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The effects of the immunosuppressant agent, mechlorethamine-HCl, on the immune response of domestic turkeys to Histomonas meleagridis infection

by

Yosiya Niyo

A Thesis Submitted to the Graduate Faculty in Partial Fulfillment of The Requirements for the Degree of MASTER OF SCIENCE

Major Subject: Veterinary Pathology

Signatures have been redacted for privacy

Iowa State University
Ames, Iowa
1971
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INTRODUCTION

*Histomonas meleagridis* is the etiologic agent of an acute fatal disease of turkey poults known as infectious enterohepatitis or histomonosis. The disease is characterized by the development of caseonecrotic typhlitis and focal necrotic hepatitis. Mortality is high in untreated cases. Use of dimetridazole, an anti-histomonal drug, results in remission of clinical signs and lesions and birds so treated are subsequently highly resistant to challenge with virulent histomonads. In these birds, the characteristic residual tissue change is the presence of numerous foci of lymphoid cells in the liver and cecal necks.

Immunization with attenuated cultures of histomonads establishes partial protection apparently expressed in cecal mucosa. This protection is easily broken down by challenge with embryonated *Heterakis gallinarum* eggs known to produce histomonosis. Precipitating and complement-fixing antibodies are demonstrable in sera from clinically ill and immune-recovered birds but transfer of such sera does not confer any protection to susceptible birds.

The nature of immunity established in birds that recover from the disease spontaneously or as a result of drug therapy is incompletely understood. However, the presence of large numbers of lymphoid cell accumulations in the liver and ceca in immune recovered birds suggests that these cells may be...
involved in mediation of immunity which is established in these birds.

This study was designed to investigate the response of recovered immune birds to challenge with virulent histomonads after these residual lymphoid foci have been destroyed by the use of nitrogen mustard, a chemical immunosuppressant agent. It is believed that knowledge obtained from this study will serve as a basis for future studies involving identification and transplantation of specific cells involved in immunity to this protozoan disease.
REVIEW OF LITERATURE

Histomonosis or infectious enterohepatitis is a protozoan disease of many gallinaceous birds. In the turkey, it is an acute disease with a high mortality rate. Smith (1895) reported the disease in turkeys and attributed it to a protozoan parasite which he named Amoeba meleagridis. The organism was later reclassified in Zoomastigina as Histomonas meleagridis by Tyzzer (1920) after he studied its pleomorphic nature and determined that it was a flagellate. Since then, the disease has been extensively studied by several investigators with regard to etiology (Bradley and Reid, 1966; Goedbloed and Bool, 1962; Kemp and Reid, 1966b; Tyzzer, 1920, 1927, 1932, 1934a; Tyzzer and Collier, 1925; Tyzzer and Fabyan, 1922) and transmission (Graybill and Smith, 1920; Horton-Smith and Long, 1956; Lund and Burtner, 1957; McGuire and Morehouse, 1958; Tyzzer and Fabyan, 1920). It is generally agreed that Histomonas meleagridis is the etiologic agent of the so-called "blackhead" or infectious enterohepatitis of turkeys.

Graybill and Smith (1920) produced the disease in the turkeys by feeding them embryonated Heterakis gallinarum eggs. Two years later, Tyzzer and Fabyan (1922) clearly demonstrated the transmission of Histomonas meleagridis by Heterakis ova and this finding was later substantiated by other workers (Gibbs, 1962; Lund and Burtner, 1957; McKay and Morehouse,
Lund et al. (1966) provided conclusive evidence showing that earthworms are biologic vectors for *Heterakis gallinarum*. Poultry may acquire the disease (histomonosis) by ingesting embryonated *Heterakis gallinarum* eggs provided these eggs are harboring virulent histomonads.

The disease has been extensively studied with respect to pathogenesis and development of the lesions (Clarkson, 1962; Farmer et al., 1951; McGuire and Morehouse, 1958; Malewitz et al., 1958). Infection is thought to start in the ceca where the initial response is characterized by hyperemia, leukocytic infiltration of submucosa and thickening of the cecal wall. There is sloughing of cecal epithelium. Later a caseonecrotic core forms in the cecal lumen. Rupture of the capillaries allows histomonads to enter the liver via the hepatic portal veins (Clarkson, 1962; McGuire and Morehouse, 1958). Once in the liver, histomonads continue to multiply and destroy much of the parenchyma. The affected birds finally die due to loss of functional liver tissue, dehydration, and inadequate feed consumption. Histological examination of turkeys that die from the disease shows a severe caseonecrotic typhlitis and a multiple focal necrotic hepatitis. Birds that recover from the disease naturally or as a result of drug therapy show numerous lymphoid foci in both the ceca and liver.

Doll and Franker (1963) were unable to induce histomono-
sis in bacteria-free turkeys and suggested that the pathogenesis and development of lesions seen in this disease may be due to a combined action of Histomonas and the normal intestinal flora. Franker and Doll (1964) produced the disease in previously bacteria-free hosts by administering certain of the normal bacterial species along with histomonads. Bradley and Reid (1966) were unable to induce the disease in turkeys using Histomonas meleagridis in the absence of E. coli and suggested a dual etiology involving a protozoan (H. meleagridis) and a bacterium (E. coli) for histomonosis.

Some of the host responses to the disease have been partially characterized by several investigators. Johnson and Lange (1939) studied blood smears from experimentally infected turkeys and compared these results with those they had obtained from a study of natural cases. In both instances, blood cell alterations were similar. They reported finding a marked heterophilia which appeared 24 hours post-infection and persisted until death of the birds. Infected birds also showed a myelocytosis and anemia in terminal stages of the disease.

McGuire and Cavett (1952) reported a progressive increase in total leukocyte count beginning with the appearance of "early clinical signs" and continuing throughout the course of the disease. There was a sixfold increase in the number of heterophils just before death. Lymphocytes increased early
in the course of the disease but began to decrease rapidly as the disease progressed.

Malewitz and Calhoun (1957) studied blood cell response of the infected turkeys and reported that those that eventually died from infection showed a persistent heterophilia and lymphopenia. They did not find any significant changes in monocyte, eosinophil, or basophil counts. They also reported a drop in hemoglobin levels and lowered total erythrocyte count.

Bierer (1969) analysed turkey serum and established that the usual normal serum protein fractions were present. Alterations in serum protein values of histomonas-infected turkeys were reported by Clarkson (1959). He found that serum gamma globulins increased fivefold while serum albumin levels fell to approximately one-half the normal level. Clarkson (1966) attempted to correlate serum protein changes in histomonas-infected poults with pathological changes observed in the liver and ceca. He suggested that the escape of albumin from inflamed ceca into the cecal lumen resulted in the initial fall in serum albumin level. Further reduction in albumin, noted later in the disease, was attributed to the inability of the damaged liver to adequately produce albumin. He also suggested that "either an immunologic response" and/or "a non-specific response to tissue damage" accounted for the rise in gamma globulins.

Histomonosis has also been studied in chickens, a species
Venkataratnam and Clarkson (1963) studied alterations in blood cell response of chicken infected with *Histomonas meleagridis* and observed an increase in the total number of leukocytes from 30,000 to 70,000 cells/cu. mm., 10 days postinfection. This rise was chiefly because of an increase in total number of heterophils and lymphocytes. Eosinophils and monocytes were also increased but no significant changes were observed in either total erythrocytes or basophil counts. All counts had returned to within normal range by 21 days postinfection. Histopathologic studies of the involved tissues revealed that lesions in both ceca and liver coincided with increases in heterophil response in tissues and peripheral blood while lymphocytes, monocytes, and eosinophils were most prominent in the recovery phase.

Serum protein changes in histomonas-infected chickens have been partially investigated (Beg and Clarkson, 1970; McDougald and Hansen, 1969). Serum albumin levels tended to fall early in the course of the disease but returned to near normal levels as the lesions resolved. Total globulin levels increased during the course of the disease and were significantly higher than in the control birds, 12 days postinfection (McDougald and Hansen, 1969). Beg and Clarkson (1970) found marked increases primarily in gamma globulin levels.

Serum enzyme changes associated with the disease have been reported by McDougald and Hansen (1970). These workers
found significant increases in both lactic dehydrogenase and serum glutamic oxalacetic transaminase (SGOT) in histomonas-infected turkeys and chickens. Increases in enzyme levels correlated with tissue breakdown in the liver and ceca.

McGuire and Cavett (1952) reported on changes in blood uric acid content and non-protein nitrogen during the course of the disease. The level of blood uric acid dropped early in the course of the disease, returned to near normal as the clinical signs became severe, and was markedly elevated in the terminal stages of the disease. Non-protein nitrogen values decreased as the disease progressed except on the day of death when the values were near normal.

Several workers have contributed to the study of histomonosis immunity. Tyzzer (1932, 1934b, 1936) used culture-attenuated strains of histomonads in his immunity studies of the disease. He found that he could establish only partial protection, since challenge with a virulent strain of histomonads produced the disease.

Lund (1959) challenged turkeys which he had immunized with a non-pathogenic strain of Histomonas and obtained variable results. These turkeys were refractory to the disease when challenged by intra-rectal inoculation of histomonads but this resistance broke down when it was challenged by means of embryonated Heterakis eggs. From these findings he suggested that an immune component was established on the surface of cecal mucosa, but was not effective against migrating
Heterakis larvae, which penetrated the epithelium.

Ruff and Hansen (1970) have shown that use of gamma-irradiated histomonads does not confer solid immunity to susceptible turkeys.

Several investigators have studied the immunity in turkeys that had recovered from the disease after drug therapy. Swales (1950) found that birds developed resistance to reinfection if treatment with 2-amino-5-nitrothiazole (Enheptin-T) was instituted after early cecal lesions had developed while complete suppression of early cecal lesions left these birds susceptible to reinfection. Kendall (1957) found that turkeys which recovered from experimental infection after sodium acetarsol therapy resisted reinfection. Clarkson (1963) reported that chickens that spontaneously recovered from the disease and turkeys that recovered from infection after acinitrazole (Entramin A) therapy developed "protective immunity". Clarkson (1966) suggested that immunization against histomonosis was best accomplished by initiating chemotherapy after the disease was well established in the cecal mucosa.

Precipitating antibodies are detectable in Histomonas-infected birds and in immune, recovered birds (Clarkson, 1963), but attempts to immunize susceptible birds by means of whole blood or serum transfer (Clarkson, 1963) have failed to confer any protective immunity.

Pertinent information on some of the immune mechanisms
in avian species has come from studies of cecal coccidiosis. Protective immunity develops in chickens that recover from *Eimeria tenella* infection. Work by Burns and Challey (1959) and Horton-Smith et al. (1961) demonstrated that resistance to cecal coccidiosis could be transferred from an infected cecum to a previously isolated and uninfected cecum, presumably via the circulation. Leathem and Burns (1967) pointed out that while sporozoites of *Eimeria tenella* are capable of invading cecal mucosa of immune birds, their developmental stages are suppressed. Tyzzer (1929) and Pierce and Long (1965) were unable to transfer protective immunity from birds immune to *Eimeria tenella* infection to susceptible chickens by means of blood or serum. However, Rose (1971) has indicated that serum taken from birds infected with *Eimeria maxima* will protect susceptible chickens. She points out that, transfer of large quantities of serum between days 14 and 21 postinfection offers the best protection.

When immune birds are challenged, the characteristic tissue response is massive infiltration of cecal submucosa by "pyroninophilic cells" which resemble plasma cells (Horton-Smith, 1963). The glandular crypts and surrounding connective tissue are heavily infiltrated by heterophils. Immunity established by *Eimeria tenella* infection is species specific (Rose and Long, 1962; Tyzzer, 1929). Evidence presented by Pierce and Long (1965) suggests that acquired immunity to cecal coccidiosis is largely cellular rather than
humoral in nature since destruction of the bursa of Fabricius without destroying the thymus does not appear to significantly influence the response to challenge.

Although whole body irradiation, immunosuppressive drugs, thymectomy, and bursaectomy have been used extensively in a variety of studies on the immune responses of the chicken (Cooper et al., 1966; Dent and Good, 1965; Glick et al., 1957; Graetzer et al., 1963; Jankovic and Isakovic, 1966; Lerman and Weidanz, 1970; St. Pierre and Ackerman, 1965; Warner and Szenberg, 1962; Warner et al., 1962; Weber and Weidanz, 1969), few investigators have utilized these techniques in the study of immune response to protozoan infections. Studies by Farmer and Breitenback (1968) and Longenecker et al. (1966) indicate that bursaectomy lowers resistance to *Plasmodium lophiurae* infections in chicken.

The immunosuppressive property of nitrogen mustard is due to its cytotoxic activity on all rapidly dividing cells in the body with the primary action probably being the alkylation of nucleic acids, thus blocking replication and cell division. However, lymphocytes tend to be more sensitive to the action of mechlorethamine than do any of the cells of the granulocytic series (Calabrensi and Parks, 1970).

Taliaferro and Taliaferro (1948) reported that administration of nitrogen mustard to chickens lowered their acquired immunity to malaria infections. Similar immune suppression had been reported by Philip et al. (1947) in
immune goats. Seto and Henderson (1968) used nitrogen mustard and irradiation to suppress immune responses of young chickens to mammalian erythrocytes and obtained comparable results with the two techniques.

Suppression of immune responses of Histomonas-infected turkeys were partially investigated by Kemp (1970). He found that birds which had been treated with mechlorethamine HCl either developed less severe or no lesions. The histopathologic alterations in the liver consisted of coagulation necrosis with minimal inflammatory reaction. Numerous histomonads were present in the liver and ceca. Total leukocyte count was markedly depressed and survival time was longer in these birds than in the infected control group. A suggestion that "normal host inflammatory response to histomonads in the liver may contribute to the virulence of the disease" was advanced.

The drug, 1,2-dimethyl-5-nitroimidazole (dimetridazole), is an effective cure for histomonosis (Joyner et al., 1966; J.M.S. Lucas et al., 1961, 1962, 1963; McGuire et al., 1964), even when treatment is delayed until both cecal and liver lesions have developed (Morehouse et al., 1968).
MATERIALS AND METHODS

Trial I

Source and care of animals

Twenty-five Williams broadwhite day-old poult s used in this trial were purchased from a commercial hatchery. They were wing-banded for identification and maintained in a brooder battery for the first 3 weeks before being transferred to a growing battery where they were kept throughout the course of the experiment. All birds were maintained ad libitum on a commercial, non-medicated starter ration, and water.

Initial infection with Heterakis gallinarum eggs

At 7 days of age, each poult was given per os approximately 500 embryonated Heterakis eggs from a stock that had been shown to induce fatal histomonosis in susceptible turkeys. This dose served as the initial immunizing infection.

Weights

All birds were weighed each time prior to collection of blood samples.

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1Jerome Turkey Hatchery, Inc., Barron, Wisconsin.
Collection of blood samples, total and differential leukocyte counts

Starting on the 7th day postinfection approximately 1 ml. blood was collected from each poult twice weekly throughout the course of the experiment. Disposable tuberculin syringes were used to collect blood from the jugular vein. Blood was immediately transferred into 12 by 75 mm. glass tubes. A drop of blood from each sample was used for leukocyte and differential counts. Total leukocyte counts were estimated using the Rees-Ecker Method as reported by Lucas and Jamroz (1961). The total number of cells counted from the four corner squares of a hemocytometer counting chamber were multiplied by 50 to give the total leukocyte count per cubic millimeter. Slide smears were air-dried and stained with standard Wright's Stain for differential leukocyte counts. Myelocytes were counted as heterophils.

Collection of serum samples

Approximately 1 ml. of the blood sample collected was allowed to stand (in tubes) at room temperature for 1 hour or until the clot had retracted. The blood was centrifuged at 2000 r.p.m. for 20 minutes. By means of Pasteur pipettes, serum was removed from the clot and placed in evacuated, silicone-coated glass tubes¹ provided with rubber stoppers.

¹"B-D Vacutainers", Becton-Dickinson and Co., Columbus, Nebraska.
The serum was kept frozen until total serum protein, serum protein fractions and serum glutamic oxalacetic transaminase (SGOT) determinations were made, usually 1-3 weeks later.

**Treatment with 1,2-dimethyl-5-nitroimidazole**

Poults were observed daily for any clinical signs of the disease. After the disease was well established in the liver, as indicated by passage of "sulfur-yellow" droppings, each poult was treated with an oral dose of the drug, 1,2-dimethyl-5-nitroimidazole (Dimetridazole)\(^1\), at the rate of 62.5 mg/kg. Daily observations were continued until all the birds appeared to have recovered. Passage of normal droppings and the apparent return of total leukocyte counts to within the normal range, were taken as indicators of recovery. Poults that died during this period were necropsied. Gross observations of the tissues were made and results were recorded. Tissues from these necropsies were fixed in 10% buffered formalin and saved for further processing for histopathologic studies.

Fifteen recovered birds were divided into 3 groups, of 5 birds each, as follows:

- **Group 1** - Immune control birds.
- **Group 2** - Heterakis-egg challenged birds.
- **Group 3** - Chemical immunosuppression followed by challenge with Heterakis eggs.

---

\(^1\)Dimetridazole was kindly donated by Dr. T. A. Rude, from Salsbury Laboratories, Charles City, Iowa.
Administration of an immunosuppressant

After recovery, each of the poults in Group 3 received intravenous mechlorethamine-HCl, Methylbis(-Chloroethyl)-amine HCl\(^1\), (HN\(_2\)) at the rate of 1 1/3 mg/kg. every 3rd day for 2 weeks.

Challenge with embryonated Heterakis eggs

Ten days after administration of the initial dose of mechlorethamine-HCl to poults in Group 3, poults in Groups 2 and 3 were challenged with an oral dose of approximately 500 Heterakis eggs obtained from the same culture stock that was used for initial immunization infection. These 2 groups were kept in cages below that holding Group 1. This housing arrangement was designed to minimize possible reinfection of Group 1 by Groups 2 and 3, through contamination.

Necropsy examination

Birds that died during the course of the experiment were necropsied. All surviving birds in the 3 groups were necropsied 25 days after administration of challenge dose. Gross lesions were described and the following tissue samples were fixed in 10% buffered formalin and saved for further processing for histopathologic studies:

- Myocardium
- Lung

\(^1\)Methylbis(-Chloroethyl)-amine HCl by Pfaltz and Bauer, Inc.
Liver
Kidney
Spleen
Bursa of Fabricius
Ceca
Small Intestine

Serum protein determination

Total serum protein values for each serum sample were determined by the Goldberg refractometer method. Actual values expressed in gm/100 ml. were read directly from AO/TS Meter, Model 10400¹.

Serum glutamic oxalacetate assay

Serum samples which had been frozen were allowed to thaw at room temperature. Each sample was divided into aliquots. One portion was used for serum electrophoresis and the other was diluted with distilled water. The latter portion was used in 1:6 dilution for SGOT assay. The enzyme was assayed by the colorimetric method of Reitman and Frankel (1957). Procedure and reagents as outlined in Sigma Technical Bulletin No. 505² were used for the test. A Coleman, Junior Model 6A Spectrophotometer³ at 505 mu. was used for all readings. SGOT levels

¹American Optical Instrument Company, Buffalo, N.Y. 14215
²Sigma Chemical Company, St. Louis, Missouri.
were expressed in Sigma-Frankel units/ml. of serum.

Serum electrophoresis

Serum electrophoretic separations were done on cellulose acetate electrophoresis membranes. A freshly prepared, high resolution barbital buffer, pH 8.6 with an ionic strength of 0.075, was used. Electrophoretic separation was carried out at a constant voltage of 250 V and 15-20 mA for 1 hour in a Brinkmann electrophoresis chamber\(^1\). The membranes were stained in Ponceau-S-dye\(^2\), decolorized in 5% acetic acid, dehydrated in ethanol, cleared, and dried. These cleared membrane strips were later scanned on a recording densitometer/integrator\(^3\). The concentration of each serum fraction was expressed as grams per cent of total and as a relative percent of the total serum protein.

Preparation of tissues for histopathologic studies

All tissues were prepared for sectioning by the standard ethanol dehydration and paraffin embedding techniques. The routine stain used was hematoxylin and eosin. Selected tissues were also stained with the periodic acid-Schiff (PAS) procedure.

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\(^1\)Brinkmann Instruments, Inc., New York, N.Y.

\(^2\)Industrial Chemicals Division, Morristown, N.J.

\(^3\)Gelman Instruments Company, Ann Arbor, Mich.
technique for better visualization of histomonads (Kemp and Reid, 1966a).

**Trial II**

In this trial, 25 poults were purchased as day old poults from the same source as those used in Trial I. Experimental procedures were similar to those of Trial I with few exceptions. Thirteen recovered birds were divided into 3 groups as follows:

- **Group 1** - Immune control birds (4 birds).
- **Group 2** - *Heterakis*-egg challenged birds (4 birds).
- **Group 3** - Chemical immunosuppression and challenge with *Heterakis* eggs (5 birds).

In this trial the immunosuppressant, HN2, was given to Group 3 on the same day that Groups 2 and 3 were challenged with embryonated *Heterakis* eggs as opposed to Trial I in which immunosuppression was started 10 days prior to challenge. The dosage was also increased from $1 1/3$ mg/kg. every 3 days to $4$ mg/kg. and was given on days 0, 4, and 9 postchallenge.

**Trial III**

Twenty-nine poults in this trial were purchased as day-old poults from Thompson Hatchery, Ellsworth, Iowa. Care of animals and handling of blood samples were similar to that in
Trials I and II. However, the mechanics of this trial varied slightly from those of previous trials. The timing of HN2 administration was altered in order to determine if this would make any difference in the immunosuppressive effects already detected in Trials I and II. Birds in Trial III were divided into 5 groups as follows:

Group 1 - Consisted of 5 uninfected control birds.
Group 2, 3, and 4 - Nineteen birds which had been infected, treated, and recovered were arbitrarily divided into 3 groups of 6, 7, and 6 birds each, respectively.

Group 2 - Birds in this group were later challenged with Heterakis eggs.
Group 3 - Each bird in this group was given HN2, intravenously, at the rate of 1 1/3 mg/kg/day for 5 days starting 2 days before challenge.
Group 4 - Birds in Group 4 were not given HN2 until 7 days postchallenge. Dosage and duration of treatment were identical to those used in Group 3.
Group 5 - Which consisted of birds that had not been previously infected, was infected at the time of challenge. This group served as the infected control group.
At challenge, all birds in Groups 2, 3, 4, and 5 were infected *per os* with approximately 500 *Heterakis* eggs/bird from the original culture.
RESULTS

Trial I

Mortality

Mortality in Groups 1, 2, and 3 were 2/5, 1/5, and 3/5, respectively.

Body Weights

Data for body weights of different groups are given in Table 1. There were no significant differences with regard to weight gains among all groups until a few days after challenge when birds in Group 3 began to lose weight (Figure 1).

Hematologic Observations

Total leukocyte counts

Detailed results of the total leukocyte counts for the 3 groups are summarized in Table 2. The typical leukocyte response in all groups was an initial leukocytosis which was quite marked 12 to 14 days postinfection. This was followed by a gradual decrease in leukocytes after treatment with dimetridazole and the counts soon fell to within the normal range (Figure 2). The total leukocyte numbers in Group 2, rose after challenge with Heterakis eggs and remained slightly above control values (Group 1) for the remainder of the trial period. Leukopenia developed in Group 3 while
Table 1. Comparison of average weights (in grams) of three groups of turkeys during the experimental period

<table>
<thead>
<tr>
<th>Days Post-infection</th>
<th>Group 1</th>
<th>Group 2</th>
<th>Group 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>7</td>
<td>115 (5)</td>
<td>126 (5)</td>
<td>116 (5)</td>
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<tr>
<td>12</td>
<td>126 (5)</td>
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<td>19</td>
<td>192 (5)</td>
<td>221 (5)</td>
<td>200 (5)</td>
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<tr>
<td>22</td>
<td>228 (5)</td>
<td>263 (5)</td>
<td>236 (5)</td>
</tr>
<tr>
<td>26</td>
<td>304 (5)</td>
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<td>372 (5)</td>
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<tr>
<td>33</td>
<td>408 (4)</td>
<td>592 (5)</td>
<td>426 (5)</td>
</tr>
<tr>
<td>35</td>
<td>531 (4)</td>
<td>644 (5)</td>
<td>416 (5)</td>
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<td>40</td>
<td>669 (4)</td>
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<td>44</td>
<td>729 (4)</td>
<td>959 (4)</td>
<td>635 (2)</td>
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<tr>
<td>47</td>
<td>957 (3)</td>
<td>1,132 (4)</td>
<td>780 (2)</td>
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<tr>
<td>50</td>
<td>1,098 (3)</td>
<td>1,224 (4)</td>
<td>881 (2)</td>
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<td>54</td>
<td>1,166 (3)</td>
<td>1,181 (4)</td>
<td>767 (2)</td>
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<tr>
<td>57</td>
<td>1,227 (3)</td>
<td>1,193 (4)</td>
<td>727 (2)</td>
</tr>
</tbody>
</table>

*aTotal number of birds used.

Table 2. Comparison of average total leukocyte counts of three groups of turkeys during the experimental period

<table>
<thead>
<tr>
<th>Days Post-infection</th>
<th>Group 1</th>
<th>Group 2</th>
<th>Group 3</th>
</tr>
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<tbody>
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<td>7</td>
<td>19,600 (5)a</td>
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<td>12</td>
<td>54,550 (5)</td>
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<td>32,750 (5)</td>
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<td>13,000 (2)</td>
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<td>23,050 (3)</td>
<td>43,900 (4)</td>
<td>54,850 (2)</td>
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<td>50,600 (4)</td>
<td>72,250 (2)</td>
</tr>
</tbody>
</table>

*aTotal number of birds used.
Figure 1. Progressive changes in the body weights of the following groups in Trial I:

Group 1 - Immune-control.
Group 2 - Immune-challenged.
Group 3 - HN₂-treated.

Infection at 7 days of age
TRIAL I

- GROUP ONE
- GROUP TWO
- GROUP THREE

DIMETRIDAZOLE
HN₂
CHALLENGE

AVERAGE BODY WEIGHT IN 100'S GRAMS

AGE OF BIRDS, IN DAYS.
Figure 2. Total leukocyte response pattern of the following groups in Trial I:

- Group 1 - Immune-control.
- Group 2 - Immune-challenged.
- Group 3 - HN2-treated.

Infection at 7 days of age
DIMETRIDAZOLE

HN₂

CHALLENGE

TRIAL I

GROUP ONE

GROUP TWO

GROUP THREE

AGE OF BIRDS, IN DAYS

AVERAGE TOTAL LEUKOCYTE NUMBERS IN THOUSANDS/CU. MM.

AGE OF BIRDS, IN DAYS

14 19 20 24 29 34 36 39 44 49 54 59 64 69

0 8 16 24 32 40 48 56 64
birds in this group were being treated with HN2. During this time, circulating leukocyte numbers fell below 3,000 cells/cu. mm. Following challenge with Heterakis eggs, there was a marked leukocytosis which persisted until the trial was terminated (Figure 2). This group had an average cell count of over 72,000 cells/cu. mm. when the trial was terminated, 57 days after infection.

**Differential leukocyte counts**

Results of differential leukocyte counts are summarized in Tables 3 through 7. Total heterophil and lymphocyte counts were markedly elevated 12 to 14 days postinfection. This was followed by a gradual fall in numbers of both cell types to normal counts after treatment with dimetridazole. Transient increases in absolute numbers of heterophils were detected in Group 1 on days 44 and 57 postinfection but there was no corresponding increase in the total number of lymphocytes. Significant and persistent increases of heterophils and lymphocytes were observed in Group 2 starting with day 47 postinfection (12 days postchallenge).

Group 3 had a progressive decrease in absolute heterophil and lymphocyte numbers while on treatment with HN2. The decrease was more marked in heterophil counts than in the lymphocyte counts (Figures 3, 4, 5, 6). After withdrawal of HN2, counts of both cell types began to increase rapidly, particularly the heterophil counts which averaged well over
Table 3. Comparison of the average total heterophil counts of three groups of turkeys during the experimental period

<table>
<thead>
<tr>
<th>Days Post-infection</th>
<th>Group 1</th>
<th>Group 2</th>
<th>Group 3</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(63.80)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>(69.60)</td>
<td>(58.80)</td>
</tr>
<tr>
<td></td>
<td>12,300&lt;sup&gt;b&lt;/sup&gt;</td>
<td>19,300</td>
<td>15,150</td>
</tr>
<tr>
<td>12</td>
<td>(49.20)</td>
<td>(57.00)</td>
<td>(57.20)</td>
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<tr>
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<td>(62.40)</td>
<td>(62.00)</td>
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<td>26,550</td>
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<td>(61.40)</td>
<td>(57.80)</td>
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<td>16,350</td>
<td>10,950</td>
</tr>
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<td>(54.40)</td>
<td>(58.80)</td>
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<td>15,950</td>
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<td>(57.80)</td>
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<tr>
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<td>8,600</td>
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<td>7,950</td>
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<td>(54.20)</td>
<td>(64.00)</td>
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</table>

<sup>a</sup>Reported as percentage.

<sup>b</sup>Reported as total numbers of cells/cu. mm.
Figure 3. Absolute numbers of heterophils in the following groups in Trial I:

Group 1 - Immune-control.
Group 2 - Immune-challenged.
Group 3 - HN₂-treated.

Infection at 7 days of age
DIMETRIDAZOLE \( \text{HN}_2 \) CHALLENGE

TRIAL I

- ○ GROUP ONE
- △ GROUP TWO
- ■ GROUP THREE

AGE OF BIRDS, IN DAYS

AVERAGE ABSOLUTE HETEROPHIL NUMBERS IN THOUSANDS/CU. MM. OF BLOOD
Figure 4. Relative numbers of heterophils (expressed in per cent) for the following groups in Trial I:

Group 1 - Immune-control.
Group 2 - Immune-challenged.
Group 3 - HN₂-treated.

Infection at 7 days of age
Table 4. Comparison of the average total eosinophil counts of three groups of turkeys during the experimental period

<table>
<thead>
<tr>
<th>Days Post-infection</th>
<th>Group Numbers 1</th>
<th>Group Numbers 2</th>
<th>Group Numbers 3</th>
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<tbody>
<tr>
<td>7</td>
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<td>(0.20)</td>
</tr>
<tr>
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<td>43\textsuperscript{b}</td>
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<td>(0.40)</td>
</tr>
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</tr>
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<td>(0.40)</td>
<td>(0.00)</td>
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<tr>
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<td>0</td>
<td>166</td>
<td>0</td>
</tr>
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<td>(0.40)</td>
<td>(0.20)</td>
</tr>
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<td>(0.00)</td>
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<td>(0.40)</td>
<td>(0.00)</td>
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<td>(0.80)</td>
<td>(0.20)</td>
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<td>61</td>
<td>163</td>
<td>29</td>
</tr>
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<td>(0.20)</td>
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<td>(1.25)</td>
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<td>1,688</td>
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</table>

\textsuperscript{a}Reported as percentage.

\textsuperscript{b}Reported as total numbers of cells/cu. mm.
Table 5. Comparison of the average total monocyte counts of three groups of turkeys during the experimental period.

<table>
<thead>
<tr>
<th>Days Post-infection</th>
<th>1</th>
<th>2</th>
<th>3</th>
</tr>
</thead>
<tbody>
<tr>
<td>7</td>
<td>(0.00)\textsuperscript{a}</td>
<td>(0.80)</td>
<td>(0.80)</td>
</tr>
<tr>
<td></td>
<td>0 \textsuperscript{b}</td>
<td>164</td>
<td>179</td>
</tr>
<tr>
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<td>(0.00)</td>
<td>(0.00)</td>
</tr>
<tr>
<td></td>
<td>100</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>15</td>
<td>(0.60)</td>
<td>(0.00)</td>
<td>(0.20)</td>
</tr>
<tr>
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<td>41</td>
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<tr>
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<td>(0.20)</td>
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</tr>
<tr>
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<td>(0.60)</td>
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<td>270</td>
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</table>

\textsuperscript{a}Reported as percentage.

\textsuperscript{b}Reported as total numbers of cells/cu. mm.
Table 6. Comparison of the average total lymphocyte counts of three groups of turkeys during the experimental period

<table>
<thead>
<tr>
<th>Days Post-infection</th>
<th>Group 1</th>
<th>Group 2</th>
<th>Group 3</th>
</tr>
</thead>
<tbody>
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<td>6,850</td>
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</tr>
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<td>23,350</td>
<td>17,800</td>
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<td>(48.60)</td>
<td>(32.20)</td>
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<td>(41.75)</td>
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<td>9,000</td>
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</table>

*aReported as percentage.

*bReported as total numbers of cells/cu. mm.
Figure 5. Absolute numbers of lymphocytes in the following groups in Trial I:

- Group 1 - Immune-control.
- Group 2 - Immune-challenged.
- Group 3 - HN2-treated.

Infection at 7 days of age
DIMETRIDAZOLE

HN2 CHALLENGE

TRIAL I

GROUP ONE

GROUP TWO

GROUP THREE

AVERAGE ABSOLUTE LYMPHOCYTE NUMBERS IN THOUSANDS/CC.

AGE OF BIRDS, IN DAYS

0 4 8 12 16 20 24 28 32

0 14 19 24 29 34 36 39 44 49 54 59 64 69
Figure 6. Relative numbers of lymphocytes (expressed in per cent) for the following groups in Trial I:

Group 1 - Immune-control.
Group 2 - Immune-challenged.
Group 3 - HN2-treated.

Infection at 7 days of age
Trial I

- **Group One**
- **Group Two**
- **Group Three**

Relative lymphocyte numbers in %

Age of birds, in days
Table 7. Comparison of the average total basophil counts of three groups of turkeys during the experimental period

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<th>Days Post-infection</th>
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<th>3</th>
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<td>(4.60)</td>
<td>(7.20)</td>
<td>(4.60)</td>
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<td>(6.60)</td>
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<td>(9.00)</td>
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<td>(7.20)</td>
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<td>(6.75)</td>
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<td>47</td>
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<td>(6.00)</td>
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<td>787</td>
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<td>0</td>
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<tr>
<td>57</td>
<td>(4.00)</td>
<td>(4.00)</td>
<td>(1.50)</td>
</tr>
<tr>
<td></td>
<td>1,051</td>
<td>716</td>
<td>1,448</td>
</tr>
</tbody>
</table>

\(^a\)Reported as percentage.

\(^b\)Reported as total numbers of cells/cu. mm.
48,000 cells/cu. mm. at the time the trial was terminated. Eosinophils were infrequently seen and when present, they accounted for less than 2 per cent of the cells counted. No significant changes were observed in either the monocyte or basophil counts among all groups.

SGOT Values

Data for SGOT values for the 3 groups are given in Table 8. Levels for serum glutamic-oxalacetate (SGOT) activity did not vary markedly from group to group. Instead, greater variations were observed among individual birds than between groups.

Serum Protein Studies

Results for total serum protein and serum protein fractions are summarized in Tables 9 through 14. After challenge with *Heterakis* eggs, slightly higher total serum protein levels were observed in Group 2 than in Group 3 (Figure 7). Significant variations were observed in the serum albumin and gamma globulin fractions. A reduction of as much as 30 to 50 per cent in serum albumin levels was detected in all groups 12 days postinfection (Figures 8 and 9). This was followed by a rapid rise to "normal levels" after all birds were treated with dimetridazole.

After challenge with *Heterakis* eggs, albumin levels in
Table 8. Comparison of serum glutamic-oxalacetic transaminase (SGOT) activity in three groups of turkeys during the experimental period

<table>
<thead>
<tr>
<th>Days Post-infection</th>
<th>Group 1</th>
<th>Group 2</th>
<th>Group 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>7</td>
<td>379.20a (5)b</td>
<td>355.50 (4)</td>
<td>278.40 (5)</td>
</tr>
<tr>
<td>12</td>
<td>279.60 (5)</td>
<td>318.00 (5)</td>
<td>278.40 (5)</td>
</tr>
<tr>
<td>15</td>
<td>313.20 (5)</td>
<td>333.20 (5)</td>
<td>376.40 (5)</td>
</tr>
<tr>
<td>19</td>
<td>320.80 (5)</td>
<td>300.80 (5)</td>
<td>376.40 (5)</td>
</tr>
<tr>
<td>22</td>
<td>319.20 (5)</td>
<td>274.80 (5)</td>
<td>308.40 (5)</td>
</tr>
<tr>
<td>26</td>
<td>288.00 (5)</td>
<td>278.50 (4)</td>
<td>279.60 (5)</td>
</tr>
<tr>
<td>30</td>
<td>284.80 (5)</td>
<td>312.00 (5)</td>
<td>285.60 (5)</td>
</tr>
<tr>
<td>33</td>
<td>198.00 (1)</td>
<td>268.80 (5)</td>
<td>336.00 (4)</td>
</tr>
<tr>
<td>35</td>
<td>358.50 (4)</td>
<td>259.50 (4)</td>
<td>240.00 (2)</td>
</tr>
<tr>
<td>40</td>
<td>237.00 (4)</td>
<td>262.50 (4)</td>
<td>318.00 (4)</td>
</tr>
<tr>
<td>44</td>
<td>201.00 (4)</td>
<td>249.00 (4)</td>
<td>216.00 (2)</td>
</tr>
<tr>
<td>47</td>
<td>238.00 (3)</td>
<td>184.50 (4)</td>
<td>327.00 (2)</td>
</tr>
<tr>
<td>50</td>
<td>238.00 (3)</td>
<td>186.00 (4)</td>
<td>168.00 (2)</td>
</tr>
<tr>
<td>54</td>
<td>262.00 (3)</td>
<td>333.00 (4)</td>
<td>300.00 (2)</td>
</tr>
<tr>
<td>57</td>
<td>224.00 (3)</td>
<td>178.00 (3)</td>
<td>342.00 (2)</td>
</tr>
</tbody>
</table>

aSGOT reported in Sigma-Frankel Units.
bTotal number of birds used.

Table 9. Comparison of total serum protein values of three groups of turkeys during the experimental period

<table>
<thead>
<tr>
<th>Days Post-infection</th>
<th>Group Numbers 1</th>
<th>Group Numbers 2</th>
<th>Group Numbers 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>7</td>
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<td>2.60 (5)</td>
<td>2.60 (5)</td>
</tr>
<tr>
<td>12</td>
<td>2.82 (5)</td>
<td>3.34 (5)</td>
<td>2.94 (5)</td>
</tr>
<tr>
<td>15</td>
<td>3.02 (5)</td>
<td>3.58 (5)</td>
<td>3.38 (5)</td>
</tr>
<tr>
<td>19</td>
<td>3.38 (5)</td>
<td>3.78 (5)</td>
<td>3.50 (5)</td>
</tr>
<tr>
<td>22</td>
<td>3.50 (5)</td>
<td>3.84 (5)</td>
<td>3.38 (5)</td>
</tr>
<tr>
<td>26</td>
<td>3.52 (5)</td>
<td>3.72 (5)</td>
<td>3.36 (5)</td>
</tr>
<tr>
<td>30</td>
<td>3.80 (5)</td>
<td>4.00 (5)</td>
<td>3.30 (5)</td>
</tr>
<tr>
<td>33</td>
<td>3.82 (4)</td>
<td>4.12 (5)</td>
<td>3.56 (5)</td>
</tr>
<tr>
<td>35</td>
<td>4.05 (4)</td>
<td>4.68 (5)</td>
<td>3.28 (5)</td>
</tr>
<tr>
<td>40</td>
<td>4.55 (4)</td>
<td>3.63 (4)</td>
<td>2.72 (4)</td>
</tr>
<tr>
<td>44</td>
<td>4.07 (4)</td>
<td>3.77 (4)</td>
<td>3.25 (2)</td>
</tr>
<tr>
<td>47</td>
<td>5.03 (3)</td>
<td>4.15 (4)</td>
<td>3.45 (2)</td>
</tr>
<tr>
<td>50</td>
<td>4.90 (3)</td>
<td>4.10 (4)</td>
<td>2.95 (2)</td>
</tr>
<tr>
<td>54</td>
<td>3.77 (3)</td>
<td>4.07 (4)</td>
<td>3.40 (2)</td>
</tr>
<tr>
<td>57</td>
<td>4.07 (3)</td>
<td>3.75 (4)</td>
<td>3.30 (2)</td>
</tr>
</tbody>
</table>

aReported as grams/100 ml. of serum.
bTotal number of birds used.
Figure 7. Progressive changes in total serum protein in the following groups in Trial I:

Group 1 - Immune-control.
Group 2 - Immune-challenged.
Group 3 - HN2-treated.

Infection at 7 days of age
DIMETRIDAZOLE CHALLENGE

TRIAL I

GROUP ONE

GROUP TWO

GROUP THREE

TOTAL SERUM PROTEIN CONCENTRATION IN GRAMS %

AGE OF BIRDS, IN DAYS

14 19 20 24 29 34 36 39 44 49 54 59 64 69
Table 10. Comparison of total serum albumin concentration in three groups of turkeys during the experimental period

<table>
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<th>Group Numbers</th>
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<th>3</th>
</tr>
</thead>
<tbody>
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<td>0.98 (5)</td>
<td>0.94 (5)</td>
</tr>
<tr>
<td></td>
<td>(40.30)c</td>
<td>(37.42)</td>
<td>(36.13)</td>
</tr>
<tr>
<td>12</td>
<td>0.74 (5)</td>
<td>0.65 (5)</td>
<td>0.65 (5)</td>
</tr>
<tr>
<td></td>
<td>(25.38)</td>
<td>(19.39)</td>
<td>(21.83)</td>
</tr>
<tr>
<td>15</td>
<td>0.78 (5)</td>
<td>0.92 (5)</td>
<td>0.95 (5)</td>
</tr>
<tr>
<td></td>
<td>(26.03)</td>
<td>(25.64)</td>
<td>(27.75)</td>
</tr>
<tr>
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<td>1.19 (5)</td>
<td>1.30 (5)</td>
<td>1.17 (5)</td>
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<tr>
<td></td>
<td>(35.66)</td>
<td>(34.63)</td>
<td>(33.72)</td>
</tr>
<tr>
<td>22</td>
<td>1.30 (5)</td>
<td>1.46 (5)</td>
<td>1.31 (5)</td>
</tr>
<tr>
<td></td>
<td>(37.15)</td>
<td>(38.43)</td>
<td>(39.57)</td>
</tr>
<tr>
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<td>1.42 (5)</td>
<td>1.37 (5)</td>
<td>1.27 (5)</td>
</tr>
<tr>
<td></td>
<td>(40.63)</td>
<td>(36.93)</td>
<td>(37.87)</td>
</tr>
<tr>
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<td>1.39 (5)</td>
<td>1.58 (5)</td>
<td>1.26 (5)</td>
</tr>
<tr>
<td></td>
<td>(36.65)</td>
<td>(39.57)</td>
<td>(37.87)</td>
</tr>
<tr>
<td>33</td>
<td>1.54 (4)</td>
<td>1.62 (5)</td>
<td>1.21 (5)</td>
</tr>
<tr>
<td></td>
<td>(40.38)</td>
<td>(39.32)</td>
<td>(33.20)</td>
</tr>
<tr>
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<td>1.34 (4)</td>
<td>1.58 (5)</td>
<td>1.02 (5)</td>
</tr>
<tr>
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<td>(31.75)</td>
<td>(33.91)</td>
<td>(30.07)</td>
</tr>
<tr>
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<td>1.12 (4)</td>
<td>1.34 (4)</td>
<td>0.87 (4)</td>
</tr>
<tr>
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<td>(26.64)</td>
<td>(37.21)</td>
<td>(27.79)</td>
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<td>44</td>
<td>1.56 (4)</td>
<td>1.48 (4)</td>
<td>1.26 (2)</td>
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<td>(36.01)</td>
<td>(39.96)</td>
<td>(38.64)</td>
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<td>1.34 (4)</td>
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<td>(32.82)</td>
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<td>(41.08)</td>
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<td>0.87 (2)</td>
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<td>(35.02)</td>
<td>(27.19)</td>
<td>(29.45)</td>
</tr>
<tr>
<td>54</td>
<td>1.25 (3)</td>
<td>0.93 (4)</td>
<td>0.45 (2)</td>
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<td>(32.52)</td>
<td>(22.68)</td>
<td>(13.31)</td>
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<td>0.77 (4)</td>
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<td>(31.42)</td>
<td>(20.78)</td>
<td>(6.24)</td>
</tr>
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</table>

a Reported as grams percent.
b Total number of birds used.
c Reported as relative percent.
Figure 8. Progressive changes in serum albumin concentration (expressed in grams per cent) for the following groups in Trial I:

- **Group 1** - Immune-control.
- **Group 2** - Immune-challenged.
- **Group 3** - HN₂-treated.

Infection at 7 days of age
DIETRIDIAMOLE CHALLENGE

1.60
1.40
1.20
1.00
0.80
0.60
0.40
0.20
0.00

AVG. SERUM ALBUMIN CONCENTRATION IN GRAMS %

14 19 24 29 34 39 44 49 54 59 64 69

AGE OF BIRDS, IN DAYS

DIMERTRIPAZOLE

HN2

CHALLENGE

TRIAL 1

GROUP ONE

GROUP TWO

GROUP THREE

1.60
1.40
1.20
1.00
0.80
0.60
0.40
0.20
0.00
Figure 9. Progressive changes in serum albumin concentration (expressed as percent of the total serum protein) in the following groups in Trial I:

Group 1 - Immune-control.
Group 2 - Immune-challenged.
Group 3 - HN2-treated.

Infection at 7 days of age.
Table 11. Comparison of total serum alpha 1 globulin concentration in three groups during the experimental period

<table>
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<th>Days Post-infection</th>
<th>Group 1</th>
<th>Group 2</th>
<th>Group 3</th>
</tr>
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<tbody>
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<td>0.26</td>
<td>0.24</td>
<td>0.21</td>
</tr>
<tr>
<td></td>
<td>(9.32)</td>
<td>(9.11)</td>
<td>(8.20)</td>
</tr>
<tr>
<td>12</td>
<td>0.22</td>
<td>0.34</td>
<td>0.32</td>
</tr>
<tr>
<td></td>
<td>(7.77)</td>
<td>(9.94)</td>
<td>(11.01)</td>
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<td>0.31</td>
<td>0.39</td>
<td>0.31</td>
</tr>
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<td>(10.45)</td>
<td>(10.87)</td>
<td>(9.14)</td>
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<td>0.38</td>
<td>0.36</td>
<td>0.37</td>
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<td>(11.39)</td>
<td>(9.48)</td>
<td>(10.73)</td>
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<td>0.37</td>
<td>0.35</td>
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<tr>
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<td>(11.13)</td>
<td>(9.62)</td>
<td>(10.55)</td>
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<td>0.35</td>
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<td>(10.99)</td>
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<td>0.37</td>
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<td>(11.44)</td>
<td>(11.42)</td>
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<td>0.36</td>
<td>0.41</td>
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<td>(10.29)</td>
<td>(8.84)</td>
<td>(11.74)</td>
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<td>0.49</td>
<td>0.31</td>
</tr>
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<td></td>
<td>(11.69)</td>
<td>(10.62)</td>
<td>(9.79)</td>
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<tr>
<td>40</td>
<td>0.48</td>
<td>0.41</td>
<td>0.40</td>
</tr>
<tr>
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<td>(11.14)</td>
<td>(11.45)</td>
<td>(15.56)</td>
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<tr>
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<td>0.46</td>
<td>0.38</td>
<td>0.32</td>
</tr>
<tr>
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<td>(11.10)</td>
<td>(10.30)</td>
<td>(9.81)</td>
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<td>0.41</td>
<td>0.32</td>
</tr>
<tr>
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<tr>
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<td>(7.97)</td>
<td>(10.73)</td>
<td>(12.56)</td>
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<td>0.32</td>
<td>0.41</td>
<td>0.43</td>
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<tr>
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<td>(8.79)</td>
<td>(10.24)</td>
<td>(12.86)</td>
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<td>0.28</td>
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<td>(8.17)</td>
<td>(8.58)</td>
<td>(8.39)</td>
</tr>
</tbody>
</table>

a Reported as grams percent.

b Reported as relative percent.
Table 12. Comparison of total serum alpha II globulin concentration in three groups of turkeys during the experimental period

<table>
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<th>Days Post-infection</th>
<th>Group 1</th>
<th>Group 2</th>
<th>Group 3</th>
</tr>
</thead>
<tbody>
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<td>0.45</td>
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<td>0.47</td>
</tr>
<tr>
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<td>(16.00)^b</td>
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<td>(18.47)</td>
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<td>0.63</td>
<td>0.72</td>
<td>0.63</td>
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<td>(23.33)</td>
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<td>0.57</td>
<td>0.56</td>
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<td>(13.11)</td>
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<td>0.48</td>
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<td>(13.59)</td>
<td>(14.25)</td>
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<td>(15.93)</td>
<td>(12.81)</td>
<td>(14.74)</td>
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<td>(13.92)</td>
<td>(18.28)</td>
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^aReported as grams percent.

^bReported as relative percent.
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*aReported as grams percent.

*bReported as relative percent.
### Table 14. Comparison of total serum gamma globulin concentration of three groups of turkeys during the experimental period

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*Reported as grams percent.

bReported as relative percent.
Figure 10. Progressive changes in serum gamma globulin concentration (expressed in grams per cent) for the following groups in Trial I:

Group 1 - Immune-control.
Group 2 - Immune-challenged.
Group 3 - HN<sub>2</sub>-treated.

Infection at 7 days of age
DIMETRIDAZOLE

HN₂

CHALLENGE

TRIAL I

AVERAGE SERUM GAMMA GLOBULIN CONCENTRATION IN GRAMS%

AGE OF BIRDS, IN DAYS

GROUP ONE

GROUP TWO

GROUP THREE
Figure 11. Progressive changes in serum gamma globulin concentration (expressed as per cent of total serum protein) in the following groups in Trial I:

- Group 1 - Immune-control.
- Group 2 - Immune-challenged.
- Group 3 - HN2-treated.

Infection at 7 days of age
Average serum gamma globulin concentration in %

Trial 1

Group One
Group Two
Group Three

Age of birds, in days

Dimetridazole
HN2
Challenge
Groups 2 and 3 gradually fell below normal levels and remained within this range for the remainder of the experimental period. The fall was most remarkable in Group 3 where the albumin levels dropped to 0.21 gm. per cent the day the experiment was terminated. In contrast, a twofold increase in gamma globulin levels was detected in all 3 groups 12 days postinfection (Figures 10 and 11). The level dropped to within the normal range after treatment with dimetridazole. Transient increases in gamma globulin levels were detected in Group 1 on days 40 and 47 postinfection (two birds in this group had very high gamma globulin levels on these days). Following challenge with Heterakis eggs, marked increases in gamma globulin levels were detected in both Groups 2 and 3. There were no significant changes in either alpha or beta globulin fractions among all the 3 groups.

Histopathologic Studies

Group 1 - immune-control birds

Of the 2 birds which died before the trial was terminated, gross lesions were observed in the liver and ceca of one while lesions in the other bird were confined to the ceca. The remaining 3 birds which were killed and necropsied at the end of the trial period did not have any significant lesions. Liver lesions The histopathologic alterations of the gross lesions consisted of focal necrotic areas diffusely
scattered throughout the liver parenchyma. Multinucleated giant cells were numerous within these necrotic areas and many contained degenerating histomonads. There was an intense mononuclear cell infiltration in the surrounding tissue. Histomonads were frequently observed in disrupted hepatic sinusoids and bile duct proliferation was quite marked. Discrete areas of resolving lesions were present in liver sections from one other bird.

Liver sections from birds which had no gross lesions did not contain histomonads (Figures 12 and 13). Well circumscribed lymphoid cell accumulations, the so-called "bursa-dependent follicles", were frequently found scattered throughout the parenchyma and tended to be more numerous near blood vessels.

Cecal lesions The cecal lumina of birds which had gross lesions were filled with necrotic masses consisting of cellular debris, fibrin, and bacterial colonies. The mucosal lining was ulcerated and a granulomatous inflammation involved all layers of the cecal wall. There was an intense mononuclear cell infiltration into the lamina propria, submucosa, and serosa. Giant cells were numerous in both the mucosa and submucosa. Serosal vessels were congested and the mesentery was infiltrated by large numbers of mononuclear cells and a few polymorphonuclear leukocytes. Sections from ceca which did not have gross lesions were characterized by an intense lymphocytic cell infiltrate in mucosa and sub-
mucosa (Figures 14 and 15). Lymphoid foci, similar to those found in the liver, were frequently found in lamina propria and occasionally in other layers. No histomonads were observed.

Lesions in other tissues Well-circumscribed lymphoid foci were frequently observed in the spleen (Figures 16 and 17), small intestine, and bronchial mucosa. Definitive microscopic lesions were not observed in the kidney, myocardium, or the bursa of Fabricius (Figures 18 and 19).

Group 2 - immune-challenged birds

One bird which died before this group was challenged with virulent histomonads did not have gross or microscopic lesions. All the remaining birds were killed 25 days post-challenge. Two birds had cecal lesions but no gross lesions were observed in either the liver or any other tissues.

Liver lesions Focal areas of lymphoid cell accumulation surrounded by scanty, fibrous stroma were observed near hepatic vessels (Figures 20 and 21). A focal resolving lesion was observed in one section.

Cecal lesions The microscopic lesions in birds which did not have gross lesions consisted of an intense lymphocytic infiltration into all layers of the cecal wall. The reaction was most marked in the mucosa and submucosa. Well circumscribed lymphoid foci (similar to those seen in the liver) were present in lamina propria and submucosa (Figures
Figure 12. Liver section from an immune control bird. Hematoxylin and eosin stain. X 64

Figure 13. Higher magnification of a portion of Figure 12. Hematoxylin and eosin stain. X 400
Figure 14. Section of cecum from an immune control bird. 
Hematoxylin and eosin stain. X 64

Figure 15. Higher magnification of a portion of Figure 14. 
Hematoxylin and eosin stain. X 400
Figure 16. Section of spleen from an immune control bird. Hematoxylin and eosin stain. X 64

Figure 17. Higher magnification of a portion of Figure 16. Hematoxylin and eosin stain. X 400
Figure 18. Typical section of the bursa of Fabricius from immune control birds. Hematoxylin and eosin stain. X 64

Figure 19. Higher magnification of a portion of Figure 18. Hematoxylin and eosin stain. X 400
Figure 20. Lymphoid follicles in liver section from an immune-challenged bird. Hematoxylin and eosin stain. X 64

Figure 21. Higher magnification of the lymphoid follicle in Figure 20. Hematoxylin and eosin stain. X 400
Figure 22. Numerous lymphoid follicles and extensive mononuclear cell infiltration in cecal wall of an immune-challenged bird. Hematoxylin and eosin stain. X 64

Figure 23. Higher magnification of one of the follicles in Figure 22. Hematoxylin and eosin stain. X 400
In one bird, the cellular response consisted of polymorphonuclear leukocytes, principally heterophils.

The histopathologic alterations in the ceca which had gross lesions were a granulomatous tissue reaction involving all layers of the cecal wall and extending into the adjacent mesentery. Histomonads were found free in lamina propria or surrounded by numerous multinucleated giant cells. The mucosal lining was ulcerated and the cecal lumen contained necrotic cellular debris, epithelial cells, and colonies of bacteria.

Lymphoid follicles (bursa-dependent follicles) were frequently observed in the spleen (Figures 24 and 25) and small intestine and were occasionally seen in bronchial mucosa. The bursa of Fabricius was enlarged and its follicles were prominent. A thin connective tissue stroma separated individual follicles (Figures 26 and 27).

No significant microscopic changes were observed in the myocardium, large intestine, or the lungs.

Group 3 - HN2-treated birds

Three birds died between 6 and 9 days after challenge and the remaining 2 birds were killed and necropsied 25 days after challenge (the day the trial was terminated). Gross lesions were observed in the livers and ceca of all birds. Small granulomas were occasionally observed in the lungs,
Figure 24. Spleen section from an immune-challenged bird. Hematoxylin and eosin stain. X 64

Figure 25. Higher magnification of a portion of Figure 24. Hematoxylin and eosin stain. X 400
Figure 26. Section through the bursa of Fabricius from an immune-challenged bird. Bursal follicles are filled with round, dark staining cells. Hematoxylin and eosin stain. X 64

Figure 27. Higher magnification of a portion of Figure 26. Hematoxylin and eosin stain. X 400
kidneys and the bursa of Fabricius of some of these birds.

**Liver lesions** Microscopic liver lesions consisted of large areas of coagulative necrosis with poorly defined borders. Giant cells were numerous in these necrotic areas and often contained degenerated histomonads. Individual or "nested" histomonads were present at the peripheries of these necrotic areas, around blood vessels and in hepatic sinusoids (Figures 28 and 29). The associated cellular response was quite mild and consisted of mononuclear and epithelioid cells. Macrophages filled with pigment were frequently found in these sections.

**Cecal lesions** Microscopic lesions consisted of massive invasion of all layers of cecal wall by histomonads (Figures 30 and 31). The mucosa was ulcerated and small necrotic foci were frequently observed in the submucosa. Large numbers of giant cells and macrophages were present in the lamina propria. No bursa-dependent follicles were observed in any sections.

**Lesions in other tissues**

**Spleen** There was an apparent loss of basophilic staining cells of the white pulp and a concurrent increase in the number of reticular cells (Figures 32 and 33). Bursa-dependent follicles and histomonads were not observed in these sections.

**Kidney** Focal granulomas consisting of histomonads surrounded by mononuclear cells were found in kidney sections.
Figure 28. Numerous histomonads and giant cells in the liver section typical of HN2-treated group. Hematoxylin and eosin stain. X 64

Figure 29. Higher magnification of a portion of Figure 28. Hematoxylin and eosin stain. X 400
Figure 30. Ulcerated mucosal lining of cecum from HN$_2$-treated group. Numerous histomonads are present in cecal wall. Hematoxylin and eosin stain. X 64

Figure 31. Higher magnification of a portion of Figure 30. Hematoxylin and eosin stain. X 400
Figure 32. Typical section of spleen from HN₂-treated group. There is depletion of lymphoid cells. Hematoxylin and eosin stain. X 64

Figure 33. Higher magnification of a portion of Figure 32. Hematoxylin and eosin stain. X 400
from 2 birds. Microscopic changes from other kidney sections were not remarkable.

**Lung**  
Histomonads were not observed in any of the lung sections. However, 2 birds with lung lesions had a chronic granulomatous pneumonia. A mycotic agent, probably *Aspergillus* sp. was observed in air sacs and in many of the blood vessels.

**Bursa of Fabricius**  
This structure was generally smaller in this group than in Groups 1 and 2. Follicles appeared smaller and contained far fewer cells than equivalent-sized follicles of immune-control birds (Figures 34 and 35). There was a marked increase in interfollicular connective tissue. Giant cells were occasionally observed in some follicles. Histomonads were present in sections of this structure from 2 different birds (Figures 36 and 37).

**Myocardium, duodenum, small intestine, and pancreas**  
The histopathologic alterations observed in these tissues were not remarkable.

**Trial II**

**Mortality**

Mortality in Groups 1, 2, and 3 were 0/4, 0/4, and 3/5, respectively.

**Body Weights**

Data on body weights for the 3 groups are given in Table
Figure 34. Section of the bursa of Fabricius from a HN2-treated bird. There is atrophy of the bursal follicles and depletion of follicular cells. Hematoxylin and eosin stain. X 64

Figure 35. Higher magnification of a portion of Figure 34. Hematoxylin and eosin stain. X 400
Figure 36. Protozoal granuloma in the bursa of Fabricius from a HN₂-treated bird. Single and clusters of histomonads are present. Periodic acid-Schiff (PAS) stain. X 64

Figure 37. Higher magnification of the granuloma in Figure 36. Periodic acid-Schiff (PAS) stain. X 400
15. There were no significant differences between Groups 1 and 2 with regard to weight gains (Figure 38). Birds in Group 3 gained comparatively less weight than birds in Groups 1 and 2.

Hematologic Observations

Detailed results of hematologic observations for all groups are summarized in Tables 16 through 21. The responses were similar in kind and magnitude to those described for Trial I (Figures 39 through 43) except that, in this trial, the total lymphocyte numbers first rose then steadily dropped to normal values (Figures 42 and 43).

SGOT Studies

Data for SGOT values are given in Table 22. Marked variations in SGOT values were observed among individual birds and between groups. These changes were similar to those observed in Trial I.

Serum Protein Studies

Results of serum protein determinations were essentially similar to those obtained in Trial I and are summarized in Tables 23 through 28. Following challenge, total serum protein concentration was slightly higher in Group 3 than in
Table 15. Comparison of average weights (in grams) of three groups of turkeys during the experimental period

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*aTotal number of birds used.

Table 16. Comparison of average total leukocyte counts of three groups of turkeys during the experimental period

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<td>32,900 (5)</td>
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</table>

*aTotal number of birds used.*
Figure 38. Progressive changes in the body weights of the following groups in Trial II:

Group 1 - Immune-control.
Group 2 - Immune-challenged.
Group 3 - HN₂-treated.

Infection at 7 days of age
Figure 39. Total leukocyte response pattern of the following groups in Trial II:

Group 1 - Immune-control.
Group 2 - Immune-challenged.
Group 3 - HN2-treated.

Infection at 7 days of age
HN₂ TRIAL II

DI METRIDAZOLE

AND

GROUP ONE

CHALLENGE

GROUP TWO

GROUP THREE

TRIAL II

○ GROUP ONE

△ GROUP TWO

■ GROUP THREE

AGE OF BIRDS, IN DAYS

AGE OF BIRDS, IN DAYS

AVERAGE TOTAL LEUKOCYTE NUMBERS

IN THOUSANDS/CU. MM. OF BLOOD

14 19 24 29 34 39 44 49 54 59 64 69

45

40

35

30

25

20

15

10

5

0

20

25

30

35

40

45
Table 17. Comparison of the average total heterophil counts of three groups of turkeys during the experimental period

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<th>Groups 1 Numbers</th>
<th>Groups 2 Numbers</th>
<th>Groups 3 Numbers</th>
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<td>(40.60)</td>
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<td>(74.40)</td>
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<td>25,900</td>
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<td>(49.50)</td>
<td>(52.00)</td>
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<td>21,900</td>
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<td>(47.60)</td>
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<td>20,400</td>
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<td>(39.50)</td>
<td>(36.40)</td>
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<td>11,150</td>
<td>7,950</td>
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<td>(57.75)</td>
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<td>12,850</td>
<td>14,700</td>
<td>7,500</td>
</tr>
</tbody>
</table>

*Reported as percentage.*

*aReported as total numbers of cells/cu. mm.*
Figure 40. Absolute numbers of heterophils in the following groups in Trial II:

Group 1 - Immune-control.
Group 2 - Immune-challenged.
Group 3 - HN2-treated.

Infection at 7 days of age
DIMETRIDAZOLE

HN$_2$ AND CHALLENGE

TRIAL II
- GROUP ONE
- GROUP TWO
- GROUP THREE

AGE OF BIRDS, IN DAYS

AVG. ABSOLUTE HETEROPHIL NUMBERS IN THOUSANDS/CU.MM. OF BLOOD
Figure 41. Relative numbers of heterophils (expressed in per cent) for the following groups in Trial II:

- Group 1 - Immune-control.
- Group 2 - Immune-challenged.
- Group 3 - HN₂-treated.

Infection at 7 days of age
DIMETRIDAWE

HN₂ AND CHALLENGE

TRIAL II
- GROUP ONE
- GROUP TWO
- GROUP THREE

RELATIVE HETEROPHIL NUMBERS IN %

AGE OF BIRDS, IN DAYS

14 19 24 29 34 39 44 49 54 59 64 69
Table 18. Comparison of the average total eosinophil counts of three groups of turkeys during the experimental period

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<th>3</th>
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<td>(0.40)</td>
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<td>59 b</td>
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<td>82</td>
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<td>(1.00)</td>
<td>(0.20)</td>
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<td>70</td>
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</tr>
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<td>(0.25)</td>
<td>(0.20)</td>
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<td>(0.40)</td>
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<td>113</td>
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<td>64</td>
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<td>(0.00)</td>
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<td>(0.50)</td>
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</table>

aReported as percentage.
bReported as total numbers of cells/cu. mm.
Table 19. Comparison of the average total monocyte counts of three groups of turkeys during the experimental period

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<th>Group 2</th>
<th>Group 3</th>
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<td>(0.25)</td>
<td>(0.60)</td>
</tr>
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<td>263</td>
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\(^a\) Reported as percentage.

\(^b\) Reported as total numbers of cells/cu. mm.
Table 20. Comparison of the average total lymphocyte counts of three groups of turkeys during the experimental period

<table>
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<tr>
<th>Days Post-infection</th>
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<th>Group 3 (as percentage)</th>
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<td>11,450</td>
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<td>(34.75)</td>
<td>(41.75)</td>
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<td>10,050</td>
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<td>8,200</td>
<td>18,700</td>
<td>4,000</td>
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<td>57</td>
<td>(39.00)</td>
<td>(34.75)</td>
<td>(33.50)</td>
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<td>8,100</td>
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<td>(41.00)</td>
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<td>8,250</td>
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<td>6,750</td>
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<td>64</td>
<td>(38.00)</td>
<td>(40.67)</td>
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<tr>
<td></td>
<td>9,600</td>
<td>11,350</td>
<td>3,300</td>
</tr>
</tbody>
</table>

\textsuperscript{a}Reported as percentage.

\textsuperscript{b}Reported as total numbers of cells/cu. mm.
Figure 42. Absolute numbers of lymphocytes in the following groups in Trial II:

- Group 1 - Immune-control.
- Group 2 - Immune-challenged.
- Group 3 - HN2-treated.

Infection at 7 days of age
TRIAL II
• GROUP ONE
• GROUP TWO
• GROUP THREE

DIMETRIDAZOLE

HN₂ AND CHALLENGE

AVERAGE ABSOLUTE LYMPHOCYTE NUMBERS IN THOUSANDS/CU. MM. OF BLOOD

AGE OF BIRDS, IN DAYS

14 19 24 29 34 39 44 49 54 59 64 69
Figure 43. Relative numbers of lymphocytes (expressed in per cent) for the following groups in Trial II:

Group 1 - Immune-control.
Group 2 - Immune-challenged.
Group 3 - HN₂-treated.

Infection at 7 days of age
TRIAL II

60

GROUP ONE

HN₂

• GROUP TWO

• GROUP THREE

IN:

z

50

..........

(/)

0::::

~

45

::>

z

~

40 >-

u 0

0

DIMETRIDAZONE

55

50

45

40

35

30

25

20

15

10

5

0

RELATIVE LYMPHOCYTE NUMBERS IN %

AGE OF BIRDS, IN DAYS

TRIAL II

O GROUP ONE

A GROUP TWO

■ GROUP THREE

HN₂ AND

CHALLENGE

14 19 24 29 34 39 44 49 54 59 64 69
Table 21. Comparison of the average total basophil counts of three groups of turkeys during the experimental period

<table>
<thead>
<tr>
<th>Days Post-infection</th>
<th>Group 1</th>
<th>Group 2</th>
<th>Group 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>6</td>
<td>(3.00)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>(4.75)</td>
<td>(3.60)</td>
</tr>
<tr>
<td></td>
<td>569&lt;sup&gt;b&lt;/sup&gt;</td>
<td>1,080</td>
<td>788</td>
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<tr>
<td>13</td>
<td>(2.00)</td>
<td>(2.75)</td>
<td>(2.20)</td>
</tr>
<tr>
<td></td>
<td>574</td>
<td>1,384</td>
<td>768</td>
</tr>
<tr>
<td>16</td>
<td>(2.50)</td>
<td>(4.50)</td>
<td>(4.20)</td>
</tr>
<tr>
<td></td>
<td>792</td>
<td>1,991</td>
<td>1,401</td>
</tr>
<tr>
<td>23</td>
<td>(3.00)</td>
<td>(2.75)</td>
<td>(5.60)</td>
</tr>
<tr>
<td></td>
<td>611</td>
<td>858</td>
<td>1,245</td>
</tr>
<tr>
<td>27</td>
<td>(6.00)</td>
<td>(7.00)</td>
<td>(3.60)</td>
</tr>
<tr>
<td></td>
<td>1,105</td>
<td>1,476</td>
<td>772</td>
</tr>
<tr>
<td>30</td>
<td>(3.25)</td>
<td>(5.50)</td>
<td>(6.20)</td>
</tr>
<tr>
<td></td>
<td>591</td>
<td>1,230</td>
<td>1,075</td>
</tr>
<tr>
<td>35</td>
<td>(3.75)</td>
<td>(5.75)</td>
<td>(2.60)</td>
</tr>
<tr>
<td></td>
<td>765</td>
<td>926</td>
<td>536</td>
</tr>
<tr>
<td>37</td>
<td>(3.25)</td>
<td>(5.00)</td>
<td>(2.60)</td>
</tr>
<tr>
<td></td>
<td>748</td>
<td>885</td>
<td>376</td>
</tr>
<tr>
<td>41</td>
<td>(3.00)</td>
<td>(3.00)</td>
<td>(2.00)</td>
</tr>
<tr>
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<td>1,008</td>
<td>555</td>
<td>533</td>
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<td>44</td>
<td>(2.75)</td>
<td>(6.00)</td>
<td>(4.60)</td>
</tr>
<tr>
<td></td>
<td>1,185</td>
<td>1,260</td>
<td>843</td>
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<tr>
<td>47</td>
<td>(4.25)</td>
<td>(2.75)</td>
<td>(6.20)</td>
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<td>2,014</td>
<td>818</td>
<td>668</td>
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<tr>
<td>50</td>
<td>(4.25)</td>
<td>(3.75)</td>
<td>(5.75)</td>
</tr>
<tr>
<td></td>
<td>1,068</td>
<td>1,209</td>
<td>745</td>
</tr>
<tr>
<td>54</td>
<td>(5.25)</td>
<td>(3.25)</td>
<td>(4.67)</td>
</tr>
<tr>
<td></td>
<td>1,022</td>
<td>1,612</td>
<td>554</td>
</tr>
<tr>
<td>57</td>
<td>(5.50)</td>
<td>(4.50)</td>
<td>(7.00)</td>
</tr>
<tr>
<td></td>
<td>1,016</td>
<td>1,615</td>
<td>934</td>
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<tr>
<td>61</td>
<td>(4.50)</td>
<td>(7.25)</td>
<td>(2.50)</td>
</tr>
<tr>
<td></td>
<td>1,067</td>
<td>2,017</td>
<td>554</td>
</tr>
<tr>
<td>64</td>
<td>(5.00)</td>
<td>(8.00)</td>
<td>(5.00)</td>
</tr>
<tr>
<td></td>
<td>1,020</td>
<td>2,339</td>
<td>574</td>
</tr>
</tbody>
</table>

<sup>a</sup>Reported as percentage.

<sup>b</sup>Reported as total numbers of cells/cu. mm.
Table 22. Comparison of serum glutamic-oxalacetic transaminase (SGOT) activity in three groups of turkeys during the experimental period

<table>
<thead>
<tr>
<th>Days Post-infection</th>
<th>Group Numbers</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>6</td>
<td>272.00a (3)b</td>
<td>212.00 (3)</td>
<td>297.60 (5)</td>
</tr>
<tr>
<td>13</td>
<td>217.00 (4)</td>
<td>218.00 (3)</td>
<td>307.50 (4)</td>
</tr>
<tr>
<td>16</td>
<td>213.00 (4)</td>
<td>210.00 (4)</td>
<td>222.00 (4)</td>
</tr>
<tr>
<td>23</td>
<td>208.50 (4)</td>
<td>213.00 (4)</td>
<td>208.80 (5)</td>
</tr>
<tr>
<td>27</td>
<td>219.00 (4)</td>
<td>240.00 (4)</td>
<td>253.20 (5)</td>
</tr>
<tr>
<td>30</td>
<td>253.50 (4)</td>
<td>236.00 (3)</td>
<td>254.40 (5)</td>
</tr>
<tr>
<td>35</td>
<td>205.50 (4)</td>
<td>258.00 (4)</td>
<td>301.20 (5)</td>
</tr>
<tr>
<td>37</td>
<td>187.50 (4)</td>
<td>220.50 (4)</td>
<td>264.00 (5)</td>
</tr>
<tr>
<td>41</td>
<td>282.00 (4)</td>
<td>331.50 (4)</td>
<td>259.20 (5)</td>
</tr>
<tr>
<td>44</td>
<td>190.50 (4)</td>
<td>228.00 (4)</td>
<td>182.00 (3)</td>
</tr>
<tr>
<td>47</td>
<td>238.00 (3)</td>
<td>223.50 (4)</td>
<td>256.30 (4)</td>
</tr>
<tr>
<td>50</td>
<td>262.00 (3)</td>
<td>238.00 (3)</td>
<td>248.00 (3)</td>
</tr>
<tr>
<td>54</td>
<td>241.50 (4)</td>
<td>276.00 (4)</td>
<td>190.00 (3)</td>
</tr>
<tr>
<td>57</td>
<td>282.00 (4)</td>
<td>261.00 (4)</td>
<td>249.00 (2)</td>
</tr>
<tr>
<td>61</td>
<td>241.50 (4)</td>
<td>225.00 (4)</td>
<td>258.00 (2)</td>
</tr>
<tr>
<td>64</td>
<td>298.50 (4)</td>
<td>228.00 (3)</td>
<td>249.00 (2)</td>
</tr>
</tbody>
</table>

aSGOT reported in Sigma-Frankel Units.
bTotal number of birds used.

Table 23. Comparison of total serum protein values of three groups of turkeys during the experimental period

<table>
<thead>
<tr>
<th>Days Post-infection</th>
<th>Group Numbers</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>6</td>
<td>2.63a (4)b</td>
<td>2.50 (3)</td>
<td>2.96 (5)</td>
</tr>
<tr>
<td>13</td>
<td>2.60 (4)</td>
<td>2.17 (3)</td>
<td>2.50 (5)</td>
</tr>
<tr>
<td>16</td>
<td>2.97 (4)</td>
<td>2.88 (4)</td>
<td>3.10 (5)</td>
</tr>
<tr>
<td>23</td>
<td>3.32 (4)</td>
<td>3.27 (4)</td>
<td>3.50 (5)</td>
</tr>
<tr>
<td>27</td>
<td>3.50 (4)</td>
<td>3.47 (4)</td>
<td>3.56 (5)</td>
</tr>
<tr>
<td>30</td>
<td>3.50 (4)</td>
<td>3.47 (4)</td>
<td>3.52 (5)</td>
</tr>
<tr>
<td>35</td>
<td>2.77 (4)</td>
<td>3.32 (4)</td>
<td>3.22 (5)</td>
</tr>
<tr>
<td>37</td>
<td>2.45 (4)</td>
<td>3.00 (4)</td>
<td>3.16 (5)</td>
</tr>
<tr>
<td>41</td>
<td>3.15 (4)</td>
<td>3.25 (4)</td>
<td>4.54 (5)</td>
</tr>
<tr>
<td>44</td>
<td>4.80 (4)</td>
<td>3.75 (4)</td>
<td>4.42 (5)</td>
</tr>
<tr>
<td>47</td>
<td>4.90 (4)</td>
<td>4.27 (4)</td>
<td>4.42 (5)</td>
</tr>
<tr>
<td>50</td>
<td>4.80 (4)</td>
<td>4.90 (4)</td>
<td>4.47 (4)</td>
</tr>
<tr>
<td>54</td>
<td>4.67 (4)</td>
<td>5.97 (4)</td>
<td>4.23 (3)</td>
</tr>
<tr>
<td>57</td>
<td>4.90 (4)</td>
<td>6.92 (4)</td>
<td>4.25 (2)</td>
</tr>
<tr>
<td>61</td>
<td>4.17 (4)</td>
<td>5.87 (4)</td>
<td>4.45 (2)</td>
</tr>
<tr>
<td>64</td>
<td>4.25 (4)</td>
<td>5.40 (3)</td>
<td>4.70 (2)</td>
</tr>
</tbody>
</table>

aReported as grams/100 ml. of serum.
bTotal number of birds used.
Figure 44. Progressive changes in total serum protein in the following groups in Trial II:

Group 1 - Immune-control.
Group 2 - Immune-challenged.
Group 3 - HN₂-treated.

Infection at 7 days of age
TRIAL II
- GROUP ONE
- GROUP TWO
- GROUP THREE

TOTAL SERUM PROTEIN CONCENTRATION IN GRAMS %

AGE OF BIRDS, IN DAYS

14 19 20 24 29 34 39 44 49 54 59 64 69

DIMETRIDAZOLE

HN₂ AND CHALLENGE
Table 24. Comparison of total serum albumin concentration in three groups of turkeys during the experimental period

<table>
<thead>
<tr>
<th>Days Post-infection</th>
<th>Group Numbers 1</th>
<th>Group Numbers 2</th>
<th>Group Numbers 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>6</td>
<td>1.04a (4)b</td>
<td>1.05 (3)</td>
<td>1.19 (5)</td>
</tr>
<tr>
<td></td>
<td>(39.58c)</td>
<td>(41.86)</td>
<td>(40.28)</td>
</tr>
<tr>
<td>13</td>
<td>0.87 (4)</td>
<td>0.27 (3)</td>
<td>0.62 (5)</td>
</tr>
<tr>
<td></td>
<td>(33.11)</td>
<td>(12.67)</td>
<td>(24.46)</td>
</tr>
<tr>
<td>16</td>
<td>1.09 (4)</td>
<td>0.80 (4)</td>
<td>0.83 (5)</td>
</tr>
<tr>
<td></td>
<td>(36.92)</td>
<td>(27.63)</td>
<td>(27.27)</td>
</tr>
<tr>
<td>23</td>
<td>1.37 (4)</td>
<td>1.18 (4)</td>
<td>1.39 (5)</td>
</tr>
<tr>
<td></td>
<td>(40.98)</td>
<td>(36.31)</td>
<td>(39.94)</td>
</tr>
<tr>
<td>27</td>
<td>1.46 (4)</td>
<td>1.34 (3)</td>
<td>1.52 (5)</td>
</tr>
<tr>
<td></td>
<td>(41.74)</td>
<td>(37.08)</td>
<td>(42.81)</td>
</tr>
<tr>
<td>30</td>
<td>1.47 (4)</td>
<td>1.34 (4)</td>
<td>1.46 (5)</td>
</tr>
<tr>
<td></td>
<td>(41.95)</td>
<td>(38.30)</td>
<td>(41.56)</td>
</tr>
<tr>
<td>35</td>
<td>1.09 (4)</td>
<td>1.33 (4)</td>
<td>1.24 (5)</td>
</tr>
<tr>
<td></td>
<td>(38.06)</td>
<td>(39.86)</td>
<td>(37.83)</td>
</tr>
<tr>
<td>37</td>
<td>0.80 (4)</td>
<td>1.13 (4)</td>
<td>0.76 (5)</td>
</tr>
<tr>
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<td>(31.88)</td>
<td>(36.59)</td>
<td>(23.96)</td>
</tr>
<tr>
<td>41</td>
<td>0.29 (4)</td>
<td>1.10 (4)</td>
<td>0.87 (5)</td>
</tr>
<tr>
<td></td>
<td>(9.54)</td>
<td>(34.76)</td>
<td>(18.62)</td>
</tr>
<tr>
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<td>0.78 (4)</td>
<td>1.09 (4)</td>
<td>1.00 (5)</td>
</tr>
<tr>
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<td>(16.76)</td>
<td>(30.01)</td>
<td>(22.16)</td>
</tr>
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<td>1.34 (4)</td>
<td>0.89 (4)</td>
<td>0.96 (5)</td>
</tr>
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<td>(27.31)</td>
<td>(23.48)</td>
<td>(21.24)</td>
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<td>50</td>
<td>1.63 (4)</td>
<td>0.91 (4)</td>
<td>1.06 (4)</td>
</tr>
<tr>
<td></td>
<td>(33.94)</td>
<td>(18.58)</td>
<td>(22.82)</td>
</tr>
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<td>1.61 (4)</td>
<td>1.25 (4)</td>
<td>0.84 (2)</td>
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<td>(34.55)</td>
<td>(21.27)</td>
<td>(19.26)</td>
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<td>57</td>
<td>1.47 (4)</td>
<td>1.86 (4)</td>
<td>1.64 (2)</td>
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<td>(31.18)</td>
<td>(26.81)</td>
<td>(38.44)</td>
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<td>1.60 (4)</td>
<td>1.90 (4)</td>
<td>1.58 (2)</td>
</tr>
<tr>
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<td>(38.36)</td>
<td>(32.34)</td>
<td>(35.67)</td>
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<td>1.45 (4)</td>
<td>2.11 (3)</td>
<td>1.98 (2)</td>
</tr>
<tr>
<td></td>
<td>(32.96)</td>
<td>(39.12)</td>
<td>(42.14)</td>
</tr>
</tbody>
</table>

aReported as grams percent.
bTotal number of birds used.
cReported as relative percent.
Figure 45. Progressive changes in serum albumin concentration (expressed in grams per cent) for the following groups in Trial II:

Group 1 - Immune-control.
Group 2 - Immune-challenged.
Group 3 - HN2-treated.

Infection at 7 days of age
Average serum albumin concentration in grams.

**Trial II**
- **Group One**
- **Group Two**
- **Group Three**

**Variables:**
- **Dimetridazole**
- **HN$_2$ and Challenge**

**Axes:**
- Y-axis: Average serum albumin concentration in grams.
- X-axis: Age of birds, in days.

**Legend:**
- Circles: Group One
- Triangles: Group Two
- Squares: Group Three
Figure 46. Progressive changes in serum albumin concentration (expressed as percent of the total serum protein) in the following groups in Trial II:

- Group 1 - Immune-control.
- Group 2 - Immune-challenged.
- Group 3 - HN2-treated.

Infection at 7 days of age
TRIAL II

- DIMETRIDAZOLE
- HN₂ AND CHALLENGE

AVERAGE SERUM ALBUMIN CONCENTRATION IN %

AGE OF BIRDS, IN DAYS

GROUP ONE
- GROUP TWO
- GROUP THREE
Table 25. Comparison of total serum alpha 1 globulin concentration in three groups of turkeys during the experimental period

<table>
<thead>
<tr>
<th>Days Post-infection</th>
<th>Group 1</th>
<th>Group 2</th>
<th>Group 3</th>
</tr>
</thead>
<tbody>
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<td>0.27 \textsuperscript{a}</td>
<td>0.28</td>
<td>0.28</td>
</tr>
<tr>
<td></td>
<td>(10.39) \textsuperscript{b}</td>
<td>(11.55)</td>
<td>(9.39)</td>
</tr>
<tr>
<td>13</td>
<td>0.37</td>
<td>0.31</td>
<td>0.36</td>
</tr>
<tr>
<td></td>
<td>(14.59)</td>
<td>(14.26)</td>
<td>(14.61)</td>
</tr>
<tr>
<td>16</td>
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<td>0.20</td>
<td>0.26</td>
</tr>
<tr>
<td></td>
<td>(9.25)</td>
<td>(6.84)</td>
<td>(8.20)</td>
</tr>
<tr>
<td>23</td>
<td>0.31</td>
<td>0.24</td>
<td>0.28</td>
</tr>
<tr>
<td></td>
<td>(9.47)</td>
<td>(7.32)</td>
<td>(7.96)</td>
</tr>
<tr>
<td>27</td>
<td>0.31</td>
<td>0.25</td>
<td>0.31</td>
</tr>
<tr>
<td></td>
<td>(8.75)</td>
<td>(6.82)</td>
<td>(8.85)</td>
</tr>
<tr>
<td>30</td>
<td>0.35</td>
<td>0.31</td>
<td>0.25</td>
</tr>
<tr>
<td></td>
<td>(9.93)</td>
<td>(9.00)</td>
<td>(7.10)</td>
</tr>
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<td>35</td>
<td>0.26</td>
<td>0.29</td>
<td>0.24</td>
</tr>
<tr>
<td></td>
<td>(9.50)</td>
<td>(8.57)</td>
<td>(7.52)</td>
</tr>
<tr>
<td>37</td>
<td>0.13</td>
<td>0.27</td>
<td>0.29</td>
</tr>
<tr>
<td></td>
<td>(5.38)</td>
<td>(9.07)</td>
<td>(9.13)</td>
</tr>
<tr>
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<td>(8.45)</td>
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<td>(7.37)</td>
<td>(4.67)</td>
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<td>0.32</td>
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</tr>
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<td>(4.11)</td>
<td>(6.72)</td>
<td>(6.24)</td>
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<td>57</td>
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<tr>
<td></td>
<td>(4.04)</td>
<td>(6.48)</td>
<td>(8.00)</td>
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<td>61</td>
<td>0.32</td>
<td>0.35</td>
<td>0.25</td>
</tr>
<tr>
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<td>(5.74)</td>
<td>(5.56)</td>
</tr>
<tr>
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<td>0.25</td>
</tr>
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<td>(6.72)</td>
<td>(7.79)</td>
<td>(5.37)</td>
</tr>
</tbody>
</table>

\textsuperscript{a} Reported as grams percent.

\textsuperscript{b} Reported as relative percent.
Table 26. Comparison of total serum alpha II globulin concentration of three groups of turkeys during the experimental period.

<table>
<thead>
<tr>
<th>Days Post-infection</th>
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<th>Group 3</th>
</tr>
</thead>
<tbody>
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<td>0.44</td>
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<tr>
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<td>(20.56)</td>
<td>(29.88)</td>
<td>(25.75)</td>
</tr>
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<td>0.58</td>
<td>0.50</td>
</tr>
<tr>
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<td>(16.83)</td>
<td>(20.14)</td>
<td>(16.30)</td>
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<td>0.47</td>
<td>0.45</td>
<td>0.50</td>
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<td>(14.18)</td>
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<td>(14.85)</td>
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</tr>
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<td>30</td>
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<td>0.46</td>
<td>0.51</td>
</tr>
<tr>
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<td>(13.11)</td>
<td>(14.54)</td>
</tr>
<tr>
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<td>0.50</td>
<td>0.45</td>
<td>0.58</td>
</tr>
<tr>
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<td>(18.94)</td>
<td>(13.68)</td>
<td>(18.86)</td>
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<tr>
<td>37</td>
<td>0.62</td>
<td>0.56</td>
<td>0.81</td>
</tr>
<tr>
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<td>(25.69)</td>
<td>(19.55)</td>
<td>(26.10)</td>
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<tr>
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<td>0.71</td>
<td>0.51</td>
<td>0.87</td>
</tr>
<tr>
<td></td>
<td>(23.23)</td>
<td>(15.26)</td>
<td>(19.33)</td>
</tr>
<tr>
<td>44</td>
<td>0.59</td>
<td>0.65</td>
<td>0.92</td>
</tr>
<tr>
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<td>(12.54)</td>
<td>(17.72)</td>
<td>(20.57)</td>
</tr>
<tr>
<td>47</td>
<td>0.71</td>
<td>0.72</td>
<td>1.08</td>
</tr>
<tr>
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<td>(14.43)</td>
<td>(17.11)</td>
<td>(24.08)</td>
</tr>
<tr>
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<td>0.66</td>
<td>0.91</td>
<td>1.00</td>
</tr>
<tr>
<td></td>
<td>(13.71)</td>
<td>(18.67)</td>
<td>(22.03)</td>
</tr>
<tr>
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<td>0.71</td>
<td>0.97</td>
<td>0.92</td>
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<td>(14.99)</td>
<td>(16.52)</td>
<td>(23.81)</td>
</tr>
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<td>0.69</td>
<td>0.99</td>
<td>0.68</td>
</tr>
<tr>
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<td>(14.18)</td>
<td>(14.21)</td>
<td>(16.08)</td>
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<tr>
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<td>1.00</td>
<td>0.86</td>
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<td>(19.01)</td>
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<td>0.95</td>
<td>0.83</td>
</tr>
<tr>
<td></td>
<td>(15.55)</td>
<td>(17.87)</td>
<td>(17.70)</td>
</tr>
</tbody>
</table>

aReported as grams percent.

bReported as relative percent.
Table 27. Comparison of total serum beta globulin concentration of three groups of turkeys during the experimental period

<table>
<thead>
<tr>
<th>Days Post-infection</th>
<th>1</th>
<th>Group Numbers</th>
<th>2</th>
<th>3</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0.72(^a)</td>
<td>0.59</td>
<td>0.79</td>
<td>0.59(^a)</td>
</tr>
<tr>
<td>13</td>
<td>0.51(^b)</td>
<td>0.66</td>
<td>0.61</td>
<td>0.51(^b)</td>
</tr>
<tr>
<td>16</td>
<td>0.68(^b)</td>
<td>0.70</td>
<td>0.74</td>
<td>0.68(^b)</td>
</tr>
<tr>
<td>23</td>
<td>0.57(^b)</td>
<td>0.55</td>
<td>0.63</td>
<td>0.57(^b)</td>
</tr>
<tr>
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<td>0.74(^b)</td>
<td>0.76</td>
<td>0.73</td>
<td>0.74(^b)</td>
</tr>
<tr>
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<td>0.71</td>
<td>0.70(^b)</td>
</tr>
<tr>
<td>35</td>
<td>0.59(^b)</td>
<td>0.71</td>
<td>0.70</td>
<td>0.59(^b)</td>
</tr>
<tr>
<td>37</td>
<td>0.64(^b)</td>
<td>0.65</td>
<td>0.85</td>
<td>0.64(^b)</td>
</tr>
<tr>
<td>41</td>
<td>0.83(^b)</td>
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<td>0.83(^b)</td>
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<tr>
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<td>1.07(^b)</td>
</tr>
<tr>
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<td>0.88</td>
<td>1.01</td>
<td>0.89(^b)</td>
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<tr>
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<td>1.00</td>
<td>0.88(^b)</td>
</tr>
<tr>
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<td>0.82(^b)</td>
<td>1.01</td>
<td>0.90</td>
<td>0.82(^b)</td>
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<tr>
<td>57</td>
<td>0.83(^b)</td>
<td>1.36</td>
<td>0.85</td>
<td>0.83(^b)</td>
</tr>
<tr>
<td>61</td>
<td>0.89(^b)</td>
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<td>0.89(^b)</td>
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<tr>
<td>64</td>
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<td>1.09</td>
<td>0.88</td>
<td>0.72(^b)</td>
</tr>
</tbody>
</table>

\(^a^\) Reported as grams percent.

\(^b^\) Reported as relative percent.
<table>
<thead>
<tr>
<th>Days Post-infection</th>
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<th>2</th>
<th>3</th>
</tr>
</thead>
<tbody>
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<td>0.19</td>
<td>0.27</td>
</tr>
<tr>
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<td>(6.90)(^a)</td>
<td>(7.68)</td>
<td>(9.06)</td>
</tr>
<tr>
<td>13</td>
<td>0.32</td>
<td>0.27</td>
<td>0.27</td>
</tr>
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<td>(12.53)</td>
<td>(10.84)</td>
</tr>
<tr>
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<td>0.43</td>
<td>0.61</td>
<td>0.76</td>
</tr>
<tr>
<td></td>
<td>(14.21)</td>
<td>(21.16)</td>
<td>(23.84)</td>
</tr>
<tr>
<td>23</td>
<td>0.61</td>
<td>0.85</td>
<td>0.70</td>
</tr>
<tr>
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<td>(18.22)</td>
<td>(25.71)</td>
<td>(19.62)</td>
</tr>
<tr>
<td>27</td>
<td>0.50</td>
<td>0.72</td>
<td>0.53</td>
</tr>
<tr>
<td></td>
<td>(14.16)</td>
<td>(20.03)</td>
<td>(14.57)</td>
</tr>
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<td>(16.47)</td>
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<tr>
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<td>(13.67)</td>
</tr>
<tr>
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<td>0.39</td>
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<tr>
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<td>(10.88)</td>
<td>(13.00)</td>
<td>(13.50)</td>
</tr>
<tr>
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<td>1.05</td>
<td>0.63</td>
<td>1.47</td>
</tr>
<tr>
<td></td>
<td>(31.74)</td>
<td>(18.61)</td>
<td>(32.63)</td>
</tr>
<tr>
<td>44</td>
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<td>0.87</td>
<td>1.16</td>
</tr>
<tr>
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<td>(40.64)</td>
<td>(21.38)</td>
<td>(26.77)</td>
</tr>
<tr>
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<td>1.69</td>
<td>1.48</td>
<td>1.17</td>
</tr>
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<td>(34.55)</td>
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<td>(26.86)</td>
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<td>1.44</td>
<td>1.78</td>
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<td>(36.02)</td>
<td>(26.52)</td>
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<td>1.27</td>
<td>2.49</td>
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</tr>
<tr>
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<td>(26.90)</td>
<td>(40.38)</td>
<td>(24.83)</td>
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<td>57</td>
<td>1.72</td>
<td>2.28</td>
<td>0.74</td>
</tr>
<tr>
<td></td>
<td>(33.61)</td>
<td>(32.88)</td>
<td>(17.43)</td>
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<td>0.80</td>
<td>1.58</td>
<td>0.80</td>
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</tr>
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<td>0.83</td>
<td>0.75</td>
</tr>
<tr>
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<td>(28.02)</td>
<td>(14.96)</td>
<td>(16.04)</td>
</tr>
</tbody>
</table>

\(^a\)Reported as grams percent.

\(^b\)Reported as relative percent.
Figure 47. Progressive changes in serum gamma globulin concentration (expressed in grams per cent) for the following groups in Trial II:

- Group 1 - Immune-control.
- Group 2 - Immune-challenged.
- Group 3 - HN2-treated.

Infection at 7 days of age
DIMETRIDA ZOLE

TRIAL II
- GROUP ONE
- GROUP TWO
- GROUP THREE

HN₂ AND CHALLENGE

AVERAGE SERUM GAMMA GLOBULIN CONCENTRATION IN GRAMS %

AGE OF BIRDS, IN DAYS

14 19 20 24 29 34 39 44 49 54 59 64 69
Figure 48. Progressive changes in serum gamma globulin concentration (expressed as per cent of total serum protein) in the following groups in Trial II:

- Group 1 - Immune-control.
- Group 2 - Immune-challenged.
- Group 3 - HN2-treated.

Infection at 7 days of age
Groups 1 and 2 (Figure 44). Significant changes were observed in both serum albumin and gamma globulin fractions (Figures 45, 46, 47, 48). Changes in other protein fractions were not remarkable.

Histopathologic Studies

**Group 1 - immune-control birds**

Birds in this group did not have either gross or microscopic lesions referable to histomonosis. Focal areas of lymphoid cell accumulations (similar to those described in Trial I) were numerous in the liver, cecal mucosa, spleen, and were occasionally seen in bronchial and intestinal mucosa.

**Group 2 - immune-challenged birds**

Gross cecal lesions were present in only 2 birds. Other birds in this group, did not have gross lesions either in the liver or ceca.

**Liver lesions** Histopathologic alterations were confined to 2 liver sections and consisted of discrete areas of resolving lesions. No histomonads were found in these areas.

**Cecal lesions** Microscopic examination of ceca with gross lesions revealed large numbers of polymorphonuclear leukocytes in the mucosa and submucosa. Giant cells containing degenerated forms of histomonads were present in these areas. Sections from ceca free of gross lesions were his-
to logically similar to those described in Group 2, Trial I.

Lesions in other tissues Lesions in other tissues were not remarkable and closely paralleled those described in Group 2 of Trial I.

Group 3 - HN2-treated birds

Gross lesions were present in livers of 3 of the 5 birds. Lesions in the other 2 birds were restricted to the ceca.

Liver lesions Microscopic liver lesions consisted of large necrotic areas with irregular borders. Macrophages, multinucleated giant cells and many histomonads were present in these areas. Frequently, giant cells contained one or more histomonads. A mild mononuclear cell infiltrate was present at the periphery of these necrotic areas. Sections from livers without gross lesions had a few focal resolving lesions.

Cecal lesions Microscopic cecal lesions were similar to those described for Group 3, Trial I.

Lesions in other tissues Marked lymphoid depletion was observed in the spleen (Figures 32 and 33) and the bursa of Fabricius (Figures 34 and 35). The histopathologic alterations found in the lungs, kidneys and small intestine were not remarkable.
Trial III
Mortality

Mortality rates in Groups 1, 2, 3, 4, and 5 were 0/5, 0/6, 1/7, 0/6, and 2/5, respectively.

Body Weights

Results of body weight gains were similar to those reported for Trial I and are summarized in Table 29. Slight weight gain depressions were evident in Groups 3 and 4 following treatment with HN₂ (Figure 49).

Hematologic Observations

**Total leukocyte counts**

Detailed results of the total leukocyte counts for the 5 groups are given in Table 30. No significant changes in total leukocyte counts were detected in Group 1, which consisted of uninfected control birds. In general, the average total leukocyte counts varied between 16,000 and 30,000 cells/cu. mm.

The leukocyte response pattern in infected groups (Groups 2, 3, and 4) was similar to that observed in Trial I. All groups except Group 1, had a marked increase in leukocytes following challenge with virulent histomonads (Figure 50).

**Differential leukocyte counts**

The results of differential leukocyte counts are sum-
Table 29. Comparison of average weights (in grams) of five groups of turkeys during the experimental period

<table>
<thead>
<tr>
<th>Days Post-infection</th>
<th>Group Numbers 1</th>
<th>Group Numbers 2</th>
<th>Group Numbers 3</th>
</tr>
</thead>
<tbody>
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<td>137 (4)</td>
<td>131 (3)</td>
</tr>
<tr>
<td>17</td>
<td>(0)</td>
<td>154 (4)</td>
<td>157 (3)</td>
</tr>
<tr>
<td>21</td>
<td>165 (5)</td>
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</tr>
<tr>
<td>24</td>
<td>193 (5)</td>
<td>204 (4)</td>
<td>215 (3)</td>
</tr>
<tr>
<td>28</td>
<td>231 (5)</td>
<td>245 (6)</td>
<td>223 (7)</td>
</tr>
<tr>
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<td>274 (5)</td>
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</tr>
<tr>
<td>38</td>
<td>365 (5)</td>
<td>452 (6)</td>
<td>370 (7)</td>
</tr>
<tr>
<td>42</td>
<td>442 (5)</td>
<td>523 (6)</td>
<td>412 (7)</td>
</tr>
<tr>
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<td>513 (5)</td>
<td>600 (6)</td>
<td>495 (7)</td>
</tr>
<tr>
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<td>593 (5)</td>
<td>663 (6)</td>
<td>564 (7)</td>
</tr>
<tr>
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<td>662 (5)</td>
<td>666 (6)</td>
<td>549 (7)</td>
</tr>
<tr>
<td>56</td>
<td>783 (5)</td>
<td>723 (6)</td>
<td>617 (6)</td>
</tr>
</tbody>
</table>

a No weights recorded.
b Total number of birds used.

Table 30. Comparison of average total leukocyte counts of five groups of turkeys during the experimental period

<table>
<thead>
<tr>
<th>Days Post-infection</th>
<th>Group Numbers 1</th>
<th>Group Numbers 2</th>
<th>Group Numbers 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>14</td>
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<td>31,050 (4)</td>
<td>35,700 (3)</td>
</tr>
<tr>
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<td>(0)</td>
<td>29,800 (4)</td>
<td>21,050 (3)</td>
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<tr>
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<td>23,300 (5)</td>
<td>28,050 (4)</td>
<td>23,050 (3)</td>
</tr>
<tr>
<td>24</td>
<td>26,450 (5)</td>
<td>20,950 (4)</td>
<td>19,950 (3)</td>
</tr>
<tr>
<td>28</td>
<td>16,400 (5)</td>
<td>25,000 (6)</td>
<td>23,950 (7)</td>
</tr>
<tr>
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<td>23,650 (5)</td>
<td>21,750 (6)</td>
<td>26,700 (7)</td>
</tr>
<tr>
<td>35</td>
<td>21,550 (5)</td>
<td>22,650 (6)</td>
<td>19,800 (7)</td>
</tr>
<tr>
<td>38</td>
<td>19,800 (5)</td>
<td>15,450 (6)</td>
<td>9,850 (7)</td>
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<td>32,700 (6)</td>
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<td>38,000 (7)</td>
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<td>56</td>
<td>28,600 (5)</td>
<td>50,300 (6)</td>
<td>50,650 (6)</td>
</tr>
</tbody>
</table>

a No samples recorded.
b Total number of birds used.
<table>
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<tr>
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<th>5</th>
</tr>
</thead>
<tbody>
<tr>
<td>117</td>
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<td>-</td>
</tr>
<tr>
<td>137</td>
<td>(4)</td>
<td>-</td>
</tr>
<tr>
<td>154</td>
<td>(4)</td>
<td>187</td>
</tr>
<tr>
<td>177</td>
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<td>216</td>
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<tr>
<td>223</td>
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<td>258</td>
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<td>273</td>
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<td>306</td>
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<tr>
<td>333</td>
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<td>374</td>
</tr>
<tr>
<td>381</td>
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<td>425</td>
</tr>
<tr>
<td>470</td>
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<td>509</td>
</tr>
<tr>
<td>491</td>
<td>(6)</td>
<td>598</td>
</tr>
<tr>
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<td>(6)</td>
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<td>729</td>
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<tr>
<td>463</td>
<td>(6)</td>
<td>830</td>
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<table>
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<tr>
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<td>23,600</td>
</tr>
<tr>
<td>20,950</td>
<td>(4)</td>
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<td>20,600</td>
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<tr>
<td>21,550</td>
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</tr>
<tr>
<td>18,150</td>
<td>(6)</td>
<td>19,950</td>
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</tr>
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<td>36,950</td>
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<td>31,700</td>
<td>(6)</td>
<td>39,900</td>
</tr>
<tr>
<td>41,600</td>
<td>(6)</td>
<td>54,500</td>
</tr>
</tbody>
</table>
Figure 49. Progressive changes in the body weights of the following groups in Trial III:

Group 1 - Uninfected-control.
Group 2 - Immune-challenged.
Groups 3 and 4 - HN2-treated.
Group 5 - Infected-control.

Infection at 7 days of age
Figure 50. Total leukocyte response pattern of the following groups in Trial III:

- Group 1 - Uninfected-control.
- Group 2 - Immune-challenged.
- Groups 3 and 4 - HN2-treated.
- Group 5 - Infected-control.

Infection at 7 days of age
marized in Tables 31 through 35. Changes in total leukocyte counts were reflected in absolute heterophil numbers (Figure 51). Marked heterophilia was observed in all infected groups before treatment with dimetridazole (Figures 51 and 52). Heterophil numbers below 6,000 cells/cu. mm. were seen in Group 3 which was being treated with HN2. After challenge, the absolute heterophil numbers were markedly increased in all groups except the control group (Figure 51).

The lymphocyte response pattern in all the groups except Group 3 was similar to that of the control group (Figures 53 and 54). In Group 3, total lymphocyte numbers fell below control levels following treatment with HN2. Total lymphocyte numbers above control values were observed in Group 5 on the day the experiment was terminated (Figure 53).

Changes in other cell types were not remarkable. A twofold increase in eosinophils was found in Group 5 on the last day of the experiment. One bird in this group had a marked eosinophilia (total eosinophil count of over 2,900 cells/cu. mm.) on this day, which was reflected in the high average total eosinophil count for the whole group. There was an increase in total number of monocytes in all groups except Group 1, in the terminal stages of the experiment. Basophils accounted for 3 to 6 per cent of the total leukocyte counts in all groups.
Table 31. Comparison of average total heterophil counts of five groups of turkeys during the experimental period

<table>
<thead>
<tr>
<th>Days Post-infection</th>
<th>Group Numbers 1</th>
<th>Group Numbers 2</th>
<th>Group Numbers 3</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>14</td>
<td>a</td>
<td>(66.25)b</td>
<td>(68.00)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>21,450 c</td>
<td>24,150</td>
</tr>
<tr>
<td>17</td>
<td></td>
<td>(55.00)</td>
<td>(49.00)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>16,600</td>
<td>10,550</td>
</tr>
<tr>
<td>21</td>
<td>(54.80)</td>
<td>(52.00)</td>
<td>(55.67)</td>
</tr>
<tr>
<td></td>
<td>12,850</td>
<td>14,700</td>
<td>13,350</td>
</tr>
<tr>
<td>24</td>
<td>(49.20)</td>
<td>(53.50)</td>
<td>(51.33)</td>
</tr>
<tr>
<td></td>
<td>13,200</td>
<td>11,250</td>
<td>10,400</td>
</tr>
<tr>
<td>28</td>
<td>(50.40)</td>
<td>(49.50)</td>
<td>(40.86)</td>
</tr>
<tr>
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<td>8,200</td>
<td>12,100</td>
<td>9,950</td>
</tr>
<tr>
<td>31</td>
<td>(55.00)</td>
<td>(56.17)</td>
<td>(50.14)</td>
</tr>
<tr>
<td></td>
<td>13,750</td>
<td>12,100</td>
<td>14,500</td>
</tr>
<tr>
<td>35</td>
<td>(47.20)</td>
<td>(44.00)</td>
<td>(47.57)</td>
</tr>
<tr>
<td></td>
<td>10,450</td>
<td>9,650</td>
<td>9,650</td>
</tr>
<tr>
<td>38</td>
<td>(41.40)</td>
<td>(47.17)</td>
<td>(56.00)</td>
</tr>
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<td></td>
<td>8,350</td>
<td>7,350</td>
<td>5,400</td>
</tr>
<tr>
<td>42</td>
<td>(39.60)</td>
<td>(43.33)</td>
<td>(43.71)</td>
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<td>10,850</td>
<td>7,100</td>
<td>5,800</td>
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<tr>
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<td>(33.60)</td>
<td>(42.00)</td>
<td>(32.71)</td>
</tr>
<tr>
<td></td>
<td>8,400</td>
<td>8,950</td>
<td>6,000</td>
</tr>
<tr>
<td>49</td>
<td>(41.80)</td>
<td>(60.50)</td>
<td>(47.29)</td>
</tr>
<tr>
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<td>14,850</td>
<td>20,550</td>
<td>16,000</td>
</tr>
<tr>
<td>52</td>
<td>(35.20)</td>
<td>(62.50)</td>
<td>(59.29)</td>
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<tr>
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<td>7,600</td>
<td>31,600</td>
<td>22,800</td>
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<tr>
<td>56</td>
<td>(48.40)</td>
<td>(59.00)</td>
<td>(61.17)</td>
</tr>
<tr>
<td></td>
<td>13,800</td>
<td>31,650</td>
<td>34,150</td>
</tr>
</tbody>
</table>

aNo samples recorded.

bReported as percentage.

cReported as total numbers of cells/cu. mm.
<table>
<thead>
<tr>
<th>4/(75.50)</th>
<th>5/(52.60)</th>
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</tr>
<tr>
<td>44,00</td>
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</tr>
<tr>
<td>10,400</td>
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<tr>
<td>12,650</td>
<td>12,250</td>
</tr>
<tr>
<td>10,750</td>
<td>11,100</td>
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<td>7,450</td>
<td>10,450</td>
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<td>10,600</td>
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<tr>
<td>7,450</td>
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<td>9,650</td>
<td>13,350</td>
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<tr>
<td>25,750</td>
<td>12,300</td>
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<tr>
<td>21,000</td>
<td>23,100</td>
</tr>
<tr>
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<td>13,350</td>
</tr>
<tr>
<td>22,050</td>
<td>25,450</td>
</tr>
</tbody>
</table>
Figure 51. Absolute numbers of heterophils in the following groups in Trial III:

- Group 1 - Uninfected-control.
- Group 2 - Immune-challenged.
- Groups 3 and 4 - HN2-treated.
- Group 5 - Infected-control.

Infection at 7 days of age
TRIAL III

- GROUP ONE
- GROUP TWO
- GROUP THREE
- GROUP FOUR
- GROUP FIVE

AGE OF BIRDS, IN DAYS

HN₂ TO
GROUP 3 CHALLENGE GROUP 4
Figure 52. Relative numbers of heterophils (expressed in per cent) for the following groups in Trial III:

- Group 1 - Uninfected-control.
- Group 2 - Immune-challenged.
- Groups 3 and 4 - HN2-treated.
- Group 5 - Infected-control.

Infection at 7 days of age
TRIAL III

- GROUP ONE
- GROUP TWO
- GROUP THREE
- GROUP FOUR
- GROUP FIVE

AGE OF BIRDS, IN DAYS

RELATIVE HETEROPIHIL NUMBERS IN %

HN₂ TO GROUP 3 CHALLENGE GROUP 4
Table 32. Comparison of average total eosinophil counts of five groups of turkeys during the experimental period

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<tr>
<th>Days Post-infection</th>
<th>1</th>
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<th>Group Numbers</th>
<th>3</th>
<th>4</th>
<th>5</th>
</tr>
</thead>
<tbody>
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<td>14</td>
<td>a</td>
<td>(0.75)</td>
<td>(0.33)</td>
<td>(0.25)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>212 c</td>
<td>135</td>
<td>166</td>
<td></td>
<td></td>
</tr>
<tr>
<td>17</td>
<td></td>
<td></td>
<td>(0.33)</td>
<td>(1.50)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>62</td>
<td>369</td>
<td></td>
<td></td>
</tr>
<tr>
<td>21</td>
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<td>(0.25)</td>
<td>(1.00)</td>
<td>(0.25)</td>
<td>(0.00)</td>
<td></td>
</tr>
<tr>
<td></td>
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<td>183</td>
<td>44</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>24</td>
<td>(0.60)</td>
<td>(0.25)</td>
<td>(0.33)</td>
<td>(0.25)</td>
<td>(0.60)</td>
<td></td>
</tr>
<tr>
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<td>180</td>
<td>50</td>
<td>53</td>
<td>63</td>
<td>158</td>
<td></td>
</tr>
<tr>
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<td>(0.00)</td>
<td>(0.33)</td>
<td>(0.86)</td>
<td>(0.00)</td>
<td>(0.00)</td>
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</tr>
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<td>0</td>
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<td>(0.33)</td>
<td>(0.71)</td>
<td>(0.50)</td>
<td>(0.40)</td>
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</tr>
<tr>
<td></td>
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<td>79</td>
<td>112</td>
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</tr>
<tr>
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<td>(0.00)</td>
<td>(0.14)</td>
<td>(0.00)</td>
<td>(0.20)</td>
<td></td>
</tr>
<tr>
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<td></td>
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<td>(0.00)</td>
<td>(0.14)</td>
<td>(0.00)</td>
<td>(0.00)</td>
<td></td>
</tr>
<tr>
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<td>0</td>
<td>0</td>
<td>15</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>42</td>
<td>(0.20)</td>
<td>(0.83)</td>
<td>(0.43)</td>
<td>(0.20)</td>
<td>(0.20)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>42</td>
<td>132</td>
<td>59</td>
<td>50</td>
<td>60</td>
<td></td>
</tr>
<tr>
<td>45</td>
<td>(0.00)</td>
<td>(0.17)</td>
<td>(0.29)</td>
<td>(0.17)</td>
<td>(0.00)</td>
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<tr>
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<td>0</td>
<td>33</td>
<td>57</td>
<td>22</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>49</td>
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<td>(0.00)</td>
<td>(0.00)</td>
<td>(0.33)</td>
<td>(0.20)</td>
<td></td>
</tr>
<tr>
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<td>0</td>
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<td>0</td>
<td>102</td>
<td>64</td>
<td></td>
</tr>
<tr>
<td>52</td>
<td>(0.00)</td>
<td>(0.00)</td>
<td>(0.00)</td>
<td>(0.17)</td>
<td>(0.00)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>119</td>
<td>0</td>
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</tr>
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<td>(0.17)</td>
<td>(0.33)</td>
<td>(0.00)</td>
<td>(1.25)</td>
<td></td>
</tr>
<tr>
<td></td>
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<td>158</td>
<td>165</td>
<td>0</td>
<td>732</td>
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</tbody>
</table>

aNo sample recorded.

bReported as percentage.

cReported as total numbers of cells/cu. mm.
Table 33. Comparison of average total monocyte counts of five groups of turkeys during the experimental period

<table>
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<tr>
<th>Days Post-infection</th>
<th>1</th>
<th>2</th>
<th>Group Numbers</th>
<th>4</th>
<th>5</th>
</tr>
</thead>
<tbody>
<tr>
<td>14</td>
<td>a (0.75)</td>
<td>212 c (0.67)</td>
<td>(0.25)</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>17</td>
<td>— (0.00)</td>
<td>0</td>
<td>87 (0.75)</td>
<td>193 (0.75)</td>
<td>—</td>
</tr>
<tr>
<td>21</td>
<td>(0.00)</td>
<td>0</td>
<td>0 214 (0.75)</td>
<td>0 (0.25)</td>
<td>(0.40)</td>
</tr>
<tr>
<td>24</td>
<td>(0.80)</td>
<td>188</td>
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<td>53 (0.25)</td>
<td>63 (0.40)</td>
</tr>
<tr>
<td>28</td>
<td>(0.40)</td>
<td>63</td>
<td>99 (0.33)</td>
<td>361 (0.67)</td>
<td>121 (0.00)</td>
</tr>
<tr>
<td>31</td>
<td>(0.40)</td>
<td>135</td>
<td>0 (0.00)</td>
<td>93 (0.29)</td>
<td>54 (0.20)</td>
</tr>
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<td>(0.40)</td>
<td>79</td>
<td>119 (0.50)</td>
<td>95 (0.33)</td>
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<td>0</td>
<td>21 (0.17)</td>
<td>44 (0.17)</td>
<td>40 (0.80)</td>
</tr>
<tr>
<td>42</td>
<td>(0.00)</td>
<td>0</td>
<td>30 (0.17)</td>
<td>135 (0.60)</td>
<td>140 (0.20)</td>
</tr>
<tr>
<td>45</td>
<td>(0.60)</td>
<td>136</td>
<td>119 (0.67)</td>
<td>61 (0.00)</td>
<td>0 (0.00)</td>
</tr>
<tr>
<td>49</td>
<td>(0.40)</td>
<td>170</td>
<td>120 (0.33)</td>
<td>105 (0.33)</td>
<td>42 (1.00)</td>
</tr>
<tr>
<td>52</td>
<td>(0.60)</td>
<td>134</td>
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<td>392 (1.14)</td>
<td>567 (1.50)</td>
</tr>
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<td>69</td>
<td>484 (0.67)</td>
<td>1,018 (1.50)</td>
<td>529 (0.75)</td>
</tr>
</tbody>
</table>

a No samples recorded.

b Reported as percentage.

c Reported as total numbers of cells/cu. mm.
Table 34. Comparison of average total lymphocyte counts of five groups of turkeys during the experimental period

<table>
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<th>Group Numbers 2</th>
<th>3</th>
</tr>
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<td>(29.25)b</td>
<td>(29.33)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>8,150 c</td>
<td>10,600</td>
</tr>
<tr>
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<td></td>
<td>(42.75)</td>
<td>(47.00)</td>
</tr>
<tr>
<td></td>
<td></td>
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<td>9,750</td>
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<td>(42.20)</td>
<td>(41.75)</td>
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</tr>
<tr>
<td></td>
<td>9,850</td>
<td>11,550</td>
<td>9,200</td>
</tr>
<tr>
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<td>(45.60)</td>
<td>(41.25)</td>
<td>(43.67)</td>
</tr>
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<td>8,600</td>
<td>8,550</td>
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<td>28</td>
<td>(46.00)</td>
<td>(45.17)</td>
<td>(51.57)</td>
</tr>
<tr>
<td></td>
<td>7,550</td>
<td>11,500</td>
<td>12,150</td>
</tr>
<tr>
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<td>(42.40)</td>
<td>(39.67)</td>
<td>(45.57)</td>
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<td>9,400</td>
<td>8,650</td>
<td>11,550</td>
</tr>
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<td>(47.20)</td>
<td>(51.83)</td>
<td>(47.29)</td>
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<td>9,200</td>
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<tr>
<td>38</td>
<td>(55.60)</td>
<td>(48.17)</td>
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<td>3,750</td>
</tr>
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<td>(55.20)</td>
<td>(49.33)</td>
<td>(46.43)</td>
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<td>15,200</td>
<td>8,700</td>
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<tr>
<td>45</td>
<td>(60.40)</td>
<td>(52.00)</td>
<td>(63.43)</td>
</tr>
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<td>14,400</td>
<td>10,350</td>
<td>8,850</td>
</tr>
<tr>
<td>49</td>
<td>(55.20)</td>
<td>(34.83)</td>
<td>(50.29)</td>
</tr>
<tr>
<td></td>
<td>17,850</td>
<td>10,850</td>
<td>13,850</td>
</tr>
<tr>
<td>52</td>
<td>(60.40)</td>
<td>(32.50)</td>
<td>(36.71)</td>
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<td>56</td>
<td>(46.00)</td>
<td>(37.17)</td>
<td>(33.67)</td>
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<tr>
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<td>13,100</td>
<td>16,950</td>
<td>14,200</td>
</tr>
</tbody>
</table>

aNo sample recorded.

bReported as percentage.

cReported as total numbers of cells/cu. mm.
Figure 53. Absolute numbers of lymphocytes in the following groups in Trial III:

Group 1 - Uninfected-control.
Group 2 - Immune-challenged.
Groups 3 and 4 - HN₂-treated.
Group 5 - Infected-control.

Infection at 7 days of age
Figure 54. Relative numbers of lymphocytes (expressed in per cent) for the following groups in Trial III:

- Group 1 - Uninfected-control.
- Group 2 - Immune-challenged.
- Groups 3 and 4 - HN₂-treated.
- Group 5 - Infected-control.

Infection at 7 days of age
Table 35. Comparison of average total basophil counts of five groups of turkeys during the experimental period

<table>
<thead>
<tr>
<th>Days Post-infection</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
</tr>
</thead>
<tbody>
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<td>14</td>
<td>a</td>
<td>(3.00)(^b)</td>
<td>(1.67)</td>
<td>(2.25)</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1,008(^c)</td>
<td>554</td>
<td>1,580</td>
<td>-</td>
</tr>
<tr>
<td>17</td>
<td>-</td>
<td>(2.25)</td>
<td>(3.33)</td>
<td>(3.75)</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td></td>
<td>736</td>
<td>617</td>
<td>804</td>
<td>-</td>
</tr>
<tr>
<td>21</td>
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<td>(5.25)</td>
<td>(3.00)</td>
<td>(4.75)</td>
<td>(4.80)</td>
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<td>1,119</td>
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<td>(4.75)</td>
<td>(4.33)</td>
<td>(3.50)</td>
<td>(4.40)</td>
</tr>
<tr>
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<td>980</td>
<td>900</td>
<td>729</td>
<td>1,045</td>
</tr>
<tr>
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<td>(3.20)</td>
<td>(4.67)</td>
<td>(5.57)</td>
<td>(5.83)</td>
<td>(2.60)</td>
</tr>
<tr>
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<td>1,213</td>
<td>1,345</td>
<td>1,073</td>
<td>528</td>
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<td>(3.83)</td>
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<td>(5.33)</td>
<td>(3.40)</td>
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<td>841</td>
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<td>965</td>
<td>684</td>
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<td>(4.50)</td>
<td>(5.29)</td>
<td>(3.50)</td>
<td>(5.40)</td>
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<td>600</td>
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<td>(6.33)</td>
<td>(8.29)</td>
<td>(6.40)</td>
<td>(7.00)</td>
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<td>954</td>
<td>1,002</td>
<td>1,532</td>
<td>1,890</td>
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<td>(5.40)</td>
<td>(4.17)</td>
<td>(2.86)</td>
<td>(4.83)</td>
<td>(4.00)</td>
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<td>765</td>
<td>1,312</td>
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<td>(2.00)</td>
<td>(3.67)</td>
<td>(4.60)</td>
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<td>(2.86)</td>
<td>(3.00)</td>
<td>(4.60)</td>
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<td>941</td>
<td>1,201</td>
<td>619</td>
<td>1,579</td>
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<td>(3.00)</td>
<td>(3.00)</td>
<td>(2.67)</td>
<td>(7.75)</td>
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<tr>
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<td>1,215</td>
<td>1,043</td>
<td>1,128</td>
<td>1,177</td>
<td>4,523</td>
</tr>
</tbody>
</table>

\(^a\) No samples recorded.

\(^b\) Reported as percentage.

\(^c\) Reported as total numbers of cells/cu. mm.
Results of SGOT analyses are given in Table 36. Changes in SGOT values were not remarkable in any one group. Some sick birds had elevated SGOT levels but this was not reflected in the mean value for the group.

Serum Protein Studies

Results of serum protein determinations are given in Tables 37 through 42. No significant changes were detected in the total serum protein levels among all groups (Figure 55). Changes in albumin and globulin fractions in all infected groups were similar to those described for Trial I (Figures 56, 57, 58, 59). However, gamma globulin levels in Group 5 (infected at the day of challenge) did not differ significantly from those of the uninfected control group (Group 1) (Figures 58 and 59).

Histopathologic Studies

Group 1 - uninfected-control birds

All birds in the group were killed at the end of the trial and no gross lesions were observed. On microscopic examination small necrotic foci were found scattered throughout the liver parenchyma. Coagulative necrosis had occurred without cellular response. No significant microscopic lesions
**Table 36.** Comparison of serum glutamic-oxalacetic transaminase (SGOT) activity of five groups of turkeys during the experimental period

<table>
<thead>
<tr>
<th>Days Post-infection</th>
<th>1</th>
<th>2</th>
<th>Group Numbers</th>
<th>3</th>
<th>4</th>
<th>5</th>
</tr>
</thead>
<tbody>
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<td>14</td>
<td>-a</td>
<td>252.00</td>
<td>318.00</td>
<td>358.00</td>
<td>-</td>
<td></td>
</tr>
<tr>
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<td>-a</td>
<td>204.00</td>
<td>240.00</td>
<td>250.50</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>21</td>
<td>304.80</td>
<td>268.50</td>
<td>324.00</td>
<td>282.00</td>
<td>300.00</td>
<td></td>
</tr>
<tr>
<td>24</td>
<td>277.50</td>
<td>292.50</td>
<td>298.00</td>
<td>336.00</td>
<td>250.00</td>
<td></td>
</tr>
<tr>
<td>28</td>
<td>262.00</td>
<td>267.00</td>
<td>251.00</td>
<td>249.20</td>
<td>285.00</td>
<td></td>
</tr>
<tr>
<td>31</td>
<td>290.00</td>
<td>218.00</td>
<td>223.29</td>
<td>209.33</td>
<td>249.00</td>
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</tr>
<tr>
<td>35</td>
<td>267.00</td>
<td>206.00</td>
<td>211.71</td>
<td>189.00</td>
<td>204.00</td>
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</tr>
<tr>
<td>38</td>
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<td>231.00</td>
<td>220.00</td>
<td>212.00</td>
<td>190.50</td>
<td></td>
</tr>
<tr>
<td>42</td>
<td>258.00</td>
<td>254.00</td>
<td>213.43</td>
<td>184.80</td>
<td>226.80</td>
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</tr>
<tr>
<td>45</td>
<td>240.00</td>
<td>248.00</td>
<td>207.43</td>
<td>199.20</td>
<td>204.00</td>
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<tr>
<td>49</td>
<td>282.00</td>
<td>217.67</td>
<td>202.29</td>
<td>187.00</td>
<td>207.00</td>
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</tr>
<tr>
<td>52</td>
<td>255.60</td>
<td>233.33</td>
<td>284.71</td>
<td>314.00</td>
<td>207.20</td>
<td></td>
</tr>
<tr>
<td>56</td>
<td>277.20</td>
<td>217.00</td>
<td>274.00</td>
<td>356.00</td>
<td>226.50</td>
<td></td>
</tr>
</tbody>
</table>

* a No samples recorded.
* b SGOT reported in Sigma-Frankel Units.

**Table 37.** Comparison of total serum protein values of five groups of turkeys during the experimental period

<table>
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<tr>
<th>Days Post-infection</th>
<th>1</th>
<th>2</th>
<th>Group Numbers</th>
<th>3</th>
<th>4</th>
<th>5</th>
</tr>
</thead>
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<td>2.47b</td>
<td>2.67</td>
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<td></td>
</tr>
<tr>
<td>17</td>
<td>-</td>
<td>3.17</td>
<td>3.87</td>
<td>2.97</td>
<td></td>
<td></td>
</tr>
<tr>
<td>21</td>
<td>2.98</td>
<td>3.15</td>
<td>3.20</td>
<td>3.15</td>
<td>2.84</td>
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<tr>
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<td>3.00</td>
<td>3.25</td>
<td>3.17</td>
<td>3.35</td>
<td></td>
<td></td>
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<tr>
<td>28</td>
<td>3.00</td>
<td>3.47</td>
<td>3.36</td>
<td>3.27</td>
<td></td>
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<td>3.12</td>
<td>3.33</td>
<td>3.07</td>
<td>3.13</td>
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<td></td>
</tr>
<tr>
<td>35</td>
<td>2.98</td>
<td>3.27</td>
<td>3.06</td>
<td>2.95</td>
<td></td>
<td></td>
</tr>
<tr>
<td>38</td>
<td>3.14</td>
<td>3.30</td>
<td>3.55</td>
<td>3.33</td>
<td></td>
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<tr>
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<td>2.58</td>
<td>2.86</td>
<td>2.80</td>
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<td></td>
</tr>
<tr>
<td>45</td>
<td>3.24</td>
<td>3.10</td>
<td>3.17</td>
<td>2.90</td>
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</tr>
<tr>
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<td>3.02</td>
<td>3.05</td>
<td>3.04</td>
<td>2.87</td>
<td></td>
<td></td>
</tr>
<tr>
<td>52</td>
<td>3.04</td>
<td>3.52</td>
<td>2.83</td>
<td>2.73</td>
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<td>56</td>
<td>3.64</td>
<td>4.63</td>
<td>3.85</td>
<td>3.47</td>
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</tr>
</tbody>
</table>

* a No samples recorded.
* b Reported as grams/100 ml. of serum.
Figure 55. Progressive changes in total serum protein in the following groups in Trial III:

Group 1 - Uninfected-control.
Group 2 - Immune-challenged.
Groups 3 and 4 - HN₂-treated.
Group 5 - Infected-control.

Infection at 7 days of age
Table 38. Comparison of total serum albumin concentration of five groups of turkeys during the experimental period

<table>
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<tr>
<th>Days Post-infection</th>
<th>Group Numbers</th>
</tr>
</thead>
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<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>17</td>
<td></td>
</tr>
<tr>
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<td></td>
</tr>
<tr>
<td>21</td>
<td>1.21</td>
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<tr>
<td></td>
<td>(42.04)</td>
</tr>
<tr>
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<td>(43.86)</td>
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<td>1.28</td>
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<td>(43.21)</td>
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<td>1.49</td>
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<td>(41.06)</td>
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</table>

a No samples recorded.

b Reported as grams percent.

c Reported as relative percent.
Figure 56. Progressive changes in serum albumin concentration (expressed in grams per cent) for the following groups in Trial III:

- Group 1 - Uninfected-control.
- Group 2 - Immune-challenged.
- Groups 3 and 4 - HN2-treated.
- Group 5 - Infected-control.

Infection at 7 days of age
Figure 57. Progressive changes in serum albumin concentration (expressed as per cent of the total serum protein) in the following groups in Trial III:

Group 1 - Uninfected-control.
Group 2 - Immune-challenged.
Groups 3 and 4 - HN2-treated.
Group 5 - Infected-control.

Infection at 7 days of age
Table 39. Comparison of total serum alpha 1 globulin concentration of five groups of turkeys during the experimental period

<table>
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<th>Days Post-infection</th>
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<td>0.11</td>
<td>0.15</td>
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</tr>
<tr>
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<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>(8.67)c</td>
<td>(4.10)</td>
<td>(6.36)</td>
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</tr>
<tr>
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<td>0.26</td>
<td>0.28</td>
<td>0.25</td>
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<td>(8.84)</td>
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<tr>
<td></td>
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<td>(8.13)</td>
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<td>(7.73)</td>
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<td>0.27</td>
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<td>(10.18)</td>
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<td>0.24</td>
</tr>
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<td></td>
<td></td>
</tr>
<tr>
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<td></td>
<td>(8.73)</td>
<td>(10.02)</td>
<td>(8.06)</td>
<td>(8.31)</td>
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<td>0.35</td>
<td>0.33</td>
<td>0.27</td>
<td>0.29</td>
<td>0.35</td>
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</tr>
<tr>
<td></td>
<td></td>
<td>(10.56)</td>
<td>(10.77)</td>
<td>(8.50)</td>
<td>(9.79)</td>
</tr>
<tr>
<td>49</td>
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<td>0.20</td>
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</tr>
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</tr>
<tr>
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<td></td>
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<td>(10.39)</td>
<td>(10.42)</td>
<td>(7.17)</td>
</tr>
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<td>52</td>
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<td></td>
<td></td>
</tr>
<tr>
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<td></td>
<td>(9.73)</td>
<td>(7.28)</td>
<td>(8.39)</td>
<td>(7.09)</td>
</tr>
<tr>
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<td>0.27</td>
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</tr>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>(8.06)</td>
<td>(5.16)</td>
<td>(7.05)</td>
<td>(4.84)</td>
</tr>
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</table>

a No samples recorded.

b Reported as grams percent.

c Reported as relative percent.
Table 40. Comparison of total serum alpha II globulin concentration of five groups of turkeys during the experimental period

<table>
<thead>
<tr>
<th>Days Post-infection</th>
<th>Group Numbers</th>
<th>1</th>
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<th>3</th>
<th>4</th>
<th>5</th>
</tr>
</thead>
<tbody>
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<td>14</td>
<td>a</td>
<td>0.68 b</td>
<td>0.67</td>
<td>0.75</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>17</td>
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<td>0.66</td>
<td>0.73</td>
<td>0.50</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>21</td>
<td>0.52</td>
<td>(18.03)</td>
<td>0.64</td>
<td>0.64</td>
<td>0.62</td>
<td>0.53</td>
</tr>
<tr>
<td>24</td>
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<td>(17.99)</td>
<td>0.61</td>
<td>0.48</td>
<td>0.51</td>
<td>0.54</td>
</tr>
<tr>
<td>28</td>
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<td>0.57</td>
<td>0.45</td>
<td>0.55</td>
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<tr>
<td>31</td>
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<td>(12.46)</td>
<td>0.40</td>
<td>0.39</td>
<td>0.45</td>
<td>0.44</td>
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<tr>
<td>35</td>
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<td>(11.84)</td>
<td>0.35</td>
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<td>0.39</td>
<td>0.40</td>
</tr>
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<td>42</td>
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<td>0.34</td>
</tr>
<tr>
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<td>(11.86)</td>
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<td>0.41</td>
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<td>0.38</td>
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<tr>
<td>49</td>
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<td>(13.00)</td>
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<td>0.63</td>
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<tr>
<td>52</td>
<td>0.41</td>
<td>(13.16)</td>
<td>0.71</td>
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<td>0.81</td>
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<td>0.52</td>
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\*No samples recorded.
\*Reported as grams percent.
\*Reported as relative percent.
Table 41. Comparison of total serum beta globulin concentration of five groups of turkeys during the experimental period

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<th>Days Post-infection</th>
<th>Group Numbers</th>
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<th></th>
<th></th>
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</thead>
<tbody>
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<td>1</td>
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<td>3</td>
<td>4</td>
<td>5</td>
</tr>
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<td>14</td>
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<td>0.77</td>
<td>0.60</td>
<td>-</td>
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<tr>
<td></td>
<td>(28.65) c</td>
<td>(28.76)</td>
<td>(24.93)</td>
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<td></td>
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<tr>
<td>17</td>
<td>-</td>
<td>0.68</td>
<td>0.87</td>
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<td>-</td>
</tr>
<tr>
<td></td>
<td>(21.22)</td>
<td>(23.30)</td>
<td>(21.44)</td>
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<td></td>
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<tr>
<td>21</td>
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<td>0.68</td>
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<td>0.60</td>
</tr>
<tr>
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<td>0.66</td>
<td>0.58</td>
</tr>
<tr>
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<td>(19.76)</td>
<td>(21.02)</td>
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<td>0.66</td>
<td>0.65</td>
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</tr>
<tr>
<td></td>
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<td>(21.77)</td>
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</tr>
<tr>
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<td>0.63</td>
<td>0.53</td>
<td>0.61</td>
</tr>
<tr>
<td></td>
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<td>(17.87)</td>
<td>(17.06)</td>
<td>(19.99)</td>
<td></td>
</tr>
<tr>
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<td>0.64</td>
<td>0.66</td>
<td>0.57</td>
<td>0.52</td>
</tr>
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<td>(19.75)</td>
<td>(18.74)</td>
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<td>0.55</td>
<td>0.73</td>
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</tr>
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<td></td>
<td>(18.72)</td>
<td>(16.11)</td>
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</tr>
<tr>
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<td>(19.11)</td>
<td>(17.79)</td>
<td>(19.32)</td>
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<tr>
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<td>0.67</td>
<td>0.59</td>
<td>0.75</td>
</tr>
<tr>
<td></td>
<td>(21.33)</td>
<td>(18.73)</td>
<td>(20.25)</td>
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<tr>
<td>49</td>
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<td>0.70</td>
<td>0.72</td>
<td>0.72</td>
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</tr>
<tr>
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<td>(24.26)</td>
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<td>0.70</td>
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<td>(25.94)</td>
<td>(25.54)</td>
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<td>0.78</td>
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<tr>
<td></td>
<td>(19.64)</td>
<td>(18.05)</td>
<td>(19.09)</td>
<td>(22.53)</td>
<td></td>
</tr>
</tbody>
</table>

a No samples recorded.

b Reported as grams percent.

c Reported as relative percent.
Table 42. Comparison of total serum gamma globulin concentration in five groups of turkeys during the experimental period

<table>
<thead>
<tr>
<th>Days Post-infection</th>
<th>Group Numbers</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
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<tr>
<td>14</td>
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<td>17</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
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<td>0.29</td>
</tr>
<tr>
<td></td>
<td>(10.34)</td>
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<td>0.27</td>
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<tr>
<td></td>
<td>(8.98)</td>
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<td>0.34</td>
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<tr>
<td></td>
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<td>(11.89)</td>
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<td></td>
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<td>(14.11)</td>
</tr>
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</tr>
<tr>
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<td>(12.38)</td>
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<td>(14.37)</td>
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<td>0.64</td>
</tr>
<tr>
<td></td>
<td>(17.67)</td>
</tr>
</tbody>
</table>

a No samples recorded.

b Reported as grams percent.

c Reported as relative percent.
Figure 58. Progressive changes in serum gamma globulin concentration (expressed in grams per cent) for the following groups in Trial III:

Group 1 - Uninfected-control.
Group 2 - Immune-challenged.
Groups 3 and 4 - HN2-treated.
Group 5 - Infected-control.

Infection at 7 days of age
TRIAL III

- GROUP ONE
- GROUP TWO
- GROUP THREE
- GROUP FOUR
- GROUP FIVE

AVERAGE SERUM GAMMA GLOBULIN CONCENTRATION IN GRAMS %

- HN₂ TO
- GROUP 3 CHALLENGE GROUP 4

AGE OF BIRDS, IN DAYS
Figure 59. Progressive changes in serum gamma globulin concentration (expressed as per cent of total serum protein) in the following groups in Trial III:

Group 1 - Uninfected-control.
Group 2 - Immune-challenged.
Groups 3 and 4 - HN2-treated.
Group 5 - Infected-control.

Infection at 7 days of age
TRIAL III

○ GROUP ONE
△ GROUP TWO
■ GROUP THREE
● GROUP FOUR
□ GROUP FIVE

AGE OF BIRDS, IN DAYS

HN₂ TO GROUP 3 CHALLENGE

HN₂ TO GROUP 4
were observed in other tissues.

**Group 2 - immune-challenged birds**

All birds were killed at the end of the trial. Both gross and microscopic lesions were similar to those seen in Group 2 of Trial II.

**Group 3 - HN2-treated birds (-2 to +2 days pre- and postchallenge)**

Cecal lesions similar to those in Group 3 of Trial II were observed in all 7 birds but liver lesions were found in 4 birds only. There was a slight lymphoid depletion in the spleen and much of the bursal tissue had been replaced by connective tissue. Microscopic changes observed in other tissues were not remarkable.

**Group 4 - HN2-treated birds (+7 to +11 days postchallenge)**

Gross lesions were present in the livers and ceca of all birds.

**Liver lesions** Microscopic liver lesions consisted of massive areas of coagulative necrosis surrounded by mononuclear inflammatory cells. Giant cells containing individual or "nested" histomonads were frequently seen in the necrotic areas and adjacent tissue. Bile duct proliferation was quite marked in less damaged portions of the liver parenchyma.

**Cecal lesions** Cecal lesions were similar to those seen in Group 3 of the same trial.
Lesions in other tissues  Lymphoid depletion of the spleen was observed in 4 out of the 6 birds used in this group. One bird had a mycotic granulomatous pneumonia and Aspergillus sp. was present in air sacs and in thrombosed vessels in the lung. The bursa of Fabricius was reduced in size and fewer cells were present in its follicles. There was an increase in interfollicular connective tissue.

Group 5 - infected-control birds

Three birds had typical histomonosis lesions in the ceca and liver. Lesions in the 4th bird were confined to the ceca while the 5th bird had no gross lesions.

Liver lesions  The histopathologic alterations of liver sections from birds which had gross lesions, consisted of necrotic areas randomly scattered throughout liver parenchyma. There was a marked mononuclear cell infiltration in these necrotic areas. Macrophages and giant cells were present in large numbers. Histomonads could be seen in some of the giant cells and also in disrupted hepatic sinusoids.

Cecal lesions  The cecal lesions consisted of massive invasion of all layers by macrophages, lymphocytes, plasma cells and polymorphonuclear leukocytes. Histomonads had penetrated all cecal layers but were most numerous in the lamina propria. The ceca without gross lesions were found to have large numbers of polymorphonuclear leukocytes in the wall.
Lesions in other tissues

Microscopic changes observed in other tissues were not remarkable except that in some birds large numbers of polymorphonuclear cells had infiltrated into the bursa of Fabricius, bronchial mucosa, and small intestine.
DISCUSSION

This study demonstrated that turkey poults which recovered from experimental histomonosis infection as a result of drug therapy were refractory to the disease when challenged by the same infective agent. Administration of an immunosuppressant agent to immune recovered poults broke down this resistance and these birds succumbed to the disease when challenged. Parameters used in studying the host's responses to the disease included mortality rates, weight gains, alterations in hematologic and serum protein values, changes in SGOT activity levels and histopathologic changes.

Mortality Rates

Fewer deaths were recorded in HN₂-treated groups of Trial III than in the corresponding groups in Trials I and II in which the disease was allowed to run its normal course. Based on the extent of tissue damage observed in some birds in Groups 3 and 4 of Trial III, it is believed that these birds would probably have died within the next 4 or 5 days.

Weight Gains

Throughout the trial period, observed weight gain depressions were consistent with the reduction in feed and water consumption normally encountered in sick birds.
Hematologic Values

Circulating leukocyte numbers were markedly increased in all groups prior to treatment with dimetridazole primarily because of increased heterophil numbers although lymphocytes were also increased, particularly in Trial I. These findings are consistent with those of other workers (Johnson and Lange, 1939; McGuire and Cavett, 1952). The increase in leukocyte numbers coincided with the appearance of sulfur-yellow droppings. This suggested that the disease had extended from the ceca to the liver and the marked leukocytosis was a reflection of increased tissue demand for heterophils brought about by the increasingly extensive tissue damage. The return of circulating leukocyte numbers to the normal range in all groups after the birds were treated with dimetridazole is similar to the pattern reported by Venkataratnam and Clarkson (1963) for chickens recovering from histomonosis infection. In the present study, the return of leukocyte numbers to normal levels was probably associated with the resolution of liver and cecal lesions as a result of drug therapy.

The reduction of leukocyte numbers to levels below control values observed in birds which were being treated with nitrogen mustard (HN₂) indicates that its cytotoxicity was effectively expressed in these trials. However, its anti-leukemic effect did not appear to be permanent since peripheral leukocyte counts rose to values above control values
after the drug was withdrawn.

The increase in total leukocyte numbers following challenge of HN2-treated and immune groups was a response to reinfection established by the challenging dose. Leukocytosis which developed in some of the immune control birds was probably due to relapse of the original infection. Relapses of this disease are not unusual because of the difficulty of completely eliminating all tissue histomonads. The lack of significant changes observed in eosinophil, basophil or monocyte counts, reflects the findings of Malewitz and Calhoun (1957).

Serum Protein Changes

The reduction in serum albumin levels in all groups, 12 to 15 days after infection, was similar to changes reported by Clarkson (1959, 1966). Clarkson attributed the fall in albumin to loss of large quantities of albumin into cecal lumen and to the inability of the damaged liver to produce adequate quantities of albumin. In the present study, albumin levels returned to normal after treatment with dimetridazole. This response pattern was similar to that reported in chickens that were recovering from the disease by other investigators (Beg and Clarkson, 1970; McDougald and Hansen, 1969) and was associated with resolution of histomonosis lesions.
The fall in albumin levels observed in HN\textsubscript{2}-treated birds, following challenge, correlated with the development of cecal and liver lesions. Several factors may account for the rise in serum gamma globulins, observed between days 7 and 12 of infection. Precipitating antibodies which are produced in \textit{Histomonas}-infected turkeys or chickens (Clarkson, 1963) appear in the gamma globulin fraction and are responsible, in part, for the rise in serum gamma globulins (Clarkson, 1966). The rise may also be caused by the production of "non-specific immunoglobulins" by the reticuloendothelial system in response to tissue destruction or to a decrease in osmotic pressure (Clarkson, 1966). Madden and Zeldis (1958) have suggested that immunoglobulin-producing cells are probably stimulated by plasma amino acids which tend to accumulate in the damaged liver. These workers also suggest that a decrease in albumin production may stimulate production of gamma globulins. Dougherty and White (1946) suggested that the rate of release of gamma globulin from lymphocytes was under pituitary-adrenal cortical control. They associated increase in serum gamma globulins with increased pituitary-adrenal cortical secretions. It is difficult to say which, if any, of these factors are responsible for the rise in serum gamma globulins, in the present study.

Changes in other globulin fractions were not very remarkable and no reasonable explanation can be advanced until normal metabolic fates of these fractions have been
thoroughly worked out in the turkey.

**SGOT Values**

Results of SGOT studies were unexpected. McDougald and Hansen (1970) found increases in GOT levels in *Histomonas*-infected turkeys and chickens and correlated these increases with tissue breakdown in the liver and ceca. Similar changes have been observed by this author in previous studies (Niyo, 1970 unpublished). However, in the present study, there was a wide variation in enzyme level in each group from day to day. Serum enzyme levels lower than control values were sometimes observed in infected groups. Some of these birds were later found to have minimal liver lesions but had severe cecal lesions. Low transaminase levels have been reported in sera and tissues of pyridoxine-deficient mammals (Sebrell and Harris, 1968). It is conceivable that alteration in cecal lumen, because of the extensive histomonosis lesions, might affect metabolism of pyridoxine. This may indirectly be reflected in low transaminase activities which are dependent on this vitamin, but is not known whether similar mechanisms prevail in avian species. In any event, birds in these trials did not show clinical signs referable to pyridoxine deficiency. The large technical error inherent in this method of analysis and differences in rate of lesion development in individual birds may account for much of the varia-
tions in enzyme levels observed in these trials.

Histopathologic Studies

The histologic response of immune birds to challenge with Histomonas-bearing Heterakis eggs consisted of extensive lymphocytic infiltration in all layers of the cecal wall. In addition, numerous well-circumscribed lymphoid foci were observed, primarily in the liver, ceca, and spleen. Similar lymphoid foci were occasionally found in other tissues. No histomonads were observed in the tissues except in a few cases in which lesions were found in either the liver or the ceca. In contrast, HN2-treated birds developed histomonosis lesions in the ceca and livers. Large numbers of histomonads were present in these tissues and were closely associated with giant cells and macrophages. Liver lesions had fewer infiltrating cells compared to normal birds, suggesting that there was a reduction in the cells associated with the protection of the host against the disease. It is known that use of cytotoxic drugs in treatment of neoplastic diseases suppresses immune response of human patients and renders them susceptible to other infections (Schwartz and Borel, 1968). In this study, two birds that had been treated with HN2 developed mycotic (granulomatous) pneumonia, probably as a result of drug-induced tolerance.

The destruction of lymphoid cells of the spleen, bursa
of Fabricius and cecal tonsils observed in HN₂-treated birds was attributed to the lymphocytotoxic action of the drug. Although histopathologic studies of the thymus were not carried out due to technical problems, the destruction of lymphocyte populations of this organ by the use of nitrogen mustard (HN₂) has been reported (Kemp, 1970). Depletion of follicular cells of the bursa of Fabricius was attributed to the action of HN₂ rather than to the normal involution of this lympho-epithelial organ since no similar (regressive) changes were observed in either the immune-control or immune-challenged birds which were of the same age and breed.

Well circumscribed lymphoid foci, the bursa-dependent follicles, were prominent in immune-control and immune-challenged birds but were absent in HN₂-treated birds. These lymphoid foci are thought to constitute an important integral part of the lymphoid system in the chicken and probably in the turkey as well. They tend to enlarge in response to antigenic stimulus and consequently are prominent in certain avian diseases. Rhoades (1971) reported that they were prominent in reproductive tracts and air sacs of turkeys infected with Mycoplasma meleagridis and Taliaferro (1967) remarked on the increase of lymphoid nodules in avian malaria. It has been suggested that such nodules are related to the mechanism of immunity (Soulsby, 1967).

Evidence for morphologic and functional similarity between bursal lymphocytes and the large lymphocytes of the
splenic germinal centers has been presented by several workers
(Clawson et al., 1967; Cooper et al., 1965). It has been
pointed out that the function of the bursa-dependent system
is the production of immunoglobulins (Cooper et al., 1967;
Glick et al., 1956; Janković and Mitrović, 1967). In the
present study, serum-immunoglobulins were not greatly reduced
in the HN2-treated groups despite the fact that there was a
marked depletion of the bursa-dependent system. Some of these
immunoglobulins may indeed be the serum precipitins described
by Clarkson (1963) in Histomonas-infected turkeys or they
may be non-specific immunoglobulins produced in response to
catabolic by-products.

Although immunoglobulin synthesis has been detected in
bursaless chickens such birds are unable to produce anti-
 bodies in response to antigenic stimulus (Cooper et al.,
1967). It is possible that total destruction of the bursa-
dependent cells was not accomplished so that the residual
foci of these cells were still capable of producing these
gamma globulins. In any event, these gamma globulins seem to
provide little or no protection against histomonosis since
infection was re-established in HN2-treated birds despite
the presence of these globulins. Clarkson (1963) was unable
to transfer solid protection from immune birds to susceptible
birds by means of serum. Similar failures have been encounter-
ed with Besnoitia infections in hamsters (Frankel, 1967).

It has been stated that typical histomonosis lesions are
confined to the ceca and liver and there are indications that histomonads will infrequently invade other tissues such as spleen, kidney, and proventriculus (Johnson and Lange, 1939; Malewitz et al., 1958). In this study, histomonosis lesions were found in the kidneys of some HN2-treated birds. In addition, Histomonas-granulomas were found in the bursa of Fabricius of 2 birds that had been treated with HN2. Invasion of the bursa of Fabricius by histomonads has not been reported previously and while this may be a coincidental finding, it nevertheless leads one to some interesting speculations. Since these lesions were found in a structure that is associated with antibody production, it was assumed that treatment with HN2 had suppressed immune responses of this structure and rendered it susceptible to Histomonas invasion.

Use of HN2 on recovered birds eliminated acquired resistance so that they succumbed to challenge with histomonads introduced by Heterakis eggs. The severity of lesions was more pronounced in birds in which immunosuppression was started several days before challenge (Trial I) than in those birds in which the immunosuppressant agent was given together with or following challenge. This suggests that immunosuppression in this instance is best accomplished when nitrogen mustard (HN2) administration is started before challenge. Loss of the acquired resistance correlated with depletion of lymphoid cell population of the bursa of Fabricius, the spleen and cecal nodules and the disappearance of the bursa-depend-
ent follicles which were quite prominent in the liver and ceca of the immune-challenged birds. It is tempting to speculate that acquired resistance to histomonosis is mediated by these residual lymphoid cells and that humoral factors probably play a minor protective role, if any. It would be interesting to find out if transplantation of these cells from immune to susceptible birds can provide protective immunity to the disease.
CONCLUSIONS AND SUMMARY

This study has produced a successful new model host/parasite system for the study of cellular immune phenomena in protozoan diseases. It is superior to previous models in that the effects are well-defined, the host/parasite system is a naturally occurring one, and the nature of the experimental animals and parasites is such that it is a convenient system to set up and allows numerous easy experimental manipulations to test various parameters of host/parasite interaction.

The various hematologic and serologic values, while reflecting little response relative to the immune state of the hosts, nevertheless represent a more complete summary of values than have been collected heretofore in this host/parasite system.

Other specific findings from this study are summarized below:

1. Mortality was higher and weight gain depressions were more pronounced in HN2-treated birds than in immune-control or immune-challenged birds.

2. Leukopenia observed in HN2-treated birds was not permanent and was attributed to the cytotoxic action of the drug on all rapidly dividing cells. Following its withdrawal, these birds developed a marked leukocytosis in response to challenging dose of virulent histomonads.
3. Changes observed in serum protein fractions were correlated with the development of histomonosis lesions. Administration of HN2 did not appear to exert any significant effect on serum proteins.

4. SGOT activity levels varied markedly among individual birds and the possible reasons for such patterns were discussed.

5. Use of nitrogen mustard, HN2, destroyed lymphoid follicles of the liver, spleen, and cecal necks. In addition, lymphoid cells of the bursa of Fabricius were also destroyed. Birds devoid of such cells were highly susceptible to Histomonas meleagridis infection. These birds developed severe cecal and liver lesions following challenge with virulent histomonads. This is the first time that acquired resistance to this disease has been eliminated by artificial means. In contrast, residual lymphoid cells were prominent in birds which had recovered from the disease but were not treated with HN2. These birds were highly resistant to reinfection.

While results of this study are not completely definitive, they nevertheless suggest that these residual lymphoid cells are involved in mediation of acquired resistance to histomonosis infection. The major limitation of this study resides in the broad spectrum of immunosuppressive activity of mechlorethamine-HCl which prevented specific analysis of the roles of individual components of the reticulo-endothelial
system. However, it is clearly indicated that acquired immunity to this disease can be suppressed, and selective ablative techniques such as bursectomy, splenectomy, thymectomy or combinations of such procedures, along with immunocyte transplantation studies could well result in a definitive description of the immune phenomena operating in this condition. Such a result could be a significant addition to our understanding of protozoan host/parasite relationships in other domestic animals, and perhaps man.
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