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Hypothermia, Hypoglycemia, and Hypothyrosis Associated with Poult Enteritis and Mortality Syndrome[1,2]

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ABSTRACT A metabolic dysfunction contributes to the poor performance and mortality associated with Poult Enteritis and Mortality Syndrome (PEMS). Within 2 d after contact-exposed poults were removed from the presence of PEMS-infected poults and returned to their respective treatment rooms to infect experimental poults, the experimental poults began to huddle together and show signs of the disease. When separated from the huddle, body temperatures of exposure poults were depressed significantly. Body temperatures decreased progressively through 8 d after exposure with a maximum depression of 2 C and returned to a normal level at 18 d after PEMS exposure. Similar decreasing patterns in serum glucose, inorganic phosphorus, triiodothyronine, and thyroxine were observed, with maximum decreases in these serum constituents being found between 8 and 13 d after PEMS exposure. There were significant correlations among decreasing body temperatures, decreasing serum constituents, and mortality in the PEMS-exposed poults. Daily mortality rates associated with PEMS began at 6 d and peaked at 9 d after PEMS exposure. Mortality rates decreased from 9 to 15 d after experimental PEMS exposure. Depressions in serum constituents, body temperature, and increased mortality rates did not coincide with decreased feed intake associated with PEMS. Therefore, it was concluded that the agent(s) causing PEMS may have a direct effect on energy metabolism in afflicted poults.

(*Key words*: poult enteritis, mortality, thyroxine, triiodothyronine, body temperature)

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INTRODUCTION

Poult Enteritis and Mortality Syndrome (PEMS) has been described as the most significant poultry disease to have emerged since infectious bursal disease in chickens (Barnes, 1997). It is an acute infectious, transmissible disease without a definitive etiology that is characterized by severe immunodysfunction (Qureshi *et al*., 1997). It has been reported that atypical *Escherichia coli* isolates and several other enteric pathogens have a close involvement with the disease (Edens *et al*., 1997a,b, 1998; Qureshi *et al*., 1997).

Among the many signs of the disease, which include decreased feed intake, diarrhea, dehydration, atrophy of primary lymphoid organs, and wasting of musculature (Edens *et al*., 1997a,b, 1998; Qureshi *et al*., 1997), is a strong behavioral tendency to huddle into very tight and oftentimes piled-up groups that appears shortly after field cases of PEMS develop and after experimental exposure to the unidentified etiologic agent(s) that cause PEMS (Edens *et al*., 1998). In a preliminary examination of PEMS-infected birds separated from these huddles, body temperatures (BT) of those birds were depressed. Hypothermia in both young and adult chickens has been associated with administration of some prostaglandins and bacterial endotoxins (Pittman *et al*., 1976) and with administration of *Bordetella avium* endotoxin to turkey poults (Edens *et al*., 1987).

Edens and Doerfler (1997) reported that glucose metabolism in PEMS-infected poults appeared to be impaired because hepatic glycogen was depleted along with a significant increase in hepatic glucose-6-phosphatase activity without concomitant increases in serum glucose. These responses were not corrected with addition of sucrose to the drinking water of the infected poults (Edens and Doerfler, 1997).

Furthermore, it has been reported that hypothyroidism is a major problem in some animals

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Abbreviation Key: BT = body temperature; PEMS = Poultry Enteritis and Mortality Syndrome; T_3 = triiodothyronine; T_4 = thyroxine.

experiencing diarrhea (Kowalewski and Kolodej, 1977; Miller *et al*., 1978). The hypothyroidism-related diarrhea caused hypomotility characterized in the intestinal tract as a loss of rhythmic segmentation that is responsible for retardation of passage of intestinal contents. Hypothyroidism is also associated with decreased BT in birds (Freeman, 1970, 1971) and could be related to the condition that prevails in PEMS. Therefore, the objective of these studies was to determine the relationship among BT, serum thyroid hormones, glucose, and inorganic phosphorus (P_i) levels, and mortality profiles in turkey poults afflicted with PEMS.

MATERIALS AND METHODS

Animal Welfare

This project was approved and conducted under the supervision of the North Carolina State University Animal Care and Use Committee, which has adopted Animal Care and Use Guidelines governing all animal use in experimental procedures.

Poults and Husbandry

British United Turkey female poults from a commercial hatchery were obtained and transported to North Carolina State University, where they were wing-banded and weighed before placement on pine wood shavings-covered floors in controlled environment isolation rooms. The poults were not subjected to hatchery services such as beak or nail trimming, antibiotic administrations, or vaccinations. The North Carolina Agricultural Research Service turkey starter feed (Table 1) and water were provided in plastic containers for *ad libitum* consumption. Continuous lighting was provided by incandescent lamps in the ceiling of each room. At the time of placement, the poults were assigned to Control and PEMS treatment groups. There were a total of 150 poults in each treatment group in each of eight different trials that served as experimental replicates that were conducted over a period of 18 mo. This design provided a grand total of 1,200 poults in each of the control and PEMS-exposed groups. The eight different trials were originally designed to be conducted over a 21-d period, but extensions to some trials added 2 d (two trials) or 7 d (two trials) to the durations. In these extended trials, periodic measurements continued on the same basis as in the 21-d trials. Although there were differences in the duration of trials, the data were pooled for presentation, and data represented in the figures represent all birds in all trials. Analysis of the data was based on individual bird observations.

Brooding Temperatures

Ambient temperature for brooding was maintained by room air conditioning using a thermostatically controlled hot water-cold water heat exchange system mediated by a forced draft. Initial room brooding temperature for both the Control and PEMS rooms was set at 34 1 C, and this temperature was decreased 3 C in each room at 7, 14, and 21 d of brooding. Final brooding temperatures at 23 and 28 d of age was 25 C. Humidity in the experimental rooms was not controlled and varied from 47 to 63% relative humidity.

TABLE 1. Composition[1] of the turkey starter diet

Ingredients	Feed composition	
	(kg/1,000 kg)	(%)
Ground corn	456.0	45.568
Poultry fat	19.0	1.899
Poultry byproduct meal	80.0	7.994
Soybean meal (48% protein)	398.0	39.772
Limestone	15.0	1.499
Dicalcium phosphate (P: 21%, Ca: 16%)	23.0	2.298
Salt	2.0	0.200
Trace mineral premix	1.0	0.100
Vitamin premix[2]	1.0	0.100
Methionine, DL, 99%	2.2	0.220
Choline chloride, 60%	2.0	0.200
Lysine, 78%	1.5	0.150
Total, kg	1,000.7	100.000

[1]Calculated analyses: Metabolizable energy: 2,915 kcal/kg; crude protein: 28.13%; arginine: 2.04%; lysine: 1.62%; methionine: 0.67%; total sulfur amino acids: 1.10%; tryptophan: 0.34%; available phosphorus: 1.09%; calcium: 1.50%; sodium: 0.17%; xanthophyll: 11 mg/kg; fat: 5.14%.

[2]Vitamin premix: vitamin A: 13,200 IU/kg; cholecalciferol: 4,000 IU/kg; menadione (K_3): 4 mg/kg; vitamin E: 66 IU/kg; riboflavin: 13.2 mg/kg; d-pantothenate: 22 mg/kg; niacin: 110 mg/kg; choline: 1,200 mg/kg; vitamin B_{12}: 39.6 mg/kg; d-biotin 253 mg/kg; pyridoxine: 7.9 mg/kg; thiamine 4 mg/kg; folic acid 2.2 mg/kg; sodium selenite: 0.3 mg/kg; ethoxyquin: 100 mg/kg.

PEMS Exposure

At 5 d of age, a total of 15 poults (15 from a total of 150) from the group to be exposed with PEMS were removed randomly and were taken to the College of Veterinary Medicine. These poults were placed into pens containing poults with a documented PEMS disease for a period of 16 h (overnight), and these contact-exposed poults (seeders) were then returned to their respective treatment rooms to induce PEMS infection in their "exposed" treatment pen mates. Control poults were not removed from their respective rooms.

Measurements

Body temperatures in four different trials (three trials to 21 d of age and one trial to 28 d of age) were determined daily on randomly selected poults in both the Control and PEMS-exposed isolation rooms. Care was taken to not use the same thermistor probe for both the Control and PEMS exposed poults because it was determined earlier by the staff in this laboratory that feces-contaminated vinyl probes could be a means of transmission of PEMS. Poults randomly selected for BT determinations were held in

cages for 10 min before BT were determined. This procedure minimized handling and also allowed poults to regain basal BT after being caught or after being removed from a huddle of poults experiencing PEMS. On a daily basis between 0900 and 1030 h using 10 poults per treatment, a 3-mm diameter vinyl-covered thermistor probe connected to a TUC model 46 telethermometer[4] with a response time of less than 30 s was inserted 3 cm through the cloaca into the large intestine of each poult. After 30 s, the BT was recorded from the analogue dial on the telethermometer (Edens *et al.*, 1987). Body weights were determined at placement and at 7, 14, and 21 d of age. At intervals of 2 or 3 d, depending upon the trial, beginning at 1 d of age, 10 poults per treatment were selected at random for blood sampling via cardiac puncture and were then killed by carbon dioxide asphyxiation. Serum was collected from individual samples using Vacutainer serum separation tubes,[5] and all serum samples were analyzed spectrophotometrically for glucose (Dubowski, 1962) and P_i (Goldenberg and Fernandez, 1966) and by radioimmunoassay for thyroxine (T_4) and triiodothyronine (T_3) using commercial kits.[6] Mortality was observed and recorded twice daily, when necessary, in each of the eight trials represented here. During the first 7 d after hatch, mortality was corrected for normal poult mortality due to accidental deaths.

Analysis of Data

All blood serum and body weight data were subjected to analysis of variance using the General Linear Models procedure of the SAS (SAS Institute, 1990). Total mortality rates for the treatment groups were transformed to arc sine square root percentage, which were then subjected to analysis of variance using the procedures of the SAS (SAS Institute, 1990). Correlations among variables were calculated using procedures of the General Linear Models procedure of the SAS (SAS Institute, 1990). Statements of significance are based on P 0.05.

RESULTS

Colonic BT were depressed significantly in PEMS-exposed turkey poults (Figure 1A). Within 2 d after seeder poults were exposed to PEMS-infected poults and were returned to their respective treatment groups, BT declined. By 6 d postexposure (11 d of age), a significant depression in BT was evident and persisted through 23 d of age (18 d postexposure). At 9 d after PEMS exposure, the most severe hypothermia was detected and was more than 2 C below the BT of Control poults. At 20 and 22 d postexposure, BT of the PEMS-exposed poults was not different from that of Controls.

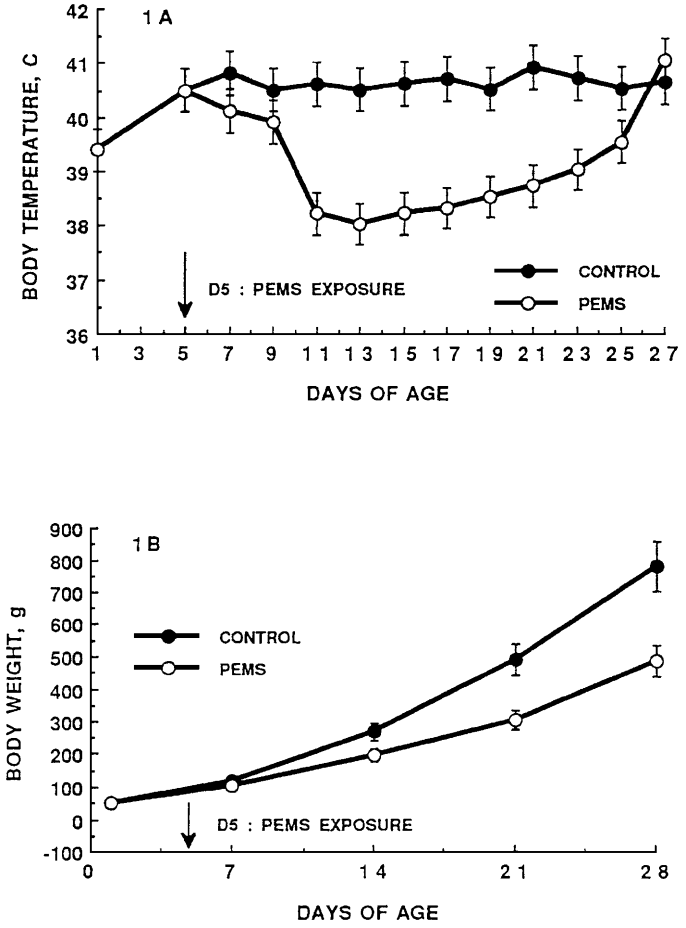

FIGURE 1. Effect of poult enteritis and mortality syndrome induced by overnight exposure of seeder poults at 5 d of age to poults infected with Poult Enteritis and Mortality Syndrome (PEMS) on the development of hypothermia and decreased growth rate. Vertical bars on the graph represent mean SEM.

At 2 d after PEMS exposure there was an evidence that body weight of the PEMS-exposed poults was less than the body weight of the Control poults (Figure 1B). At 14 d of age (9 d after PEMS exposure), there was a significant depression in body weight, which remained depressed in comparison with Controls through 28 d of age. Body weight depressions at 9, 16, and 23 d after PEMS exposure were 41, 29, and 36%, respectively, less than that of Controls.

Serum glucose levels were not different between Control and PEMS-exposed poults at 4 d after PEMS exposure (Figure 2A). However, at 6 d postexposure, serum glucose was depressed significantly and remained depressed through 16 d postexposure (21 d of age). The greatest difference between Control and PEMS serum glucose levels (76 mg/dL) was observed at 11 d postexposure (16 d of age). The maximum depression in serum glucose (i.e., the difference between Control and PEMS-exposed poults) was approximately 20% and implied that the difference was probably due to inanition associated with PEMS.

Serum P_i (Figure 2B) was decreased significantly in response to PEMS. A significant difference between the

[4]Yellow Springs Instrument Co., Yellow Springs, OH 45387.
[5]Becton Dickinson Vacutainer Systems, Franklin Lakes, NJ 07417-1885.
[6]Diagnostic Products, Inc., Los Angeles, CA 90045.

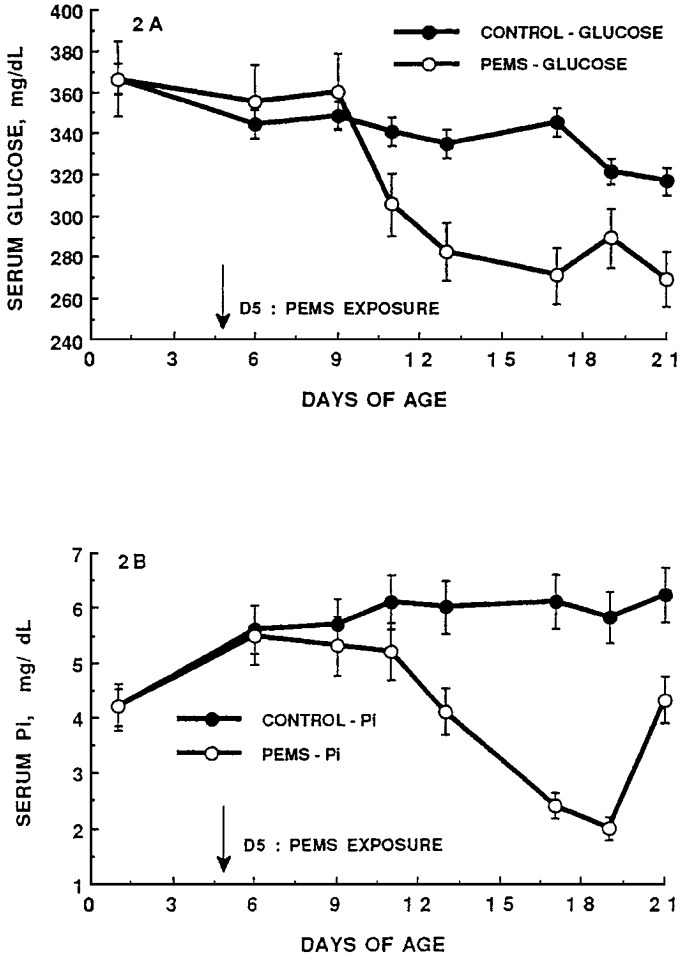

FIGURE 2. Effect of poult enteritis and mortality syndrome induced by overnight exposure of seeder poults at 5 d of age to poults infected with Poult Enteritis and Mortality Syndrome (PEMS) on the development of serum hypoglycemia and hypophosphatemia. Vertical bars on the graph represent mean SEM.

two treatment groups was seen at 8 d postexposure, and this difference continued to increase through 19 d of age (14 d postexposure). At 21 d of age (16 d postexposure) serum P_i was beginning to increase to Control P_i concentrations but was still depressed significantly in comparison to P_i in Controls.

Serum thyroid hormone profiles of Control and PEMS exposed poults are presented in Figure 3. Within 2 d after PEMS exposure, serum T_3 concentrations were depressed significantly in the exposed poults (Figure 3A). The T_3 concentrations in exposed poults decreased to a minimum at 8 d postexposure, which was maintained through 23 d of age (18 d postexposure). In contrast, a biphasic response for serum T_4 was observed (Figure 3B) in PEMS-exposed poults. At 1 d postexposure, T_4 in the PEMS poults was significantly higher than the control value, but by 11 d of age (6 d postexposure) T_4 was depressed significantly and remained depressed through 18 d postexposure (23 d of age) when the experiment ended.

Serum T_3:T_4 ratios revealed a decreasing profile in both Control and PEMS-infected poults from 6 through 23 d of age (Figure 3C). However, in PEMS-exposed poults, the decreases were significantly larger than those observed in Controls. Furthermore, the decreasing T_3:T_4 ratios in the PEMS-exposed poults were nonlinear, implying that there were periods during the postex-

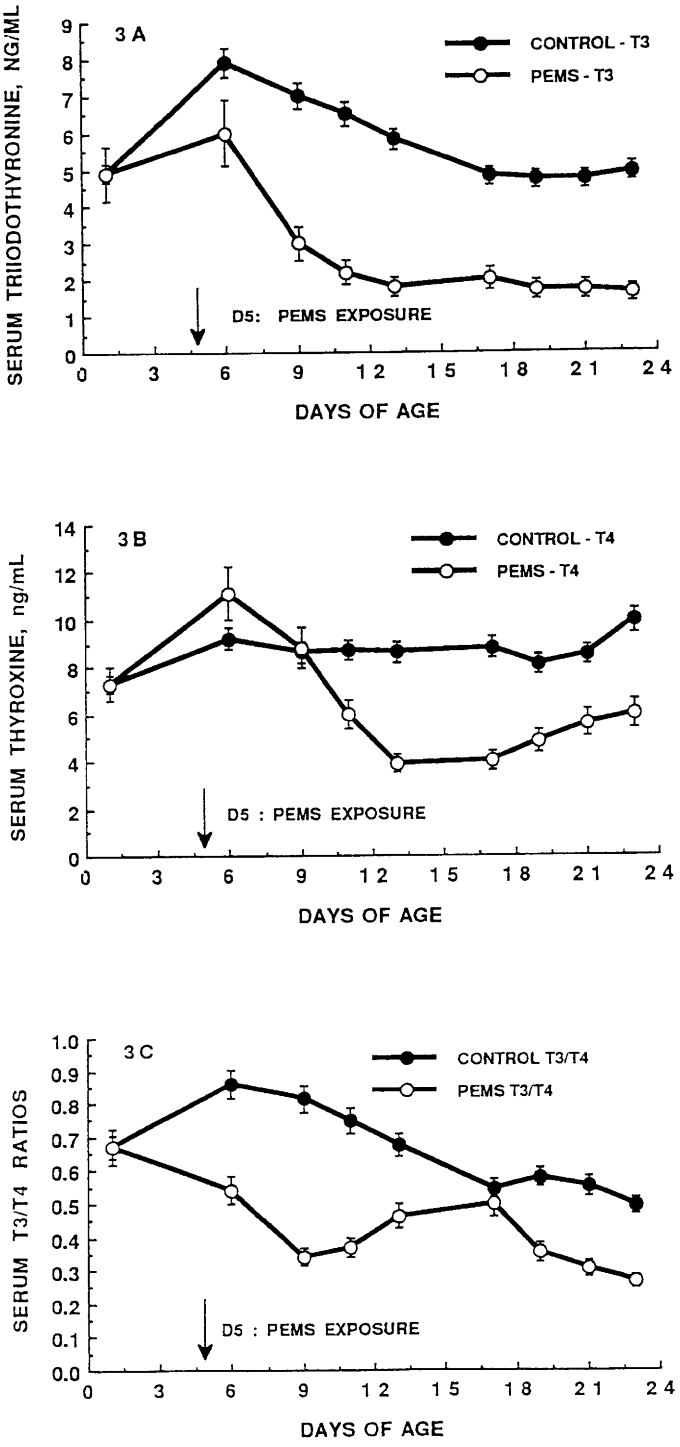

FIGURE 3. Development of hypothyrosis as evidenced by significantly decreased serum triiodothyronine, thyroxine and triiodothyronine/thyroxine ratios due to poult enteritis and mortality syndrome induced by overnight exposure of seeder poults at 5 d of age to poults infected with Poult Enteritis and Mortality Syndrome (PEMS). Vertical bars on the graph represent mean SEM.

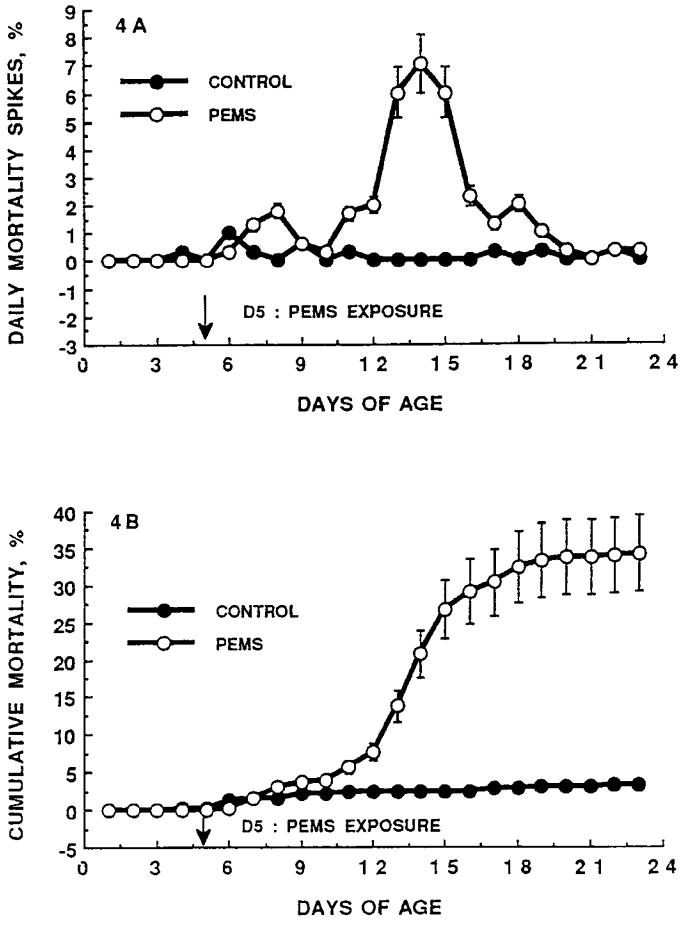

FIGURE 4. Daily and cumulative percentage mortality rates due to poult enteritis and mortality syndrome (PEMS) induced by overnight exposure of seeder poults at 5 d of age to PEMS-infected poults. Vertical bars on the graph represent mean SEM.

posure PEMS response when the poults did consume larger amounts of feed and assimilate nutrients (between 6 and 8 d postexposure). Unfortunately, the interpretation of the PEMS T_3:T_4 profile was difficult due to differences between trials.

On a daily basis, PEMS related mortality (Figure 4A) was somewhat variable until 6 d postexposure, when a sustained increase in mortality occurred and reached its maximum at 9 d postexposure. Percentage mortality showed a declining profile from 10 through 14 d postexposure, when it reached Control levels. Cumulative mortality rate due to PEMS exposure for the eight trials reached approximately 35% (Figure 4B). Mortality due to exposure increased significantly at 6 d postexposure (11 d of age) and continued to increase over the following 8 consecutive d (through 19 d of age, when a plateau was reached). Total mortality in Controls was less than 4% during the eight trials (Figure 4B).

The beginning of daily mortality spikes associated with PEMS was related to the maximum depressions in BT, serum glucose, T_3, and the T_3:T_4 ratios, whereas peak daily mortality was associated with maximum depressions in serum P_i (8 d postexposure) and serum T_4 (8 d postexposure). Termination of the daily spikes in mortality was related to a small and nonsignificant shift in serum T_4 (11 d postexposure) and the small upward trend in BT at 11 d postexposure.

DISCUSSION

Body temperature depressions associated with PEMS reached a minimum level at 6 d after exposure. Concurrently, daily spikes in mortality associated with the disease increased significantly. With continued BT depression in the PEMS exposed poults, mortality rates on a daily and cumulative basis continued to increase through 10 to 11 d after the PEMS exposure. In this same time reference, growth rates of the PEMS-afflicted poults decreased significantly, indicating that feed consumption rates were depressed (data not shown) or that the ability of the poult to assimilate nutrient from the intestinal tract had been impaired. Based upon examinations of the intestinal tracts, we concluded that feed remained largely undigested even in the lower bowel of PEMS-afflicted poults. Thus, malabsorption was a result of the PEMS disease.

Depressed BT in the PEMS-infected poults was accompanied by highly significant depressions in serum T_3 and T_4 concentrations. A well-known relationship between BT and levels of serum thyroid hormones has been established in domestic species of poultry (May, 1989). Normally, increased serum concentrations of thyroid hormones are accompanied by significant increases in heat production in poultry (Klandorf *et al.*, 1981) especially when birds are exposed to cold environments (Bobek *et al.*, 1980; Freeman, 1970, 1971; May *et al.*, 1974). In the present experiments, PEMS-infected poults were maintained in controlled, apparently ideal, environments closely resembling normal brooding temperature conditions. Nevertheless, BT and serum thyroid hormones were depressed. Because ambient temperatures were within a thermoneutral range commonly used for brooding, there should have been little if any change in serum thyroid hormone levels (Cogburn and Freeman, 1987; Klandorf *et al.*, 1981; May *et al.*, 1974).

It has been suggested that poults experiencing PEMS will become anorexic (Barnes, 1997), and feed intake by PEMS-afflicted poults may be 20 to 40% lower than the intake by Controls during the acute mortality phase (Doerfler and Edens, unpublished observations). The influence of feed intake during PEMS exposure has not been addressed fully, but such severely reduced feed intake should have serious consequences. Certainly, reduced feed intake (Barnes, 1997) should result in reduced heat production.

May (1989) reported that T_4 acts as a prohormone, and under conditions of hypothyroidism, maximum conversion of T_4 to T_3 takes place via the action of action of 5 -deiodinase. There are factors that control conversion of T_4 to T_3 and these include the quantity and metabolizable energy content of feed (Klandorf and

Harvey, 1985). Examination of the T_3:T_4 ratio indicated that PEMS infection had decreased the conversion of T_4 to T_3, but this occurred without a concomitant increase in T_4 except at 2 d postexposure. This observation implied that feed consumption was low but had not ceased in the PEMS-infected poults. In chickens, feed deprivation for short periods of time causes a reduction in plasma T_3 and a concomitant increase in plasma T_4 (May, 1978, 1989). Therefore, the decreased serum thyroid hormone concentrations in PEMS-afflicted poults would suggest a primary hypothyrosis due to damage in the thyroid gland. This hypothesis is also suggested by thyroid atrophy in PEMS-afflicted poults (H. J. Barnes and J. S. Guy, North Carolina State University, College of Veterinary Medicine, Raleigh, NC 27695).

Other diseases, such as bordetellosis due to *Bordetella avium*, also cause a prolonged hypothermia in poults (Edens *et al.*, 1991). Plasma T_3 in the *B. avium*-infected poults was not different from Control values, but there was an attenuated T_4 response to feed deprivation in the infected poults. Furthermore, significant elevations of plasma corticosterone and altered thyroid hormones in the *B. avium*-infected poults were thought to be contributing causes to decreased weight gain. Rudas *et al.* (1986) have also reported that chickens with malabsorption syndrome (runting/stunting syndrome) experience hypothyrosis. Within 2 d after exposure with intestinal homogenates that cause the malabsorption syndrome, liver 5′-deiodinase activity was depressed, causing a significant depression in serum T_3 concentrations. However, serum T_4 concentrations were also decreased significantly, and remained decreased from 6 through 29 d of age, ostensibly due to decreased nutrient absorption from the intestinal tract.

Decreased growth rates in PEMS-afflicted poults can be explained partially by the hypothyrosis associated with the disease. However, Edens *et al.* (1997a) and Edens and Doerfler (1997) have provided evidence that part of the decreased weight gain is associated with decreased absorption of glucose and P_i. The malabsorption appears to be related to damage in the intestinal epithelium on which the absorptive surfaces of microvilli of the epithelial cells are destroyed and to disruption of subcellular organelles such as the mitochondria and cell membranes associated with the endoplasmic reticulum and Golgi apparatus. Therefore, the prolonged period of depressed weight gain after the passage of the acute mortality phase of the PEMS disease is due to a malabsorption condition. Malabsorption in PEMS-afflicted poults appeared to have been confirmed by the observation by Edens and Doerfler (1997). Neither serum glucose nor serum P_i were elevated by consumption of water supplemented with sucrose and potassium phosphate. Additionally, increased hepatic glucose-6-phosphatase activity and depletion of hepatic glycogen were observed in PEMS-afflicted poults given drinking water with and without sucrose + potassium phosphate supplements.

Even though decreased weight gain and greatly elevated feed conversion ratios in association with PEMS appears to be a sequel of malabsorption, the pathophysiological evidence suggests that the disease is rooted extra-intestinally. Specifically, the hypothyroid condition associated with PEMS can explain the decreased weight gain (Edens *et al.*, 1991; Rudas *et al.*, 1986; May, 1978), and the hypothyroid condition can also explain the prolonged hypothermia associated with PEMS as heat production driven by T_3 (Freeman, 1970, 1971; Bobek *et al.*, 1980; Klandorf and Harvey, 1985; Klandorf *et al.*, 1981; May *et al.*, 1974; May, 1989) would be greatly decreased. Edens and Doerfler (1997) have also pointed out that hepatic cells in the PEMS-afflicted poult appear to be unable to utilize glucose for energy metabolism. However, utilization of structural protein from the musculature may also account for the decreased weight gain and wasting associated with such poults. The wasting of the musculature can be attributed partially to the enteroinvasive atypical *E. coli* that colonize all of the visceral organs of PEMS-afflicted poults (Edens *et al.*, 1997a,b, 1998). Additionally, there is an intense eosinophilia associated with PEMS induced with both Coronavirus-positive and Coronavirus-negative fecal inocula that cause the disease (Edens *et al.*, 1997c). It has been reported that eosinophilia is associated with immunodeficiency syndromes in mammals (Duic *et al.*, 1970; Van Scoy *et al.*, 1975; Bjorksten and Lundmark, 1976) in which there is impaired T cell functions. In PEMS-afflicted poults, there is immune system dysfunction characterized by a lower T cell-mediated lymphoproliferative response (Qureshi *et al.*, 1997).

Therefore, we concluded, on the available data, that PEMS induces a metabolic as well as an immune system dysfunction that is only partly related to inanition. The disease is exacerbated by lesions in the intestinal tract and these lesions lead to malabsorption of nutrients. The malabsorption then exacerbates the hypothyroidism associated by the disease causing development of hypothermia. Under these conditions, the reduced BT would predispose these poults to secondary bacterial infections (Ram and Hutt, 1955) that ultimately may lead to death.

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