

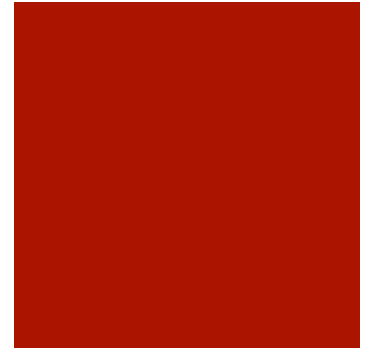


Iron Overload

Dick Wells

Outline

- A functional definition of iron overload
- Iron toxicity – from atoms to organs
- Treatment of iron overload

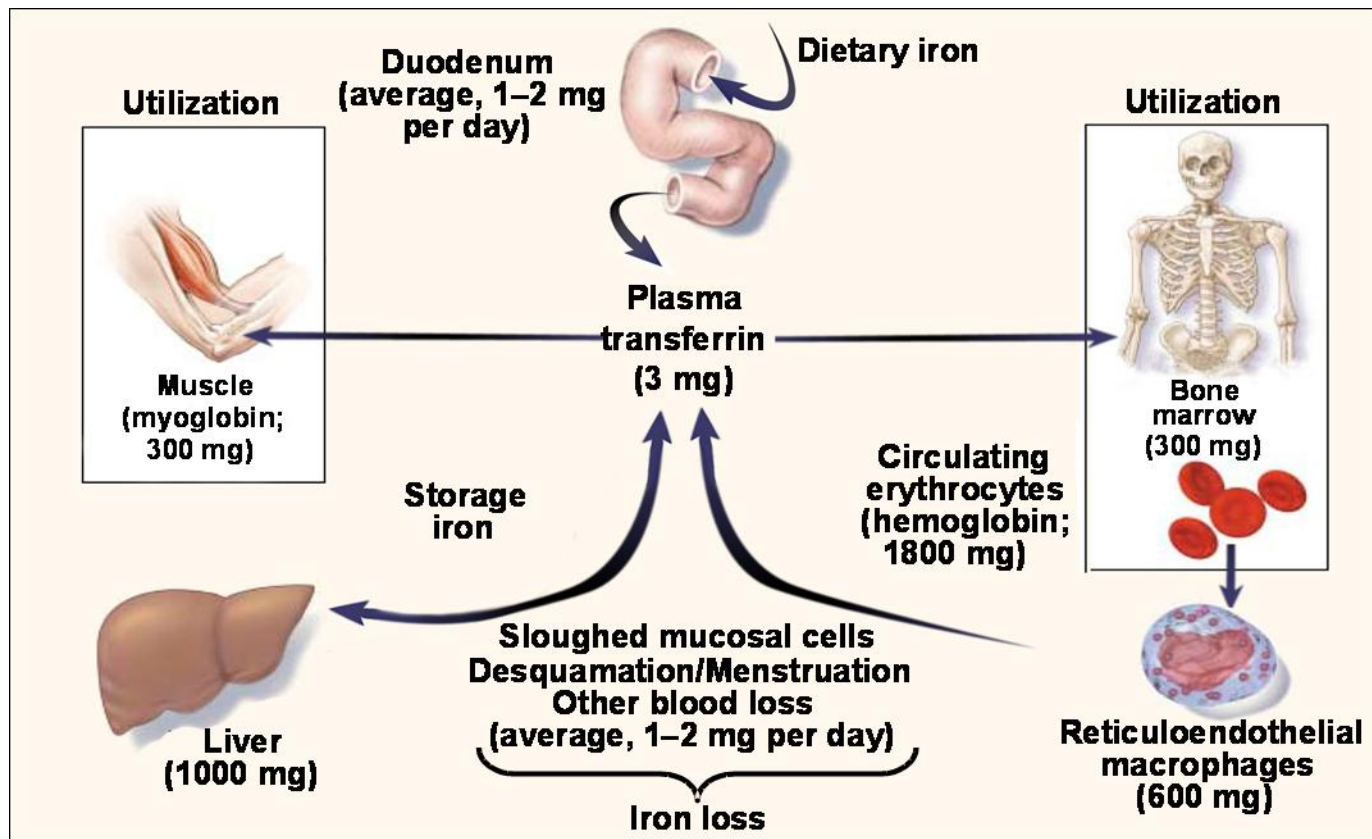




Am I overloaded yet?

A functional definition of iron overload

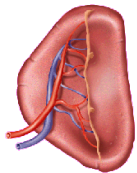
Body Iron Distribution



There is no physiologic mechanism to remove excess iron

The Iron Balance

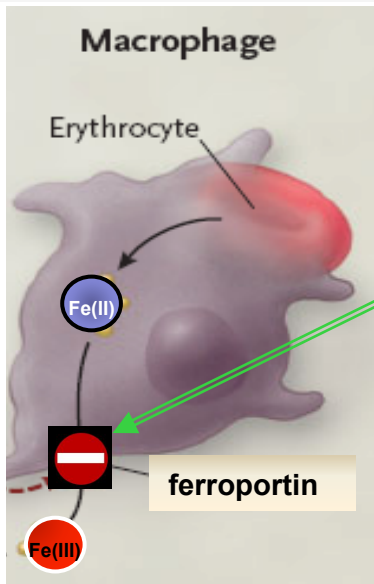
1 % blood cells digested/d
25 mg iron released



spleen

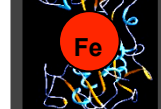
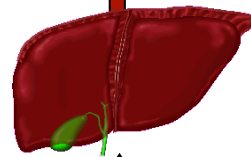
Macrophage

Erythrocyte



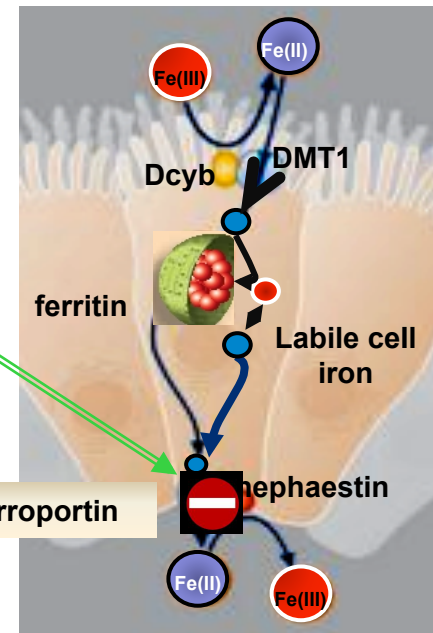
Hepcidin blocks
ferroportin, preventing
iron export into plasma

Hepcidin



Iron released into plasma is
incorporated into transferrin

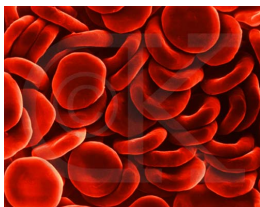
TfSat normally 0.2-0.55
(No non-Tf-bound iron)



duodenum

Absorption of iron
balances daily loss

Transferrin iron
is used for
production of
new blood cells



Transfusion therapy results in iron overload



- Normal iron influx through gut is 1–2 mg/day
- 1 blood unit contains 200–250 mg iron
- **Iron overload can occur after 10–20 transfusions**

Iron from
transfused
RBC

Iron from
increased
absorption

Free Iron:

The Essence of Iron Overload

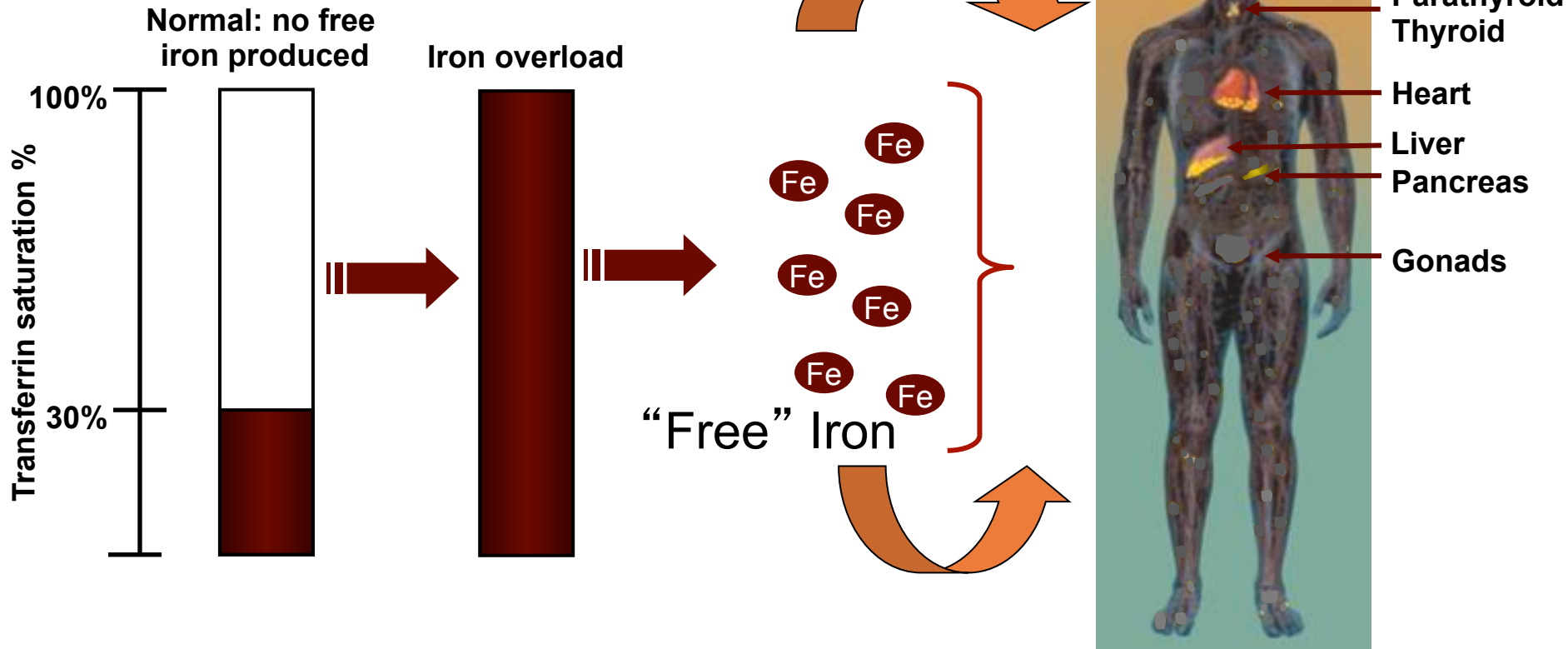


Saturation of transferrin due to

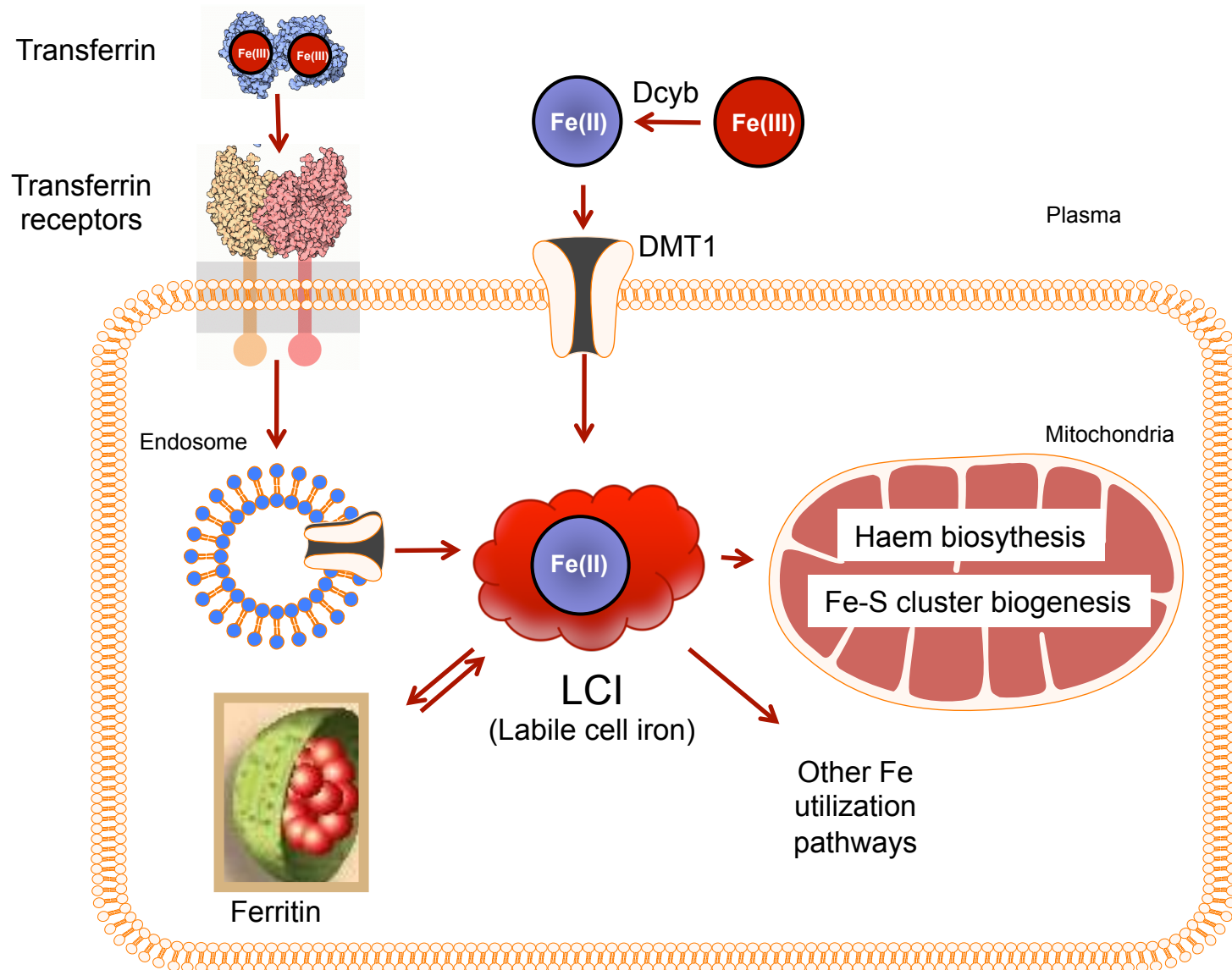
- Frequent blood transfusions, and
- Ineffective erythropoiesis leading to increased iron absorption

Subsequent
formation of free
iron in plasma

Uncontrolled iron
loading of organs



Free iron in our cells

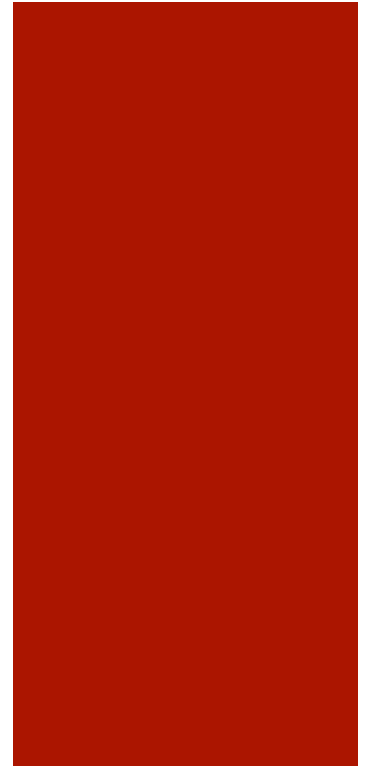


Summary

Iron Balance

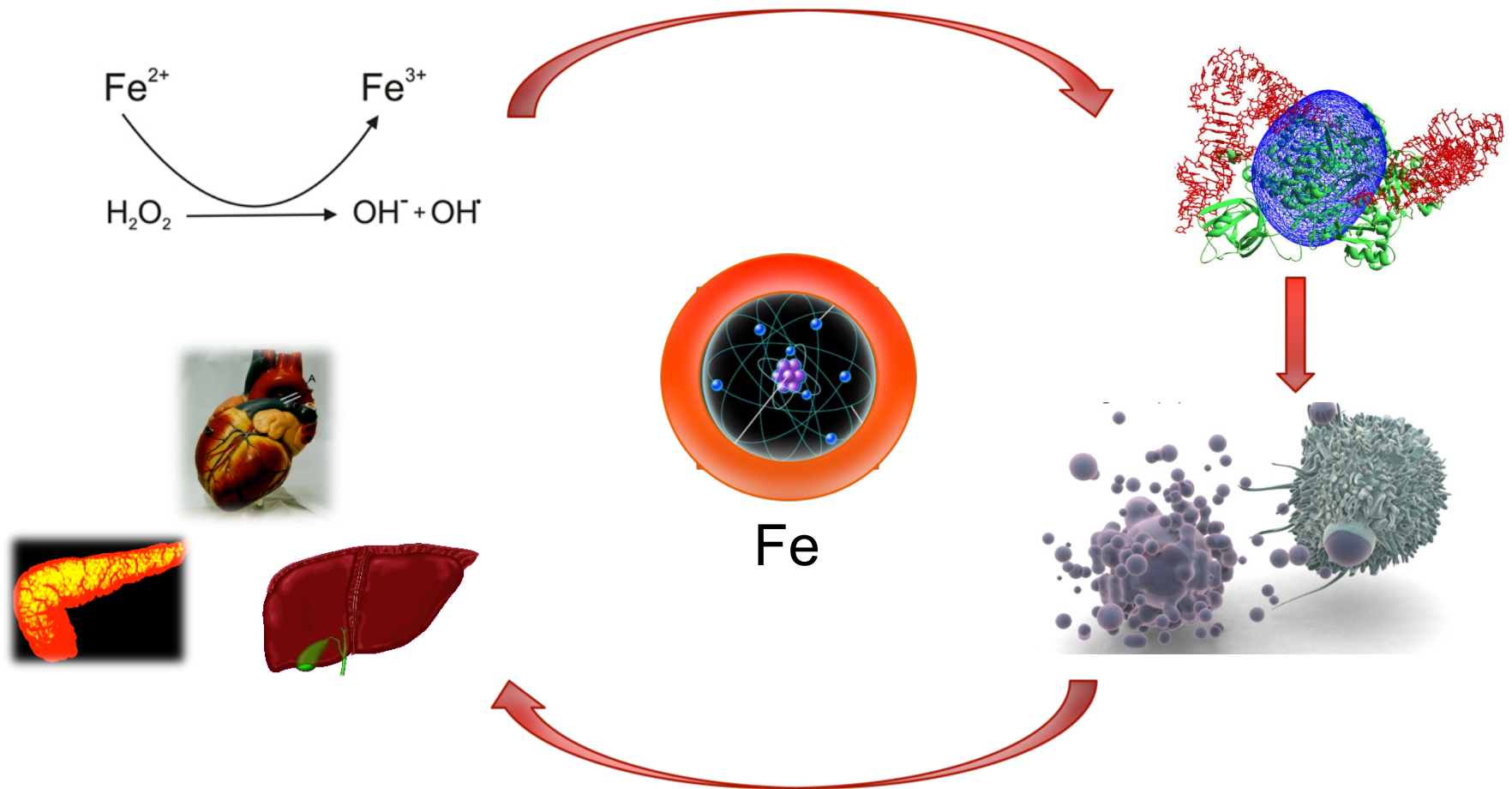
- There is no mechanism for excreting excess iron
- Iron normally is as
 - Haemoglobin and myoglobin
 - Transferrin (plasma)
 - Ferritin (intracellular)
- “Free” iron is rare
- When iron stores are high, free iron appears in the plasma and can get into cells

What problems
are caused by
free iron?



Iron supports dangerous radicals

Iron Toxicity: From Atoms to Organs

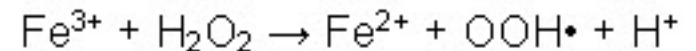
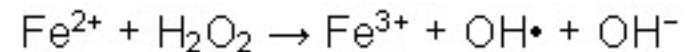


Iron and Free Radicals

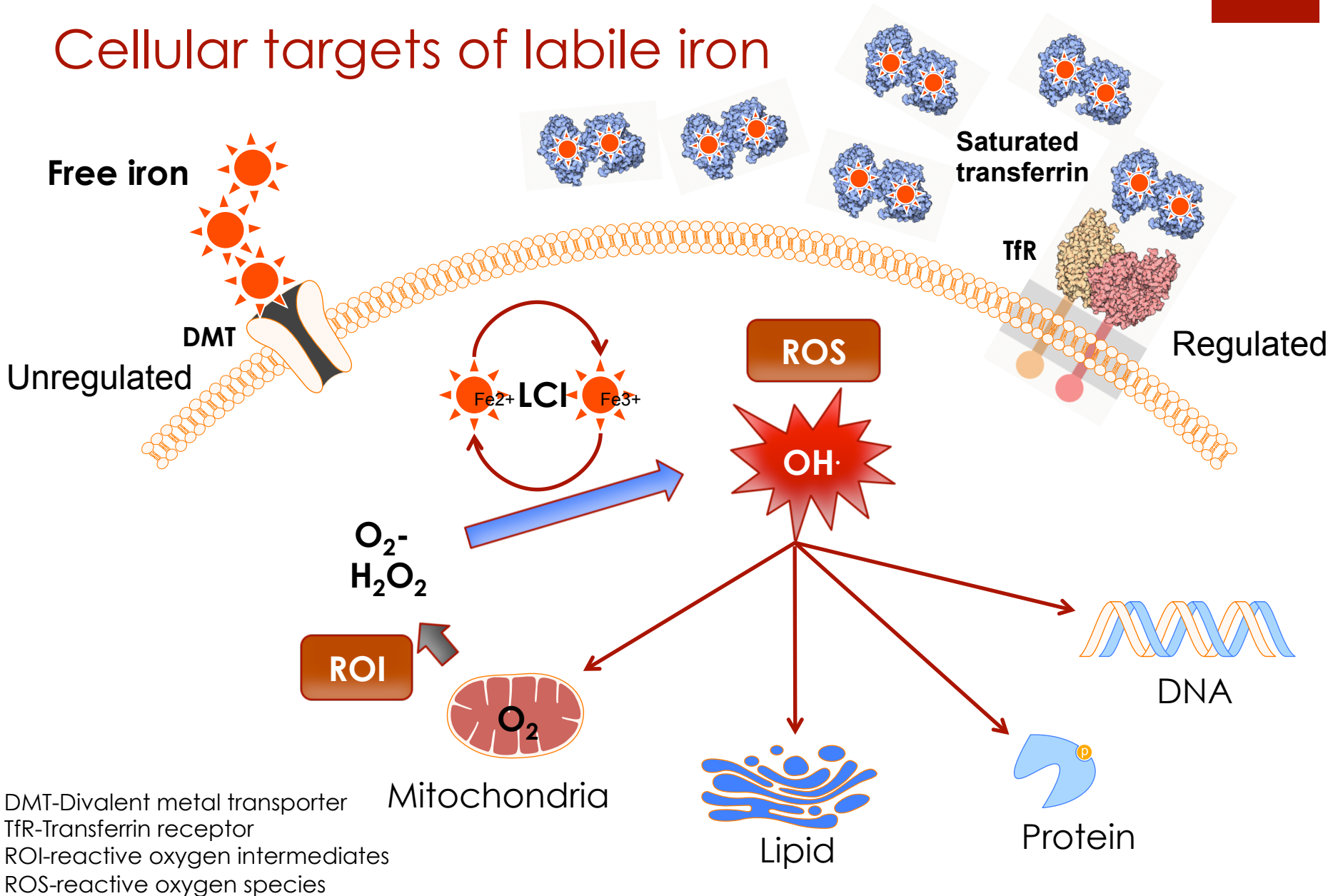
- Cell metabolism produces **hydrogen peroxide** (H_2O_2) as a biproduct
- H_2O_2 is not itself very toxic
 - Reactive oxygen intermediate (ROI)
- **Free iron** reacts with H_2O_2 to form highly toxic free radicals
 - Reactive oxygen species (ROS)

H_2O_2 Reactions

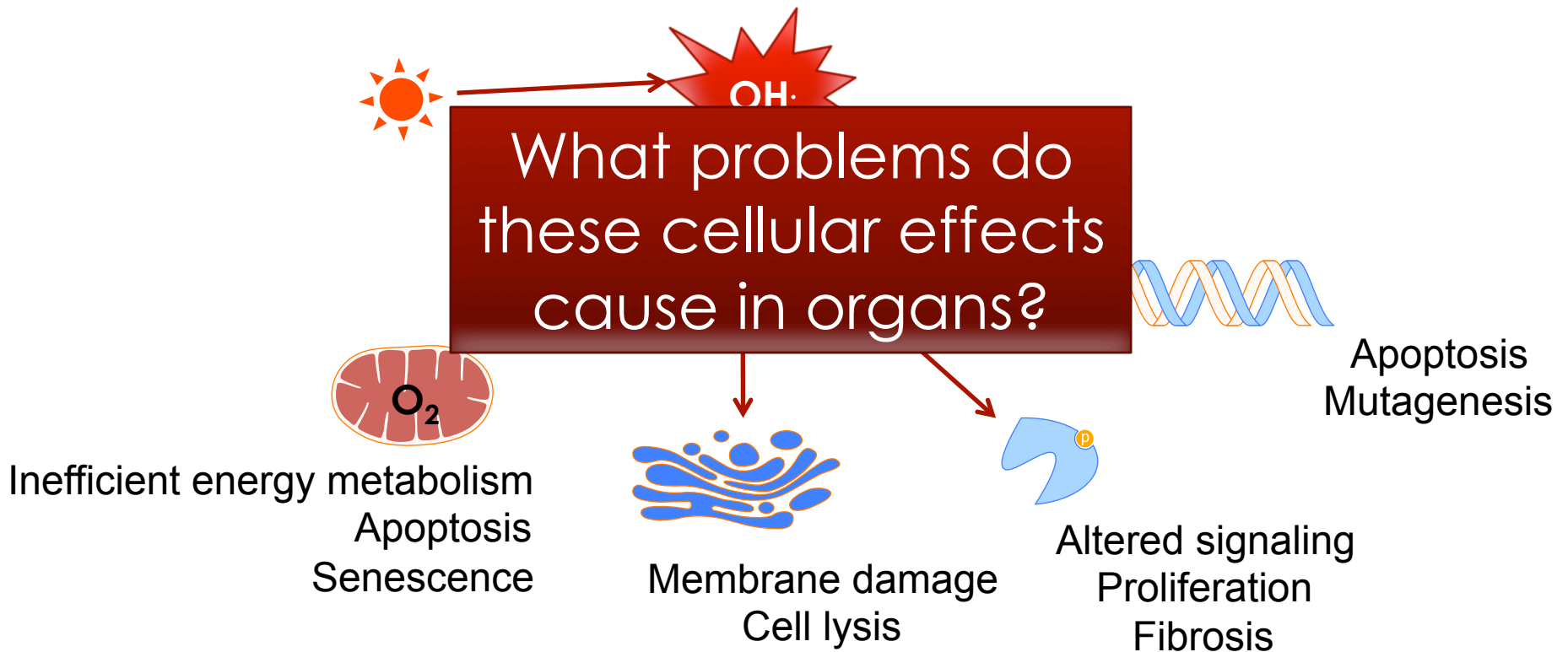
Fenton Reaction



Cellular targets of labile iron

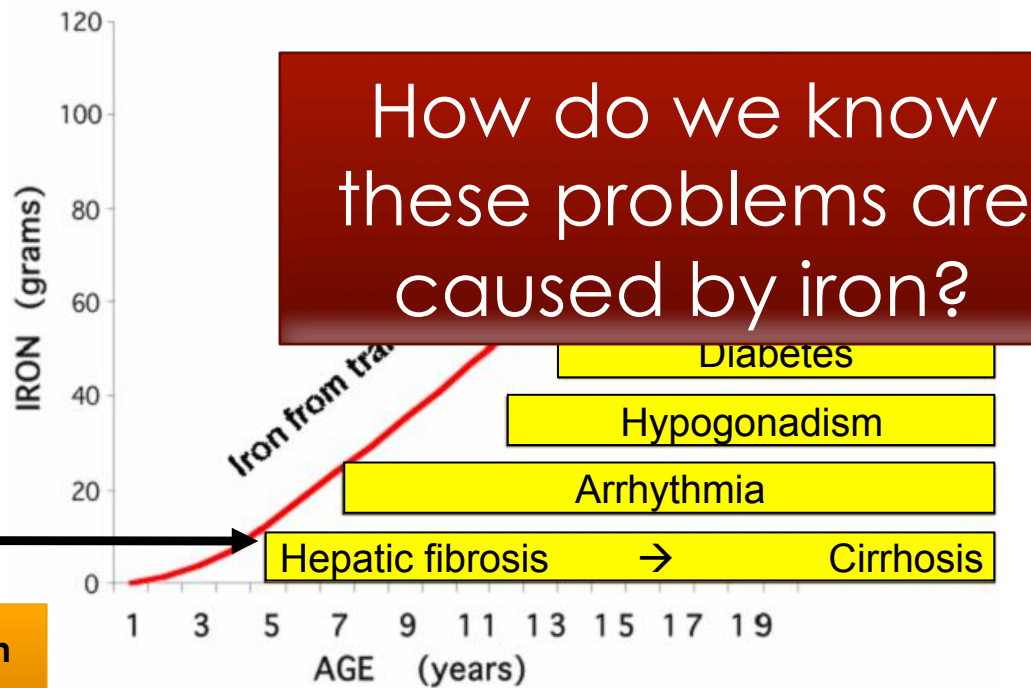


Cellular Effects of Free Iron

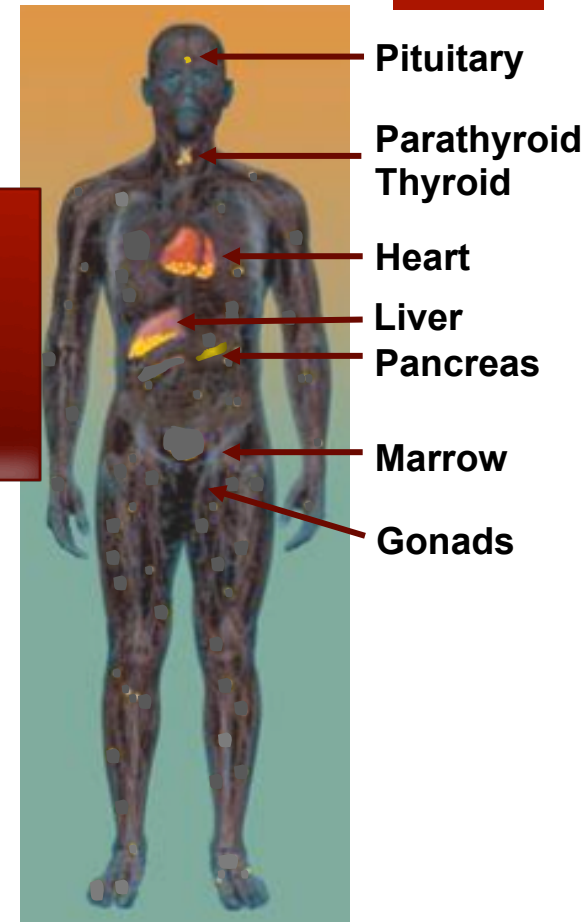


Iron Overload

Morbidity and Mortality

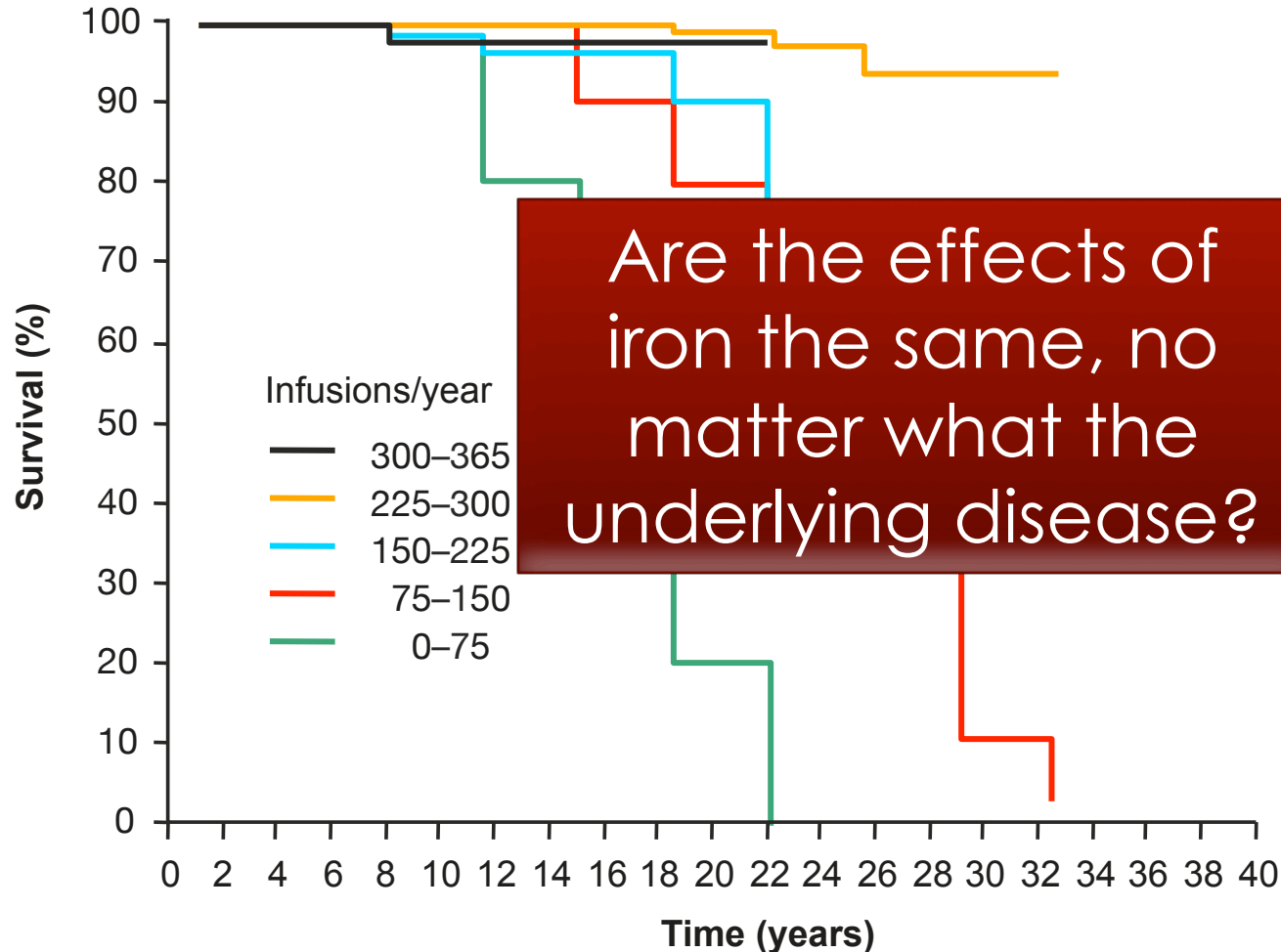


Uncontrolled iron loading of organs



Iron Overload

Effect of iron chelation



Are the effects of iron the same, no matter what the underlying disease?

ation = survival

Comparison of organ dysfunction in thalassaemia major and sickle cell disease

Characteristic	Thalassaemia major	Sickle cell disease	p value
Age	18.4 ± 2.1	14.8 ± 1.0	NS
Duration of transfusion	12 years	6 years	
Serum ferritin (µg/L)	2,122 ± 289	2,916 ± 233	0.04
Liver iron (mg Fe/g dry wt)	14.8 ± 2.2	14.3 ± 1.4	NS
Transfusions (n/year)	12.2 ± 1.8	6.0 ± 0.6	0.002
Cardiac disease	20%	0%	0.002
Gonadal failure	33%	0%	< 0.001
Growth delay	27%	9%	NS
Hypothyroidism	7%	0%	NS
Viral hepatitis	33%	2%	< 0.001
Fibrosis	81%	29%	0.02

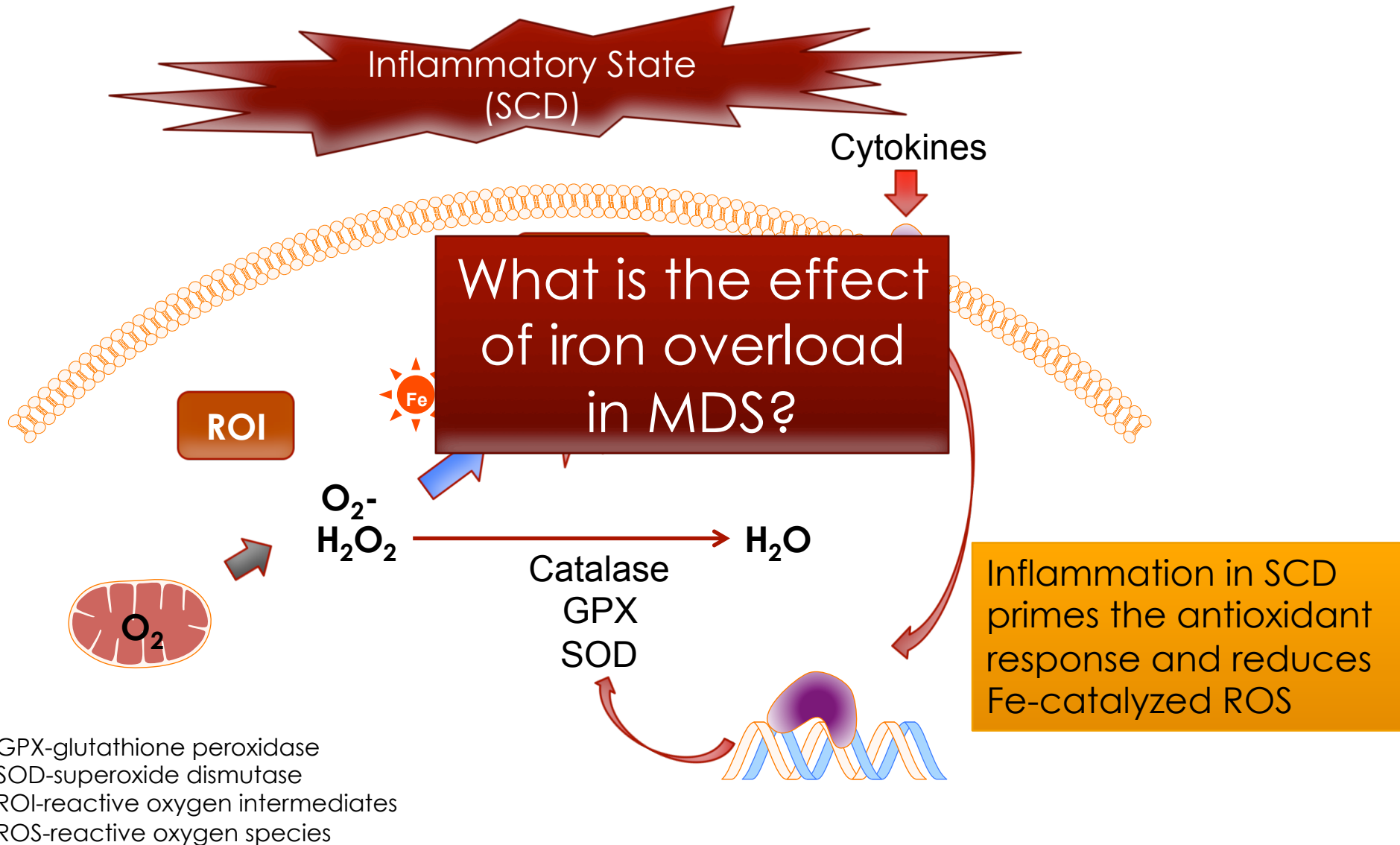
Despite similar Fe measures, SCD patients have fewer end-organ complications

Factors

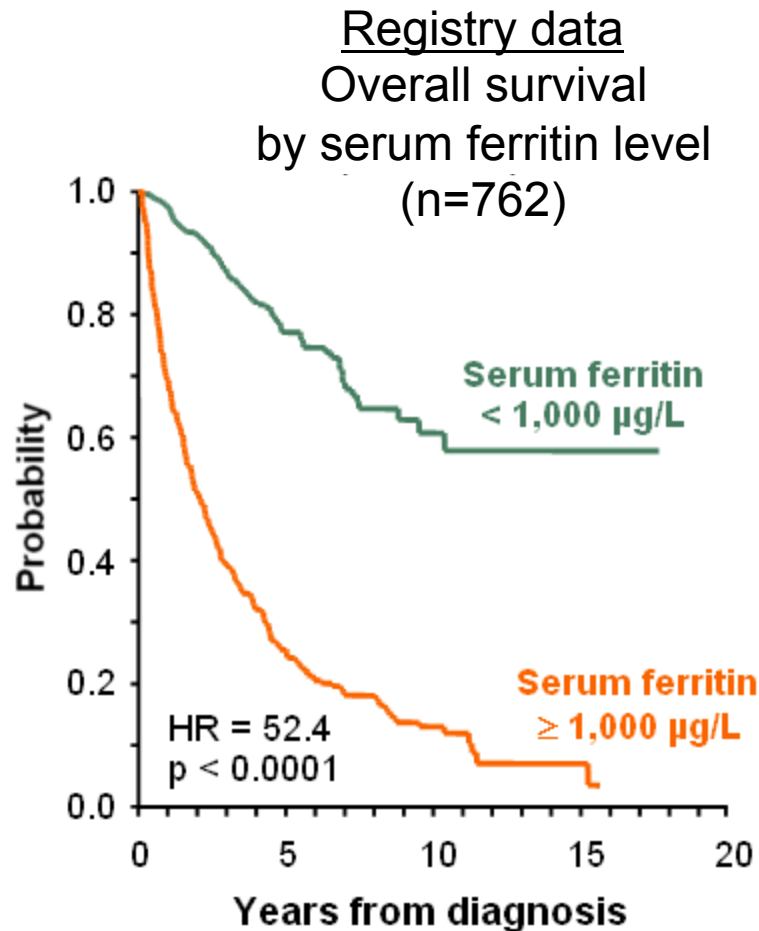
1. Duration of transfusion
2. TM vs. SCD

Why should this be?

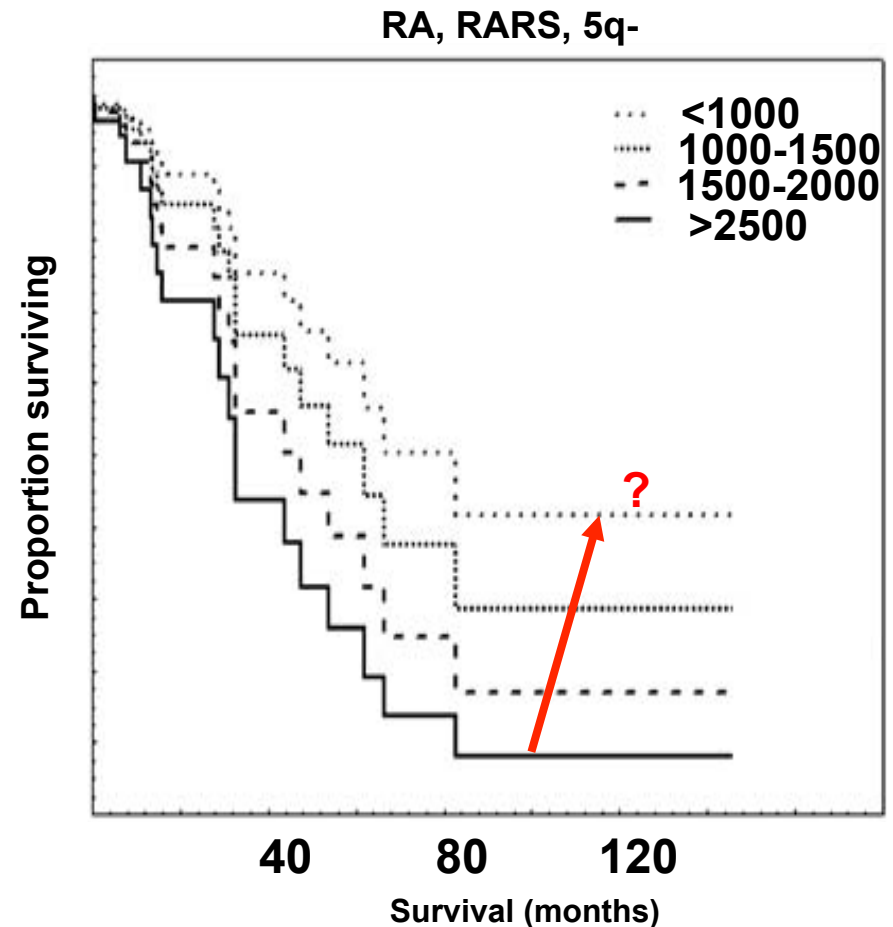
Inflammation Primes the Antioxidant Response



Does iron overload contribute to mortality in MDS?



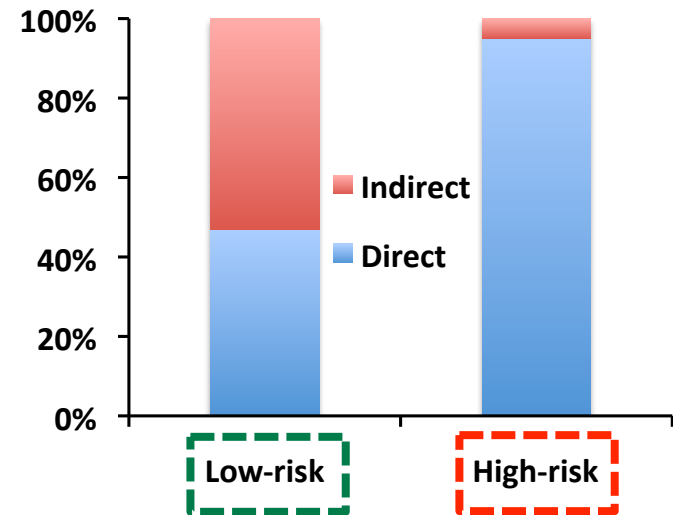
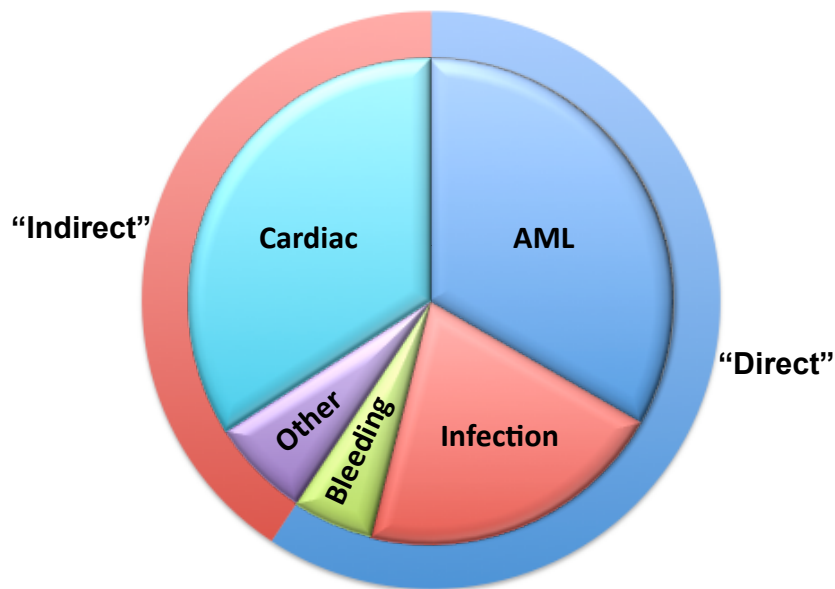
Sanz et al., Blood 2008 112 (abstract 640)



Malcovati et al., Haematologica, 2007

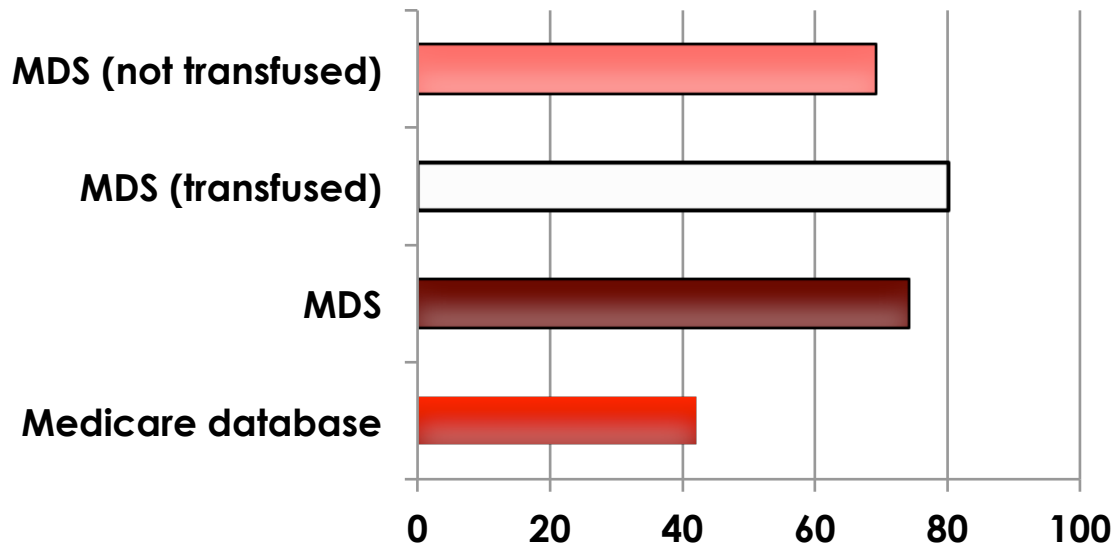
MDS Classification:

Causes of death in MDS



The goals of therapy are different in low-risk and high risk MDS

The heart in MDS



Rates of heart
disease in US
medicare patients

“MDS cardiomyopathy”: chronic anaemia + iron overload + the aged myocardium

Cardiac iron in patients with MDS

	N	Cardiac iron	Units transfused	Serum ferritin (µg/L)	Chelated
Jensen et al. 2003	12	9	44–254	1,740–8,715	0
Chacko et al.					6
Konen et al.					7
Di Tucci et al.					2
Pascal et al.					54

HOWEVER: There is no obvious relationship between cardiac iron and heart problems in MDS

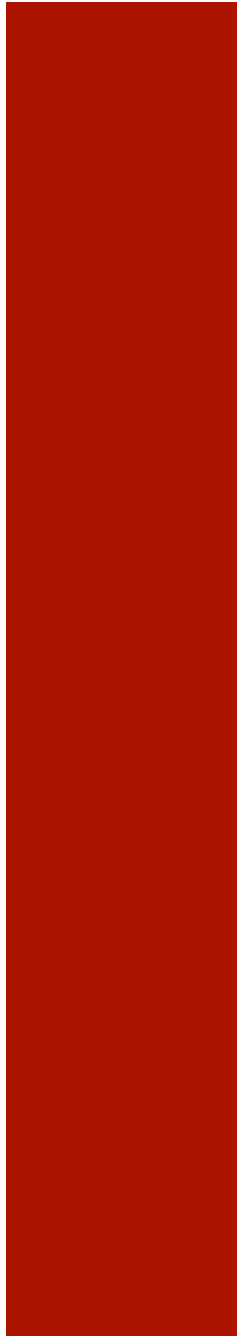
Di Tucci AA, et al. Haematologica. 2008;93:1385-8.

Chacko J, et al. Br J Haematol. 2007;138:587-93.

Jensen PD, et al. Blood. 2003;101:4632-9.

Konen E, et al. Am J Hematol. 2007;82:1013-6.

Should iron chelation
be given in MDS?



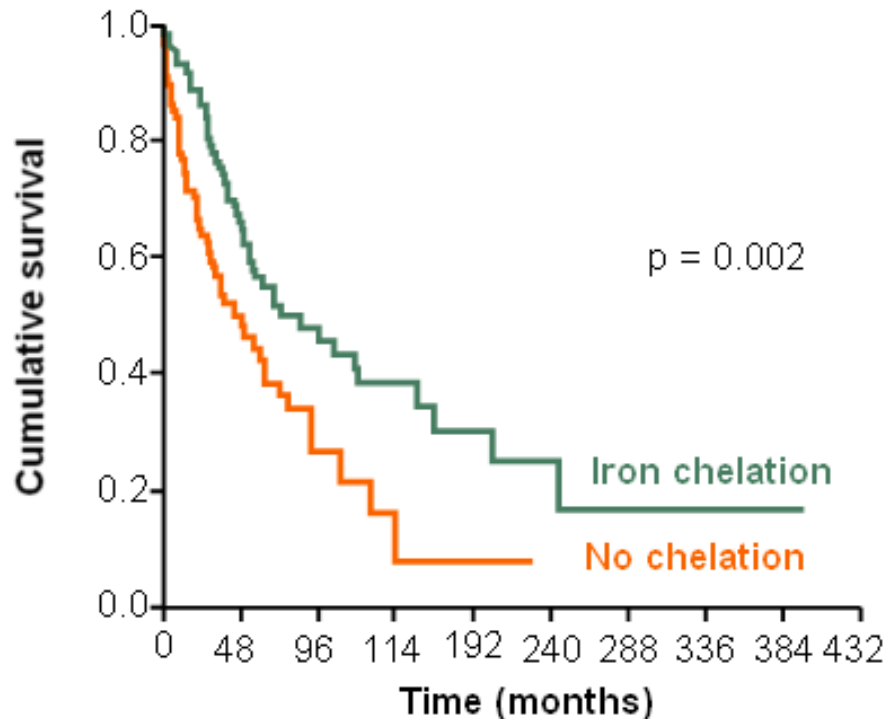
Ferroscepticism



TELESTO

- DeLoughery TG. Iron: The fifth horseman of the apocalypse? Am J Hematol. 2009
- Tefferi A, Stone RM. Iron chelation therapy in myelodysplastic syndrome—Cui bono? Leukemia. 2009

Iron chelation and survival in MDS



Fox Blood 2009; 114 (abstract 1747)

Leitch (Clin Leuk Res 2008)

- 178 pt
- OS in ICT >160 mo
- OS in non-ICT = 40 mo
- $p < 0.03$

□ **Rose** (ASH 2007)

- 170 pt
- OS 115 vs. 51 mo
- $p < 0.0001$

■ **Fox** (ASH 2009)

- 186 pt (matched pairs)
- OS in ICT = 75 mo
- OS in non-ICT = 49 mo
- $P = 0.002$



Available online at www.sciencedirect.com



Leukemia Research 32 (2008) 1338–1353

**Leukemia
Research**

www.elsevier.com/locate/leukres

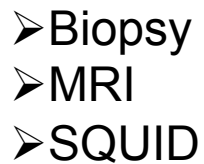
Invited editorial

Iron overload in myelodysplastic syndromes: A Canadian consensus guideline

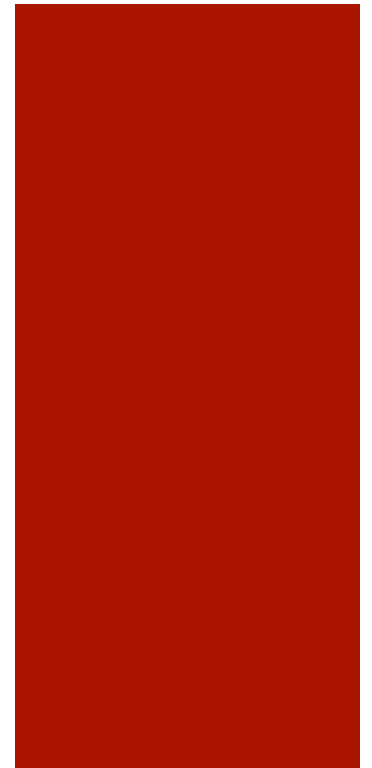
Richard A. Wells^{a,*}, Brian Leber^b, Rena Buckstein^a, Jeffrey H. Lipton^c,
Wanda Hasegawa^d, Kuljit Grewal^e, Karen Yee^c, Harold J. Olney^f,
Loree Larratt^g, Linda Vickars^h, Alan Tinmouthⁱ

- Lower-risk MDS if life exp > 1 y
- Higher-risk MDS if BMT candidate
- Either desferal or exjade as first line
- Target ferritin < 1000 ng/mL

1999, 2000, 2001, 2002, 2003, 2004, 2005, 2006, 2007, 2008, 2009, 2010, 2011, 2012, 2013, 2014, 2015, 2016, 2017, 2018, 2019, 2020, 2021, 2022, 2023, 2024, 2025, 2026, 2027, 2028, 2029, 2030, 2031, 2032, 2033, 2034, 2035, 2036, 2037, 2038, 2039, 2040, 2041, 2042, 2043, 2044, 2045, 2046, 2047, 2048, 2049, 2050, 2051, 2052, 2053, 2054, 2055, 2056, 2057, 2058, 2059, 2060, 2061, 2062, 2063, 2064, 2065, 2066, 2067, 2068, 2069, 2070, 2071, 2072, 2073, 2074, 2075, 2076, 2077, 2078, 2079, 2080, 2081, 2082, 2083, 2084, 2085, 2086, 2087, 2088, 2089, 2090, 2091, 2092, 2093, 2094, 2095, 2096, 2097, 2098, 2099, 2100, 2101, 2102, 2103, 2104, 2105, 2106, 2107, 2108, 2109, 2110, 2111, 2112, 2113, 2114, 2115, 2116, 2117, 2118, 2119, 2120, 2121, 2122, 2123, 2124, 2125, 2126, 2127, 2128, 2129, 2130, 2131, 2132, 2133, 2134, 2135, 2136, 2137, 2138, 2139, 2140, 2141, 2142, 2143, 2144, 2145, 2146, 2147, 2148, 2149, 2150, 2151, 2152, 2153, 2154, 2155, 2156, 2157, 2158, 2159, 2160, 2161, 2162, 2163, 2164, 2165, 2166, 2167, 2168, 2169, 2170, 2171, 2172, 2173, 2174, 2175, 2176, 2177, 2178, 2179, 2180, 2181, 2182, 2183, 2184, 2185, 2186, 2187, 2188, 2189, 2190, 2191, 2192, 2193, 2194, 2195, 2196, 2197, 2198, 2199, 2200, 2201, 2202, 2203, 2204, 2205, 2206, 2207, 2208, 2209, 2210, 2211, 2212, 2213, 2214, 2215, 2216, 2217, 2218, 2219, 2220, 2221, 2222, 2223, 2224, 2225, 2226, 2227, 2228, 2229, 2230, 2231, 2232, 2233, 2234, 2235, 2236, 2237, 2238, 2239, 2240, 2241, 2242, 2243, 2244, 2245, 2246, 2247, 2248, 2249, 2250, 2251, 2252, 2253, 2254, 2255, 2256, 2257, 2258, 2259, 2260, 2261, 2262, 2263, 2264, 2265, 2266, 2267, 2268, 2269, 2270, 2271, 2272, 2273, 2274, 2275, 2276, 2277, 2278, 2279, 2280, 2281, 2282, 2283, 2284, 2285, 2286, 2287, 2288, 2289, 2290, 2291, 2292, 2293, 2294, 2295, 2296, 2297, 2298, 2299, 2300, 2301, 2302, 2303, 2304, 2305, 2306, 2307, 2308, 2309, 2310, 2311, 2312, 2313, 2314, 2315, 2316, 2317, 2318, 2319, 2320, 2321, 2322, 2323, 2324, 2325, 2326, 2327, 2328, 2329, 2330, 2331, 2332, 2333, 2334, 2335, 2336, 2337, 2338, 2339, 2340, 2341, 2342, 2343, 2344, 2345, 2346, 2347, 2348, 2349, 2350, 2351, 2352, 2353, 2354, 2355, 2356, 2357, 2358, 2359, 2360, 2361, 2362, 2363, 2364, 2365, 2366, 2367, 2368, 2369, 2370, 2371, 2372, 2373, 2374, 2375, 2376, 2377, 2378, 2379, 2380, 2381, 2382, 2383, 2384, 2385, 2386, 2387, 2388, 2389, 2390, 2391, 2392, 2393, 2394, 2395, 2396, 2397, 2398, 2399, 2400, 2401, 2402, 2403, 2404, 2405, 2406, 2407, 2408, 2409, 2410, 2411, 2412, 2413, 2414, 2415, 2416, 2417, 2418, 2419, 2420, 2421, 2422, 2423, 2424, 2425, 2426, 2427, 2428, 2429, 2430, 2431, 2432, 2433, 2434, 2435, 2436, 2437, 2438, 2439, 2440, 2441, 2442, 2443, 2444, 2445, 2446, 2447, 2448, 2449, 2450, 2451, 2452, 2453, 2454, 2455, 2456, 2457, 2458, 2459, 2460, 2461, 2462, 2463, 2464, 2465, 2466, 2467, 2468, 2469, 2470, 2471, 2472, 2473, 2474, 2475, 2476, 2477, 2478, 2479, 2480, 2481, 2482, 2483, 2484, 2485, 2486, 2487, 2488, 2489, 2490, 2491, 2492, 2493, 2494, 2495, 2496, 2497, 2498, 2499, 2500, 2501, 2502, 2503, 2504, 2505, 2506, 2507, 2508, 2509, 2510, 2511, 2512, 2513, 2514, 2515, 2516, 2517, 2518, 2519, 2520, 2521, 2522, 2523, 2524, 2525, 2526, 2527, 2528, 2529, 2530, 2531, 2532, 2533, 2534, 2535, 2536, 2537, 2538, 2539, 2540, 2541, 2542, 2543, 2544, 2545, 2546, 2547, 2548, 2549, 2550, 2551, 2552, 2553, 2554, 2555, 2556, 2557, 2558, 2559, 2560, 2561, 2562, 2563, 2564, 2565, 2566, 2567, 2568, 2569, 2570, 2571, 2572, 2573, 2574, 2575, 2576, 2577, 2578, 2579, 2580, 2581, 2582, 2583, 2584, 2585, 2586, 2587, 2588, 2589, 2590, 2591, 2592, 2593, 2594, 2595, 2596, 2597, 2598, 2599, 2600, 2601, 2602, 2603, 2604, 2605, 2606, 2607, 2608, 2609, 2610, 2611, 2612, 2613, 2614, 2615, 2616, 2617, 2618, 2619, 2620, 2621, 2622, 2623, 2624, 2625, 2626, 2627, 2628, 2629, 2630, 2631, 2632, 2633, 2634, 2635, 2636, 2637, 2638, 2639, 2640, 2641, 2642, 2643, 2644, 2645, 2646, 2647, 2648, 2649, 2650, 2651, 2652, 2653, 2654, 2655, 2656, 2657, 2658, 2659, 2660, 2661, 2662, 2663, 2664, 2665, 2666, 2667, 2668, 2669, 2670, 2671, 2672, 2673, 2674, 2675, 2676, 2677, 2678, 2679, 2680, 26



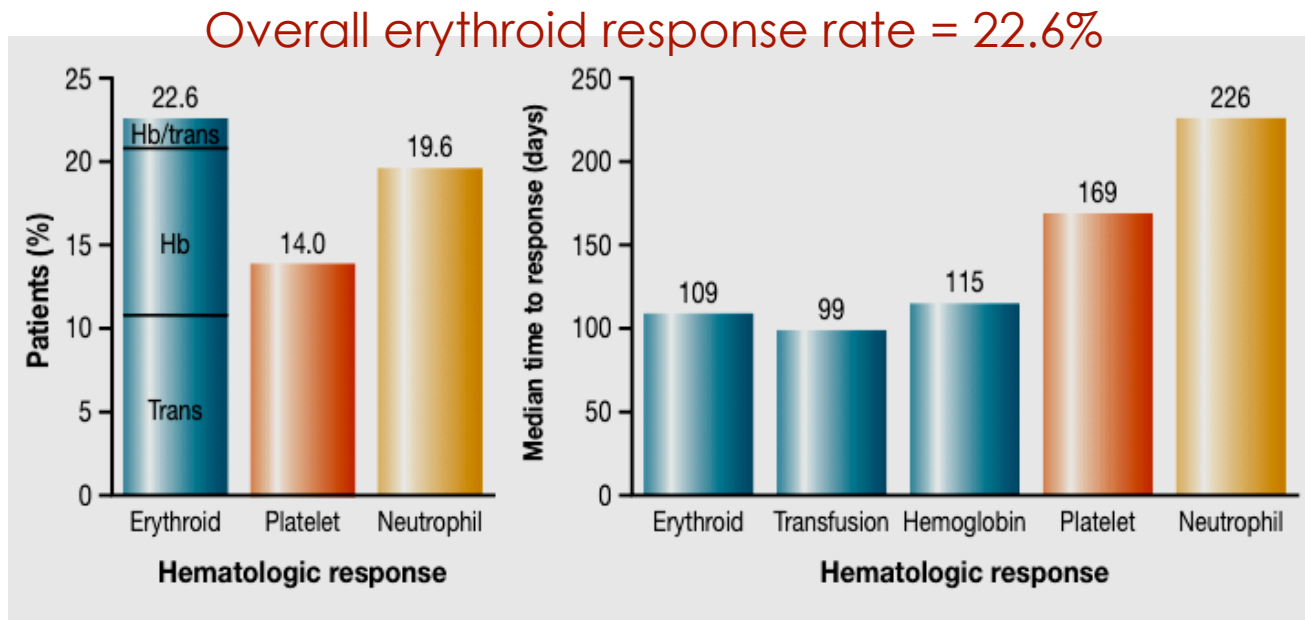
Serum ferritin



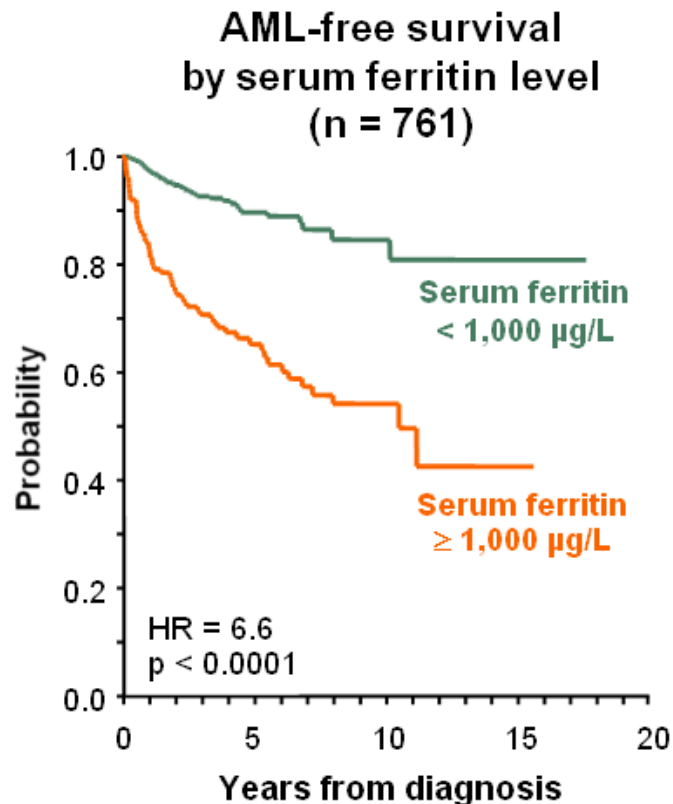
Unexpected effects of iron in MDS

Iron and Haematopoiesis in MDS

Analysis of trial data to study haematological responses in the MDS patients in EPIC (N=341)

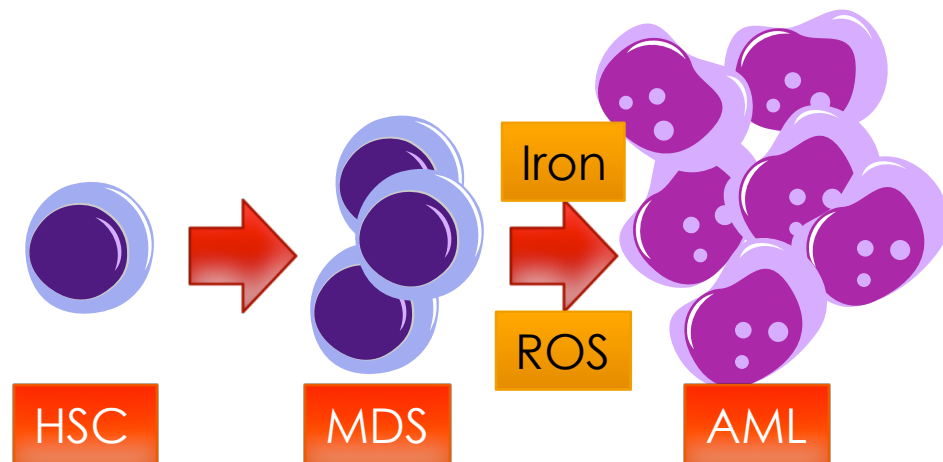


Iron and AML in MDS



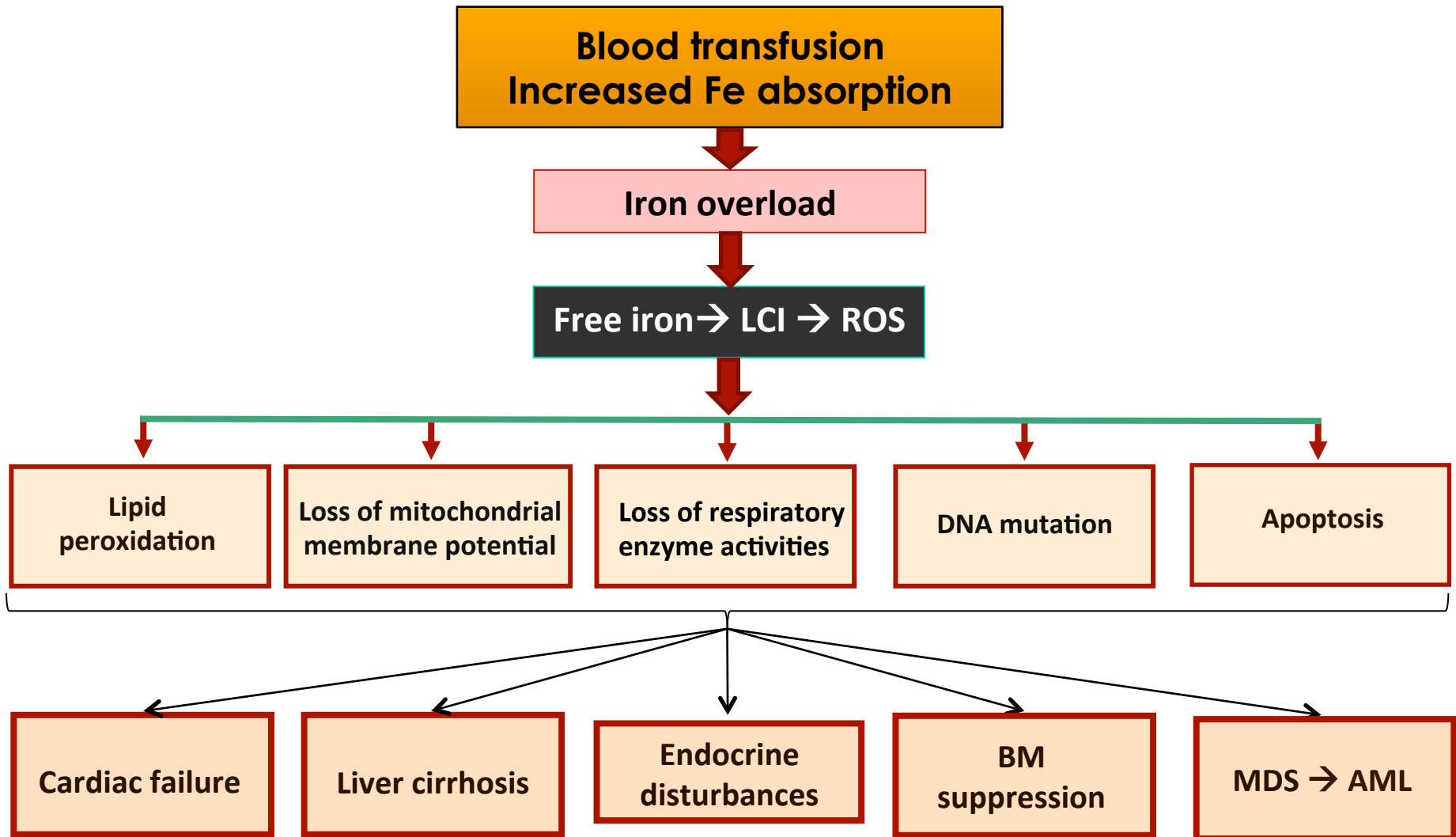
Sanz G, et al. Blood. 2008;112:[abstract 640].

How could IOL promote development of AML?



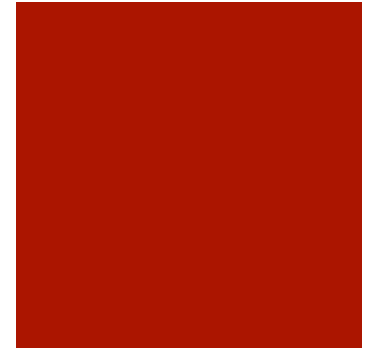
- Fe causes DNA damage in vitro
- Fe accelerates development of AML in mouse model

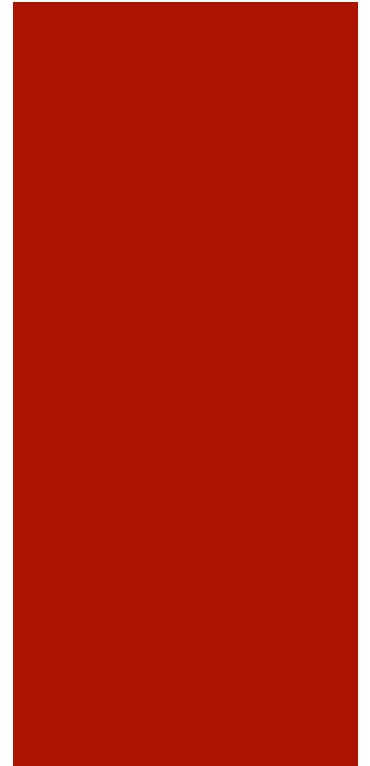
Summary Iron Toxicity



Conclusions

- Iron is both essential and toxic -- balance is maintained by an intricate network of proteins
- Chronic RBC transfusion overwhelms this network, resulting in the presence of “free iron”, which causes cell and organ damage via generation of free radicals
- Fe toxicity leaves different footprints in TM, SCD, and MDS
- Chelation therapy can prevent chronic Fe toxicity but must be monitored by indirect (ferritin) or direct (LIC) means





Any questions?