Dear Sir,

We wanted to investigate closely the mechanisms which bring about the onset of hypertensive episodes in a subgroup of uraemic subjects treated with recombinant human erythropoietin (rHuEPO). Although different factors, such as increase of hematocrit, decrease of 6-keto-PGF levels and changes of the endothelium-derived relaxing factors, were hypothesized as moments responsible for the increase of the pressure which sometimes follows the administration of rHuEPO, these have not yet been completely understood within the context pertaining with the real hypertensive factors induced by rHuEPO. Both the importance of the Ca\(^{2+}\) increase within the muscular vessel cells for the establishment and the maintenance of a hypertensive condition, and the necessity of an interaction between Ca\(^{2+}\) and erythropoietin for carrying out the events which will lead to the maturity of the erythroid cells are well known. We wanted to evaluate in vitro the changes of the Ca-mediated K\(^{+}\) set, in the presence of scalar doses of rHuEPO, in whole red blood cells (RBC) from 10 normal normotensive subjects without familial anamnesis for hypertension, 16 normotensive uraeics, 16 uraemics with essential hypertension and from some fishes (Boops-Boops), whose nucleated erythrocytes have receptors for the erythropoietin and show a membrane phospholipidic composition which is different from the erythrocyte membrane of healthy human subjects.

The investigation was carried out by using the Gardos effect (evaluation of the efflux of Ca-mediated K). To the medium of the incubation of the erythrocytes the rHuEPO alone or in association with a membrane Ca antagonist, isradipine (40 µM), was added. The RBC from hypertensive subjects showed an efflux of the Ca-mediated K\(^{+}\) significantly increased compared to the normotensive subjects without hypertensive familial anamnesis (table...
1). In the RBC from fishes, the Ca$^{2+}$ influx was superimposable to the influx noticed in the hypertensive subjects, and this proves the importance of

Table 1. Percent of intracellular K$^{+}$ concentration

* $p < 0.01$ vs. controls; ** $p < 0.01$ vs. Ca$^{2+}$. I = Isradipine.

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the anomaly of the membrane in the hypertensive subject in eliciting hypertension.
The administration of a Ca antagonist, isradipine, caused in all the examined subjects, as well as in the fishes, a clear reduction of the K$^{+}$ efflux.
The addition of rHuEPO in the medium did not show in human RBC any change of Ca$^{2+}$-induced K$^{+}$ flux compared to the basal conditions, whereas in the RBC from fishes, such an addition has subsequently increased the K$^{+}$ efflux, which was then annulled by isradipine.
The different behaviour of fishes RBC in response to the rHuEPO, compared to the behaviour of RBC from uraemic hypertensive subjects, might be explained by the fact that in man RBC there are no receptors for the rHuEPO, usually present only in the erythroid precursors.
If we extrapolate the data obtained from the fishes RBC and compare them with those from the human muscular fibre cells, where some erythropoietin receptors are probably present, we can suppose that the rHuEPO, on helping the Ca$^{2+}$ flux into the muscular fibre cells, might determine an increase of the peripheral resistances and subsequently of the arterial pressure in subjects genetically predisposed to hypertension.