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Pathogenicity and chemotherapy of *Plasmodium durae* in experimentally infected domestic turkeys

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ABSTRACT

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Only 3 out of 8 South African isolates of *Plasmodium durae* used in 524 turkeys in 161 passages caused approximately 50 % mortality, a further 3 produced approximately 10 % mortality while 2 were found to be apathogenic. Exoerythrocytic schizonts were the main pathogenic stage. In most survivors the effect on mass gains was minimal.

Twelve drugs currently available for use in poultry, as well as chloroquin phosphate, were tested for their activity against experimental infections with *Plasmodium durae* in domestic turkeys. While chloroquin phosphate showed a certain degree of effectivity, Amprolium, Amprolium + Ethopabate, Maduramycin, Toltrazuril, Metronidazole, Furazolidone, Enrofloxacin and Sulfamethoxypyridazine + Trimethoprim were ineffective. Halofuginone and Penta-Sulfa at a high dose had some protective effect. At high doses Sulfachloropyrazine protected from mortality without affecting the parasitaemia, while Sulfamonomethoxine suppressed parasitaemia without entirely protecting from mortality. From these data it is concluded that Halofuginone has a potential as possible chemoprophylactic. While a combination of Sulfamonomethoxine and Sulfachloropyrazine could be used in the treatment of outbreaks in the field.

INTRODUCTION

The occurrence of *Plasmodium durae* in Africa was reviewed and its presence in South Africa confirmed by isolation by Huchzermeyer (1993). A high degree of pathogenicity of this parasite for domestic turkeys has been reported from Kenya (Herman 1941; Purchase 1942; Mackenzie & Simpson 1953) and Zimbabwe (Huchzermeyer 1975, 1976).

Herman (1941) mentions "extensive splenic involvement", whereas Purchase (1942) and Garnham (1966) particularly emphasize hypertension, which causes blood to spurt "with some violence" (Garnham 1966) from punctured veins. Right ventricular hypertrophy caused by the South African isolates has already been reported (Huchzermeyer 1988). An absence of rise in temperature was reported by Purchase (1942), who also first reported the presence in the capillaries of the brain of numerous exoerythrocytic schizonts (EES) as cause for cerebral symptoms preceding death. The effect of *P. durae* infections on mass gain has not been reported previously.

The action of chinins on experimental avian malarias was investigated by Brumpt, Bovet & Brumpt (1937), Missiroli (1937), Mudrow (1940) and Singh, Basu & Ray (1952), mainly in an attempt to use the avian infection as a model for human malaria. Sulfamonomethoxine with pyrimethamine and sulfamethoxine with pyrimethamine were used successfully against human *P. falciparum* infections in Indochina (Ebisawa, Muto, Mitsui & Kameko 1971). Sulphamonomethoxine alone and in combination with pyrimethamine was found an effective prophylactic against leucocytozoonosis due to *Leucocytozoon (Akiba) caullery*i in fowls in the Phillipines (Manuel & Mora-

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TABLE 1 Drugs tested for activity against *P. durae*

Abbreviation	Generic name	Commercial name	Company	Trial no.
AM+	Amprolium + Ethopabate	Amprol plus	MSD	1
AMS	Amprolium	Amprol soluble	MSD	2
COL	Sulphamethoxypyridazine + Trimethoprim	Colimix		1
CYG	Maduramicin	Cygro	Cyanamid	1
DAI	Sulfamonomethoxine	Daimeton WS Plus	Chemveld	3; 8; 9
EMT	Metronidazole	Emtryl soluble	MayBaker	1
ENR	Enrofloxacin	Baytril	Bayer	13
ESB	Sulfachloropyrazine	ESB3	Ciba Geigy	9; 10; 11
FUR	Furazolidone	Furazolidone 96 %	Phenix	1
HAL	Halofuginone	Stenorol	Roussel	7
MAL	Chloroquine phosphate	Malaquin	CABS	4; 6
PEN	Sulphathiazole + Sulpha-cetamide + Sulphamerazine + Sulphadimidine + Sulphaquinoxaline + Trimethoprim	Penta-Sulfa	Pharma-Link (Milborrow)	8; 9
TOL	Toltrazuril	Baycox	Bayer	5; 6; 12

TABLE 2 Dosages, applications and regimes used in the antimalarial trials

Trial no.	Date Y	M	Strain	Passage	n[1]	Drug	Dosage	Application	Regime[2]
1	84	12	M	16	2	AM+	100 mg x 1 kg^{-1}	Feed	0 to end
					2	CYG	5 mg x 1 kg^{-1}	Feed	0 to end
					2	EMT	0,63 mg x 1 ℓ^{-1}	Water	0 to end
					2	FUR	2 mg x 1 ℓ^{-1}	Water	0 to end
					2	COL	0,22 mg x 1 ℓ^{-1}	Water	0 to end
2	85	01	M	18	2	AMS	0,5 mg x 1 ℓ^{-1}	Water	2 to end
					2	AMS	1mg x 1 ℓ^{-1}	Water	2 to end
3	85	06	M	28	2	DAI	1mg x 1 ℓ^{-1}	Water	4–8; 11–15
					2	DAI	5 mg x 1 ℓ^{-1}	Water	4–6
4	86	01	M	15	2	MAL	5 mg x 1 kg^{-1} live mass	Per os	0; D21
5	86	02	M	43	2	TOL	5 mg x 1 kg^{-1} live mass	Per os	3
6	86	02	M	44	2	MAL	5 mg x 1 kg^{-1} live mass	Per os	0; 7; 14
						TOL	2,5 mg x 1 ℓ^{-1}	Water	0–5
7	86	10	O	12	2	HAL	3 mg x 1 kg^{-1}	Feed	0 to end
8	87	01	O	15	4	PEN	0,5 mg x 1 ℓ^{-1}	Water	1
						PEN	0,25 mg x 1 ℓ^{-1}	Water	2; 3; 6; 7; 10; 13
					4	DAI	2 mg x 1 ℓ^{-1}	Water	0–3
9	87	01	O	16	4	DAI	2 mg x 1 ℓ^{-1}	Water	After onset of parasitaemia: 5–7
					4	ESB	1 mg x 1 ℓ^{-1}	Water	1–3
					4	PEN	1 mg x 1 ℓ^{-1}	Water	1–3; 6; 9–11
10	87	02	O	17	4	ESB	1 mg x 1 ℓ^{-1}	Water	1–3; 6–8
					4	ESB	2 mg x 1 ℓ^{-1}	Water	1–3
11	87	03	O	20	4	ESB	4 mg x 1 ℓ^{-1}	Water	1–3; 6–8
12	87	04	N	10	4	TOL	10 mg x 1 kg^{-1} live mass	Per os	0; 1; 6
13	89	04	N	12	3	ENR	0,5 mg x 1 ℓ^{-1}	Water	1–3
					3	ENR	0,5 mg x 1 ℓ^{-1}	Water	After onset of parasitaemia: 9–11

[1] n = number of birds per group

[2] numbers denote day post infection on which treatment was given

les 1974; Manuel, Morales & Trovela 1977). Combinations of halofuginone and furazolidone have also been used successfully against leucocytozoonosis in fowls (Wickramanayake 1979). Halofuginone is a chlorobromated derivative of febrifugine which was used for centuries in China and Indochina for the treatment of human malaria (Henderson, Rose, Harris & Chen 1949). The active alcaloid of febrifugine, γ-dichroine, was found to be active against *P. relictum* in canaries (Henderson *et al.* 1949). Aureomycin (chlortetracycline) was reported to be effective against *P. gallinaceum* in fowls, even against the exoerythrocytic stages (Coatney, Greenberg, Cooper & Trembley 1949).

As *P. durae* could pose a threat to the establishment of turkey industries in endemic areas, it appeared necessary to investigate the degree of pathogenicity of local isolates and practical means of chemotherapy of such infections.

MATERIALS AND METHODS

Poults for passaging were obtained day-old from various commercial sources and later bred at the Onderstepoort Veterinary Institute. All birds were reared and kept under mosquito proof conditions.

Passaging was done by subinoculation of fresh blood by intramuscular or intravenous routes as described in detail by Huchzermeyer (1993).

The parasitaemia was monitored by taking thin blood smears 2–5 x per week. These were fixed with May-Grünwald Giemsa, stained with Giemsa and examined at a magnification of 1000. Of each smear 5–100 fields of view with approximately 100 erythrocytes per field were examined and the para sites counted. The counts were recorded as number of parasites per 100 fields of view.

Of birds that died, brain smears were taken, which were fixed and stained as described above and examined at magnifications of 100 and 1000 for EES. As it was difficult to set a standard for counting, the presence of EES was expressed as + when few EES were seen, ++ when most capillaries contained 1 or a few EES and +++ when most capillaries contained many EES.

In several passages blood samples were taken together with the blood smears and the haematocrit (hct) was determined by using a haematocrit centrifuge. At the same time the hct of uninfected birds kept under identical conditions was also determined.

In other passages the mass of birds was recorded individually with the aid of a digital scale (Mettler PK 4800 with Mettler GA40 printer) in order to determine the effect of the infection on mass gains.

From birds which died, the mass was determined on the same digital scale for the hearts without auricles (= total ventricles) and the spleens. The spleen-heart ratio (SHR) was determined by dividing spleen mass by total ventricular mass (Huchzermeyer & Van der Vyver 1991).

The drugs used in the present trials were obtained from commercial sources and are listed in Table 1. They were administered either ready-mixed in the ration or given in the drinking water or by individual dosing according to live mass. The dosages used were the same as currently used against other pathogens. If a drug appeared to show effectivity in the first trial, dosage and regime were adjusted in the repeat trial. These trials with dosage and regimes are listed in Table 2. In each trial there was an infected untreated control of as many birds as were used per trial group. A delay in onset of parasitaemia and a substantially lowered parasitaemia were taken as indication of a possible antimalarial activity, whereas failure of the parasitaemia to become patent was taken to indicate a strong antimalarial effect. Only when mortality occurred in the control group could prevention of mortality be used as a further parameter.

RESULTS

The mortality produced by the 8 isolates of *P. durae* is detailed in Table 3. Three isolates (1 from a turkey and 2 from Swainson's francolin) produced approximately 50 % mortality, while the other isolates produced either very low mortality or none at all.

The hct values of 19 uninfected turkeys ranged from 35–44 (mean 38,8; standard deviation 2,56).

The course of infection in individual birds has been illustrated by plotting the logarithm of parasite counts and hct in Fig. 1–3, logarithm of parasite counts, hct and daily mass change as % of body mass in Fig. 4, and mean logarithms of parasite counts with daily mass changes in Fig. 5. In some cases there was

TABLE 3 Percentage mortality in turkeys caused by different South African isolates of *Plasmodium durae*

Isolate	Origin	No. of passages	No. of birds	% mortality
T	Turkey	40	79	7,6
E	F.s.	2	4	50,0
M	Turkey	44	135	50,4
N	Turkey	22	72	12,5
O	F.s.	39	209	45,5
Q	Turkey	3	5	–
J	F.s.	7	11	–
N	F.l.l.	4	9	11,1
Total	–	161	524	34,5

F.s. = *Francolinus swainsoni*
F.l.l. = *F. levaillantii levaillantii*

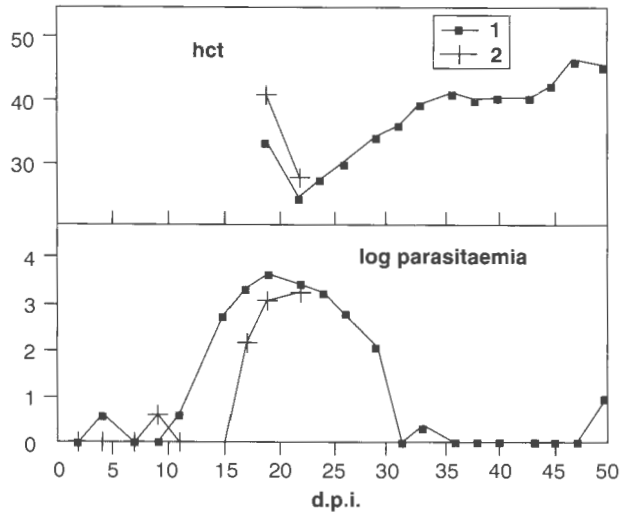

FIG. 1 Effect of parasitaemia on haematocrit. Bird 2 was found dead on Day 22 p.i. (isolate M passage 26)

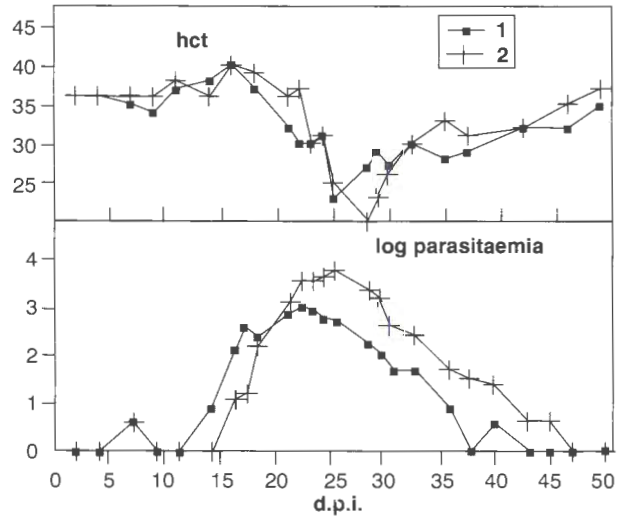

FIG. 2 Effect of parasitaemia on hct. In both birds there was initially an increase in hct, while the trough of the hct curve followed peak parasitaemia by 2–3 d (isolate M passage 29)

an increase of hct before the peak of parasitaemia followed by a short decline several days after the peak of parasitaemia.

The effect of parasitaemia on mass gains in groups of 10 infected and 10 non-infected control birds is shown in Table 4 and of 2 turkeys with a prolonged parasitaemia compared with 2 controls in Table 5. As shown in Table 6, EES were found in the brain capillaries of most birds that died from infection with *P. durae,* irrespective whether mortality occurred at the peak of parasitaemia or after recovery from parasitaemia.

TABLE 4 The effect of parasitaemia on mass gain of turkeys infected with *P. durae* (isolate O passage 18)

Dpi	Log mean parasite count	% Daily mean mass gain	
		Infected (n=10)	Controls (n=10)
4	2,20		
6	2,08	3,5	3,9
8	3,09	1,7	2,3
11		-1,6	1,7
12	3,64		

n = number of birds

TABLE 5 Total mass gain of 2 turkeys with prolonged parasitaemia 1 and 2 uninfected control birds and mean daily percentage mass gain (isolate M passage 17)

Bird	Infected		Uninfected	
	1	2	3	3
Initial mass (g)	1 005	1 220	862	1150
Final mass (g)	1 647	1 619	1440	1773
Mass gain (g)	642	399	578	623
% of initial mass	63,9	32,7	67,1	54,2
n days	31	31	31	31
Mean daily % gain	1,62	0,90	1,65	1,41
s	1,23	0,84	0,64	0,95
Mean log parasitaemia	1,88	2,26		
s	1,07	0,88		
n counts	21	21		

n = number
s = standard deviation

TABLE 6 The percentage frequency of occurrence of exoerythrocytic schizonts of *P. durae* in brain capillaries of experimentally infected turkeys

Isolate	n	% occurrence of EES			
		–	+	++	+++
M	44	4,5	13,6	25	56,8
N	6	16,7	0	33,3	50
O	62	4,8	0	29	66,1

n = number of brains examined

The spleen–heart ratios of turkeys infected with isolates N and O of *P. durae* were significantly higher than those of the controls (means ± standard deviations did not overlap) (Table 7).

The results of the drug trials are summarized in Table 8. Four of the anticoccidials tested (Amprolium, Amprolium + Ethopabate, Maduramycin and Toltrazuril) showed no antimalarial activity, while Halofuginone somewhat suppressed the parasitaemia and afforded protection from mortality. Chloroquine phosphate lowered or suppressed the parasitaemia and appeared to protect from mortality, whereas neither Metronidazole, Furazolidone nor Enrofloxacin were effective.

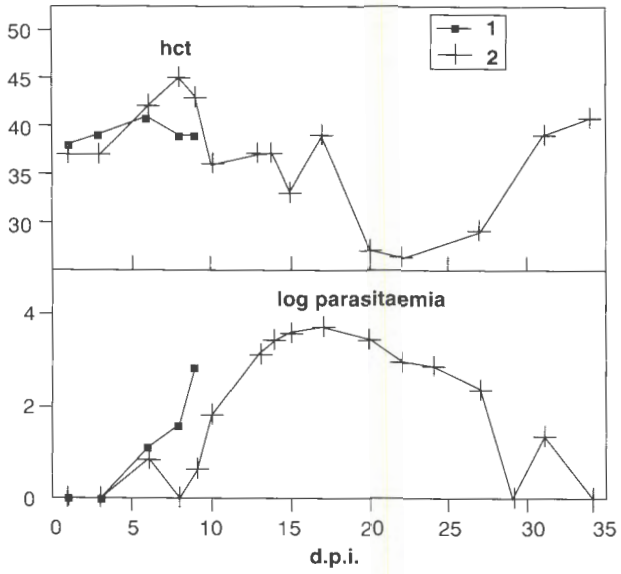

FIG. 3 Effect of parasitaemia on hct. Bird 1 was found dead on Day 9 p.i. (isolate M passage 31)

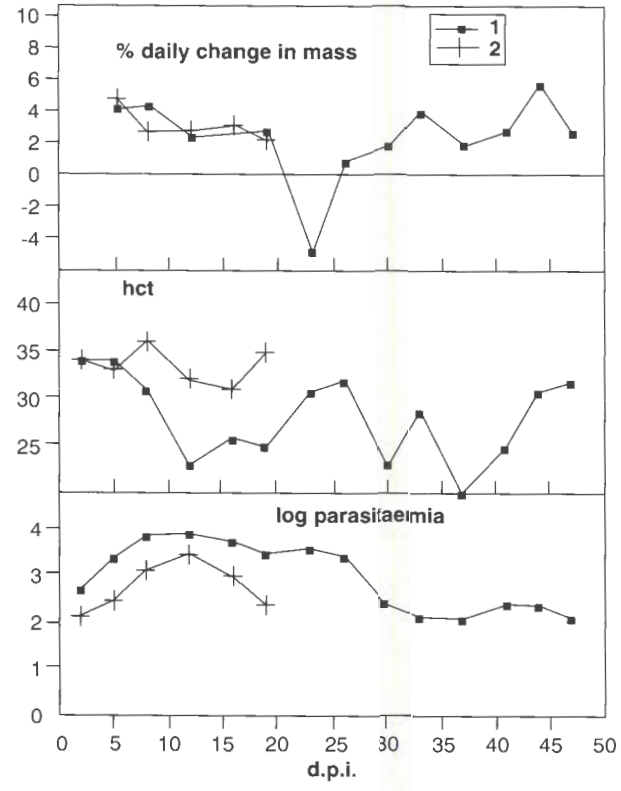

FIG. 4 Comparison of parasitaemia, hct and daily mass changes. Bird 2 was found dead on Day 19 p.i. Subsequently Bird 1 underwent severe mass loss. Both events appear to be linked to the presumably simultaneous development of EES rather than changes in parasitaemia (isolate N passage 11)

Amongst the sulfonamides and sulfonamide combinations Sulphamethoxypyridazine + Trimethoprim was ineffective; at a higher dose Penta-Sulfa slightly lowered the parasitaemia and protected from mortality; prolonged application of high doses of Sulfachloropyrazine protected from mortality while not suppressing parasitaemia, and only Sulfamonomethoxine suppressed parasitaemia, while not entirely protecting from mortality.

DISCUSSION

The South African isolates subject of this study were far less pathogenic for turkeys than those reported from other African countries: Kenya: Herman (1941): "extremely pathogenic and fatal to young

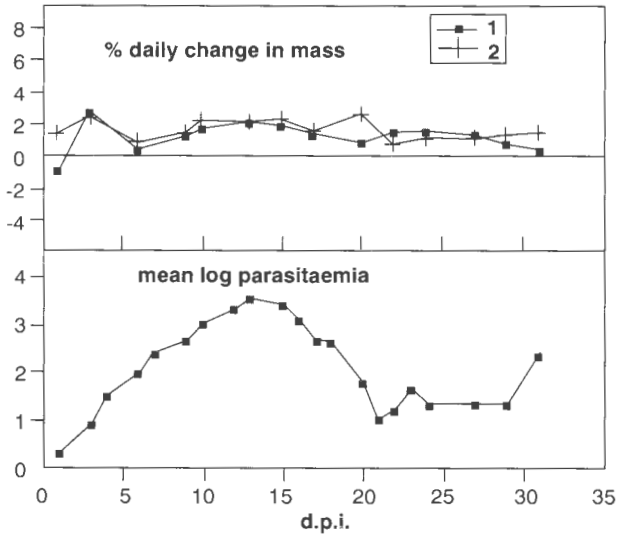

FIG. 5 Comparison of parasitaemia and daily mass changes. Even high parasitaemia did not prevent daily mass gains (isolate M passage 17)

TABLE 7 Spleen-heart ratios of turkeys experimentally infected with *P. durae* and of non-infected controls

	Isolate N	Isolate O	Controls
n	20	23	30
mean	0,889	0,889	0,293
s	0,396	0,325	0,065
range	0,4–1,86	0,17–1,66	0,21–0,53

n = number of birds
s = standard deviation

TABLE 8 Antimalarial effectivity of tested drugs

Drug	Dosage	No. days used	Parasitaemia		Mortality	
			Delayed	Suppressed	Trial	Control
AM+	100 mg x 1 kg^{-1}	23	-	-	0/2	0/2
AMS	5 g x 1 ℓ^{-1}	19	-	-	0/2	0/2
	1 g x 1 ℓ^{-1}	19	-	-	0/2	0/2
COL	0,22 g x 1 ℓ^{-1}	23	-	-	0/2	0/2
CYG	5 mg x kg^{-1}	23	-	-	0/2	0/2
DAI	1 g x 1 ℓ^{-1}	2 X 5	+	+	0/2	2/2
	5 g x 1 ℓ^{-1}	3	+	+	0/2	2/2
	2 g x 1 ℓ^{-1}	4	+	+	0/4	0/4
	2 g x 1 ℓ^{-1}	3	n/a	+	2/4	4/4
EMT	0,63 g x 1 ℓ^{-1}	23	-	-	0/2	0/2
ESB	1 g x 1 ℓ^{-1}	3	-	-	4/4	4/4
	1 g x 1 ℓ^{-1}	6	-	-	0/4	4/4
	2 g x 1 ℓ^{-1}	3	-	-	4/4	4/4
	4 g x 1 ℓ^{-1}	6	-	-	0/4	4/4
FUR	2 g x 1 ℓ^{-1}	23	-	-	0/2	0/2
HAL	3 mg x 1 kg^{-1}	26	+	(+)	0/3	1/2
MAL	5 mg x 1 kg^{-1}	2	+	-	0/2	2/2
	5 mg x 1 kg^{-1}	3	+	(+)	0/2	1/2
PEN	0,5 x 1 ℓ^{-1} / 0,25 x 1 ℓ^{-1}	1 / 6	-	-	0/4	0/4
	1 g x 1 ℓ^{-1}	8	-	(+)	0/4	4/4
TOL	0,5 x 1 ℓ^{-1}	3	-	-	0/4	0/4
	0,5 x 1 ℓ^{-1}	3	n/a	-	0/4	0/4
TRI	5 mg x 1 kg^{-1}	1	n/a	-	0/2	0/2
	2,5 ml x 1 ℓ^{-1}	6	-	-	2/2	2/2
	10 mg x 1 kg^{-1}	3	-	-	4/4	4/4

(+) denotes mild effect

turkeys"; Purchase (1942): mortality 12 out of 14; MacKenzie & Simpson (1953): mortality up to 90 %; Zimbabwe: Huchzermeyer (1975, 1976): mortality 5 out of 5. In 161 passages with 524 birds the 8 South African isolates produced 34,5 % mortality with only 3 isolates able to produce approximately 50 % mortality, while the other 5 isolates produced much lower mortality or even none (2 isolates).

EES were found in almost all birds that died, both at the peak of parasitaemia and after parasitaemia had subsided. This differs markedly from the biphasic mortality pattern found in *P. circumflexum* infections in turkeys, where EES only appeared after recovery from the parasitaemia (Huchzermeyer & Van Der Vyver 1991). The Zimbabwean isolate of *P. durae* produced large numbers of EES even in the early stages of parasitaemia (Huchzermeyer 1975, 1976). Mortality due to the early development of EES has also been found in fowls infected with *P. gallinaceum* (Haas, Wilcox, Laird, Ewing & Coleman 1948) as well as in chukars infected with *P. octamerium* (Manwell 1968). In all these cases the brain capillaries were occluded by the swollen endothelial cells, preventing normal blood flow and causing anoxic conditions in the brain or in parts of the brain resulting in a type of cerebral stroke (Seed & Manwell 1977). Consequently the EES appear to be the main pathogenic feature of *P. durae.*

Parasitaemia only had a limited effect on hct, which in some birds tended to rise in the initial stages of parasitaemia and after the peak of parasitaemia dropped for a few days below the range found in normal birds. This showed that parasitaemia and consequent destruction of erythrocytes are not the main agents of pathogenicity in *P. durae* infections. This is in contrast to the effect of experimental infections with *P. lophurae* in ducks (Rostorfer & Rigdon 1945) and with *P. circumflexum* in turkeys (Huchzermeyer & Van der Vyver 1992), where severe aneamia alone appears to be responsible for some of the mortality.

There was also only a mild effect of parasitaemia on mass gain, except where high parasitaemia was prolonged (Table 5). A short period of mass loss of the survivor of 2 birds after the death of the other 1 may have been linked with the development of EES in both birds simultaneously, causing the death of 1 of the birds and a severe crisis in the other (Fig. 4). In infections of turkeys with *P. fallax* mass gain was depressed when either erythrocytic or exo-erythro-

cytic forms were high in number (Graham, Stauber, Palczuk & Barnes 1973).

Purchase (1942) reported an absence of a rise in body temperature. Endotoxicity appears to play a role in mammalian malarias (Clark 1982a, b). However, the avian malarial parasites are not thought to act as pyrogenic agents (Hayworth, Van Riper & Weathers 1987), although a rise in rectal temperature during infections of ducks with *P. lophurae* has been reported (Hewitt 1942).

Right ventricular hypertrophy as a consequence of hypoxic pulmonary arterial hypertension caused by *P. durae* infections in turkeys has been reported previously (Huchzermeyer 1988) as well as in experimental infections of turkeys with *P. circumflexum* (Huchzermeyer & Van der Vyver 1991). These were, however, less severe than the right ventricular hypertrophy observed in broiler chickens infected with *Aegyptianella pullorum* (Huchzermeyer, Cilliers, Diaz Lavigne & Bartkowiak 1987).

"Extensive splenic involvement" in *P. durae* infections in turkeys was reported by Herman (1941). The reasons for expressing the relative mass of the spleen as spleen-heart ratio (SHR) were discussed in a previous paper (Huchzermeyer & Van der Vyver 1991). SHR's recorded in the present trials were similar to those found in experimental infections of turkeys with *P. circumflexum* (Huchzermeyer & Van der Vyver 1991).

The hypertension reported by Purchase (1942) and Garnham (1966) was investigated and could not be confirmed by De Jong (1971). In the present trials squirting of blood from the punctured brachial veins occurred commonly in infected as well as in uninfected turkeys depending somewhat on the angle at which the wing was held. It is believed to be due to a combination of the action of venous valves and the pressure exerted on the wing and its venous system and not to be dependent on an increase in arterial blood pressure.

With the exception of chloroquine phosphate only drugs currently available for use in poultry were tried and only at doses generally recommended for use in poultry. Only when some effect was seen or even suspected in the preliminary screening, were higher doses tested, with the exclusion of feed-medicated anticoccidials, where increasing the dosage would have been impracticable. The negative results, therefore, do not necessarily indicate an absolute lack of antimalarial activity, but rather a failure to act against *P. durae* at current dosage rates.

Because of the close relationship between coccidia and plasmodia, one would have expected or hoped for a better efficacy of the anticoccidials tested. The ineffectiveness of Amprolium, Amprolium + Ethopabate, Maduramycin and Toltrazuril could, however, be due to a lower absorption rate, ideal for drugs having to act on intestinal parasites. Halofuginone, the exception, is known to be related to an historically used antimalarial (Henderson *et al.* 1949).

Metronidazole is used against flagellates and as antibacterial; Furazolidone is an antibacterial with some anticoccidial action (Harwood & Stunz 1949; Reid 1973), which also showed some antimalarial activity in combination with Halofuginone against leucocytozoonosis in fowls (Wickramanayake 1979); Enrofloxacin is a quinolone carboxylic acid derivative with a broad antibacterial spectrum of activity (Scheer 1987); neither of these substances alone had any effect.

Sulfonamides alone or in combinations have been used against coccidia as well as plasmodia. Sulfachloropyrazine is widely used in the treatment of coccidiosis in fowls (Reid 1973), while Sulfamonomethoxine alone or in combination with pyrimethamine has been used against leucocytozoonosis in fowls (Manuel & Morales 1974; Manuel *et al.* 1977) and the latter combination also in human malaria (Ebisawa *et al.* 1971). In the present trials Sulfamonomethoxine suppressed parasitaemia, but was unable to give full protection from mortality when given after the onset of parasitaemia. Conversely Sulfachloropyrazine did not show any effect on parasitaemia, but at the highest dose gave protection from mortality. This effect might have been brought about by a selective action against EES which appear to be the most pathogenic form of the parasite.

In conclusion it can be stated that the local isolates of *P. durae* were less pathogenic than those reported from Kenya and Zimbabwe and some even apathogenic, that EES are the main pathogenic stage of this parasite and that drugs effective against the infection of turkeys with *P. durae* appear to be available. While Halofuginone has a potential as a chemoprophylactic, Sulfamonomethoxine and Sulfachloropyrazine, preferably in combination or alternatingly, could be used to treat outbreaks.

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