Loss of plasma proteins into the intestine occurred as a result of increased permeabiltiy of intestinal mucosa (Enigk, Schanzel, Scupin and Dey-Hazra, 1970; Kouwenhoven and Van Der Horst, 1970; Preston-Mafham and Sykes, 1967; Rose and Long, 1969). Marked leakage was noted after intravenous injection of sky-blue dye into chickens infected with E. acervulina (Preston-Mafham and Sykes, 1967). Maximum leakage was observed over the period 90-120 hours post infection, which is the time of maximum parasitization, and was correlated with a decrease in the ability to absorb histidine, glucose and fluid (Preston-Mafham and Sykes, 1967). Similar results were obtained by Long (1968b) following inoculation of 1×10^7 but not 1×10^4 or 1×10^5 oocysts of E. acervulina or E. praecox. Additional leakage of dye as early as 3.5-7 hours post infection was reported by Long (1968b). This is presumably associated with sporozoite penetration (Ryley, 1975).

Many investigators have demonstrated significant increases in intestinal acidity in chickens infected with E. acervulina (Kouwenhoven, and Van Der Horst, 1969, 1972), E. maxima (Stephens, Kowalski and Borst, 1967; Ruff and Reid, 1975) and E. brunetti (Ruff, Johnson, Dykstra and Reid, 1974). In the case of E. acervulina infection, Kouwenhoven and Van Der Horst (1969) reported a caseous substance on the mucosa of the affected part of the intestine. The appearance of this caseous material at 5 days after a heavy infection coincides with very low pH and the decreased absorption of vitamin A and carotenes.

By exposing a ligated intestinal loop to 4.5 pH buffers in vitro or diluted HCl in vivo, Kouwenhoven and Van Der Horst (1972) observed denaturation of mucosal proteins similar to those seen during the acute stages of E. acervulina infection. Accordingly, Kouwenhoven and his

coworkers believe that this acidification is the key factor on which the other intestinal changes depend. Impairment of fat hydrolysis with increased intestinal acidity has been also suggested by Sharma and Fernando (1975) in E. acervulina infections.

According to Ryley (1975), coccidia can produce lactic acid during their metabolism. It is not known whether intestinal acidification is the direct result of the metabloic activity of coccidia or if it is an indirect effect resulting from an interaction of the parasite with the host's metabolism (Ryley, 1975).

Schildt and Herick (1955) have found that the muscular activity of the crop and ceca was greatly reduced during the acute phase of E. tenella infection. The response of isolated intestinal tissue to acetylcholine was studied by Oikawa and Kawaguchi (1974) as an indicator for the contractile activity of the digestive tract of chickens infected with E. tenella and E. acervulina. They concluded that coccidial infection may cause a disorder of intestinal contractility in the host, not only directed to its parasitic location but also generally over the whole digestive tract.

3. Extra-intestinal effects

Food and water intake during coccidial infections have been investigated by many workers (Michael and Hodge, 1972; Augustine and Thomas, 1979; Reid and Pitois, 1965; Fitzgerald and Mansfield, 1972). In six Eimeria species of chickens, Reid and Pitois (1965) found that food and water consumption was decreased on the 4th and 5th days post infection. According to these authors, sick chickens were more likely to eat than to drink, which is an important point to consider when anticoccidial drugs are used for treatment (Long, 1973; Ryley,

1975). Significant reduction in water and food consumption have been also reported by Long (1968b) in chickens infected with E. acervulina and E. praecox from the 4th to the 6th days post infection. Fitzgerald and Mansfield (1972) reported that feed consumption was reduced for 13 weeks and water consumption for 4-5 weeks during and after infection of calves with 500 oocysts of E. bovis per day for 5 consecutive days. Lambs infected with E. ninakohlyakimovae and E. faurei showed reduction in food consumption but no significant decreased in water consumption (Shumard, 1957).

Body weight loss or reduced weight gain was recognized a long time ago and, and considered to be one of the most obvious effects of coccidiosis (Tyzzer, 1929). Changes in weight were considered to be the criteria that could be used to evaluate subacute coccidial infections where clinical signs and changes in feed and water consumption could not be detected (Long, 1973). No clinical signs accompanied Eimeria praecox infection in chickens and for this reason it was considered non-pathogenic, yet heavy infection caused reduced weight gain though less marked than in E. acervulina infection (Long, 1968b). In both E. acervulina and E. necatrix infections produced by repeated daily oocyst inoculation, the period of reduced weight gain was longer than in infections produced by single inoculations (Turk and Stephens, 1970; Michael and Hodge, 1971). According to Michael and Hodge (1971, 1972) anorexia is not the only factor responsible for reduced weight gain in chickens infected with E. acervulina and E. necatrix because uninfected controls, starved to the same degree as those in the infected groups, did not lose as much weight and recovered better when returned to normal feeding. Studying the pathogenic effects of single or mixed infections

with low doses (simulating field conditions) of E. acervulina, E. maxima and E. brunetti, Hein (1976a) observed that in chickens infected with any two of these species, the weight loss was greater than that due to either of them given alone. In chickens inoculated with these three species, the weight loss was slightly less than that due to infection with E. brunetti alone. This was attributed to competition between the parasites which reached a maximum when chickens received a mixture of these three species (Hein, 1976a).

According to Long (1973) parasitic diseases in general appear to cause alterations in the physiology of the host which are not yet fully understood. A muscular weakness accompanying parasitic infections in poultry has been frequently observed (Long, 1973). Stafseth (1931) described leg weakness in intestinal coccidiosis of chickens and Levine and Herrick (1954, 1957) reported that chickens infected with E. tenella were less able to perform muscular work. This muscular weakness commenced on the 3rd day post infection and became more severe during the hemorrhagic phase of the infection. Waxler (1941) and Pratt (1944) reported that the muscle of chickens infected with E. tenella contain appreciably less glycogen than that of normal birds and Stoll, Enigk and Dey-Hazra (1970) reported reduced glycogen reserves in chickens infected with E. necatrix. Freeman (1970) found that during E. tenella infection there is decreased plasma lactate concentration, decreased pectoral muscle glycogen, but no change in blood glucose or liver glycogen.

Stockdale (1978) reported that calves infected with E. zuerni showed a rapid reduction in plasma sodium and chloride ions by day 18, reaching their lowest levels about day 24, and were increased at day 30 post infection. Similarly, chickens infected with E. brunetti showed a

decrease in plasma sodium and chloride but an increase in potassium and these changes were dose dependent (Allen, Berrett and Hein, 1973).

Erythrocyte numbers, hemoglobin and packed cell volume (PCV) values were decreased in calves infected with E. zuerni (Stockdale, 1978). In chickens receiving higher dose of E. brunetti the packed cell volume (PCV) increased initially and then continued to fall after clinical recovery (Allen et al., 1973). Washburn (1975) reported that infection with 1×10^5 oocysts of E. tenella caused a highly significant decrease in PCV in chickens resulting in severe anemia. According to Long (1973), erythrocyte numbers are frequently decreased by more than 50% in E. tenella infections, but with E. necatrix, the PCV is not depressed to such an extent. No significant depression in the PCV of chickens infected with E. maxima has been found by Stephens, Kowalski and Borst (1967) but they found a significant increase at 6, 10 and 14 days post infection. Thus, the pathogenic effects of most Eimeria infections of chickens do not include a substantial effect on blood cell numbers (Long, 1973).

Several workers have experimental evidence to indicate that blood clotting is impaired in chickens with coccidial hemorrhagic enteritis (Long, 1973; Harms and Tugwell, 1956; Harms, Wakeroup and Cox, 1960; Ruff, Wyatt and Witlock, 1978). Blood loss which occurs in species like E. tenella during second generation schizont development can be extensive and has been suggested to contribute significantly to mortality (Natt and Herrick, 1955).

Various avian species, including chickens, shows a remarkable resistance to the deteriorating effects of hemorrhage (Sturkie, 1976). According to Zambraski and Schuler (1980), birds are able to withstand

blood losses of up to 75% of their total blood volume and unlike mammals, they do not demonstrate irreversible circulatory deterioration during severe hemorrhage. These observations suggest that death in infections with species of coccidia where hemorrhagic enteritis and loss of blood is the main feature is not solely due to blood loss and other factors may be involved (Bertke, 1963).

Ryley (1975) suggested that effects of coccidial infection on tissue remote from the intestine could be brought about by the activity of circulating toxins, but he added that no such substance has been isolated and it is only of academic interest. He also postulated that the changes observed could be influenced by a decrease in oxygen supply in the case of the hemorrhagic enteritis, where the oxygen carrying capacity of the blood may be reduced.

Toxic effects such as fever, hyperglycemia, hypoglycemia and blood sugar depletion at death have been reported in rabbits inoculated with disrupted oocysts of E. tenella of chickens by many workers (Burns, 1959; Rikimuri, Galysh and Shumard, 1961; Sharma and Foster, 1964). According to Long (1973) these results are difficult to interpret since the toxic effects were observed only by inoculating rabbits with oocyst material of chicken origin and no effect could be produced in chickens, mice or guinea pigs.

Bertke (1963) was of the opinion that the high mortality seen in E. tenella infection is not solely due to bleeding and destruction of cecal mucosa. Thus, he studied renal clearance and found a gradual decline in uric acid clearance during the first 3 days, followed by a temporary rise and then a further decline which continued until the 10th day post infection. He concluded that a toxic material produced by or in

response to the presence of the parasite caused the shock phenomena which was indicated by the renal clearance curve. Death was attributed to the failure to recover sufficiently before cecal bleeding occurred so that the chicken was in irreversible shock and death followed shortly (Bertke, 1963).

Challey (1960, 1962, 1966) studying the response of adrenals to E. tenella infection observed an elevation in ascorbic acid at the time of maximum stress as judged by the occurrence of mortality, weight loss and the various metabolic changes characteristic of the cecal coccidiosis syndrome. These results were unexpected in the light of previous observations of depletion as a characteristic response to stress in mammals (Challey, 1960). Challey also observed that experimental bleeding caused similar adrenal ascorbic acid elevation and concluded that the changes in ascorbic acid levels of infected chickens were due to blood loss alone and not necessarily to toxic effects of the parasite.

Immune Response to Eimeria

Animals show both natural and acquired immunity to coccidia. Rose (1973) suggests that natural immunity may be responsible for the host specificity seen in Eimeria species. Some natural immunity, related to age of the host and breed of the bird, has also been demonstrated (Ruff and Reid, 1977).

Eimeria species are considered good immunogens, and readily induce an immune response in the host. In experimentally infected chickens, immunity can be induced to all species, although there is considerable variation among them (Rose, 1976). In these birds two kinds of immunity

have been described (Rose, 1976). i. Clinical immunity - which means the disappearance of clinical signs after challenge, but without the inhibition of the reproduction of the parasite. This type of immunity usually results from a single large inoculum of oocysts of the poorly immunogenic species. ii. Complete immunity - this is characterized by complete inhibition of the developmental stages of the parasite. In the most immunogenic species, E. maxima, a single inoculum of a small number of oocysts (50-100) is sufficient to induce complete immunity. On the other hand, to achieve complete immunity in the case of the least immunogenic species (E. tenella and E. necatrix) at least three successive infections of fairly large numbers of oocysts are necessary.

Recently Long, Johnson and Wyatt (1980) found that some chickens made partially immune to E. tenella infection had cecal lesions as severe as those of birds having their first infection with the parasite, but their weight gain, PCV and prothrombin time were comparable to control birds. These authors suggested that there are at least three stages of immunity to E. tenella:

a) chickens totally immune and no parasite development occurs

b) chickens resistant to a degree where oocysts are discharged after challenge, but no lesions occur

c) chickens resistant to clinical effects of the disease in spite of having severe lesions

1. Immunogenicity

i. Immunizing properties

Eimeria species infecting chickens differ in their relative ability to stimulate immunity in the host (Rose, 1978). The usual

criteria used for comparisons between these species is the number of oocysts and doses required to induce immunity. Immunity to a particular species can be measured as a reduction in either oocyst production or clinical signs (Rose, 1978). According to Rose (1973, 1978) it is very difficult to compare the immunogenicity of different species and a true comparison can be made only when the inocula used for immunizing and their mode of administration are the same. Rose and Long (1962) studied the immunogenicity of E. acervulina, E. tenella, E. maxima and E. necatrix in chickens using two or three graded immunizing infections. This experiment was the first to show the ranking in the immunogenicity of these four species, which has been confirmed and extended by other workers (Rose, 1974a, 1978; Hein, 1976b; Joyner and Norton, 1976). The available information indicates that E. maxima is extremely immunogenic, E. tenella and E. necatrix are very poor immunogens, and the other species are between these extremes (Rose, 1978).

Lee and Fernando (1978) showed that partial immunity can be induced with a single sporocyst of E. maxima as indicated by increased weight gain of the previously exposed over the unexposed chickens upon challenge. Immunity to E. maxima also develops very rapidly (Rose, 1974a). Partial immunity to challenge inoculum developed as early as 3 days after the immunizing dose whereas with the other less immunogenic species a period of nearly 2 weeks is necessary (Rose, 1974a, 1976). Pierce, Long and Horton-Smith (1962) observed that complete immunity to E. tenella developed in chickens 14 days after they had received the last of three graded doses of oocysts.

The duration of immunity, in the absence of accidental reinfection, is difficult to determine and it is meaningful only if such infection is

avoided (Rose, 1973, 1976). Also criteria used to define immunity have been different; in some cases this has been assessed on clinical findings and in others on oocyst production (Rose, 1973). In addition, the duration of immunity probably varies directly with the method of immunization used, which include the number and magnitude of immunizing inocula as well as age of the host and other factors (Rose, 1973, 1976). Horton-Smith, Beattie and Long (1961) reported that 2-week old chicks immunized with a single inoculum of 6×10^4 oocysts of E. tenella were found susceptible 4 weeks later to a challenge dose of 1.2×10^5 oocysts, as indicated by severe parasitism. On the other hand, chickens receiving four increasing doses of oocysts at 1, 4, 7 and 10 weeks of age were fairly resistant to a challenge dose of one million oocysts at 105 days after the last immunizing inoculum (Leathem and Burns, 1968). These experiments indicate that immunity will wane, certainly within a few months (Rose, 1976).

ii. Specificity

The genus Eimeria shows remarkable host specificity and attempts to infect foreign hosts with different species have largely failed, that is, when the criteria of infection is the completion of the whole life cycle (Long, 1978; Long and Millard, 1978). This specificity also extends to the immunity they induce; accordingly, hosts immunized against one species are susceptible to infection with another (Rose, 1978). The absence of cross-protection between species has been used as one of the criteria for identification and classification of Eimeria species (Long, Joyner, Millard and Norton, 1976).

Rose and Long (1962) reported that a solid immunity to E. acervulina, E. tenella, E. necatrix or E. maxima in no way prevented