THE FETAL-PLACENTAL UNIT AS AN ALLOGRAFT:

BREAKAGE OF THE FETAL MATERNAL TOLERANCE IN PREECLAPSIA

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II. Collaborators

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This study highlights the greatest message addressed by pregnancy:

“THE TOLERANCE OF BIODIVERSITY”

In fact, the placenta acts as an immunological barrier between the mother and fetal “graft” allowing two antigenically different organisms to tolerate one another

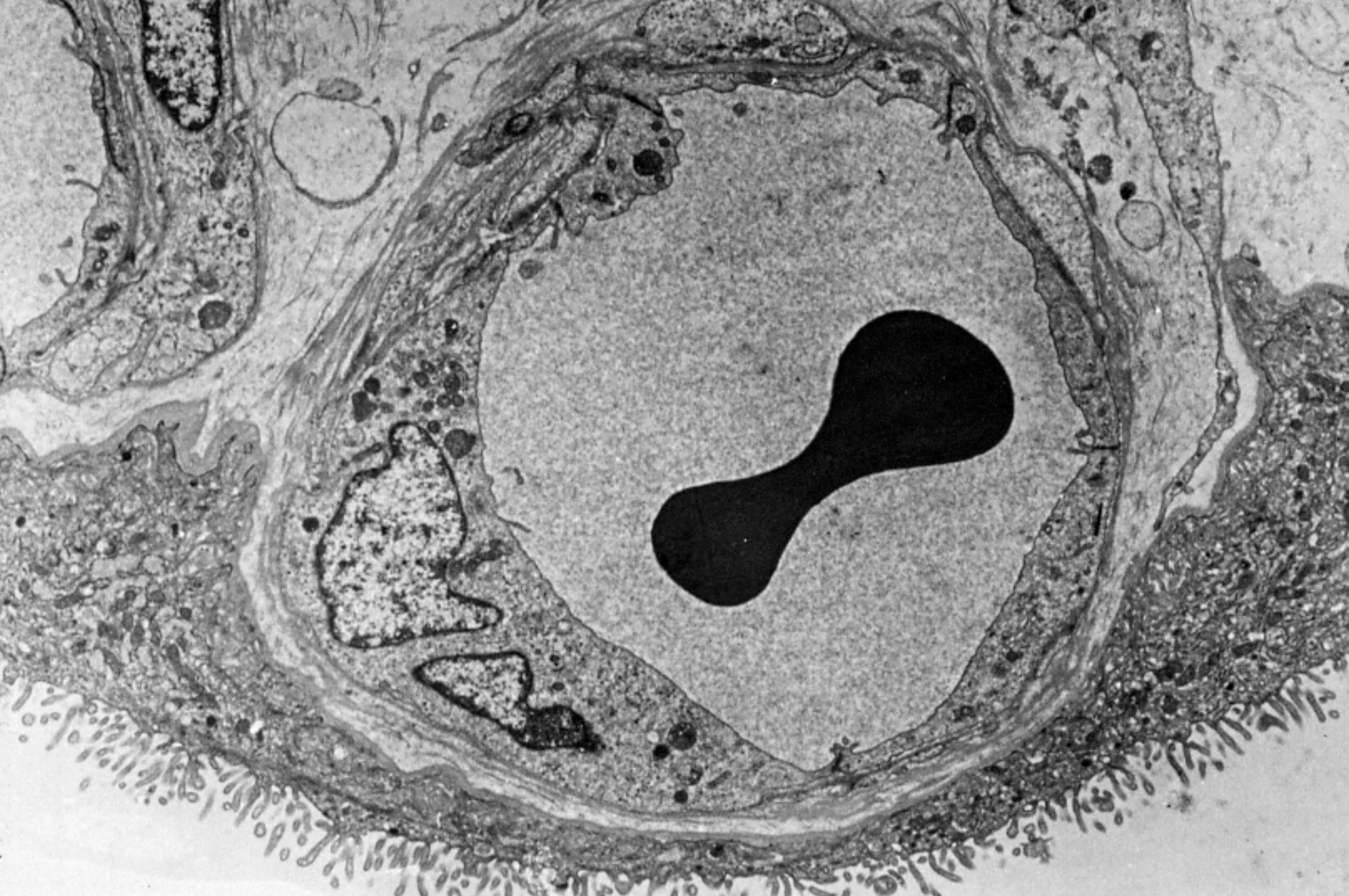
Edwards, 1995

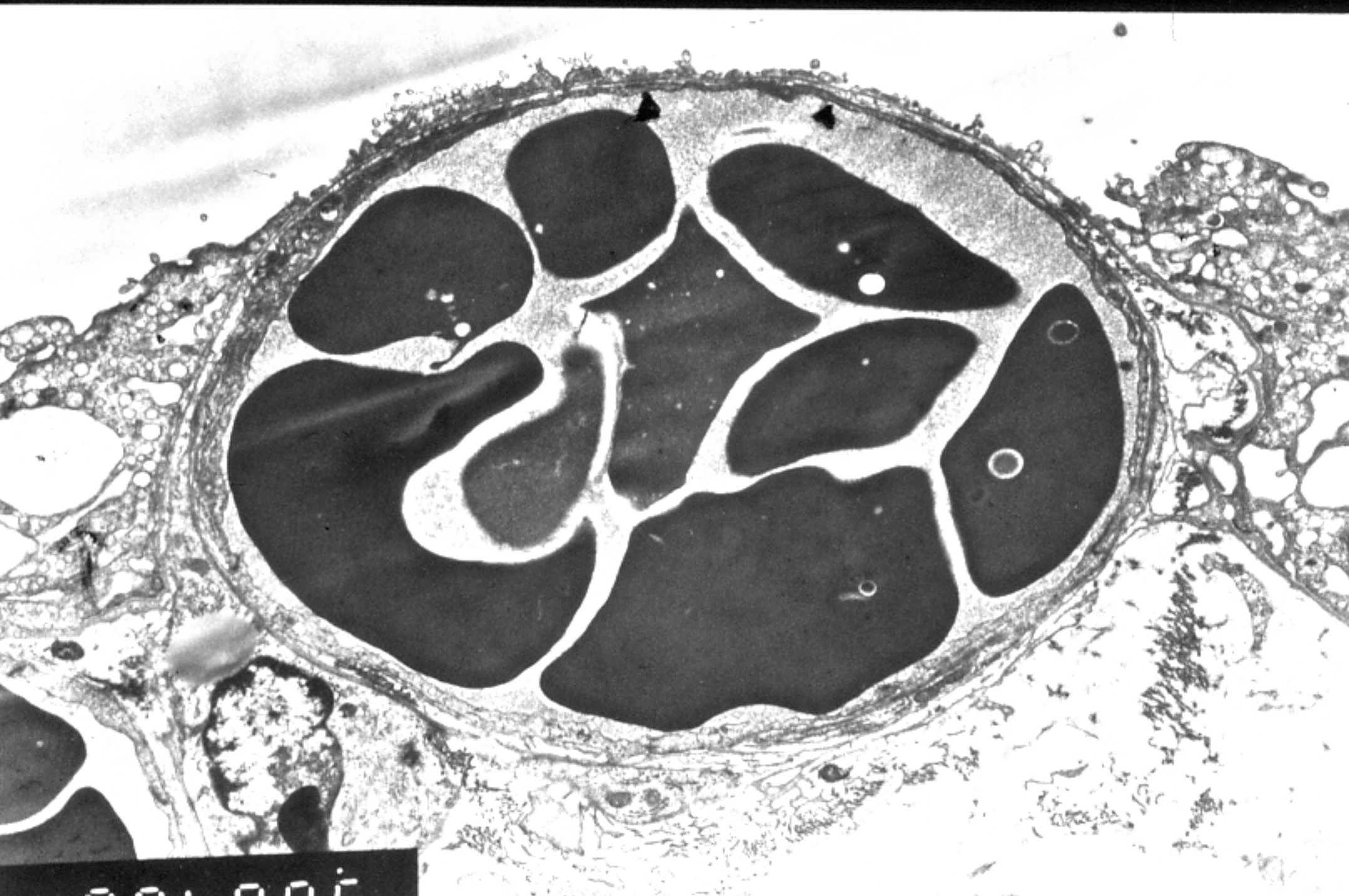
It is clear that any damage to this barrier from various ischemic risk factors (metabolic, hormonal, genetic, immunological) may be responsible for lesions of the syncytiotrophoblast and villous vessels endothelial cells as we demonstrated by electron microscopy.

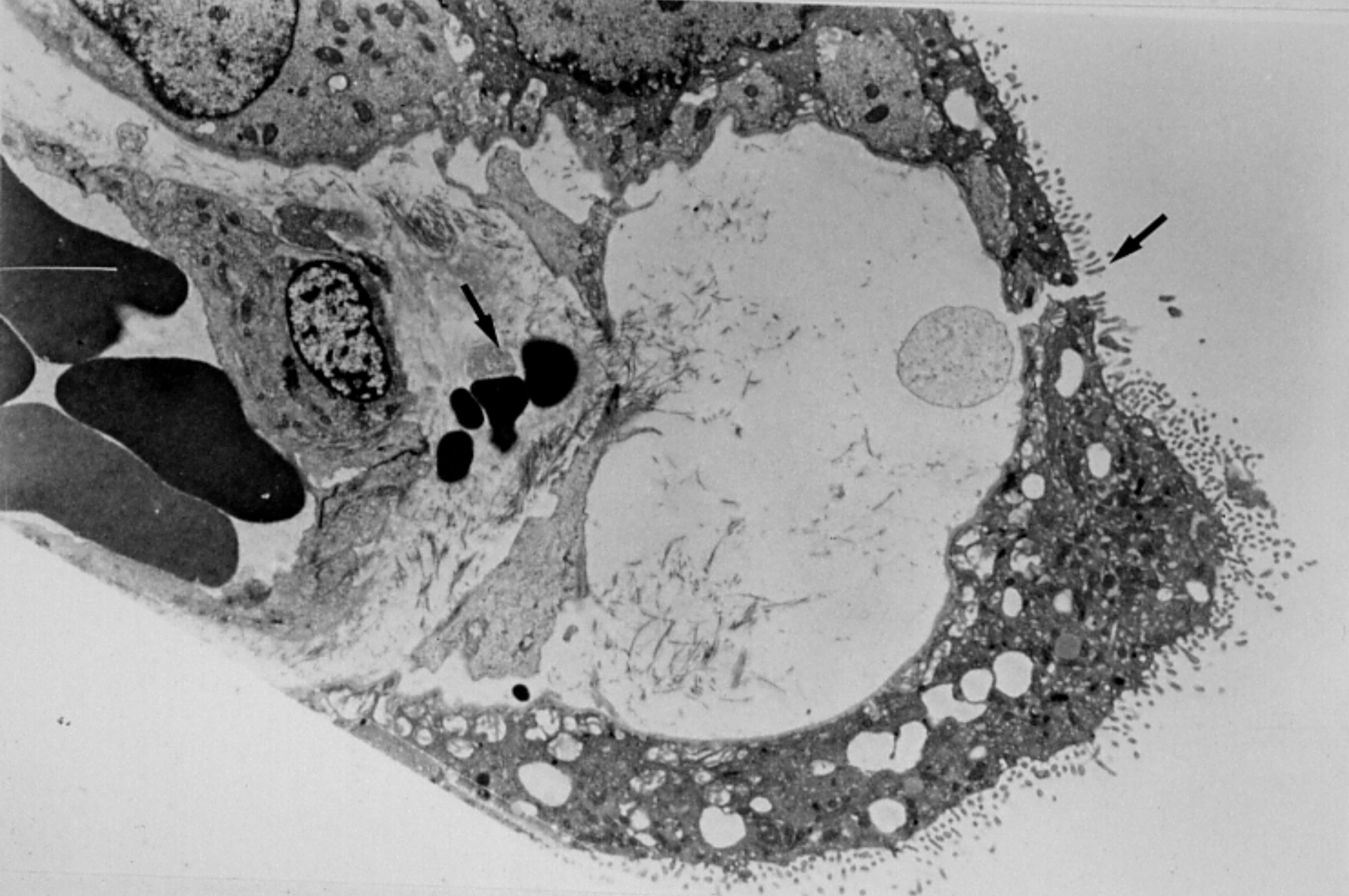
J. Anat. Embriol., **103**, 202, **1998**

Ultrastructural study of the human placental endothelium in preeclampsia

de Luca Brunori I., Lenzi P., Paparelli A. et al.







Clin Exp Obst Gyn., **21**, 228-230, **1994**.

Gestosis and fetal rejection: immunopathogenetic role of HLA-DR

de Luca Brunori I., Battini L., Simonelli M. *et al.*

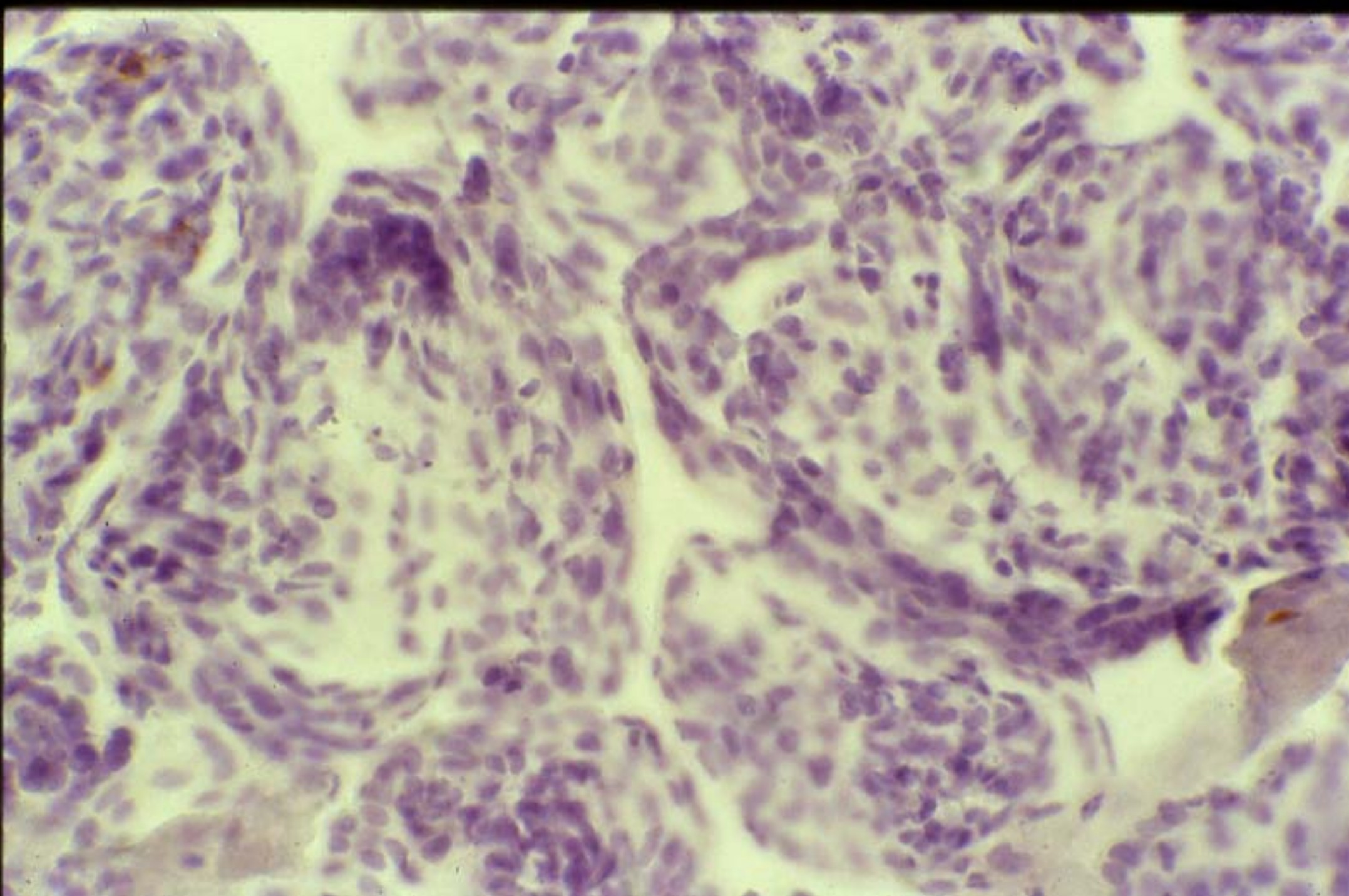
To verify this rejection's hypothesis, we examined placentae from preeclamptic patients and controls by immunohistochemical technique and HLA-DR monoclonal antibody.

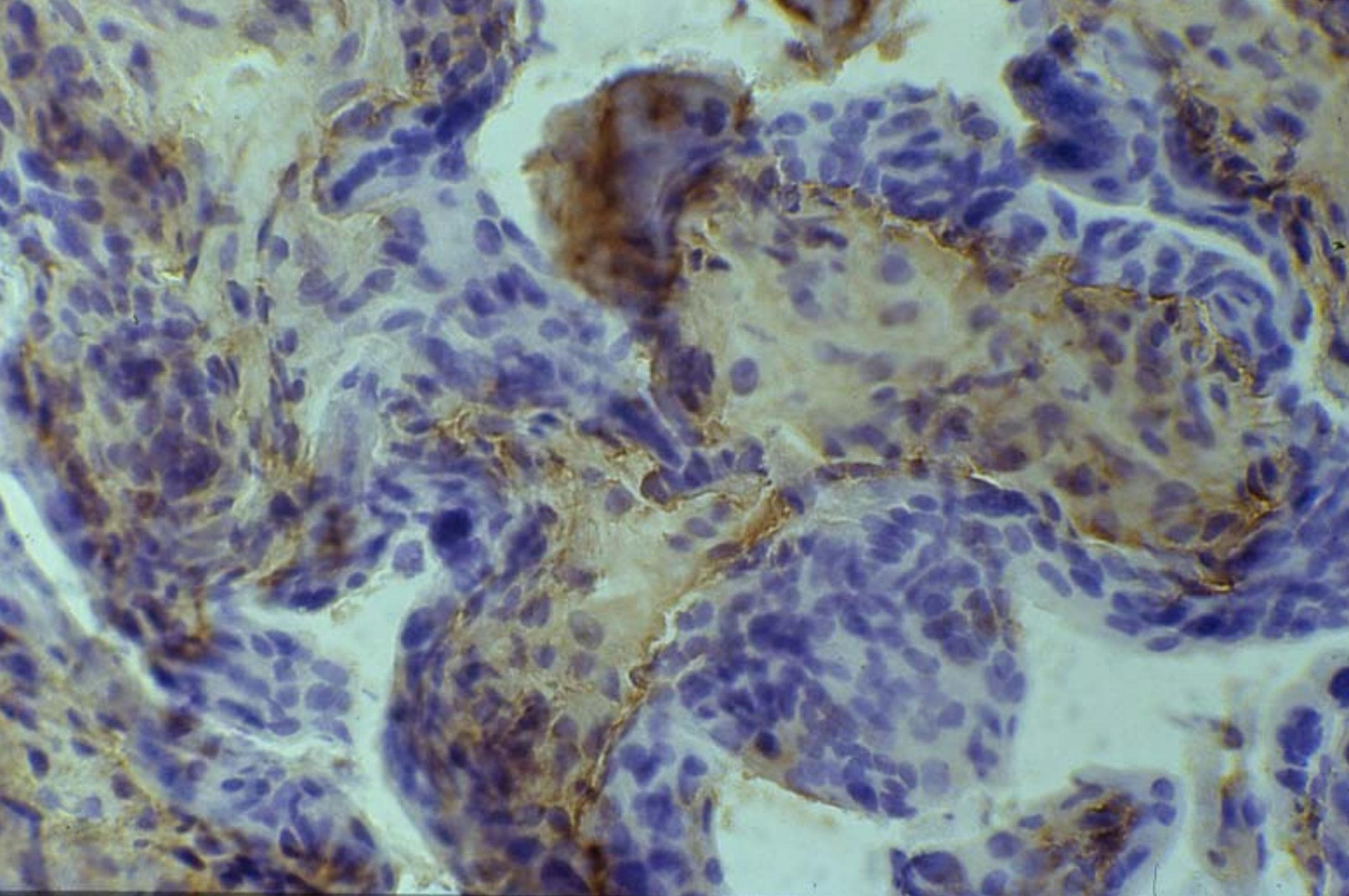
Clin Exp Obst Gyn., **21**, 192-194, **1994**.

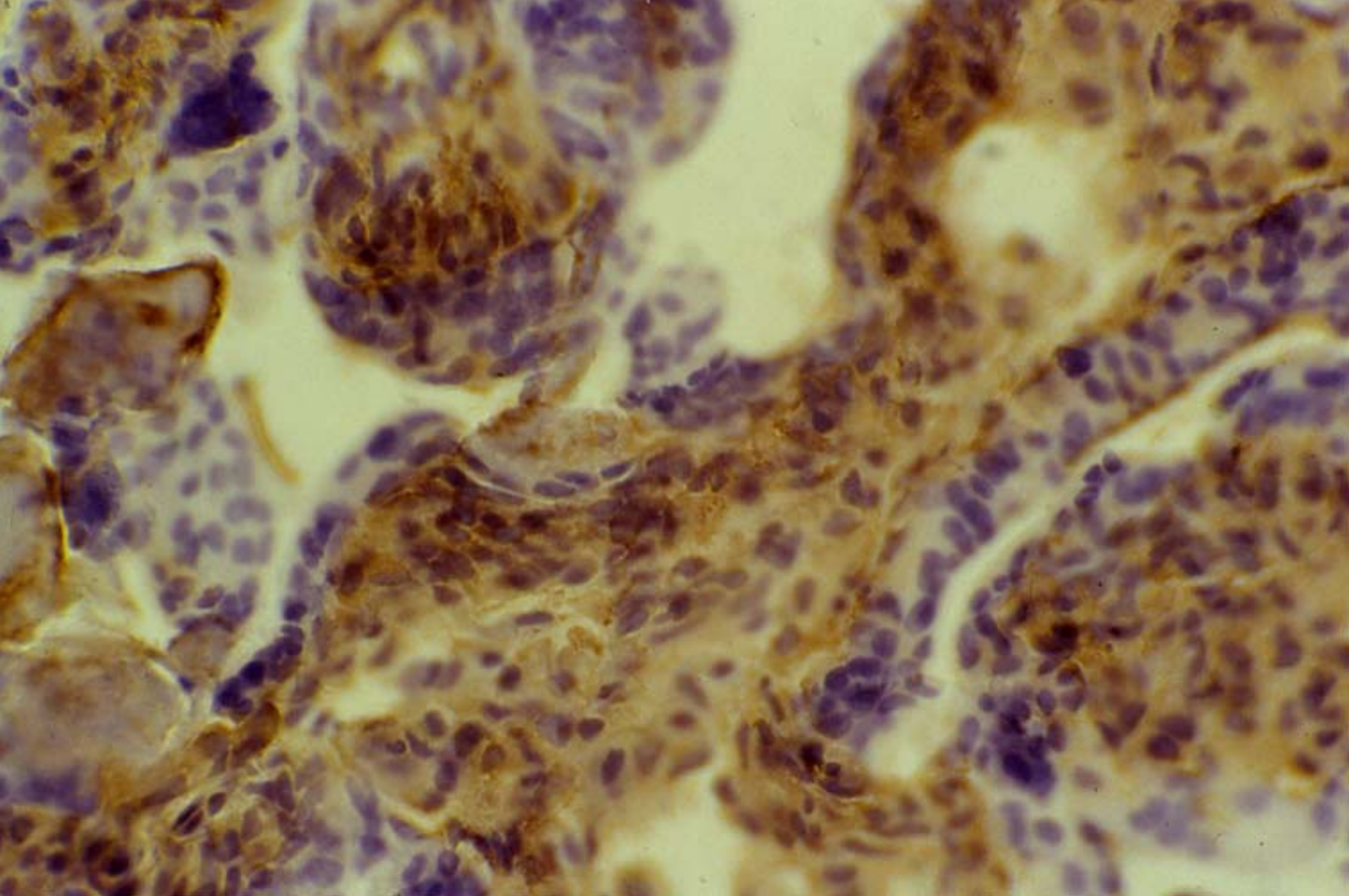
Immunohistochemical study of placental endothelium in physiologic and gestosis-complicated pregnancies by HLA-DR monoclonal antibodies

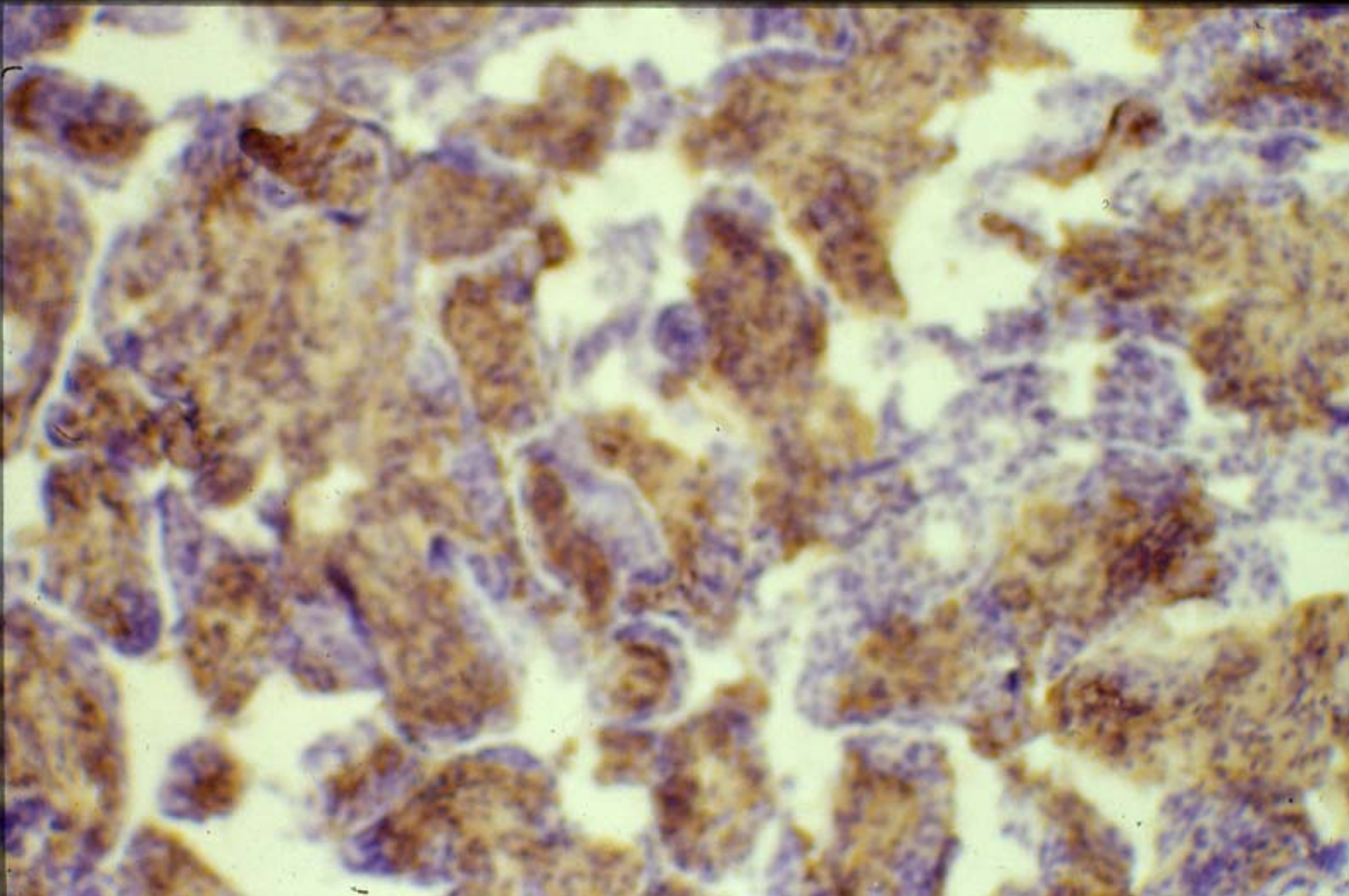
de Luca Brunori I., Battini L., Simonelli M. *et al.*

HLA-DR falls under human class II of the Major Histocompatibility Complex (MHC) and it identifies several elements involved in activating and maintaining immunitary response (limphocytes, macrophages, cell T activated, endothelial cells). Therefore, HLA-DR plays a fundamental role in self and non-self recognition and in rejective reaction.









To understand the mechanism at the basis of such an evident immunological reaction in Preeclampsia, we undertook a study to evaluate if Preeeclampsia, like transplant rejection, could be related to the immunological role of the HLA-DR Antigens.

Hum.Reprod. **15**, 1807-1812, **2000**.

Increased HLA-DR homozygosity associated with preeclampsia

de Luca Brunori, I., Battini, M. Simonelli *et al.*

In this study HLA-DR was typed in

70 preeclamptic women, their partners

70 healthy control couples

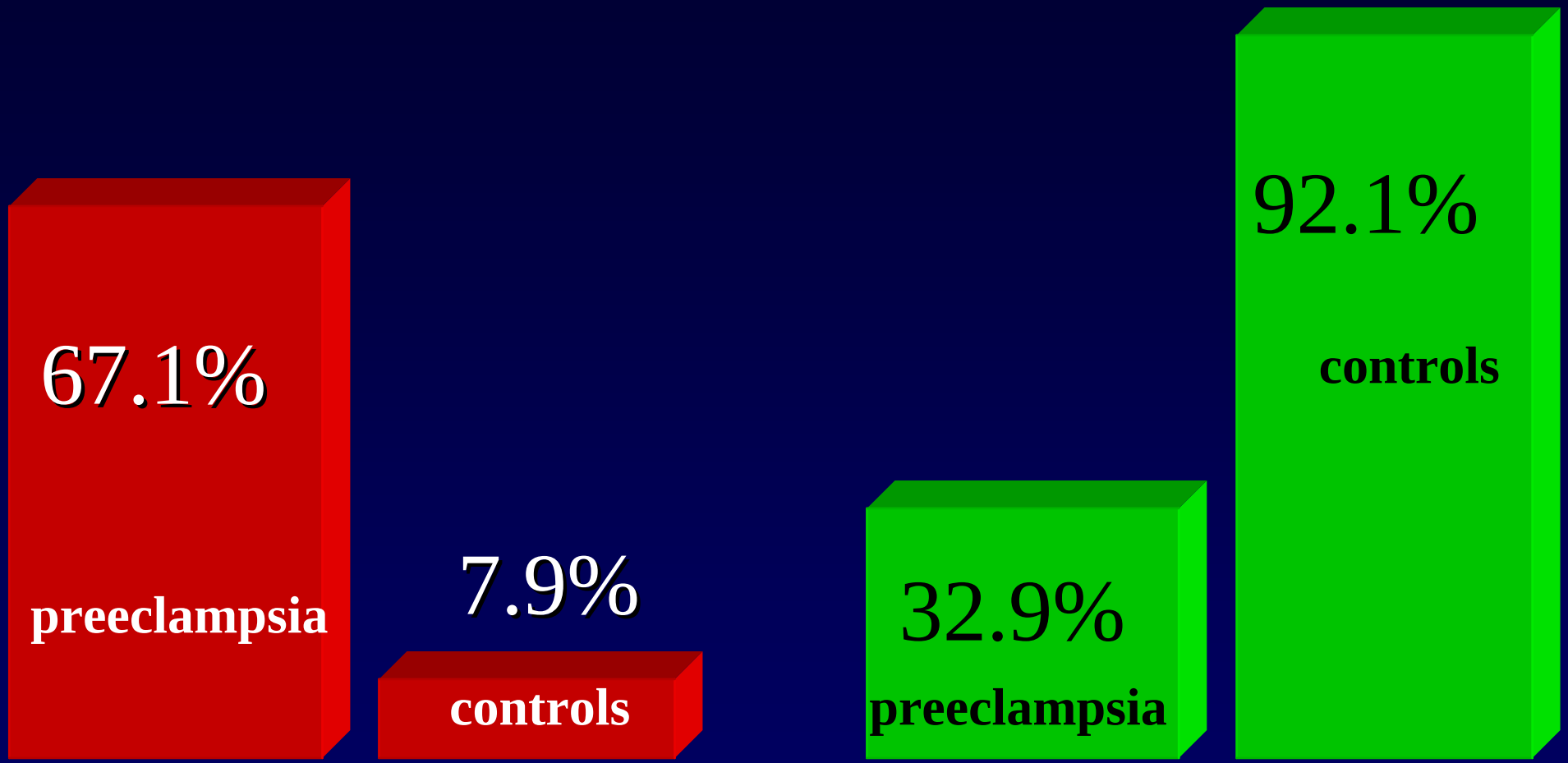
by serological Terasaki technique.

20 cases out of the preeclamptic couples

20 control couples were typed

by low resolution PCR

HLA-DR TYPING RESULTS



P<0.00001

HOMOZYGOSITY DISTRIBUTION

	♀♂	♀	♂
	N (%)	N (%)	N (%)
preeclampsia	26 (37.1)	22 (31.4)	20 (28.6)
controls	1 (1.4)	5 (7.1)	4 (5.7)

HLA-DR ANTIGENS VARIETY

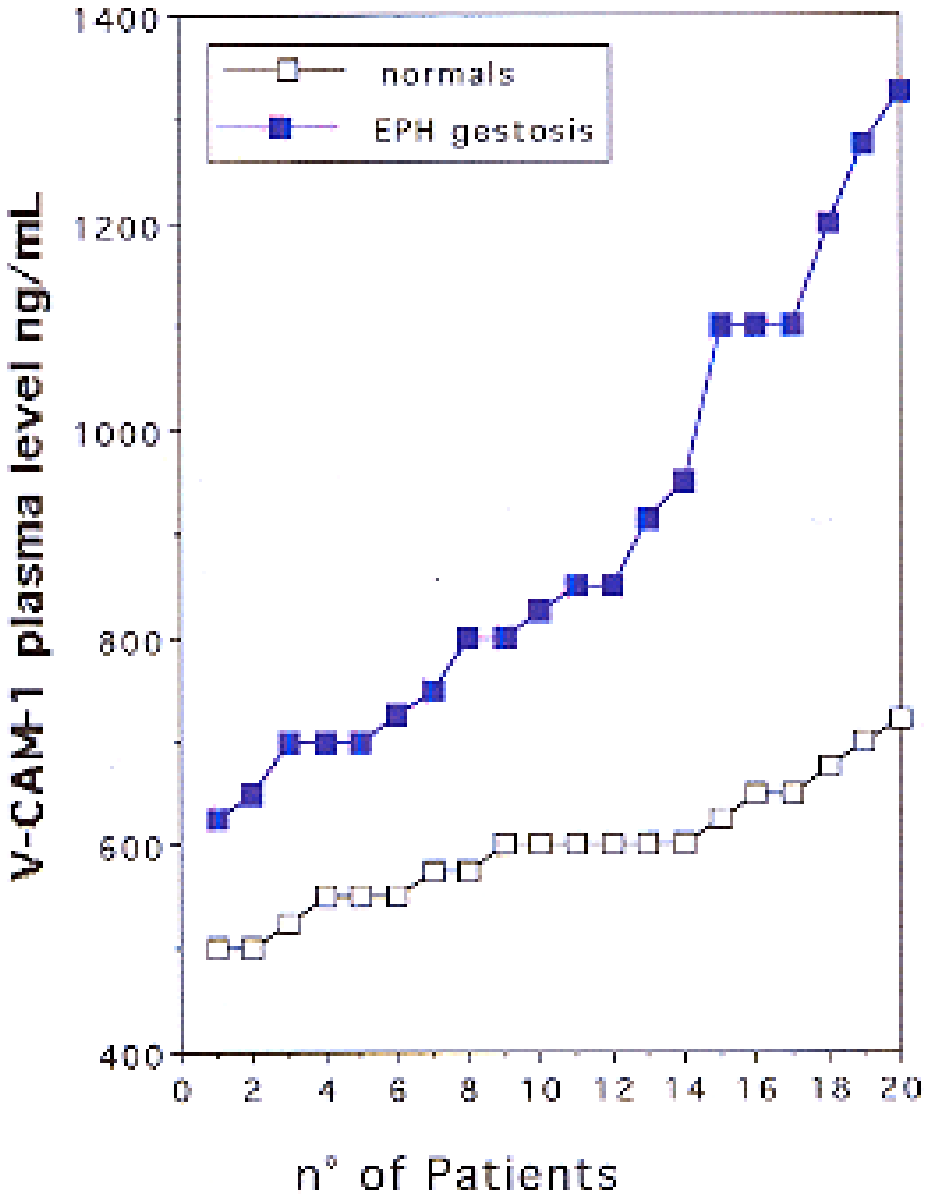
HLA-DR	4	3	2	1
preeclampsia	0	27	40	3
controls	37	28	5	0

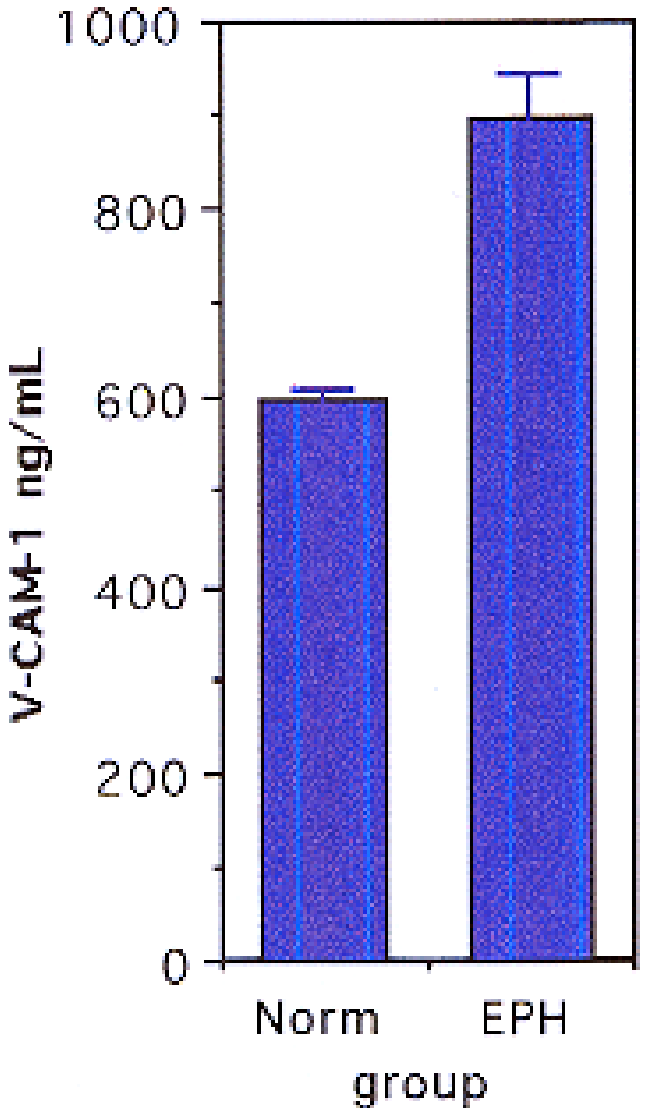
These results show that parents associated with preeclamptic pregnancies generally possess homozygosity and /or a small total number (less than 3) of different HLA-DR types than control couples according to Redman et all. 1978

Prenat. Neonat. Med 2 (1997), 325-328

INCREASED V-CAM 1 PLASMATIC LEVELS IN EPH GESTOSIS: A MARKER OF FETAL REJECTION ?

I. de Luca Brunori, L. Battini, M. Simonelli, A.R. Genazzani


normals
EPH gestosis
V-CAM-1 plasma level ng/mL
1400
1200
1000
800
600
400
0
2
4
6
8
10
12
14
16
18
20
n° of Patients


V-CAM-1 ng/mL
1000
800
600
400
200
0
Norm
EPH
group

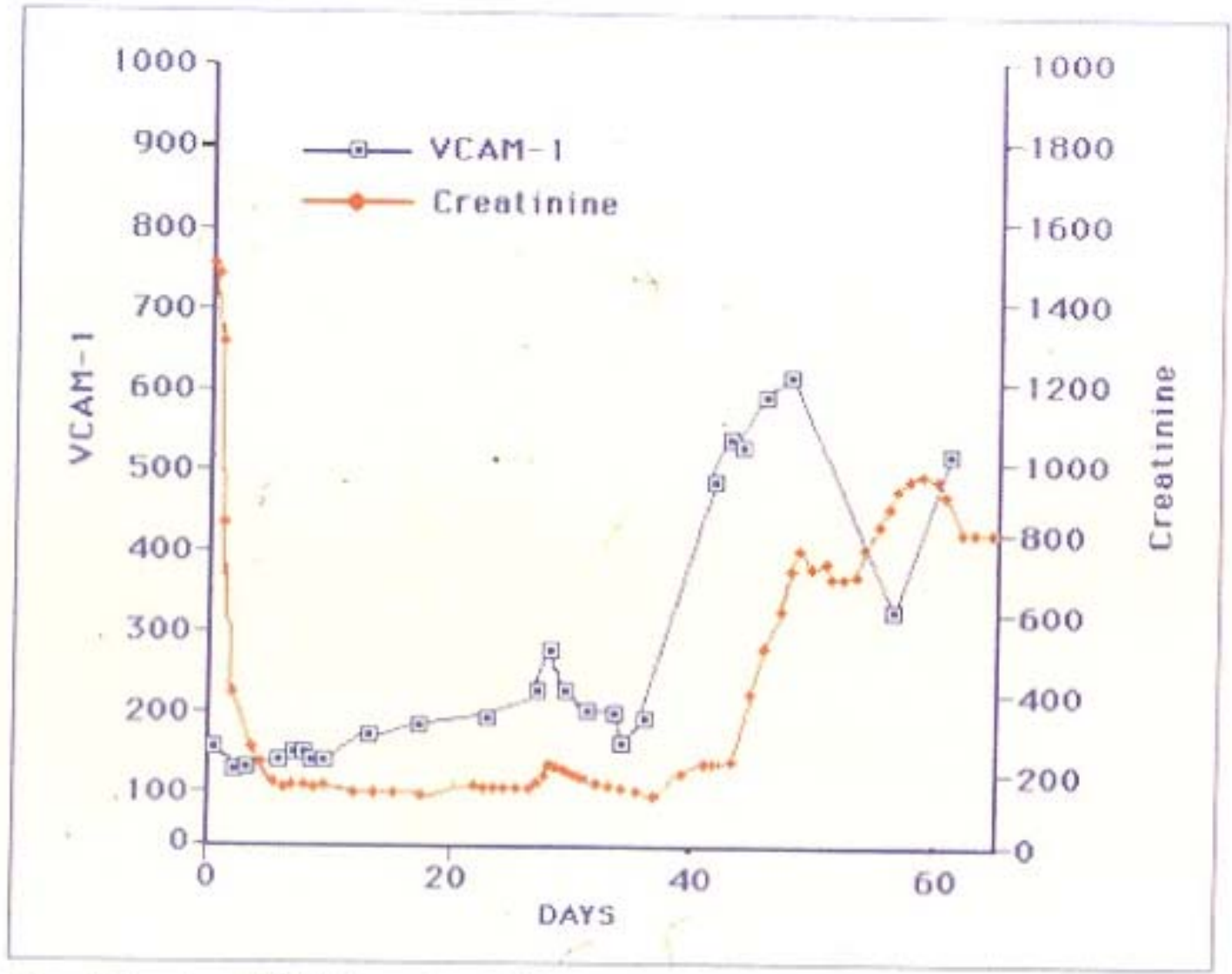
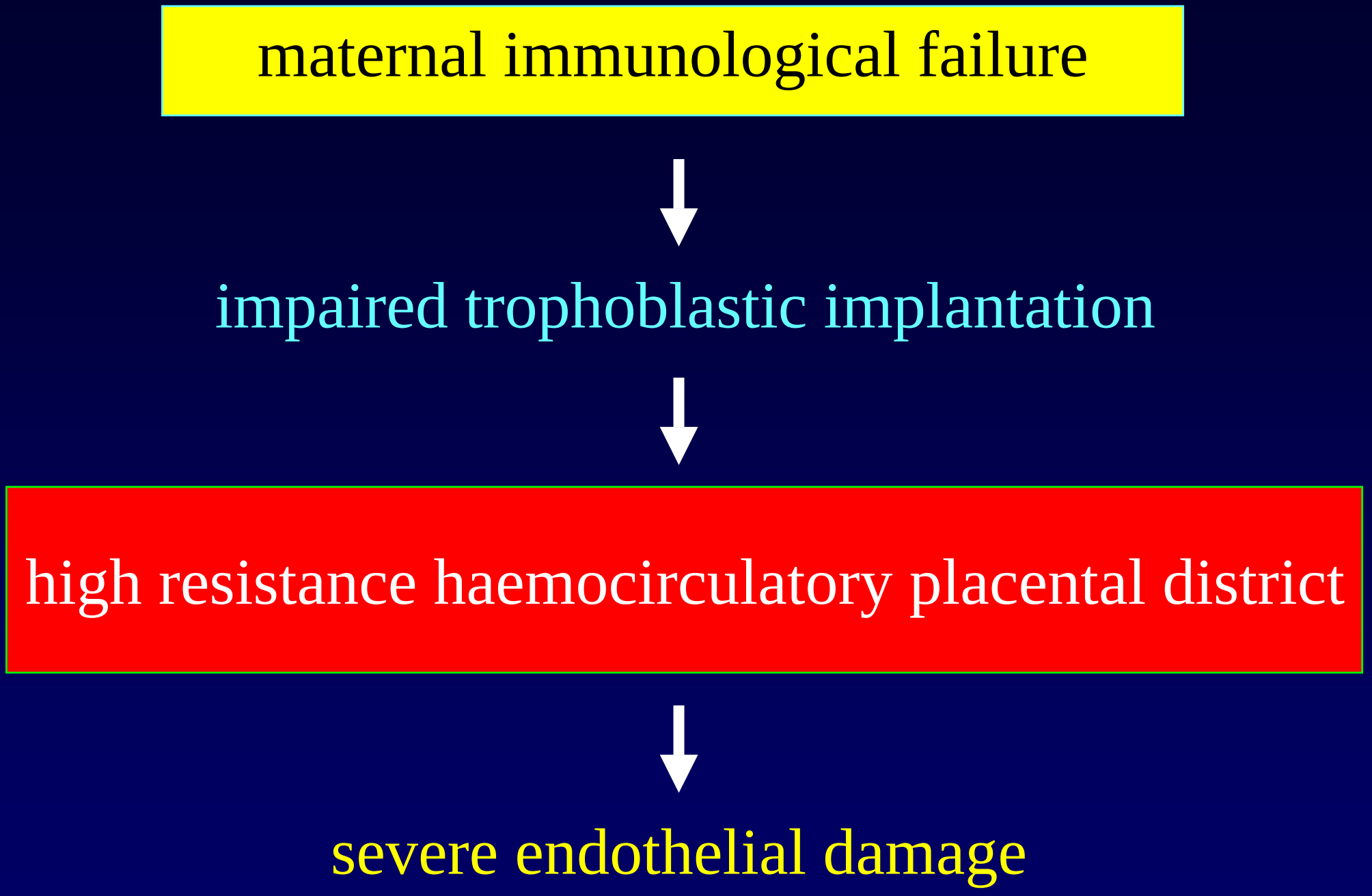


Fig. 2. Levels of VCAM-1 and creatinine were monitored in a patient following renal allograft at day 0. VCAM-1 levels appeared to rise coincident with, or slightly before, the rise in creatinine, the routine monitor of graft function. Information courtesy of Prof. A. Rees and Dr J. Hughes, Hammersmith Hospital, London, UK

DISCUSSION

Redman et al. (1978) found maternal homozygosity HLA-A and B in severe preeclampsia and asserted, in agreement with Jenkins et al., that the reduced HLA-Class I antigenical variety between partners could be the cause of the failure of maternal protective reaction


maternal immunological failure
impaired trophoblastic implantation
high resistance haemocirculatory placental district
severe endothelial damage

HLA-DR homozygosity

Reduced antigenical variety

↓

Failure of maternal immunological protective reaction

↓

Preeclampsia

This highlights an important message:

Reproductive outcome

is particularly **successful** in

couples of **heterozygous partners**.

Biodiversity enhances survival and reproduction



Welcome to biodiversity



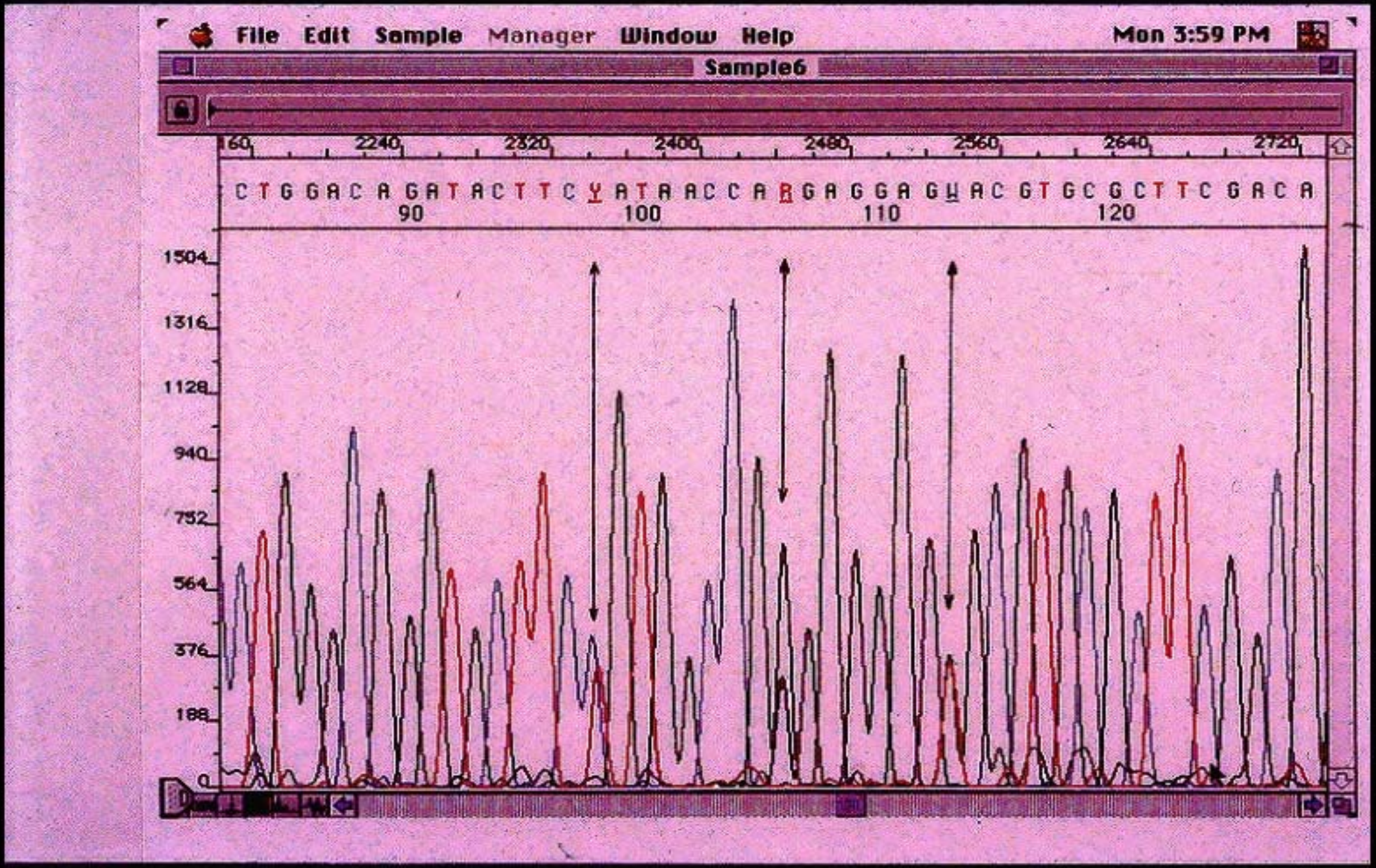



UPDATE

HLA-DRβ1 alleles DNA sequencing:

preliminary results

In this update we have examined the 2nd exon of the human gene, HLA-DRβ1, on the short arm of the cromosome 6 using the DNA sequence-based typing (S-BT) PCR


File Edit Sample Manager Window Help
Mon 3:59 PM
Sample6
2160
2240
2320
2400
2480
2560
2640
2720
C T G G A C A G A T A C T T C Y A T A A C C A R G A G G A G W A C G T G C G C T T C G A C A
90
100
110
120
1504
1316
1128
940
752
564
376
188
0

Match-tools genetic program

Sample: 1881 **Library: DRB1.L226**

Preliminary Report: **Exact match to: DRB1*1301/1302.** See Warnings Below.

Files : 1881

Polymorphic Position Report

```
                   11 1111111111 1111111111 1111111222 2222222222 2222222222 22 | nucleotide
4444577788 8888999900 0011111134 4445567777 7777799000 1111111222 3333355555 67 |   number
0268747802 4789147912 5902367930 3692990123 4578969789 0124568012 0123402478 40 |

GGCTTGTCTG CATATCACAG GAAGTGCTGT GCTCGGATGC CGGTAGAAGA CGACGGCGCG CCTACGGTKK CA <>   1881
consensus
.......... .......... .......... .......... .......... .......... .......... ..  >   1881

.......... .......... .......... .......... .......... .......... .......... ..  DRB1*1301/1302
.......... .......... .......... .......... .......... .......... ........W. ..  DRB1*1301/1316
.......... .......... .......... .......... ......M... .......... .......... ..  DRB1*1301/1329
```

Differently from other techniques like SSO-PCR or SSP-PCR, in which the alleles discrimination is indirectly performed, the **DNA sequencing** allows us to directly read the nucleotides sequences occurring in the alleles.

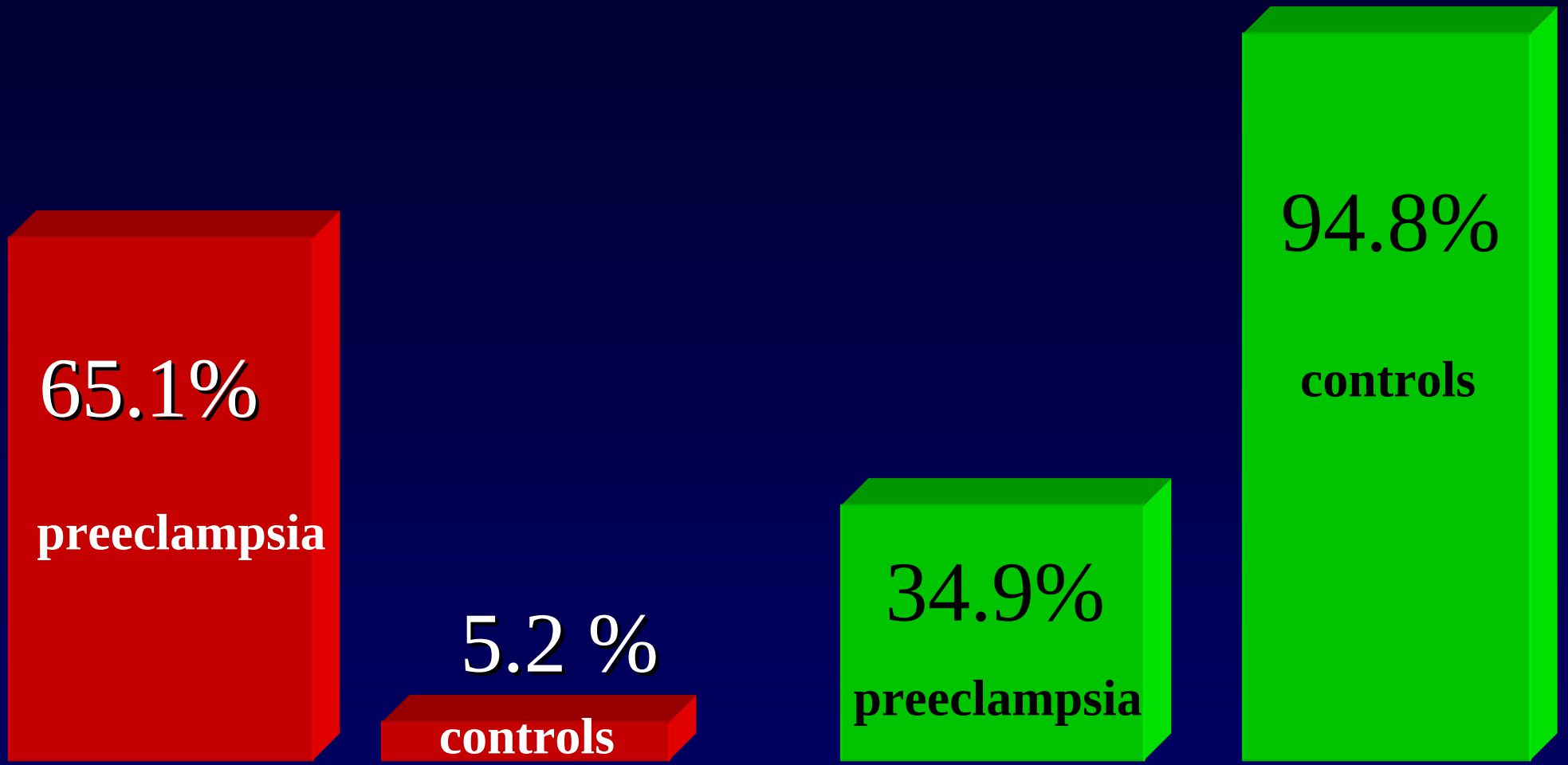
Then it is possible to truly identify the **real homozygosity** whereas the other techniques were only able to evaluate the presumed homozygosity

CASES STUDY

Study group: 56 couples of preeclamptic women

Control group: 64 couples of physiologic pregnant women

HLA-DRβ1 TYPING RESULTS



P<0.00001

The HLA-DRβ1 second exon sequencing has demonstrated:

- the presence of a real homozygosity in preeclampsia
- the not recurrence of a particular known HLA-DRβ1 allele
- the absence of a new HLA-DRβ1 allele
- the absence of punctiform mutations

HLA-DRβ1 homozygosity

Preeclampsia

Couple’s disease

SUMMARIZING

from our results various evidences seem to confirm the hypothesis of a
“ fetal rejection in preeclampsia “

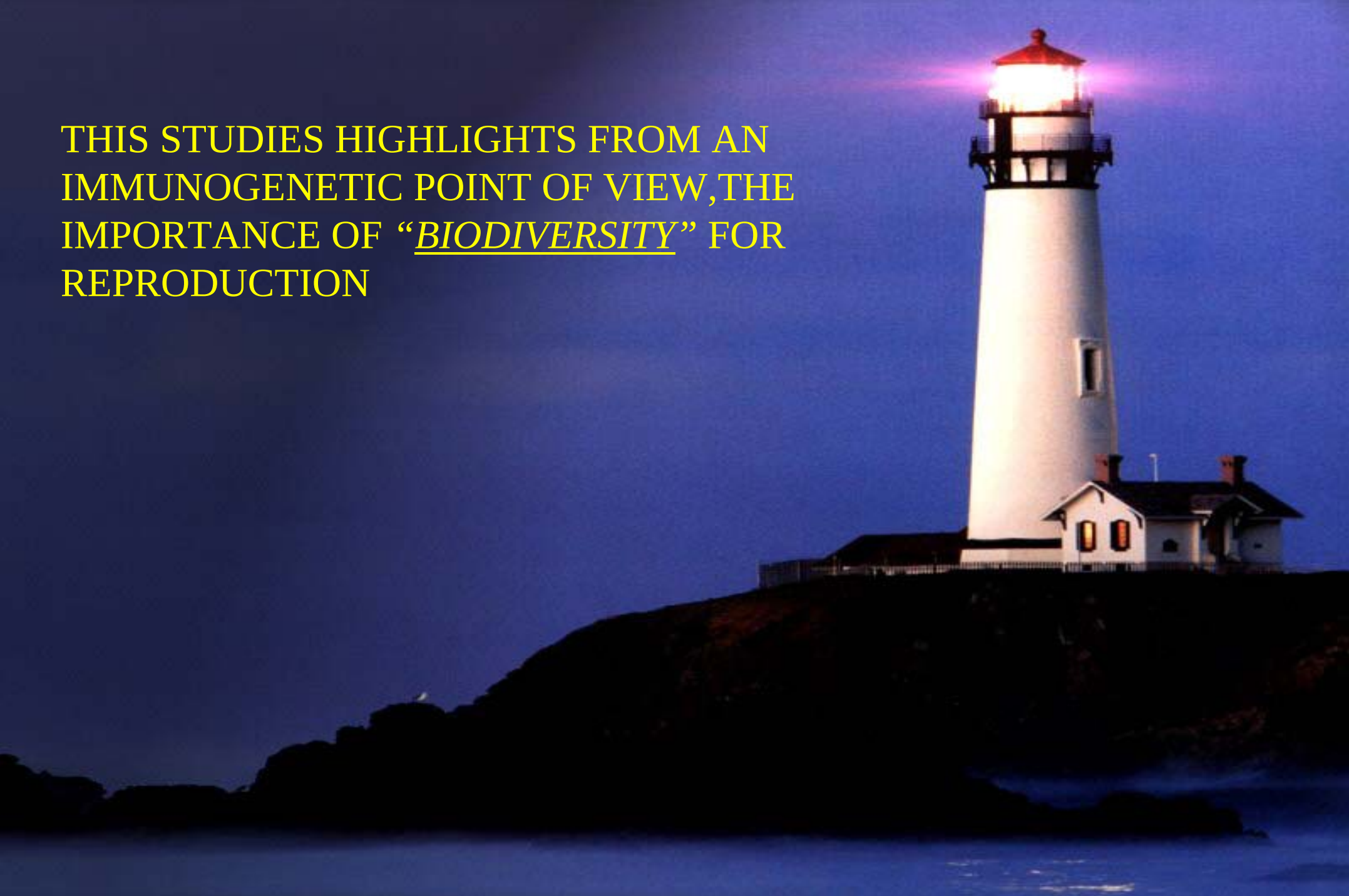
1) The ultra-microscopical evidence of the placental endothelial breakage in preeclampsia

2) The immunohistochemical evidence of the intense and widespread HLA-DR antigens expression in placentae from preeclampsia versus controls

3) The significant HLA-DR homozygosity excess in Couples of preeclamptic women versus controls, as confirmed also by DNA-sequencing.

4) The significant increase of V-CAM 1 plasmatic levels, as demonstrated in other graft rejective reactions.

5) Last, but not least, the clinical evidence that preeclamptic syndrome, quickly disappears after pregnancy interruption, as the fetus could be the cause of a maternal rejective reaction


THIS STUDIES HIGHLIGHTS FROM AN IMMUNOGENETIC POINT OF VIEW,THE IMPORTANCE OF “BIODIVERSITY” FOR REPRODUCTION

THANK YOU FOR YOUR ATTENTION