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Biochemical Observations on Blood of Rats Infected with *Toxoplasma gondii*[1)]

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トキソプラズマ感染ラットの血液生化学的所見

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In peripheral blood findings of a rat infected experimentally with the Deelen strain of *T. gondii*, mean corpusclar hemoglobin (MCH) and mean corpusclar volume (MCV) decreased slightly until the 8th week postinfection with degenerated red cells appearing occasionally. Total leukocyte count increased slightly, accompanied with a transient increase and decrease in neutrophils and lymphocytes. An abrupt increase of monocytes in the acute stage was noted, showing the degenerated figures with some vacuoles. Serum albumin showed a slight decrease, and alpha and gamma globulins, lactate dehydrogenase (LDH), glutamic oxalacetic transaminase (GOT) and glutamic pyruvic transaminase (GPT) showed an increase during acute infection, and then they nearly approached the normal values of preinfection. Histological change in the liver was a slight swelling in hepatic and reticuloendothelial cells in an acute stage. Chromophages or pigmentphagocytic cells in the spleen appeared during the 3rd week, and then increased gradually to 8 weeks postinfection. RES. BULL. OBIHIRO UNIV. 7 (1971): 15-25.

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Introduction

In spite of the large number of reports available on clinical and experimental toxoplasmosis in animal and man, only a limited information exists on the synthetic analysis of pathophysiological changes which are expressed as the body defense reaction of the host by toxoplasma infection[2-6].

Recent observations by the authors have revealed remarkable alterations in the blood findings and serum component of mice infected with the Deelen strain of toxoplasma (N. SUZUKI *et al*, in press).

It is well known that a strain of Deelen will kill a mouse within 2 or 3 weeks. Using the same strain, a rat can survive inoculation with millions of organisms. The rat is a suitable model for experimental studies of mammalian chronic toxoplasmosis. To date, however, there are only a few extensive studies of the changes produced in the blood of the animal after infection with *Toxoplasma gondii*[8]. Consequently, similar studies in rats and mice, using the same strain of Deelen, were designed to determine some of the detectable blood biochemical changes in rats which may differ from those occurring in mice.

Materials and Methods

1. Materials

20 Wistar strain female SPF rats, weighing 140 to 150 g each born in the same group within a week (produced by Versuchstierzucht GmbH & Co., Kirchborchen, Germany) were used in the experiment. Each rat was bled from the tail (0.5 ml) prior to and at various time intervals following inoculation of the parasites.

To maintain conditions for breeding and feeding, each rat was put into a separate cage, kept in an air conditioned room at 23°C, and given a limited volume of the rat standard diet (produced by the Höveler Co., Germany) and tap water freely for 2 weeks prior to the experiment.

Rats used in the experiment were inoculated intraperitoneally with 1×10^7 parasites of the Deelen strain obtained from peritoneal fluid of 3-day infected mice. To prepare the inocula, mice peritoneal fluid was centrifuged at 2,000 rpm for 15 minutes, the lower portion of fluid washed two times with physiological saline solution, and the organisms were resuspended in saline and adjusted by counting in a Thoma-Zeiss hemocytometer, to contain 1×10^7 organisms approximately in 1.0 ml of the suspension.

From each of 4 rats, blood was obtained by progressive amputation of small parts of the tail with a sharp scalpel. To prevent coagulation, 0.005 mg heparin per 0.5 ml of blood was added. To make serum, blood from other 4 rats was kept at 4°C for 30 minutes, and then centrifuged at 12,000 rpm for 5 minutes. Sera were used without delay.

2. Methods of measurement

Red blood cells were counted in a 1 : 100 dilution of blood sample in Hayem's solution, and white blood cells in a 1 : 10 dilution of blood in Türk's solution, by using the Thoma-Zeiss hemocytometer. The hematocrit was measured by a van Allen packed-cell volume tube and expressed with the value obtained by centrifugation at 3,000 rpm for 30 minutes. Hemoglobin concentration was measured by the cyanhemoglobin method. The hemogram was studied microscopically with smears fixed in methanol and stained with May-Grünwald and Giemsa stains. The percentage of each type of leukocyte was calculated from a count of 200 cells in the hemogram and a count of 500 cells in the myelogram. Reticulocytes were calculated from a count of 1,000 red blood cells stained with 0.1 percent of brilliant cresyl blue.

Total protein in serum was measured by a biurette method using a photometer, and protein fractions were ascertained by means of Sartorius-membranfolien electrophoresis using a modified barbital-phosphate buffer, pH 8.6 and 0.075 of ionic strength. Tests for serum components, total cholesterol, total bilirubin, alkaline phosphatase, glutamic oxalacetic and pyruvic transaminases (GOT and GPT), lactate dehydrogenase (LDH), cholinesterase (Ch-e), leucine amino peptidase (LAP) were all conducted with microbiochemical techniques of the Biochemica Test Combination made in Boehringer C. F. & Soehne GmbH, Germany. Sera were not used if hemolysis was present.

Histological examination was conducted with specimens fixed in 10 percent formalin saline solution, embedded in paraffin, cut at 5 microns, and stained with hematoxylin and eosin.

3. Experimental method

Rats, fed the rat standard diet for 2 weeks, were inocculated intraperitoneally with 1.0 ml of suspension contained 1×10^7 organisms of *T. gondii*, and examined preinfection, 3/7, 1, 2, 3, 6, 7 and 8 weeks postinfection as every period for each rat. Antibody titers to toxoplasma were measured by the Sabin-Feldman dye test.

Results

In this experiment all rats were infected with 1×10^7 organisms of *T. gondii* 2 weeks after the beginning of the rats standard diet. Each of 4 rats for blood and the other 4 rats for serum examinations among 10 rats, was bled every period of preinfection (b. i.), 3/7, 1, 2, 3, 6, 7 and 8 weeks after inoculation of the parasites (p. i.). All infected rats survived to the end of this experiment. The other rats were used as histopathological examinations.

1. Variations of red blood counts, hemoglobin concentration and packed cell volume (chart 1)

The average of red blood cell counts, hemoglobin concentration, and packed-cell volume (referred to as RHP) were 7.0 million per cubic millimeter, 15.0 g per

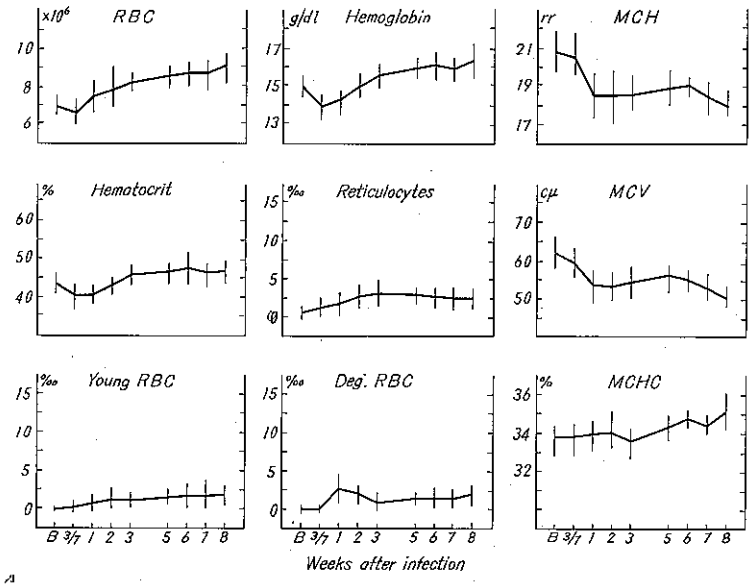

Chart 1. Changes in the Blood and Red Blood Cells in Rats During the Course of Infection

Note: RBC, Red Blood Cells; Deg. RBC, Degenerated RBC; MCH, Mean Corpusclar Hemoglobin; MCV, Mean Corpusclar Volume; and MCHC, Mean Corpusclar Hemoglobin Concentration.

100 ml of blood, and 44.5 percent b. i., indicating the average values of 4 cases of the experiment as the broader bars. RHP showed a tendency to decrease slightly to reach the minimum of 6.5 million, 14.0 g and 41 percent on the 3rd day p. i. After that, it showed a tendency to increase gradually until 8 weeks p. i., showing 9.1 million, 16.5 g and 46.8 percent. Both MCH and MCV, which were 21.1 micromicrograms and 62.7 cubic microns b. i., decreased to values of 18.2 and 51.6 on the 8th week p. i., respectively. Reticulocytes and erythroblasts as young red blood cells in the peripheral blood showed a slight increase, reaching a maximum on the 3rd week p. i. On the other hand, degenerated red cells, including basophilic stippling in the red cells, appeared slightly by 8 weeks p. i. In the blood smear of a rat, some of proliferative toxoplasmas were found at 3 days and 7 weeks p. i.

2. Variations in white blood cell count and the differential leukocyte count by percentage (Chart 2)

The average leukocyte count, which was 11.3 thousand per cubic millimeter b. i., increased to 15.9 thousands on the 1st week to 13.4 thousand on the 6th week p. i. Otherwise, on the 3rd day with 10.9 and the 7th week of 10.4 thousand, respectively, they showed a slightly lower values than the day of infection. By differential leukocyte count, neutrophils (15.5 percent or 1.3 thousand as an absolute value per cubic millimeter b. i.) revealed a transient increase and decrease

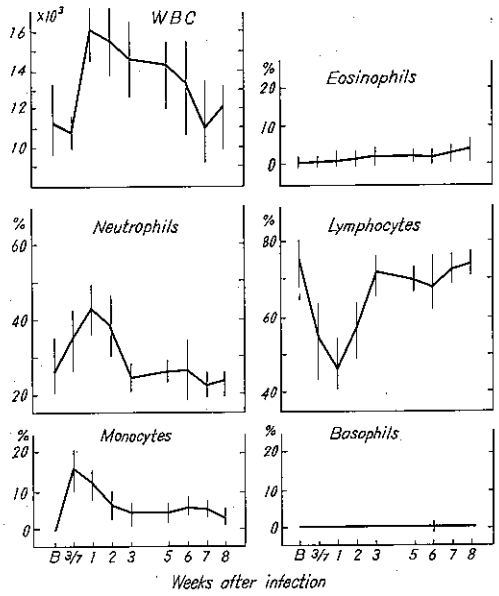

Chart 2. Changes in the Leukocyte Picture of the Rats Infected with *T. gondii*

Note: WBC, white blood cells.

of 34 percent or 3.8 thousand on the 1st week and of 7.5 percent or 0.9 thousand on the 8th week p. i. Lymphocytes (80.5 percent or 9.5 thousand b. i.) showed a transient decrease and increase of 53.5 percent or 8.5 thousand on the 1st week and of 84 percent or 9.8 thousand on the 8th week p. i. Monocyte counts, which were 0.9 percent or 0.1 thousand b. i., showed an increase of 12.5 percent or 2.1 thousand on the 1st week p. i., and then decreased gradually to the 8th week p. i., showing 2.5 percent or 0.3 thousand.

3. Variations in erythroid and myeloid cells in bone marrow (Table 1)

In the myelogram, in which two rats were killed every period of preinfection, 3/7, 1, 3, 6 and 8 weeks p. i., respectively, averages of the ratio of myeloids to erythroids for two rats (2.4 to 1 in rats b. i.) showed a lower ratio of 1.4 to 1 in the 8th week p. i. Lymphocytes, plasma cells and reticulum cells, were present at 4.8, 1.2 and 0.4 percent b. i. and showed an increase 1 to 6 weeks p. i., reaching a maximum of lymphocytes and plasma cells (13.1 and 11.8 percent) on the 3rd week, and reticulum cells 2.7 percent on the 1st week p. i., respectively.

On the other hand, monocytes, which were 1.6 percent b. i., increased to 3.1, 4.1 and 2.8 percent on the 1st, 3rd and 6th week p. i. No remarkable change was noted in the proportion of eosinophils.

4. Variations in total serum protein and serum protein fractions in the serum and serology (Table 2)

Regarding the Sabin-Feldman dye test titers from pooled sera during each

Table 1. Changes in Myelogram in Rats Infected and Non-Infected with *T. gondii*

	Before infection	Weeks after infection				
		3/7	1	3	6	8
ERYTHROPOIESIS						
Proerythroblasts	0.8	0.9	1.8	0.2	0.6	1.2
Macroblasts	5.6	4.2	11.2	9.8	4.3	6.6
Normoblasts	22.8	18.0	30.8	28.7	23.8	33.7
Erythroid: Total	29.2	23.1	43.8	38.7	28.7	41.5
GRANULOPOIESIS						
Myeloblasts	0.8	0.4	0.2	0.3	0.7	0.1
Promylocytes	3.5	2.5	0.9	1.0	1.7	0.6
Myelocytes						
neutrophile	9.0	4.9	4.4	1.4	1.6	2.3
eosinophile	2.7	1.5	0.3	0	0.5	0.6
basophile	0	0	0.1	0	0	0
Metamyelocytes						
neutrophile	5.2	9.2	2.6	2.4	2.4	4.1
eosinophile	1.2	3.1	0.2	0.5	0.6	1.7
basophile	0	0.1	0	0	0	0
Stab leukocytes						
neutrophile	11.2	9.8	12.1	3.2	5.6	9.7
eosinophile	2.8	6.3	4.9	0.9	6.2	4.9
basophile	0.6	0	0	0	0	0
Segment leukocytes						
neutrophile	22.2	22.6	26.1	23.1	21.8	29.6
eosinophile	3.2	2.1	0.9	0	3.6	0.6
basophile	0.4	0	0	0	0	0
NON-GRANULOPOIESIS						
Lymphocytes	4.8	1.5	5.4	13.1	12.6	2.7
Monocytes	1.6	1.3	3.1	4.1	2.8	0.5
Plasma cells	1.2	4.1	8.5	11.8	7.3	1.1
Myeloid: Total	70.4	69.4	69.7	61.8	67.4	58.4
Myeloid/Erythroid ratio	2.4	3.0	1.6	1.6	2.3	1.4
Megakaryocytes	0.8	0.9	3.2	0.6	1.2	0.1
Reticulum cells	0.4	6.2	2.7	1.3	1.6	0.9
Mast cells	0	0	0.4	0	0	0
Unclassified cells	0.2	0.3	0.6	0.1	0.6	0.2

time period, antibodies began appearing on the 3rd day with a titer of 1 : 256, and began to increase by the 1st week with a titer of 1 : 16,000 and showing the same titer of 1 : 16,000 by the 8th week p.i.

Averages in total serum protein in all samples obtained from the 4 rats each did not reveal a significant variation from the values of preinfection at any time during the period of 8 weeks p.i.

Table 2. Changes of Total Protein and the Fractions in Rats Infected with *T. gondii*

	Total (g/dl)	Percentage of the fraction						*Sabin-Feldman dye test
		Albumin	Alpha 1	Alpha 2	Alpha 3	Beta	Gamma	
Before infection	6.2	60.3	11.2	5.4	5.7	12.4	5.0	0
Weeks after infection								
3/7	5.5	45.8	16.1	8.6	10.2	14.6	4.9	1: 256
1	6.3	49.2	11.4	6.0	7.8	14.9	10.7	1:16,000
2	6.5	53.6	11.2	5.0	6.9	14.4	9.0	1:16,000
3	6.2	57.2	11.4	4.6	5.9	14.1	7.0	1:16,000
6	6.1	57.0	10.6	5.2	7.2	13.1	7.0	1:16,000
7	6.3	56.7	11.4	5.2	6.5	12.7	7.6	1:16,000
8	6.2	57.4	10.9	4.6	5.6	14.5	7.2	1:16,000

Note: Sabin-Feldman dye test for every period was examined as a pooled serum.

By percentage of protein fractions, there was a slight decrease in the albumin fraction by the 1st week, showing a minimum value, and began returning toward the approximate value of preinfection on the 3rd week p.i. The alpha globulins increased remarkably on the 3rd day p.i., and then tended to return gradually to the value of preinfection. In the beta globulins, there was a tendency to increase gradually to 2 weeks, and to decrease slightly until 8 weeks p.i. The remarkable increase in gamma globulin was found in the 1st week p.i., and then it was at a slightly higher level than that in preinfection until the 8th week p.i.

5. Variations in enzymes in the serum (Chart 3)

In contrast with preinfection data for LDH, GOT and GPT in the serum, which were 91, 22 and 11 milliUnits per ml, experimental data revealed an increase to 228, 55 and 25 on the 3rd day p.i., respectively. Then they showed a slightly higher level until 8 weeks p.i. as compared with those in preinfection. No remarkable change was noted in LAP. In alkaline phosphatase, which was 131 milliUnits preinfection, a mod-

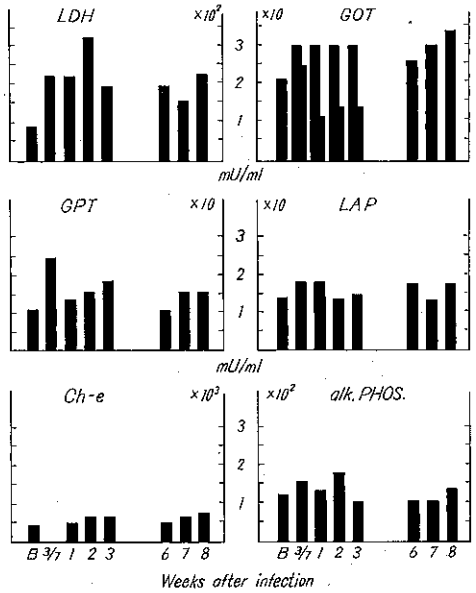

Chart 3. Serum Enzymes in Rats Infected with *T. gondii*

Note: LDH, Lactate Dehydrogenase; LAP, Leucine Amino Peptidase; GOT, Glutamic Oxalacetic Transaminase; GPT, Glutamic Pyruvic Transaminase; Ch-e, Cholinesterase; and alk. PHOS., alkaline Phosphatase.

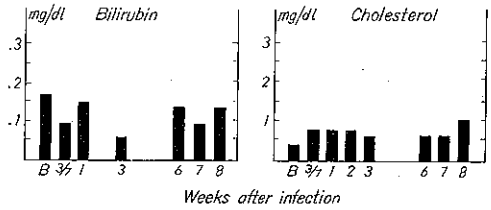

Chart 4. Variations of Bilirubin and Total Cholesterol in the Serum of Infected-rats

8 weeks p.i. than that in preinfection. the total serum bilirubin.

erately higher level was observed in the period from 3 days to 2 weeks p.i.

6. Variations of total bilirubin and total cholesterol in the serum (Chart 4)

Total cholesterol, which was 37 mg per 100 ml preinfection, increased to 75 mg 3 days p.i., and remained at a more than twice the level until No consistent changes were noted in

7. Histological findings

Specimens, which were liver, spleen, lymph node, adrenal gland, thyroid gland and brain, weren taken from rats on day 3 and the week of 1, 2, 3, 6 and 8 p.i. There was no significant difference in the severity of damage between the infected-rats and the non-infected ones, although the infected one exhibited a slight liver damage in the acute stage and a change in spleen at the latter stage during the examination at 8 weeks p.i.

Findings on the liver: The liver on the 3rd day p.i. showed an irregular stainability of the cytoplasm, and slight swelling was observed in hepatic and reticuloendothelial cells. The changes in the liver in the 1st week were less than on the 3rd day p.i. No remarkable change was observed in the liver during 3 to 8 weeks p.i. The structure of the liver lobule, the form of hepatic and endothelial cells, and the stainability of the cytoplasm were almost the same as compared with that of the non-infected.

Findings on the spleen: Passive hyperemia occurred extensively in the spleen on the 3rd and a week p.i. In the spleen on the 1st week p.i. large mononuclear cells and neutrophils were observed to increase markedly with a slight swelling of reticuloendothelial cells in the red pulp, showing an increase of erythroblasts. From on the 3rd week, chromophages or pigment-phagocytic cells were found. These cells appeared to increase gradually by 8 weeks p.i., although no pigmentphagocytic cells were observed in non-infected rats.

Findings on the lymph node: In the lymph node on the 3rd to 7th day p.i., there was observed that reticulum cells were markedly swollen in parts, and that lymphocytes and plasma cells increased. On the 8th week p.i. the reactions, which were seen in the 1st week, tended to return generally to normal.

Findings on the other tissues: In the adrenal glands on the 3rd day and a week p.i., incomplete necrobiotic changes and a congregation of cells were observed in some lesions of the cortex. Otherwise, there was no remarkable change in the adrenal during the 2nd to 8th week p.i. In the thyroid gland and brain, there were not observed remarkable differences between infected and non-infected rats.

Discussion

In mice infected with the Deelen strain of *T. gondii*, extensive and progressive damage to the liver, seen by histopathological findings and changes of protein fractions, GOT, GPT, LDH or SDH in sera, might have been caused by the remarkable proliferation of organisms, as recently reported (SUZUKI *et al.* in press). Similar studies in rats, which can survive inoculation with millions of organisms of toxoplasma, were made in this study. Although slight swelling of hepatic and reticuloendothelial cells occurred in the rat liver by the 1st week postinfection, there was no remarkable change in the liver during 3 to 8 weeks postinfection. In enzymes activities in the rat serum, (such as GOT, GPT and LDH), they appeared to increase on the 3rd day, showing a moderately higher activity until 8 weeks postinfection than that of preinfection. In cosequence, the degree of damage in the rat liver was much less in the acute stage than that in the mice infected with the same strain of toxoplasma.

As for the serum proteins of rats, alpha and beta globulins increased and albumin decreased in the acute stage of infection, and a remarkable increase in gamma globulin was observed. Sabin-Feldman dye test antibodies were observed on the 3rd day of infection and maximum titers were present the 1st week. Titers remained at high levels by the 8th week postinfection. Titers appeared to rise in almost parallel with the rise in serum gamma globulins, as REMINGTON reported.[7]

In peripheral blood findings of red blood cells in this study, the appearance of a slight decrease was noted on the 3rd day of infection, and then appeared to increase more gradually than that of preinfection until the 8th week postinfection. Otherwise, MCH and MCV in the 8th week decreased as compared with those in the preinfection. In some cases of the present experiment, anisocytic, poikilocytic or degenerated red cells appeared slightly by 8 weeks postinfection. On the other hand, there was a trend for the total leukocyte count to increase by 6 weeks with a transient increase and decrease in neutrophils, monocytes and lymphocytes. In the bone marrow, the percentage of plasma cells, lymphocytes and reticulum cells increased slightly in the acute stage, and also showed a slight hyperfunction of erythropoiesis on the 8th week postinfection. It is more notable that chromophages or pigment-phagocytic cells were found in the spleen on the 3rd week postinfection, with the cells appearing to increase in number by the 8th week postinfection.

These changes, mentioned above, in an acute and a chronic stages of the rat infection probably represent a manifestation of whole body reaction to an external stressor, namely, *T. gondii*. It is known that the principle of hematopoiesis in the bone marrow is mitosis in the monophasis of the red blood cells and in the diphasis of the white blood cells.[9] It is believed that the normal production of red cells and the increased production following an anemic stress,

is under the control of erythropoietin.[11] STOHLMAN[10] has presented results indicating that a second mechanism may also operate in the control of erythropoiesis. It is also thought that erythropoietin acts by increasing the proportion of stem cells which differentiate into the erythroid series and not by shortening the intermitotic intervals.[1] In consequence, the changes which occurred in erythrocytes of the rats infected chronically with *T. gondii* might be thought as a reflection and improvement of adaptation capability of the body to the parasites.

The systemic body reactions in the rat, which might reflect differences in resistance to toxoplasma, were less severe than those in the mouse infected with the same strain. The authors, however, feel that the toxoplasma organisms in the rat in the chronic stage may cause a slight effect to the red blood cells in hematopoietic system.

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摘　　要

急性および慢性トキソプラズマ症の病態生理を実験的に明確にするための第1段階として，強毒株トキソプラズマ (Deelen) をウイスター SPF ラットに 10^7 個，腹腔内接種して感染動物の血液諸成分を経日的に観察した。

検査項目は，1) 一般血液検査 (赤血球・白血球数，血色素量，血球容積，網赤血球数，ハインツ小体，赤血球抵抗，白血球百分率) と血球超生体，酵素，鉄などの染色，2) 血清諸酵素 (alk. phosphatase, GOT, GPT, LAP, LDH, SDH, GLDH, Cholinesterase), 3) 血清諸成分 (蛋白，コレステロール，ビリルビン，鉄，銅) および，4) 病理組織に分けて検索した。

感染後56日まで観察したラットの赤・白血球数では，その変動は著しくないが，MCH および MCV の減少，そして白血球数の増加傾向が認められた。感染初期単球が著増し，それらの多くは空胞を有し退行性変化を示すものが存在した。そしてまた，時として異常染色性赤血球の出現を認めた。血清諸酵素，総蛋白および蛋白分屑などでは，感染初期に軽度の変動を認めるが，感染後期では殆んど有意の変動を示さなかった。諸臓器病変像においても，ほぼ同様な傾向を観察した。しかし，脾内には色素貪喰細胞が42日目にきわめて軽度に認められ，56日目では，その出現の傾向を強めた。SFT 抗体は感染後7日目から16,000倍を示した。