

damage and complications associated with diabetes. The molecular mechanism by which chromium supplementation is beneficial in preventing complications of diabetes is not known. Using RBC as a model, this study has examined the effect of trivalent chromium on GSH levels in cells exposed to AA (a metabolite of ketosis in diabetes) and TBH (a standard oxidant). Normal RBC (25% hematocrit suspended in PBS) were treated with AA (0-5 mM) or TBH (0-2  $\mu$ M) with and without CrCl<sub>3</sub> in a shaking water bath at 37°C for 24 hrs. Result show a significant decrease in GSH both in AA (to 27%) and TBH (to 50%) treated RBC; and preincubation of RBC with CrCl<sub>3</sub> (0-1  $\mu$ M) prevented the decrease in GSH in AA and TBH treated RBC. To delineate the mechanism, we determined that GR activity was 70-90% higher ( $p < 0.01$ ) in RBC with prior Cr-treatment compared with those without Cr, in cells incubated with AA or TBH. There was no effect of Cr on glutathione peroxidase activity. GSH supplementation is known to improve insulin sensitivity, lower hyperglycemia and prevent complications in animal models of diabetes. This study demonstrates that Cr<sup>3+</sup> supplementation can activate GR activity and prevent GSH depletion and cellular damage, and thus can be beneficial in preventing the complications of diabetes. (supported by the NIH and Amer Diab Assoc).

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### THE OXIDATIVE STRESS ROSETTE

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Convincing data indicate that oxidative stress play a crucial role in the ageing process and the development of age-related diseases. It is, however, of primordial importance to dispose of routine methods to control and manage oxidative stress status and, overall, to give precise interpretation of the data. In this way, we have developed an oxidative stress profile based on the determination of antioxidants, trace elements, markers of oxidative damage and iron metabolism. Additionally, an original graphic representation of the data is given as the oxidative stress rosette ®. Each radius represents an assay.

For each investigated test, the normal inferior and superior values established on a healthy population of 123 subjects (mean age : 36 +/-12 years) are respectively represented at 2/5 and 3/5 of the radius. By this way, it was therefore possible to draw the pink circle which defines a normal oxidative stress status. The red line links each value of investigated assays for an individual and allows to establish his oxidative stress picture. The present case relates to an apparent healthy 31 years woman taking oral contraception. The rosette will be of great helpful for the medical corps in order to check up the oxidative stress and, therefore, to afford corrections as changes in diet or supplementation in antioxidants.

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### DIFFERENTIAL ANTIOXIDANT ENZYME ACTIVITIES IN SURFACTANT PREPARATIONS

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Broncho Pulmonary Dysplasia (BPD) following exposure to hyperoxia affects premature infants and is believed to involve oxidative damage to the lungs. Curosurf®, Survanta®, and Infasurf® are surfactant preparations routinely used in the neonatal clinics in children prone to developing BPD. Since the antioxidant enzyme activity of surfactant preparations could potentially impact upon the efficacy of these preparations at inhibiting the development of BPD, the present study was designed to determine the catalase and glutathione peroxidase activities in surfactant preparations. Catalase and Glutathione

Peroxidase (GPx) activities were determined using established spectrophotometric activity assays (*J Biol Chem* 195:133-140; *BBRC* 71:952-958). The catalase activities were 127 ± 41 mk units/mg (Curosurf®), 10 ± 5 mk units/mg (Survanta®), and 121 ± 40 mk units/mg (Infasurf®). The selenium dependent GPx activities were measured to be 840 ± 238 m units/mg (Curosurf®), 191 ± 94 m units/mg (Survanta®), and 550 ± 150 m units/mg (Infasurf®). These results show the peroxide metabolizing enzyme activities, catalase and GPx, were significantly greater ( $p < 0.05$ ) in Curosurf® and Infasurf® relative to Survanta®. These results suggest that different surfactant preparations could vary in their ability to scavenge hydrogen peroxide and/or other organic hydroperoxides. These results support the hypothesis that variations in antioxidant enzyme activities present in surfactant preparations might represent a contributing factor to outcomes in clinically relevant settings where oxidative lung injury is occurring. Supported by Dey L.P.

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### INCREASED IRON STORES AND HIGH PREVALENCE OF THE HEMOCHROMATOSIS (HFE) C282Y ALLELE IN A BREAST CANCER COHORT

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An association between the hemochromatosis (HFE) C282Y allele, which accelerates iron absorption, and breast cancer has not been previously reported. Due to the pro-oxidant properties of iron, altered iron metabolism in C282Y carriers may promote breast carcinogenesis. We determined C282Y genotypes in 168 patients undergoing high-dose chemotherapy for cancer at Vanderbilt University Medical Center: 41 with breast cancer and 127 with hematological cancers. The frequency of C282Y genotypes in breast cancers was compared with the frequency in non-breast cancers, an outpatient sample (n=169), and published U.S. national figures. Serum soluble transferrin receptor (STR) levels, which are inversely proportional to iron stores, and plasma F(2)-isoprostane levels were measured at baseline in 30 patients and compared between patients with and without C282Y alleles. The frequency of at least one C282Y allele in breast cancers was higher (36.6%, 5 homozygotes/10 heterozygotes) than frequencies in Tennessee (12.7%,  $p < 0.001$ ), the general population (12.4%,  $p < 0.001$ ), and similarly selected non-breast cancers (17.0%,  $p = 0.008$ ). The likelihood of breast cancer in this cohort increased with C282Y allele dose ( $p_{\text{trend}} = 0.010$ ). HFE C282Y carriers had lower STR levels than HFE wild-type patients (mean ± SEM 16.6 ± 2.2 and 23.5 ± 5.7, respectively;  $p$ -value = ns due to power limitations), suggesting higher iron stores. Plasma isoprostane levels were similar. A high prevalence of C282Y alleles in women with poor-risk breast cancer suggests that higher iron stores in C282Y carriers may promote local oxidant injury in the breast, leading to an increased risk of breast cancer and/or more aggressive forms of the disease.

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### DIFFERENTIAL ROLE OF TUMOR NECROSIS FACTOR RECEPTOR I AND RECEPTOR II IN ADRIAMYCIN-INDUCED CARDIAC INJURY

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Adriamycin (ADR) is one of the most potent chemotherapeutics, but its application is limited by its dose-related cardiomyopathy. Previously our laboratory has demonstrated that lacking both TNF receptors (DKO mice) exacerbates ADR-induced cardiac injury. However, the role of each receptor in mediating the protection is unknown. In this study, we investigate the contribution of each receptor in cardioprotection using TNFR-I knockout mice and