delaying their rate of decomposition[8]. The residue of recalcitrant compounds contributes to colloidal soil organic matter[8].

It is clear that secondary plant chemicals also have a role to play in deterring herbivores and pathogens in many situations. This role is not inconsistent with that of manipulating decomposers, and the evolution of one will also involve the other. Sometimes the dividing line between these two is not clear – a good example of ambiguity is the role of bark toxins in preserving the dead heart wood of a living tropical tree[3]. In other cases the linkage may involve a sequence in evolutionary time. Just as toxicity to vertebrates may originate as an incidental consequence of toxicity to invertebrate seed-predators[2], so also may toxicity to predators originate as an incidental consequence of toxic manipulation of decomposers.

The anti-predator interpretation of plant toxins is sometimes supported by citing the lack of evidence for any other direct metabolic importance to the adult plant[2,6]. However, there is evidence that toxic manipulation of decomposition is of direct ecological significance to the adult plant in its ecosystem. Consideration of all the evidence will, I think, change our estimation of the importance of anti-predator and anti-decomposer influences in driving the evolution of plant toxins, and assign a greater, and perhaps primary role to the effect on decomposition.

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Pulmonary edema in mice infected with *Plasmodium berghei*. Involvement of catecholamines[1]

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Summary. Mice inoculated with *Plasmodium berghei* developed a drastic and significant pulmonary edema. Treatment of animals with phenoxybenzamine rendered mice hyporeactive to this physiopathological alteration.

We have previously described that the lungs of mice inoculated with *Plasmodium berghei* showed dramatic edema beginning on the 4th day of infection[3]. Pulmonary edema in malaria has been reported in animal species other than rodents[4], and was described in humans more than 70 years ago[5]. Hyperactivity of the sympathetic nervous system has been observed in malaria[6], and it is known that catecholamines injected i.v. cause pulmonary edema in mice and rats[7]. Since it was shown that the phenomenon is inhibited by alpha-adrenergic receptor antagonists in rats[8], the present investigations were designed to examine the existence of any causative relation between catecholamines and pulmonary edema associated with malaria in mice.

Material and methods. Male mice of the Swiss-44 strain, weighing 18–20 g, were used for the study. The strain of *Plasmodium berghei*[9] used was the Pasteur strain[3]. The strain was maintained by successive inoculations, every 5 or 6 days, in Swiss-44 mice, by the i.p. route, with oxalated blood containing about 5×10^6 parasitized erythrocytes. The laboratory temperature was kept constant at 27 °C.

This work was conducted using 4 experimental groups: group I, normal animals injected with saline; group II, animals inoculated with *P. berghei* only (5×10^6 parasitized erythrocytes, i.p.); group III, animals injected with phenoxybenzamine in 3 separate doses of 1.0; 3.0 and 3.0 mg/kg at 1-h intervals, i.p., and group IV, animals injected with phenoxybenzamine as above and inoculated with the parasite 1h after the last dose of alpha-sympatholytic drug. Additional doses of 3.0 mg/kg of phenoxybenzamine were given each day from the 1st to 7th (the last day of infection) day to groups III and IV.

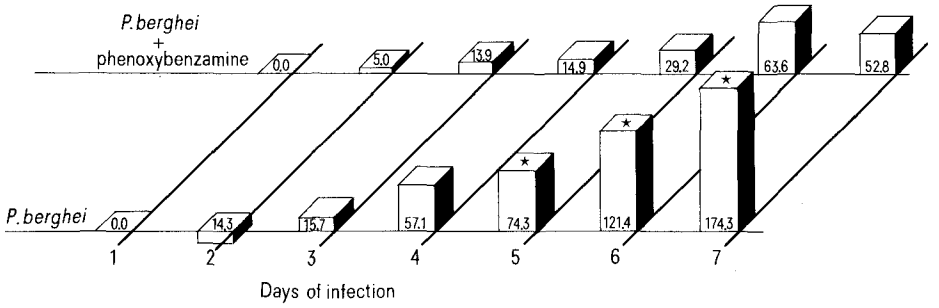
Each day, 5 animals of each group described above were anesthetized with sodium pentobarbital (40 mg/kg, i.p.) and killed by exsanguination through the aorta and inferior vena cava. The lungs were dissected free from trachea and weighed. Significant changes in lung wet weight/body weight ratios were considered to reflect pulmonary edema[10].

To verify if phenoxybenzamine could be interfering with the parasitemia of *P. berghei*-infected animals, thin blood films were obtained from infected animals only and phenoxybenzamine-treated and infected animals.

The thin blood films were stained with May-Grünwald-Giemsa and parasitemia was expressed as:

$$\text{Percentage of parasitemia} = \frac{\text{number of parasitized erythrocytes}}{\text{number of total erythrocytes}} \times 100$$

Statistical analysis was performed using Student's t-test.



Percentage changes in lung wet weight/body weight ratios caused by *P. berghei* in normal and phenoxybenzamine-treated mice. The percentages verified in *P. berghei*-inoculated animals were obtained in relation to animals injected with saline (inferior horizontal line). The percentages verified in *P. berghei* + phenoxybenzamine animals were obtained in relation phenoxybenzamine-treated mice (superior horizontal line). Each result represents a mean of 5 animal daily per group. *Results are significantly different ($p < 0.01$) from controls. Phenoxybenzamine-treated mice showed no estatistically significant differences of Staub's ratio in relation to saline injected animals.

Results and discussions. The findings have been summarized in figure 1. As can be observed, mice infected with *Plasmodium berghei* presented a progressive and significant increase of Staub's ratio (i.e. lung wt/body wt) beginning on day 5 and reaching 2-3-fold increases in values in relation to normal animals at day 7 of infection. The treatment of animals with phenoxybenzamine was shown to have profound effects on the development of pulmonary edema. This alpha-blocking agent was effective in reducing edema at day 5, 6 and 7 in animals infected with *P. berghei*. Furthermore, phenoxybenzamine did not alter the degree of parasitaemia of infected animals (table) or the lung wet weight/body weight ratios of uninfected mice (normals: $5.33 \times 10^{-3} \pm 0.28 \times 10^{-3}$; phenoxybenzamine $5.56 \times 10^{-3} \pm 0.38 \times 10^{-3}$; $n = 11$). Animals infected with the parasite presented no significant changes in body weight in relation to controls.

There is evidence that i.v. administration of adrenaline, in rats, causes pulmonary edema and that this alterations could be due to a hemodynamic effect[11] or to an increase in the vascular permeability in the lungs caused by the release of chemical mediators[12].

From our results, we suggest that pulmonary edema in *P. berghei*-malaria is fundamentally due to a permeability alteration of the vascular bed in the lungs. The hemodynamic component in malaria-edema is probably not important because it has been reported that systemic arterial pressure in the mice infected with *P. berghei* falls from normal levels of 80.2, to 51.4 mm Hg terminally[13], and hyperactivity of the sympathetic nervous system in malaria has been well demonstrated[6]. Moreover, it has been suggested that adrenalinic edema may be mediated by the release of kinin, a strong vasodilatator and permeabilizing agent[14]. Adrenaline can promote the activation of plasma kallikrein, kininogen consumption and kinin release, concomitantly with pulmonary edema[15]. We think that this pathway is the likely one, since we have noted a progressive decrease of kininic precursor beginning at day 5-7 of mouse malaria[3].

Although the results of the present work tend to implicate catecholamines as intermediate mediators of vascular permeability changes in lung edema of mice, we cannot disregard the known anti-serotonin action of phenoxybenzamine[16]. Results from our laboratory have suggested a possible participation of serotonin in this pathologic alteration in mice infected with *P. berghei*[17]. More work is needed to resolve the mechanisms of lung alterations in malaria, but it seems likely that the edema could be partially explained by the actions fo released catecholamines on alpha-adrenergic receptors during *P. berghei* infections.

Effect of phenoxybenzamine on erythrocyte infection rate of mice infected with *Plasmodium berghei*

Day after inoculation	Erythrocyte infection rate (%) *P. berghei*	*P. berghei* + phenoxybenzamine
1	–	–
2	0.51 ± 0.14	0.49 ± 0.17
3	1.80 ± 0.20	2.67 ± 0.40
4	8.71 ± 0.88	5.33 ± 1.25
5	31.06 ± 5.57	30.14 ± 3.16
6	53.46 ± 5.13	48.40 ± 5.37
7	60.33 ± 8.95	64.23 ± 5.31

Parasitemia caused by *Plasmodium berghei* in normal and phenoxybenzamine-treated mice. Day 1 equals the 24 h following inoculation. Results are mean ± SEM. The number of animals tested was 5 in each experiment.

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