ROLE OF SODIUM/POTASSIUM ATPase INHIBITORS IN HYPERTENSIVE AND CARDIOVASCULAR DISORDERS AND IN KIDNEY DISEASE PROGRESSION

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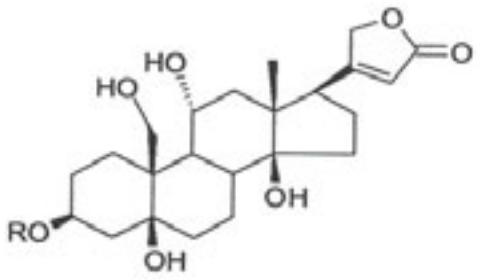
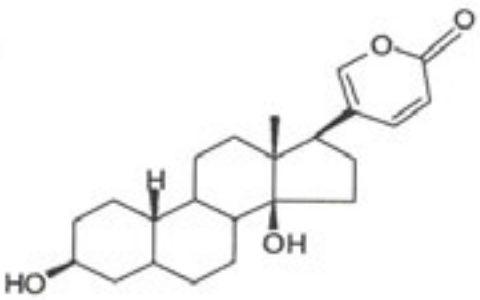
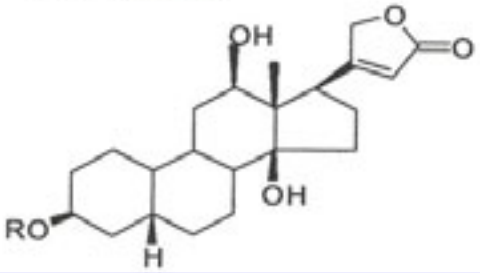


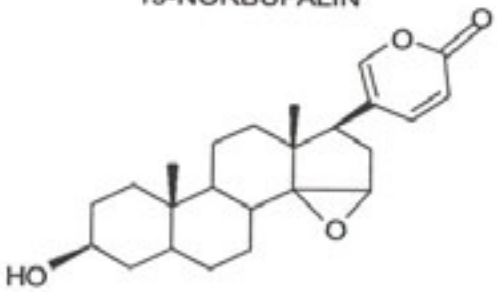
OUABAIN
R = Rhamnose



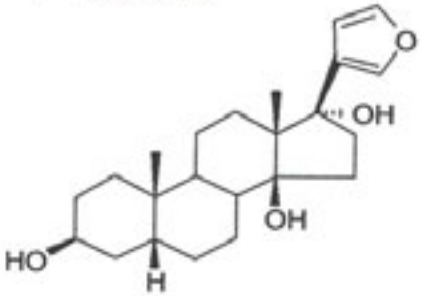
19-NORBUFALIN



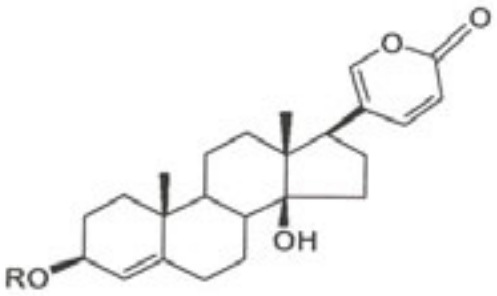
DIGOXIN LIKE INHIBITOR
R = Digitoxose



MARINOBUFAGENIN



PST 2238
Ouabain antagonist



PROSCILLARIDIN LIKE INHIBITOR
R = Rhamnose

Endogenous Cardiac Glycosides.

Cardenolides (left column) Bufodienolides (right column). H Kost, 2001

CARDIAC GLYCOSIDES

Characteristics

- Act as inhibitors of Na^+/K^+ ATPase
- Transport enzyme inhibition results in natriuresis
- Are vasoconstrictive, often causing hypertension
- Act as cardiac intropes

CARDIAC GLYCOSIDES

Differences

1. Structural

   a. Cardenolides: unsaturated 5-membered lactone ring

   b. Bufodienolides: doubly unsaturated 6-membered lactone ring

2. Activity

   a. Cardenolides: predilection for the α-2 and α-3 isoforms of Na^+/K^+ ATPase

   b. Bufodienolides: act primarily on the α-1 isoform (predominant form in the kidney)

3. The bufodienolides may be more important in the pathogenesis of disease states (e.g., preeclampsia, kidney fibrosis)

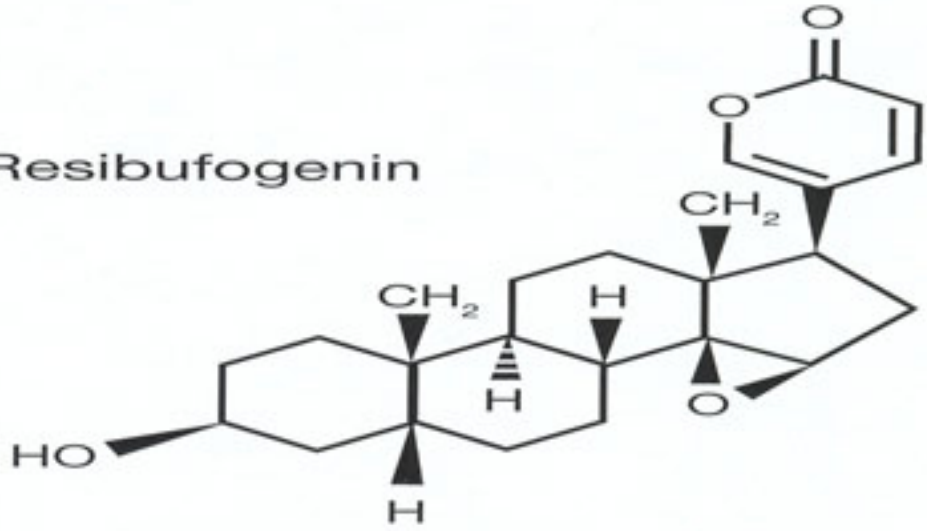
Blood Levels of Marinobufagenin

Group	Marinobufagenin (nMol/L)
Healthy individuals (n = 38)	0.225 ± 0.045
Chronic renal failure (n = 24	16.6[a] ± 5.3
Primary aldosteronism (n = 5)	13.5[a] ± 12.9
Congestive heart failure (n = 7)	1.69[a] ± 1.29
Essential hypertension (n = 27)	1.74[a] ± 0.67

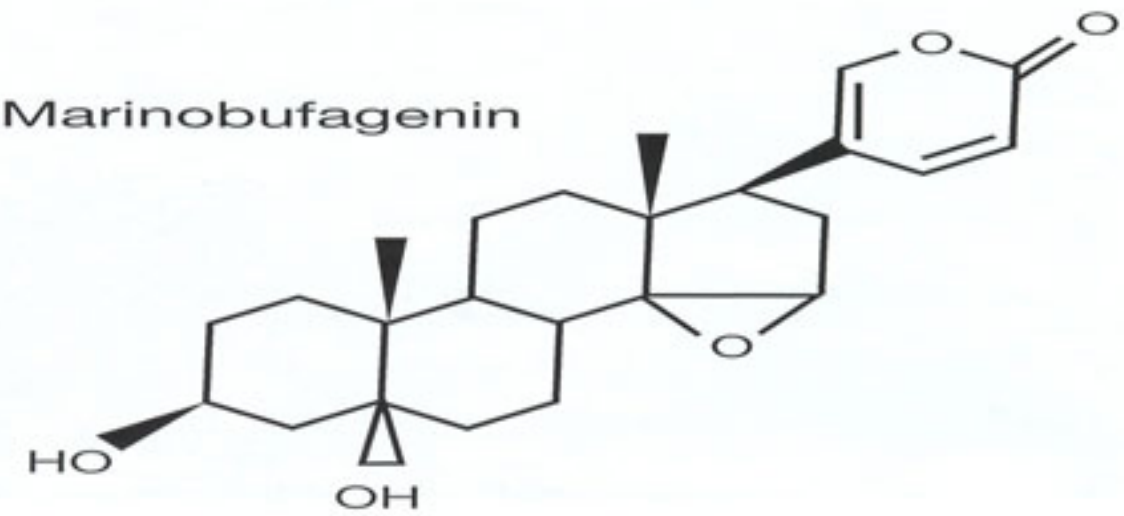
Modified and reproduced from Gonick et al,
Clin Exp Hypertens, **20**: 617-627, 1998

[a]$p < 0.05$ versus healthy controls.

Resibufogenin



Marinobufagenin



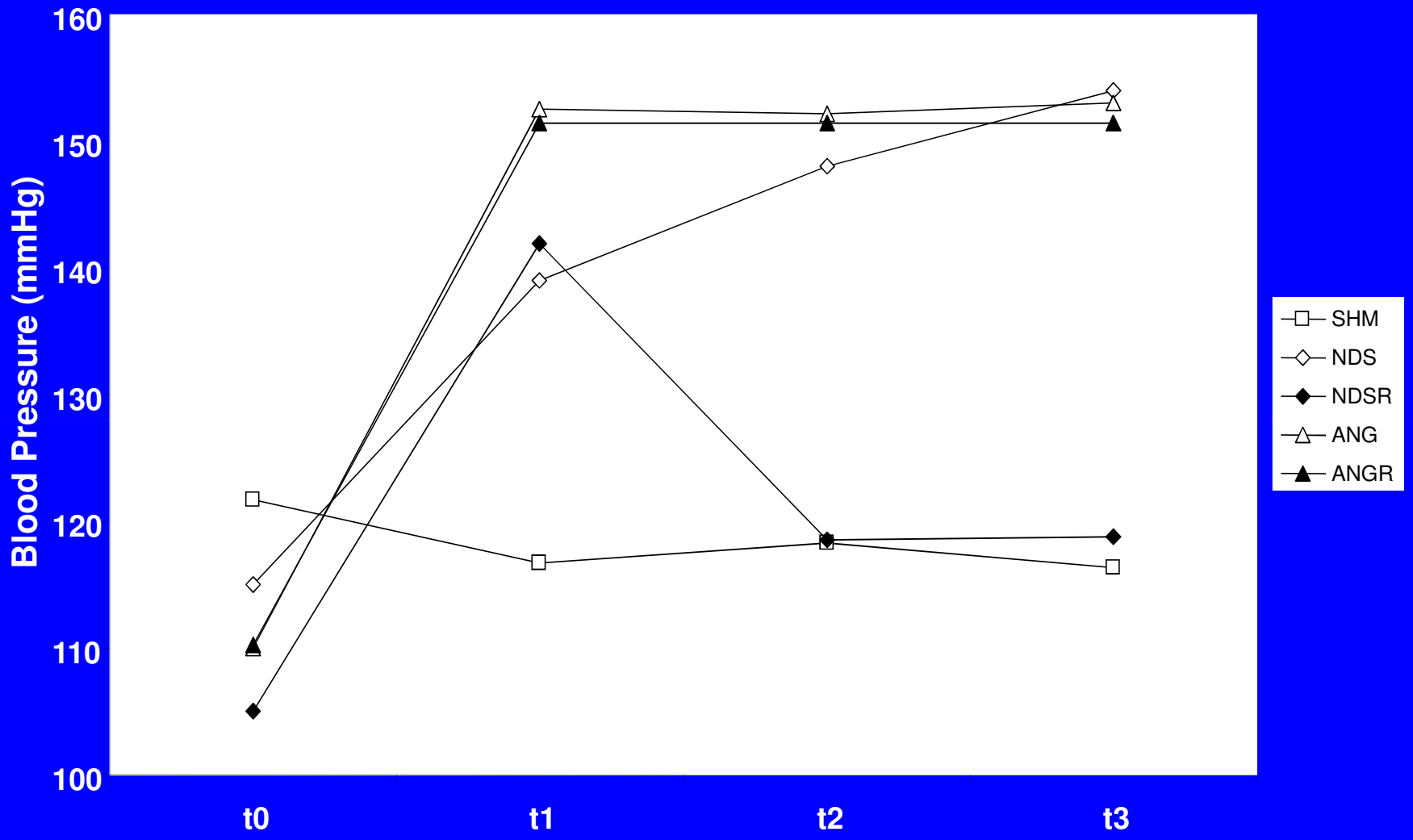
Circulating Vasoactive Substances in the Pathogenesis of Essential Hypertension

- Dahl
- deWardener and Clarkson
- Blaustein and Hamlyn

Essential Hypertension

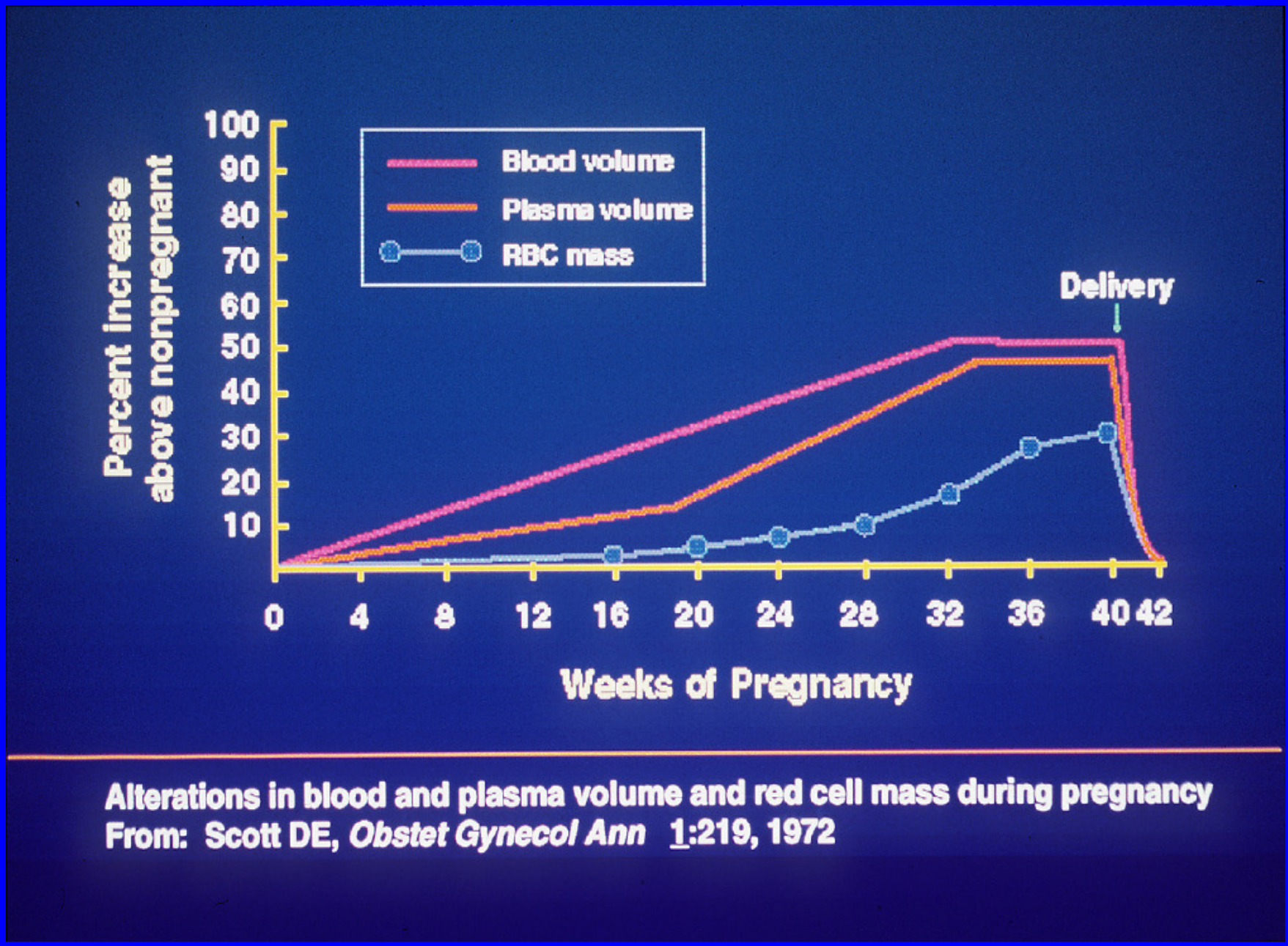
Major Etiologic Factors

- Expanded extracellular fluid volume
- Increased peripheral vascular resistance


Blood Pressure (mmHg)
160
150
140
130
120
110
100
t0
t1
t2
t3
SHM
NDS
NDSR
ANG
ANGR

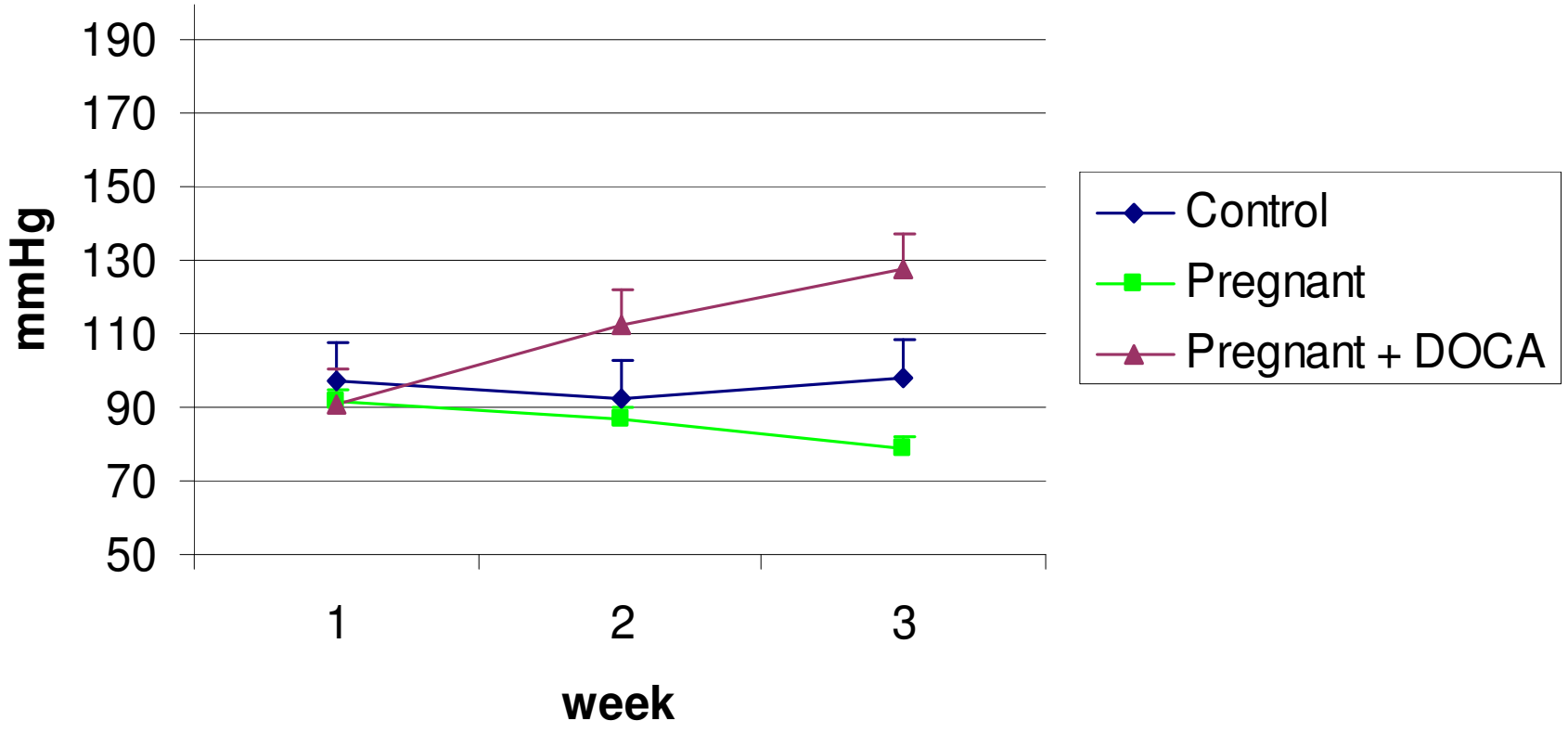
PREECLAMPSIA

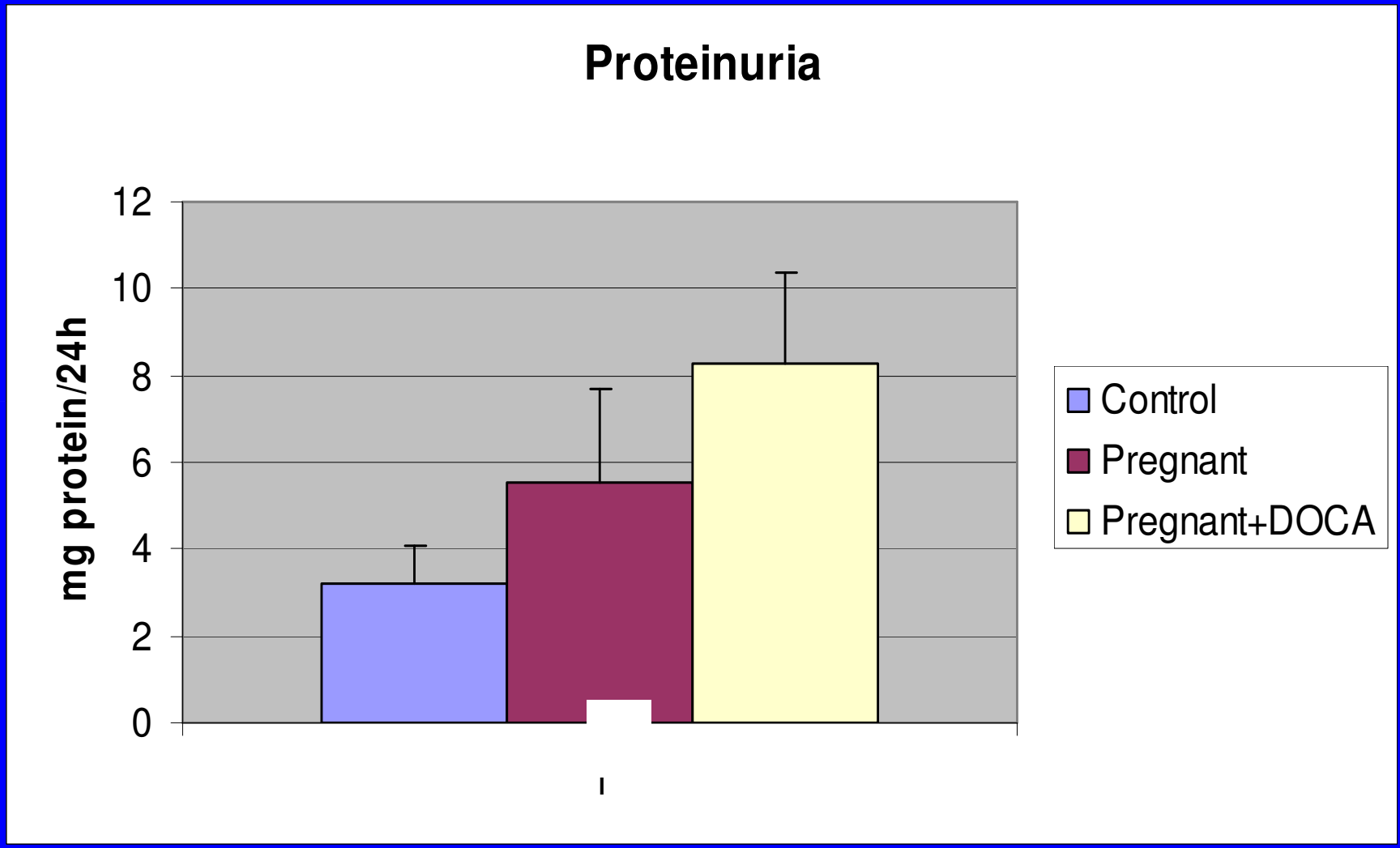
- New onset hypertension (>140/90 mmHg)
- Proteinuria (>300 mg/24 hr)
- Onset after 20 weeks of gestation
- Excessive edema often present
- Intrauterine growth restriction (IUGR) common
- Second leading cause of fetal wastage and maternal morbidity and mortality
- Syndrome remits by 12 weeks postpartum



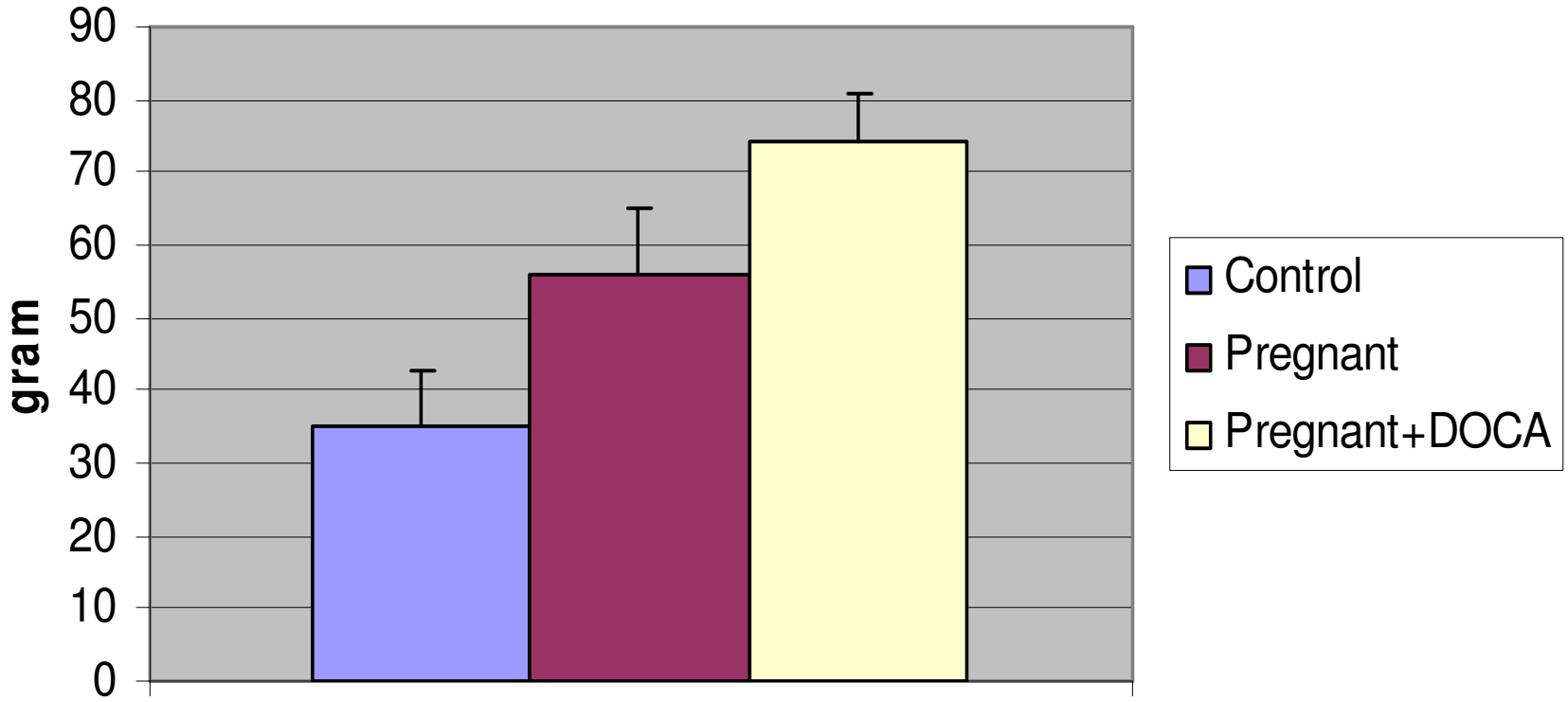
Alterations in blood and plasma volume and red cell mass during pregnancy
From: Scott DE, *Obstet Gynecol Ann* 1:219, 1972

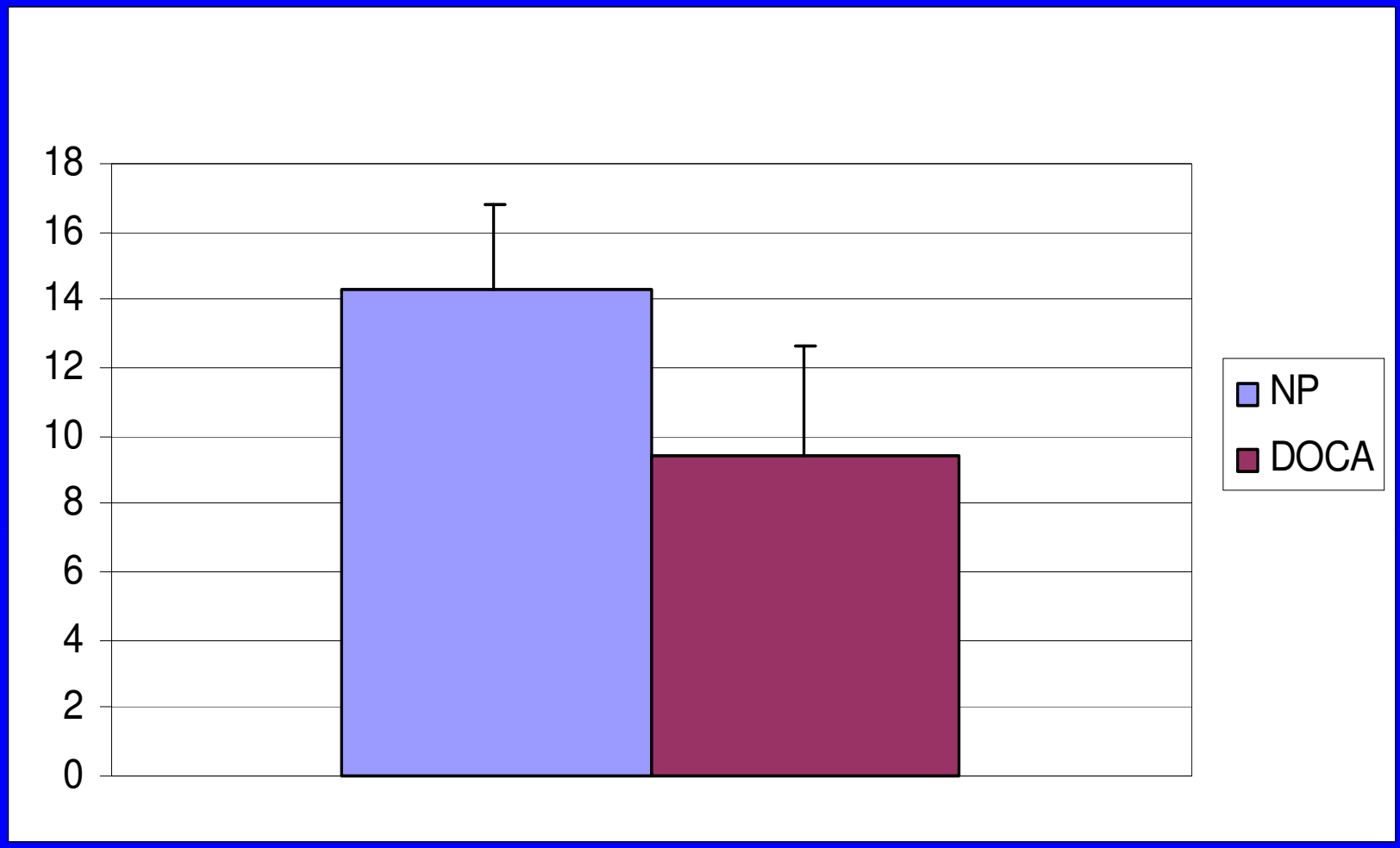
Blood Pressure Modification during Pregnancy (all groups)




Proteinuria
mg protein/24h
12
10
8
6
4
2
0
Control
Pregnant
Pregnant+DOCA

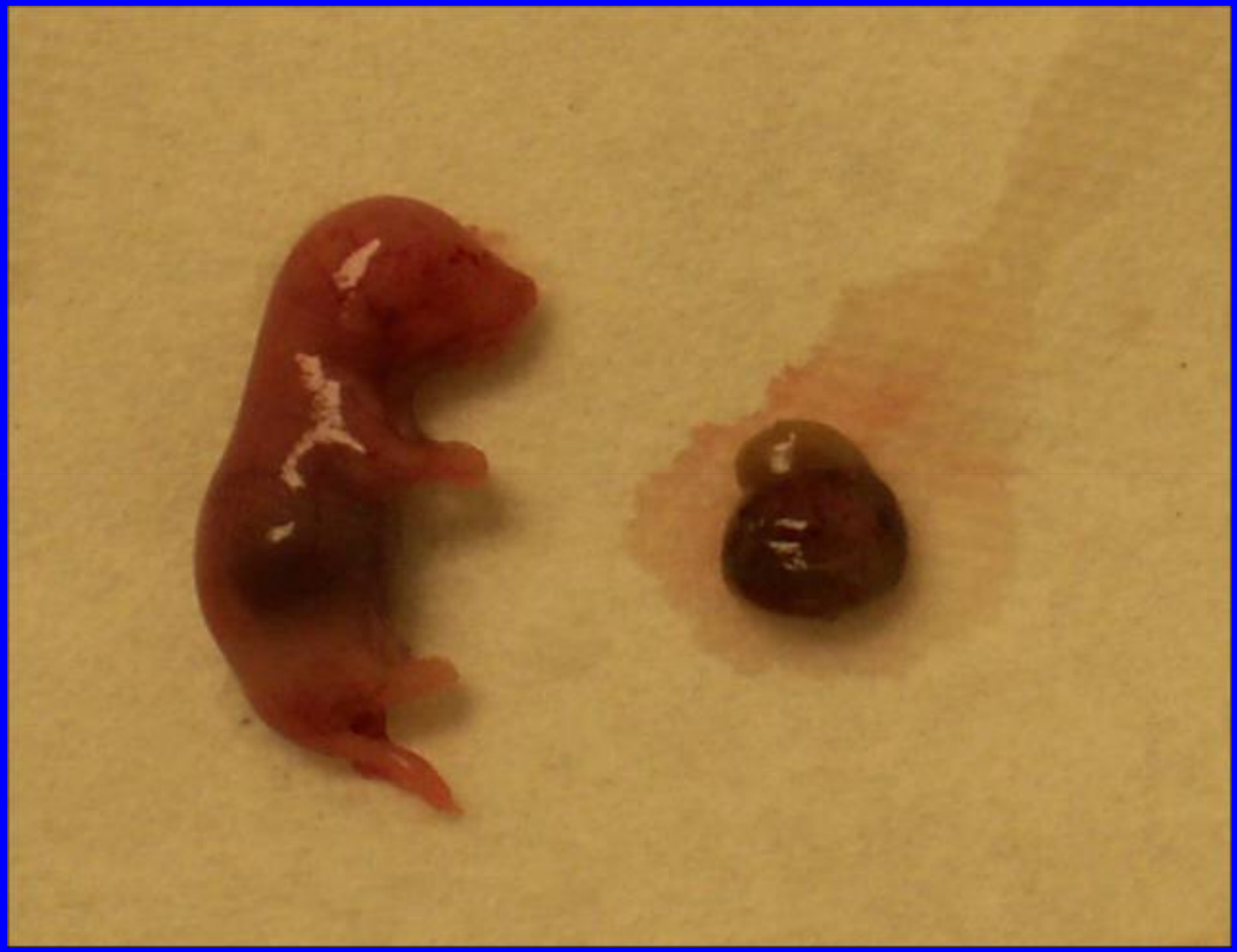
Weight Gain after 2 Weeks of Pregnancy



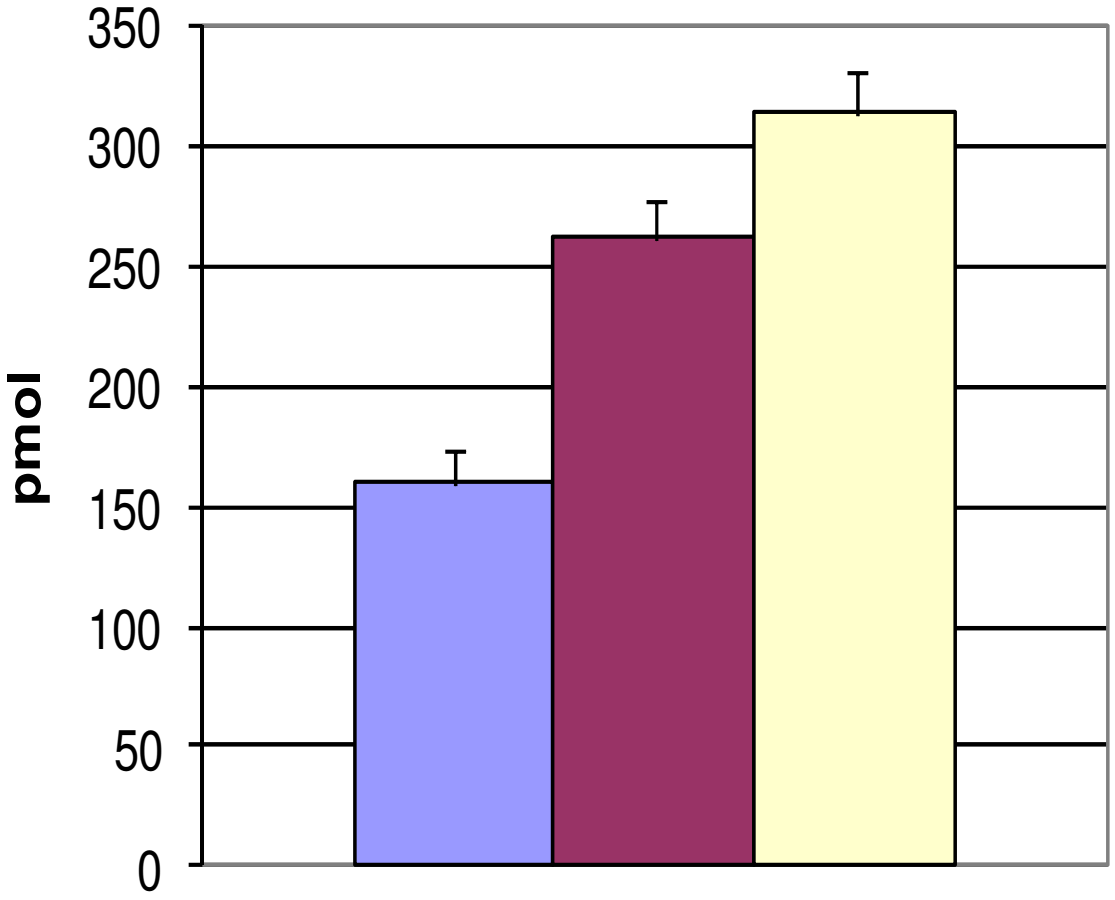


Number of pups from normal pregnant (NP) and pregnant + DOCA (DOCA) animals. The difference between the two groups was significant

(NP = 14.28 +/-2.56 vs. DOCA = 9.43 +/- 3.2, p=0.002).



Marinobufagenin Excretion (pmol/24h)

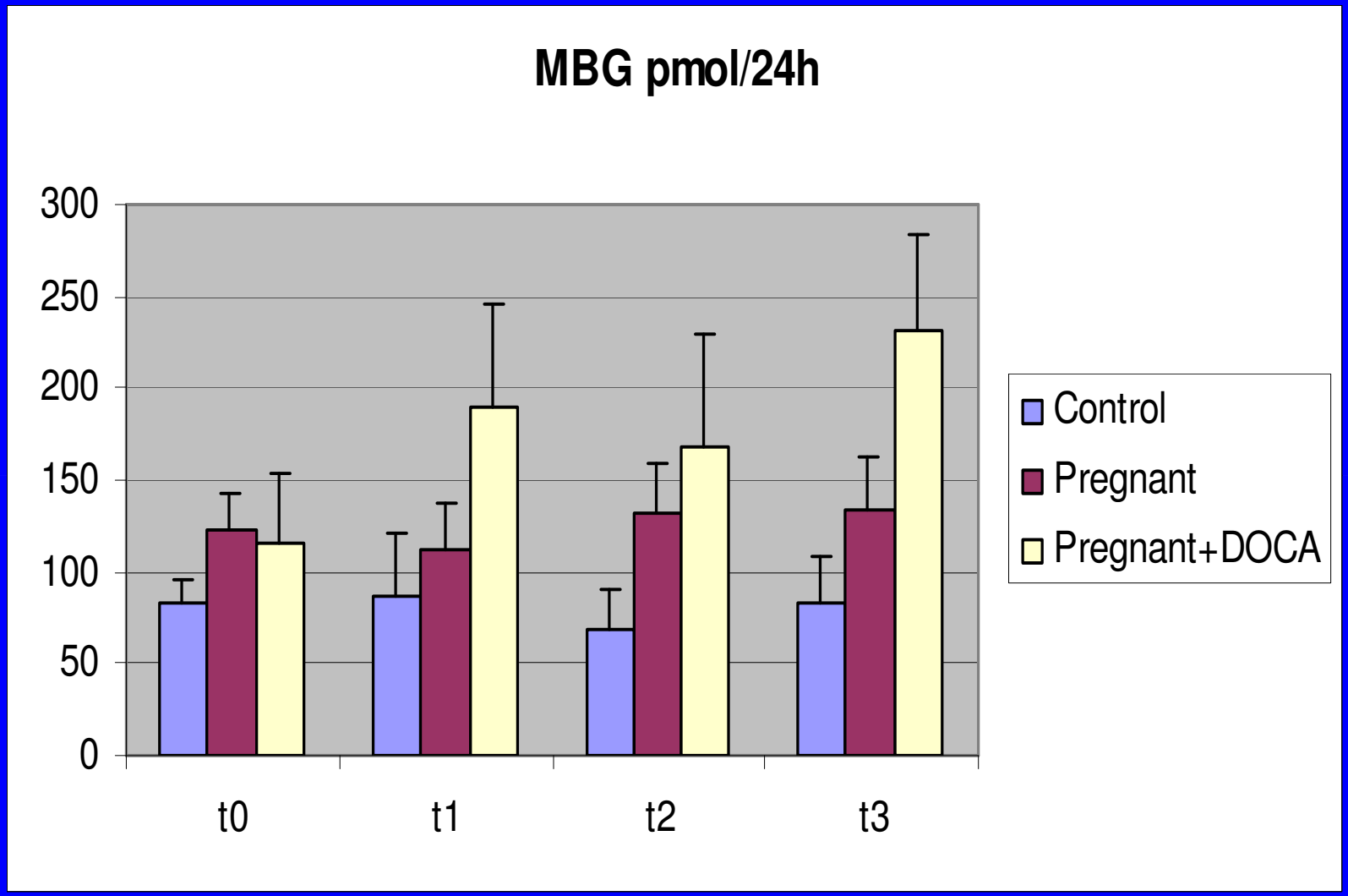


	Control	NP	Preg + DOCA
Average	160	262	314
St. Dev.	14	16	17
p vs Control		<0.01	<0.001
p vs Normal pregnant			<0.05

Control

Normal Pregnant

Pregnant + DOCA


MBG pmol/24h
300
250
200
150
100
50
0
t0
t1
t2
t3
Control
Pregnant
Pregnant+DOCA

Hematocrit Change In Preeclampsia Indicates Hemoconcentration

HEMATOCRIT VALUES IN NONPREGNANT, NORMAL PREGNANT, AND "PREECLAMPTIC" RATS

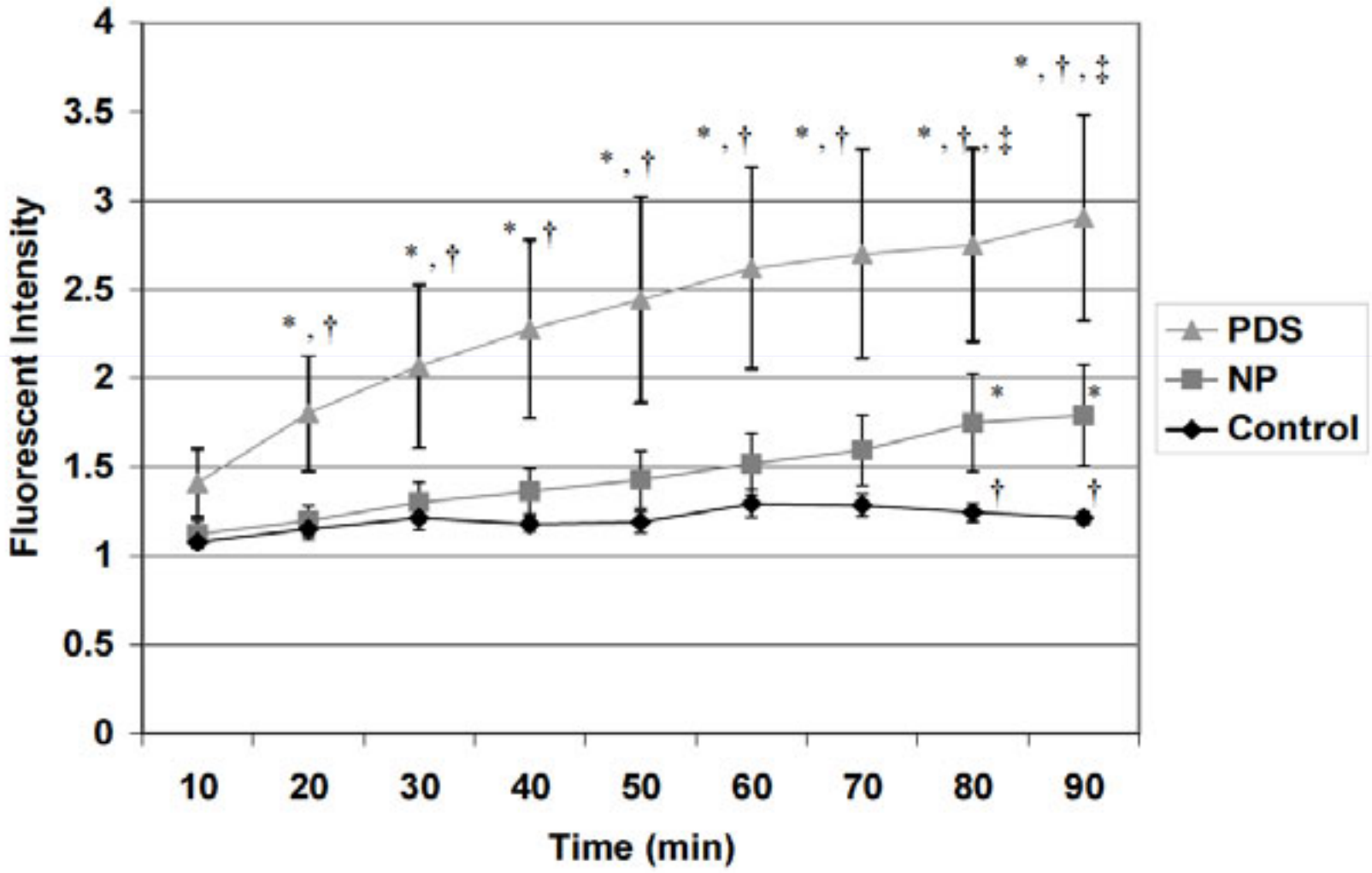
Animal Group	Number of Rats	Hematocrit
Control, nonpregnant (C)	9	0.44 +/- 0.01†
Normal pregnant (NP)	10	0.34 +/- 0.02‡
"Preeclamptic" (PDS)*	8	0.38 +/- 0.02

* "Preeclamptic" (PDS) rats = animals given saline as drinking water and weekly DOCA injections.

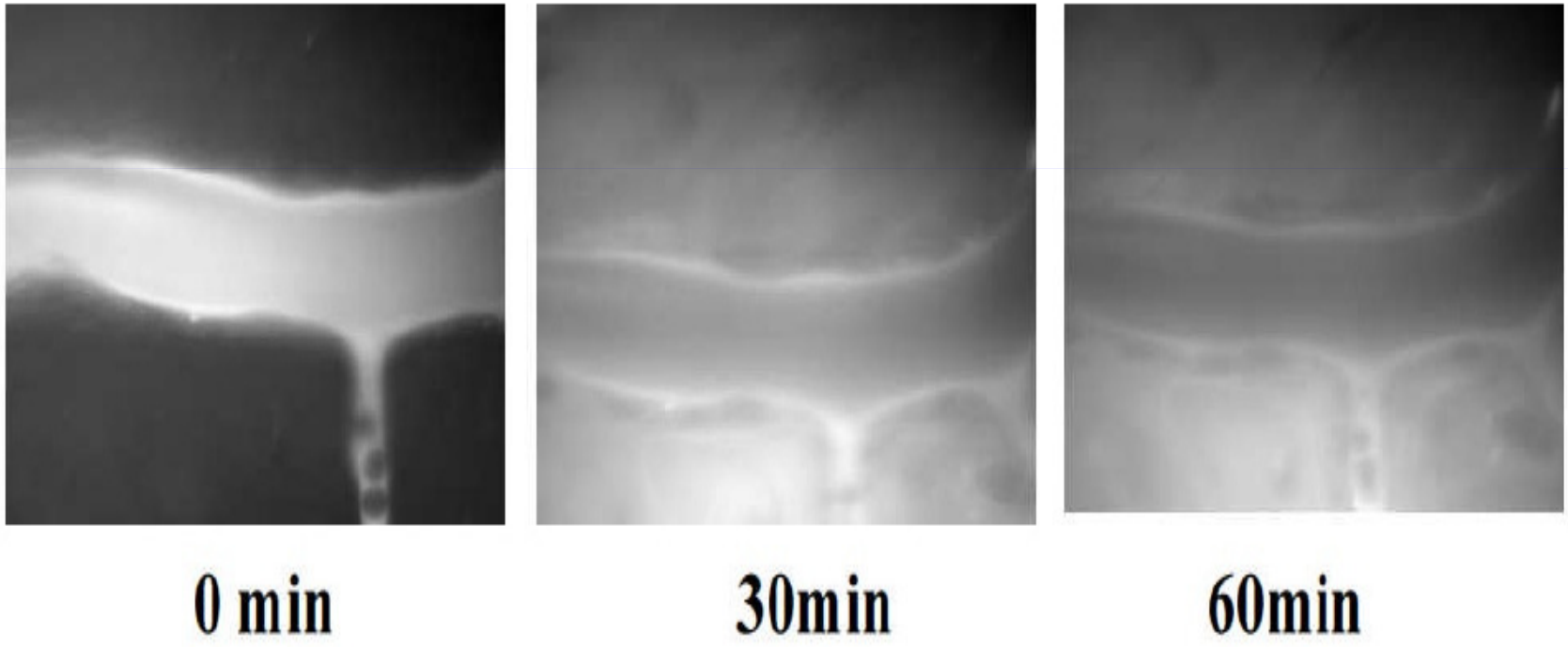
† Control rats differ from all other groups ($p < 0.001$).

‡ NP differs from PDS ($p < 0.05$).

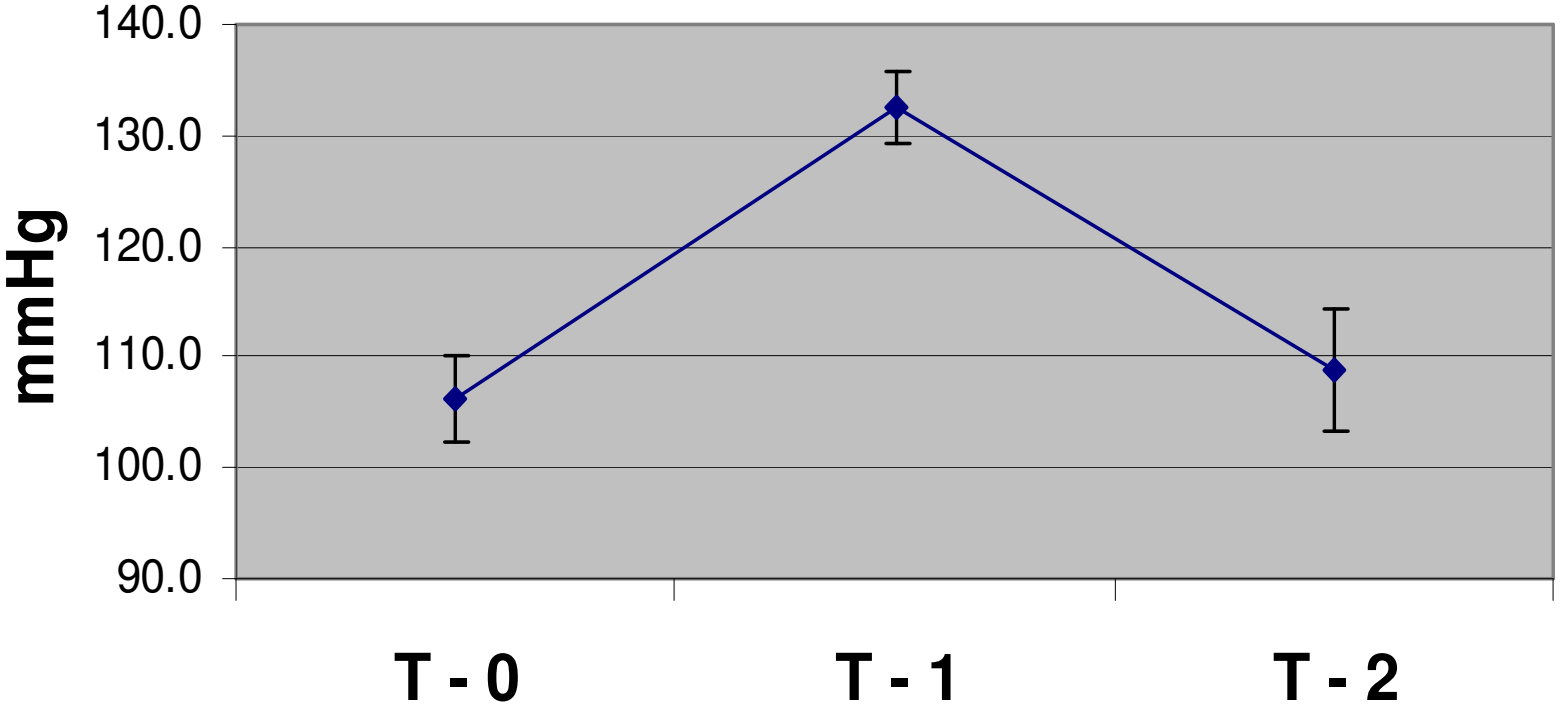
VASCULAR LEAKAGE IN NON-PREGNANT, NORMAL PREGNANT AND "PREECLAMPTIC" RATS



MBG CAUSES VASCULAR LEAK IN A MESENTERIC POST-CAPILLARY VENULE

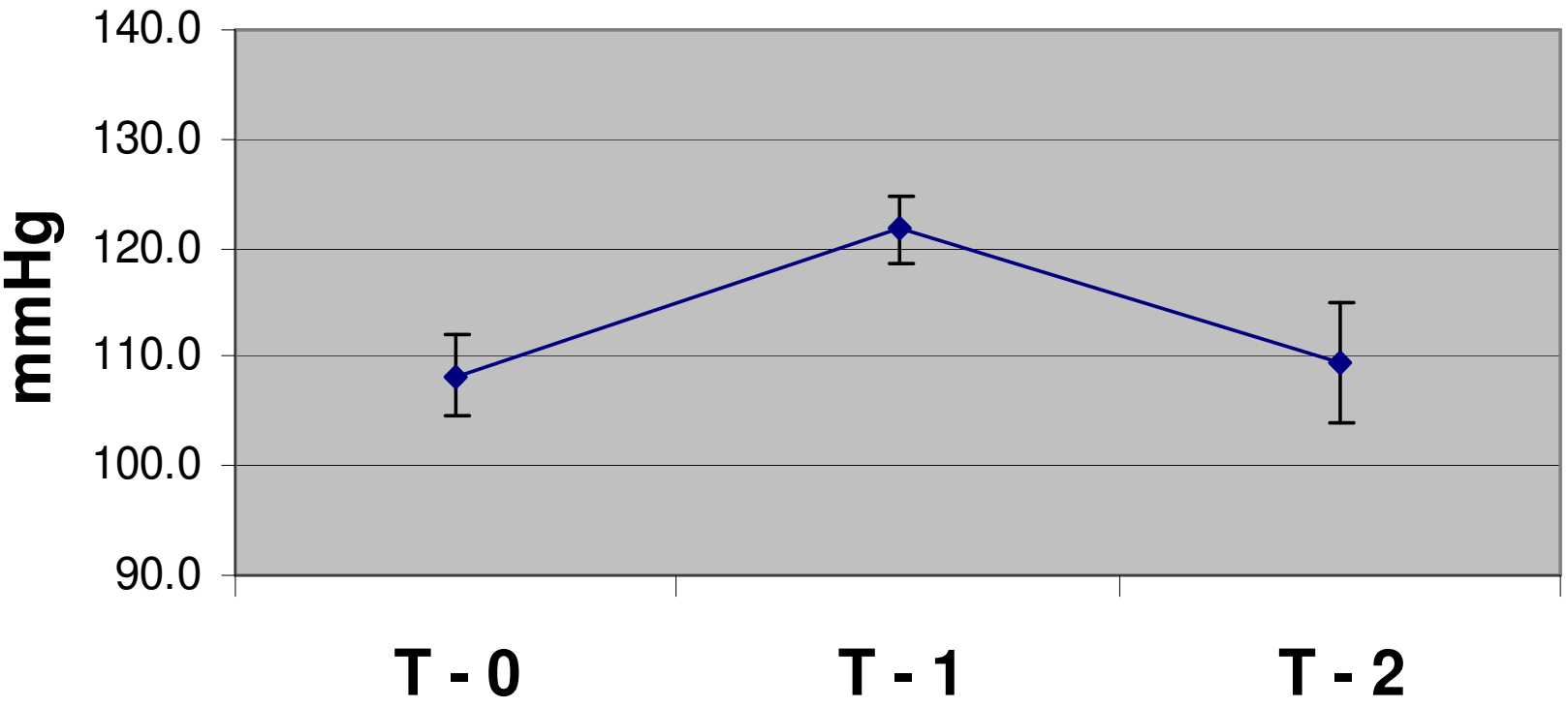


PDS + RBG



Ave BP	106.3	132.5	108.8
St. Error	3.8	3.2	5.5
		p < 0.05	p < 0.05

MBG + RBG



Ave BP	108.3	121.7	109.6
St. Error	4.2	4.2	3.2
		p < 0.01	p < 0.01

BLOOD PRESSURE, 24 HOUR PROTEIN EXCRETION, PUP NUMBER, PERCENT ABNORMAL PUPS AND HEMATOCRIT VALUES♦

Groups	Number of Rats	Baseline BP	Final BP	Protein (mg/24hr)
C	9	104 ± 5	102 ± 4 †	1.1 ± 0.9 †
NP	10	105 ± 4	90 ± 6 ‡	2.4 ± 1.2
PDS	8	103 ± 7	140 ± 8 * ‡	5.6 ± 1.8 *
PDSR	8	106 ± 6	87 ± 5 ‡	2.5 ± 1.1

Groups	Number of Rats	Pups	% Malformed	Hematocrit
C	9			0.44†
NP	10	15.0 ± 1.9	0	0.34
PDS	8	11.1 ± 1.4 *	18	0.38*
PDSR	8	14.7 ± 1.3	0	0.33

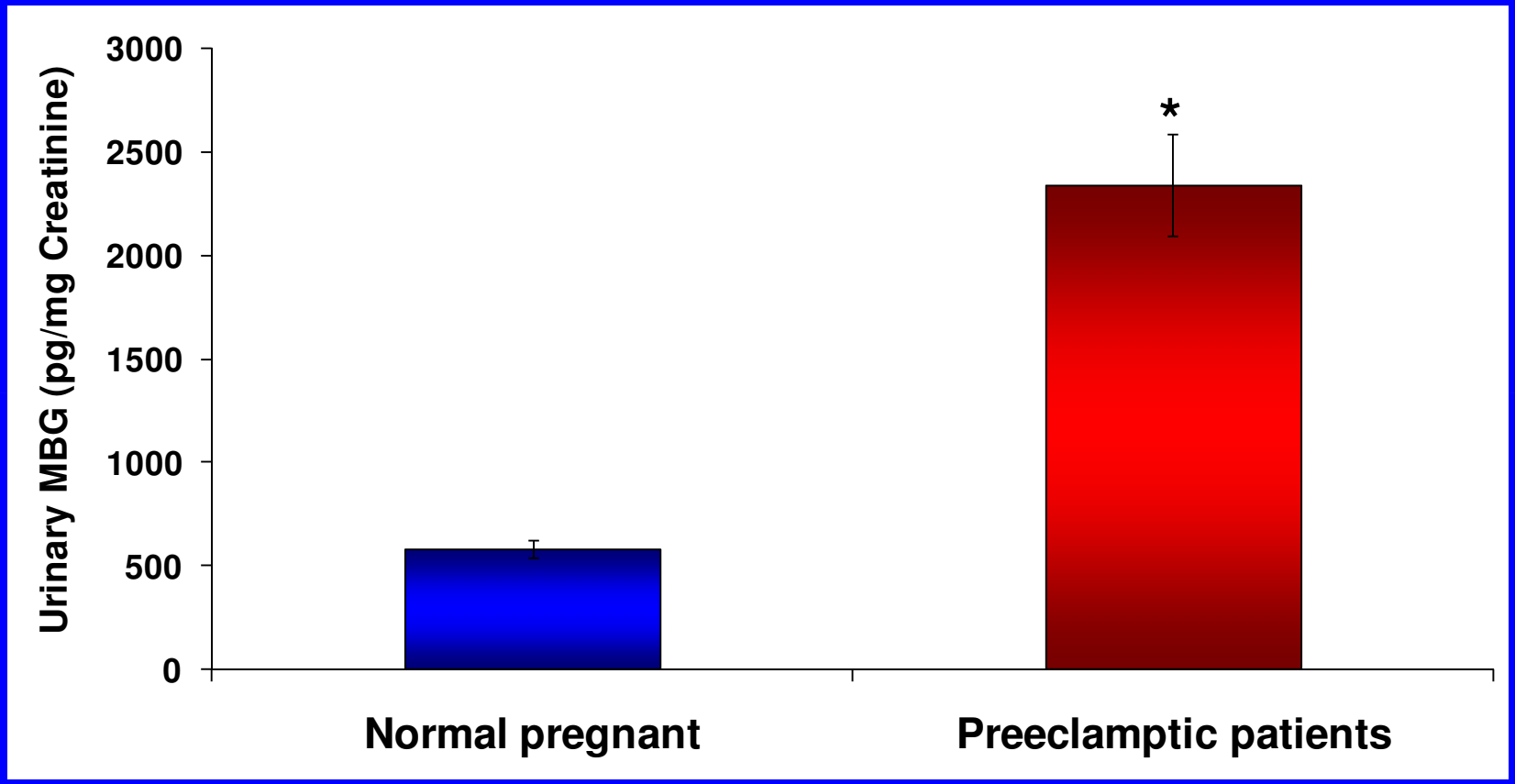
♦Abbreviations: C = Control, Non-pregnant; NP = Normal pregnant; PDS = Pregnant+DOCA+Saline C = "Preeclamptic" rats; PDSR = "Preeclamptic" rats given resibufagenin from early pregnancy; BP = Blood pressure

* $p<0.05$ PDS vs Control, NP and PDSR

† $p<0.05$ C vs NP, PDS and PDSR

‡ $p<0.05$ Baseline vs Final

URINARY MBG IN NORMAL PREGNANT AND PREECLAMPTIC PATIENTS



* $p < 0.001$

PREECLAMPSIA OUTCOMES

Subjects:

22 Formerly preeclamptic patients

20 Parous controls (matched for age, BMI, date of birth)

Results:

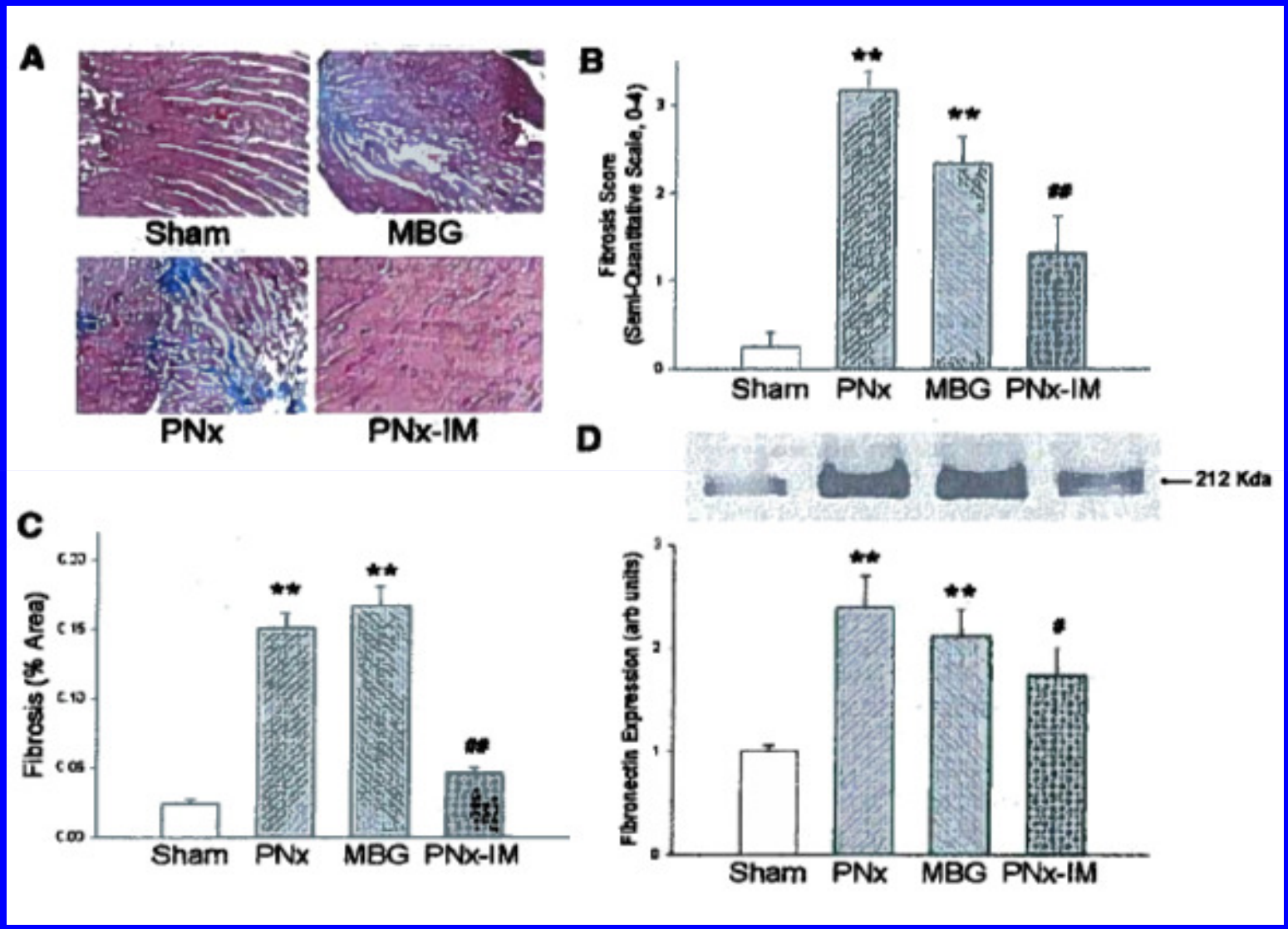
1) Hypertension was present in 55% of the formerly hypertensive patients, 7% of controls.

2) Mean arterial pressure was higher in the formerly preeclamptic women compared to the controls (100 vs. 88 mm Hg).

3) Renal blood flow was 15% lower in the formerly preeclamptic patients, unaffected in the controls.

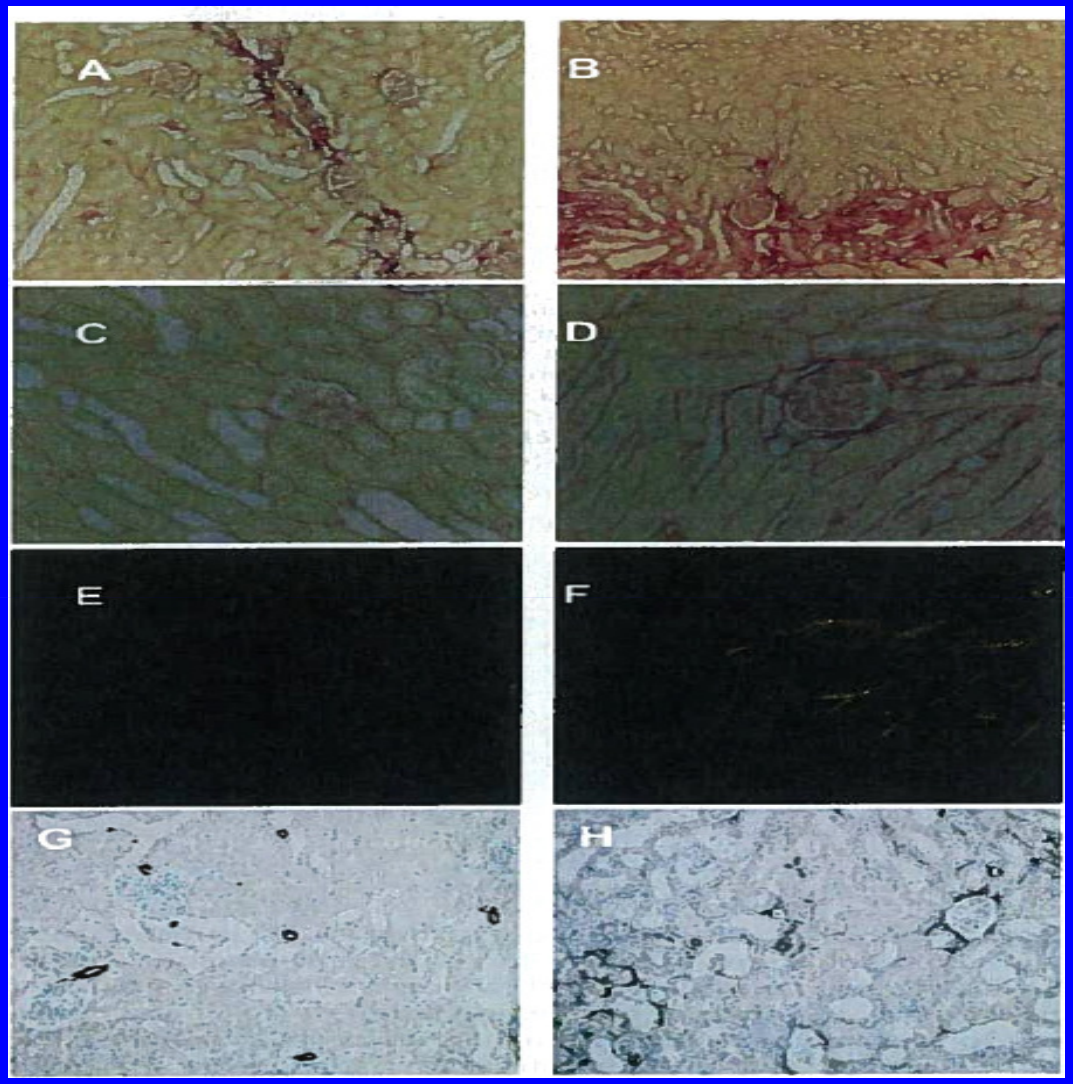
From: JJ Spaan et al, Obstet Gynecol 113: 853-859, 2009

The Induction of Cardiac Fibrosis by Marinobufagenin



* p<0.05, **p<0.01 vs. sham, # p<0.05, ## p<0.01 vs. PNx.
From: Kennedy DJ, et al, *Hypertension* **47**:488-495, 2006.

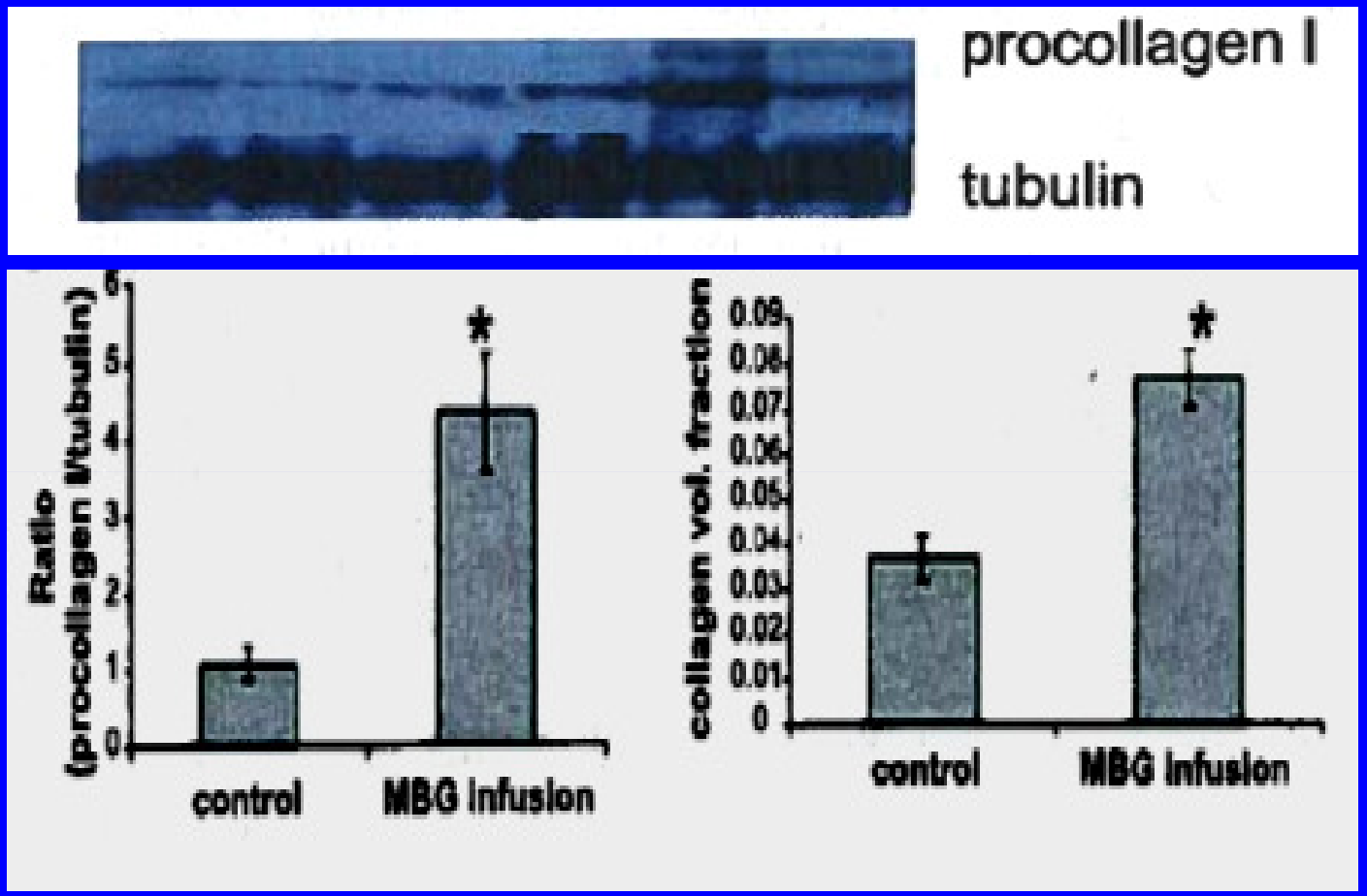
The Induction of Cardiac Fibrosis by Marinobufagenin



Accumulation of collagen in the interstitium (B) and development of fibrosis in the peritubular and periglomerular areas of the cortex (D-F). Actin deposition in the tubulointerstitium (H).

From: Federova LV, et al, *Am J Physiol, Renal Physiol* **296**: F922-F934, 2009.

MBG Causes Enhanced Procollagen Deposition



Western blots and densitometry measurements in kidney interstitium. *P< 0.05.

From: Federova LV, et al, *Am J Physiol, Renal Physiol* **296**: F922-F934, 2009.

SUMMARY

1. MBG is involved in the pathogenesis of volume expansion-mediated hypertension.
2. MBG plays an important role in the cardiomyopathy of experimental uremia.
3. MBG is a factor in the generation of kidney fibrosis and in the epithelial-to-mesenchymal transition that is characteristic of this process.
4. Further study in human subjects and CKD patients will be required to verify these findings, perhaps leading to new therapeutic measures to prevent or minimize these disorders.