plausible. The apparent inability of TS to increase the T-independent responses, however, indicates that any single interpretation may be inadequate to explain the immunopotentiating effect of this compound. Thiols have been shown to improve the viability and growth of lymphocytes in vitro as well as to enhance the action of mitogens on splenic lymphocytes[20]. While the increased spleen size in TS-treated animals might be due to the growth-promoting activity of this compound, 'sensitizing' properties might be responsible for the augmented synthesis of immunoglobulins. There is still the possibility that TS influences the humoral responses indirectly. As shown by Tormey et al.[21], transferrin greatly enhances the growth of lymphocytes in response to PHA and antigens in vitro. Since the transferrin level in TS-injected animals was always significantly increased, this might imply that TS augments the immune responses by transferrin-mediated mechanism. All these possibilities are not mutually exclusive, and further experiments along these lines are in progress.

Although it is not yet possible to draw general conclusions on the kinetics and mechanisms of TS-action, its strong stimulating effect on the mouse immune system seems obvious. The low toxicity of TS and its immunopotentiating effect encourage its therapeutic use.

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Methemoglobin in hypoxic rats

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Summary. Methemoglobin levels have been found to vary with altitude and to shift the hemoglobin-oxygen dissociation curve. In this study, hematocrits and methemoglobin levels were monitored in rats exposed to hypoxia (420 torr absolute) for various intervals. Hematocrits gradually increased throughout the period of hypoxia, while methemoglobin levels rose by 12 h, peaked at 24 h and returned to control level by day 6. These data, in the context of other work, suggest that increased methemoglobin is important in acclimation to hypoxia.

Human and animal sojourners in high altitudes respond to hypoxia with a decline in hemoglobin-oxygen affinity, indicated by a shift of the hemoglobin-oxygen dissociation curve to the right[3–5]. Presumably, this effect results from hemoglobin's interaction with 2,3-diphosphoglycerate (2,3-DPG), which sterically hinders binding with oxygen[6–8]. In lowland natives taken to high altitudes, circulating levels of 2,3-DPG increase by 48 h and remain elevated[4]. On the other hand, a relatively great hemoglobin-oxygen affinity is characteristic of animals native to high altitude[9] and of aquatic animals exposed to hypoxia[10]. Now, at extreme altitude, pulmonary oxygenation rather than tissue extraction is the limiting factor in oxygen transport; and, by artificially increasing their hemoglobin-oxygen affinity, Eaton[10] prolonged the survival of acutely hypoxic rats. In the light of this background information, one might hypothesize that the normal response of lowland species – decreased hemoglobin-oxygen affinity – is maladaptive.

Hematocrits and methemoglobin levels in response to various periods of hypoxia

Hypoxia (days)	n	Hematocrit (%) Mean ± SD	p	Methemoglobin (%) Mean ± SD	p
0	19	42.3 ± 1.70	...	4.32 ± 2.04	...
0.5	5	44.6 ± 2.60	N.S.	7.35 ± 3.88	<0.05
1	9	46.0 ± 3.33	<0.05	10.49 ± 3.01	<0.001
2	10	49.6 ± 3.62	<0.001	10.25 ± 2.52	<0.001
3	9	47.4 ± 3.40	<0.001	7.40 ± 1.23	<0.001
4	9	48.2 ± 4.07	<0.001	7.94 ± 3.07	<0.001
5	5	49.4 ± 3.65	<0.001	6.51 ± 0.93	<0.05
6	9	53.6 ± 2.80	<0.001	5.16 ± 1.71	N.S.

Rats were kept at 420 torr absolute in a hypobaric chamber. Values of control and experimental samples were compared by Student's t-test.

Methemoglobin, even though it carries no oxygen[11], has been found to increase hemoglobin-oxygen affinity[12]. The level of methemoglobin in man native to high altitude is abnormally high and is inversely related to red cell number; the level drops to normal when the subjects go to lower altitudes[13]. For a comparison, we monitored methemoglobin and hematocrits in a lowland representative, the rat, during acclimation to hypoxia.

Method. Long-Evans rats were exposed to simulated high altitude in a hypobaric chamber maintained at 420 torr absolute. Microhematocrits were determined on blood from the tail vain. Methemoglobin per 200-µl sample of blood was measured by the method of Evelyn and Malloy[14] as modified by Vandenbelt et al.[15]. Values of

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control and experimental samples were compared by Student's t-test.

Results. The erythropoietic response of rodents to hypoxia is well documented[16–18]: Hypoxia stimulates the production of erythropoietin[19], which in turn stimulates maturation of bone marrow[20] and hastens the release of reticulocytes into the peripheral blood[21]. This process is followed in the table, as hematocrit versus days of hypoxic exposure. The hematocrit gradually rises throughout the period of exposure, significantly so ($p < 0.05$) by day 1. Concurrently, a sharp rise in methemoglobin, significant ($p < 0.05$) by 12 h, peaks at 24 h ($p < 0.001$) and returns to control level by day 6.

Discussion. Normal methemoglobin levels are maintained by a balanced cycle of oxidation and reduction of hemoglobin and methemoglobin, respectively[22]. Hypoxic stress causes methemoglobin levels to elevate rapidly, significantly so ($p < 0.05$) by 12 h, far faster than the corresponding erythropoietic response (table)[18]. This drastic rise could be explained by the fact that deoxygenated hemoglobin, prevalent under hypoxia, oxidizes more readily to methemoglobin than does oxygenated hemoglobin[23]. Alternatively, a decrease in NADH levels or in NADH methemoglobin reductase activity could account for a diminished reduction of methemoglobin to hemoglobin[22]. The return of normal methemoglobin levels by the 6th day of hypoxia could occur by the reversal of these processes after the hematocrit has stabilized at a new high (table). This relationship corroborates the observation of Gourdin et al.[13] mentioned earlier.

Although observed in high-altitude residents[13], methemoglobin has not been examined for acclimative significance. Combined with what is now known about this process, our data permit the following description: In lowland natives, hypoxia evokes a rapid rise in methemoglobin (table), which increases the strength of the affinity between hemoglobin and oxygen[12], which in turn saturates the blood with oxygen for delivery to the tissues, which then facilitates survival[10] until gradual erythropoiesis can increase the blood's oxygen-carrying capacity by enlarging the erythron (table)[18]. Methemoglobin levels can only then return to normal as 2,3-DPG levels rise[4]. The process eventually leads to the high hematocrit and low hemoglobin-oxygen affinity characteristic of sojourners in high altitude.

Research is needed to determine whether a corresponding shift in the hemoglobin-oxygen dissociation curve does occur and whether elevated methemoglobin does affect survival. Meanwhile, we conclude that the dramatic though transient rise in methemoglobin revealed in our study is an effective short-term physiologic adjustment of a lowland native to an oxygen-deficient environment.

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Oxatomide, a new orally active drug which inhibits both the release and the effects of allergic mediators

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Summary. Oxatomide is a new potent inhibitor of anaphylactic and allergic reactions. After oral administration, the compound both inhibits the release of endogenous histamine and prevents the effects of exogenous histamine, at comparable doses. The combination of these effects appears to be the basis of the effectiveness of oxatomide in allergic reactions and may lead to clinical applications different from classical antihistaminics and from cromoglycate.

Allergic reactions centre on mast cells. It has long been recognized that the potent spasmogenic agent, histamine, is stored in this type of cell[1]. Antibodies of a special class, identified as IgE or reaginic antibodies, bind slowly but tightly to its surface[2] and subsequent contact of the allergen with the sensitized mast cell is a powerful, specific trigger for the release of intracellular histamine[3]. The final physiological responses depend on the topographical relation between the discharging mast cells and the mediator-sensitive smooth muscle. An unexpected feature of this relation in space is the recent finding that histamine-containing cells are found within the lumen of human bronchi[4].

The rational treatment of allergic patients started with the introduction of antihistaminic drugs in 1942[5]. After 30 years of use, however, it is widely accepted that the therapeutic effectiveness of the classical H_1-antagonists in allergic conditions has been disappointing in many respects[6] and of no or little interest in a major allergic condition, that of asthma[7]. The relative failure of these compounds in preventing human allergic bronchocon-

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