

Carboximaltosa de hierro

ferinject[®]

La nueva generación de hierro i.v.



ferinject[®]
ferric carboxymaltose



Hospital Alemán / Deutsches Hospital



Jorge E. Toblli.

Profesor Regular Titular de Medicina Interna

Universidad de Buenos Aires.

Profesor de Nefrología Universidad Católica Argentina.

Fellow of American Society of Nephrology

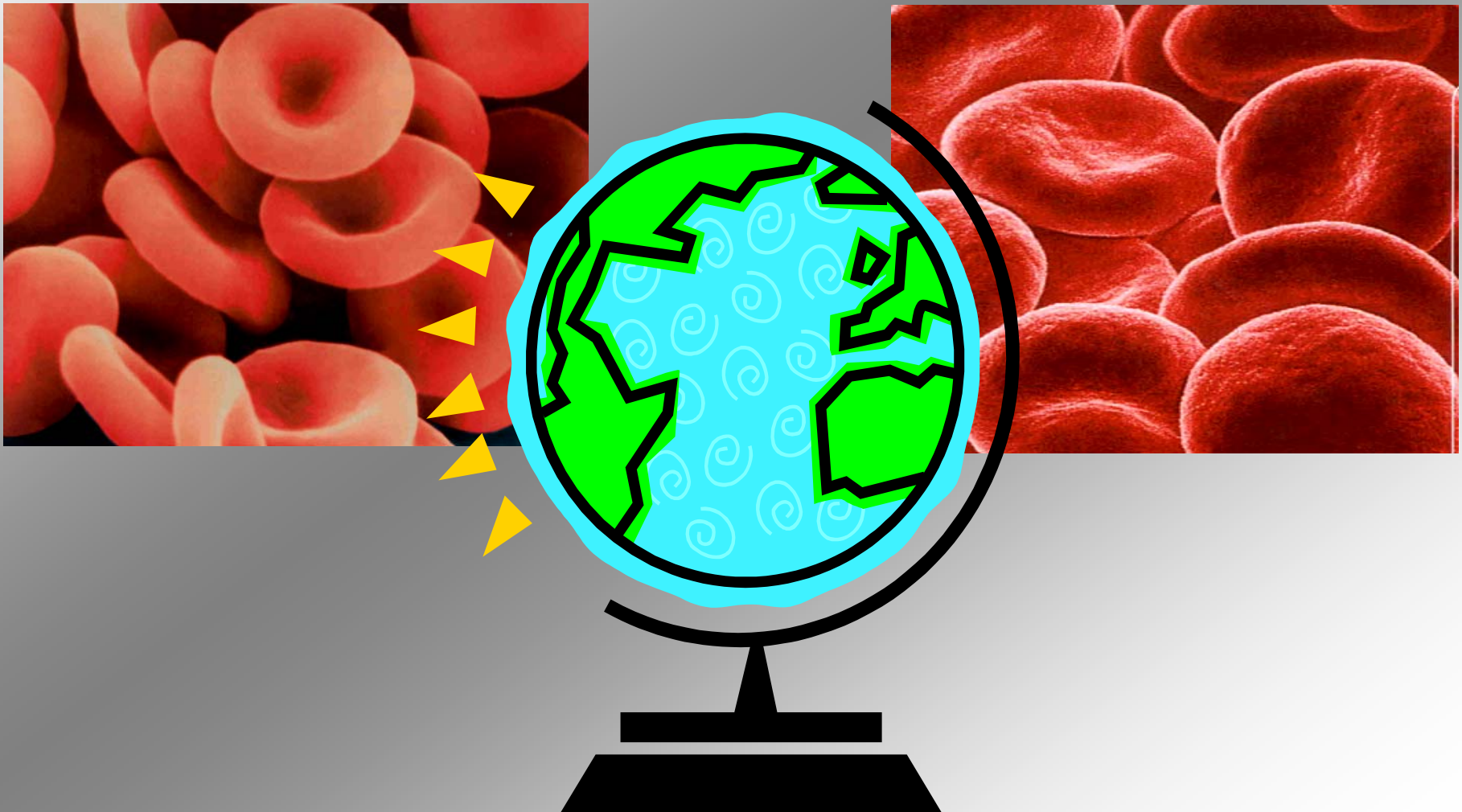
*Jefe Laboratorio de Medicina Experimental.
Hospital Alemán.*

Octubre 22, 2008

Valencia, España

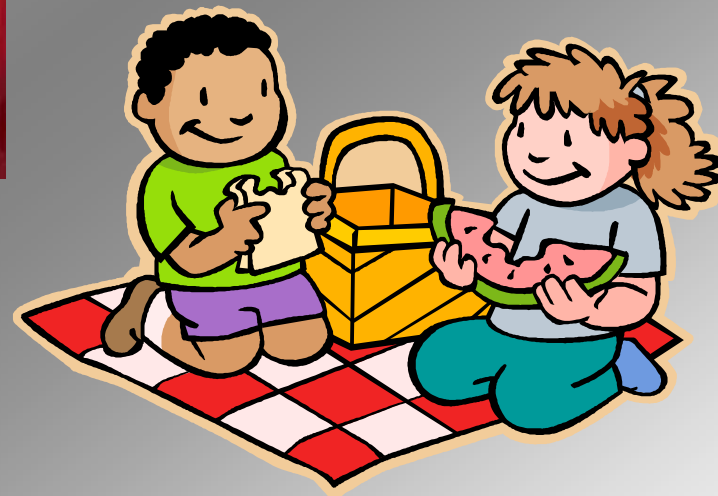
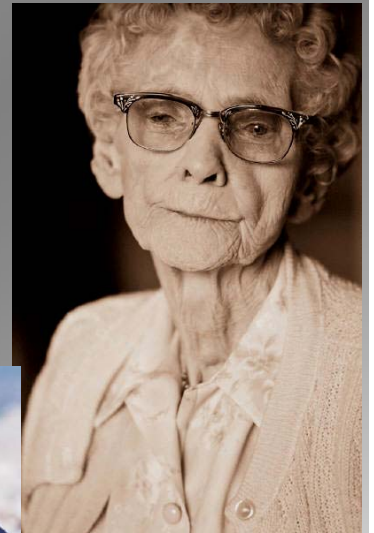
“¿Son todos los hierros I.V. iguales?”

Anaemia

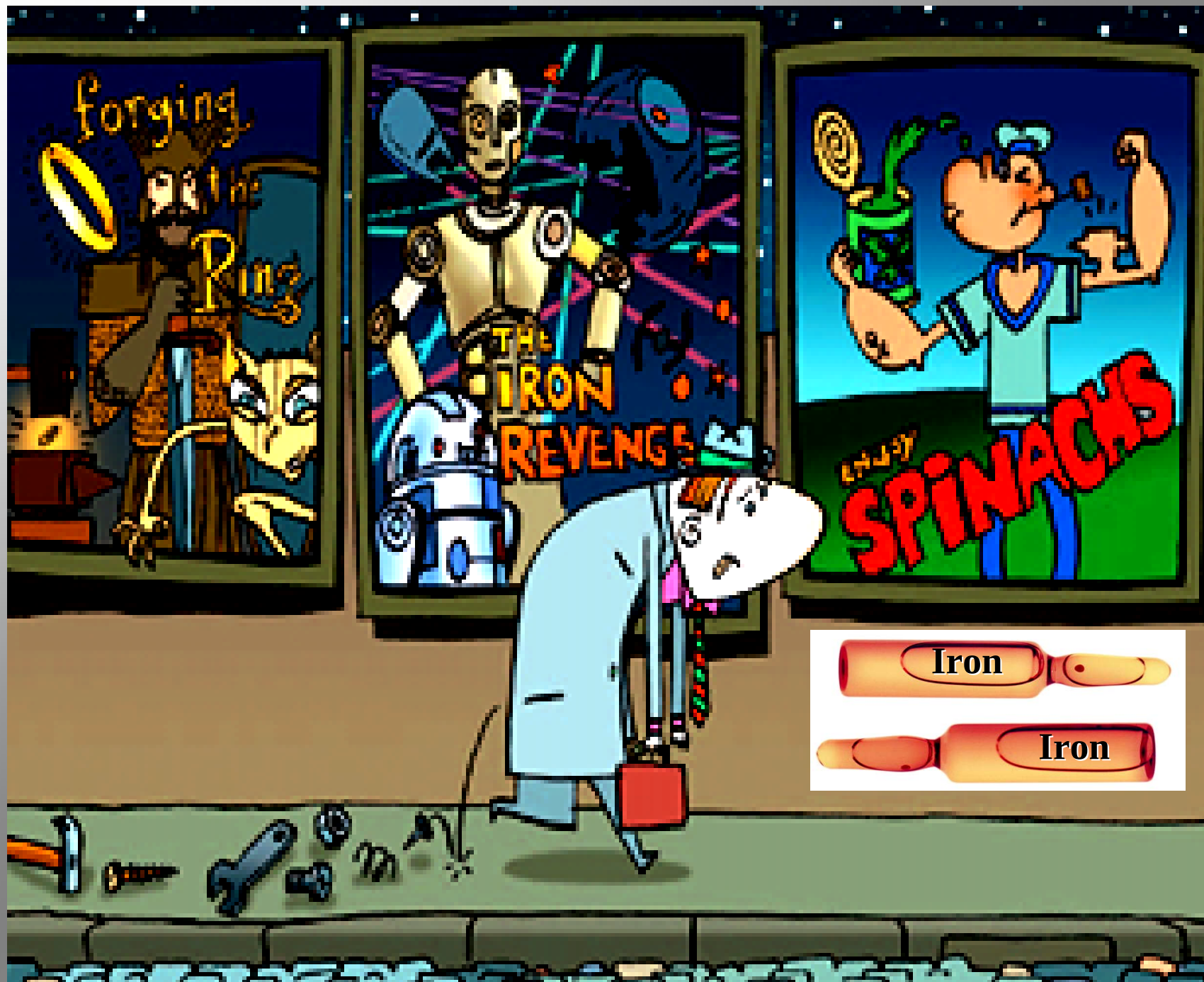


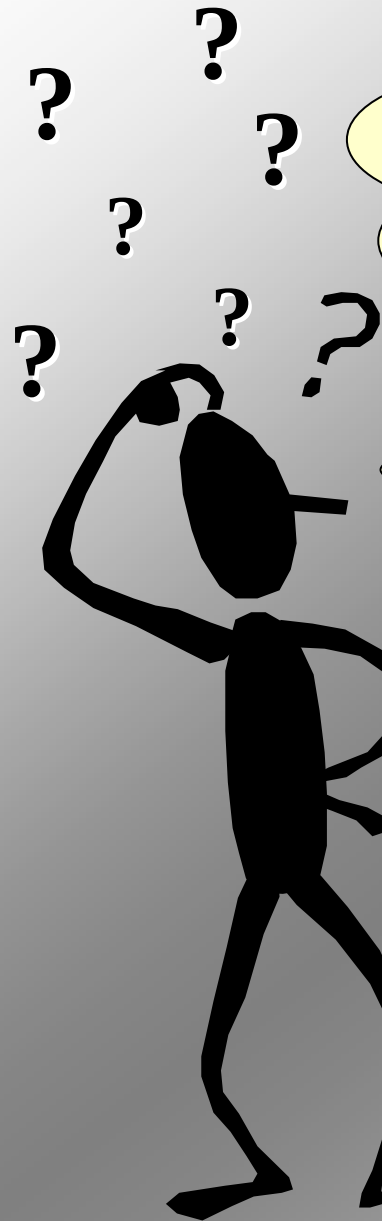
Iron Deficiency is the most
prevalent cause of Anaemia
worldwide



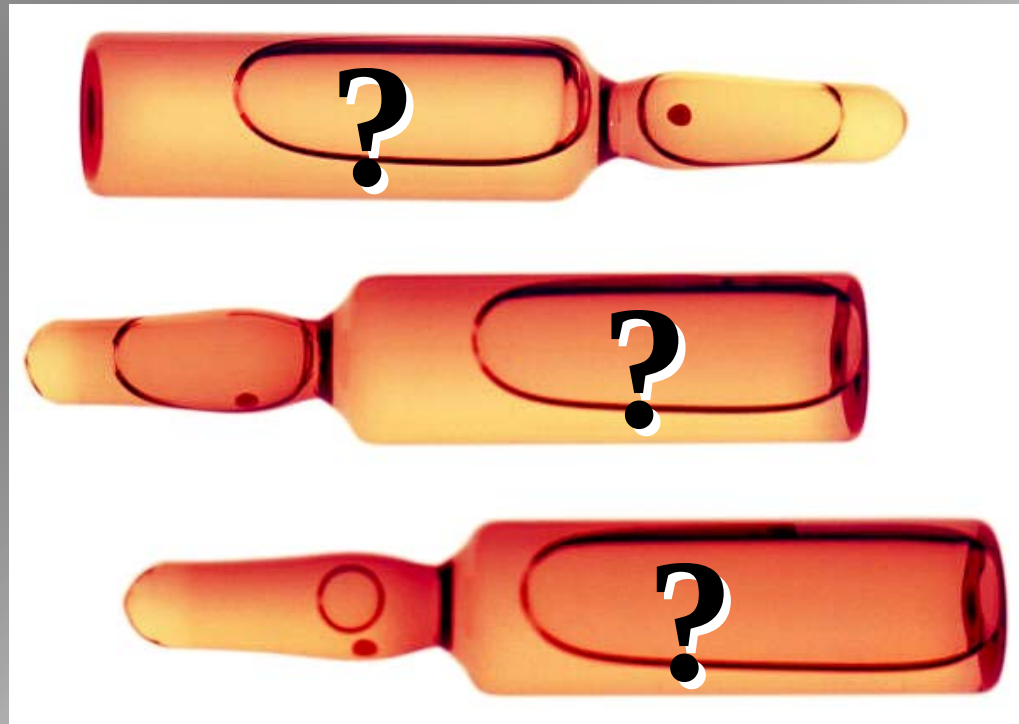








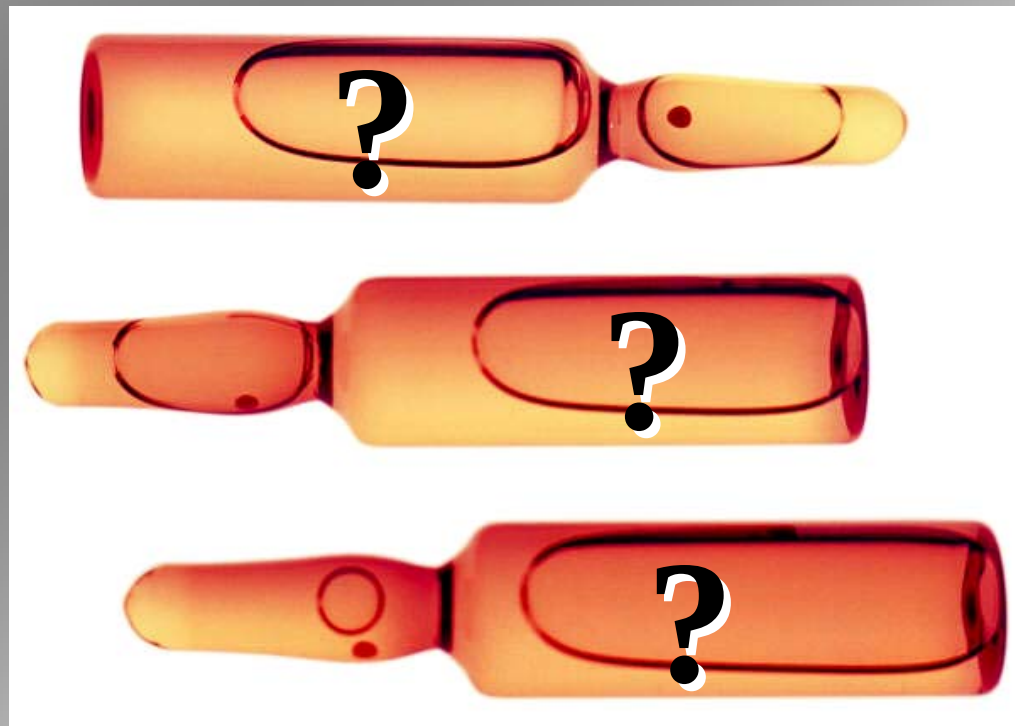
**What IV Iron are available in
the market today???**



IV Iron Preparations

- **Type I Complex.** (Iron Dextran, Ferrric Carboximaltose)
- **Type II Complex.** (Iron Sucrose Complex)
- **Type III Complex.** (Iron Gluconate, Iron ammonium citrate, Iron hydroxide sorbitol complex)

Are all “IV Iron Compounds”
the same thing ???



Objectives of the Study

To evaluate toxicity in different IV iron original preparations.



IV Iron Therapy (weekly)

**Ferric
Carboxymaltose**

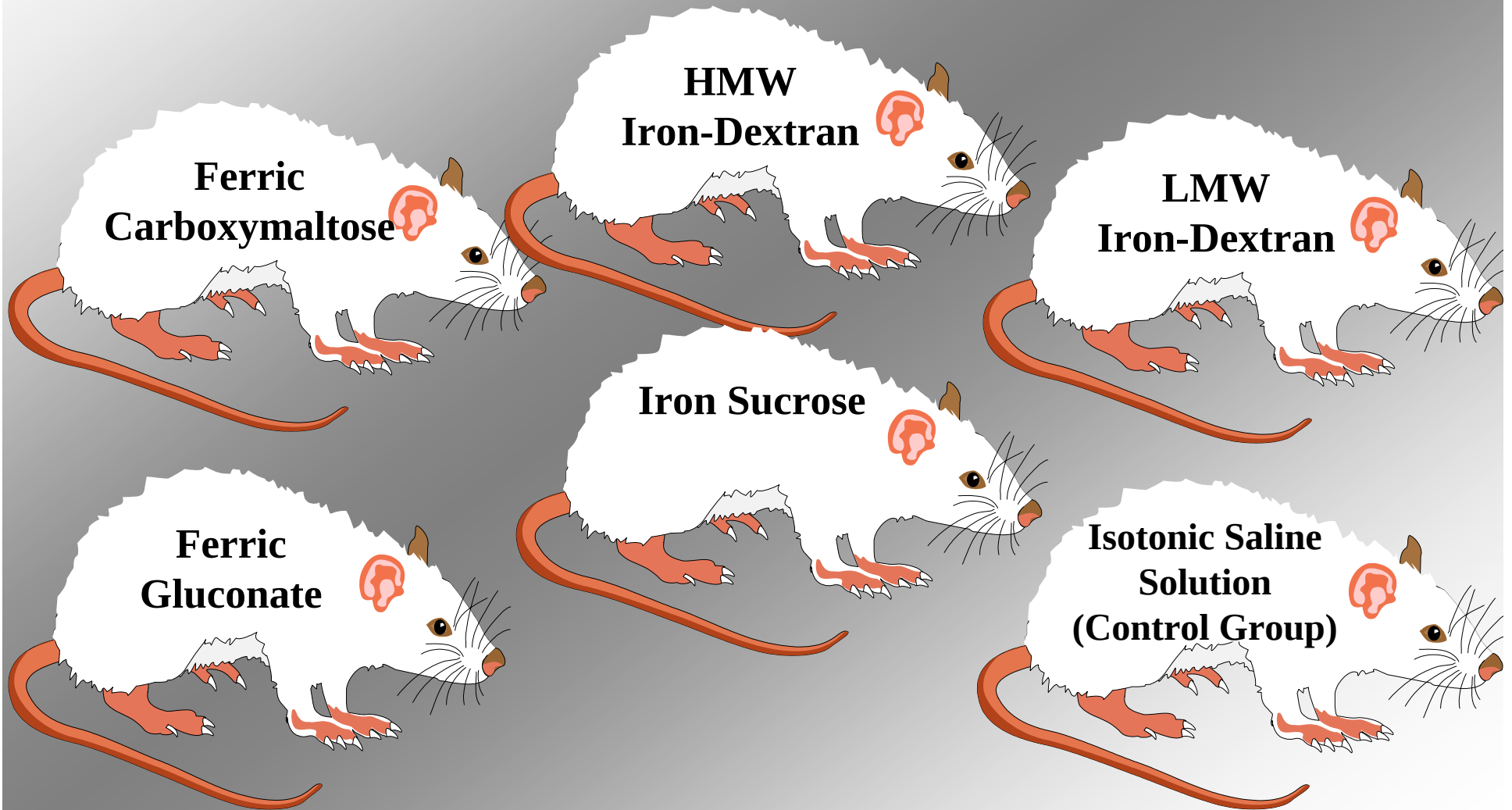
**HMW
Iron-Dextran**

**LMW
Iron-Dextran**

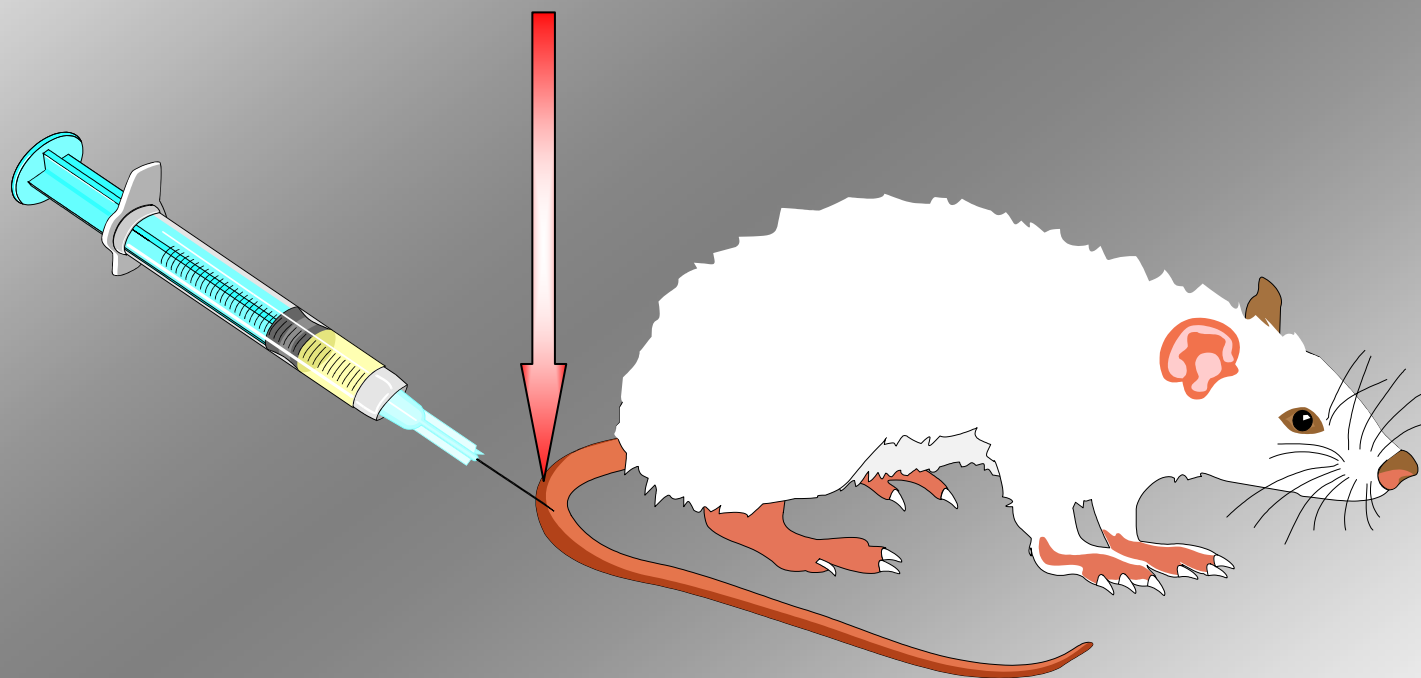
Iron Sucrose

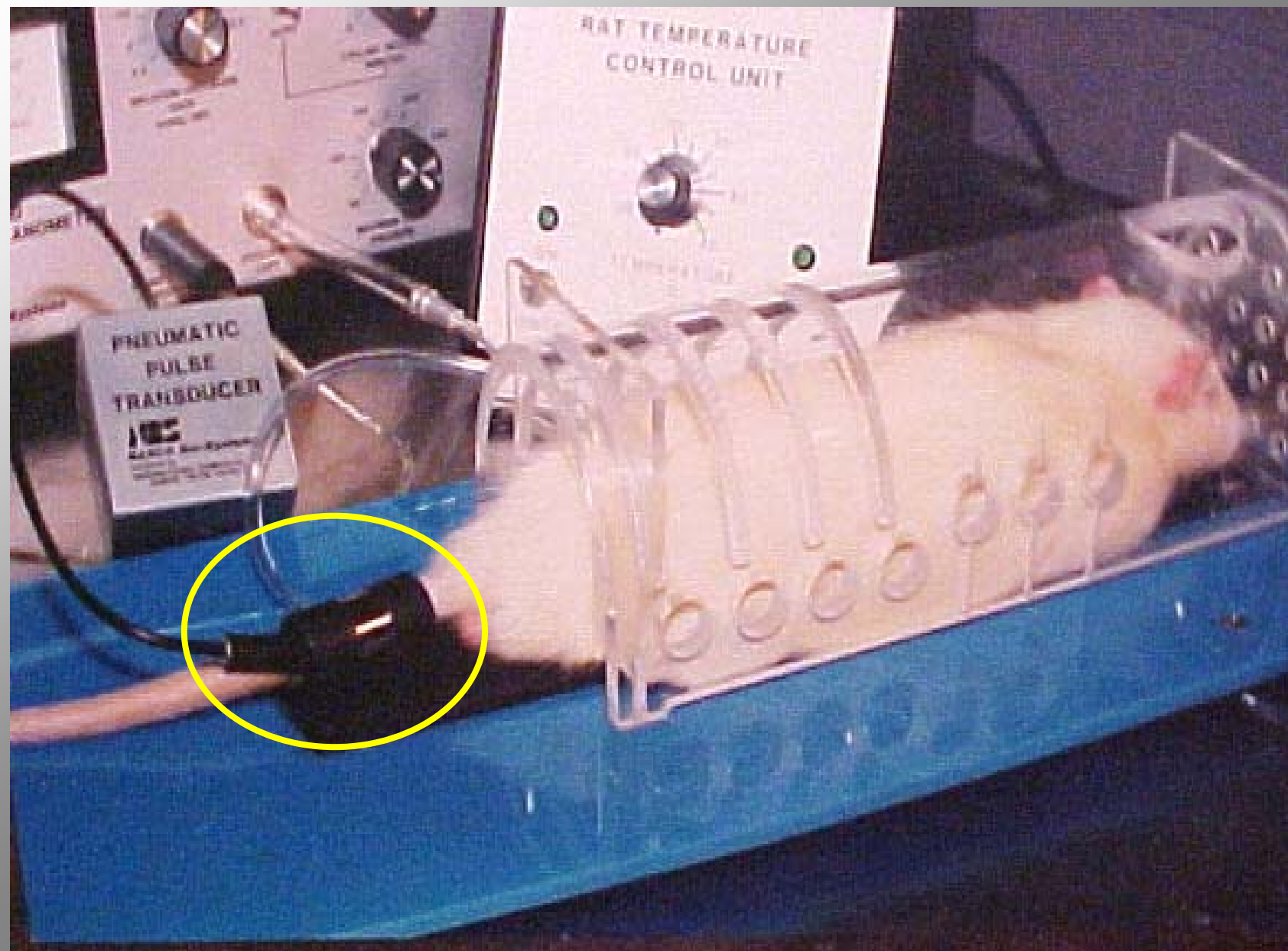
**Ferric
Gluconate**

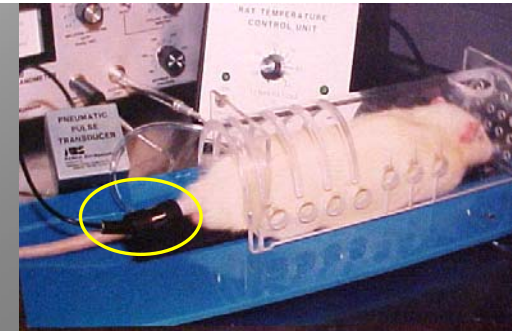
**Isotonic Saline
Solution
(Control Group)**



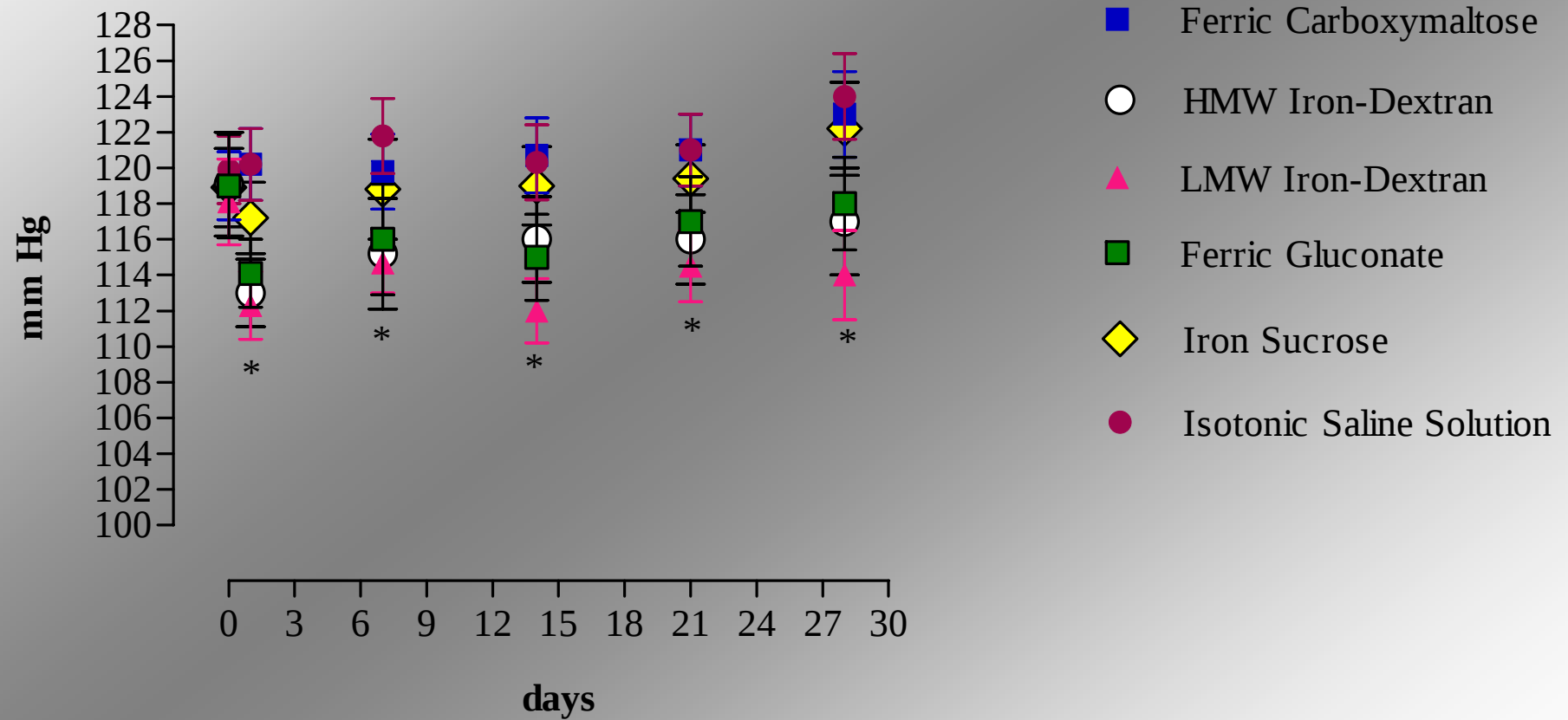
IV Iron Administration



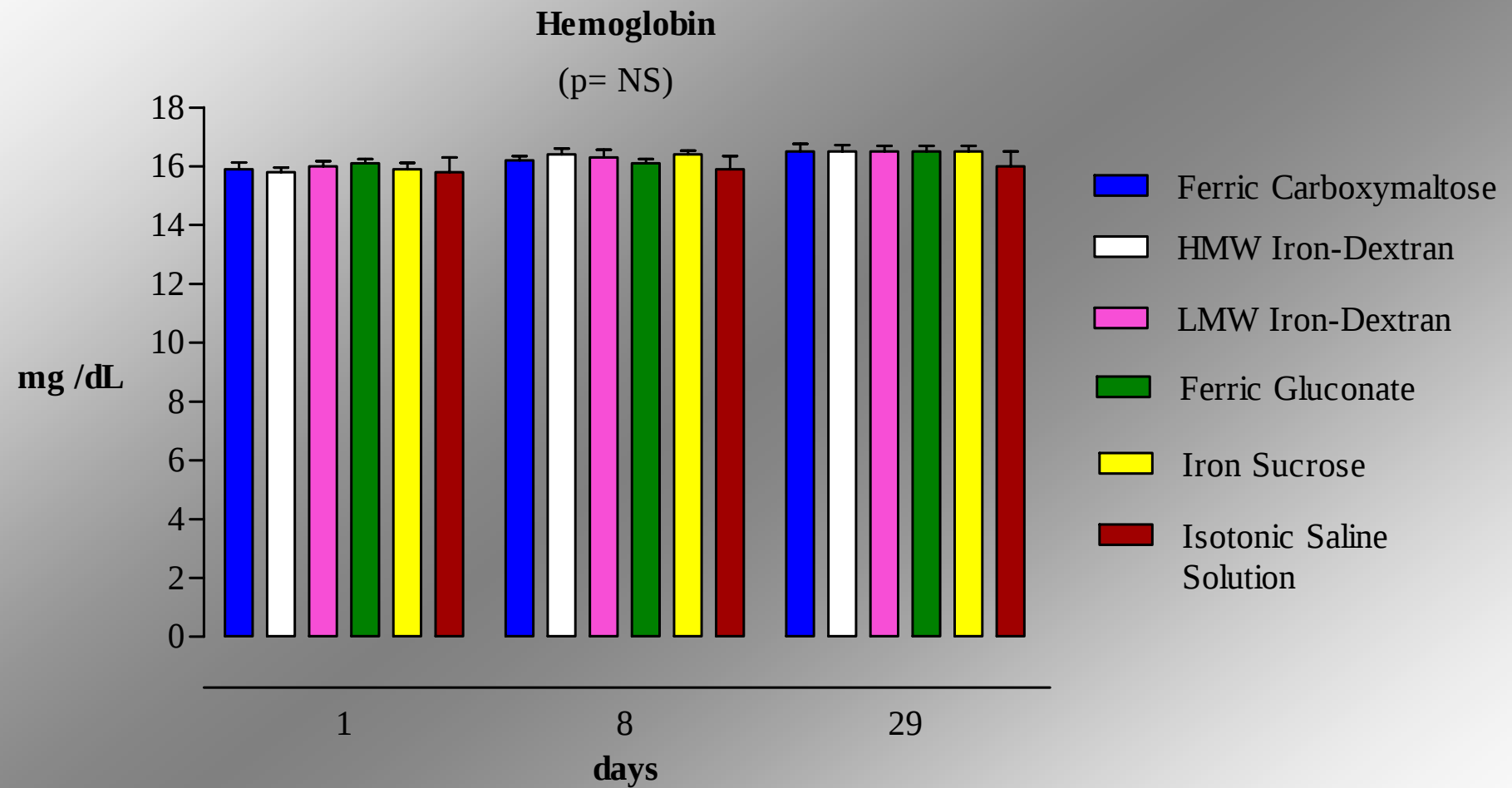




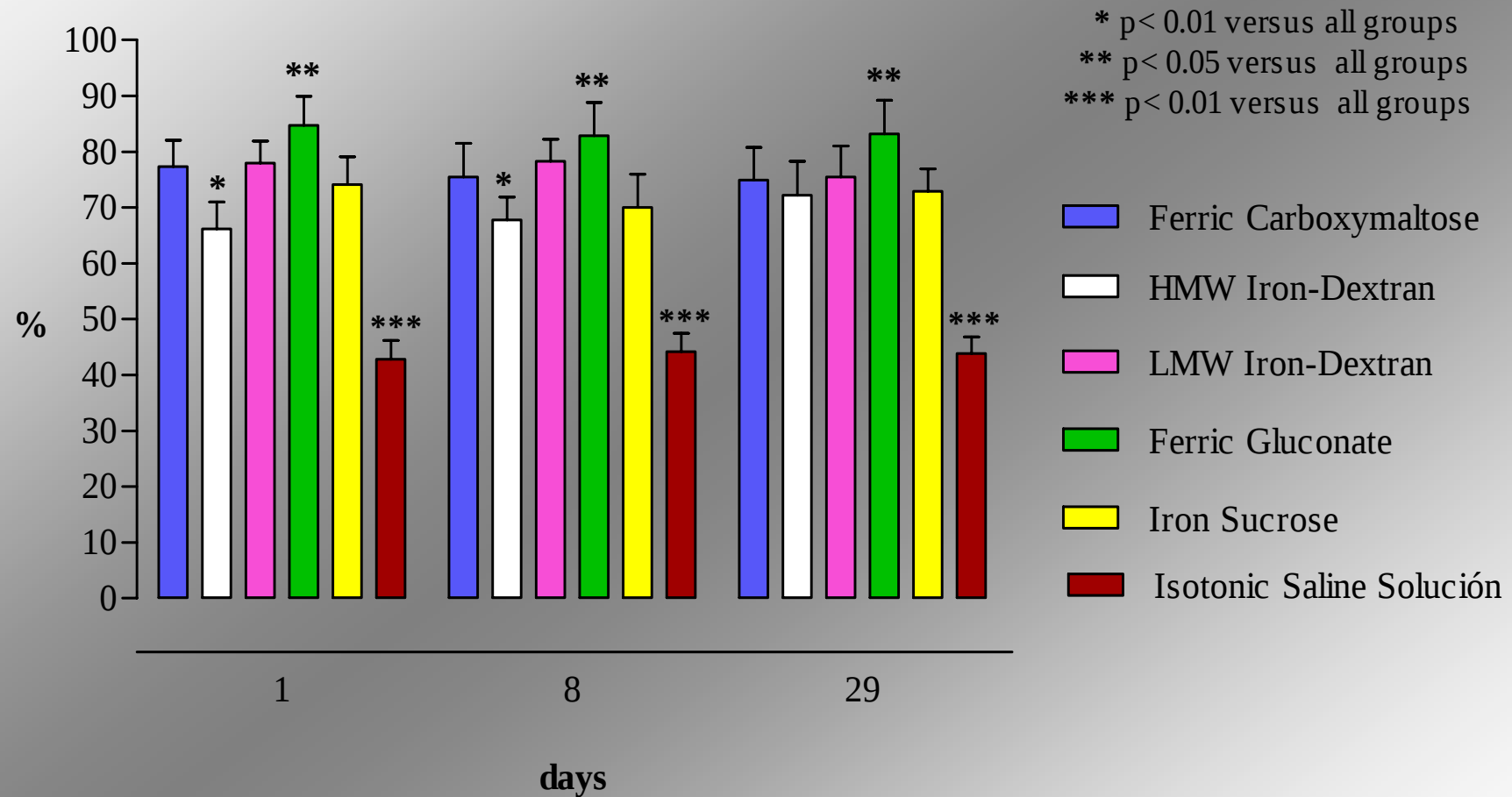
Systolic Blood Pressure



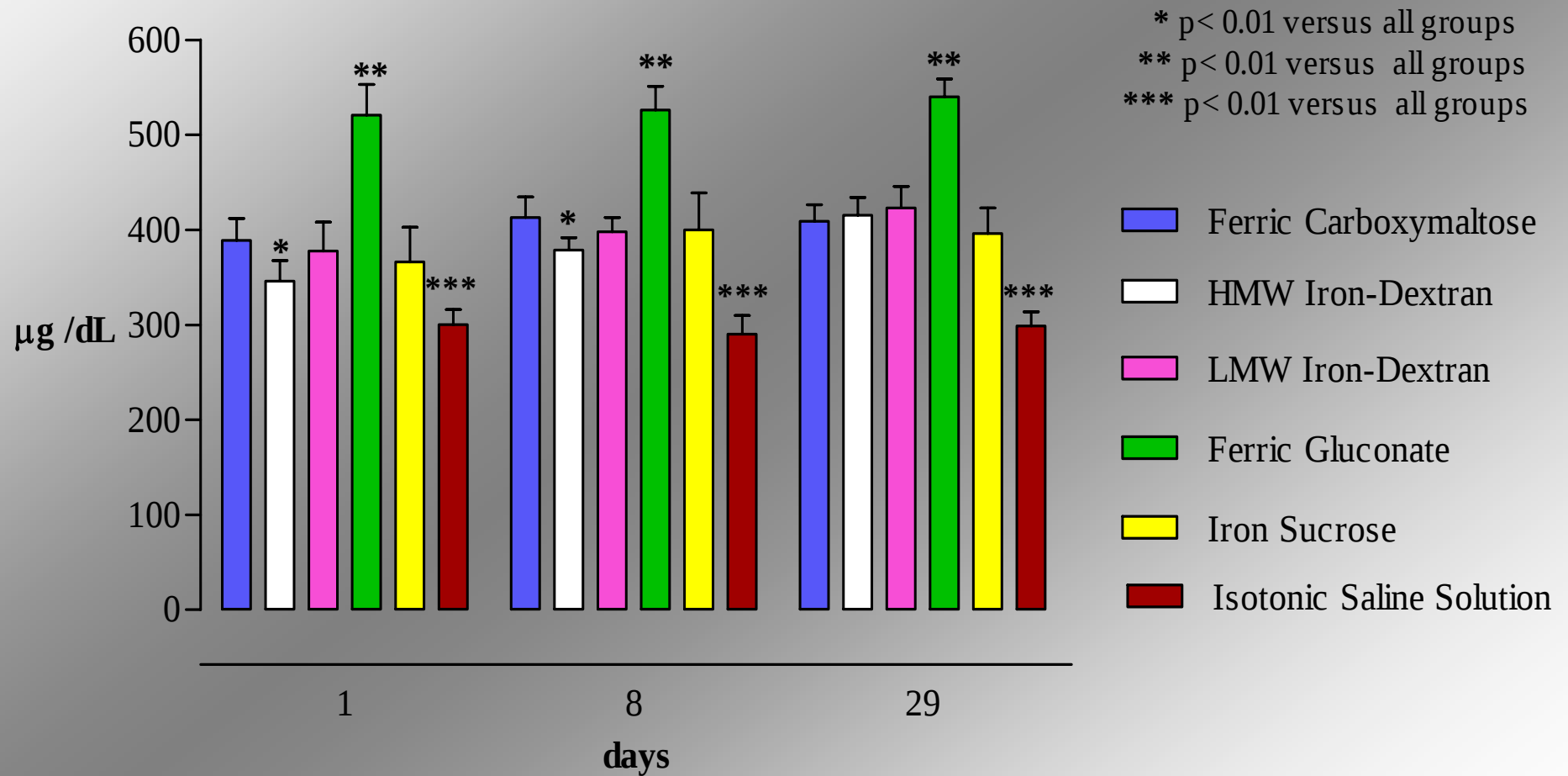




TSAT after IV Iron



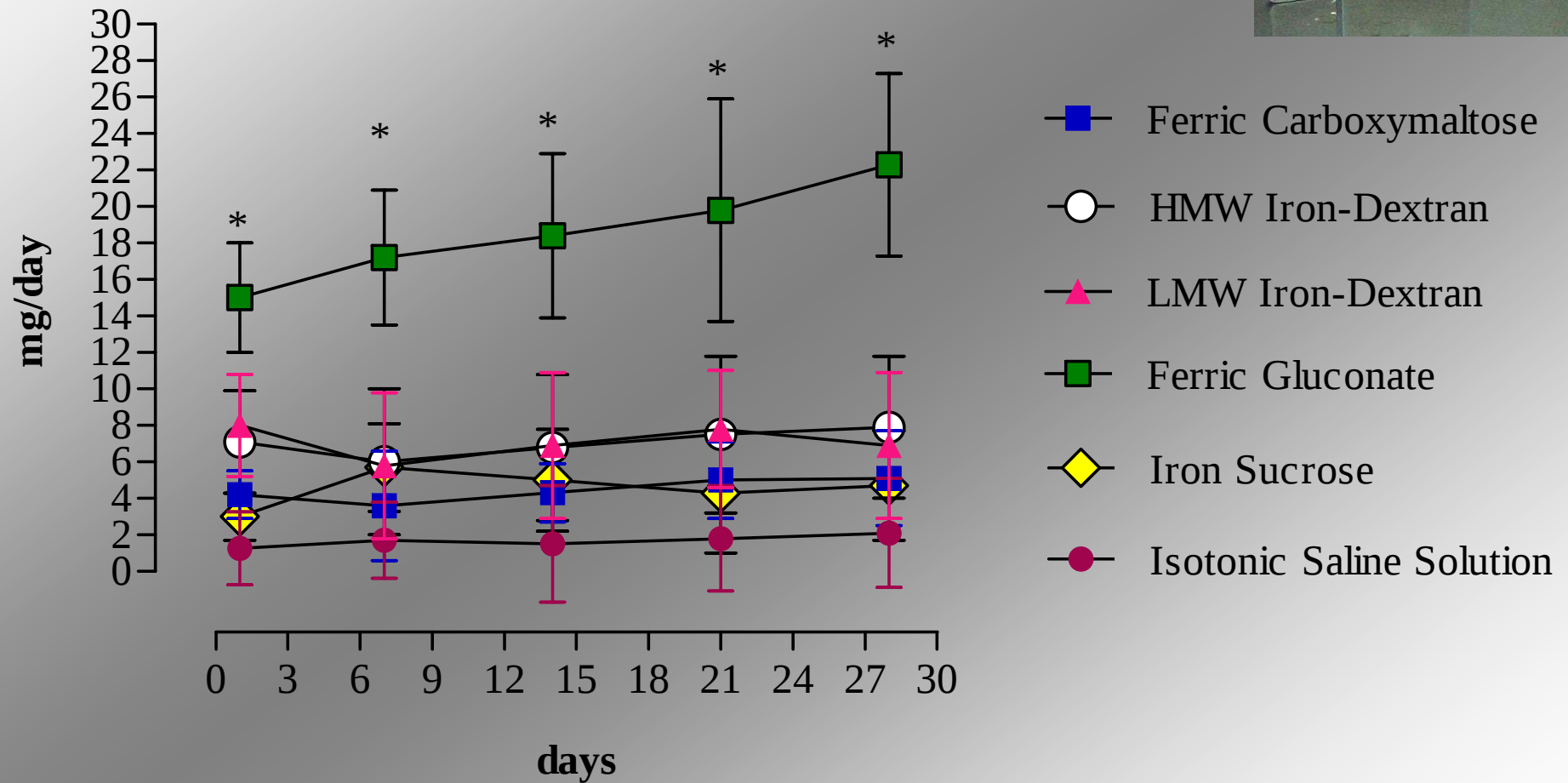
Serum Iron after IV Iron







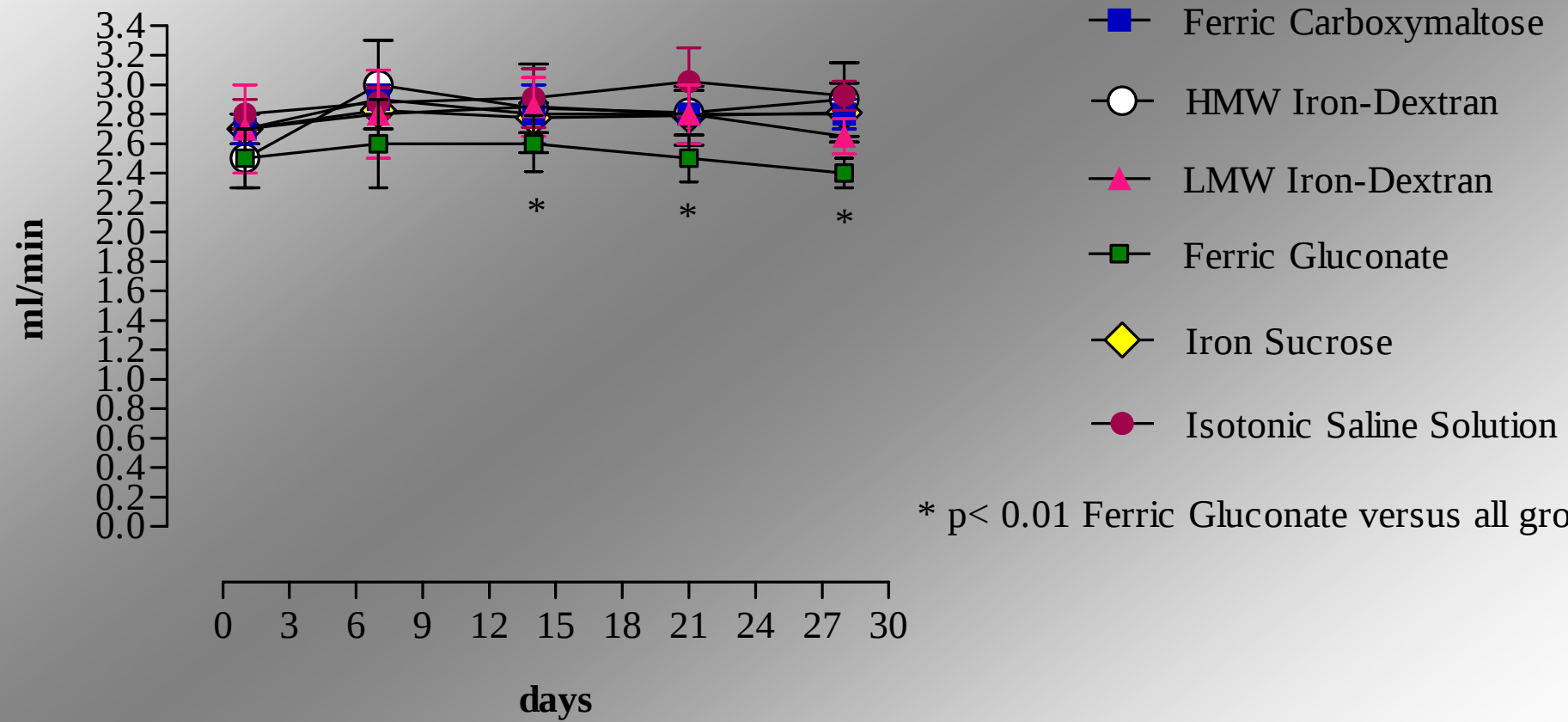
Proteinuria



* $p < 0.01$ Ferric Gluconate versus all groups

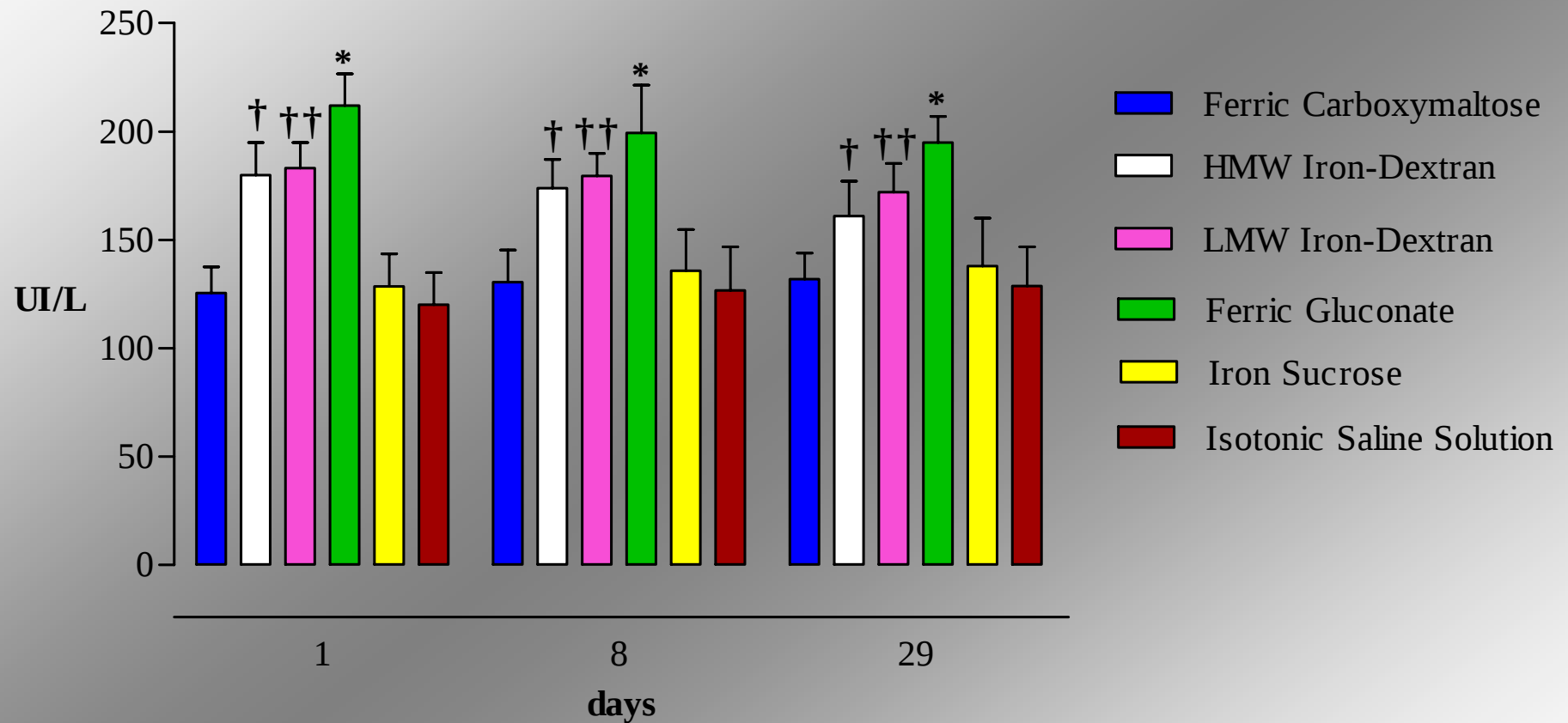


Creatinine Clearance



More Proteinuria and Lower GFR with
Ferric Gluconate

Aspartate Transferase (AST) after IV Iron

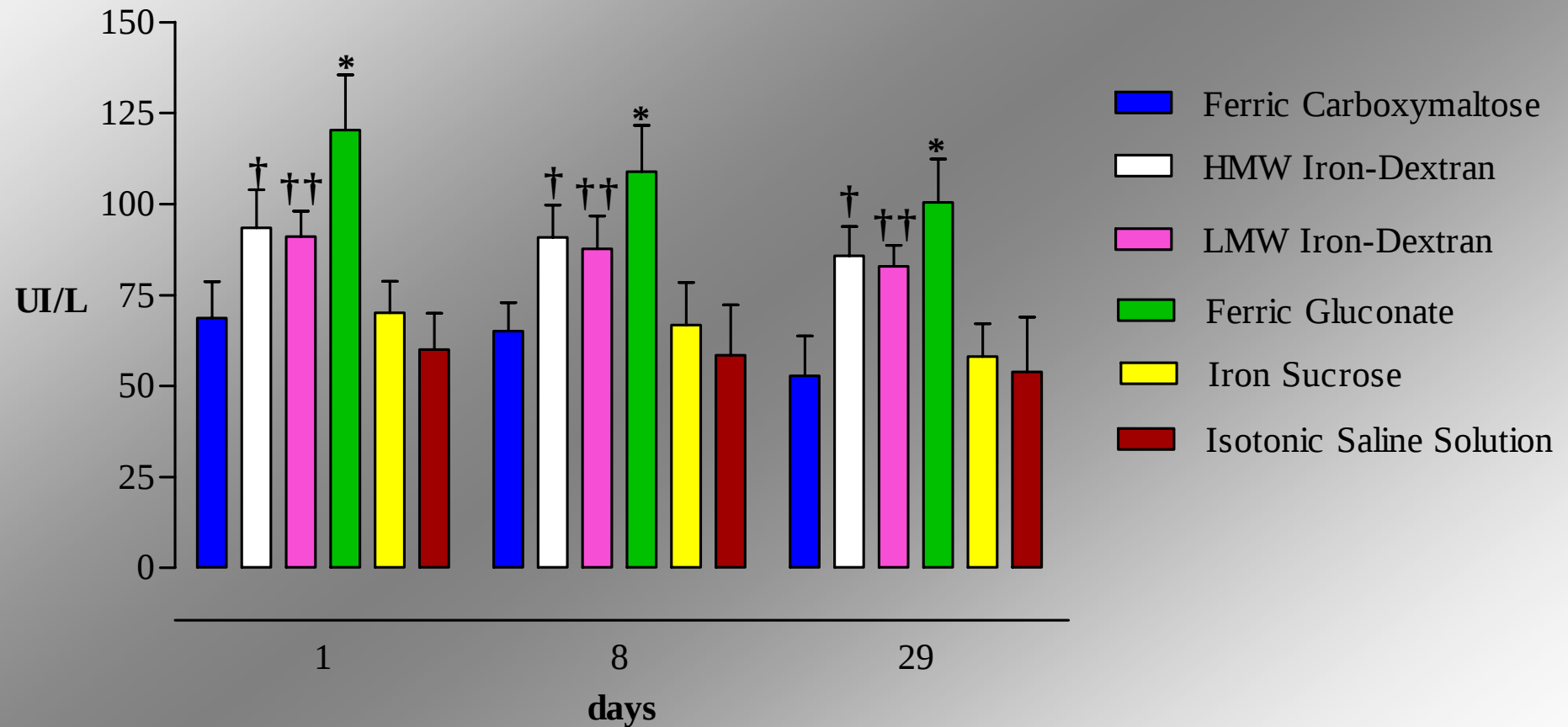


* versus all groups $p < 0.01$

† versus Ferric Carboxymaltose, Iron Sucrose and Isotonic Saline Solution $p < 0.01$

†† versus Ferric Carboxymaltose, Iron Sucrose and Isotonic Saline Solution $p < 0.01$

Alanin Transferase (ALT) after IV Iron

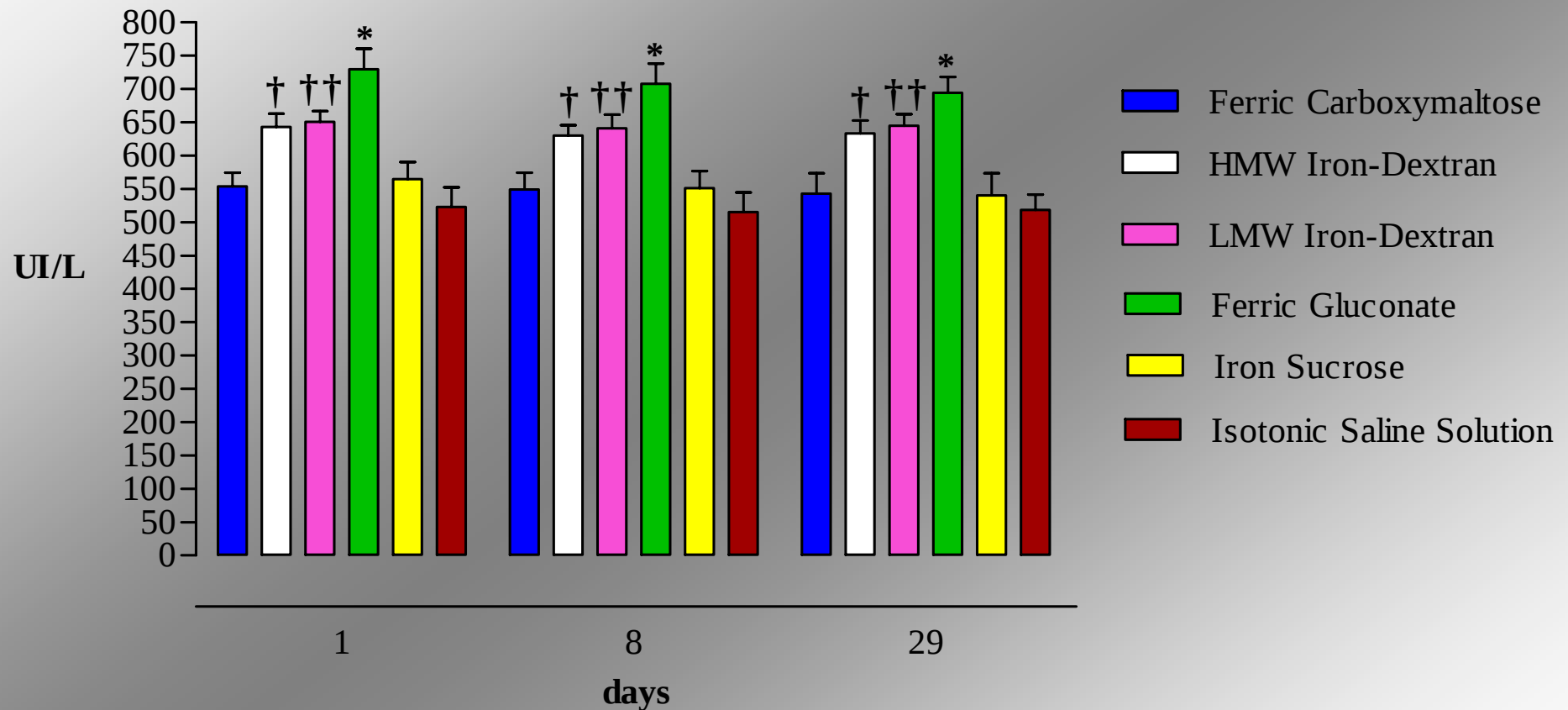


* versus all groups $p < 0.01$

† versus Ferric Carboxymaltose, Iron Sucrose and Isotonic Saline Solution $p < 0.01$

†† versus Ferric Carboxymaltose, Iron Sucrose and Isotonic Saline Solution $p < 0.01$

Alkaline Phosphatase after IV Iron



* versus all groups $p < 0.01$

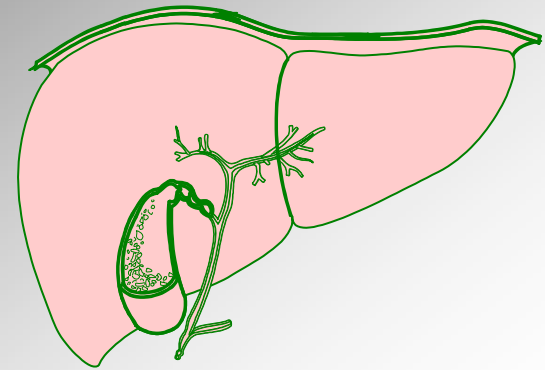
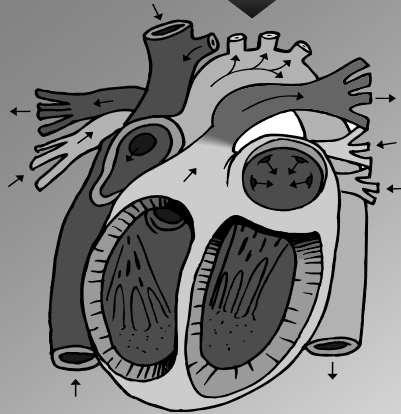
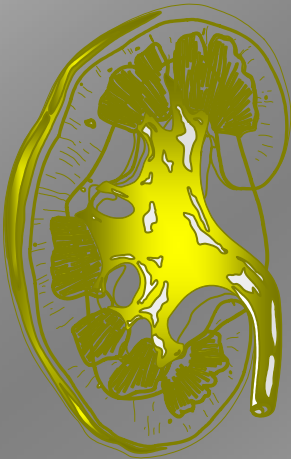
† versus Ferric Carboxymaltose, Iron Sucrose and Isotonic Saline Solution $p < 0.01$

†† versus Ferric Carboxymaltose, Iron Sucrose and Isotonic Saline Solution $p < 0.01$

More reaction in Liver enzymes in
HMW Iron-Dextran, LMW Iron-Dextran
and Ferric Gluconate



Oxidative Stress



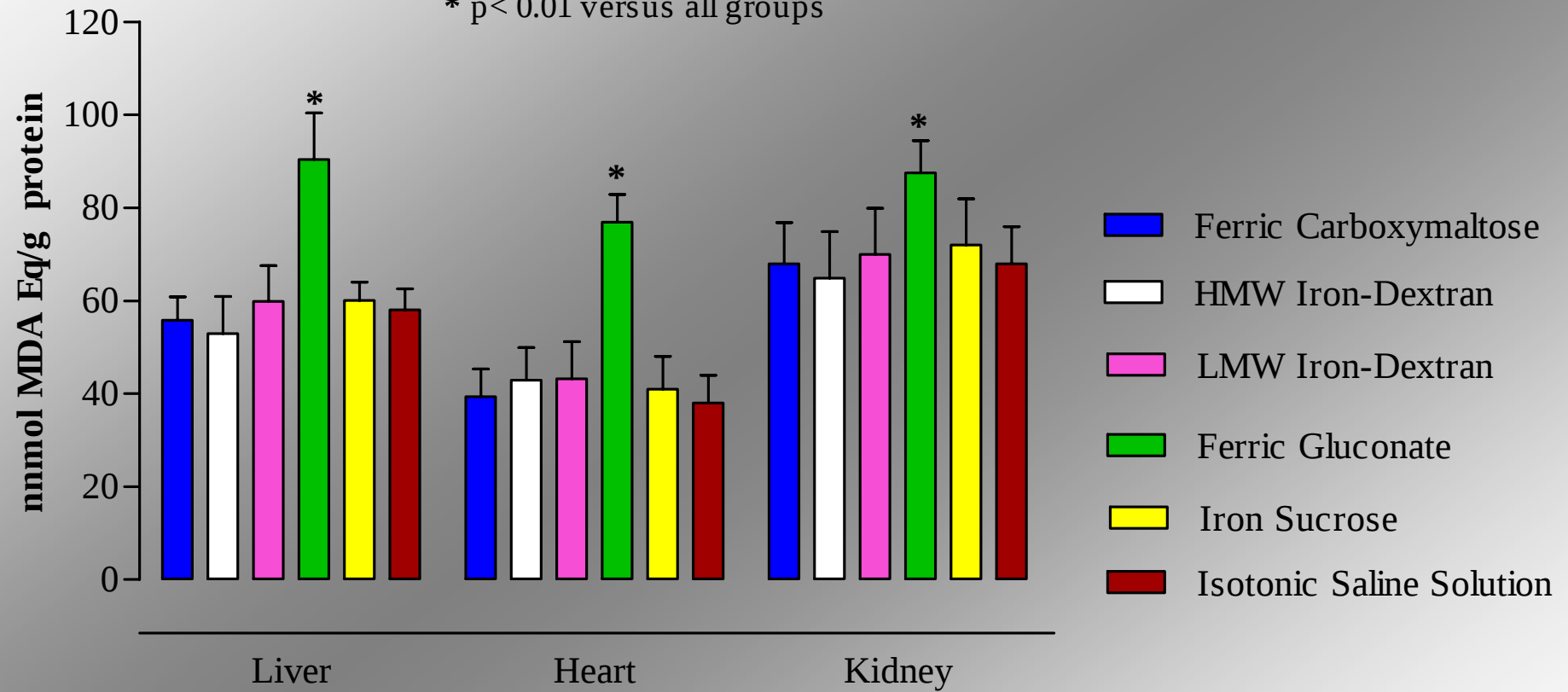
Oxidative Stress Evaluation

(After the last IV iron administration on the fourth week)

- ***Homogenates preparation***
 - 1- Lipoperoxidation by thiobarbituric reactive species (TBARS)
 - 2- Glutathione ratio (GSH/GSSG)
 - 3- Catalase activity
 - 4- CuZn Superoxide Dismutase (CuZnSOD)
 - 5- Glutathione Peroxidase (GPx)

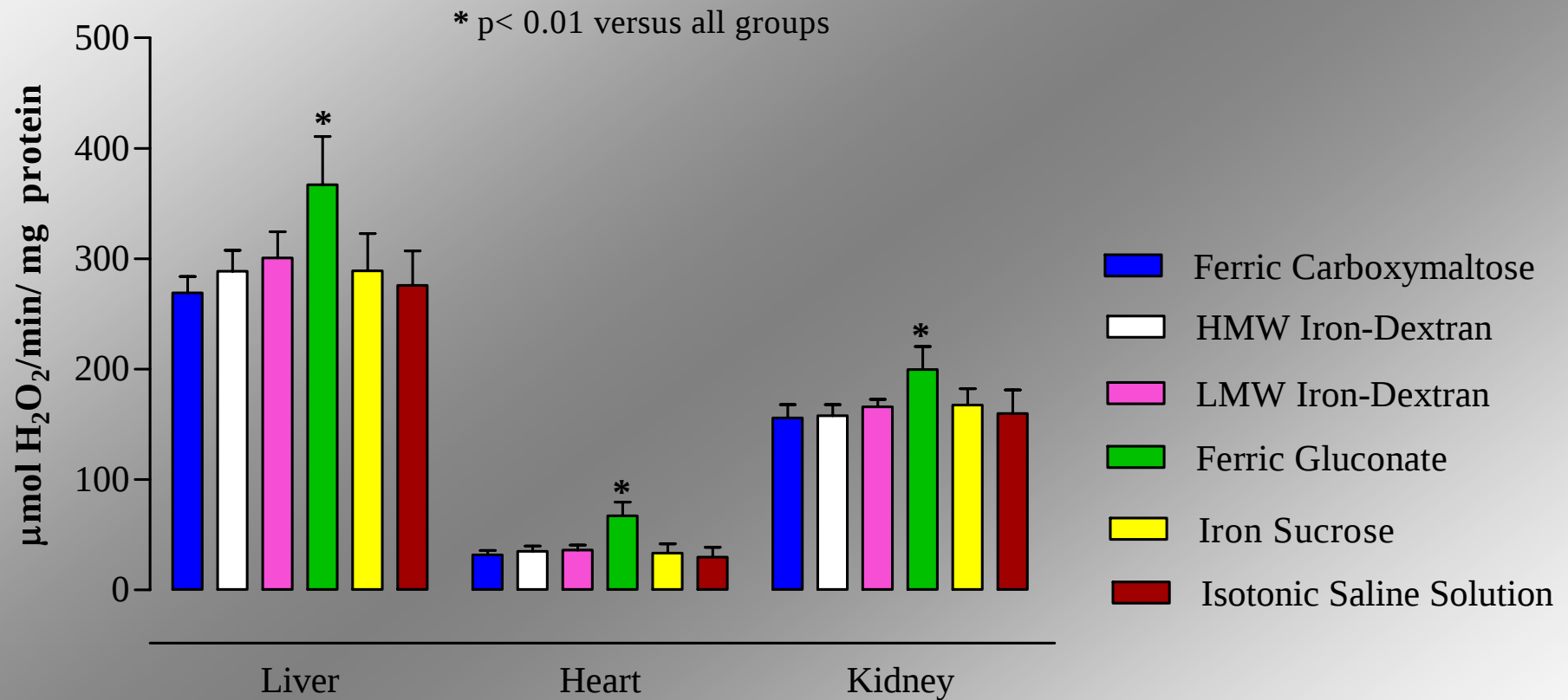
TBARs at 4 weeks after a weekly IV Iron administration

* $p < 0.01$ versus all groups



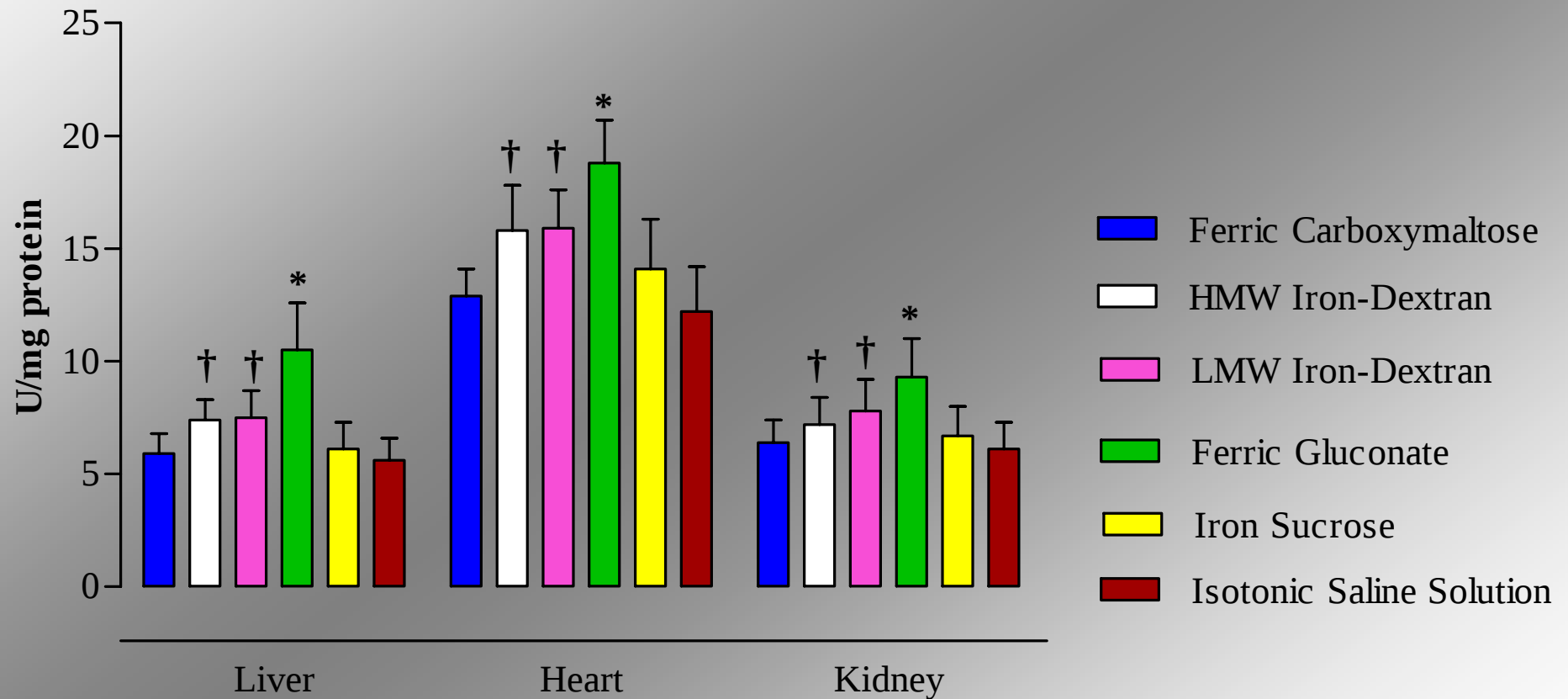
More Lipoperoxidation in “Ferric Gluconate”

Catalase at 4 weeks after a weekly IV Iron administration



**More Peroxidation in
“Ferric Gluconate”**

CuZnSOD at 4 weeks after a weekly IV Iron administration

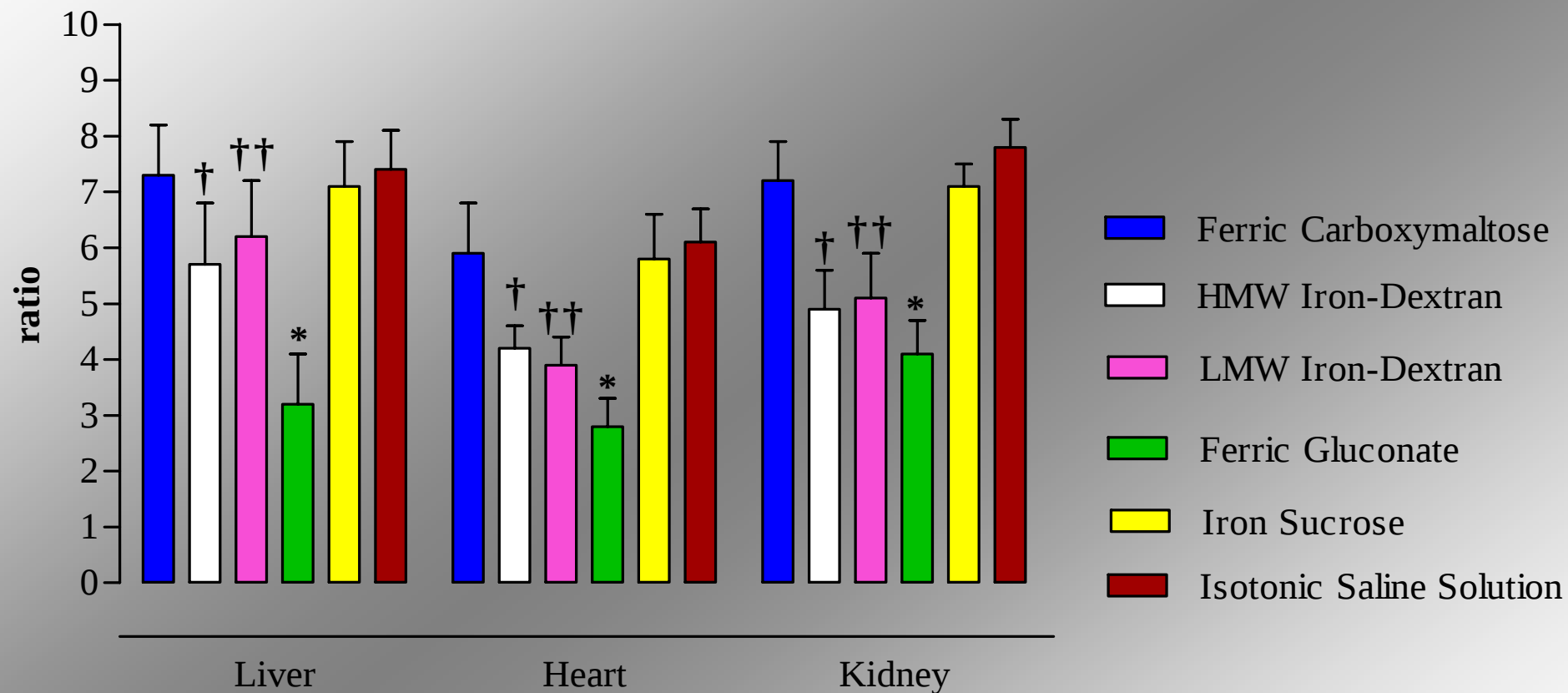


* versus all groups $p < 0.01$

† versus Ferric Carboxymaltose, Iron Sucrose and Isotonic Saline Solution $p < 0.01$

Less Production of Superoxide in Ferric Carboxymaltose and Iron Sucrose

GSH / GSSG after a weekly IV Iron administration

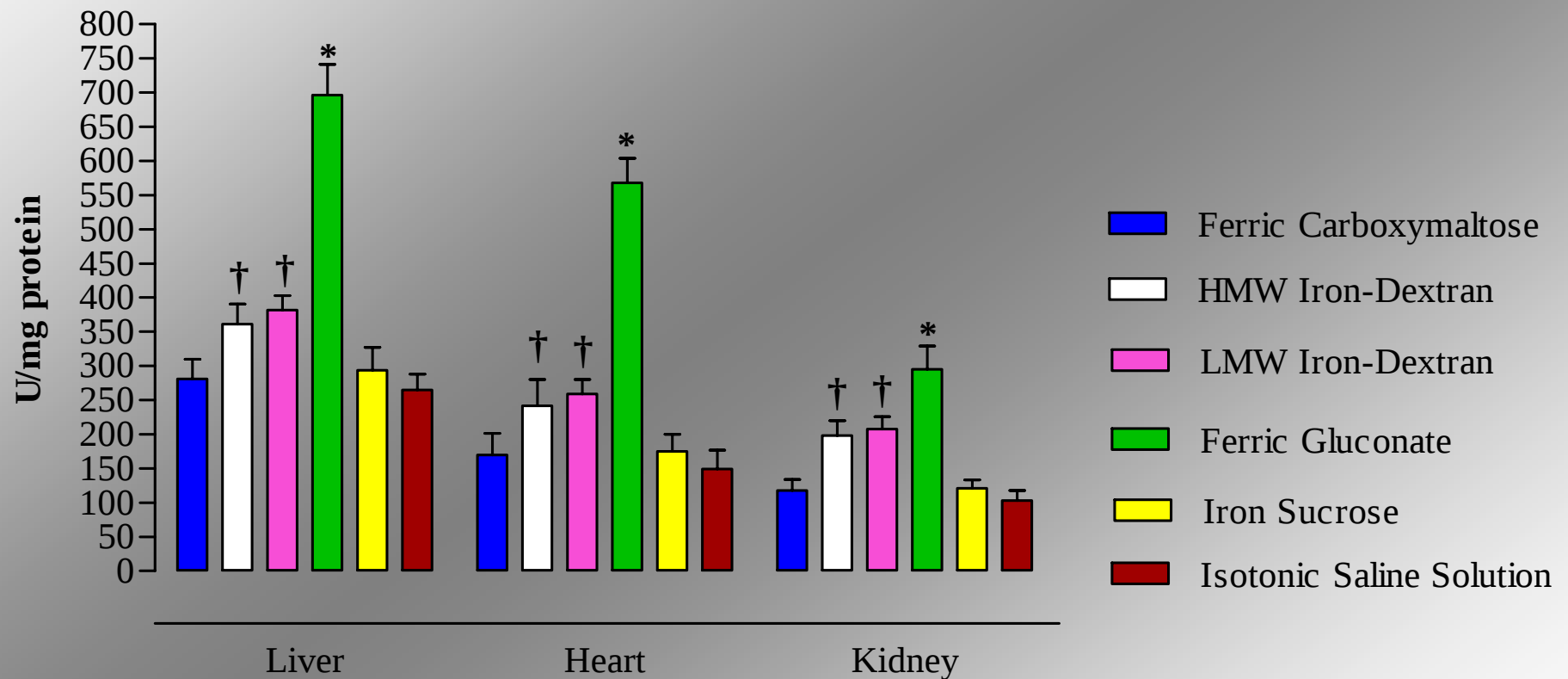


* versus all groups $p < 0.01$

† versus Ferric Carboxymaltose, Iron Sucrose and Isotonic Saline Solution $p < 0.01$

†† versus Ferric Carboxymaltose, Iron Sucrose and Isotonic Saline Solution $p < 0.01$

GPx at 4 weeks after a weekly IV Iron administration



* versus all groups $p < 0.01$

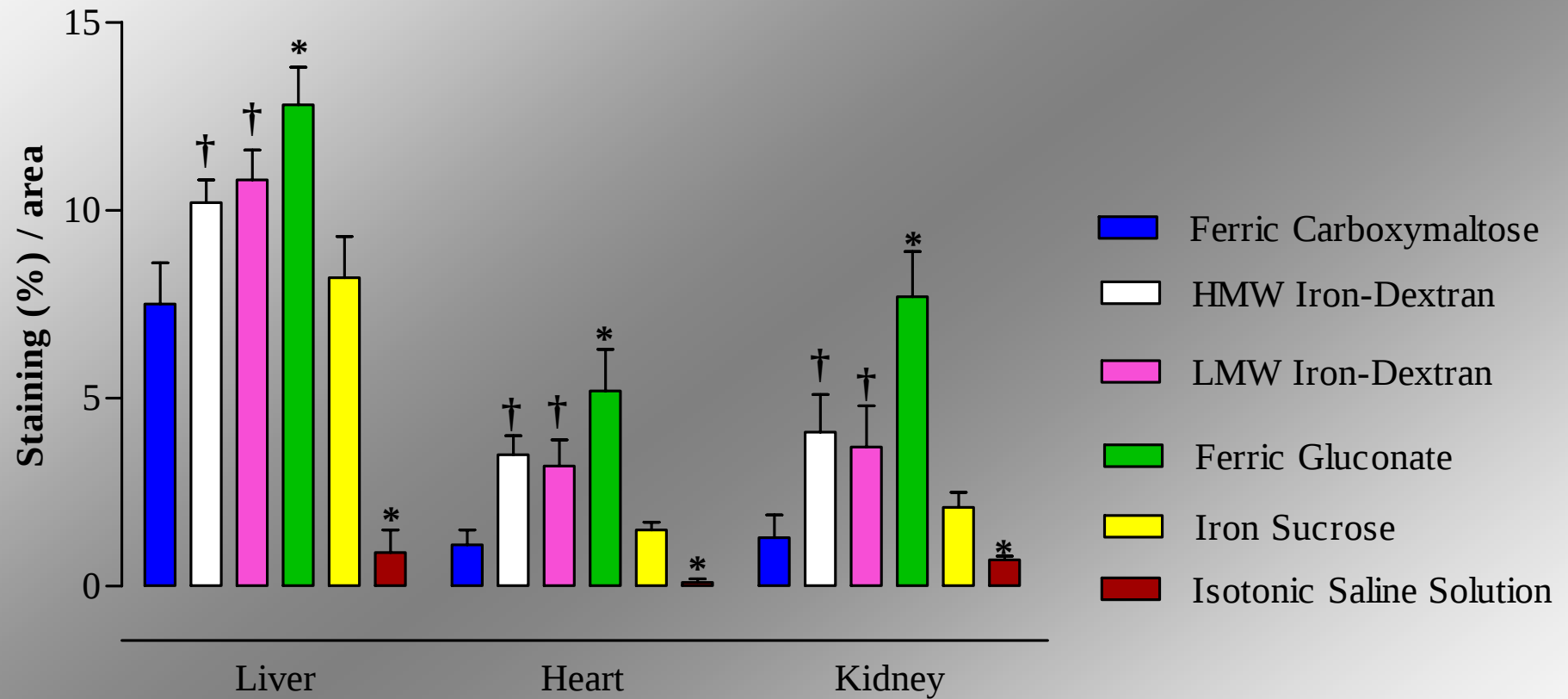
† versus Ferric Carboxymaltose, Iron Sucrose and Isotonic Saline Solution $p < 0.01$

**Less consumption of
Anti-Oxidative stress Defenses in
Ferric Carboxymaltose and Iron Sucrose**

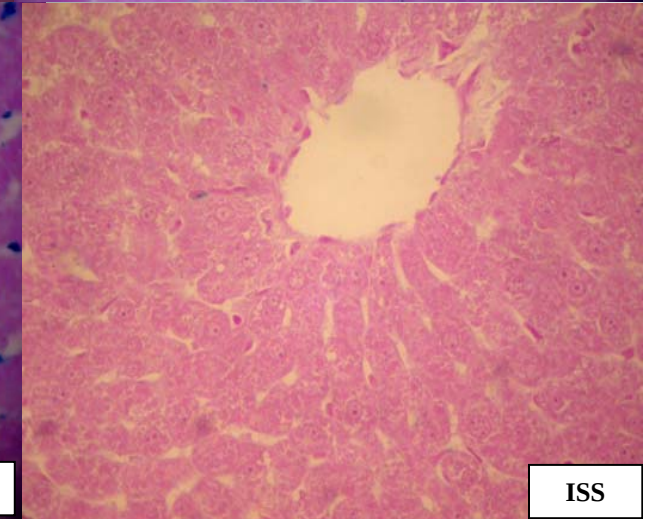
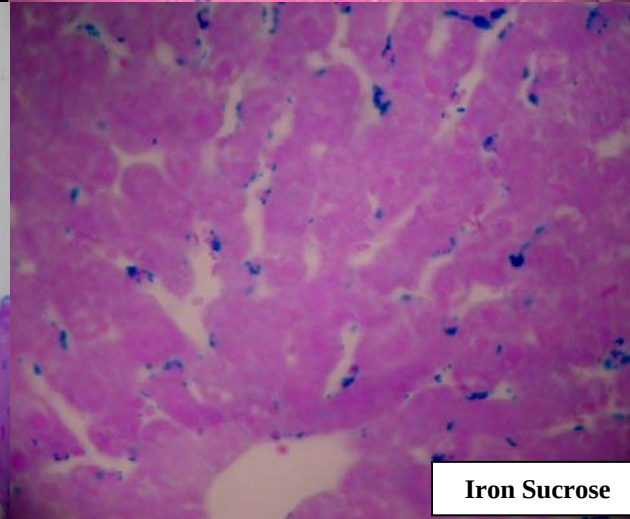
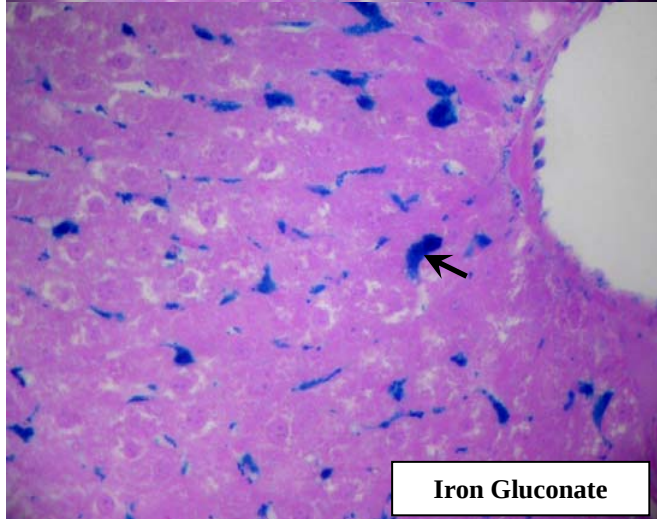
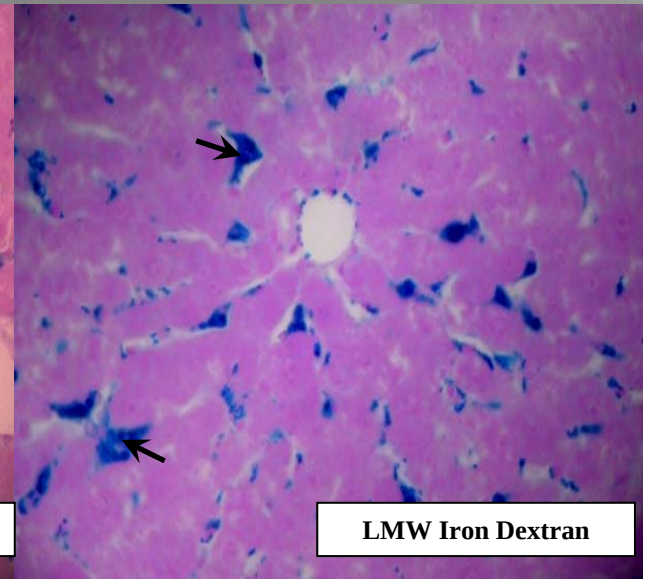
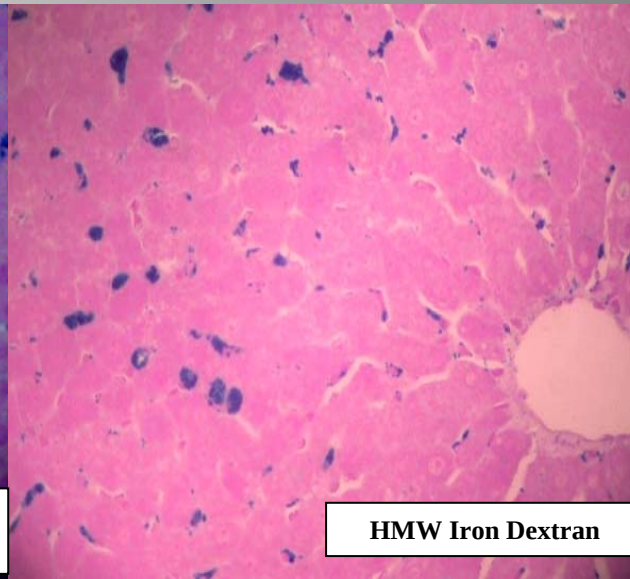
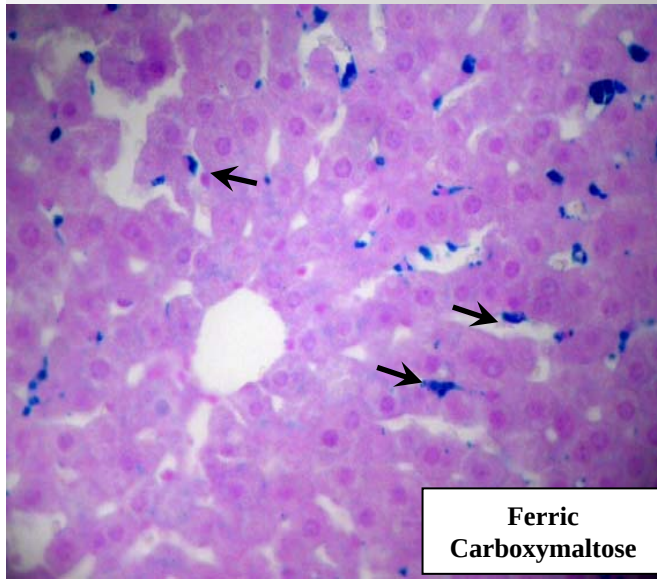
Final Remarks

Less Oxidative Stress in
Ferric Carboxymaltose & Iron Sucrose

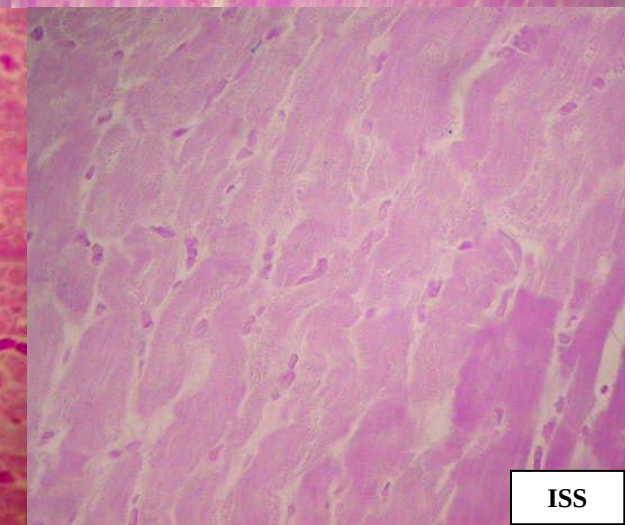
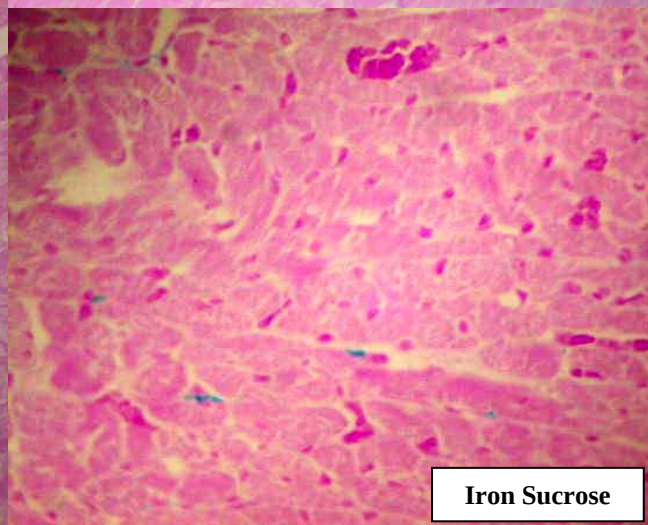
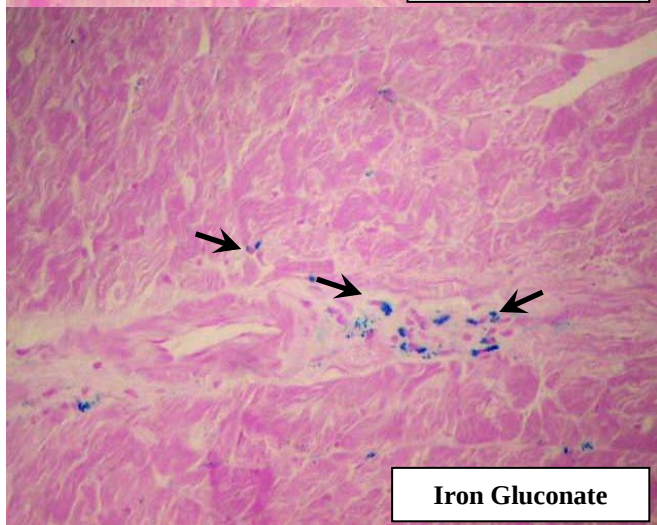
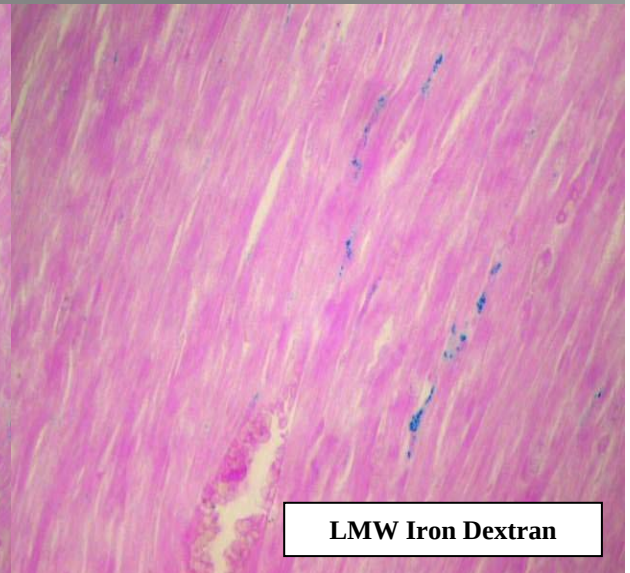
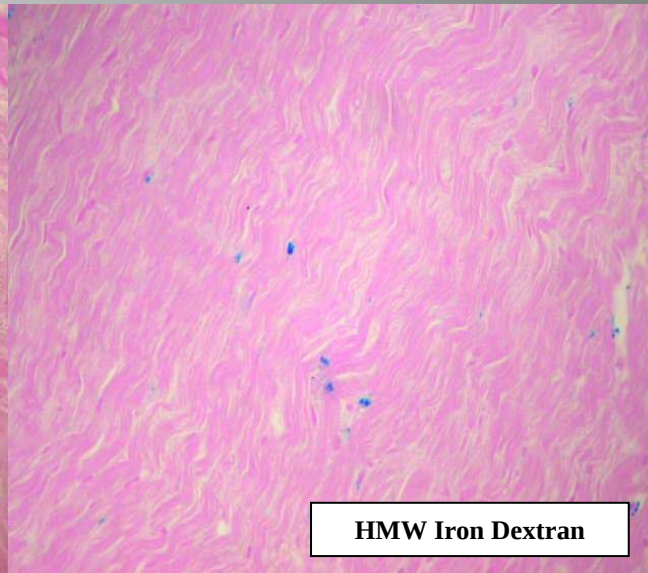
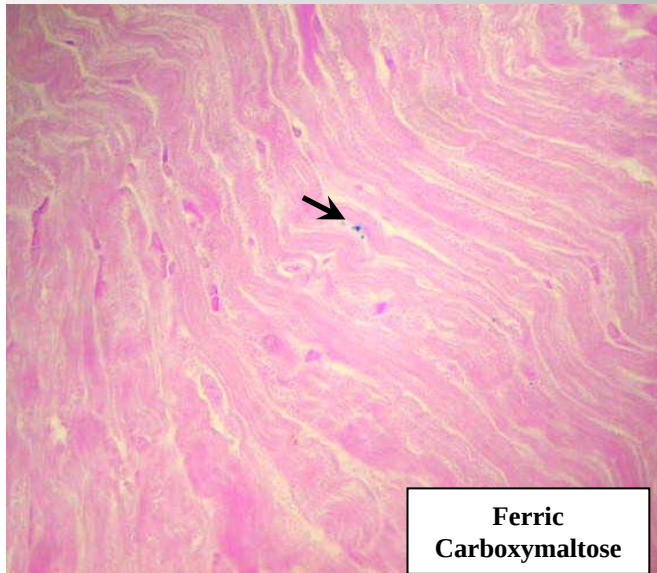
**Prussian Blue at 4 weeks
after a weekly IV Iron administration**



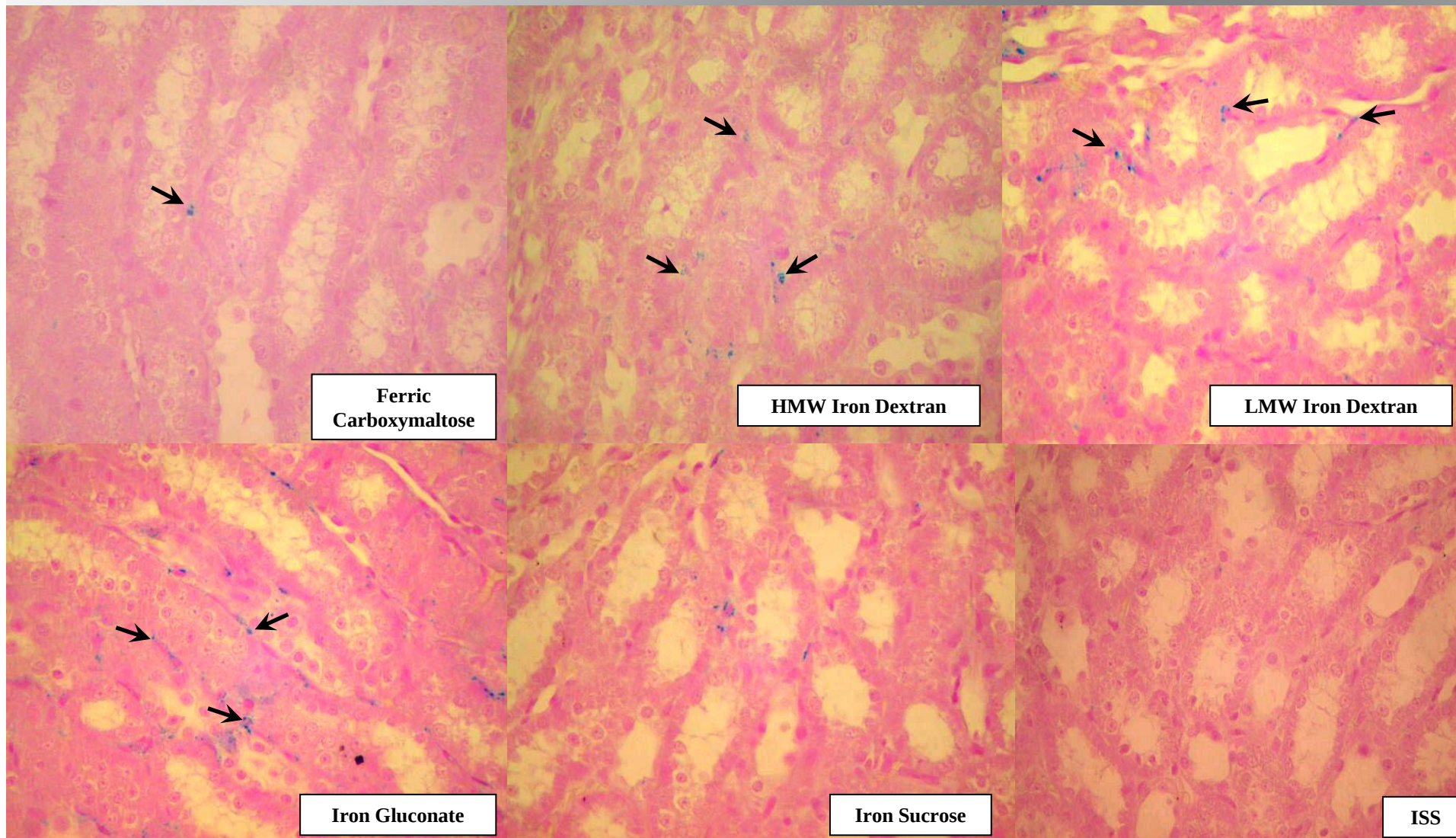
Prussian Blue in Liver at 4 weeks (x400)



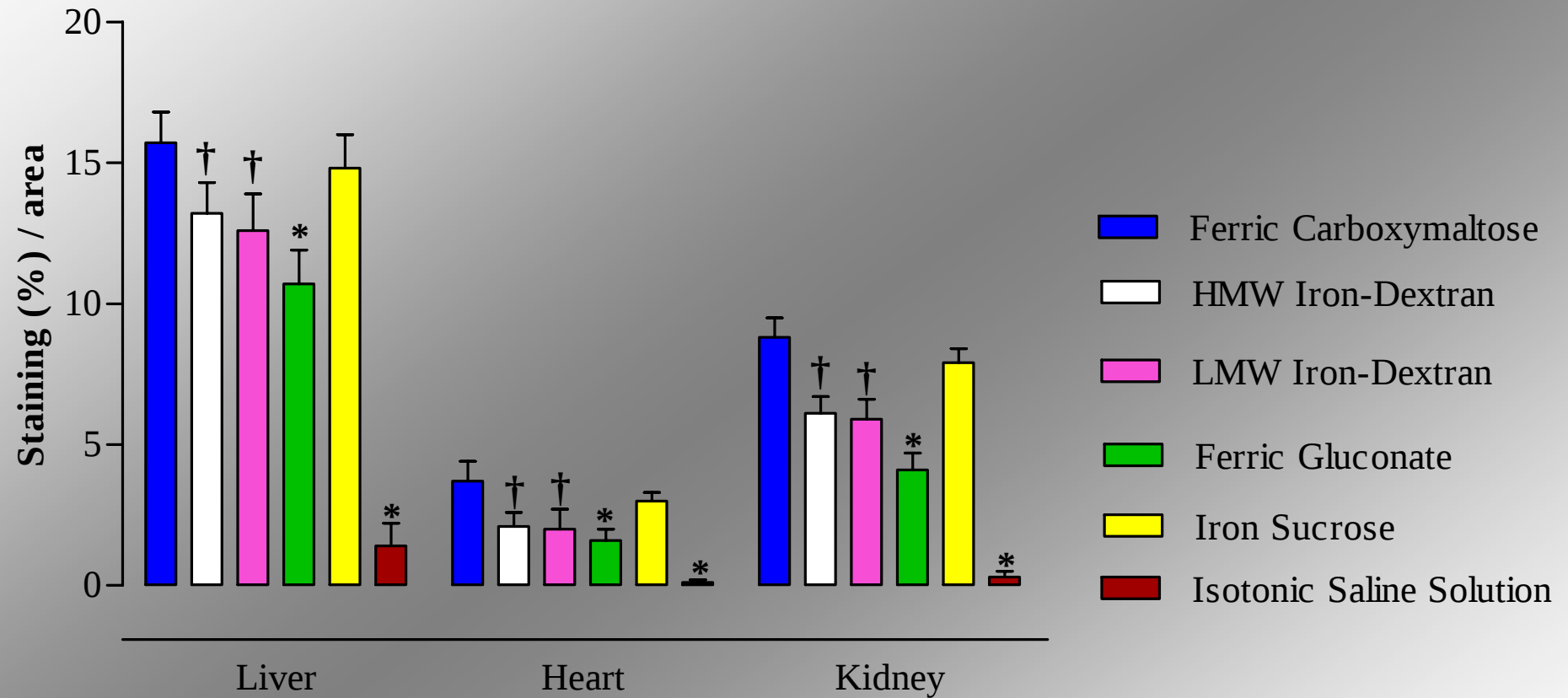
Prussian Blue in Heart 4 weeks (x400)



Prussian Blue in Kidney at 4 weeks (x400)



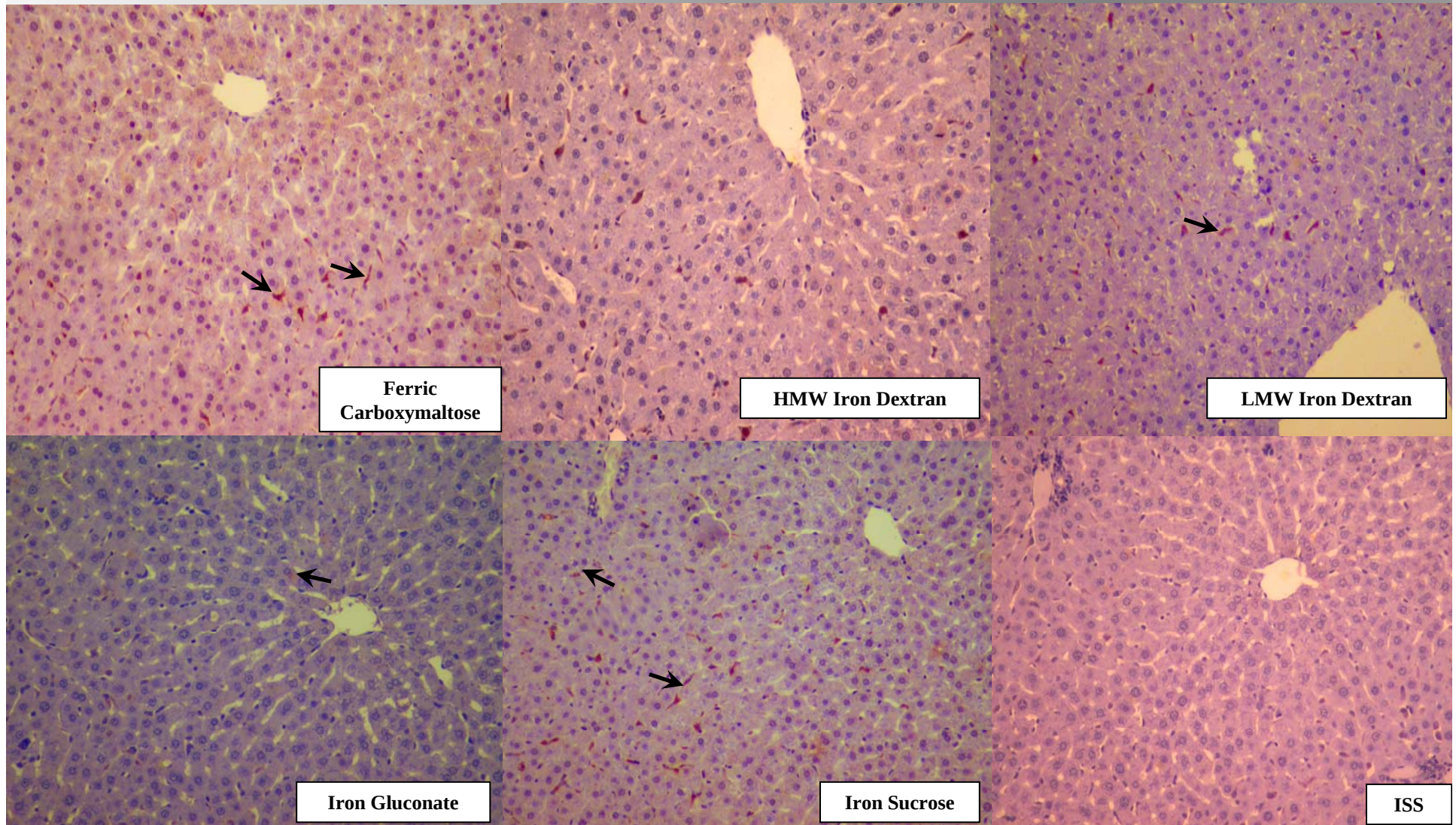
Immunostaining for Ferritin at 4 weeks after a weekly IV Iron administration



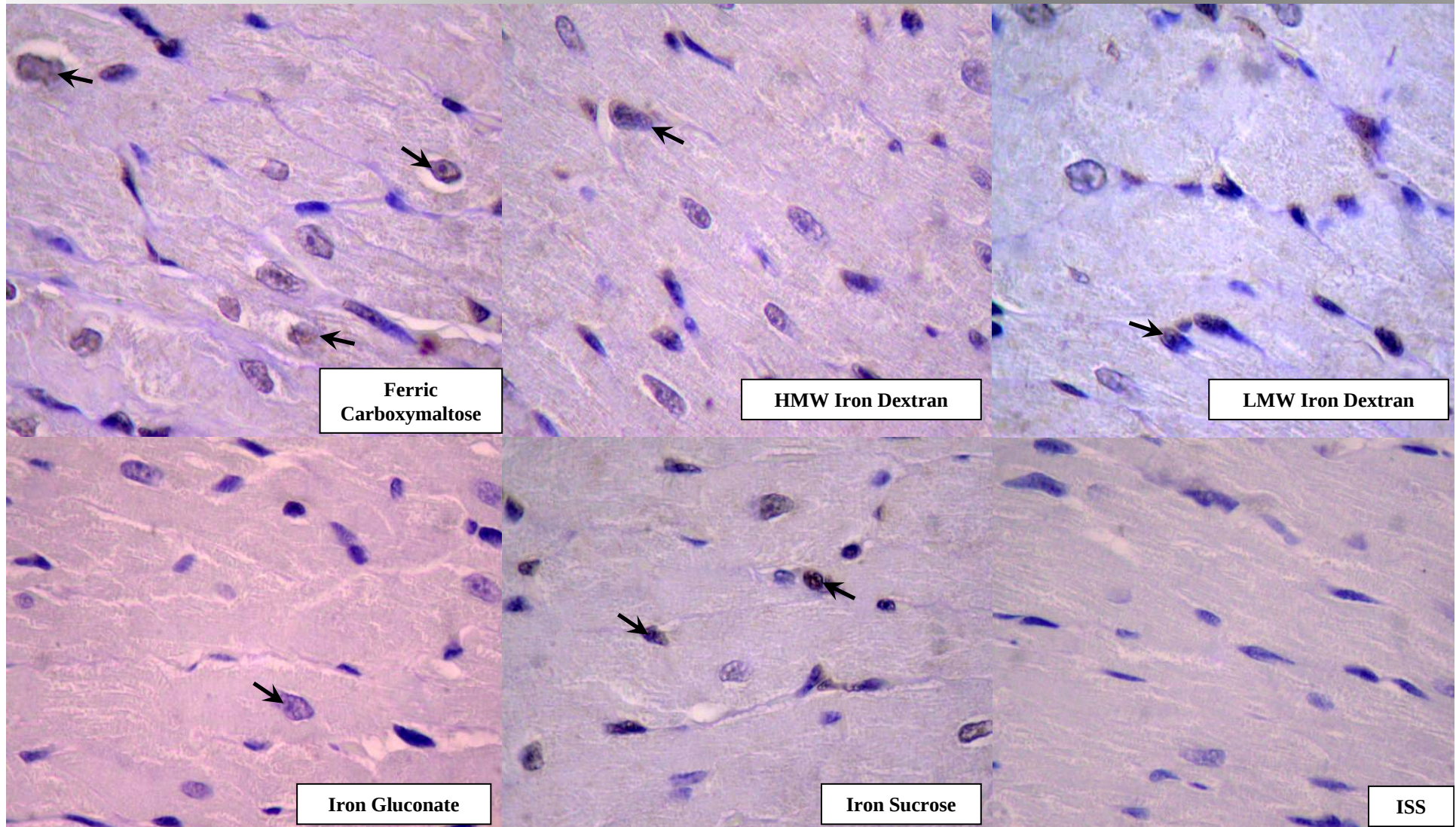
* versus all groups $p < 0.01$

† versus Ferric Carboxymaltose, Iron Sucrose and Isotonic Saline Solution $p < 0.01$

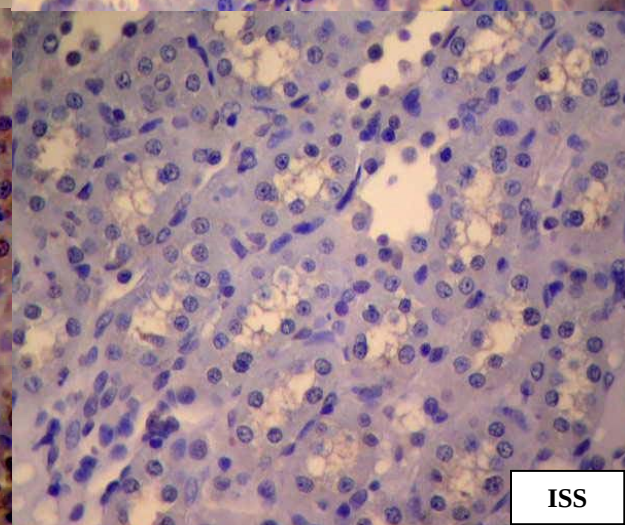
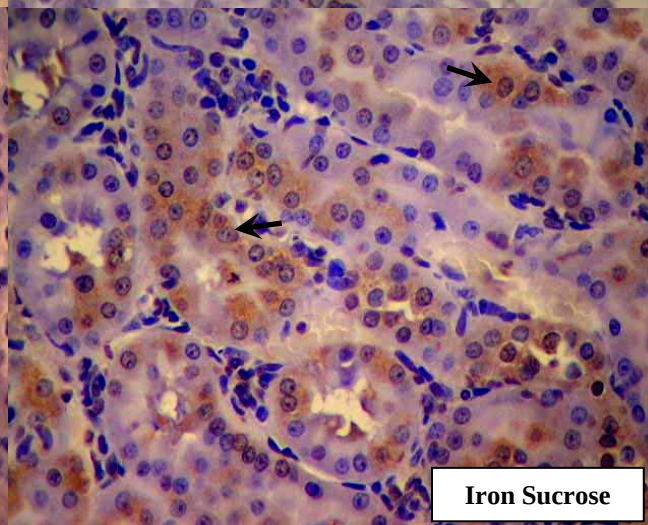
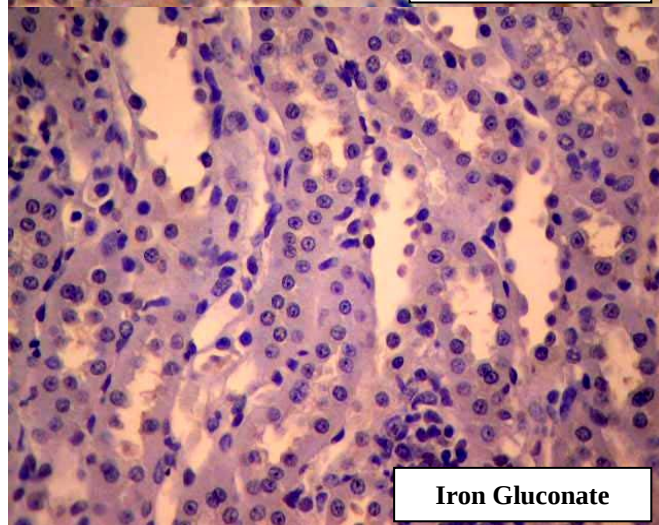
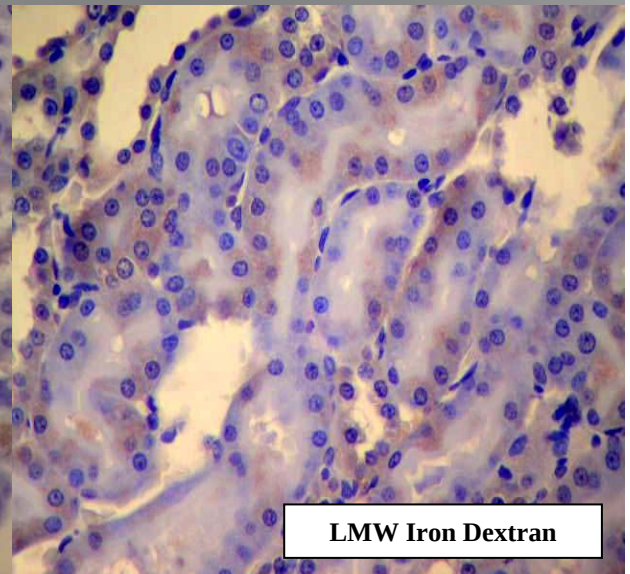
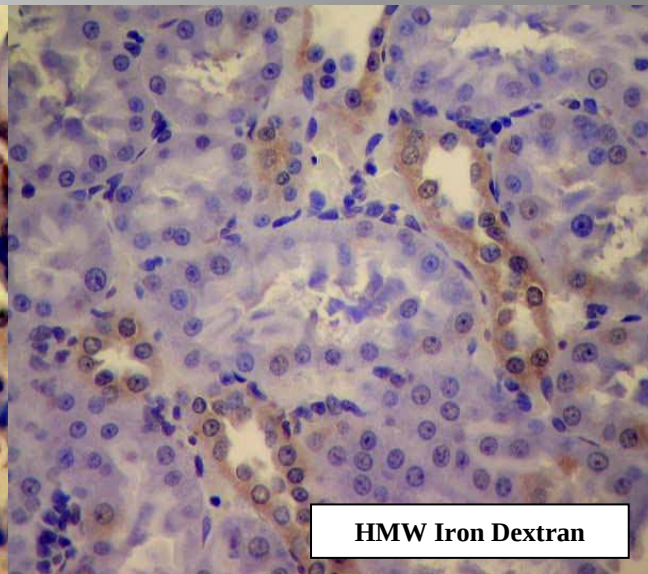
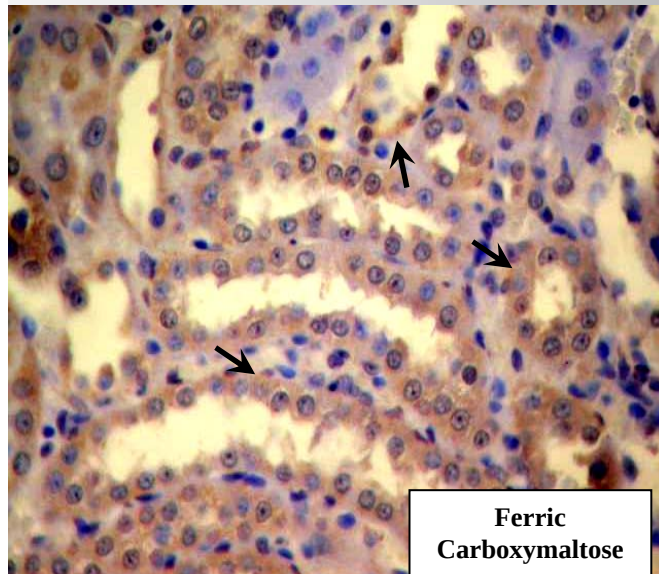
Ferritin in Liver at 4 weeks (x100)



Ferritin in Heart at 4 weeks (x1000)



Ferritin in kidney at 4 weeks (x400)

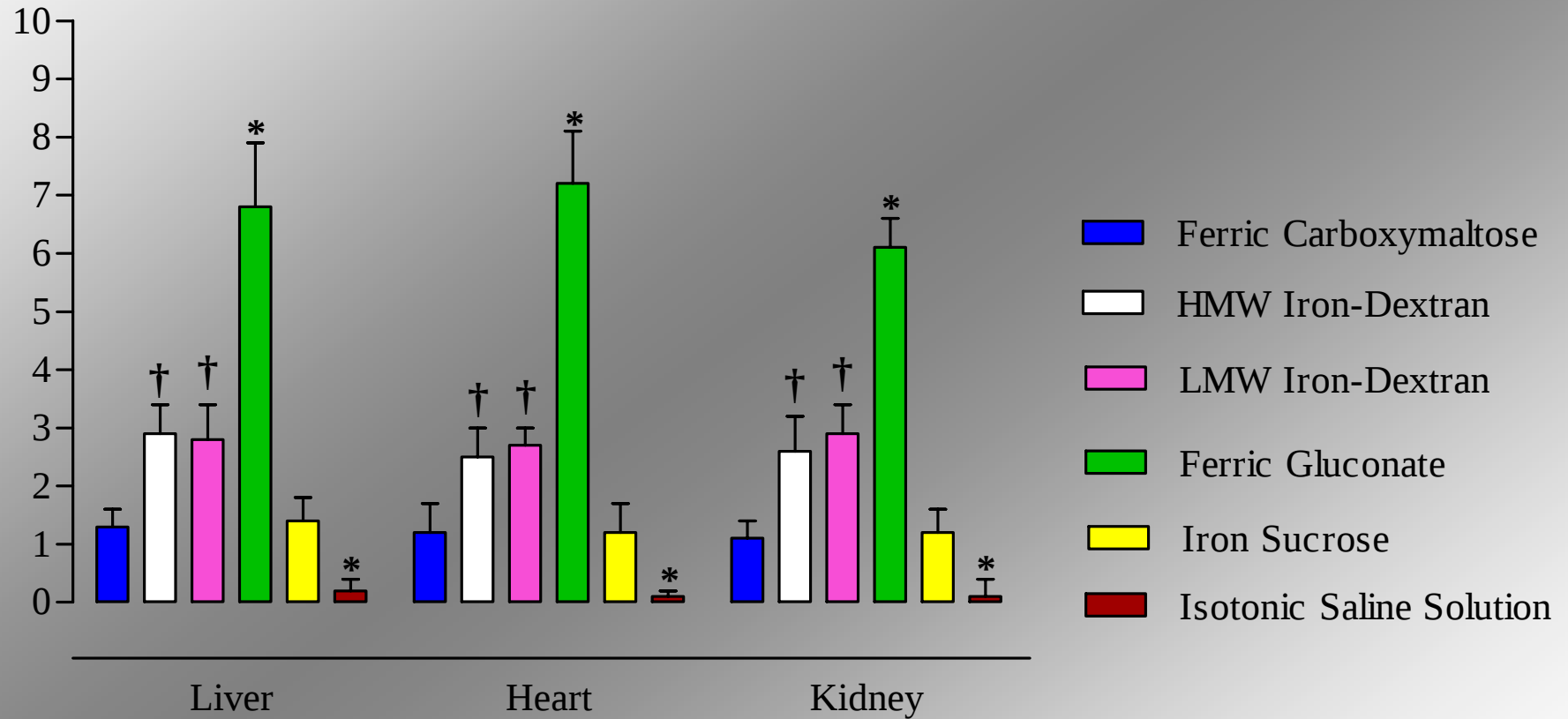


Let's go now to the inflammatory markers!!!



**IL6 immunostaining at 4 weeks
after a weekly IV Iron administration**

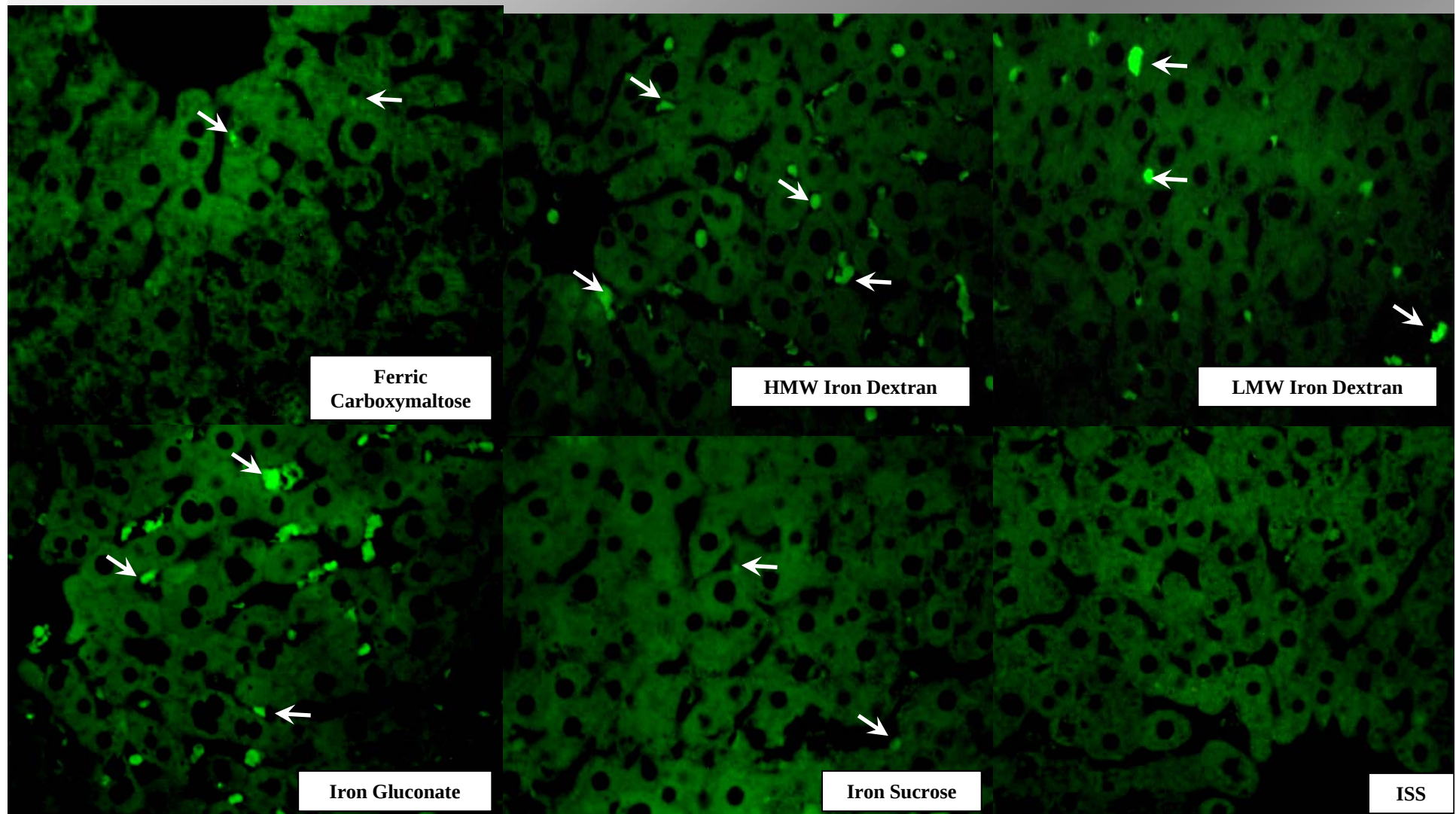
Percentage of Fluorescence / cross-sectiona area



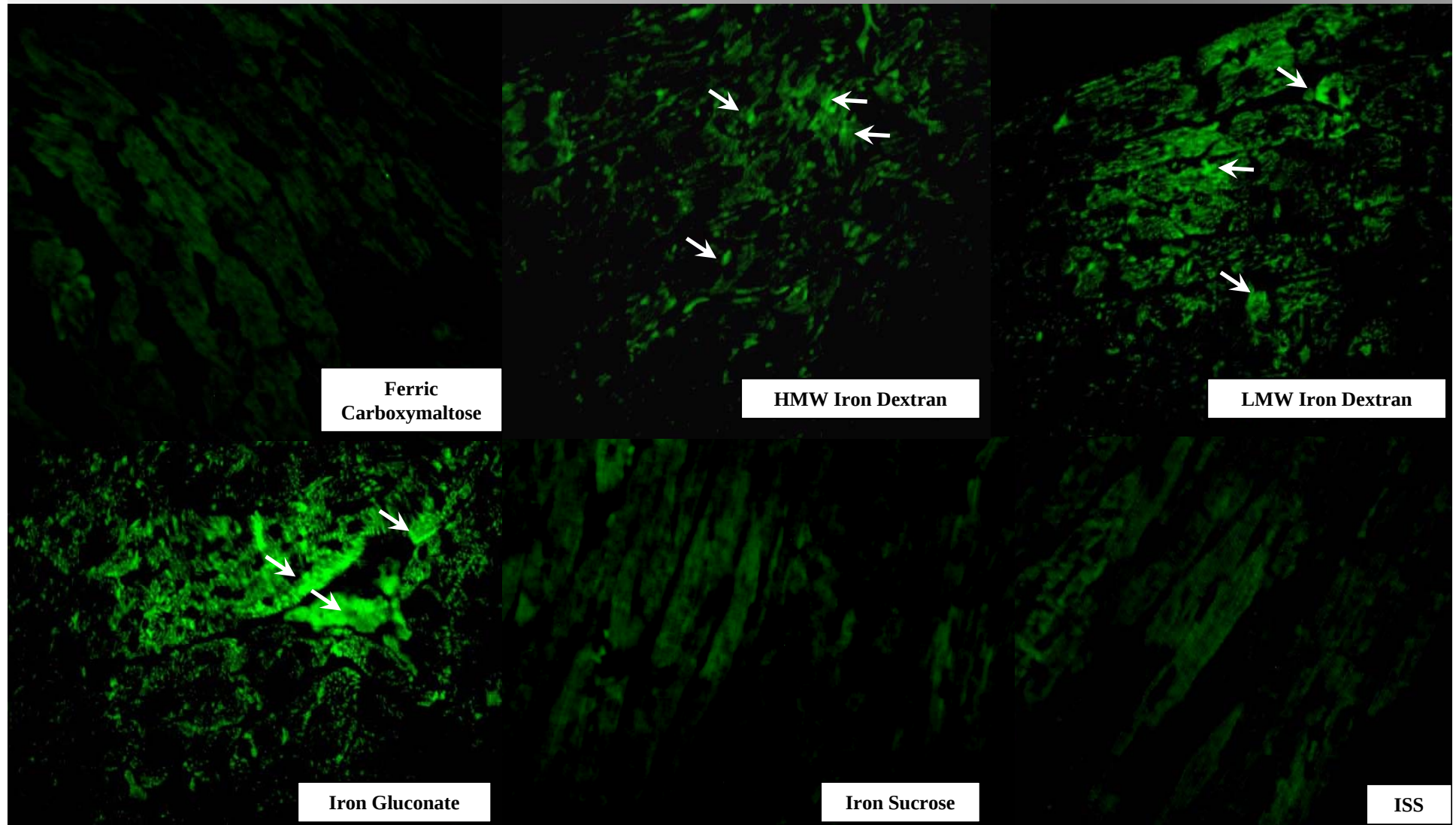
* versus all groups $p < 0.01$

† versus Ferric Carboxymaltose, Iron Sucrose and Isotonic Saline Solution $p < 0.01$

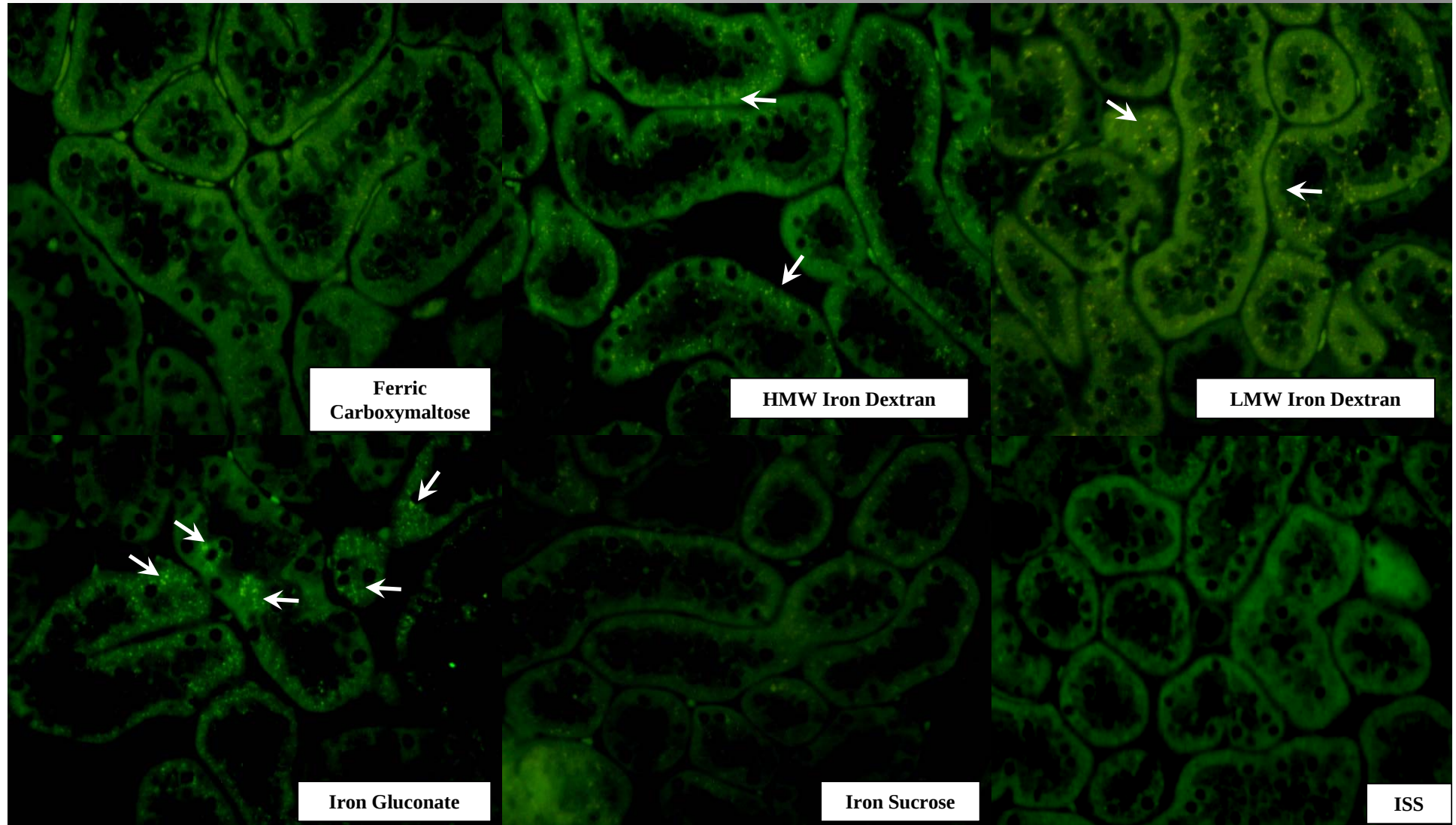
IL6 in Liver at 4 weeks (x400)



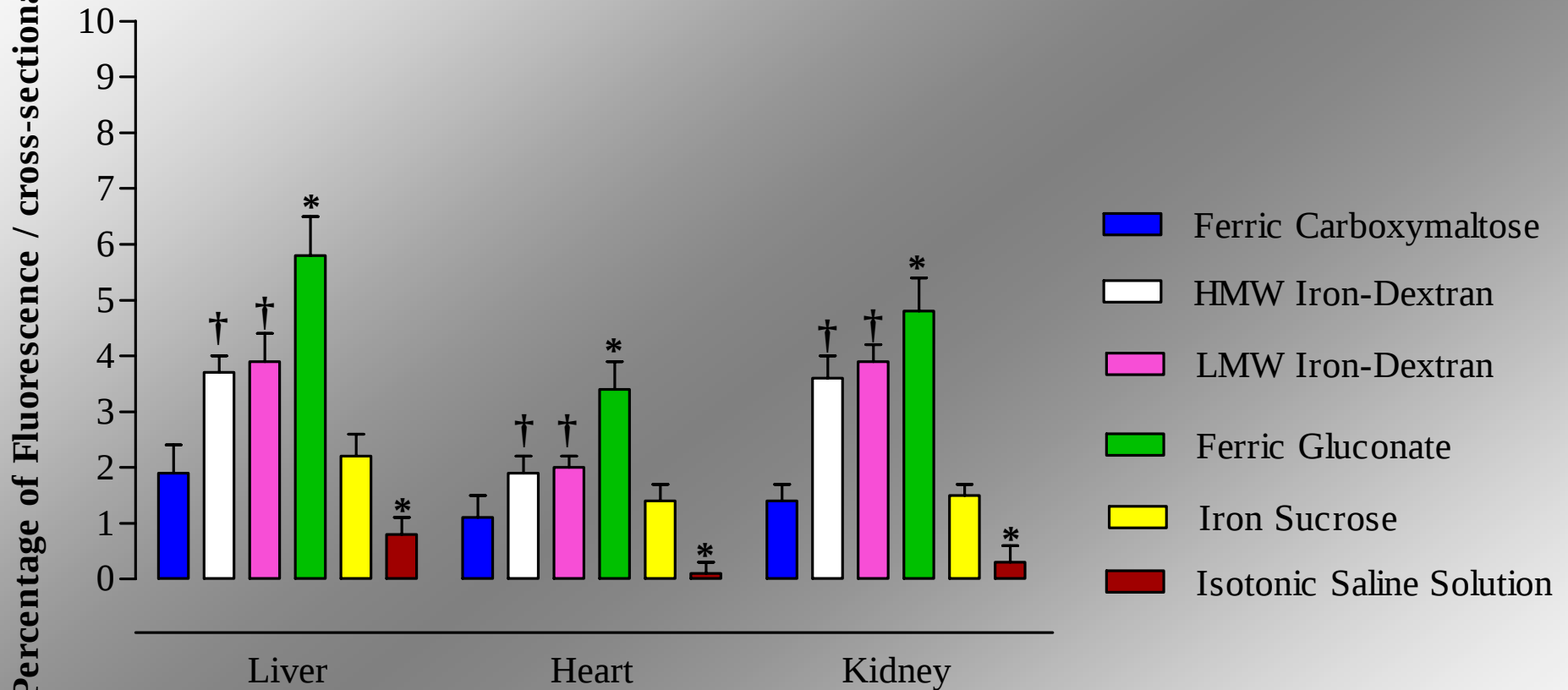
IL6 in Heart at 4 weeks (x400)



IL6 in kidney at 4 weeks (x400)



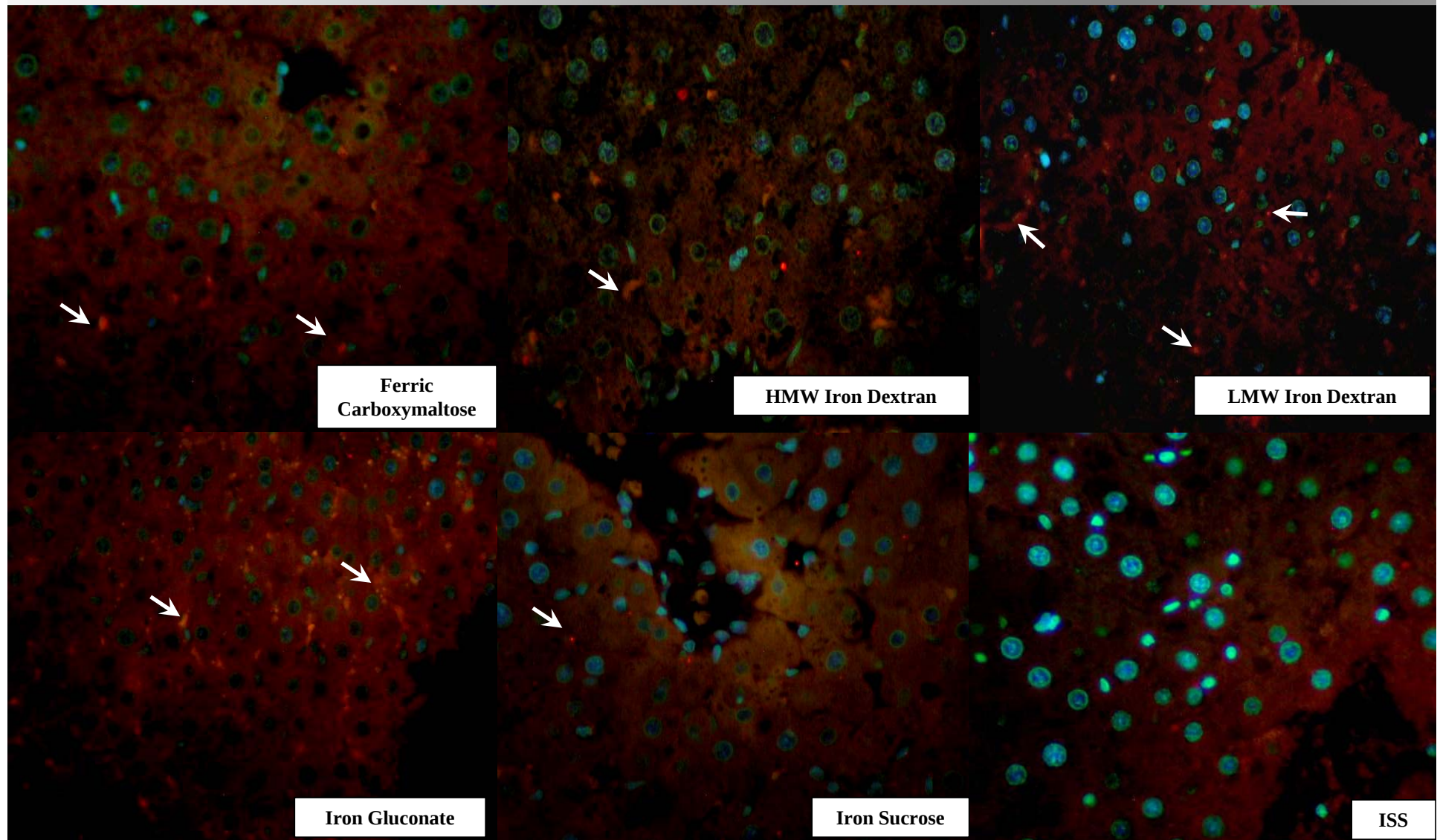
**TNF α immunostaining at 4 weeks
after a weekly IV Iron administration**



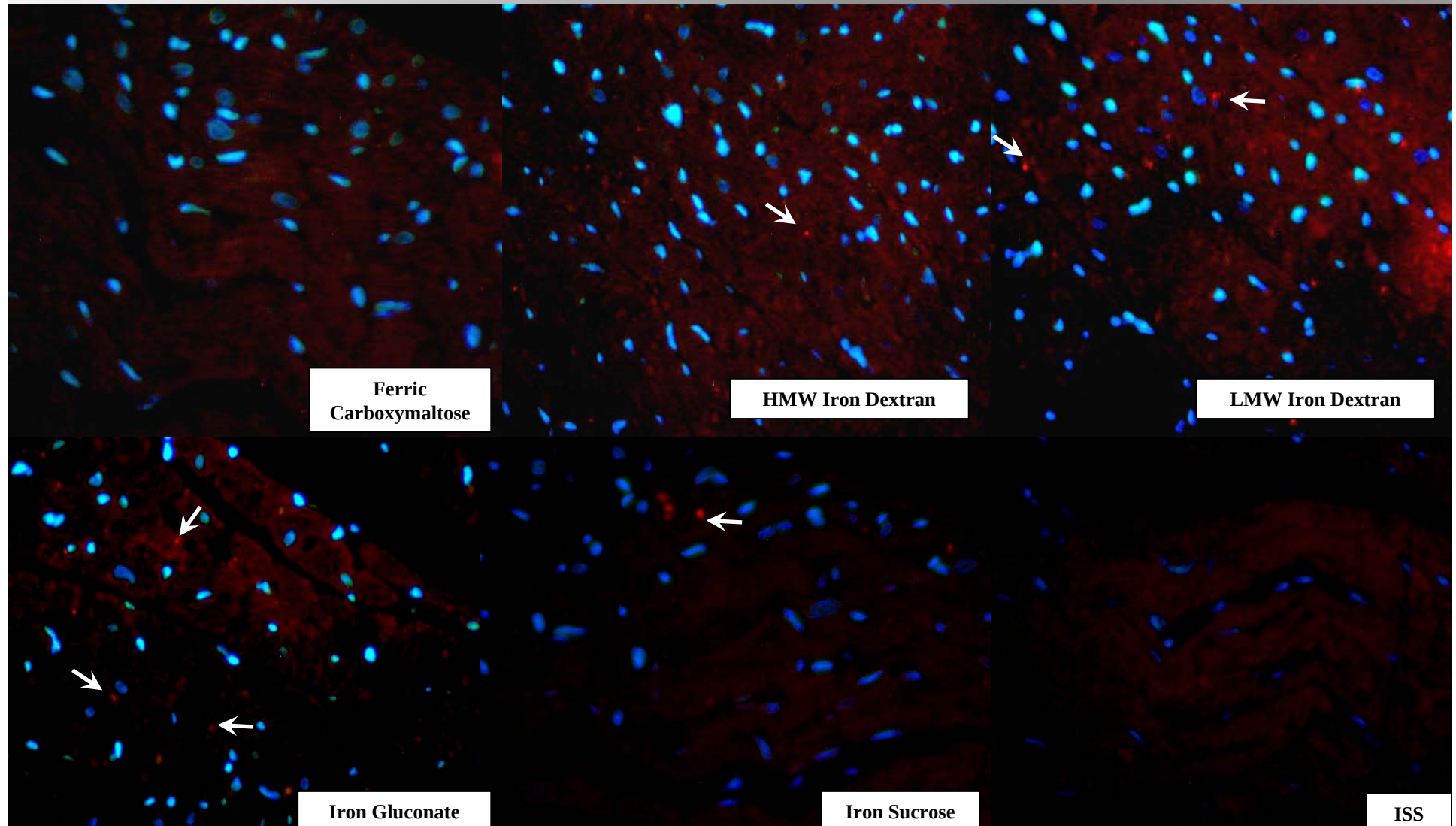
* versus all groups $p < 0.01$

† versus Ferric Carboxymaltose, Iron Sucrose and Isotonic Saline Solution $p < 0.01$

TNF α in Liver at 4 weeks (x400)

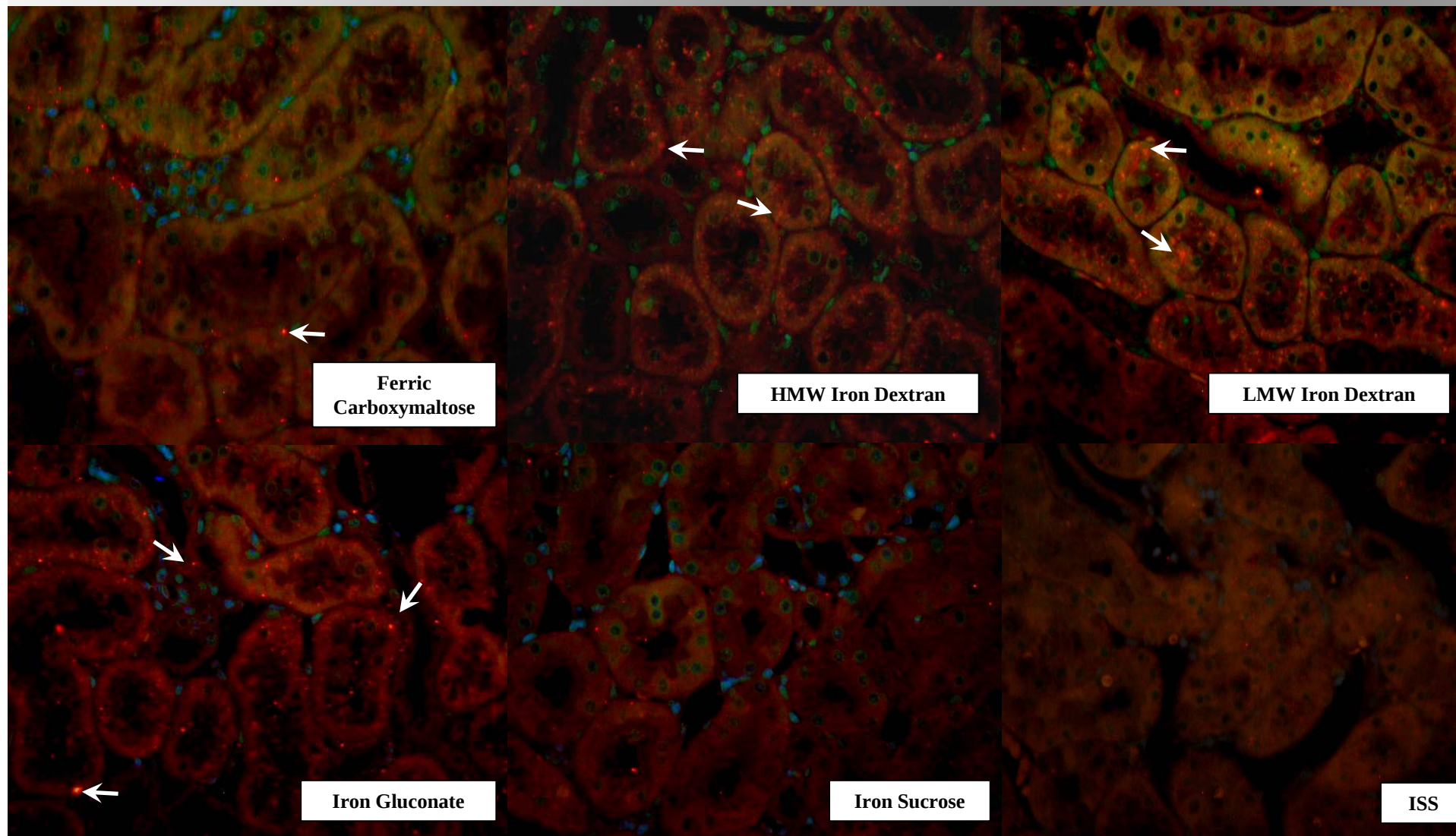


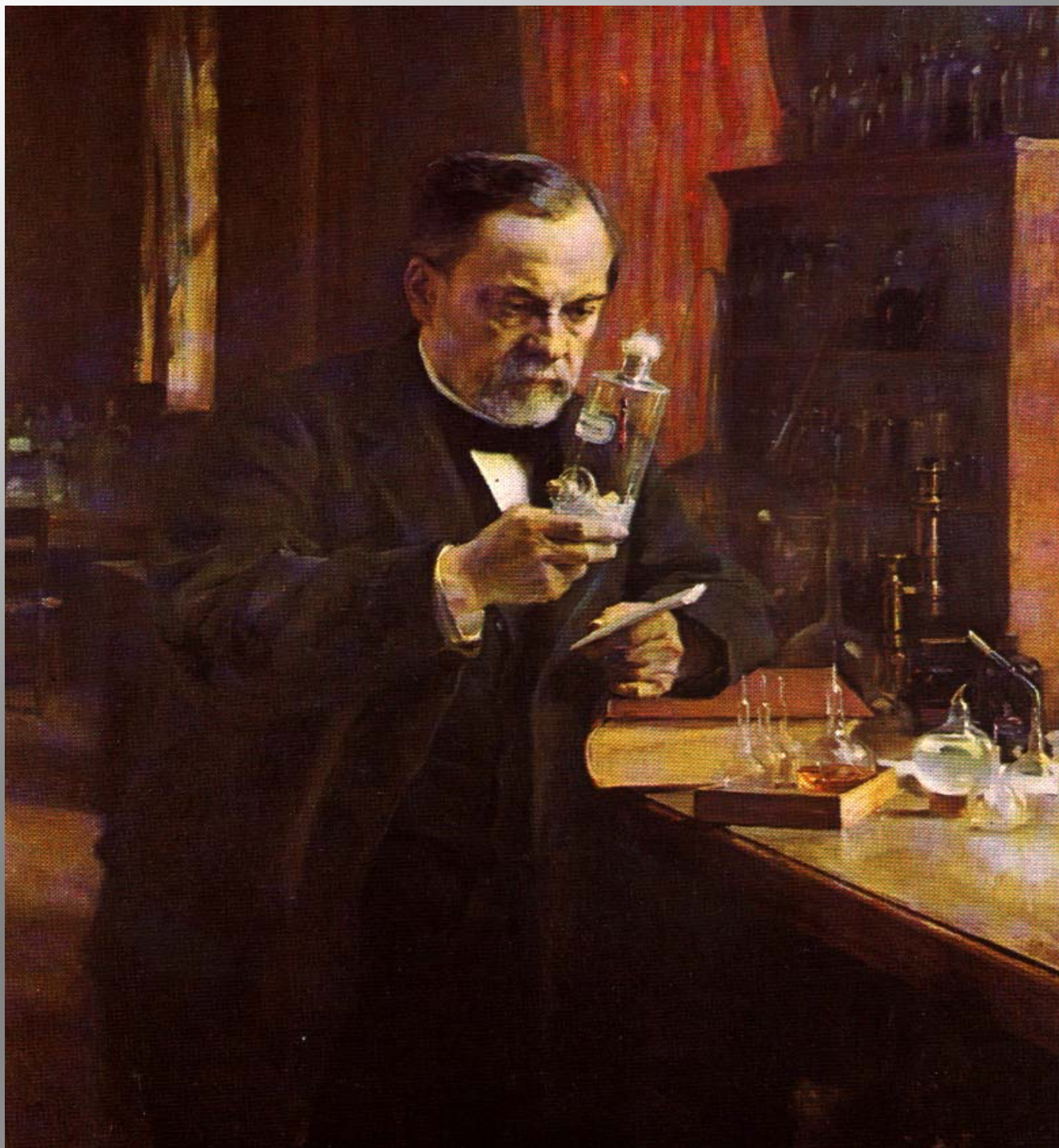
TNF α in Heart at 4 weeks
(x400)



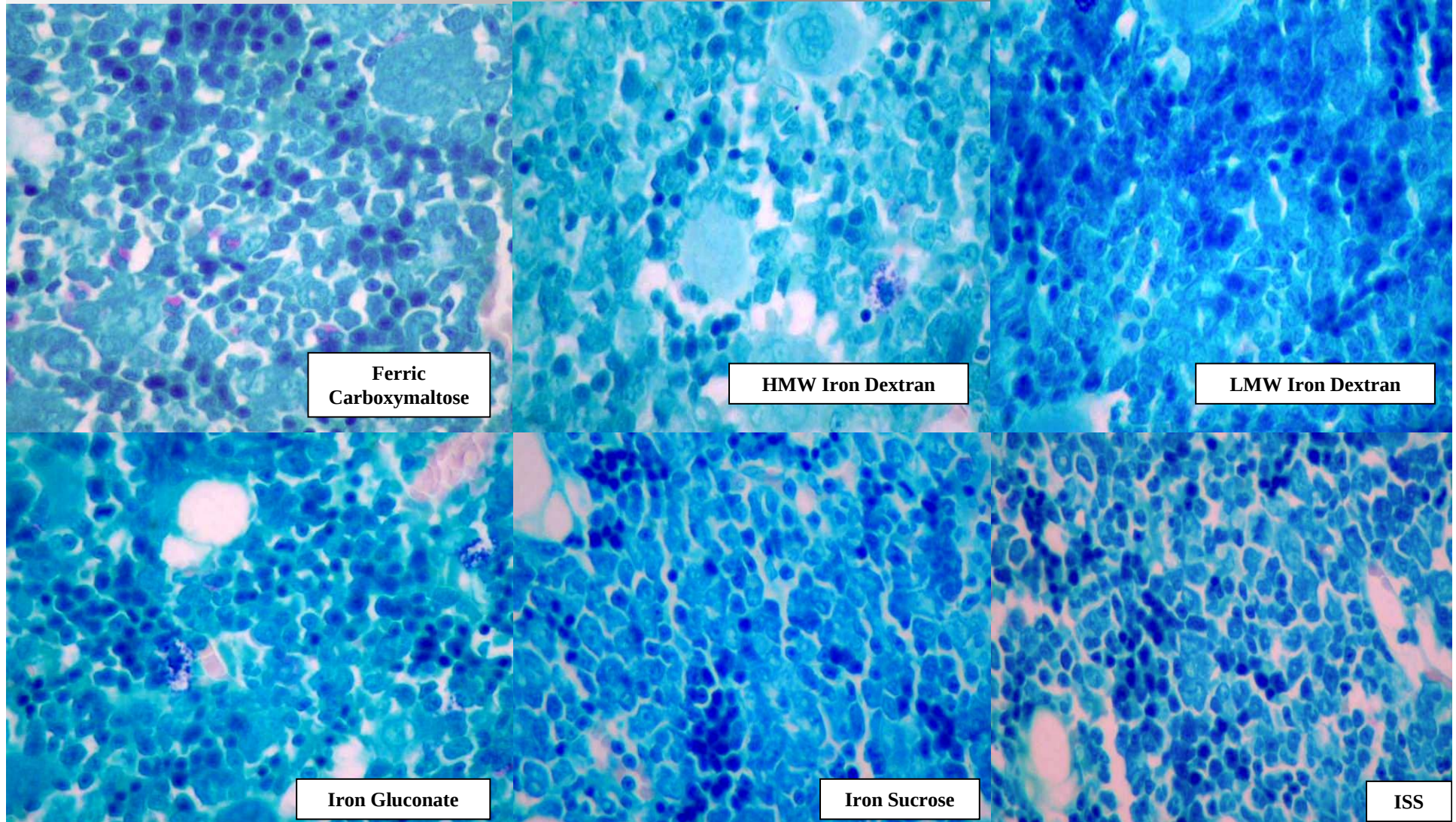
TNF α in Kidney at 4 weeks

(x400)



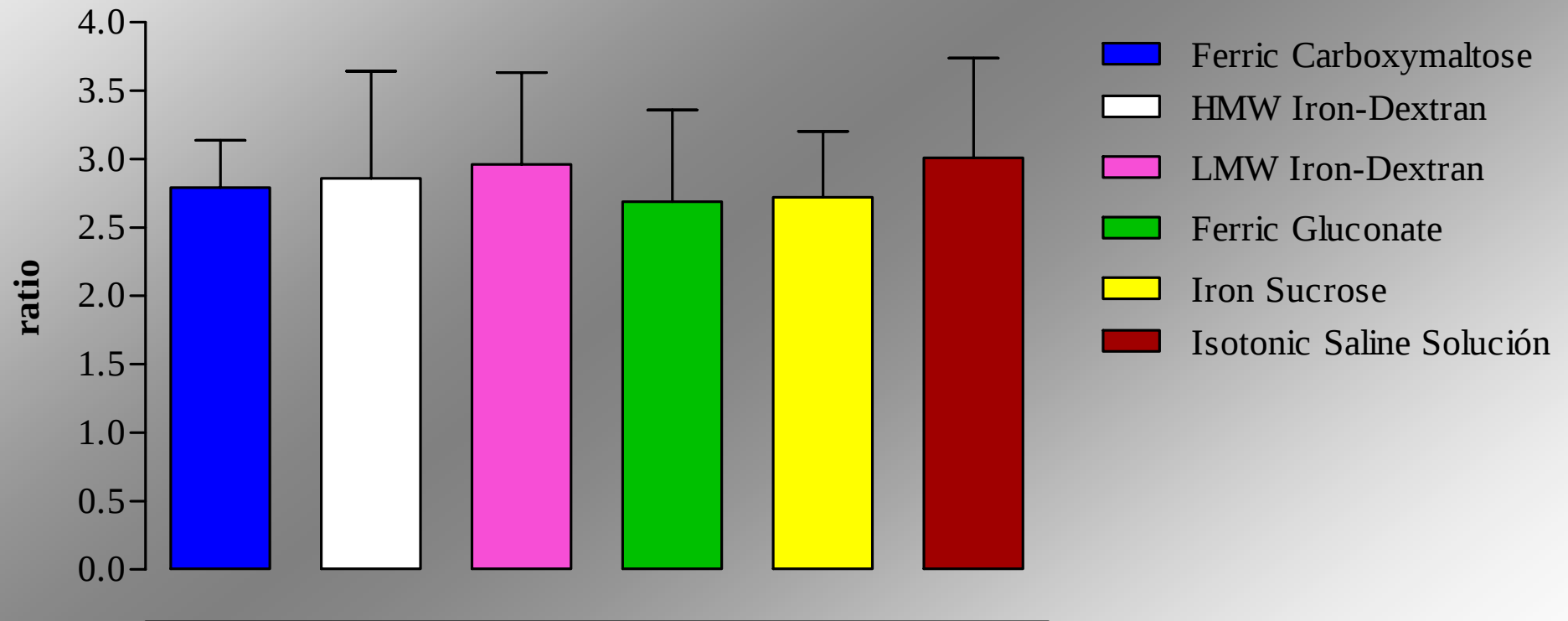


Bone Marrow at 4 weeks (Giemsa, x400)



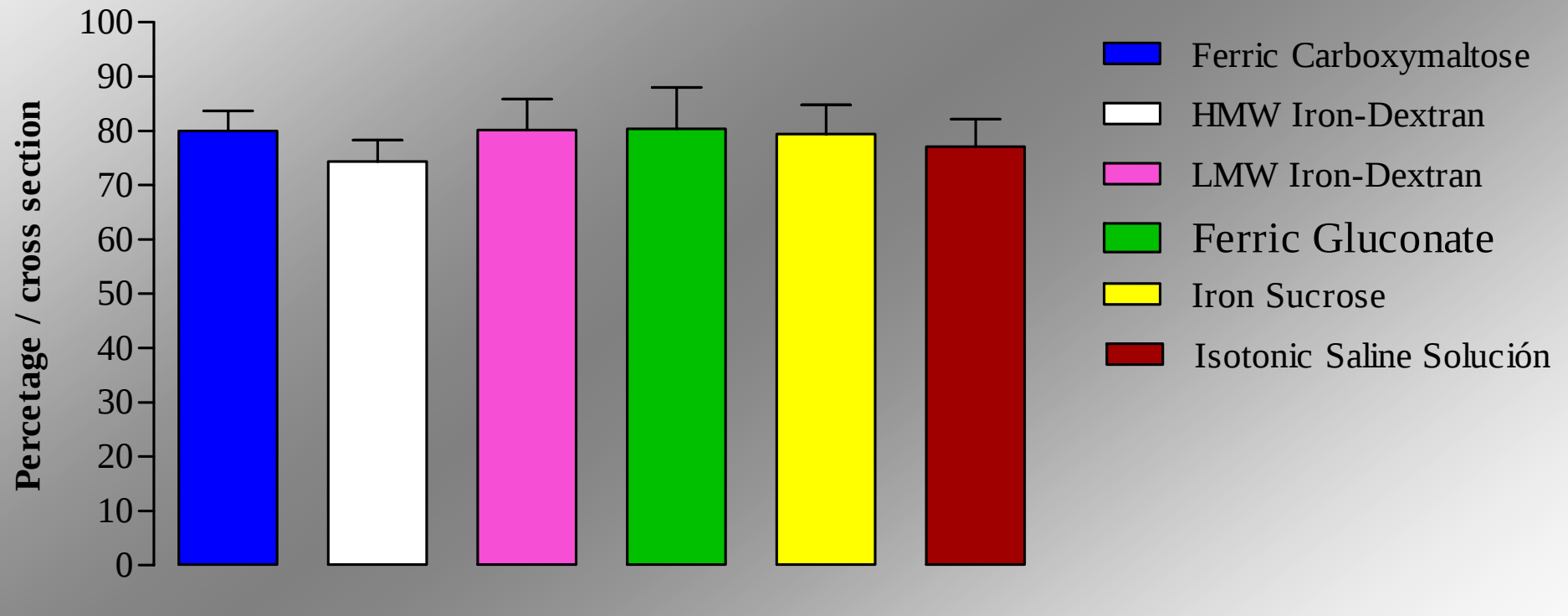
**Bone Marrow Myeloid:Erythroid ratio after
a weekly IV Iron administration**

(p=NS)

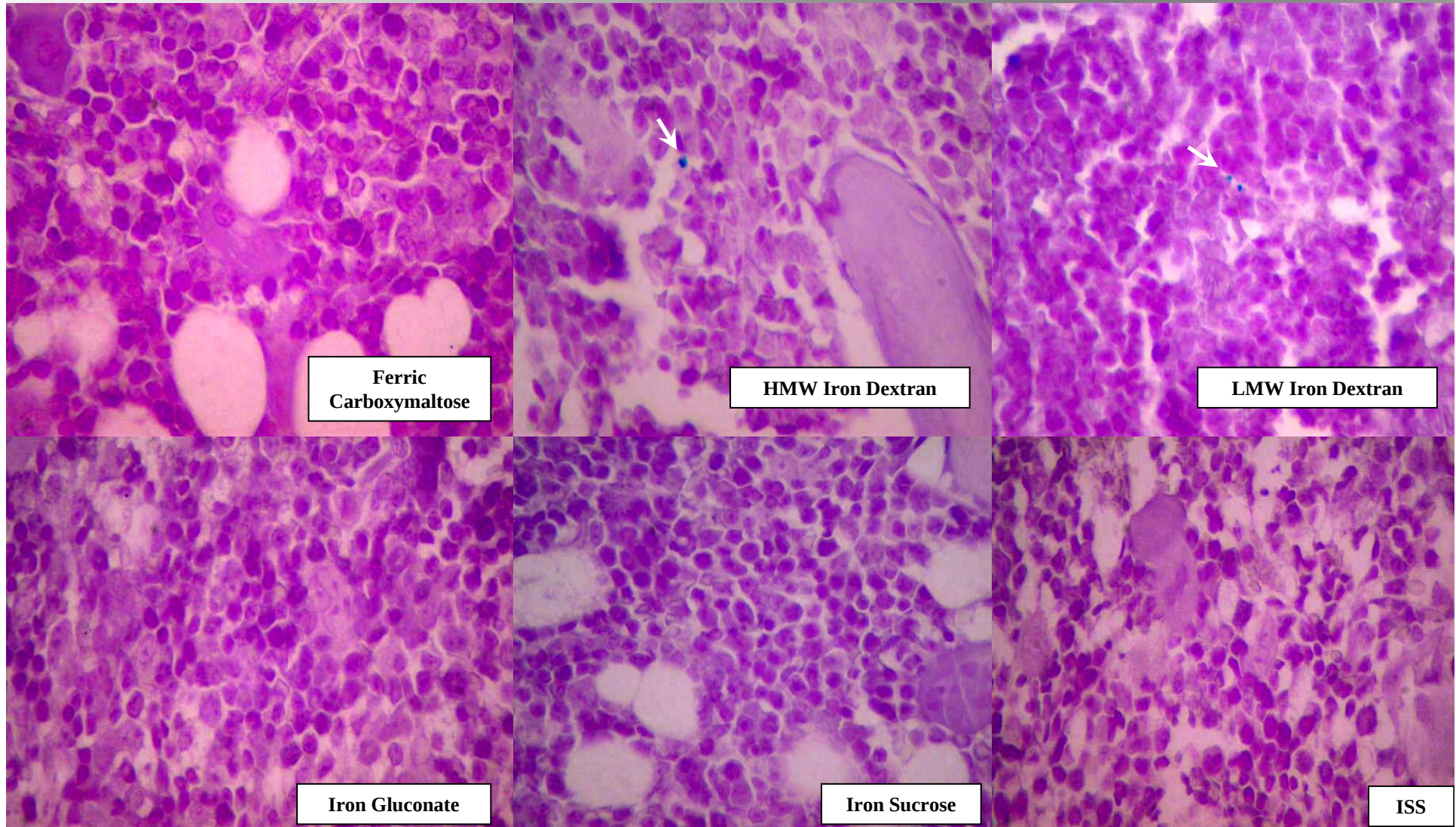


Bone Marrow Cellularity after a weekly IV Iron administration

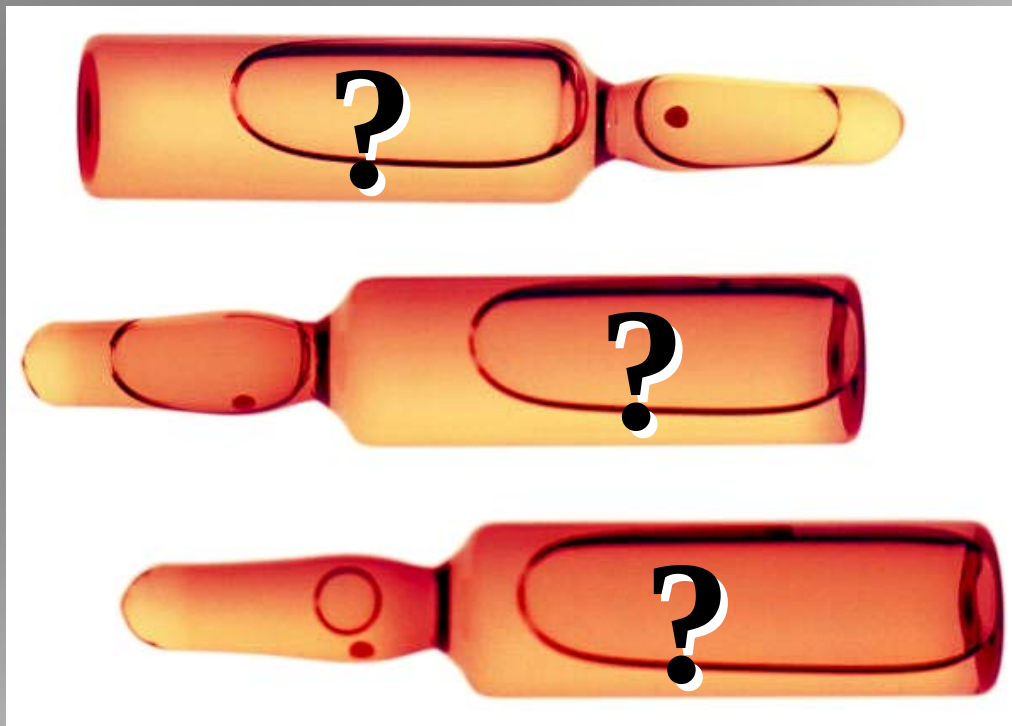
(p=NS)



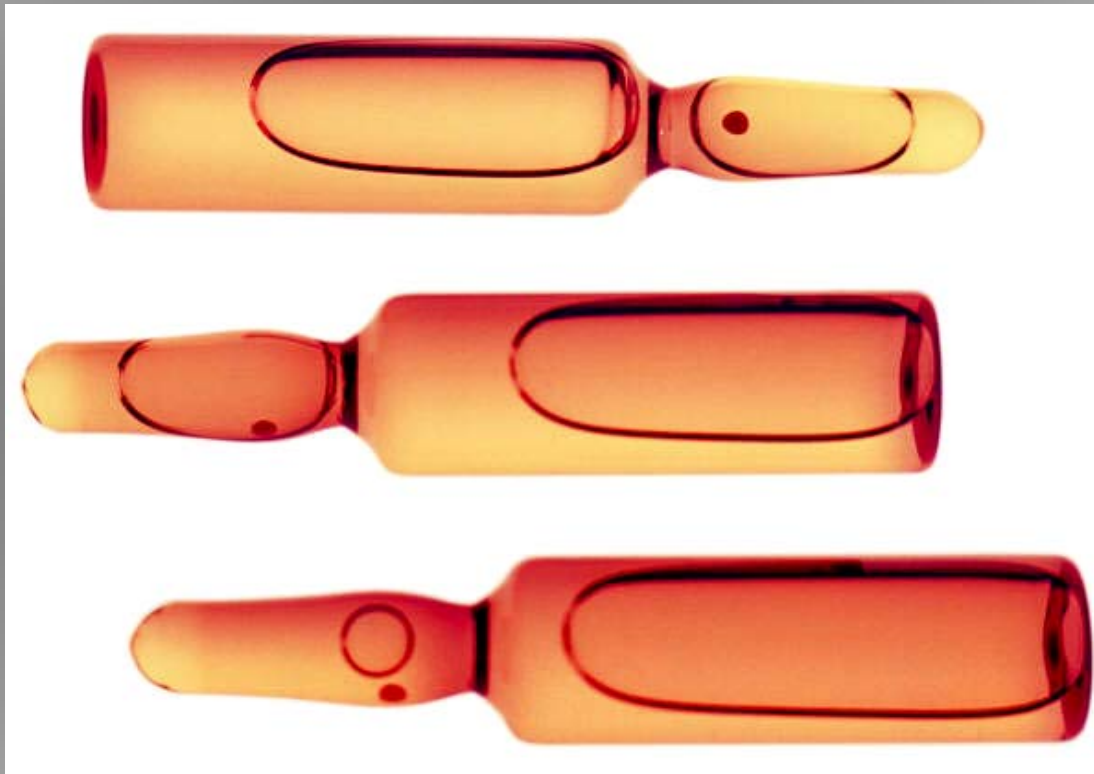
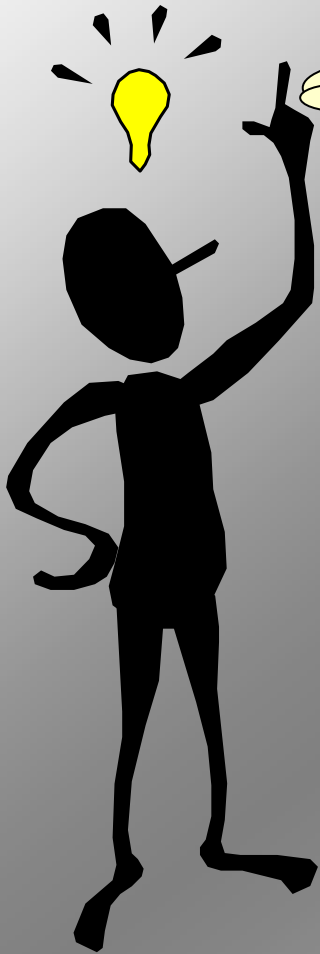
Prussian Blue in Bone Marrow at 4 weeks (x400)



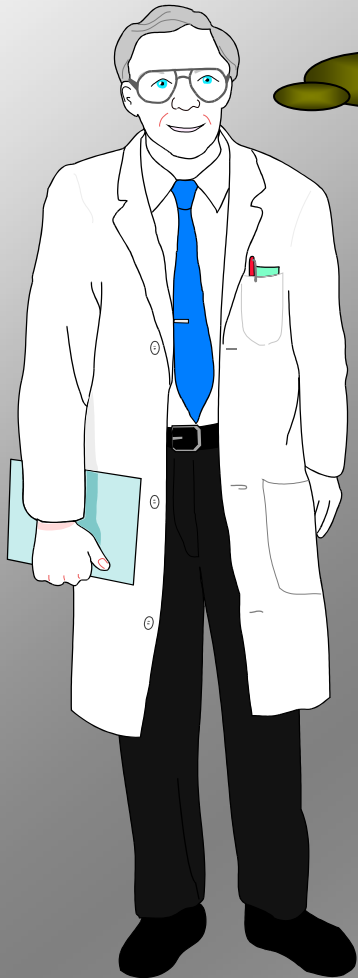
Are all “IV Iron Compounds”
the same thing ???



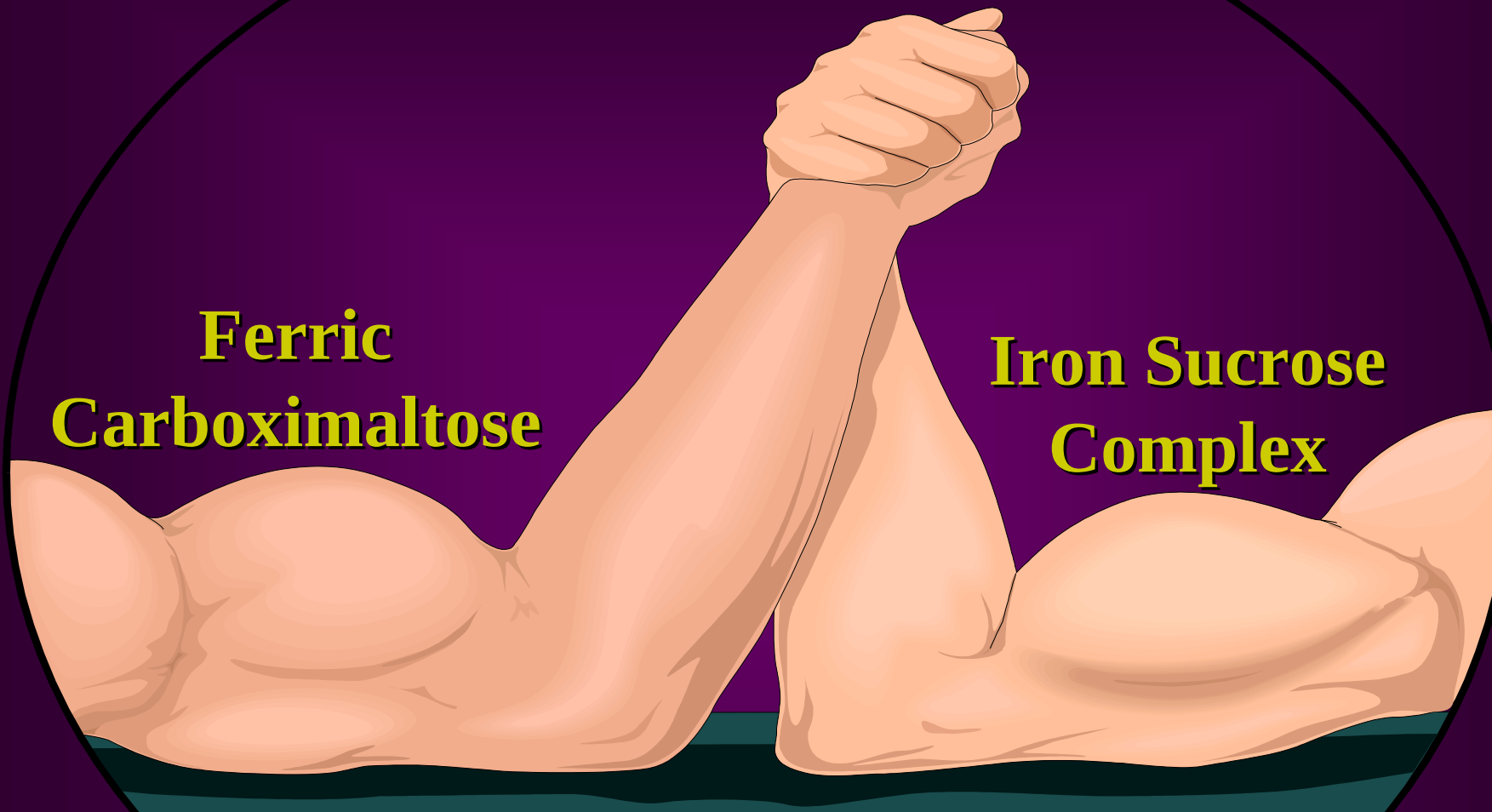
NO !!!!! All
“IV Iron Compounds” are
not the same thing



*Now, you probably
have the answer!!!*



Ferric Carboxymaltose
&
Iron Sucrose



**Ferric
Carboximaltose**

**Iron Sucrose
Complex**

Which is the best ?

Development objectives of FCM

The disadvantages of iron dextran and iron sucrose led to the aim to develop an iron compound WITH:

- A better safety and tolerance profile than existing products
- **Neutral pH and low osmolarity** and WITHOUT:
- Dextran-induced hypersensitivity reactions (DIAR)
- Low dosage limits like iron sucrose
- **Long application duration** like iron sucrose and dextran

Low reactivity with molecules in blood and living cells

Structure similar to **ferritin**

Low toxicity

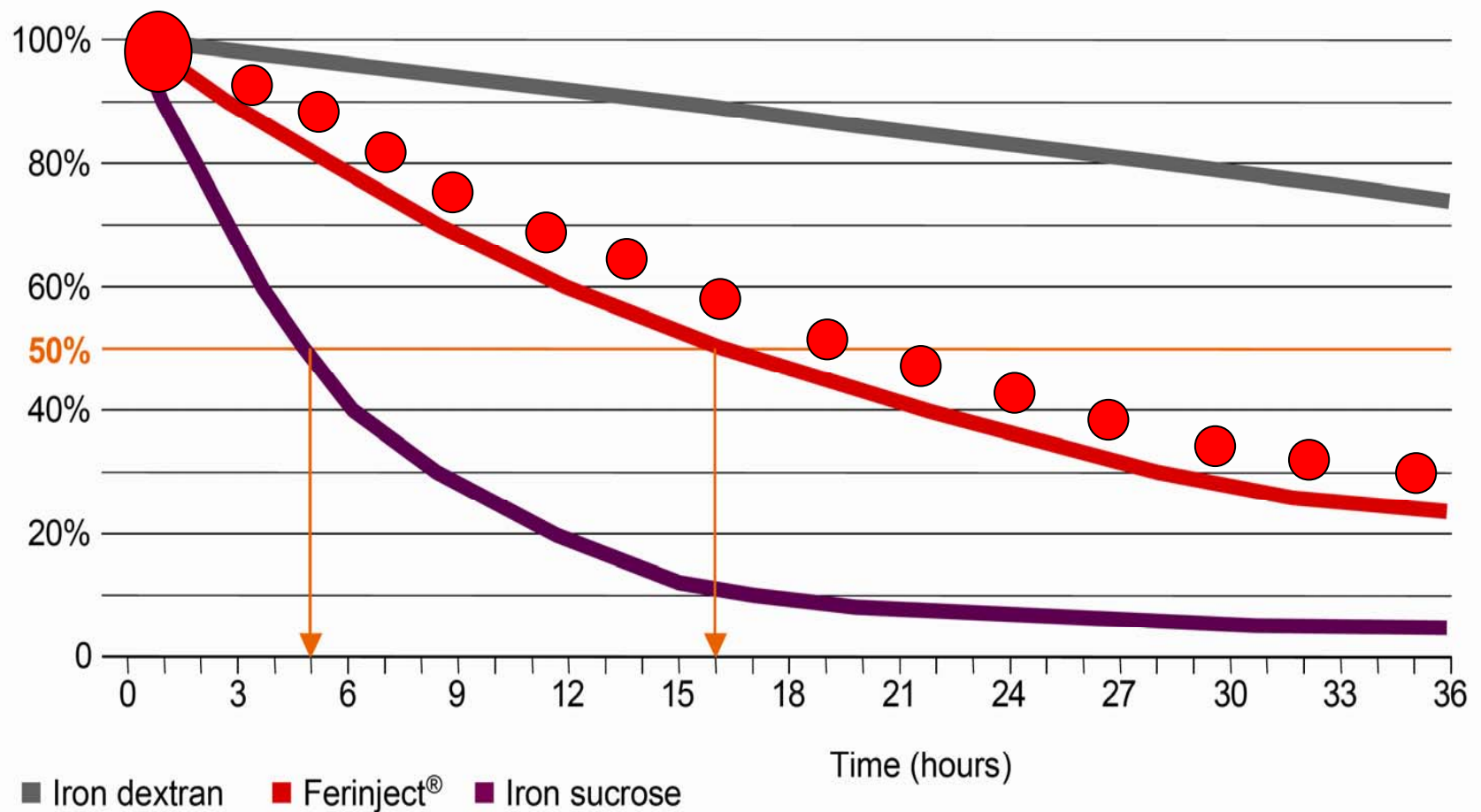
Deposition within the physiological iron stores (RES (reticuloendothelial system) in the liver) after application

No induction of oxidative stress

MW of about 150 kDa



Serum elimination^{1,6,7}

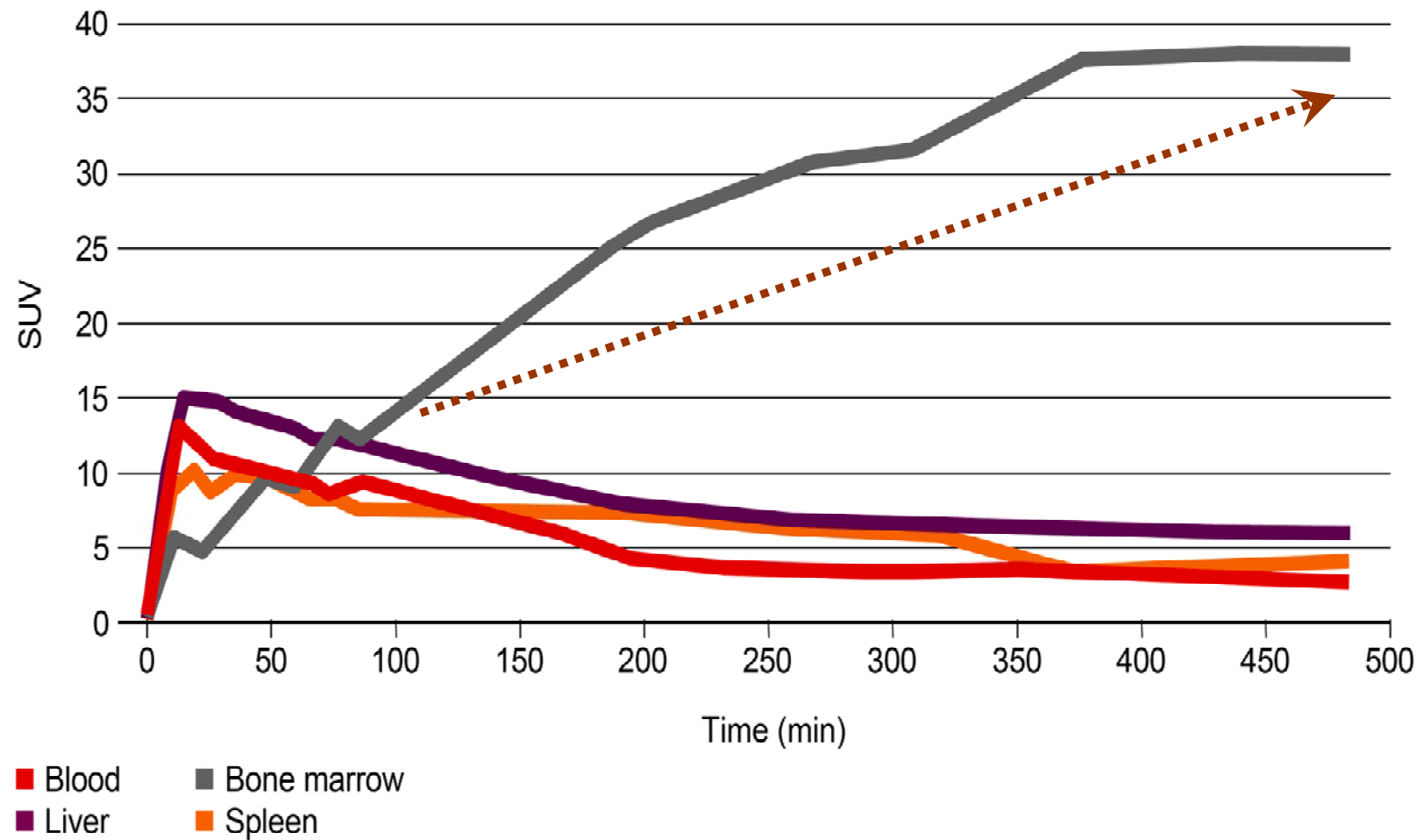


¹ Ferinject SPC

⁶ Danielson BG, 1996

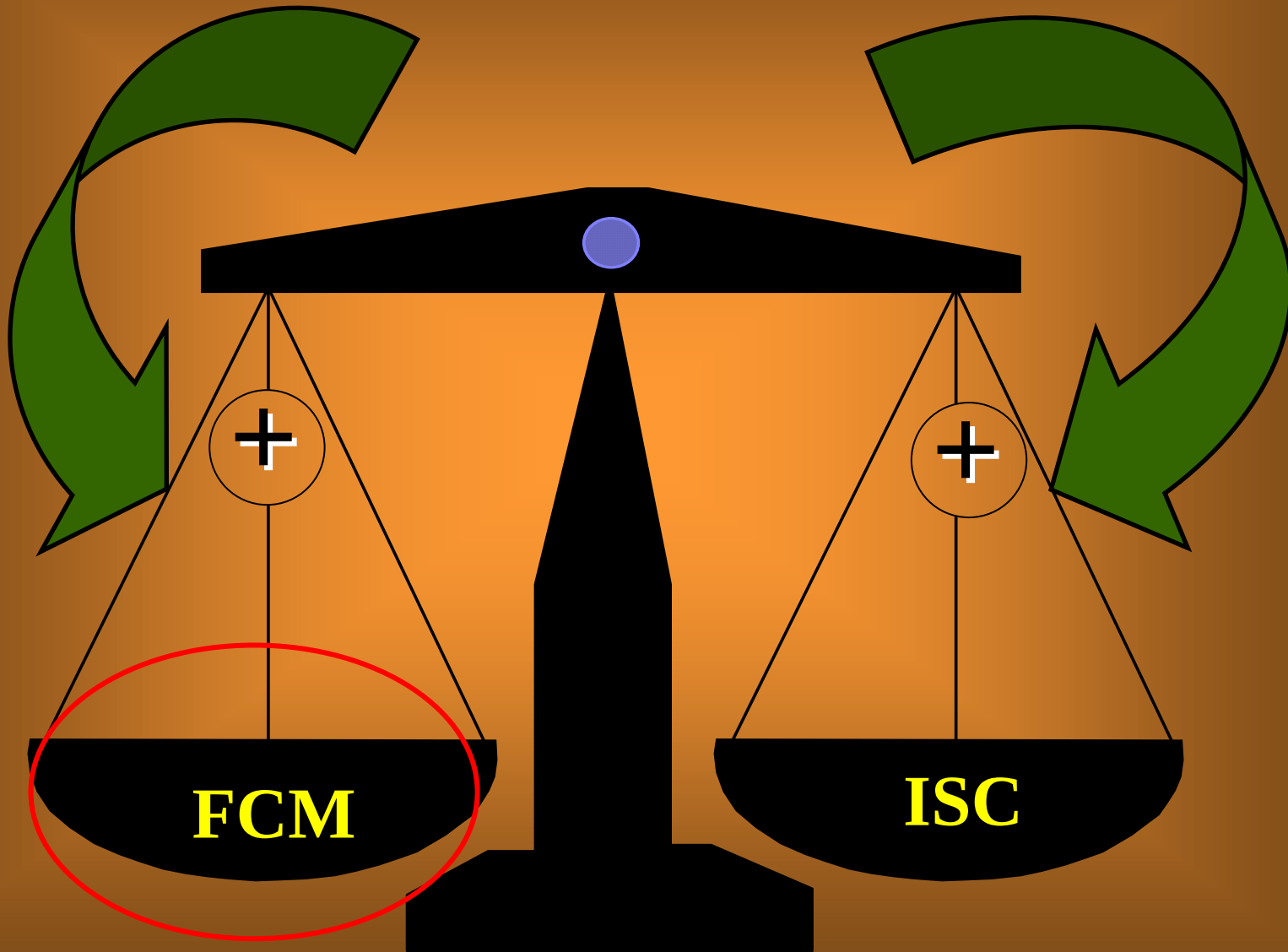
⁷ Wood JK, 1968

Iron uptake and distribution⁵



SEGURIDAD

Dosis Total de hierro







Ferric Carboximaltose





Margarita Angerosa

Ana Uceda

Mariana Feldman

Julieta Bolado

Gabriel Cao

Patricia Pagano

Pablo Piorno

Marta Costa



Hospital Alemán / Deutsches Hospital



Jorge E. Toblli.

Profesor Regular Titular de Medicina Interna

Universidad de Buenos Aires.

Profesor de Nefrología Universidad Católica Argentina.

Fellow of American Society of Nephrology

*Jefe Laboratorio de Medicina Experimental.
Hospital Alemán.*

Octubre 22, 2008

Valencia, España

Muchas gracias por vuestra atención!!!

Carboximaltosa de hierro

ferinject[®]

La nueva generación de hierro i.v.



ferinject[®]
ferric carboxymaltose