

THE EFFECT OF CORTISONE ON THE SURVIVAL OF *HYMENOLEPIS DIMINUTA* IN MICE

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ABSTRACT

Cortisone acetate, 1 mg thrice weekly, permitted *Hymenolepis diminuta* in single worm infections to survive without loss for 45 days in male CFLP mice 6 weeks old at infection. Worms grew to over 200 mg dry weight by day 18 post infection (PI), following which their weight remained steady or decreased slightly. In control mice, worms rarely exceeded 12 mg before being rejected on day 11 ± 2 PI. Termination of cortisone (commenced on day 1 of the infection) on day 6, 8, 10, or 20 PI led in each case to loss of worms starting six days later, which is believed to be 2-3 days after the cortisone given in the last dose had ceased to be effective. Tolerance was not induced. Delaying the commencement of cortisone until day 8 PI did not accelerate rejection after cortisone was terminated. Decreasing the cortisone, from 1 mg to 0.5 mg thrice weekly, after 20 days led to a reduction in the size of the worms, possibly because the worms experienced a host rejection attack when the cortisone level fell, between injections, below its protective level. There was abundant evidence that cortisone has an immediate protective effect on tapeworms, since even when cortisone treatment was delayed until after destrobilation, worms recovered and regrew as they would on transfer to a naive host. The possible sites of action of cortisone in preventing rejection are discussed.

INTRODUCTION

Six-week-old male CFLP mice reject *Hymenolepis diminuta* between day 8 and day 16 PI. The time decreases as the worm burden increases from a single to a 12-worm infection. The process usually involves worms destrobilating, leaving a scolex and neck 0.5-10 mm long, which are subsequently lost without regrowth (Hopkins, Subramanian, and Stallard, 1972a; Befus and

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Featherston, 1974). Various immunosuppressants including cortisone prevent this rejection (Hopkins, Subramanian, and Stallard, 1972b). The purpose of the present work was to determine what stage(s) in the process of worm rejection was (were) blocked by cortisone—in particular, to determine how early in an infection it was necessary to start cortisone to prevent rejection, and whether the subsequent course of an infection was the same after cortisone treatment was terminated, following different periods of administration.

MATERIALS AND METHODS

CFLP male mice (from Anglia Laboratories, formerly Carworth Europe Ltd.) 39-45 days old at time of infection were used. A single cysticercoid of *H. diminuta* was administered by stomach tube to each mouse. Mice were kept 5 or 6 per cage. Except where specified to the contrary, 1 mg of cortisone acetate (Cortisyl Roussel) in 0.05 ml of 0.9% NaCl was administered intramuscularly into right and left hind limbs alternately on Mondays, Wednesdays, and Fridays starting on day 1 (mice infected Tuesday, day 0). Mice were killed and the small intestine was removed and examined for worms. In the absence of parasites, the intestine was cut into 10 cm sections, which were placed separately in 5 cm petri dishes containing Hanks' saline and incubated for $\frac{1}{2}$ -2 hours at 37°C. Examination quickly revealed any worm bigger than 0.2 mg dry weight, i.e., over approximately 2 cm long, but more prolonged searching was necessary to find destrobilated worms, usually less than one cm in length. Destrobilated worms were not looked for, nor included when found by chance.

RESULTS

The effect of commencing cortisone at different stages of an infection

Cortisone treatment was commenced on day 1, 3, 6, 8, 10, 13, and 15 PI, in seven groups of mice to which a single cysticercoid per mouse had been administered on day 0 (Tuesday). Intramuscular injection of 1 mg of cortisone was given to each mouse on Monday, Wednesday, and Friday of each week until animals were autopsied. Mice were autopsied in groups of ten; the number infected and the mean dry weight of the worms, excluding worms < 0.2 mg, are shown in table 1. Figure 1 shows the biomass, i.e., total dry weight of worm recovered from ten mice, at different stages in the course of the infection; the various symbols indicate the day cortisone was started.

From table 1 and figure 1, it is apparent that it makes little difference whether cortisone is started 1, 3, or 6 days after infection. In each group (A, B, and C, table 1) over 90% of cysticercoids administered were recovered as worms, and in each group worm growth was at a decreasing exponential

TABLE I
THE EFFECT OF COMMENCING CORTISONE AT DIFFERENT TIMES DURING AN INFECTION ON THE SURVIVAL AND GROWTH OF *H. DIMINUTA* IN MICE (SINGLE WORM INFECTIONS)

Day post infection	1 mg cortisone administered thrice weekly starting:															
	Group A		Group B		Group C		Group D		Group E		Group F		Group G		Group H	
	Day 1		Day 3		Day 6		Day 8		Day 10		Day 13		Day 15		None	
	No./	Mean	No./	Mean	No./	Mean	No./	Mean	No./	Mean	No./	Mean	No./	Mean	No./	Mean
	10	wt.	10	wt.	10	wt.	10	wt.	10	wt.	10	wt.	10	wt.	10	wt.
8	8	4	8	4	10	2	—	—	—	—	—	—	—	—	—	—
9	10	11	9	8	10	7	7	4	—	—	—	—	—	—	6	2
10	10	24	10	18	8	8	8	12	—	—	—	—	—	—	5	8
12	10	63	10	46	10	34	8	39	—	—	—	—	—	—	3	9
14	9	106	8	88	9	110	10	71	3 + 0	75 + 0	1 + 0	86 + 0	—	—	1	21
16	10	229	10	225	10	168	9	174	2 + 3	109 + 0.4	1 + 0	95 + 0	1	0.2	1	0.9
18	10	255	8	262	10	234	9	194	4 + 1	168 + 3	1 + 2	246 + 3	1	2	2	0.7
20	9	234	9	244	9	235	10	179	3 + 4	209 + 6	2 + 2	170 + 1	1	3	0	—
22	9	240	9	211	10	232	9	183	4 + 3	202 + 6	0 + 1	0 + 11	1	214	0	—
24	10	212	10	194	10	222	10	165	6? + 2?	170 + 56	1 + 5	220 + 27	1	9	0	—
Mean No. worms (days 16-24)	9.6		9.2		9.8		9.4		6.4		3.6		1.0		0.6	

No./10, number of mice infected in a group of 10, each mouse given 1 cysticeroid on day 0; mean wt, mean dry weight (mg) of the worms recovered; —, indicates no mice examined.

The worms in Groups E and F are separated into two categories; the first figure refers to worms that did not destrobilate, the second figure to destrobilated worms that were regrowing under cortisone (see text). The two categories could not be distinguished, with certainty, on day 24 in Group E. Bottom line shows the mean number of mice infected (number of worms found) out of 10 at autopsy on days 16-24 inclusive.

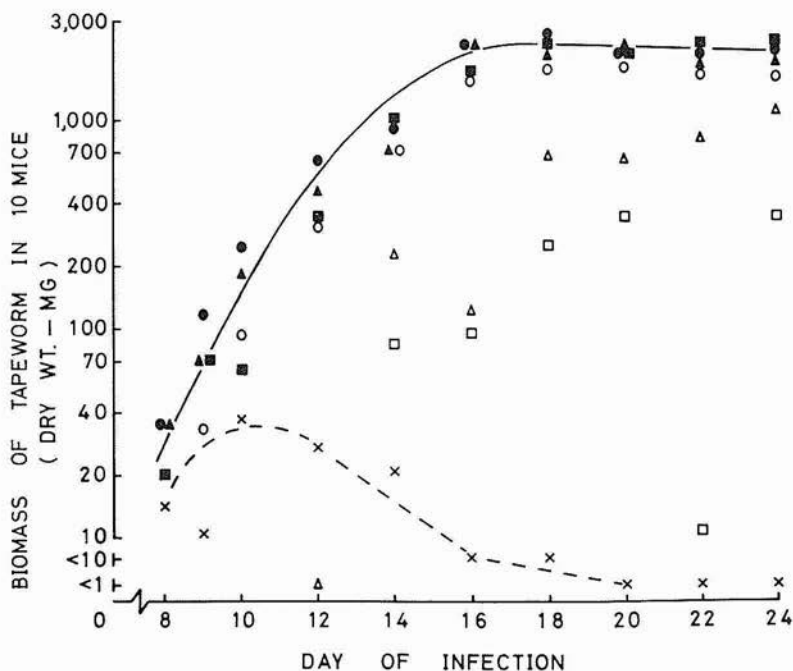


FIG. 1. THE CHANGE IN TAPEWORM BIOMASS during growth, in relation to the time when cortisone was commenced. Each point is the total dry weight of *H. diminuta* recovered from the autopsy of ten mice given one cysticercoid each on day 0. Symbols indicate time when cortisone was commenced: ● day 1, ▲ day 3, ■ day 6, ○ day 8, △ day 10, □ day 13, × Controls—no cortisone. Curves fitted by eye, solid line based on closed points, broken line on crosses, i.e., worms in control mice. See text for heterogeneity of △ and □ data, and table 1 for further details.

rate until about day 18, after which a common plateau was maintained (figure 1).

In Group D cortisone treatment was not commenced until day 8 PI, by which time growth appears to have been retarded—cf. groups A and B. No worm loss occurred, however (we recovered only 7 worms on day 9, almost certainly because one or more small worms were missed; as growth proceeded under cortisone the recovery rate rose to over 90%). The plot in figure 1 suggests that these worms, like those in Groups A, B, and C, reached a maximum size on day 18 and thereafter remained fairly constant. The implication is that growth lost in the pre-patent period (eggs appear in the feces on day 16 ± 1) is not made up.

In Group E (and F) the worm recoveries and mean weights are divided into two categories (table 1). The first figure in each column refers to large worms like those recovered in Groups A-D, the second figure to debilitated worms. We conclude:

(1) that approximately 25% of worms were rejected before cortisone had its effect (as shown by a 73% recovery on days 20-24 PI compared with over 90% in the Groups A-D)

(2) that approximately half the remaining worms destrobilated, but these were saved from expulsion and regrew. As they became bigger, the probability of finding them increased, and hence the total number of worms over 0.2 mg recovered increased from 3 on day 14 to 8 on day 24 PI.

Only 10% of the worms in Group F mice had not destrobilated and/or been expelled by the time the cortisone, started on day 13 PI, became effective. These worms, shown in the first column (table 1), persisted and reached a weight around 200 mg. As in Group E, destrobilated worms a few mm long and therefore not included started to regrow once cortisone was started. Five days after the commencement of cortisone administration, these destrobilated worms exceeded 0.2 mg (second column, Group F, table 1).

By day 15 PI, as can be seen in the controls (Group H), virtually all worms either had been rejected or were present only as destrobilated scolices. Even at this stage, however, the administration of cortisone can save destrobilated worms and permit them to re-initiate growth (Group G). The worm recovered on day 22 PI was clearly a worm in a slow or non-responder mouse (slow-responding mice, like this one in the Group G autopsied on day 22 PI, are occasionally found in control mice in similar experiments, although none happened to be found in the control mice in this experiment).

The rather low recovery of worms in the control mice (Group H) on day 9 PI was almost certainly due to the small size of the worms; rejection or destrobilation appears to have occurred on day 11 ± 2 PI.

Effect of terminating cortisone administration on the longevity of the tapeworm

One cyst of *H. diminuta* was administered to each of 430 mice on day 0. On day 1 the mice were divided into five groups: Group A, 100 control mice not receiving cortisone; Group B, 85 mice receiving cortisone on days 1, 3, and 6 PI; Group C, 75 mice receiving cortisone on days 1, 3, 6, and 8 PI; Group D, 65 mice receiving cortisone on days 1, 3, 6, 8 and 10 PI; Group E, 105 mice receiving cortisone throughout experiment, i.e., days 1, 3, 6, 8, 10, 13, 15, 17, 20, and 22 PI.

The number of worms (exceeding 0.2 mg) and their mean dry weight is shown in table 2. Each figure is based on a group of ten mice except those indicated with an asterisk, in which the number was reduced to nine because of mortality during the experiment. The results indicate that:

(1) In the control mice (Group A), worms were lost on day 11 ± 2 PI as expected.

(2) In Group E, the cortisone regimen prevented the rejection of worms throughout the 24 days of the experiment.

TABLE 2
THE EFFECT OF TERMINATING CORTISONE, AFTER DIFFERENT PERIODS, ON THE GROWTH
AND SURVIVAL OF SINGLE WORM INFECTIONS OF *H. DIMINUTA* IN SPF CFLP MALE MICE

Age of infection (days)	Group A		Group B		Group C		Group D		Group E	
	<i>No Cortisone</i>		<i>Cortisone to Day 6</i>		<i>Cortisone to Day 8</i>		<i>Cortisone to Day 10</i>		<i>Cortisone Throughout</i>	
	no. of mice	mean dry wt. of	no. of mice	mean dry wt. of	no. of mice	mean dry wt. of	no. of mice	mean dry wt. of	no. of mice	mean dry wt. of
	infected/10	worm (mg)	infected/10	worm (mg)	infected/10	worm (mg)	infected/10	worm (mg)	infected/10	worm (mg)
6	—	—	—	—	—	—	—	—	—	—
8	10	1.7	—	—	—	—	—	—	9	2.8
9	8	2.2	—	—	—	—	—	—	9	7.0
10	5	2.7	8	3.6	—	—	—	—	6	9.3
12	1	9.5	5	12	9	26	—	—	9	42
14	1	0.9	3	27	7	53	9	43	7	65
16	0		2	24	0		5	115	8	152
18	0		0		1	123	5	102	7	203
20	0		0*		1	119	2*	131	8*	197
22	0		0*		2	77	0*		8*	202
24	0		1*	54	0		0*		7*	174

Group A mice received no cortisone, mice in Groups B, C, D, and E received cortisone starting on day 1 of the infection (see text) until and including the day specified. The horizontal line shows when the cortisone treatment was terminated. —, no mice examined; 0, none of the mice infected; *, 9 mice (not 10) in the group.

(3) In Groups B, C, and D, cessation of cortisone was followed by the same sequence of events: no loss of worms occurred in the subsequent 4 days, by day 6 PI worm rejection commenced, by day 8 50% or less of the worms remained, and by day 10 80% of the worms had been rejected.

(4) Cortisone treatment led not only to the survival of the worms but to continuous increase in worm weight until day 18 PI, at which stage weight increase stopped, presumably because worms had reached sexual maturity.

(5) The mean weight of control worms was less than that of worms of the same age from mice receiving cortisone (cf. Groups A and E). This result could occur either because cortisone increases the "normal rate" of growth (cf. growth of *H. microstoma* in mice—Moss, 1972) or because the immune response of the host had begun to affect worm growth by day 8 PI in the control mice.

Tolerance

Attempts were made to induce tolerance to worm infection under cortisone, which Wakelin and Selby (1974) have shown to occur in *Trichuris muris*.

Mice were divided into three groups. Group 1, infected day 0, received cortisone from day 1 through day 20 PI (●, figure 2). On day 21, cages were randomly divided into three subgroups a, b, and c. Mice in subgroup 1a continued to receive cortisone until the experiment was terminated on day 45 PI (●, day 23-45); in subgroup 1b the mice received no further treatment (○, figure 2); and in subgroup 1c the mice had the cortisone level reduced by half, i.e., to doses of 0.5 mg (■, figure 2). Group 2 mice were controls and received no cortisone (×, figure 2). Group 3 mice were on cortisone day 8-20 PI (▲, figure 2), after day 20 the results are shown as △, figure 2.

The results show that:

(1) Following termination of cortisone on day 20 PI, rejection took place 6 ± 1 days later; it made no difference whether cortisone administration had been started on day 1 (○, figure 2) or day 8 (△, figure 2).

(2) One mg cortisone thrice weekly maintained worms without loss for 45 days (●, figure 2). Maximum weight, with maturation, was reached in the period day 16-21 PI and maintained until day 23; thereafter the worms were lighter. Without replication of the experiment, it is not possible to say whether or not the fall in mean worm weight from day 23 to day 28 PI followed by a rise is significant (cf. oscillation in weight of *Diphyllobothrium latum* in dogs [Wardle and Green, 1941], and growth of *H. citelli* [Hopkins and Stallard, 1974, figures 3 and 4]).

(3) When the level of cortisone was reduced to 0.5 mg/dose after day

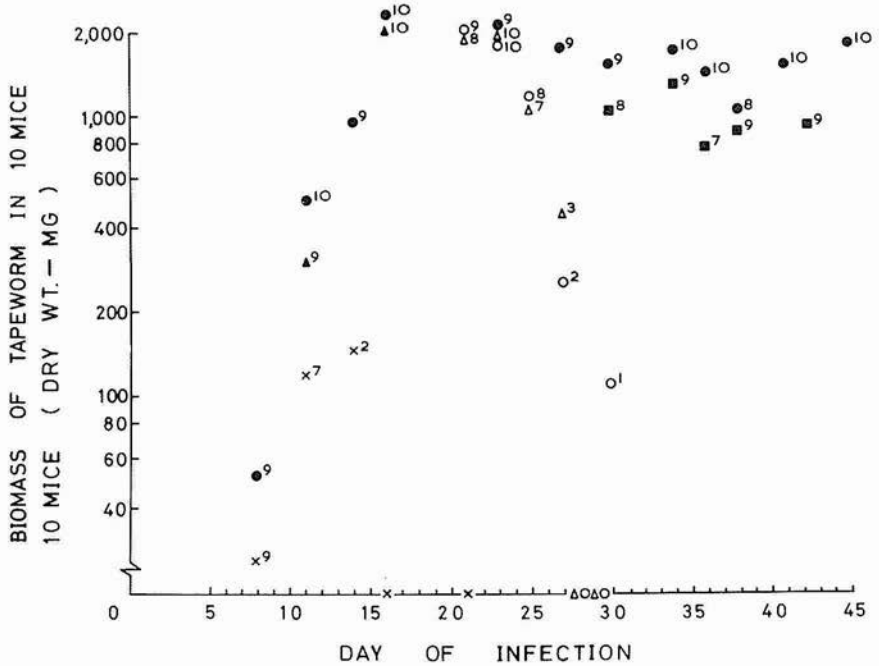


FIG. 2. THE EFFECT ON *H. diminuta* of terminating or decreasing the amount of cortisone on day 20 of an infection. Closed points indicate mice receiving cortisone up to autopsy; open points, mice in which cortisone was stopped on day 20; ×, control mice (no cortisone). Indices show number of mice in group of 10 infected (single worm infections). ●, full dose cortisone started day 1; ▲, full dose cortisone started day 8; ■, mice receiving half normal dose after day 20.

20 PI, the weight of the worms fell (■, figure 2) compared with those in mice kept on 1 mg/dose, and stabilized around 100 mg dry weight, compared with 150-190 mg in the mice on 1 mg/dose.

(4) In control mice worm growth was stunted by day 11 PI, and worm rejection was nearly complete by day 14 PI (×, figure 2).

DISCUSSION

Although many authors (e.g., Weinmann, 1966, 1970) have argued that parasitic worms living completely in the lumen of the intestine evoke immune responses, there is still a widely held belief that, since many intestinal tapeworms do not damage the gut mucosa, they are isolated outside the body of the host and are not immunogenic. Any lingering conjectures that intimate contact with the tissues (either during a migratory phase or following erosion of the mucosa by hooks on the scolex) is necessary before a protective immune response can be evoked, are no longer tenable (Hopkins, Subramian,

and Stallard, 1972a and b; Wassom et al., 1974; Befus and Featherston, 1974; Hopkins and Stallard, 1974; Befus, 1975a). It is now well established that immunologically effective amounts of proteins are readily taken up through the intestinal wall of adult mammals (Bienenstock, 1974). Thomas and Parrott (1974) have found that continued oral administration of small quantities of bovine serum albumin to mammals leads to partial immunological tolerance to this protein, an observation which is of particular relevance in intestinal parasitology, where potentially immunogenic helminths often avoid rejection by the host.

There is also no doubt that corticosteroids prevent the loss of worms from the intestine in numerous parasite infections (Wakelin, 1970). What is controversial is the point or points at which cortisone blocks the rejection mechanism. The problem is partly due to the multifaceted effects of cortisone (Claman, 1972, 1975; Berenbaum, 1974).

When cortisone was administered to mice commencing on day 1, 3, or 6 after infection, the survival and growth of the worms was similar (figure 1, table 1); presumably, therefore, the worms were up to this time unaffected by a host response. Delaying cortisone administration until day 8 PI showed that by this day worm growth had been affected; however, cortisone prevented further damage and permitted growth to resume (table 1). The most interesting result was that cortisone started on day 10, 13, or 15 PI—that is, after rejection had commenced—not only protected surviving intact worms but also permitted destrobilated worms to regrow, as they would if surgically transplanted into a previously uninfected host (Hopkins, Subramian, and Stallard, 1972a). These results resemble those obtained by Luffau and Urquhart (unpublished, but quoted by Jarrett et al., 1968) who found that cortisone started on day 14 PI stopped rejection of *Nippostrongylus brasiliensis* from rats.

It is known that *N. brasiliensis* is damaged by day 10 PI (“the antibody phase,” Jones and Ogilvie, 1971) and that subsequent rejection occurs rapidly even after transferral into naive hosts, providing there are “normal” lymphocytes present (Keller and Keist, 1972). Cortisone is, therefore, when administered late in an infection, acting on this second phase of the rejection, or on a third component (Kelly et al., 1973) possibly activated by the T-lymphocytes involved in the second phase.

The evidence at present is too fragmentary to justify building a detailed hypothesis, but there are several similarities other than the production of antibody between the rejection of *H. diminuta* and *N. brasiliensis*. *H. diminuta* is coated with immunoglobulins by day 9 PI (Befus, 1974, 1975b), though this by itself is not likely to be the only factor in the rejection of *H. diminuta*, just as antibody is not the only factor in the rejection of *Nippostrongylus*. Indeed, antiworm antibodies are produced by rats infected with *H. diminuta* (Coleman et al., 1968; Harris and Turton, 1973), and mice with

H. microstoma (Moss, 1971; Goodall, 1973), in neither of which are worms rejected. Rejection of *H. diminuta*, like *Nippostrongylus*, is also dependent on the presence of T-cells as shown by Bland's (1976) work with "nude" mice. It is reasonable to assume that T-cells sensitized to *H. diminuta* exist long before day 10 of an infection, and as sensitized T-cells are cortisone resistant (reviewed, Claman, 1972) it seems most likely that cortisone is stopping rejection by blocking the action initiated by the sensitized T-cells.

As cortisone works extremely quickly in arresting rejection, it may be surmised that its effect is either on the surface of the tapeworm where the immunological attack probably occurs, or on a process occurring in the intestinal lumen or wall. What process(es) might be involved is mere speculation at present, for there are many possibilities. It is known, for instance, that cortisone affects the permeability of the host gut wall (Jarrett et al., 1968) and the release of prostaglandins (Lewis and Piper, 1975; Dineen et al., 1974), host responses which have been incriminated in the rejection of *Nippostrongylus*. It is reasonable to speculate that the ultimate factors that damage and/or cause the rejection of tapeworms, are enzymes. These enzymes could originate from complement, which Befus's (1975b) results using fluorescein-conjugated β_1C (C_3) antisera suggest is present on the surface of *H. diminuta* (cortisone is known to be anti-complementary—see Gewurz et al., 1965), or could be released from neutrophil polymorphs, which enter the intestine in large numbers when a sensitized mucosa is exposed to homologous antigen (Bellamy and Nielsen, 1974). The role of the T-cells may well be to stimulate this immune-mediated emigration, and hence the protective function of cortisone could be the stabilization of the lysosomal membranes, thus inhibiting release of the great variety of lytic enzymes that exist in polymorphs (Baggiolini, 1972).

Termination of cortisone, commenced on day 1 PI, on day 6, 8, or 10 of an infection gave similar results: rejection started 5-6 days later. However, it is known that 1.25 mg of cortisone acetate administered every three days prevents worm loss, although the weights of the worms are statistically significantly less than those of worms in mice given cortisone every two days; when it is administered every four days there is a significant loss of worms (Subramanian, unpublished). These results suggest that the effect of cortisone acetate lasts for about 72 hours after i.m. administration. Loss of worms, therefore, starts quickly, within two or three days of the effects of cortisone waning. This suggests that part or all of the induction phase of sensitization takes place under cortisone, and that it is the efferent or effector arms of the response that are blocked. Experiments to verify this by carrying out the whole primary infection under cortisone, terminating with "Zanil" (Hopkins, Grant, and Stallard, 1973), and then testing for memory by giving a secondary infection, have given inconclusive results. Two experiments showed a considerable reduction in the anamnestic response, whereas in a third experiment

worms in the challenge infection were severely stunted, as in a normal secondary infection (Befus, 1975a).

One other result must fit into the rejection pattern. When cortisone was reduced on day 20 PI to half the normal dose, the weight of the worms in the mice decreased compared with the worms in mice kept on the full dose (figure 2). The process of rejection is therefore a quantitative phenomenon, but here again there are many interpretations. One possible explanation is that the reduced level of cortisone permits a low-level immunological attack by the host on the tapeworm, and that the parasite tolerates this attack by repairing its damaged tissues. A more probable explanation is that cortisone, given at the reduced dose of 0.5 mg thrice weekly, does not remain at a high enough level in the body to suppress attack throughout, and so, for a period immediately prior to the next dose, worm growth is impaired or stopped. The result would be a decrease in the weight of the worms until a new equilibrium was established between the smaller amount of new tissue being produced between cortisone doses and the loss of eggs and proglottids during that period. This latter explanation fits with the observation, quoted above, that 1.25 mg of cortisone every third day results in smaller worms than those found when it is given daily or every second day. There was no indication that tolerance had been induced by giving cortisone at the full effective level for the first 20 days PI.

In conclusion, cortisone is well tolerated by the host and is the most effective and most reliable way of preventing loss of *H. diminuta* (cf. Rose [1972], who wrote the same about coccidia). Its mode of action is difficult to determine, however, because of its vast array of potential effects (Baxter and Forsham, 1972; Claman, 1972, 1975). Nevertheless, in recent years much has been learned about the action of cortisone and this justifies further investigation of its function in preventing worm rejection. In particular, it would be interesting to discover what process is blocked so quickly following the injection of cortisone that worms which have destrobilated commence to grow again instead of being rejected by the host.

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