immunity. The observation that monocyte activation was not initiated by all infected human sera appears, in this respect, encouraging. Further studies of correlations with other possible parameters of immunity in human schistosomiasis are required. One important question yet to be answered is probably the understanding of the relationship between the *in vitro* mechanism described here and the IgG-eosinophil system also reported in human schistosomiasis (Butterworth *et al.*, 1976).

Although it is difficult, at our present stage of knowledge, to extrapolate from experimental observations in the rat to the human situation, it is possible that IgE molecules play an important role in the immune response to schistosome infection in man as well as in experimental animals.

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