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FURTHER DEVELOPMENT OF THE BABOON AS A MODEL FOR ACUTE SCHISTOSOMIASIS

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Baboons develop a syndrome, including eosinophilia and transient fever, after infection with carcariae of Schistosoma mansoni *that is consistent with the human syndrome of acute schistosomiasis. Radiotelemetry can be used to follow the course of fever in infected baboons. Individual variations in intensity of disease were noted in baboons. These symptoms and signs were more closely linked to the onset of oviposition by the newly matured worms than they were to the presence of migrating schistosomula or maturing worms. The baboon is concluded to be a suitable and useful model for human acute schistosomiasis mansoni.*

Key words: *Schistosoma mansoni* – experimental model – acute stage – baboon

Acute schistosomiasis (A.S.) or Katayama fever is a poorly understood, under-investigated phase of schistosomiasis whose importance is easily documentable for urbanites, tourists, and other visitors to transmission sites. The true importance of the acute stage to indigenous people in endemic areas is controversial: Neves (1986) considered it to be under-estimated for the reasons of inadequate medical attention and confusion with other common febrile diseases. Others believe A.S. to be less severe or even absent in these peoples. Many other unanswered questions about A.S. remain, from the most fundamental to the most applied; e.g. what is the relationship between intensity of cercarial exposure and intensity of disease? What mechanisms underlie the fever and other symptoms of A.S.? How are the symptoms of A.S. best managed (Lambertucci et al., 1989)?

An impediment to progress in understanding the etiology of A.S., and to its eventual management, has been the lack of, or at least the under-utilization of animal models. Smithers & Doenhoff (1982) may have been too negative in stating that no well-characterized experimental analogue of Katayama fever exists, in view of a classical parasitological and pathological study of 25 grivet monkeys that had been experimentally exposed to cercariae of *Schistosoma mansoni* or *S. haematobium* (Fairley, 1920). Nevertheless, a modern characterization of animal models would be useful. We presented evidence at the Second International Symposium on Schistosomiasis (1989, Belo Horizonte, Brazil) to support the hypothesis that the baboon (*Papio cynocephalus*) develops symptoms consistent with human A.S. after exposure to the cercariae of *S. mansoni* (Damian et al., 1989). This unpublished evidence was gathered during the course of studies designed to examine various aspects of chronic schistosomiasis and immunity to *S. mansoni* in baboons (e.g., Damian et al., 1974). In order to more fully characterize the baboon as a model for the human disease, we have recently begun a more systematic study of the early events in baboons after experimental exposure to *S. mansoni* cercariae. The present paper combines the data presented at the Second International Symposium with the first results of our new study, which considerably reinforce our contention that this species will serve adequately this purpose.

MATERIALS AND METHODS

Baboons – Baboons (*Papio cynocephalus*) used were purchased from the Southwest Foun-

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dation for Biomedical Research (San Antonio, TX). All except two (nos. S-628 and 1368) had been born in captivity in the United States. The exceptions were proved free of previous contact with schistosomes by fecal examination and serology. The animals ranged in age from 9 months to 6 years of age when first used. They were individually caged with free access to water and were fed with Purina monkey chow and fresh fruit. Animal care and experimentation practices at the University of Georgia are regularly monitored and evaluated by the University's Animal Care and Use Committee in order to ensure compliance with relevant federal regulations and guidelines.

Parasitology – Baboons were percutaneously exposed once to 100, 340, or 1,000 cercariae of a Kenyan strain (KEB) of *S. mansoni* maintained in baboons and *Biomphalaria pfeifferi* snails (Damian et al., 1972). Time of patency was determined by the Ritchie formalin-ether sedimentation technique (Ash & Orihel, 1987) on daily stool samples. Quantitative stool egg counts were done by the Bell technique as modified (Cheever & Powers, 1968). Adult worms were recovered by separate perfusion of liver and intestines, followed by careful visual inspection of the intestinal mesenteric veins for unperfused worms.

Hematology – Animals were bled at least twice prior to infection for base-line hematologic data and normal sera. They were then periodically bled until terminated. Complete and differential blood counts and serum clinical chemistry (alkaline phosphatase [AP], aspartate aminotransferase [AST/GOT], and alanine aminotransferase [ALT/GPT] were done on each sample.

Lymphocyte responses – Peripheral blood mononuclear cells (PBMC) were prepared as described (Damian et al., 1984) and stimulated with 10 µg soluble egg antigen (SEA, Boros & Warren, 1970) for 6 days in lymphocyte transformation assays conducted as described (Damian et al., 1984). Data are presented as ΔCPM (X ± SD), calculated as CPM of stimulated cultures minus CPM of unstimulated cultures. CPM (X ± SD) of unstimulated cultures (background) ranged from 259 ± 69 (Baboon # 6580) to 811 ± 620 (Baboon # 6663). The *in vitro* granuloma assay (Doughty & Phillips, 1982) using PBMC was done essentially as described by its originators except for the omission of adult worms from the cultures. 1×10^6 baboon PBMC were cultured in 1 ml of RPMI-1640 medium containing 10% fetal bovine serum with 60 *S. mansoni* eggs (produced by separately cultured, paired worms) in 24-well tissue culture plates at 37 C with 5% CO_2. Granuloma index (G.I.) score derivation was modified slightly from Doughty et al., (1984) and based on *in vitro* periovular cellular reactivity, evaluated after 7 days with an inverted microscope. For each well of the triplicated culture, cellular reactions to 50 unselected eggs were examined and a G.I. was assigned for each egg according to the following criteria: 1 – no reaction; 2 – one to five cells binding to the egg; 3 – six to ten cells binding to the egg; 4 – more than ten cells binding to the egg; 5 – one layer of cells surrounding the egg; 6 – more than one layer of cells around the egg. G.I.'s presented are the grand means of the triplicate cultures ± SEM's.

Radiotelemetry – Baboons were implanted under the trapezius muscle with a temperature-activity radiotransmitter (PhysioTel® Model TA-D70, Data Sciences, Inc., St. Paul, MN, 55113, U.S.A., purchased from Mini-mitter Co., Sun River, OR, 97707, U.S.A.) while under general anesthesia. A receiver (Model RA2000, RA2310, or RA2610, ® Data Sciences, Inc., St. Paul, MN, 55113, U.S.A., purchased from Mini-mitter Co., Sun River, OR, 97707, U.S.A.) was mounted on a plexiglass sheet over the top of each cage. Receivers were connected through a Model BCM-100 Consolidation Matrix (® Data Sciences, Inc., St. Paul, MN, 55113, U.S.A., purchased from Mini-mitter Co., Sun River, OR, 97707, U.S.A.) to a PC computer equipped with Version 4 of the Dataquest III (© Data Sciences, Inc., St. Paul, MN, 55113, U.S.A.) data aquisition and analysis program.

Severity of illness – Hiatt et al. (1979), in an attempt to quantify the severity of acute schistosomiasis in Puerto Ricans, had retrospectively developed an index of severity for the disease. This was based upon assignment of numerical values (scores) to grade the various selected symptoms, including durations of fever, diarrhea, weakness, and abdominal pain, presence or absence of myalgias, arthralgias, blood in the stools, dry coughs, nausea, vomiting, etc. For example, fever lasting up to a week was scored "1", fever lasting from 8-30 days received a score of "2", and fever extending beyond 30 days was scored "3". The index of severity was the arithmetic mean of

all of the individual scores, and ranged from 1.0 to 3.0 in individual patients. Hiatt et al. (1979) used only symptoms in the generation of their severity index, "since physical findings were not available for all patients during the symptomatic phase of their illness".

In developing an index of severity for acute schistosomiasis for experimental baboon infections, we were able to incorporate laboratory data in addition to certain symptoms. On the other hand, some symptoms could obviously not be communicated to us by the baboons. A method for scoring index of severity for baboon acute schistosomiasis, based upon the types of data already obtained or obtainable (from serum samples), is given in Table I.

RESULTS

Eosinophilia – Six young baboons exposed to 100 cercariae showed transient eosinophilia that either preceded or followed the onset of oviposition (Table II). In all cases, eosinophilia was higher after oviposition had begun.

Lymphocyte responses – Six baboons exposed to 340 cercariae had transiently elevated PBMC *in vitro* blastogenic responses to SEA at 2, 4, and in some cases 6 weeks after the onset of oviposition (Table III). Their PBMC *in vitro* granuloma response was also usually elevated after egg laying had begun (Table IV).

Radiotelemetric experiment 1 – Initially, four baboons were implanted with radiotransmitters and then infected after about one month. Because of our inexperience with the system at the time, the radiotransmitters were improperly activated and thus body temperature and activity data were not obtained. However, other desired data were gathered (Table V), enabling us to obtain severity indices, ranging from 1.62 to 2.25, for the four baboons (Table VI). Table VI also reports their worm burdens.

Radiotelemetric experiment 2 – Additional baboons were successfully implanted with properly activated radiotransmitters. This experiment is still in progress as of this writing, and the animals have yet to be terminated and their worm burdens determined. Fig. 1 shows raw temperature outputs from one control (uninfected) and three infected baboons. Uninfected baboons exhibited a circadian body temperature cycle which regularly fluctuated around a mean body temperature, for the four baboons, of 37.0 °C. Fever, manifested mainly as a rise in minimum rather than in maximum body temperatures during the circadian cycle, was observed in all baboons after infection but did not occur in the control baboon, which remained uninfected. Additionally, individual patterns of fever intensities and durations are clearly discernable. The appearance of fever was closely associated with the appearance of eggs in the stools, preceding patency by about five days.

TABLE I

Modified method for scoring severity of baboon acute schistosomiasis

Symptom or sign	Scores[a] Least severe	More severe	Most severe
Duration of fever	(1) 1-7 days	(2) 8-30 days	(3) > 30 days
Duration of diarrhea[b]	(1) none	(2) 1-14 days	(3) > 14 days
Hematochezia	(1) negative	(2) light	(3) heavy
Anorexia	(1) all biscuits eaten	(2) > half but not all eaten	(3) < half eaten
Weight loss[c]	(1) 0-0.5 kg	(2) 0.6-1 kg	(3) > 1 kg
Dry cough	(1) negative	(2) positive	
Dermatitis	(1) negative	(2) positive	
Eosinophilia	(1) negative	(2) pre or post-oviposition	(3) pre + post-oviposition
Liver function[d]	(1) all normal	(2) 1 or 2 elevated	(3) all 3 elevated
Immunoglobulins (IgM and IgG)	(1) neither elevated	(2) either elevated	(3) both elevated
Circulating immune complexes	(1) negative	(2) positive	

a: number in parentheses is the score assigned to the indicated factor.
b: Or onset of diarrhea if short-term experiment.
c: Or percentage of normal weight gain if growing animal is used.
d: Serum AP, AST, and ALT (see Materials and Methods).

TABLE II

Blood eosinophil levels[a] (as percent of total leukocytes) in young[b] baboons exposed to 100 *Schistosoma mansoni* cercariae[c]

Weeks p.i.	Baboon number S-628	A-868	A-962	B-156	B-300	1368	Remarks
Various	N.D.[d]	N.D.	N.D.	N.D.	1	N.D.	
Pre-	2	0	0	0	4	N.D.	
Exposure	2	0	0	0	0	0	
Dates	1	0	0	0	0	0	
0	2	1	0	0	2	3	Exposure day
3	0	2	2	2	0	0	
4	N.D.	0	3	1	0	0	
5	0	1	3	0	0	2	
6	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	Oviposition
7	8	2	24	11	7	7	
8	1	6	20	10	2	1	
9	3	0	8	3	3	4	
10	0	1	1	0	0	2	
12	0	1	2	1	0	2	

a: normal eosinophil values for adult baboons in parent colony: Mean % = 1.08 ± 0.06 SD, range 0-2.3% (Moor-Jankowski et al., 1965); Normal eosinophil values for 6 month-old baboons in parent colony: Mean % = 0.9, range 0-40% (Berchelman et al., 1971).
b: under 2 years of age.
c: all became infected (Damian et al., 1976).
d: N.D. = not done.

TABLE III

Soluble egg antigen (SEA) stimulated *in vitro* blastogenic responses of peripheral blood mononuclear cells from baboons exposed to 340 *Schistosoma mansoni* cercariae

Weeks post-infection	Baboon number 6580	6617	6663	6796	6861	7013
Pre-exposure	107[a] ± 90	-8 ± 220	-241 ± 85	773 ± 579	252 ± 175	29 ± 91
2	1248 ± 557	-22 ± 270	2729 ± 2127	-477 ± 96	-125 ± 35	73 ± 48
4	304 ± 195	63 ± 155	196 ± 174	71 ± 61	36 ± 85	125 ± 86
6 (oviposition)	165 ± 242	131 ± 170	417 ± 279	-119 ± 54	528 ± 547	21 ± 101
8	4799 ± 1253	2460 ± 880	66,247 ± 4560	1160 ± 188	1696 ± 754	1407 ± 550
10	6927 ± 872	7081 ± 2068	95,763 ± 14,860	5326 ± 497	3234 ± 719	982 ± 465
12	594 ± 72	316 ± 162	11,603 ± 3046	145 ± 180	1959 ± 1205	754 ± 561
14	372 ± 177	714 ± 222	2429 ± 178	1097 ± 1451	489 ± 347	294 ± 141

a: data are presented as Δ CPM ($\bar{X}$ ± S.D.) as in Materials and Methods.

DISCUSSION

The data herein presented support our contention that the baboon is a suitable model for human acute schistosomiasis mansoni. Since several hypotheses on the etiology of the A. S. syndrome implicate immunologic mechanisms, part of our thesis is based upon the correspondence of immune responses to early schistosome infections between humans and baboons (Table VII). In addition, fever, the most reliable symptom, and eosinophilia, the most reliable sign, of A.S. in humans (Hiatt et al. 1979; Neves, 1986) were also characteristic of A.S. in baboons.

Hiatt et al. (1979), in their pioneering study, found a strong positive correlation between levels of fecal egg output and index of severity in their series of 26 patients. However, not all

TABLE IV

In vitro granuloma responses to *Schistosoma mansoni* eggs by peripheral blood mononuclear cells from baboons exposed to 340 *S. mansoni* cercariae

Weeks post-infection	Baboon number					
	6580	6617	6663	6796	6861	7013
4	1.8 ± 0.08[a]	1.6 ± 0.09	1.9 ± 0.09	1.8 ± 0.06	1.9 ± 0.08	1.8 ± 0.08
6[b]	1.8 ± 0.08	1.9 ± 0.07	1.7 ± 0.09	2.0 ± 0.05	1.7 ± 0.08	1.8 ± 0.07
8	2.4 ± 0.10	1.9 ± 0.07	2.6 ± 0.11	2.4 ± 0.08	2.2 ± 0.06	2.2 ± 0.08
10	2.4 ± 0.11	1.9 ± 0.08	2.8 ± 0.13	2.4 ± 0.09	2.2 ± 0.08	2.0 ± 0.07
12	2.1 ± 0.07	1.6 ± 0.08	1.9 ± 0.11	1.9 ± 0.07	1.6 ± 0.08	2.1 ± 0.05
14	2.1 ± 0.08	1.8 ± 0.06	2.2 ± 0.07	1.9 ± 0.05	1.9 ± 0.06	1.9 ± 0.07
16	1.9 ± 0.06	1.6 ± 0.08	2.2 ± 0.09	2.0 ± 0.08	1.8 ± 0.06	2.0 ± 0.12

a: data presented as granuloma index (grand mean of triplicate cultures) ± SEM.
b: oviposition begins.

TABLE V

Data summary of experiment 1

Baboon No. & Sex	C-1057(F)	C-1058(F)	C-1319(F)	30P(M)
Date of patency[a]	4/8/91	4/10/91	4/10/91	4/7/91
Day patent p.i.[b]	46	48	48	45
Date of eosinophilia[a]	3/28/91	3/28/91	4/11/91	3/28/91
Maximum eosinophilia (%)	6	4	5	8
Post-infection dermatitis	negative	positive	positive	positive
Dry cough	negative	negative	negative	positive
Onset of diarrhea[a]	4/14/91	4/10/91	4/10/91	4/10/91
Hematochezia	moderate	severe	moderate	moderate
Δ body weight (kg.)	-0.8	-1.1	-0.6	0
AP[c] (Δ + b-l)[d]	115	16	0	0
AST[c] (Δ + b-l)[d]	10	0	0	0
ALT[c] (Δ + b-l)[d]	40	0	0	5.5

a: dates given as month/day/year.
b: p.i. = post-infection; baboons infected on 2/21/91.
c: serum enzyme levels (see Materials and Methods).
d: (Δ + b-I) = change above pre-infection base-line (b-l) average value for each baboon, in appropriate units.

individuals fitted the pattern, and some patients were intensely ill even though they were lightly infected by the criterion of egg excretion. This finding suggests that genetic or other differences in human beings might influence their response to initial infection with the parasite. In the present study, using a small series of outbred baboons, we found evidence that this may be true. The indices of severity generated from the available data of Experiment 1 showed a range (1.62 to 2.25) consistent with this hypothesis. Data from Experiment 2 on body temperature (Fig. 1) and activity (not shown) indicate variability in both of these symptoms (fever and malaise) in individual infected baboons. Other signs and symptoms from these animals (data not shown), when included, will yield a similar if not greater range in severity of acute schistosomiasis in Experiment 2 as was noted in Experiment 1. Thus baboons simulate humans very closely in their initial responses to infection with *S. mansoni*, and offer experimental opportunities to understand the mechanisms of disease and individual variations in disease severity. A larger series of baboon infections should eventually test in this model Hiatt's claim that severity of disease is directly related to intensity of infection.

Another interesting result has emerged from the research accomphished to date in the baboon model. This is that most of the symptomology of A.S., at least at cercarial exposure levels of 1,000 or less thus far used in this study, is associated with the onset of egg pro-

TABLE VI

Indices of severity and worm burdens, experiment 1

Animal No.	Scores			
Symptom or sign	C-1057	C-1058	C-1319	30P
Onset of diarrhea[a]	1	2	2	1
Hematochezia	2	3	2	2
Anorexia[b]	2	3	2	1
Weight loss	2	3	2	1
Dry cough	0	0	0	1
Dermatitis	1	2	2	2
Eosinophilia	3	3	2	3
Liver function[c]	3	2	1	2
Index of severity[d]	1.75	2.25	1.62	1.62
Worm burden	481	732	170	550

a: used instead of duration of diarrhea because short-term experiment.
b: based upon amount of biscuits and fruit consumed.
c: based upon serum AP, AST, and ALT levels.
d: arithmetic mean of scores.

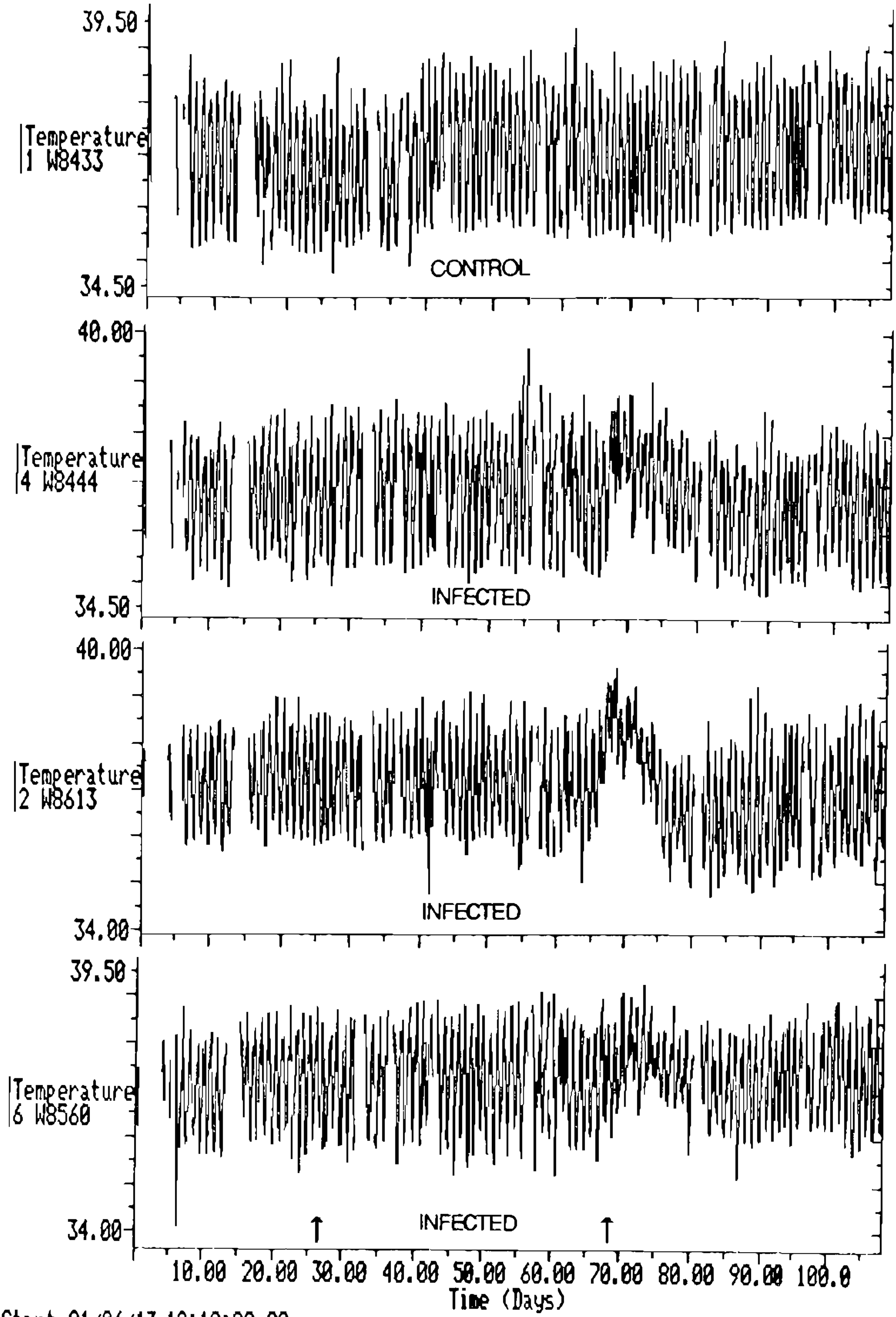
TABLE VII

Comparison of immunological reactivity during early[a] schistosomiasis mansoni in humans and in baboons

Parameter	Human[b]	Baboon[c]
Eosinophilia	Elevated	Elevated
Serum IgM level	Elevated	Elevated
Serum IgG level	Elevated	Elevated
Serum IgE level	Elevated	Perhaps elevated
Anti-cercarial Abs	Present	Present
Circumoval precipitins	Present only after oviposition begins	Present only after oviposition begins
Anti-adult worm Abs	Elevated	Elevated
Circ. immune complexes	Elevated	Unknown
PBMC Ag-specific blastogenesis	Highly responsive	Highly responsive
In vivo granulomas	Vigorous	Vigorous
In vitro granulomas	Large[d]	Large
Infection site dermatitis	Variable	Variable

a: up to 4 months post-infection.
b: references for humans are Neves (1986), Hiatt et al., (1979, 1980)), Diaz-Rivera et al., (1956), Istre et al., (1984), Zuidema et al., (1981), Clark et al., (1970), Antunes et al., (1971), Ottesen et al., (1978), Gazzinelli et al., (1985), Raso et al., (1978), Doughty et al., (1984), Lawley et al., (1979), and Mello et al., (1978).
c: references for baboons are Damian et al., (1981, 1984, 1985), Suzuki & Damian (1981), Serrano-Brizuela (1987), and Tables II-IV in this report.
d: 7-18 month infections, as compared to $>$ 5 year infections.

duction by newly matured worms rather than with the migration and maturation of schistosomula in the host. This includes eosinophilia (Table II), lymphocyte responses (Tables III and IV), and fever (Fig. 1). The onset of fever may be a very sensitive indicator of the onset of oviposition, since it preceded the appearance of the first eggs in the stool by several days. This points strongly to schistosome eggs as direct or indirect sources of pyrogens and raises several interesting questions. Egg antigens such as ω_1 (Dunne et al., 1981), which may be hepatotoxic, may also be pyrogenic. The intense immunologic granulomatous reactions, particularly during the vigorous, unregulated phase (Table IV) may result in sufficient systematic release of endogenous pyrogens (IL-1, IL-6, and TNF-α) to directly or indirectly affect the hypothalamic thermoregulatory center. Neves (1986) and others have reported



Body temperature read-outs (two minute readings averaged at hourly intervals) for four baboons, three of which were exposed to 1,000 *Schistosoma mansoni* cercariae each on the day indicated by the first arrow on the abscissa. The second arrow denotes the average day of patency for the three infected baboons, as determined by finding eggs in the stools.

fever in human A.S. that precedes oviposition by a longer period of time than herein observed. This may indicate a difference between human and baboon A.S. or it may be related to cercarial dose effects. We hope to test this point in the future by exposing baboons to larger doses of cercariae. It would also be at least as interesting to examine the cessation of fever in terms of regulatory mechanisms at the immunologic and/or hypothalamic levels. Baboons should prove useful in this and other future research relating to the acute schistosomiasis syndrome, and could help shed light on this disease as in occurs in humans.

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