Primary adrenal insufficiency (PAI)

Deficit of glucocorticoid, androgen and/or mineralcorticoid production caused by the damage, destruction or impaired function of steroid-producing adrenocortical cells

BARTHOLOMAEI
EVSTACHII

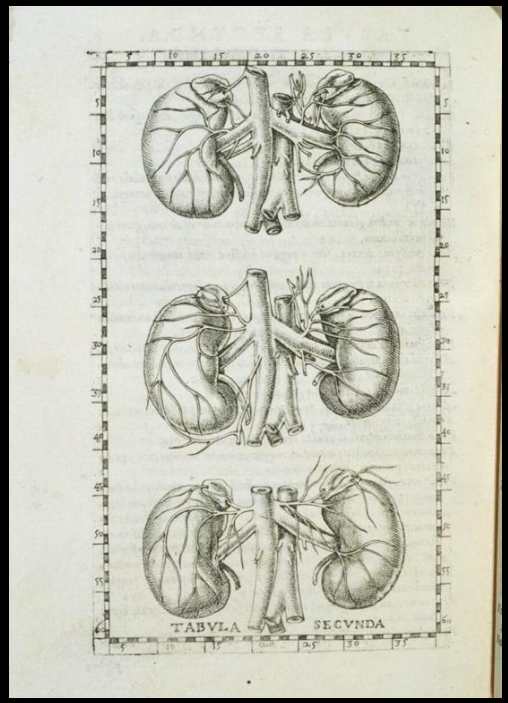
SANCTOSEVERINATIS MEDICI
AC PHILOSOPHI,
OPVSCVLA ANATOMICA.

Quorum numerum & argumenta antrsa pagina indicabit.

Cum Priuilegio Summi Pont. Illustriß. Senatus Veneti, Secundi Francorum Regis, & Catholicæ ac Cæsareæ Maiestatis.

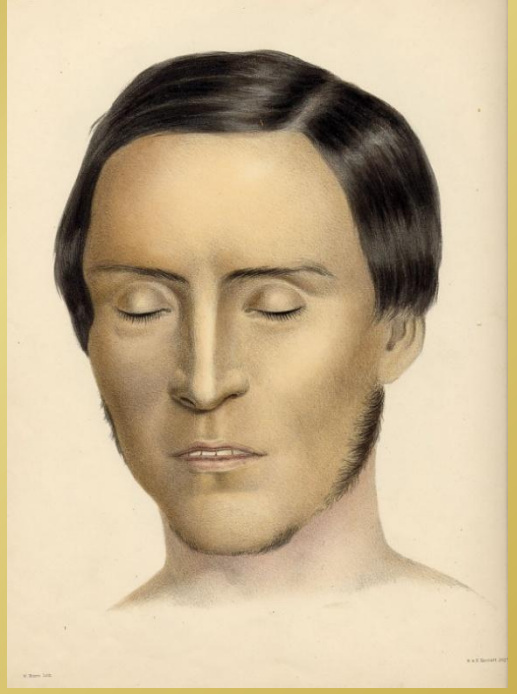
VENETIIS,
M D LXIIII.

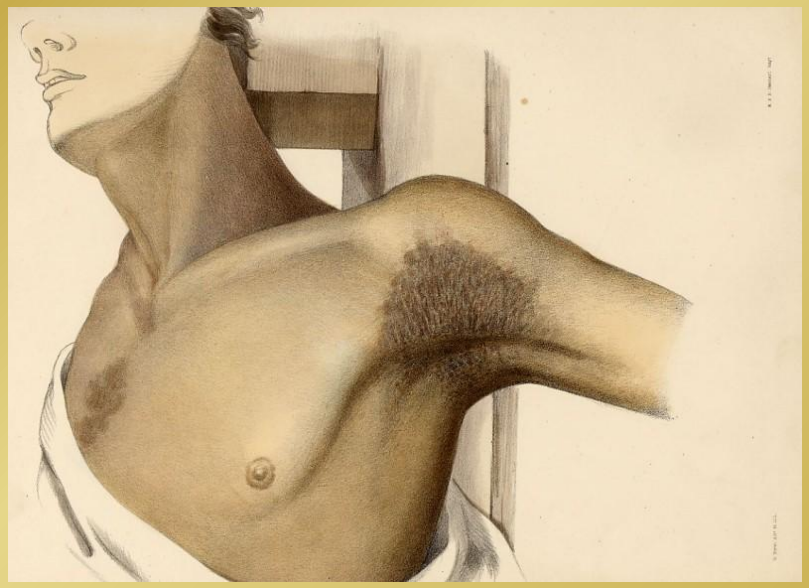
Vincentius Luchinus excudebat.

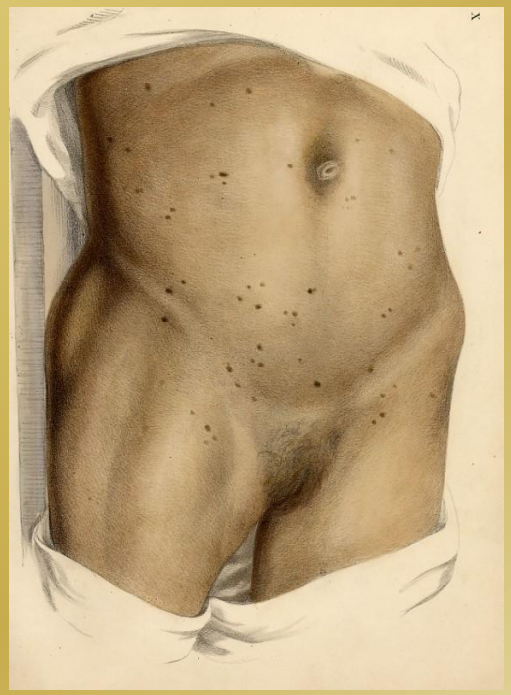


In 1855, Thomas Addison described a novel disease entity which he had observed in 11 patients:

"The leading and characteristic features of the morbid state to which I would direct attention are anaemia, general languor and debility, remarkable feebleness of the heart's action, irritability of the stomach and a peculiar change of colour in the skin, occurring in connexion with a diseased condition of the 'supra-renal capsules' ".







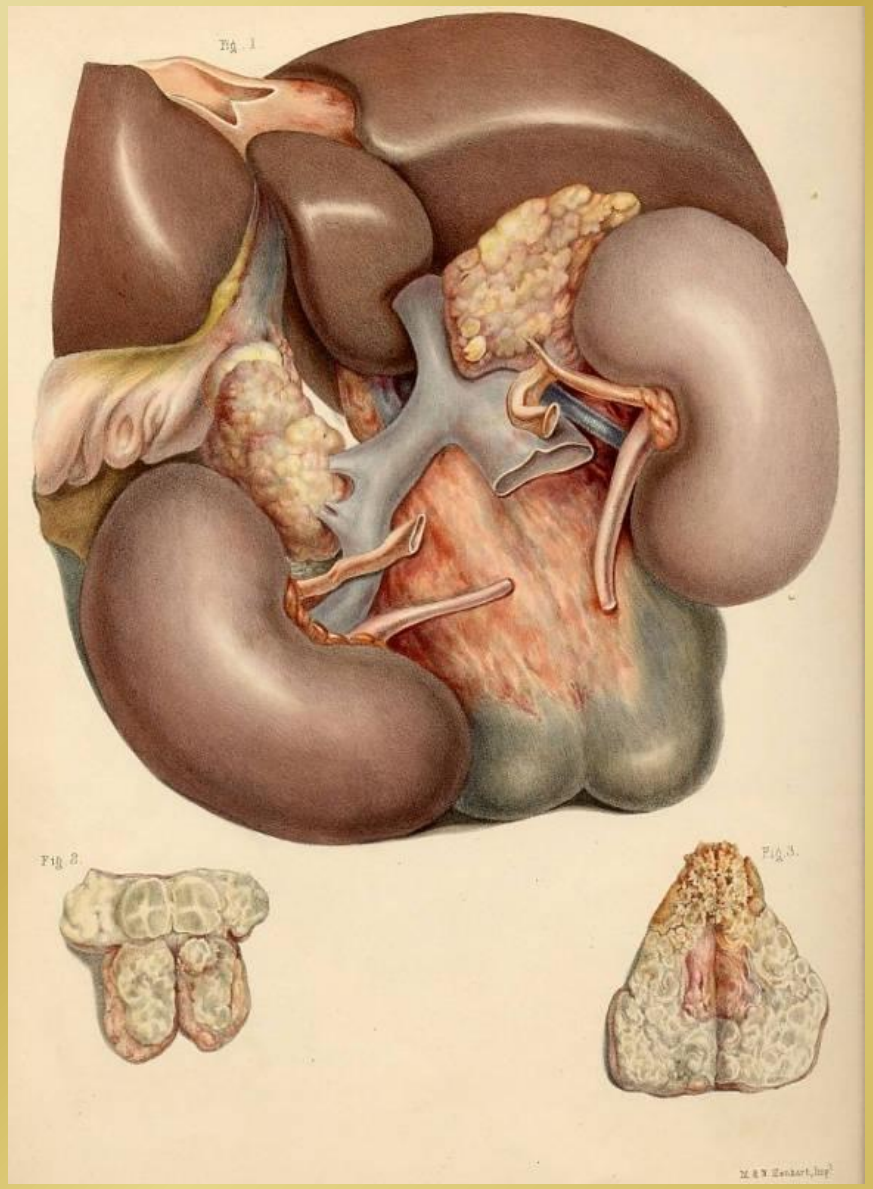


Fig. 1.
Fig. 2.
Fig. 3.

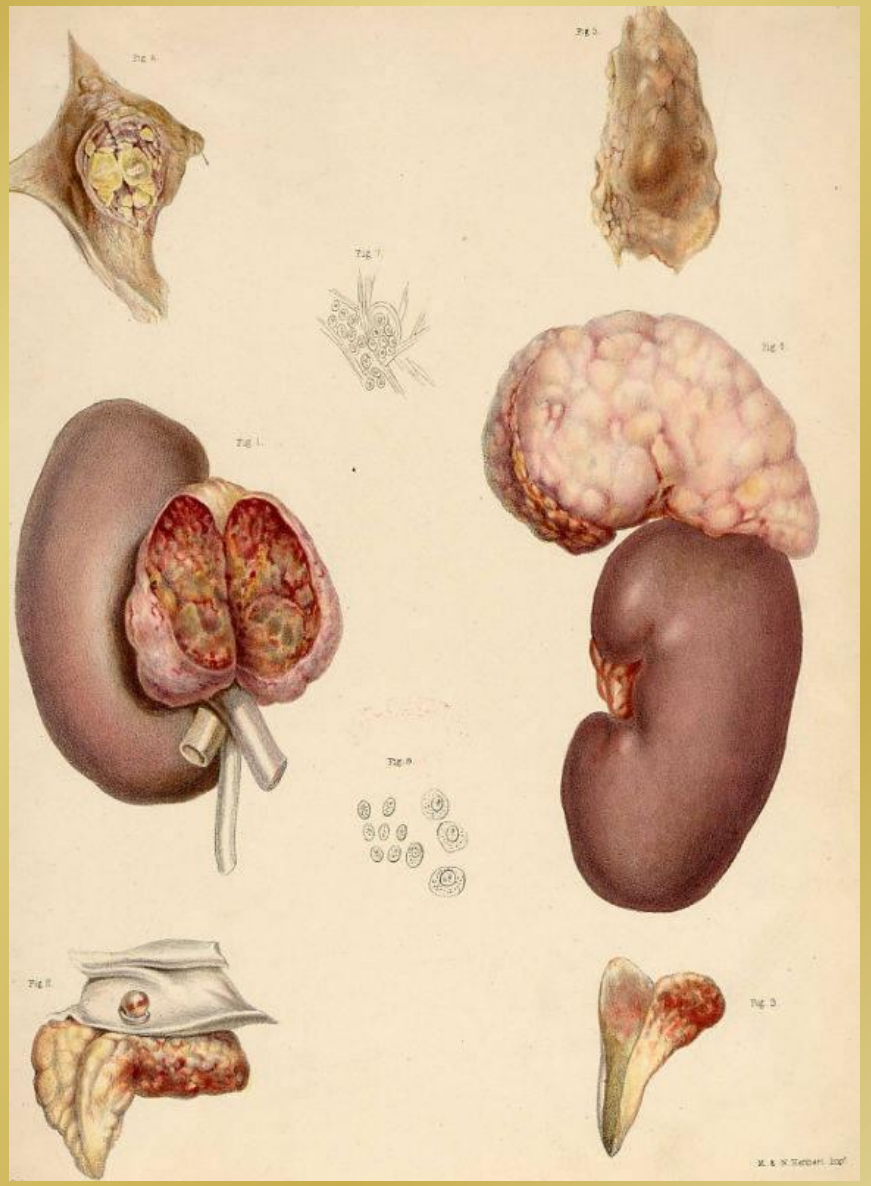


Fig. 4.
Fig. 5.
Fig. 7.
Fig. 6.
Fig. 1.
Fig. 8.
Fig. 11.
Fig. 3.

La descrizione del primo caso di Morbo di Addison autoimmune

Prevalence of PAI in Umbria 1996
(Resident population 811,887)

117 cases/million (95% CI: 95-143)

(1 case every 8,500 persons)

Prevalence in males: 106/million (95% CI: 77-144)

Prevalence in females: 127/million (95% CI: 95-166)

Ascertainment degree: 97%

(Capture/recapture analysis)

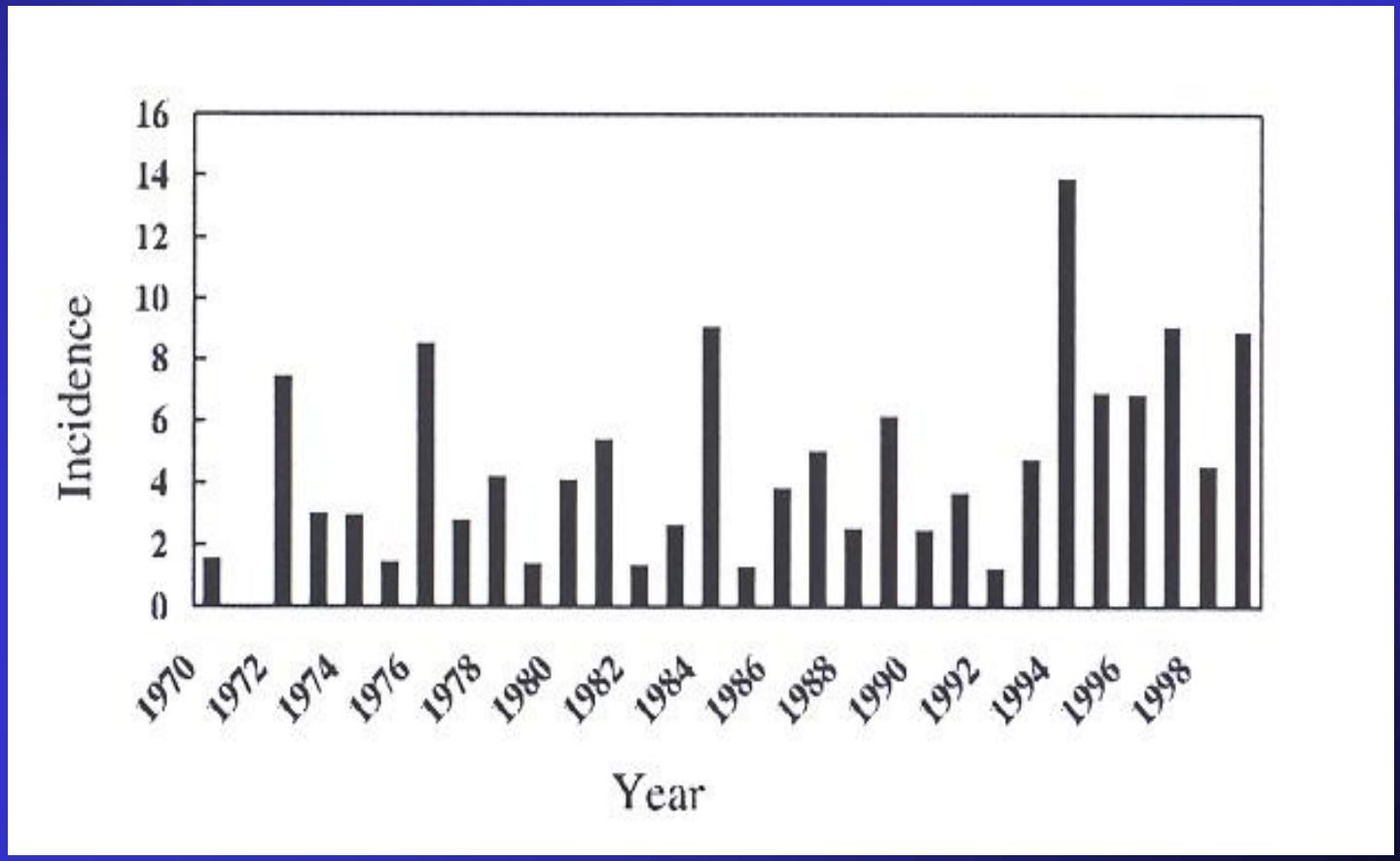
Laureti, Vecchi, Santeusanio & Falorni JCEM, 1999

High prevalence and increasing incidence of Addison's disease in western Norway

(Løvas & Husebye Clin. Endocrinology 2002)

Prevalence: 140 cases/milion inhabitants
(1 case every 7,150 persons)

Mean incidence: 0.62/100.000/year



ALMENO 100.000 PAZIENTI CON INSUFFICIENZA CORTICOSURRENALICA PRIMITIVA

ALMENO 8.000 PAZIENTI CON INSUFFICIENZA CORTICOSURRENALICA PRIMITIVA

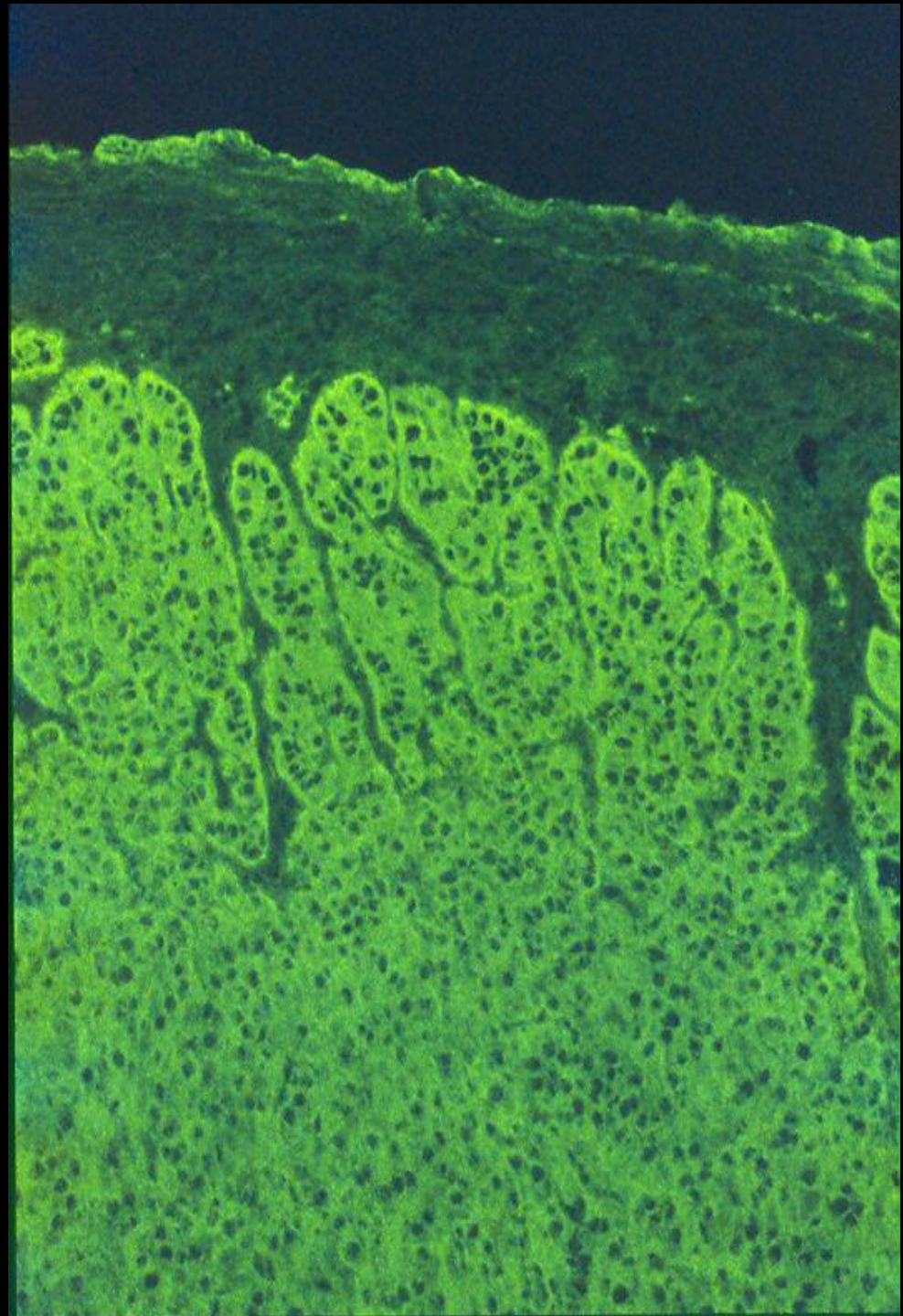
MEDIAMENTE 1 NUOVO CASO DI INSUFFICIENZA CORTICOSURRENALICA PRIMITIVA AL GIORNO

Causes of PAI

✓Autoimmune	90 %
✓Post-tuberculosis	5-8 %
✓X-linked adrenoleukodystrophy	4-5 %
✓Rare forms	1 %

Anderson JR, Goudie RB, Gray KG, Timbury GC.
Autoantibodies in Addison's disease.
Lancet 1:1123–1124 (1957)

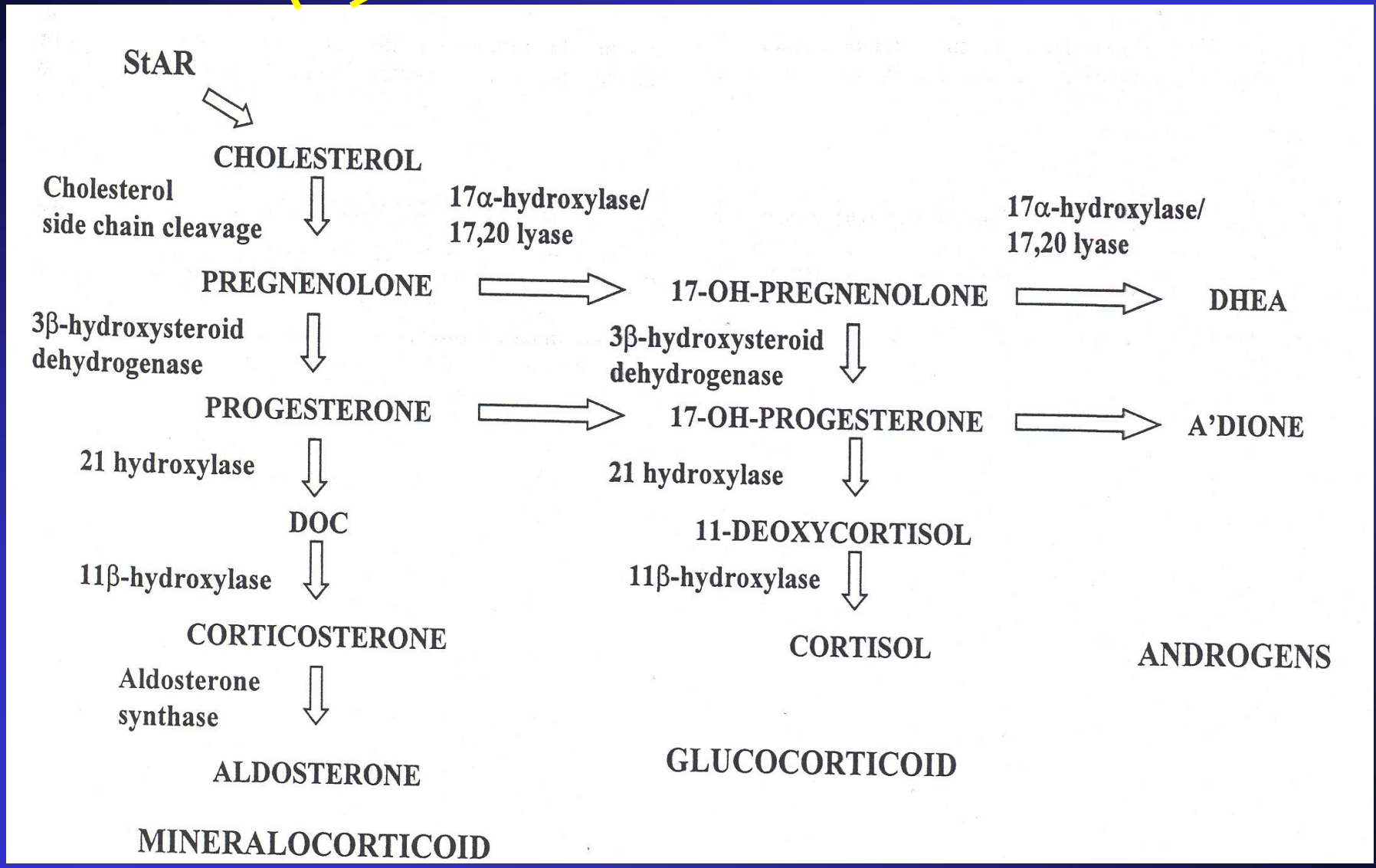
Blizzard RM, Kyle M.
Studies of the adrenal antigens and autoantibodies in Addison's disease.
J Clin Invest 42:1653–1660 (1963).



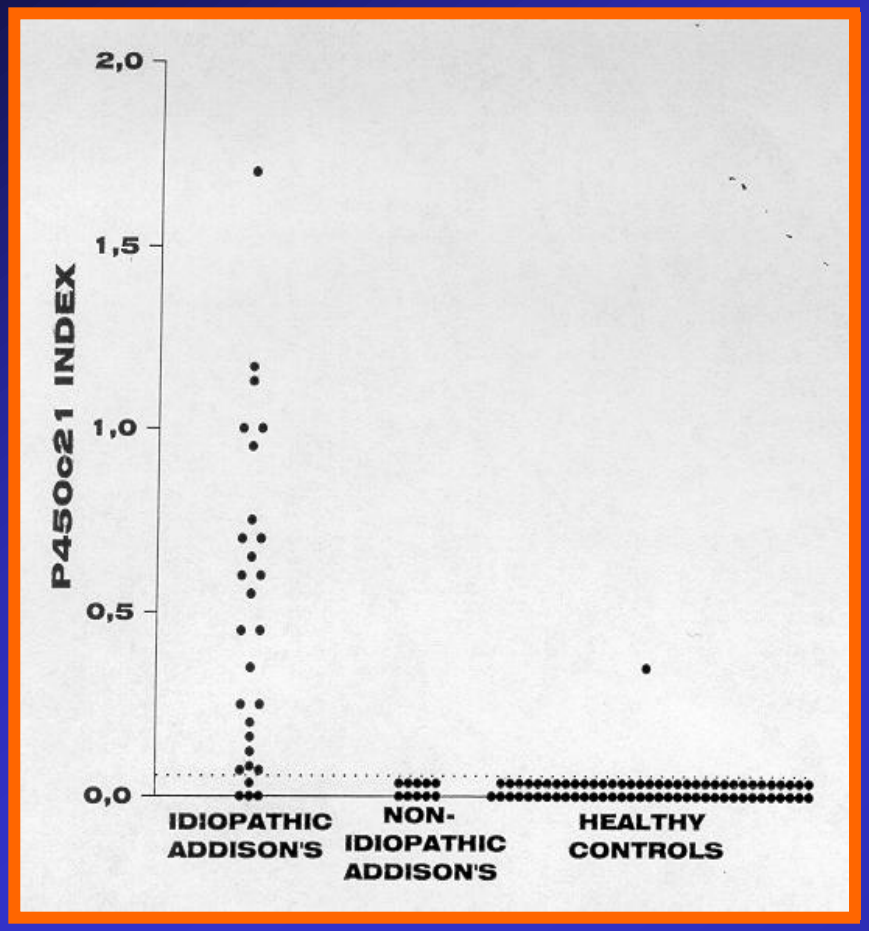
ICSP AUTOIMMUNE

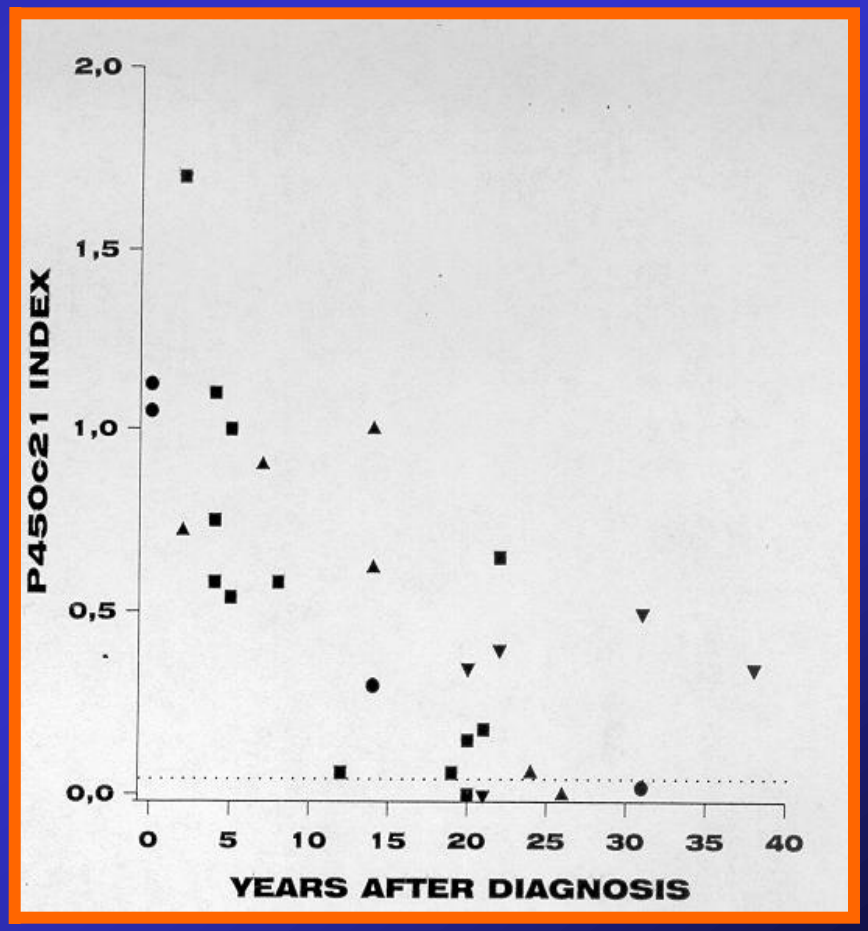
L’enzima 21-idrossilasi è il principale autoantigene cortico-surrenalico

Winqvist O et al. Lancet, 1992; Bednarek J et al. FEBS, 1992


LDL
HDL
StAR
CHOLESTEROL
Cholesterol
side chain cleavage
PREGNENOLONE
3β-hydroxysteroid
dehydrogenase
PROGESTERONE
21 hydroxylase
DOC
11β-hydroxylase
CORTICOSTERONE
Aldosterone
synthase
ALDOSTERONE
MINERALOCORTICOID
17α-hydroxylase/
17,20 lyase
17-OH-PREGNENOLONE
3β-hydroxysteroid
dehydrogenase
17-OH-PROGESTERONE
21 hydroxylase
11-DEOXYCORTISOL
11β-hydroxylase
CORTISOL
GLUCOCORTICOID
17α-hydroxylase/
17,20 lyase
DHEA
A'DIONE
ANDROGENS

21OHAb in ICSP





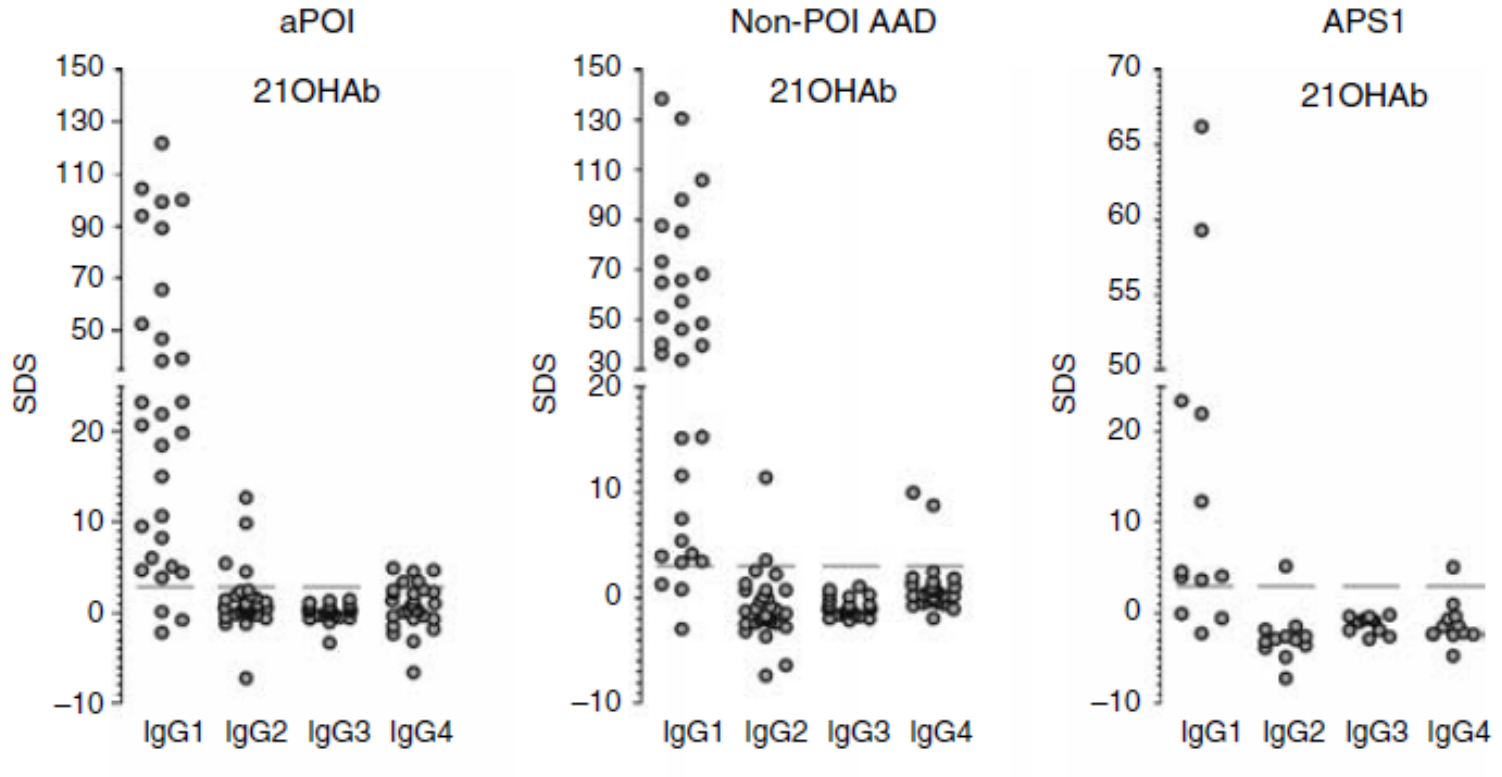
Falorni A. et al, JCEM 1995

European Journal of Endocrinology (2010) **163** 309–317 ISSN 0804-4643

CLINICAL STUDY

Autoantibody responses in autoimmune ovarian insufficiency and in Addison's disease are IgG1 dominated and suggest a predominant, but not exclusive, Th1 type of response

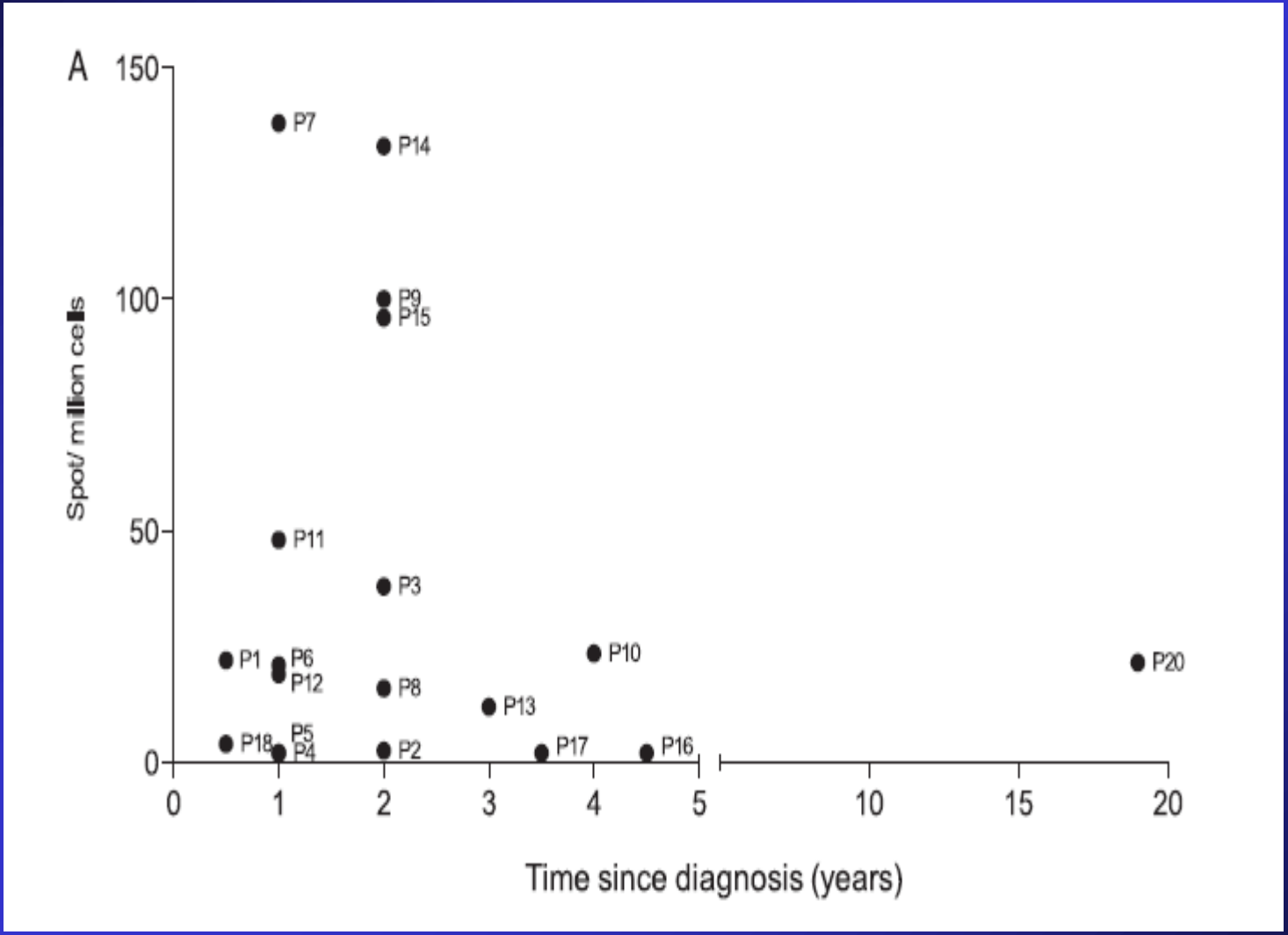
Annalisa Brozzetti, Stefania Marzotti, Daria La Torre†, Maria Luisa Bacosi, Silvia Morelli, Vittorio Bini, Bruno Ambrosi[1], Roberta Giordano[2], Roberto Perniola[3], Annamaria De Bellis[4], Corrado Betterle[5] and Alberto Falorni on behalf of the Italian Addison Network



RUOLO PATOGENETICO DEGLI ANTICORPI ANTI-21-IDROSSILASI NELLO SVILUPPO DI INSUFFICIENZA CORTICOSURRENALICA

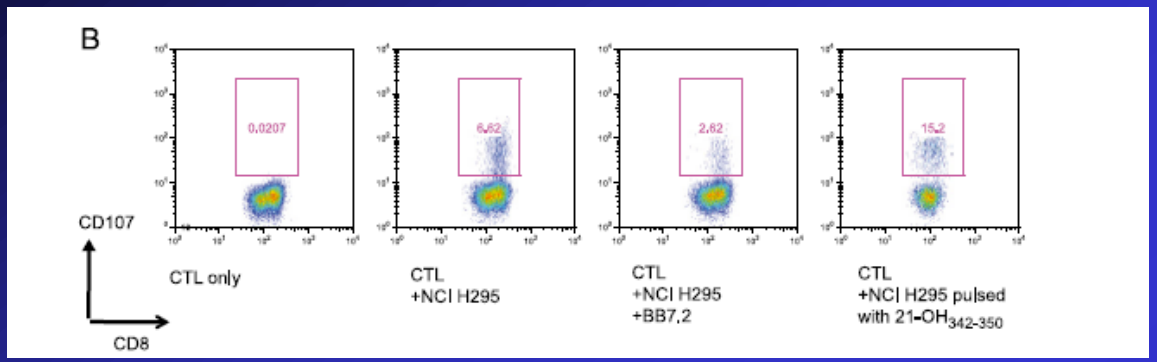
- ✓ Studi in vitro dimostrano che autoanticorpi umani anti-21OH hanno un'azione inibente l'attività enzimatica della 21OH
- ✓ Studi in vivo in pazienti con Addison autoimmune (o autoimmunità surrenalica pre-clinica) non hanno mai dimostrato un accumulo di 17OH-progesterone (il substrato della 21-idrossilasi), che si riduce consensualmente al cortisolo durante la storia naturale della malattia
- ✓ Neonati di madre con Addison autoimmune non presentano segni clinici o biochimici di insufficienza surrenalica, malgrado il passaggio transplacentare di anticorpi anti-21OH

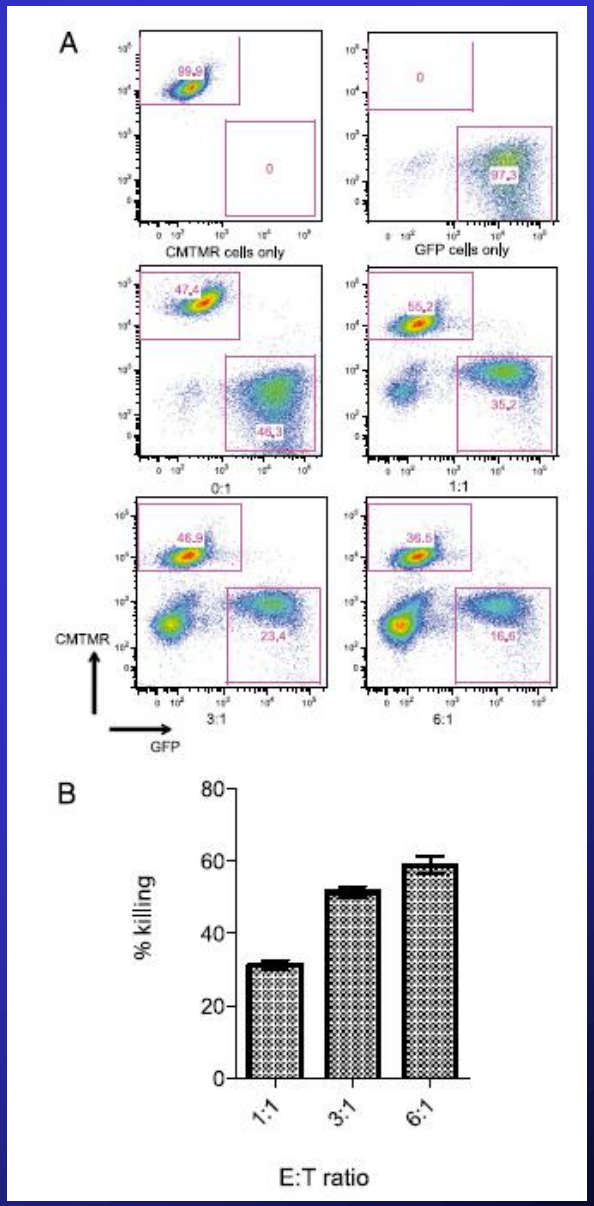
High Frequency of Cytolytic 21-Hydroxylase–Specific CD8+ T Cells in Autoimmune Addison's Disease Patients



Dawoodji et al J Immunol 2014

High Frequency of Cytolytic 21-Hydroxylase–Specific CD8+ T Cells in Autoimmune Addison's Disease Patients

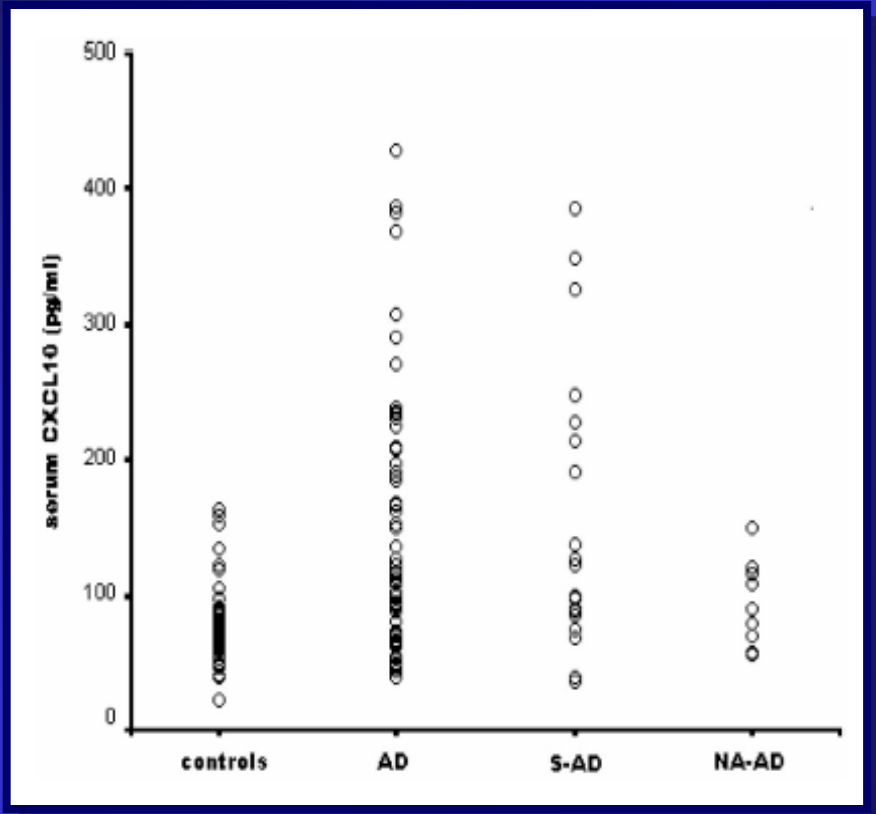


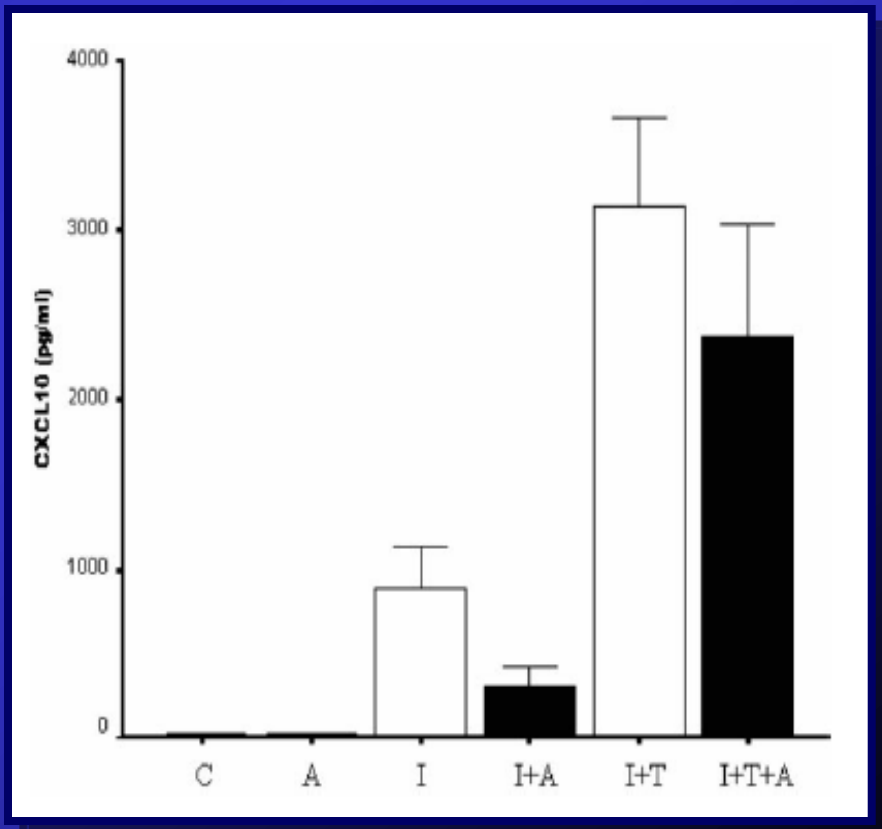


Dawoodji et al J Immunol 2014

Elevated Serum Interferon-γ-Inducible Chemokine-10/ CXC Chemokine Ligand-10 in Autoimmune Primary Adrenal Insufficiency and *in Vitro* Expression in Human Adrenal Cells Primary Cultures after Stimulation with Proinflammatory Cytokines

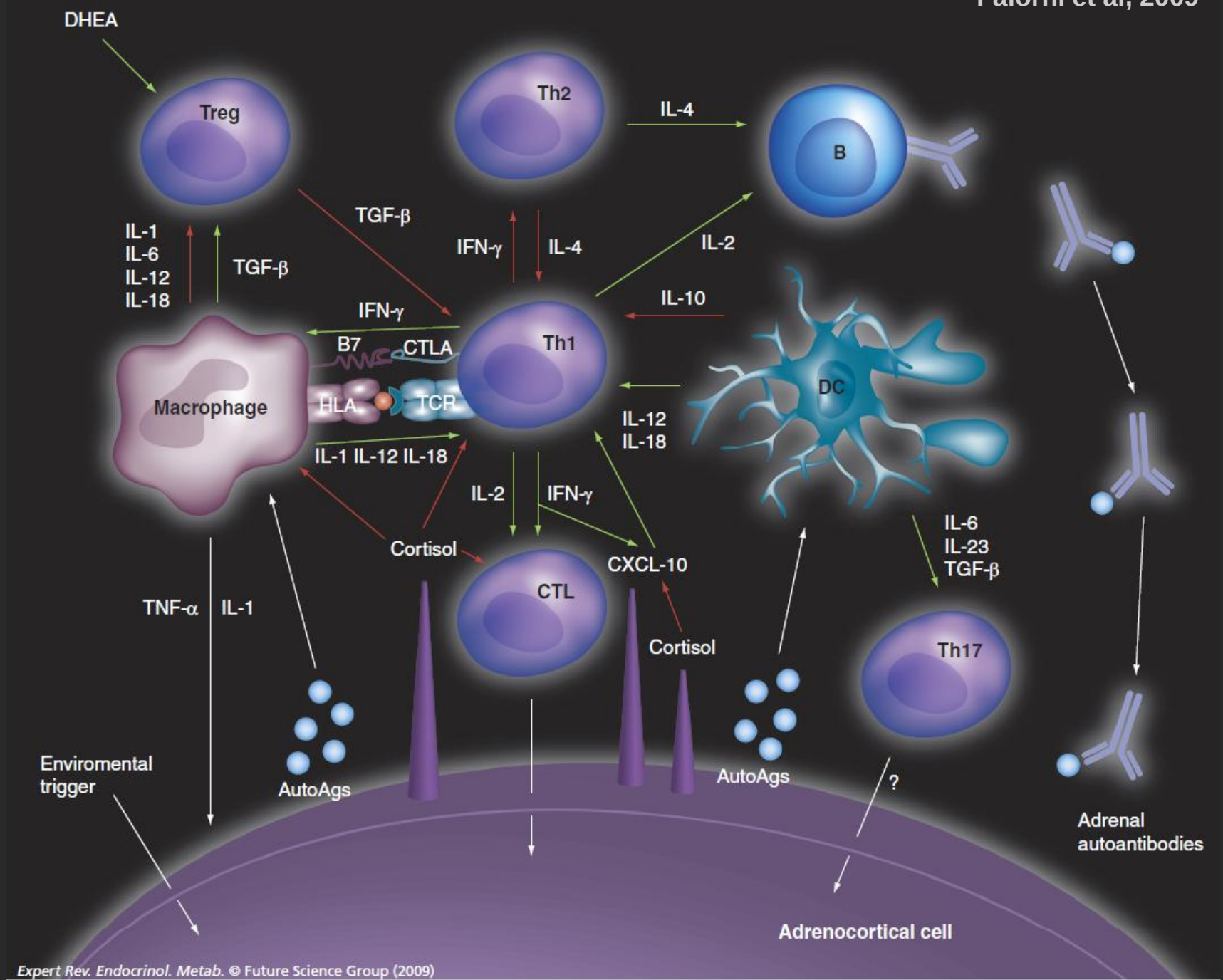
Mario Rotondi, Alberto Falorni, Annamaria De Bellis, Stefano Laureti, Pietro Ferruzzi, Paola Romagnani, Andrea Buonamano, Elena Lazzeri, Clara Crescioli, Massimo Mannelli, Fausto Santeusanio, Antonio Bellastella, and Mario Serio





J.Clin.Endocrinol.Metab. 90:2357-63,2005

Falorni et al, 2009



Estimated risk for clinical autoimmune Addison's disease

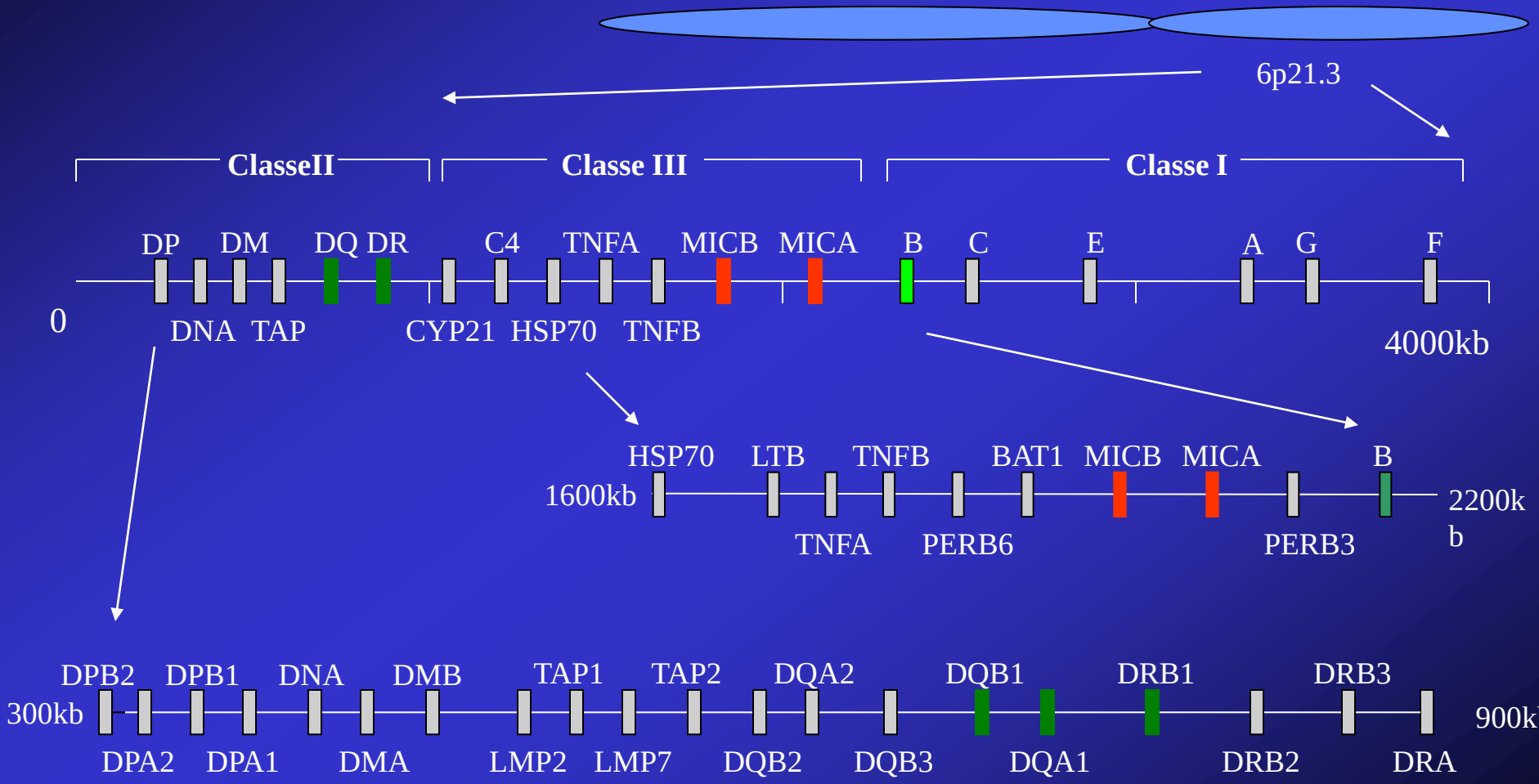
General population? 1: 7,000-7,500

First-degree relatives of AAD patients?
1:200 – 1:400

Patients with thyroid autoimmune diseases or T1DM?
1:200 – 1:400

Patients with POI or hypoparathyroidism?
1:10 – 1:20

SCHEMATIC REPRESENTATION OF HLA SYSTEM



HLA CLASS II IN AUTOIMMUNE ADDISON'S (Italian Addison Network Study 2)

Haplotypes/ Genotypes	Patients (n=166)	Controls (n=1,056)	OR	Pc
DRB1*03-DQA1*0501-DQB1*0201	94 (56%)	141 (13%)	8.47 (5.94-12.1)	<0.003
DRB1*04	56 (34%)	127 (12%)	3.72 (2.57-5.40)	<0.0015
DQA1*0301-DQB1*0302 (DQ8)	40 (24%)	86 (8%)	3.58 (2.36-5.44)	<0.003
DR3-DQ2/ DR4-DQ8	27 (16%)	12 (1.1%)	16.9 (8.37-34.1)	<0.009

Gambelunghe G et al, Diabetes 2005

HLA-DRB1*04 SUBTYPING IN T1DM AND AAD

	Healthy control subjects (n = 127) [n (%)]*	Type 1 diabetic patients (n = 113)†		AAD patients (n = 56)‡	
		n (%)	P_c	n (%)	P_c
*0401	27 (21)	36 (31)	NS	15 (27)	NS
LTR13$^+$	14/27 (52)	26/36 (72)	NS	12/15 (80)	NS
*0402	31 (24)	45 (38)	NS	20 (36)	NS
LTR13$^+$	10/31 (32)	25/45 (56)	NS	15/20 (75)	NS
*0403	34 (27)	0	<0.001	0	<0.001
LTR13$^+$	1/34 (3)§	ND		ND	
*0404	23 (18)	21 (18)	NS	7 (12)	NS
LTR13$^+$	8/23 (35)	11/21 (52)	NS	4/7 (57)	NS
*0405	7 (6)	7 (6)	NS	7 (12)	NS
LTR13$^+$	2/7 (29)	4/7 (57)	NS	5/7 (71)	NS
Others	8 (6)	8 (7)	NS	8 (14)	NS
LTR13$^+$	2/8 (25)	5/8 (62)	NS	4/8 (50)	NS

Gambelunghe G et al, Diabetes 2005

GENETICS OF AUTOIMMUNE ADDISON'S

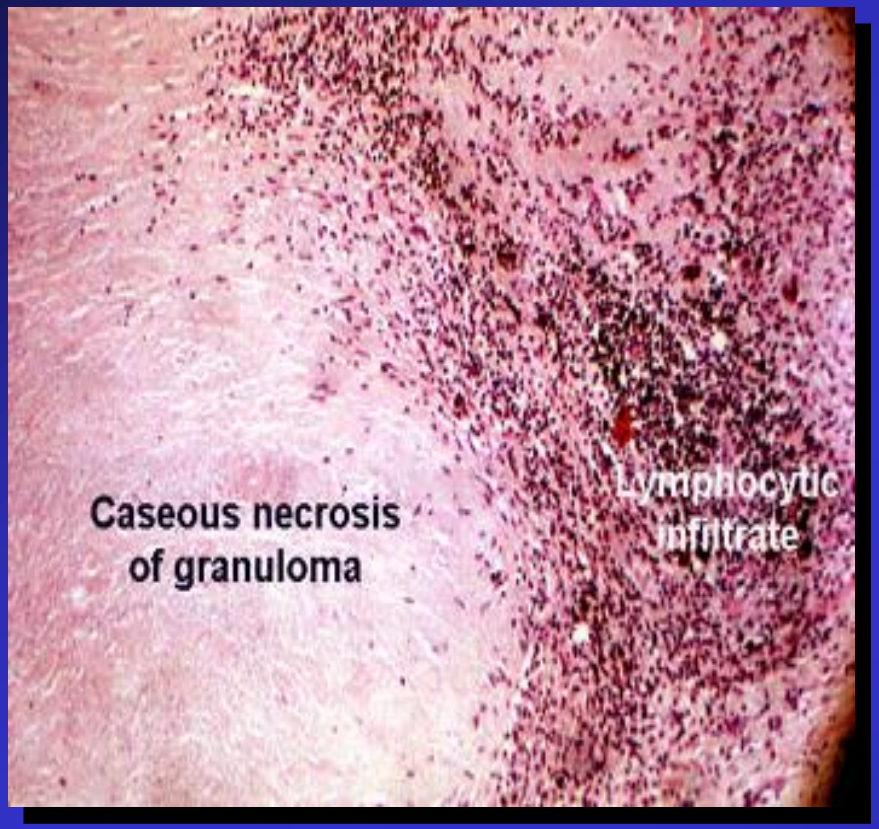
Gene	High risk	Strength of association
DRB1	*03, *04	Strong/primary
DQA1	*0501, *0301	Strong/primary
DQB1	*0201, *0302	Strong/primary
MICA	5.1	Confirmed/secondary?
HLA-B	no B15	Negatively associated
CTLA-4	G position 49	Confirmed
STAT4	*rs4274624*	Confirmed
PTPN22	T position 1858	Weak
Vitamin D receptor	ff, tt	Weak
MHC2TA/CIITA	G position -168	Confirmed
CYP27B1	CC position 1260	To be confirmed

Genes associated with Addison's disease, type 1 diabetes and autoimmune thyroid disease.

Gene class	Addison's disease	Type 1 diabetes	Autoimmune thyroid disease
	Gene or variant	Gene or variant	Gene or variant
Organ specific genes	?	*VNTR* of the Insulin promoter	*TSH Receptor* (for Graves' disease)
Immune related genes			
MHC class I		*HLA-B*	*HLA-C* and *HLA-B*
MHC class II	*DR3-DQ2*	*DR3-DQ2*	*DRB1*
	*DR4(DRB1*0404)-DQ8*	*DR4*(DRB1*0401 or DRB1*0404)-*DQ8*	*DQA1*
Non-MHC	*CTLA-4*	*CTLA-4*	*CTLA-4*
	PTPN22	*PTPN22*	*PTPN22*
	NALP1	*NALP1*	
		IL2Rα (CD25)	

Husebye & Anderson 2011

ICSP post-tubercolare



- ✓ **Localizzazione post-primaria (diffusione linfoematogena) al corticosurrene**
- ✓ **Frequente cointeressamento dell'apparato uro-genitale.**

Diagnosi di ICSP post-tubercolare

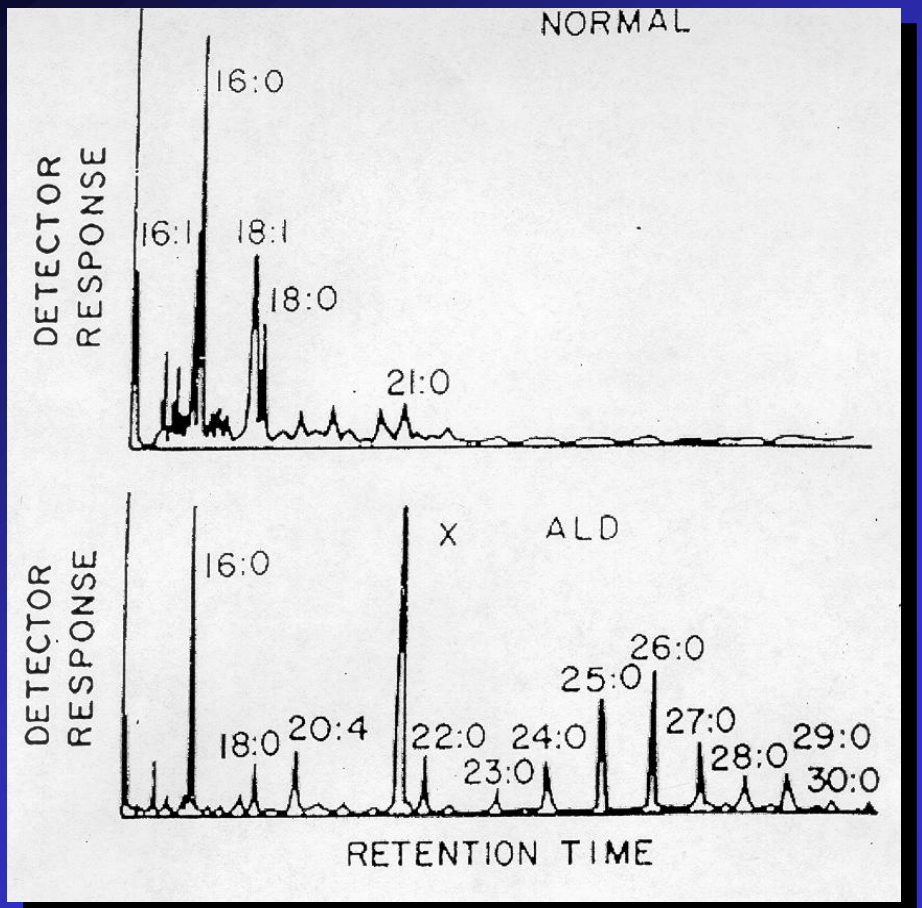
- ✓ Esame microscopico e/o colturale positivo per bacillo di Koch
- ✓ Imaging suggestivo per localizzazione tubercolare surrenalica
- ✓ Positività al PPD - Tine Test - allergometria tubercolinica
- ✓ Esiti di TBC primaria (es. evidenza di pregresso processo specifico polmonare all' RX-torace)
- ✓ Anamnesi positiva per malattia tubercolare

Imaging delle ghiandole surrenaliche per la diagnosi di ICSP post-tubercolare

- ✓ **TC-surreni: indagine gold standard**
- ✓ **RX-addome: immagini calcifiche in corrispondenza delle logge surrenali (notevoli problemi interpretativi)**
- ✓ **ECO surrenalica: ghiandole surrenaliche ingrandite bilateralmente, problemi nell'evidenziare lesioni di piccole dimensioni; immagini ipo-iperecogene intraghiandolari suggestive per fibrosi o caseosi**
- ✓ **RMN surrenali: non sono stati effettuati studi su ampie casistiche (problemi interpretativi causa la variabile densità delle componenti della ghiandola surrenalica)**

Cause di ICSP

- ✓Autoimmune 65-70 %
- ✓Tubercolosi 20-25 %
- ✓Adrenoleucodistrofia X-linked 10-20 % (dei maschi)
- ✓Forme rare 2-5 %



L'ALD è una malattia genetica che colpisce circa 1 su 20.000 maschi. E' causata da mutazioni del gene dell'ALD Protein, localizzato su Xq28.

L'alterato funzionamento della VLCFA-CoA sintetasi, conseguente alla mutazione dell'ALDp, determina una riduzione della ossidazione degli acidi grassi a catena molto lunga e quindi un

Aumento delle concentrazioni plasmatiche di VLCFA

ALD e funzione testicolare

- ✓ **Il 30-50% dei casi AMN presenta un ipogonadismo ipergonadotropo:**
  - **LH ↑ nel 42-63% dei casi**
  - **FSH ↑ nel 30-57% dei casi**
  - **Testosterone ↓ o lievemente ↓ nel 30-50% dei casi**
- ✓ **Il 50% dei casi AMN sviluppa nel corso degli anni una disfunzione erettile**

Genetic causes of primary adrenocortical failure

Disorder	Genes (chromosome)
Autoimmune Addison's disease (AAD)	
APS I	AIRE (21q22)
APS II and isolated AAD	Complex trait - HLA (p21)
Adrenoleukodystrophy (ALD)	ALD gene (Xq28)
Adrenal hypoplasia congenita (AHC)	
SF-1 linked	SF-1 gene (9q33)
X-linked	DAX-1 gene (Xp21)
Familial ACTH resistance syndromes	
Familial glucorticoid deficiency	ACTHr gene (18p11)
Triple A syndrome	AAAS (12q13)
Smith-Lemli-Opitz syndrome	Δ-7-sterol reductase gene (11q12-q13)
Kearns-Sayre syndrome	Mitochondrial DNA

Presentation of Primary Adrenal Insufficiency in Childhood

Susan Hsieh and Perrin C. White

JCEM 96: E925-E928, 2011

TABLE 1. Demographics of patients with primary adrenal insufficiency

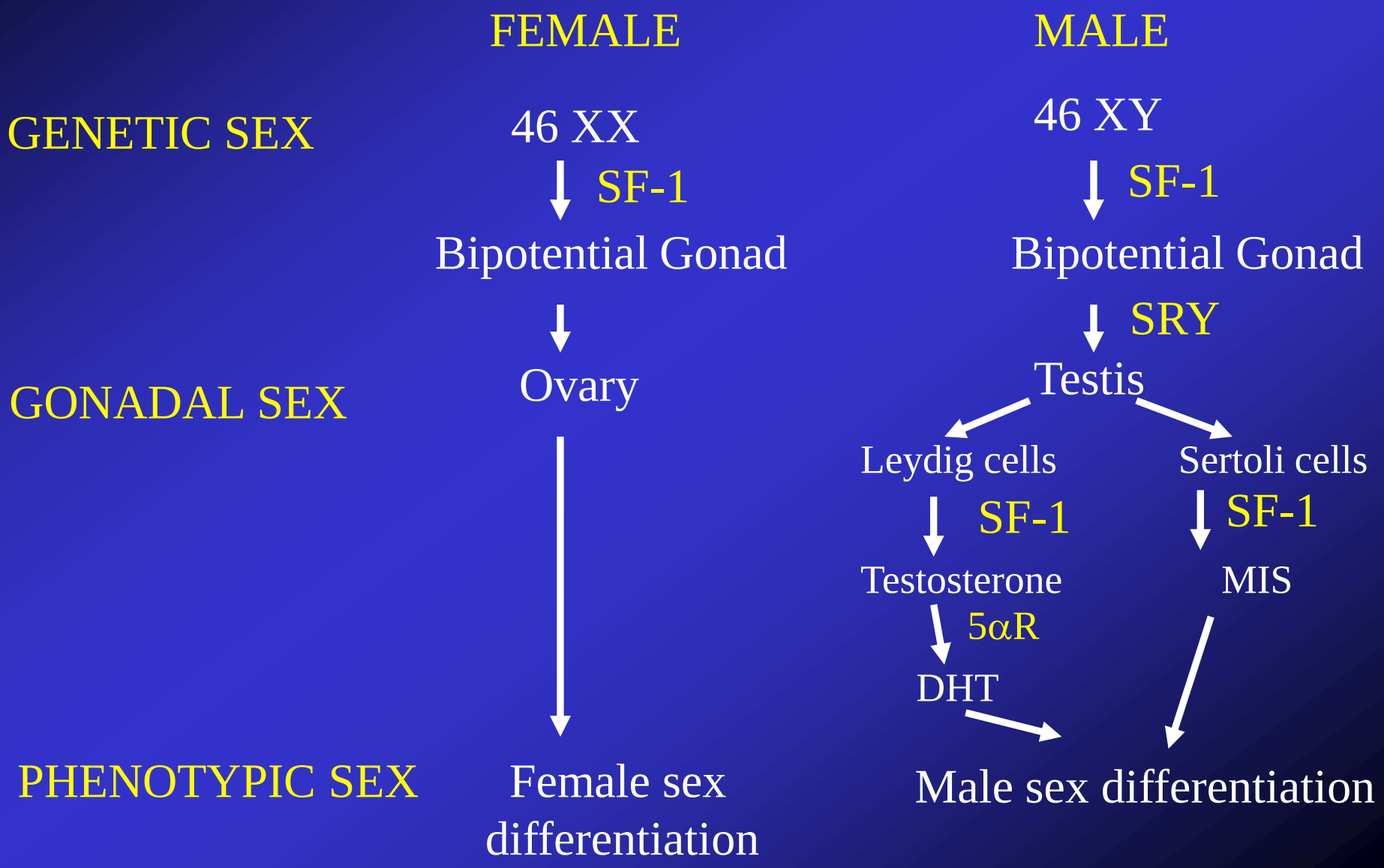
Etiology	Total, n = 42	Diagnosed at CMC, n = 20	Median (IQR) age of onset of CMC cases	Sex (male:female)	Ethnic background (W:H:A:AA)[c]
Autoimmune	18	11	14.3 (9.9–15.8)	13:5	14:3:1:0
Bilateral adrenalectomy[a]	5	0		3:2	4:1:0:0
ACTH resistance	4	0		4:0	3:1:0:0
ALD	3	3	12.1 (9.3–12.5)	3:0	1:1:0:1
APS	5	4	13.2 (10.9–14.7)	0:5	4:1:0:0
Idiopathic[b]	3	2	4.4 (4.3–4.4)	1:2	3:0:0:0
Adrenal hypoplasia congenita	2	0		2:0	2:0:0:0
Adrenal hemorrhage	2	0		0:2	1:1:0:0

[a] Adrenalectomies performed for bilateral Wilm's tumor, bilateral neuroblastoma, adrenal carcinoma due to Li Fraumeni syndrome, adrenal tumor due to Carney's complex and ectopic ACTH syndrome.

[b] Including 1 patient suspected of IMAGe syndrome.

[c] W, White; H, Hispanic; A, Asian; AA, Afro-American.

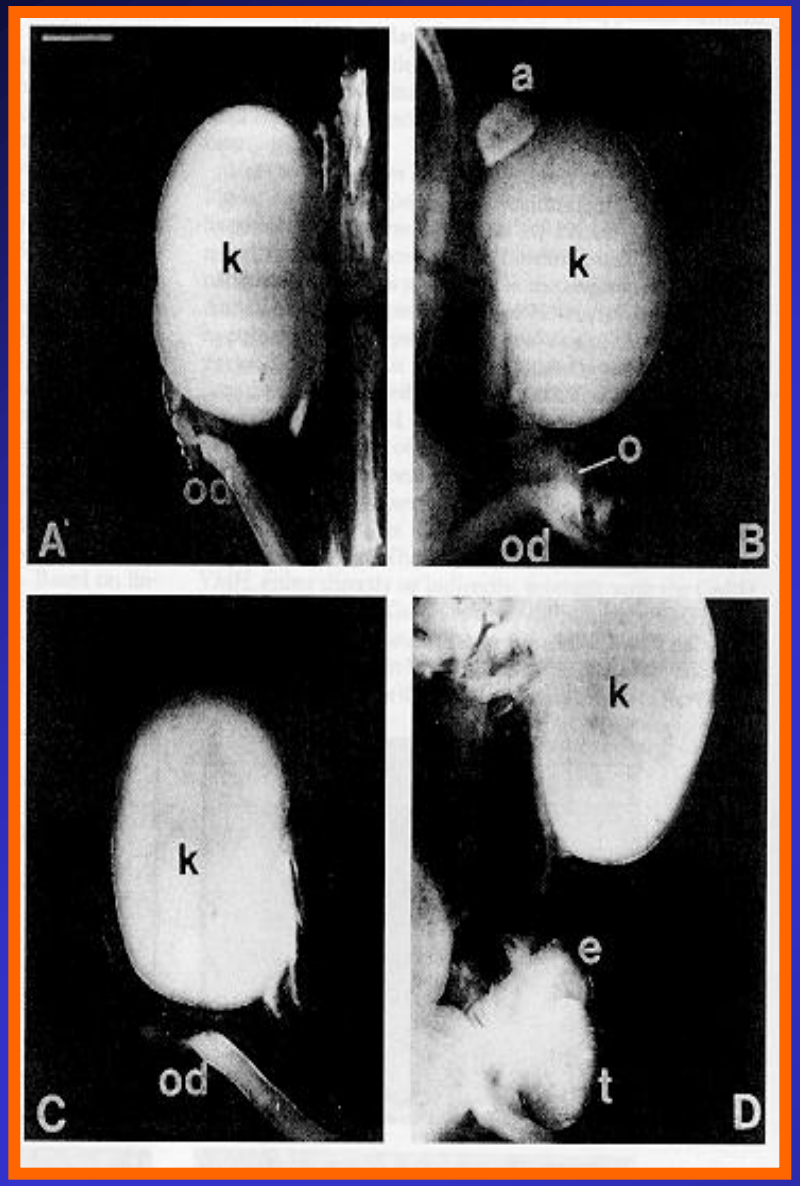
Current concepts of mammalian sexual determination and differentiation



TM WT

♀

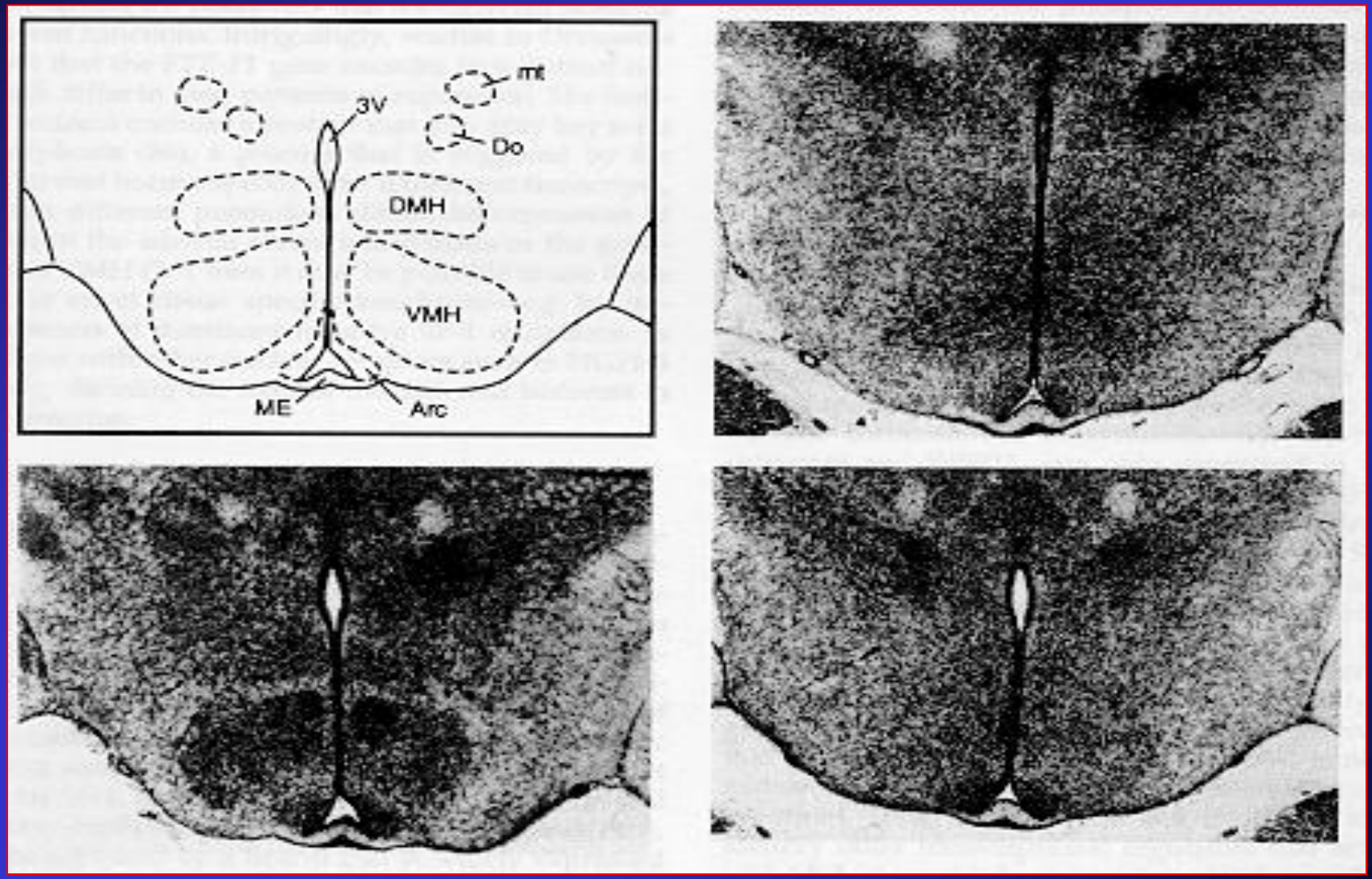
♂



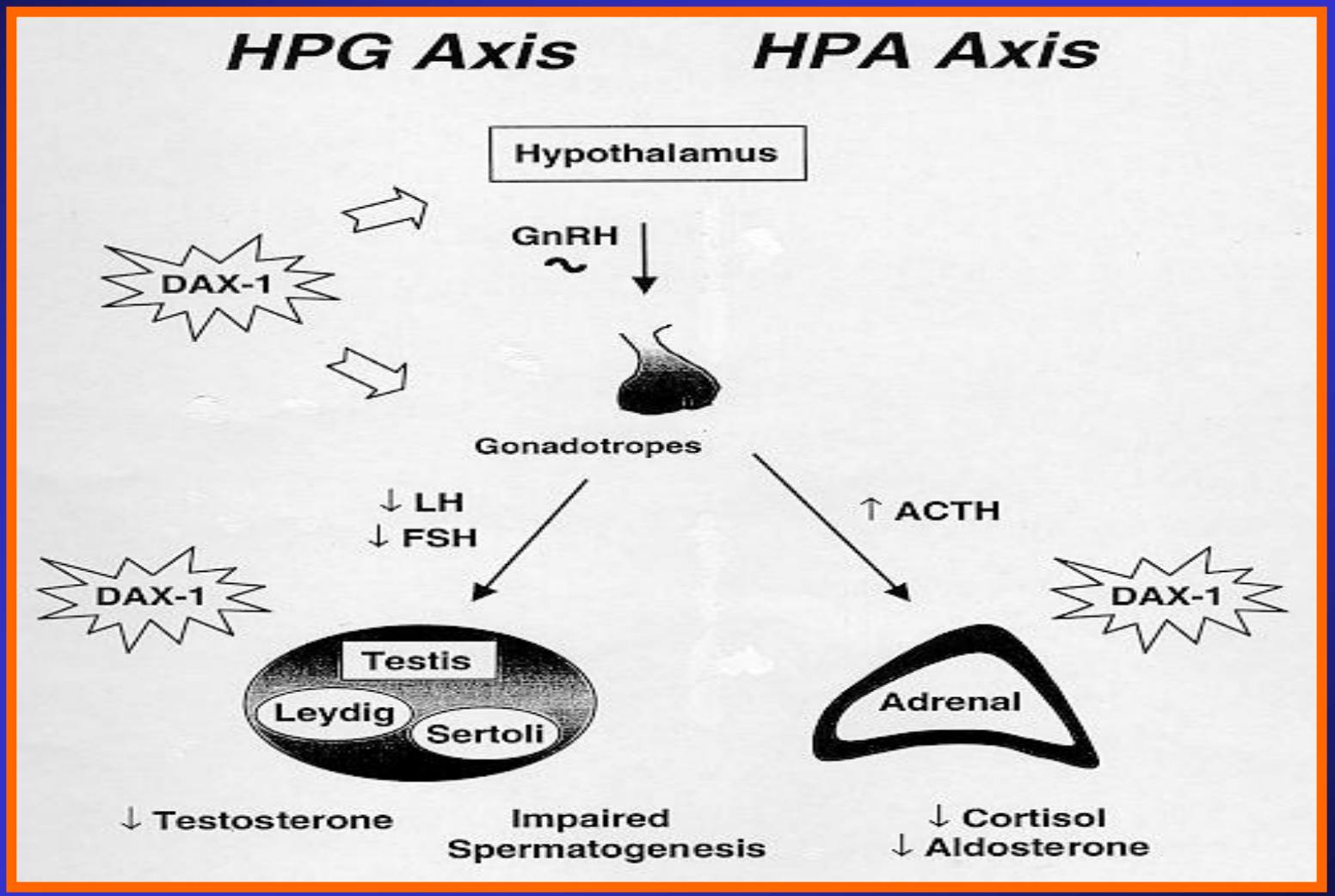
Il knock-out del gene SF-1, in topi transgenici, determina aplasia surrenalica e gonadica e persistenza di strutture di derivazione muelleriana

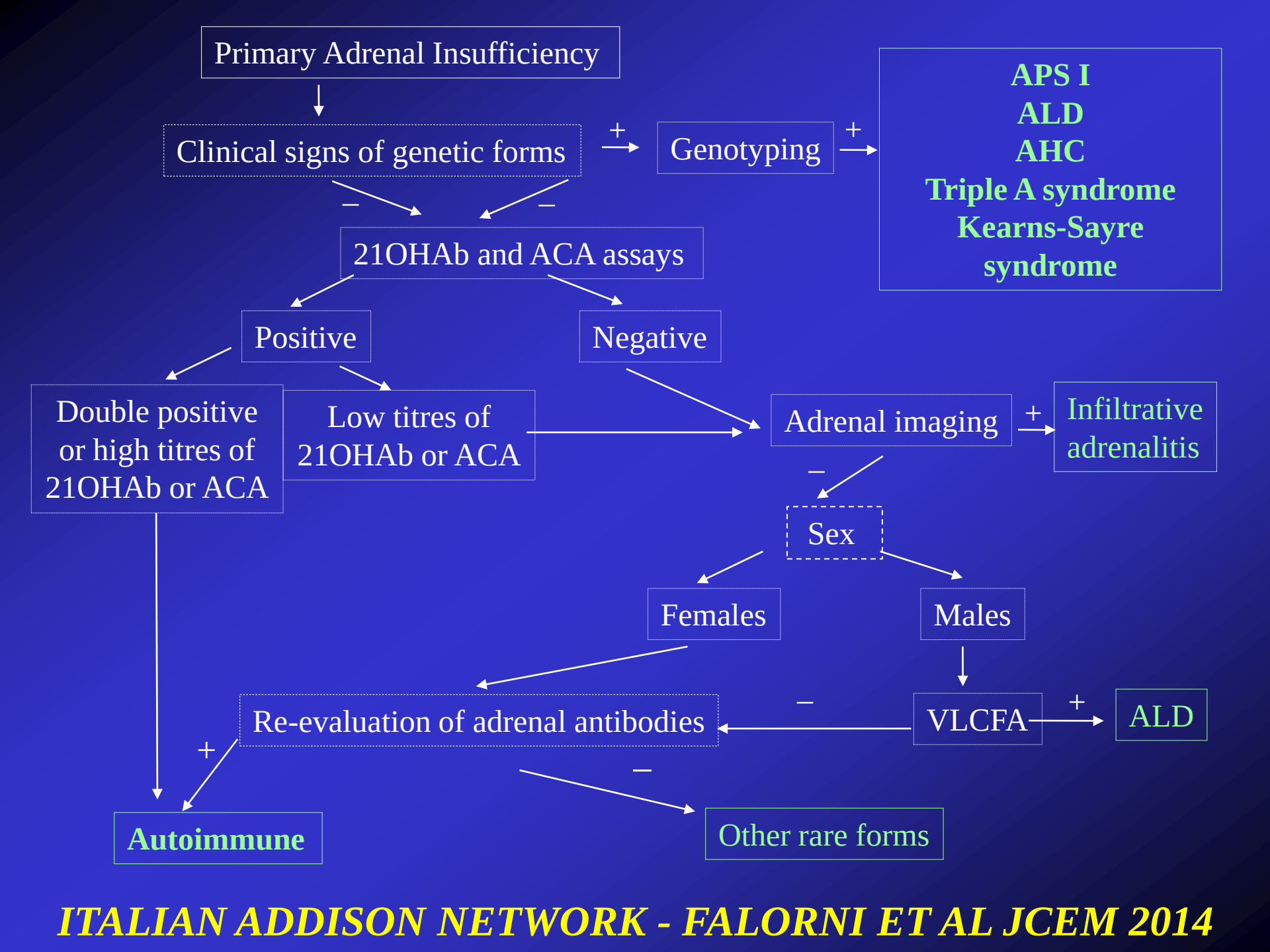
Un quadro sorprendentemente simile è stato dimostrato in due pazienti con mutazioni del gene SF-1.

Steroidogenetic factor 1 (SF-1) knockout mice lack the ventromedial hypothalamic nucleus (VMH)



Expression pattern of DAX1 and the clinical features of X-linked adrenal hypoplasia congenita




Primary Adrenal Insufficiency
Clinical signs of genetic forms
+
Genotyping
+
APS I
ALD
AHC
Triple A syndrome
Kearns-Sayre syndrome
–
–
21OHAb and ACA assays
Positive
Negative
Double positive or high titres of 21OHAb or ACA
Low titres of 21OHAb or ACA
Adrenal imaging
+
Infiltrative adrenalitis
–
Sex
Females
Males
Re-evaluation of adrenal antibodies
–
VLCFA
+
ALD
+
–
Autoimmune
Other rare forms
ITALIAN ADDISON NETWORK - FALORNI ET AL JCEM 2014

Definition and forms of adrenal insufficiency (AI)

Two main forms:[1,2]

Primary AI (Addison's disease)

- Caused by **adrenal gland destruction or dysfunction**
- Prevalence: 93–140 per million
- Peak age at diagnosis: 4th decade
- Deficit in glucocorticoid and mineralocorticoid

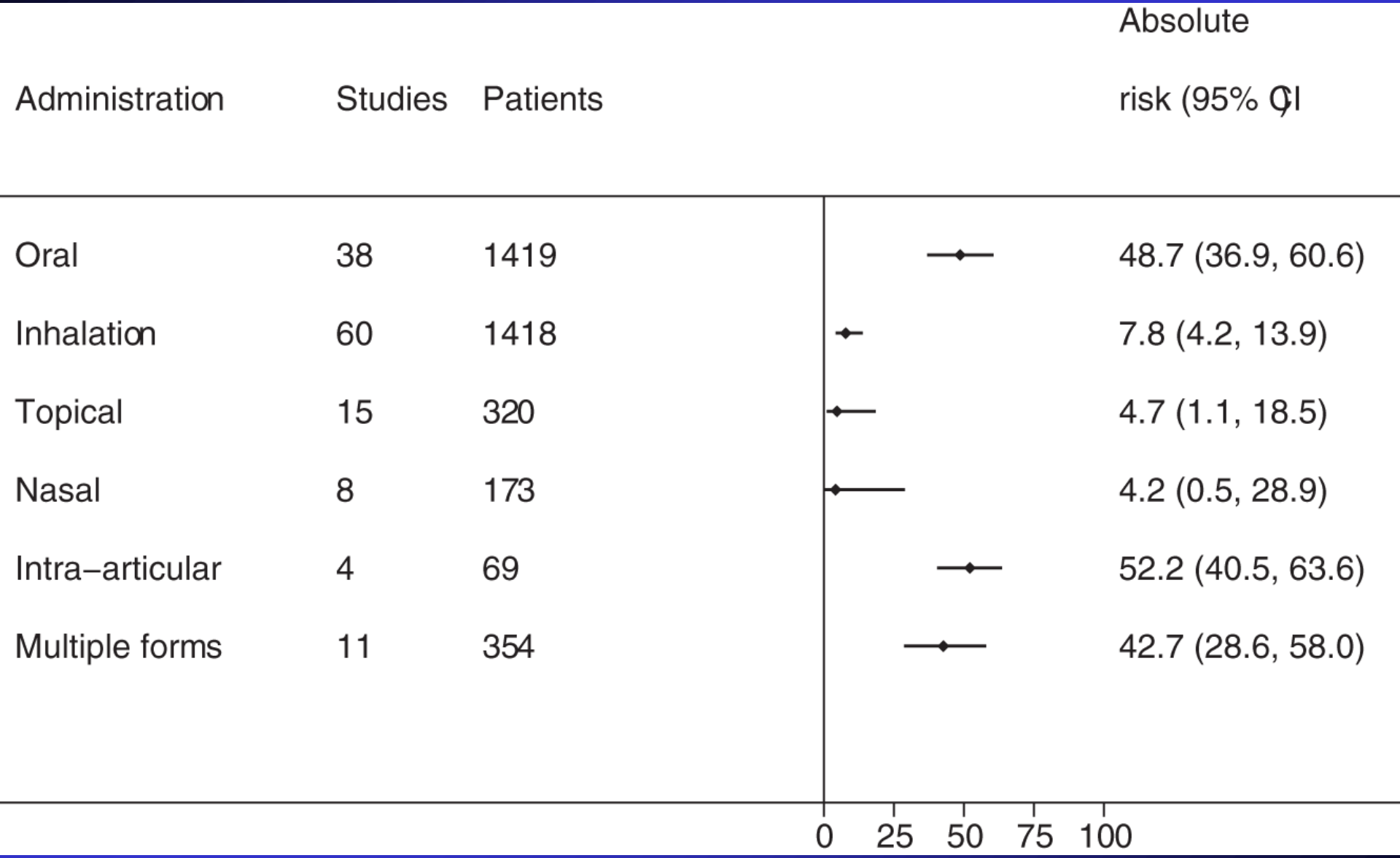
Secondary AI (Hypopituitarism)

- Caused primarily by **hypothalamic/pituitary tumours – chronic fentanyl treatment – cranial traumas**
- Prevalence: 150–280 per million
- Peak age at diagnosis: 6th decade
- Deficit in glucocorticoid (not mineralocorticoid)
- May have multiple pituitary hormone deficiencies[3]

- Tertiary/temporary AI may occur after a prolonged period of endogenous or exogenous pharmaceutical glucocorticoid exposure[1]

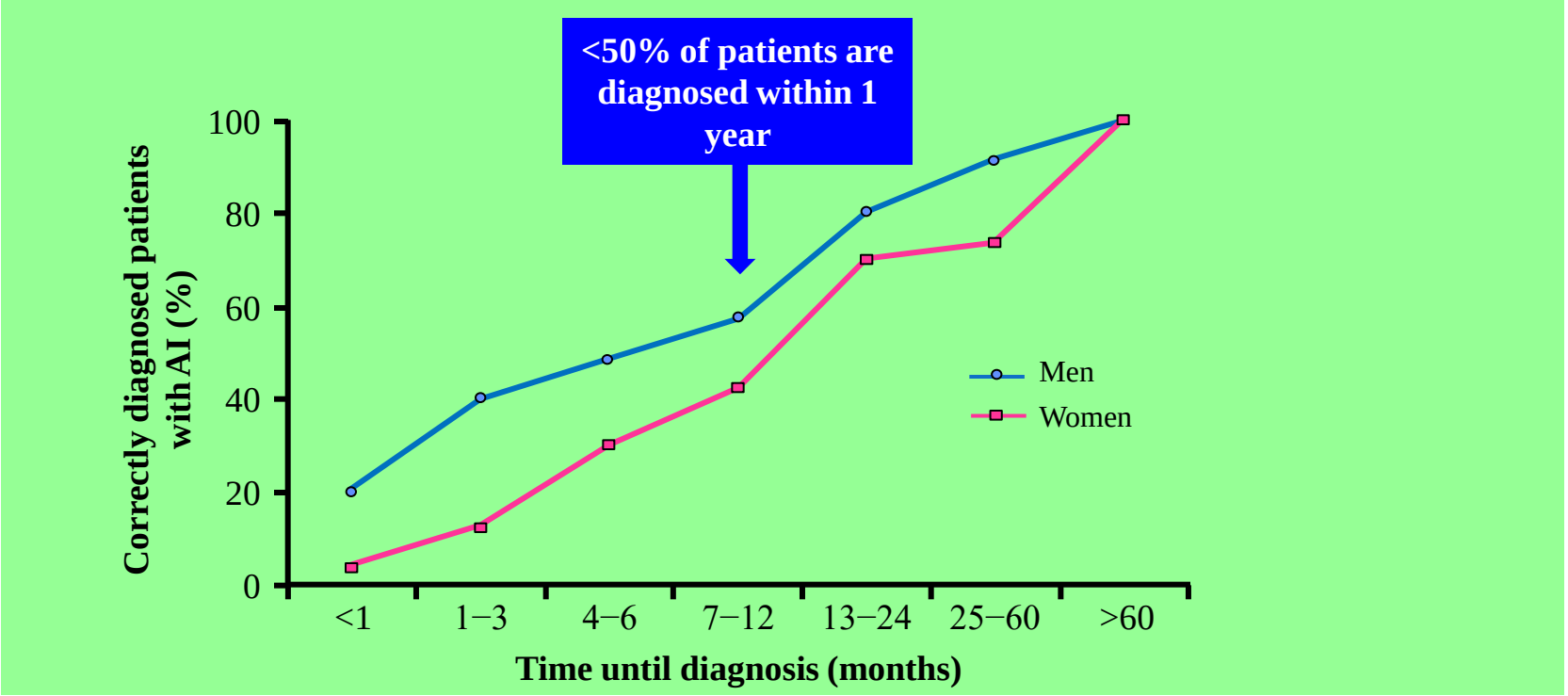
1. Arlt W. In: Harrison's Principles of Internal Medicine, 18th ed. 2012. Chapter 342, pp. 2940–2961
2. Artl W and Allolio B. Lancet 2003;361:1881–1893
3. Regal M et al. Clin Endocrinol 2001;55:735–740

Adrenal insufficiency by administration form



Broersen LH et al JCEM 2015

Delayed diagnosis of adrenal insufficiency is common in clinical practice[1]



- 67% of patients consulted ≥3 physicians before being correctly diagnosed
- 68% of patients incorrectly diagnosed initially
  - Psychiatric and gastrointestinal disorders most common incorrect diagnoses

Figure adapted from Bleicken et al. Reproduced by permission.

1. Bleicken B et al. Am J Med Sci 2010;339:525–531

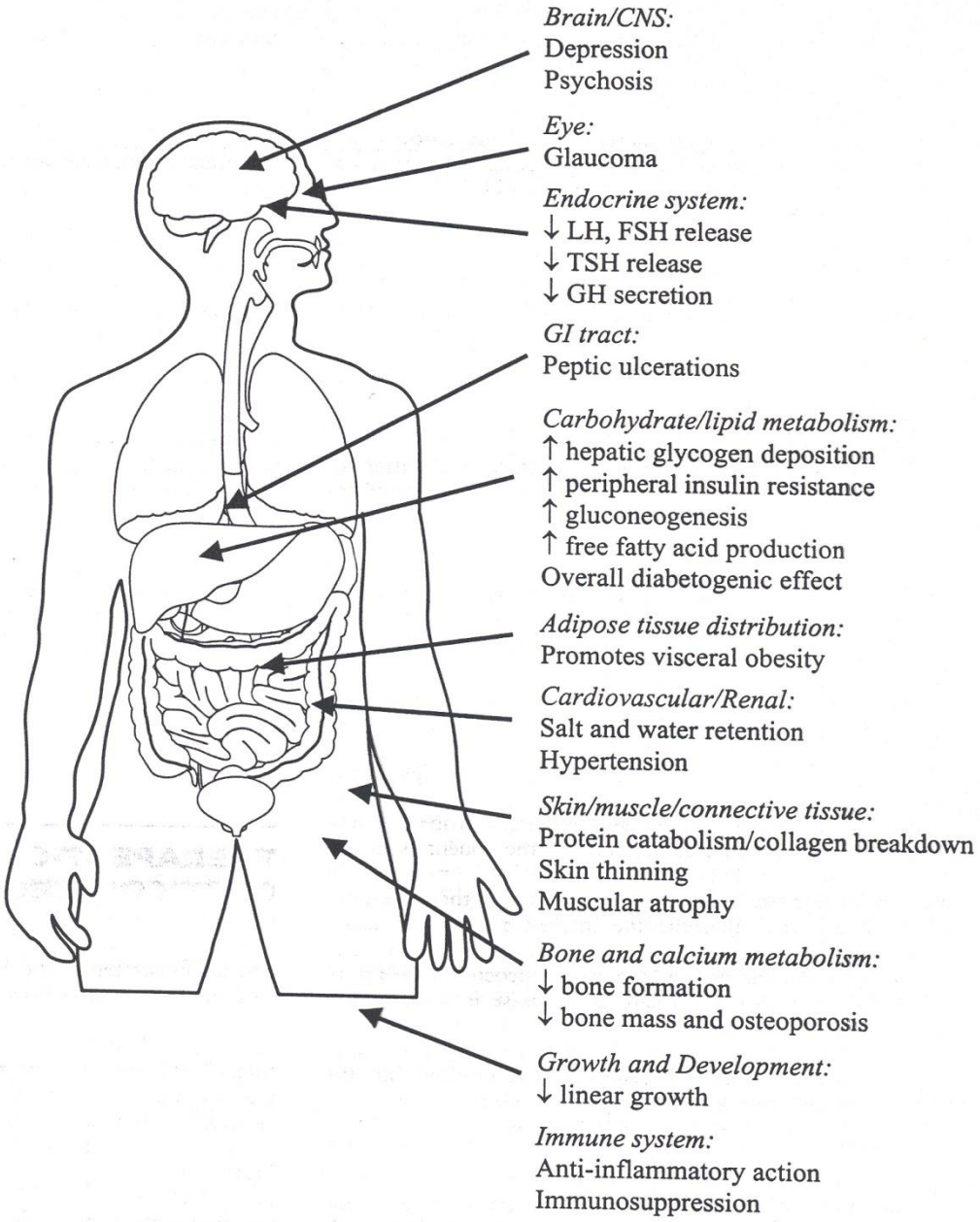
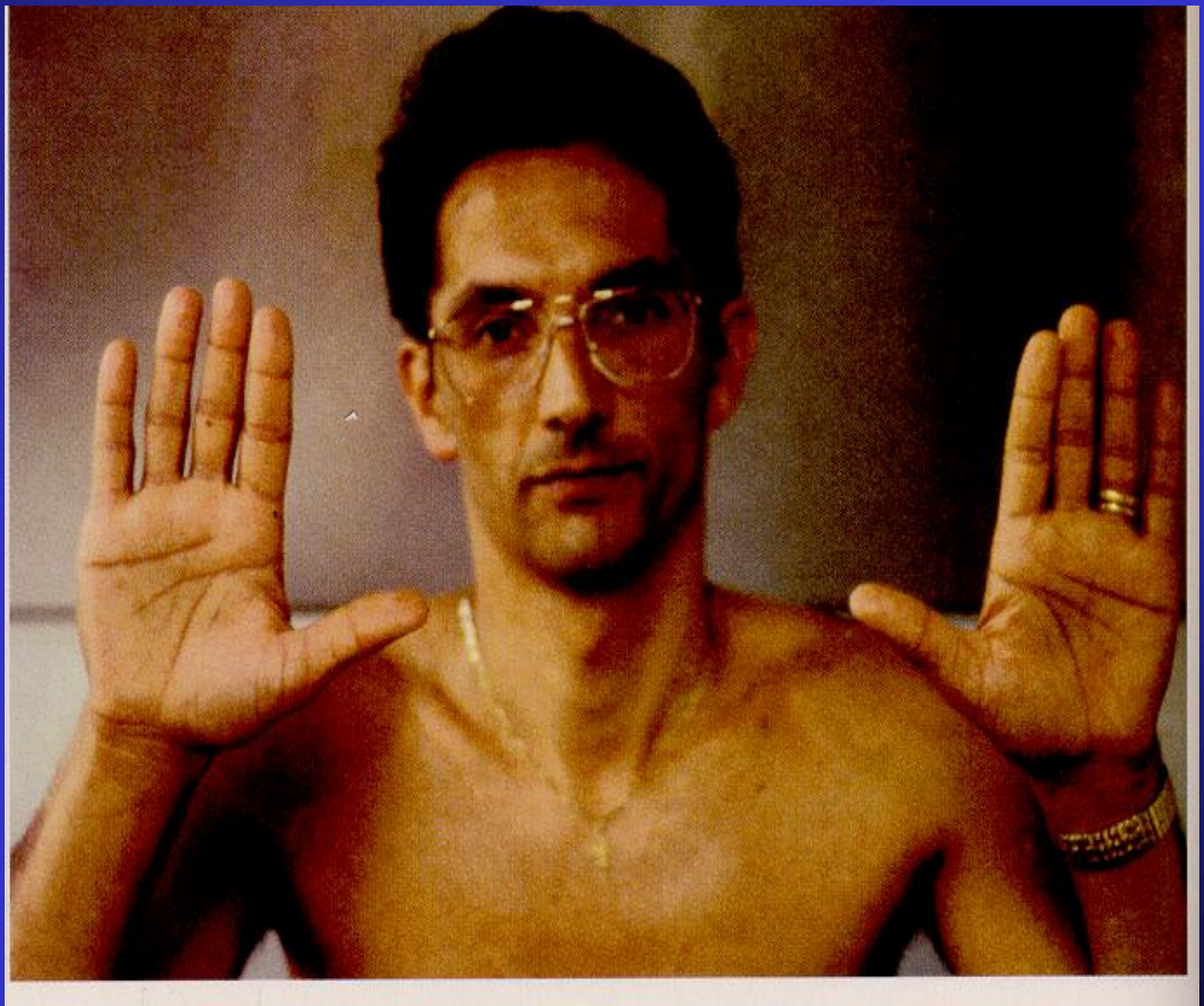
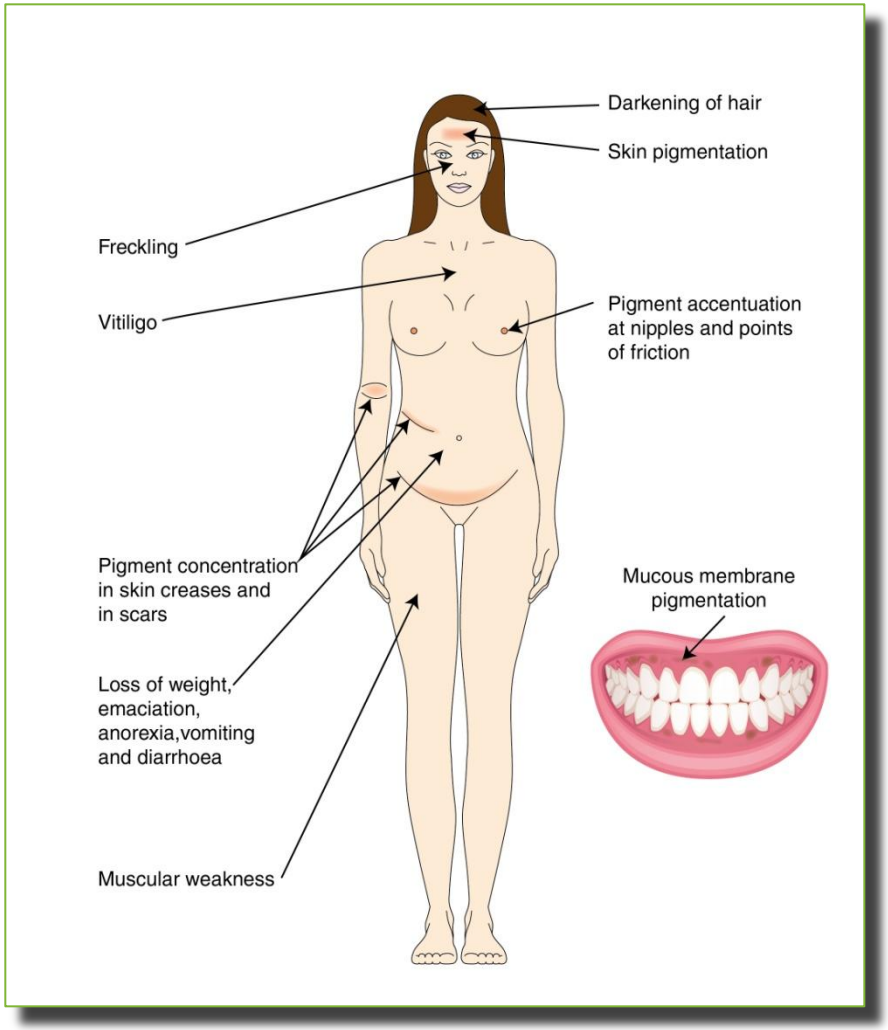


Figure 14–13. The principal sites of action of glucocorticoids in humans highlighting some of the consequences of glucocorticoid excess. CNS, central nervous system; GI, gastrointestinal; FSH, follicle-stimulating hormone; GH, growth hormone; LH, luteinizing hormone; TSH, thyroid-stimulating hormone.

Principali segni e sintomi di insufficienza cortico-surrenalica



Clinical features of Addison's disease



Signs and symptoms

- Weakness and fatiguability
- Weight loss
- Hyperpigmentation
- Hyponatraemia
- Hypotension
- Hyperkalaemia
- Gastrointestinal symptoms (abdominal pain)
- Hypercalcaemia
- Adrenal calcification
- Postural dizziness
- Muscle and joint pains
- Vitiligo

Iponatremia

- Concentrazione di sodio ≤ 135 mEq/l
- Può essere acuta (esordio prima delle 48 h) o cronica (> 48 h)
- Il più comune disordine elettrolitico in ospedale(15-30% dei pazienti)
- L'iponatremia ipotonica è classificata in base alla volemia:
  - Ipovolemica **(la crisi Addisoniana rientra nella diagnosi differenziale)**
  - Euvolemica **(le due principali cause sono la SIADH e l'insufficienza corticosurrenalica senza crisi addisoniana)**
  - Ipervolemica

References:
Miller M. *J Am Geriatr Soc*, 2006; 54:345-353
Peri A. *J Endocrinol Invest.* 2010 Oct;33(9):671-82
Douglas I. *Cleve Clin J Med.* 2006;73(3):s4-s12
Thompson CJ Eur J Endocrinol 2010 Jun; 162 Suppl. 1:S1-S3
Verbalis JG. et al. *Am J Med*, 2007;120(11 Suppl 1):S1-S21

CRISI ADDISONIANA

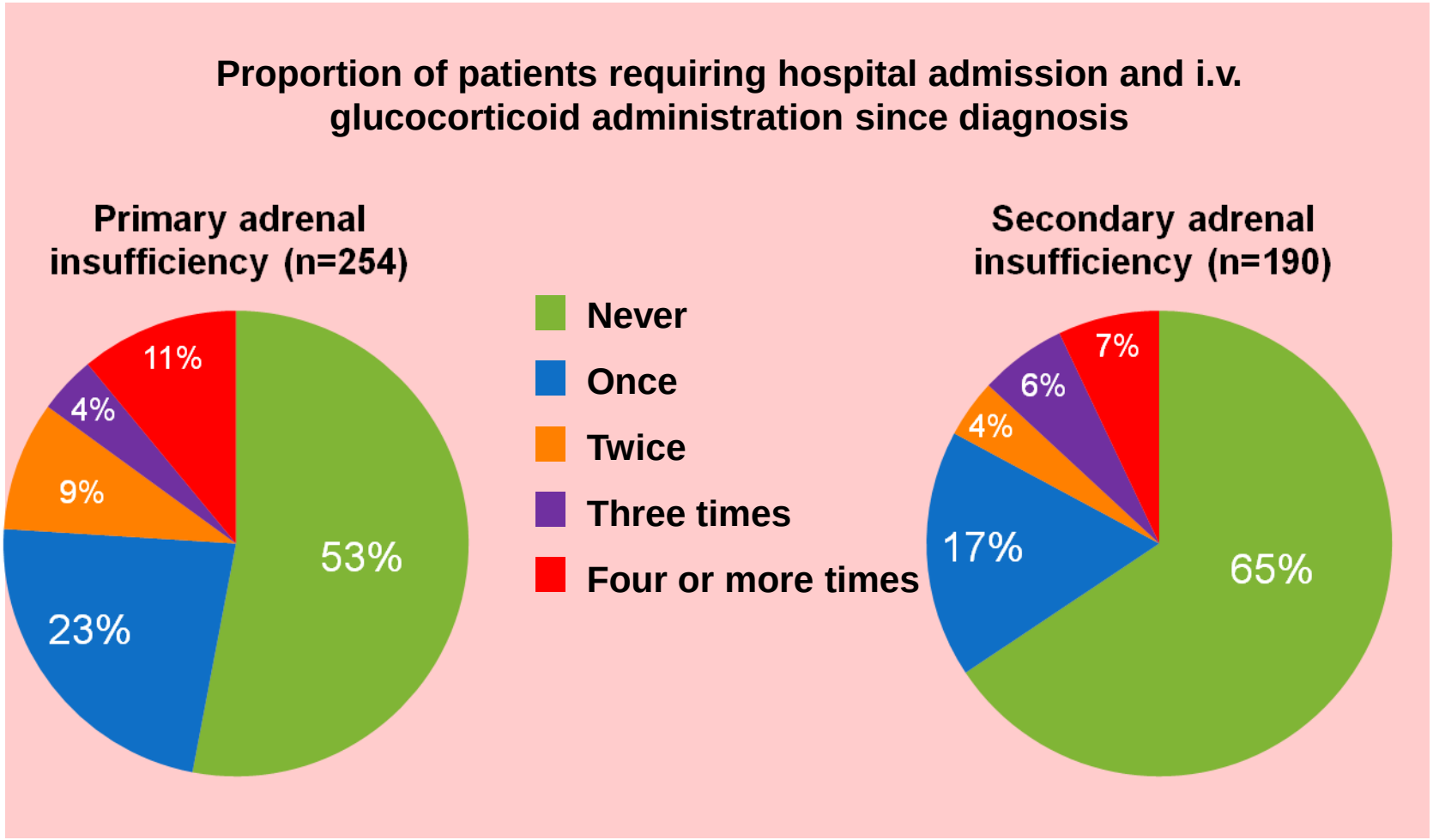
Accentuazione della sintomatologia precedente (in assenza di precedente terapia sostitutiva) o comparsa improvvisa di:

- **Nausea, vomito**
- **Dolore addominale (che diventa intrattabile)**
- **Febbre, anche elevata (ma può essere assente)**
- **Letargia e sonnolenza**
- **Disidratazione mucoso-cutanea**
- **Ipotensione fino allo shock**

I parametri ematobiochimici evidenziano spesso iponatremia e iperpotassiemia e ci può essere ipoglicemia

Se non trattata opportunamente, la morte insorge per shock ipovolemico entro 12-48 ore

Adrenal crisis still occurs despite education and treatment



- Overall incidence of adrenal crisis: 6.3 per 100 patient-years

Hahner S et al. Eur J Endocrinol 2010;162:597–602

Adrenal crisis: precipitating factors[1]

	Primary AI (181 cases) % of cases	Secondary AI (110 cases) % of cases
Gastrointestinal infection	**32.6**	**21.8**
Other infectious disease/fever	**24.3**	**17.3**
Surgery	7.2	15.5
Unknown	6.6	12.7
Strenuous physical activity	7.7	7.3
Cessation of glucocorticoid substitution by patient	5.0	6.4
Neglected glucocorticoid intake	5.0	3.6
Psychic distress	3.3	3.6
Accident	2.8	2.7
Cessation of glucocorticoid substitution by attending physician	1.1	3.6
Other reasons*	4.4	5.4

1. Hahner S et al. Eur J Endocrinol 2010;162:597–602

Functional tests in primary adrenal insufficiency (PAI)

	Cortisol μg/dl		
	Basal	ACTH test (250 μg)	ACTH pg/ml
Normal	6 – 24	> 20	5 - 45
PAI	< 3	No increase or peak value < 20	> 100
PAI in acute illness	< 15	No increase or increment < 9	> 100

Modified from Oelkers W, NEJM 1997 and from Cooper & Stewart, NEJM 2003

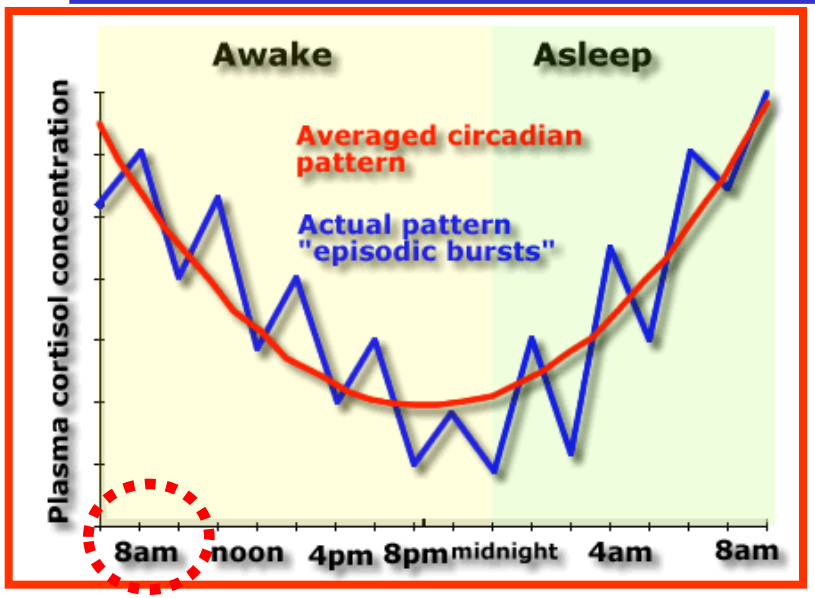
Diagnosi

Valutazioni ormonali basali

Cortisolo mattutino (h 7-9) "pazienti non stressati"

Normalità: > 10-18 µg/dl (300-500 nmol/l)

< 3-5 µg/dl (80-110 nmol/l) specificità 100%
bassa sensibilità (70%)



Grinspoon & Biller 1994; JCEM 79: 923-931
Oelkers 1996; NEJM 335: 1206-1212
Courtney et al. 2000; Clin Endocrinol 53: 431-436
Schmidt et al. 2003; JCEM 88: 4193-4198
Arlt & Allolio 2003; Lancet 361: 1881-1893
Arlt 2009; JCEM 94: 1059-1067
Grossman 2010; JCEM 95: 4855-4863

Diagnosi

Valutazioni ormonali basali

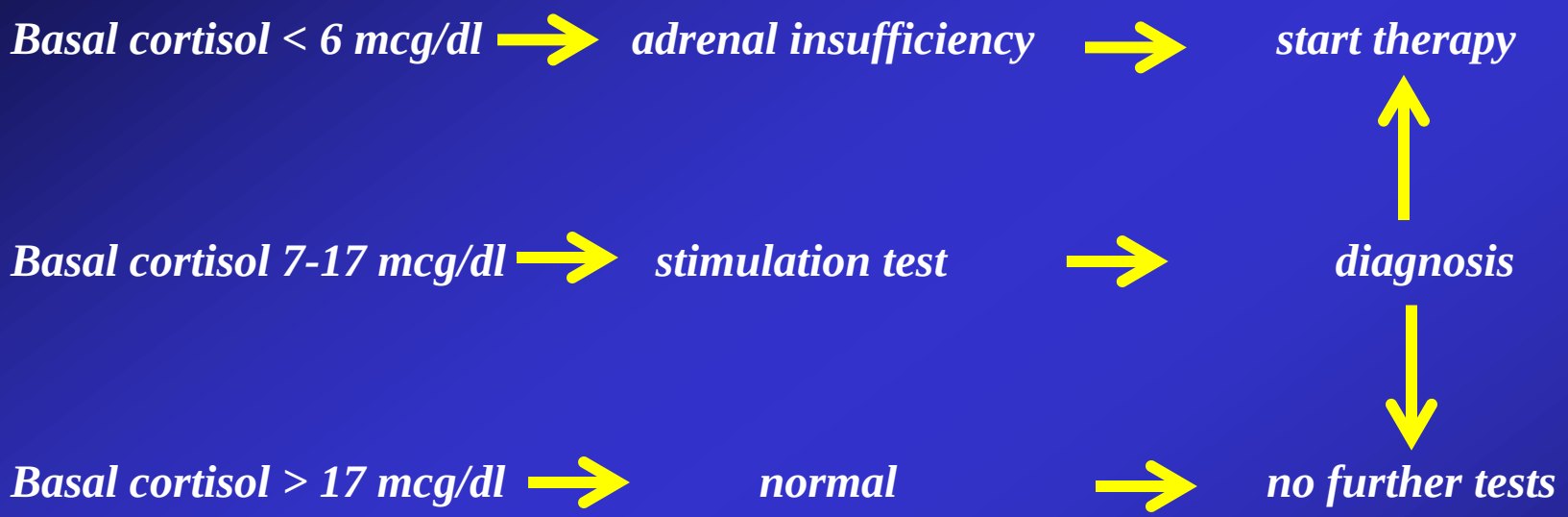
Cortisolo random "in pazienti critici"

Normalità: 20-45 µg/dl (600-1350 nmol/l)

< 10-15 µg/dl (300-390 nmol/l)

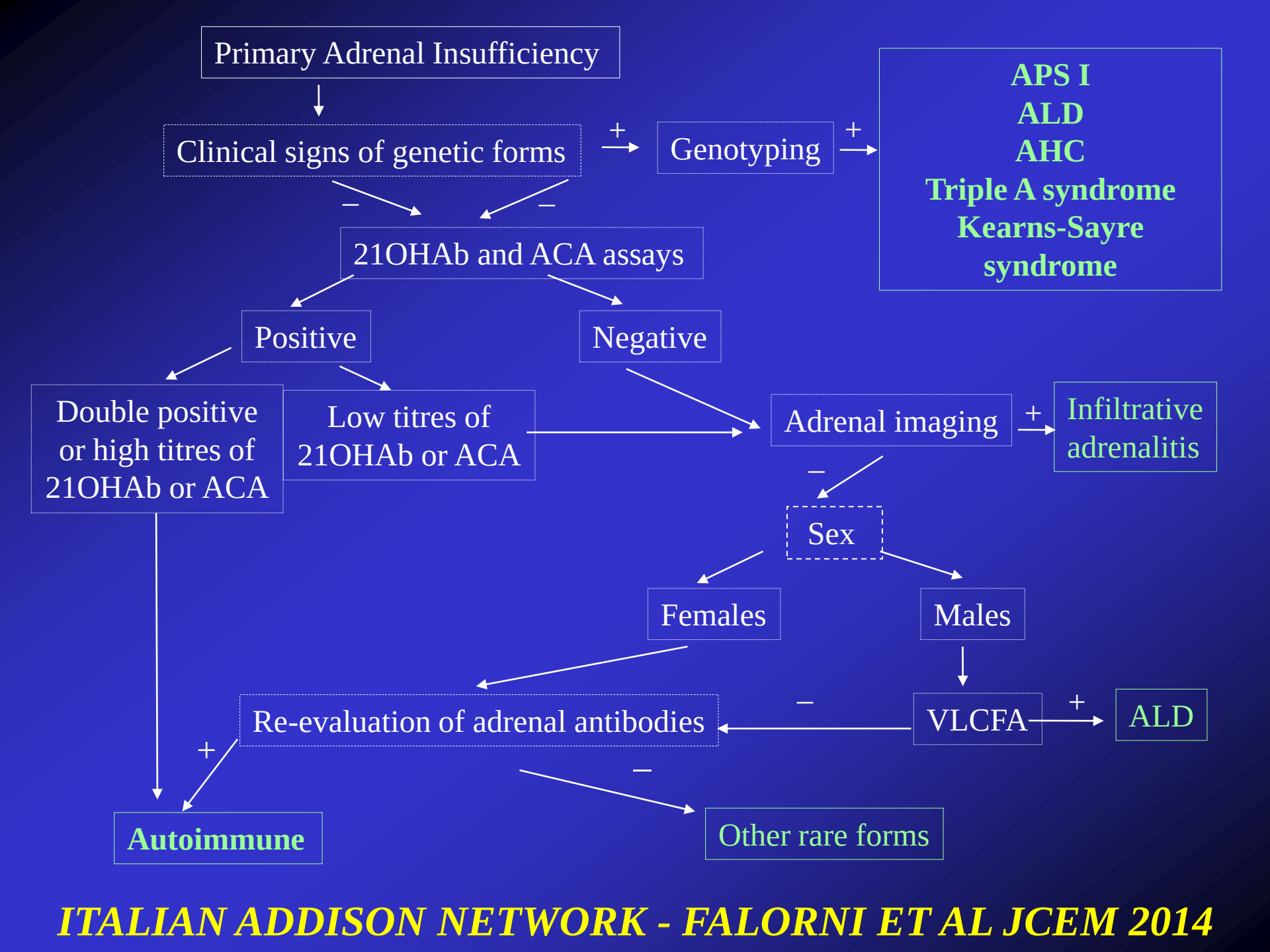
Cooper & Stewart 2003; NEJM 348: 727-734
Marik et al. 2008; Crit Care Med 36:1937-1949

How do we interpret cortisol results when adrenal insufficiency is strongly suspected



Basal cortisol 12-17 mcg/dl → *test?*

Advice the patients of possible adrenal insufficiency in stressful conditions


Primary Adrenal Insufficiency
Clinical signs of genetic forms
+
Genotyping
+
APS I
ALD
AHC
Triple A syndrome
Kearns-Sayre syndrome
–
–
21OHAb and ACA assays
Positive
Negative
Double positive or high titres of 21OHAb or ACA
Low titres of 21OHAb or ACA
Adrenal imaging
+
Infiltrative adrenalitis
–
Sex
Females
Males
Re-evaluation of adrenal antibodies
–
VLCFA
+
ALD
+
–
Autoimmune
Other rare forms
ITALIAN ADDISON NETWORK - FALORNI ET AL JCEM 2014

Frequency of ACA and 21OHAb in autoimmune organ-specific diseases

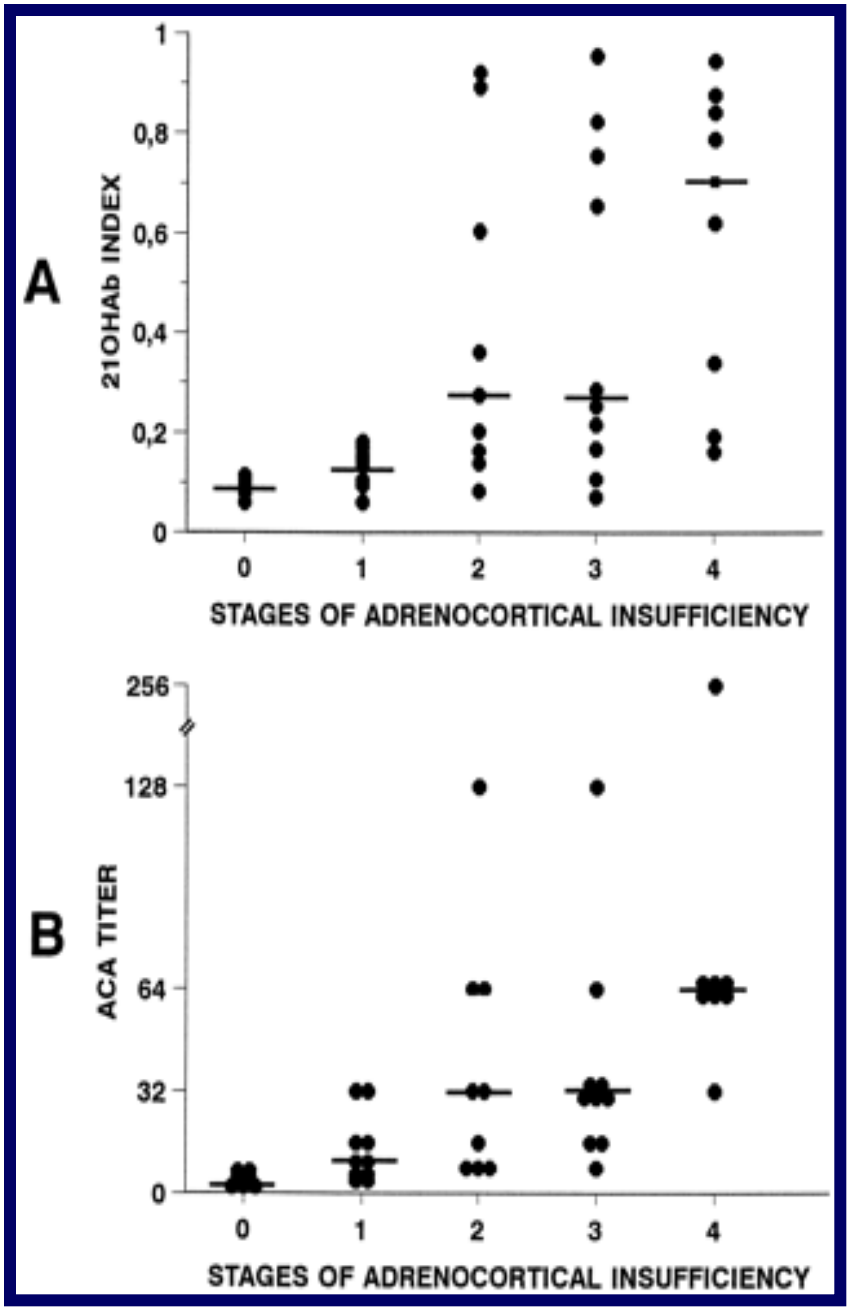
	ACA	21OHAb
Type 1 diabetes mellitus	0.2-0.9 %	0.5-1.5%
Hashimoto's thyroiditis	1.0-1.5 %	0.5-1.0%
Graves' disease	1.0-1.5 %	0.5-1.0%
Vitiligo	1.0-2.0%	1-1.5%
Primary ovarian insufficiency	4.0-8.9 %	2.0-5.0%
Primary hypoparathyroidism	5.0-15.0 %	5.0-15.0%

Falorni A, The Endocrinologist, 2000

Funzionalità cortico-surrenalica in pazienti con anticorpi anti-surrene

				Cortisolo (ACTH test)	
	PRA	Aldosterone	ACTH	0 min	60 min
Stadio 0	Normale	Normale	Normale	Normale	Normale
Stadio 1	Alto	Normale/Basso	Normale	Normale	Normale
Stadio 2	Alto	Normale/Basso	Normale	Normale	Basso
Stadio 3	Alto	Normale/Basso	Alto	Normale	Basso
Stadio 4	Alto	Basso	Alto	Basso	Basso

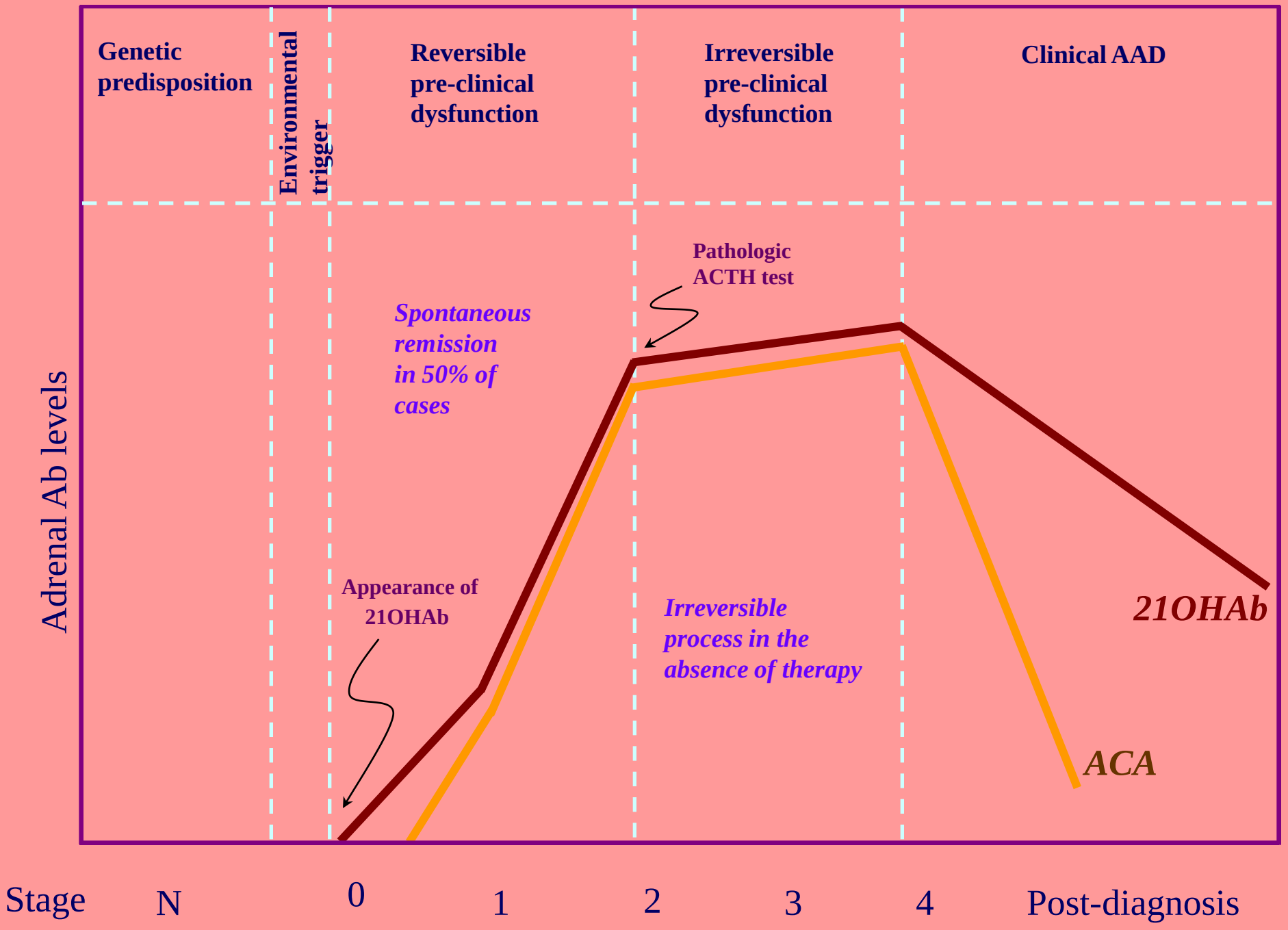
Modificato da Betterle et al. J Endocrinol 1988



Correlation between 21OHAb/ ACA titre and degree of adreno-cortical dysfunction in pre-clinical Addison's

Synacthen test	Follow-up	
Normal	Clinical PAI	15 %
	Progression	35 %
	Remission	50 %
Sub-normal	Clinical PAI	90 %
	Progression	10 %
	Remission	0 %

Laureti et al, JCEM 1998


Genetic predisposition
Environmental trigger
Reversible pre-clinical dysfunction
Irreversible pre-clinical dysfunction
Clinical AAD
Adrenal Ab levels
Pathologic ACTH test
Spontaneous remission in 50% of cases
Appearance of 21OHAb
Irreversible process in the absence of therapy
21OHAb
ACA
Stage
N
0
1
2
3
4
Post-diagnosis

What to do in routine clinical practice. Should we screen for 21OHAb…

General population?

(estimated disease risk 1: 7,000-7,500) **NO**

First-degree relatives of AAD patients?

(estimated risk of disease 0.2-0.3%) **NO**

Patients with thyroid autoimmune diseases or T1DM?

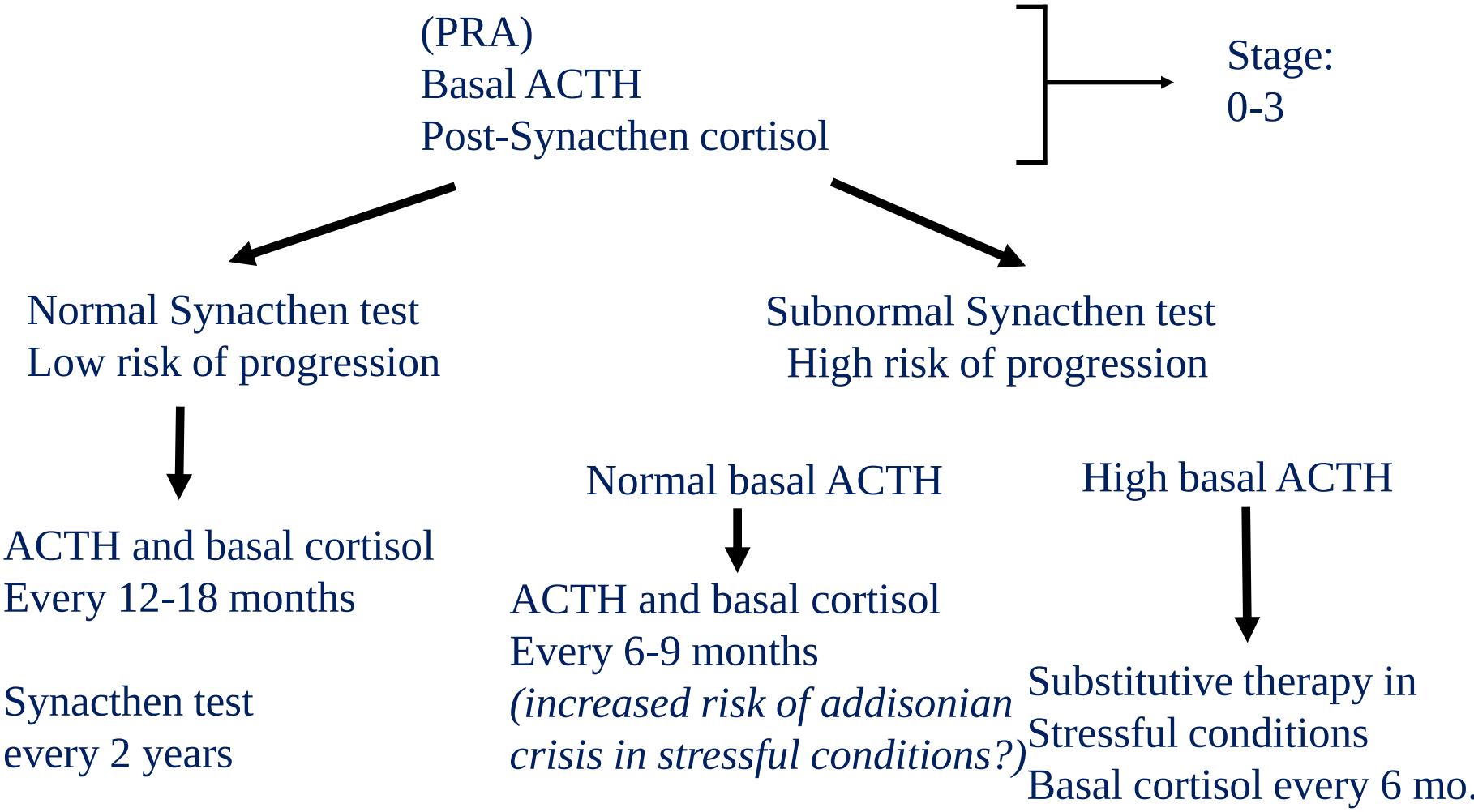
(estimated disease risk 0.1-0.3%) **MAYBE**

(estimated cost to predict a new patient: 3,000-5,000 Euros)

Patients with POI or hypoparathyroidism? **YES**

(diagnostic value and high disease risk)

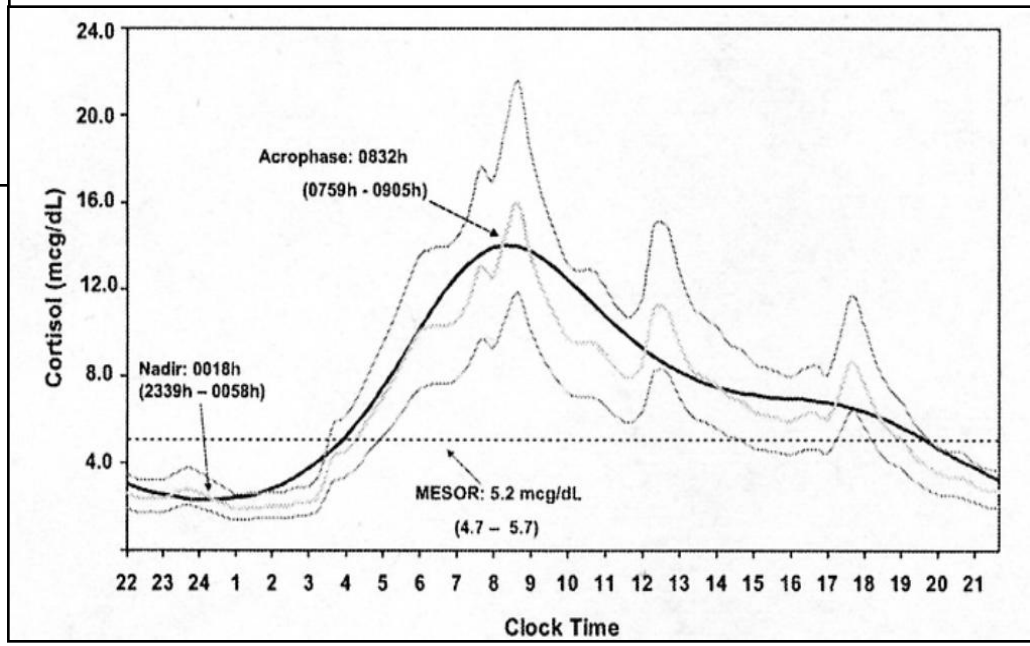
What to do in routine clinical practice.
If we have identified a 21OHAb+ individual with subclinical AAD…



FISIOLOGIA DELLA SECREZIONE DELLA CORTECCIA DEL SURRENE

La dose di cortisolo prodotta ogni giorno dai surreni varia dai 5-10 mg/m^2 di superficie corporea

Una persona normale ha una superficie corporea di **1,7m^2 circa**
Per cui la dose media di **cortisolo** prodotta giornalmente **varia tra 8-17mg**



RITMO CIRCADIANO DEL CORTISOLO

W. Arlt and B. Allolio
The Lancet 361:1881-1893; 2003

Recommended therapeutic approach to primary adrenal insufficiency

Glucocorticoid replacement

Immediate-release hydrocortisone dosing:

- Start on 15–25 mg hydrocortisone per 24 hours
- Administer in 2 or 3 divided doses
- Administer ⅔ or ½ the dose, respectively, immediately after waking

Once-daily modified-release hydrocortisone dosing:

- Dose based on clinical response, 20–40 mg/day
- Administer once daily in the morning

Mineralocorticoid replacement

Not required if hydrocortisone dose is >50 mg per 24 hours

Dosing:

- Start on 100 µg fludrocortisone as a single dose immediately after waking
- Optimised doses usually 50–250 µg/day

Adrenal androgen replacement

Consider in:

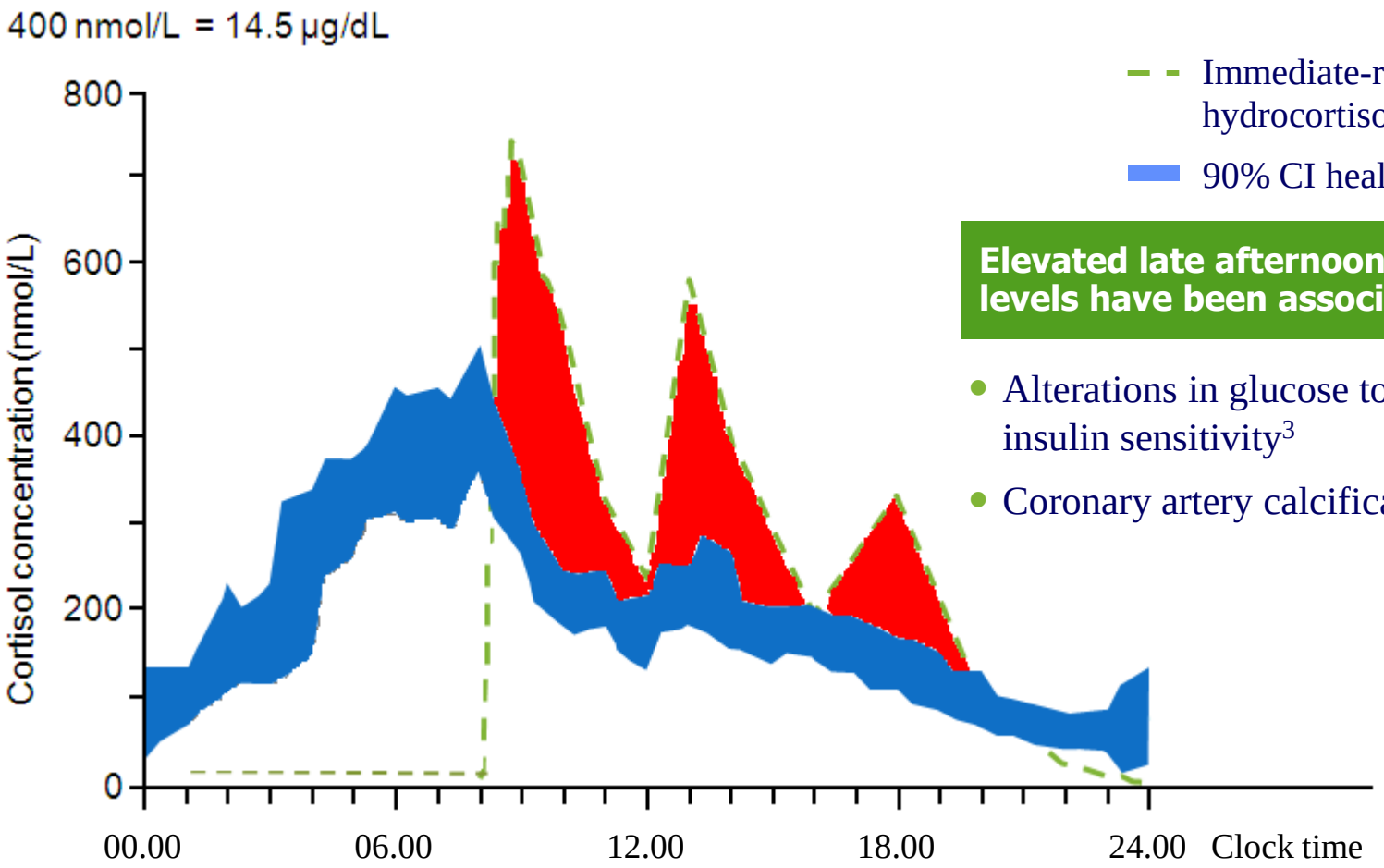
- Patients with impaired well-being and mood despite optimised glucocorticoid/ mineralocorticoid replacement therapy
- Women with symptoms and signs of androgen deficiency

Dosing:

- DHEA 25–50 mg as a single morning dose
- In women, also consider transdermal testosterone

Late afternoon/evening peaks and troughs

2



- - - Immediate-release hydrocortisone tablet TID[1]

▬ 90% CI healthy volunteers[2]

Elevated late afternoon or evening levels have been associated with:

- Alterations in glucose tolerance and insulin sensitivity[3]
- Coronary artery calcification[4]

Figure derived from Johannsson et al. and healthy volunteer data based on Vgontzas AN et al.

1. Johannsson G et al. J Clin Endocrinol Metab 2012;97:473–481; 2. Vgontzas AN et al. J Clin Endocrinol Metab 2001;86:3787–3794;
3. Plat L et al. J Clin Endocrinol Metab 1999;84:3082–3092; 4. Matthews K et al. Psychos Med 2006;68:657–661;
4. García-Borreguero D et al. J Clin Endocrinol Metab 2000;85:4201–4206.

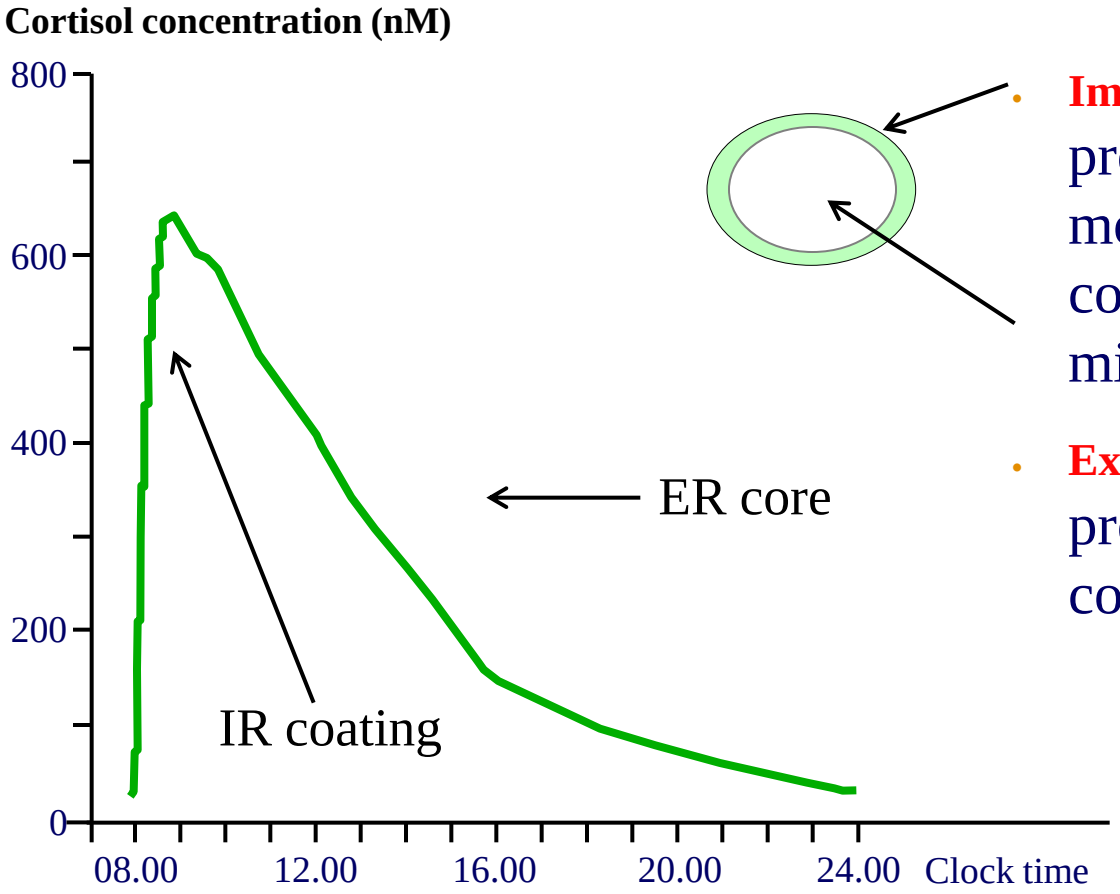
Outcome negativi associati all'attuale terapia sostitutiva dell'insufficienza corticosurrenalica

Terapia sostitutiva convenzionale con glucocorticoidi

Mortalità prematura	Alta frequenza di ospedalizzazioni/ infezioni	Ridotto benessere e qualità percepita della vita	Alterato profilo metabolico	Ridotta densità minerale ossea
CONTROVERSA				**Non associata alla terapia**

Bergthorsdottir et al. JCEM 2006, Smans LCCJ et al. ECE 2011, Hahner et al. JCEM 2007, Filipsson et al. JCEM 2007, Zelissen et al. Ann Intern Med 1994; Lövås et al EJE 2009

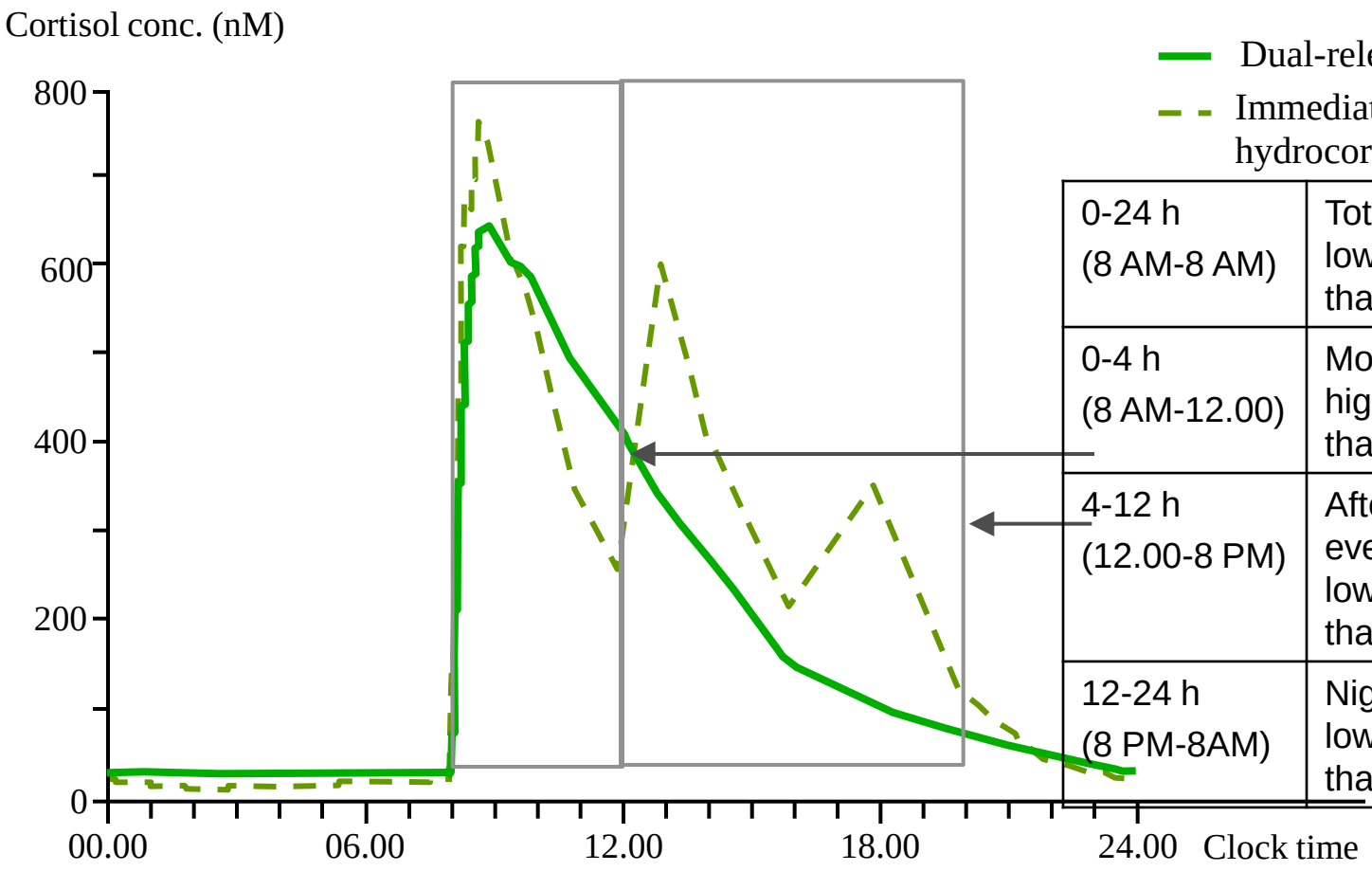
A dual-release hydrocortisone preparation
Hydrocortisone Release Profile



- **Immediate release (IR) coating** provides physiological morning cortisol concentrations within 20 minutes after intake
- **Extended release (ER) core** provides a smooth serum cortisol profile over the day

Johannsson G et al. *Eur J Endocrinol* 2009;161:119–130

Improved Serum Cortisol Profile with Dual-Release HC tablet



0-24 h (8 AM-8 AM)	Total exposure 19% lower on Dual-release than TID
0-4 h (8 AM-12.00)	Morning exposure 6% higher on Dual-release than TID
4-12 h (12.00-8 PM)	Afternoon and early evening exposure 38% lower on Dual-release than TID
12-24 h (8 PM-8AM)	Night exposure 41% lower on Dual-release than TID

Johannsson G et al. *J Clin Endocrinol Metab* 2012;97:473–481

TERAPIA SOSTITUTIVA DELL' ICSP (MINERALCORTICOIDI)

- ✓9-alfa-fluoridrocortisone (fludrocortisone)

  0.05 – 0.2 mg os. al giorno o a giorni alterni

TERAPIA DI SUPPORTO DELL' ICSP

- ✓Raddoppiare la dose standard se: febbre, chirurgia minore, stress.
- ✓ In caso di vomito praticare terapia parenterale (idrocortisone 100 mg al dì ev o im).

TERAPIA DI EMERGENZA DELL' ICSP

- ✓Idrocortisone 100 mg (ev o im) seguita da infusione di 100-200 mg di idrocortisone nelle prime 24 ore
- ✓Correggere ipovolemia (soluzione salina)
- ✓Correggere ipoglicemia (glucosata)