strate the role of information available only through the mediation of the motor-sensory feedback loop. Previous experiments have achieved this end by showing that greater compensation is achieved after self-produced movement than after equivalent passive movement, with sensory input equated under both conditions (*4*). But the head is not easily subjected to passive movement because of the difficulty of relaxing the neck musculature. Consequently, we chose to compare the effects of locomotion with equivalent passive transport of the body.

Each of eight subjects was exposed under two conditions of movement. During the "active" condition the subject walked inside the drum for one-half hour while viewing its surface. During the "passive" condition he viewed the surface while being wheeled around a similar path, for the same duration, standing on a specially designed cart. Each subject was run under each of the two conditions with both base right and base left prisms, making four runs per subject. All subjects were instructed to minimize movements of their heads in relation to their bodies and periodic inspections by the experimenter checked on this factor. The sequence of conditions was randomized among the eight subjects. Comparison of the aftereffects following the two conditions provided a test of our hypothesis that the transformed rates of displacement of parts of the retinal image will produce the aftereffect only after self-produced movement. In addition, the absence of an aftereffect following passive motion would confirm the assumption that the exposure field was not patterned in a manner that could generate the curvature aftereffect on mere scanning. As a further check, three additional subjects were run under both conditions without prisms. With the measuring procedure described above, theoretical full compensation for the curvature induced by a 20 pd prism should result in a difference between pre- and postexposure means of 20 pd of the same base orientation as the prism. This difference would indicate that what is then seen as a straight line is objectively a line either convex to the right or convex to the left, the curvature induced by the prism during exposure.

The aftereffects for the eight subjects exposed under the active condition with base right prism averaged 3.3 (range from 2.0 to 4.9) pd base right; with base left prism, 3.4 (range from 2.2 to 6.5) pd base left. They were compensatory without exception. When released from the measuring apparatus, after this condition, most of these subjects immediately noticed an apparent curvature when fixating points on straight vertical contours in their normal surroundings. After the passive condition with base right prism the mean aftereffect was 0.1 pd base left (range from 0.8 pd base right to 0.9 pd base left); with base left prism, 0.0 (range from 0.7 pd base right to 0.9 pd base left). None of the three subjects run without prisms showed a significant aftereffect under either active or passive conditions.

These results show that the presence of curved patterning in the visual field is not a necessary condition for generating the curvature aftereffect. Visual space can be warped solely as a result of transforming the relation between self-produced movement and its concurrent sensory feedback. Patterns of change in retinal stimulation are normally correlated with the movements that produce them. A prism placed in front of the eye will change the terms of the correlation but not the order entailed in it. Consequently, with exposure to the transformed condition, the central nervous system becomes informed of the new correlation which is a prerequisite for adaptation. This demonstration is consistent with our contention that the plasticity underlying adaptation to rearrangement is not attributable to changes in either response systems alone or in sensory processes alone but rather to a complex interaction between the two (*4*). The importance of this plastic process for the maintenance of stable visuospatial behavior and its development are discussed elsewhere (*7; 8*).

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Dialysis Studies in Rats on the Long-Acting Antimalarial CI-501

Abstract. *Through the use of dialysis sacks, containing the repository antimalarial CI-501, implanted intraperitoneally into rats, evidence has been obtained indicating a local rather than a systemic reservoir of the drug. These results suggest that the repository activity of CI-501 is due to drug release from the injection site and that the probability of toxic effects resulting from storage or accumulation of the drug in vital organs is remote.*

A pamoic acid salt of 4,6-diamino-1-(*p*-chlorophenyl)-1,2-dihydro-2,2-dimethyl-*s*-triazine, CI-501, is a long-acting, parenteral, antimalarial drug in mice (*1*), monkeys (*1, 2*), and man (*3*). This drug also shows repository action in rats: a single subcutaneous dose (100 mg/kg) gave protection for 10 to 11 weeks (*4*). The salt, sparingly soluble in water (0.003 percent), is slowly released from the subcutaneous or intramuscular injection sites in quantities sufficient for both protective and therapeutic activity (*1*). The purpose of this study was to determine whether CI-501 might be stored elsewhere after release from the injection site and then released from this second site in sufficient amount for activity against the malaria parasite.

We suspected that this point could be clarified by injecting the drug and then removing it before challenge with parasites. Surgical excision of the drug mass (*5*) was considered, but dismissed in favor of intraperitoneal implantation of the drug in dialysis sacks, followed by removal prior to challenge. An

Table 1. Effects of CI-501 on *P. berghei* in rats. There were six rats in group 1 and seven rats in each of the other groups. The results from day 6 to day 14 inclusive are the same as the results in day 5.

Day	Rats positive (%) in group:					
	I	II	III	IV	V	VI
1	0	0	0	0	0	0
2	0	71	28	0	0	0
3	0	100	85.7	42.8	0	57.1
4	0	100	100	100	0	71.4
5	0	100	100	100	0	100
			Analysis of parasitemia			
$\Sigma\bar{x}$*	0	105.34	87.77	58.86	0	26.43
$\bar{x}$.*	0	7.52†	6.26†	4.20†	0	1.88
$S^2(\bar{x}.)$*	0	43.31	24.06	15.55	0	4.12
$S\bar{x}$.*	0	1.75	1.31	1.05	0	0.54

* $\Sigma\bar{x}$ is the sum of the daily mean percentages of cells parasitized within groups; $\bar{x}$. is the within groups mean over all days; and $S^2(\bar{x}.)$ and $S\bar{x}$. are the variance and standard error of within groups means. † Significantly higher than group VI at $\alpha = 0.05$.

animal experiment was considered worthwhile if the poorly soluble drug would dialyze satisfactorily.

To determine if CI-501 in very dilute solution would move across a dialysis membrane in vitro, 1 ml of an aqueous suspension of CI-501 was placed in dialysis tubing (*6*), the ends were tied to form a sack, the closed sack was placed in 350 ml of 0.86-percent saline, and the whole was kept at room temperature and stirred continuously. Samples were taken from the saline bath periodically and analyzed (*7*) for drug concentration by means of the characteristic ultraviolet absorption spectrum of CI-501. These analyses indicated that the maximum predicted concentration outside the sack (26 to 30 μg/ml) was reached in approximately 65 hours. Such movement through the dialysis membrane indicated that an animal experiment would be worthwhile, although it remained conjectural whether dialysis would occur in vivo.

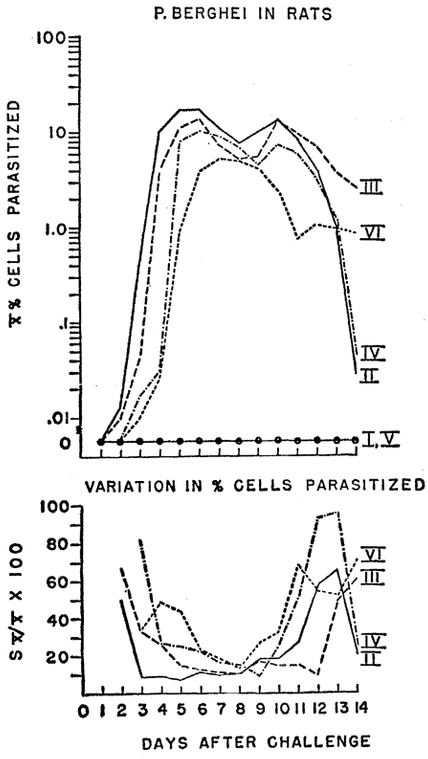

Fig. 1. Mean percentage of cells parasitized and variation in percentage of cells parasitized for 14 days after challenge with *Plasmodium berghei*. I, drug sack in; II, drug sack out; III, vehicle sack in; IV, vehicle sack out; V, free drug in; and VI, normal controls.

The animal experiment was conducted in the following manner. Six groups of seven male Rawley rats, mean weights 234 to 263 g, were used. Dialysis tubing containing an aqueous suspension of the drug or of vehicle alone was tied securely at each end to form sacks and these were inserted intraperitoneally into the indicated groups of rats through a small incision parallel to the midventral line. The drug suspension contained 100 mg of triazine base per milliliter. The groups of rats in the experiment were as follows: group I: sack containing 0.75 ml of drug suspension and 0.75 ml of saline inserted on day 0, rats sham-operated on day 7; group II: sack containing 0.75 ml of drug suspension and 0.75 ml of saline inserted on day 0, removed on day 7; group III: sack containing 0.75 ml of vehicle and 0.75 ml of saline inserted on day 0, rats sham-operated on day 7; group IV: sack containing 0.75 ml of vehicle and 0.75 ml of saline inserted on day 0, removed on day 7; group V: 0.75 ml of drug suspension given intraperitoneally on day 7; and group VI: normal intact rats. All rats were challenged intravenously on day 10 with 50×10^6 *Plasmodium berghei* procured from donor mice (rats were not used for donors due to the very low parasitemia after one passage, possibly resulting from the transfer of immune serum). Blood smears were made daily for the next 14 days and the percentage of cells parasitized was determined. The remaining sacks were removed on the 25th day and all were intact. Tissue reaction occurred only at the rough knotted ends of the sack.

The experimental results are shown in Table 1 and Fig. 1. The groups known to have at challenge either drug sacks (I) or free drug (V) were refractory to infection. The group from which the drug sack was removed before challenge (II) and the vehicle control groups (III and IV) were susceptible to infection. In Fig. 1, the upper graph depicts the course of the parasitemia and the lower graph shows the variation in percent cells parasitized [$(S\bar{x}/\bar{x}) \times 100$ gives the index of variability]. This variation was high during the periods when the parasitemia was increasing exponentially or declining rapidly; it was lowest during the peak of the parasitemia (days 6 through 9). The groups subjected to operation (II, III, and IV) developed significantly more severe infections than the normal intact controls (VI). However, the controls were heavier than the other groups and this might have accounted for their lower susceptibility.

Resistance to challenge by the rats with the drug sacks removed would have suggested that CI-501 was being stored in the tissues and secondarily released. The failure of these rats to resist infection showed that the amount of drug stored and released from other sites was insufficient to protect them. The in vitro dialysis results, metabolic data (*8*), and other antimalarial studies of the dihydrotriazine suggest that extremely small amounts would have prevented the growth of the parasite. Therefore, the evidence for negligible secondary storage and release is strong.

These observations help to elucidate the repository action of CI-501 and suggest that the possibility is small of toxic effects resulting from storage or accumulation of the drug in vital organs.

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Angiotensin Pressor Inhibition by Aldosterone in the Rabbit

Abstract. *Rabbits pretreated with aldosterone exhibited lessened response to the pressor agent angiotensin. This observation may help to explain the absence of hypertension in certain instances in which both the formation of angiotensin and the secretion of aldosterone are above normal.*

In this study we show that aldosterone dampens the pressor effect of angiotensin in the rabbit. Angiotensin, a polypeptide resulting from the interaction of kidney renin and a plasma protein, produces an increase in the secretion of aldosterone by the adrenal gland (*1*). We reported previously that aldosterone, in turn, has a blocking action on the effect of angiotensin by increasing the renin content of the rat kidney (*2*). The observation, as well as examples of the formation of increased angiotensin in the absence of hypertension in man and experimental animals, led us to the supposition that aldosterone might have inhibitory effects on angiotensin. Rabbits of a New Zealand strain were used in experiments to test this hypothesis.

On two successive days we injected adult rabbits subcutaneously with 40 μg/kg of aldosterone (Ciba *d*-aldosterone, diluted to 0.1 mg/ml in 33-percent ethyl alcohol). The control animals were given the solvent only. Several hours after the second injection, we anesthetized the animals with 20 mg/kg sodium pentobarbital (Nembutal, Abbott) and catheterized the femoral artery for recording blood pressure by the Sanborn electromanometer system. In the first group of experiments, graded doses of angiotensin II (1-L-asparaginyl-5-L-valyl angiotensin octapeptide, Ciba) were given intravenously, and the amount necessary to produce rises of 20 and 30 mm-Hg in the blood pressure was determined by titration. The average dose of angiotensin which produced these responses is given in Table I. Eight rabbits treated with aldosterone and seven control rabbits were used, but only five of the control rabbits were studied at the response level of 20 mm-Hg. The amounts of angiotensin required to produce responses of 20 and 30 mm-Hg were significantly greater in the animals pretreated with aldosterone than in the control animals.

We then used another group of five rabbits pretreated with aldosterone and five controls to determine the maximum responses in blood pressure caused by continuous infusion of angiotensin over the range of 0.2 to 1.2 μg/kg per minute. The infusion rate of a solution containing 25 μg percent of angiotensin II in 0.9 percent sodium chloride was kept constant at each dose level for a period of 5 minutes, the flow being controlled with a Sigma motor peristaltic pump. For each animal the response to the various dosages was taken as the maximum rise in blood pressure during the last minute of the infusion period. (Three control animals and two animals treated with aldosterone developed cardiac arrhythmias and respiratory distress at the 1.2 μg/kg dose rate, necessitating interruption of the infusion.) Figure 1 is constructed from the average responses in the ten animals. As can be seen, the animals treated with aldosterone were consistently less responsive to the infusion of angiotensin than the control animals. Findings similar to these have been noted in the rat and will be reported in a more extensive treatment of this subject elsewhere.

Table 1. The effect of pretreatment of rabbits with aldosterone on the response of the blood pressure to angiotensin. Logarithmic transformation of the individual doses was used to stabilize the variance. The figures in parentheses indicate the number of animals in each treatment.

Rabbits	Mean dose ($\bar{x}$) angiotensin* (μg/kg)	*t*-test	*P* (one tail)
20 mm-Hg rise in blood pressure			
Treated with aldosterone (8)	0.245	2.091	<.05
Controls (5)	0.134		
30 mm-Hg rise in blood pressure			
Treated with aldosterone (8)	0.480	3.213	<.005
Controls (7)	0.258		

* The average amount required to cause the indicated rise in blood pressure.

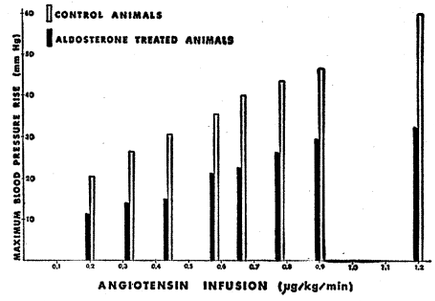

Fig. 1. Mean responses of rabbits treated with aldosterone and of control rabbits to continuous infusion with angiotensin II. The difference in the level of response of the blood pressure in the two groups is statistically significant ($P < .005$) as tested by comparison of the *y*-intercepts of the two fitted-least-squares regression lines.

In contrast to the observed effect of aldosterone on angiotensin, Raab *et al.* (*3*) noted previously that in man, the pressor effect of norepinephrine was increased after treatment with synthetic deoxycorticosterone, a salt-retaining steroid. Davis *et al.* (*4*) observed a decreased blood pressure response to angiotensin in dogs with constriction of the inferior vena cava. These animals had an increased secretion of aldosterone and presumably increased blood levels of angiotensin, yet their blood pressures were in the normal range. An increase in the activity of angiotensinase in the plasma of patients who had secondary aldosteronism was observed by Hickler *et al.* (*5*), suggesting that aldosterone may cause an increase in the activity of plasma angiotensinase and in this way may lessen the capacity of the blood pressure to respond to angiotensin.

Despite the intriguing possibility suggested by the observation of Hickler *et al.*, the actual mechanism by which aldosterone lessens the full effect of angiotensin is uncertain at present. Nevertheless, the noted antagonism of aldosterone to angiotensin provides another example of a substance acting, in turn, to inhibit or to modulate the effect of its stimulant (*6*).

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