Cushing's Syndrome In Human

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CUSHING'S SYNDROME

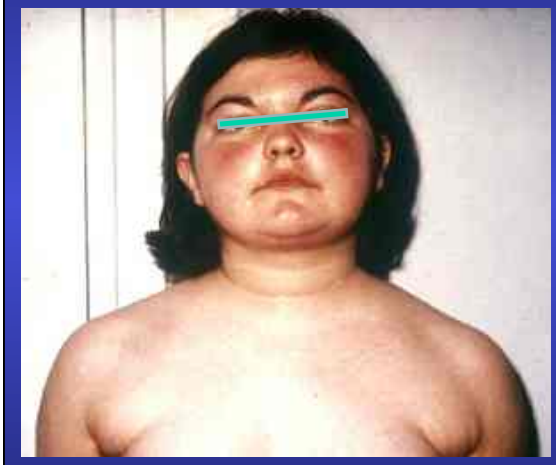
- ! The clinical (and biochemical) features associated with chronic exposition to glucocorticoid excess

Prevalence of clinical features of Cushing!'s syndrome

(prevalence of signs significantly different among patients with proven CS or without CS, in whom CS was suspected in a serie of 211 patients from Nugent)

	CS	W/O CS
Central obesity	0.90	0.03
Generalized obesity	0.03	0.62
Osteoporosis	0.64	0.03
Weakness	0.65	0.07
Ecchymosis	0.53	0.06
Serum K<3.6 mEq/l	0.25	0.04
Plethora	0.82	0.31
WBC > 11 000/mm!3	0.58	0.30
Acne	0.52	0.24
Striae (red, purple)	0.46	0.22
Diastolic BP > 105	0.39	0.17
Edema	0.38	0.17
Hirsutism	0.50	0.29

Not different: oligomenorrhea, female, abnormal GTT



CUSHING'S SYNDROME
- Diagnostic strategy -

THREE STEPS

-!Demonstrate chronic hypercortisolism

-!Establish its cause

-!Locate the responsible tumor

CUSHING'S SYNDROME
- Chronic hypercortisolism -

Three approaches :

-!Cortisol secretion is not normally suppressible.

-!Urinary cortisol is increased

-!Plasma (salivary) cortisol has lost its normal circadian variations

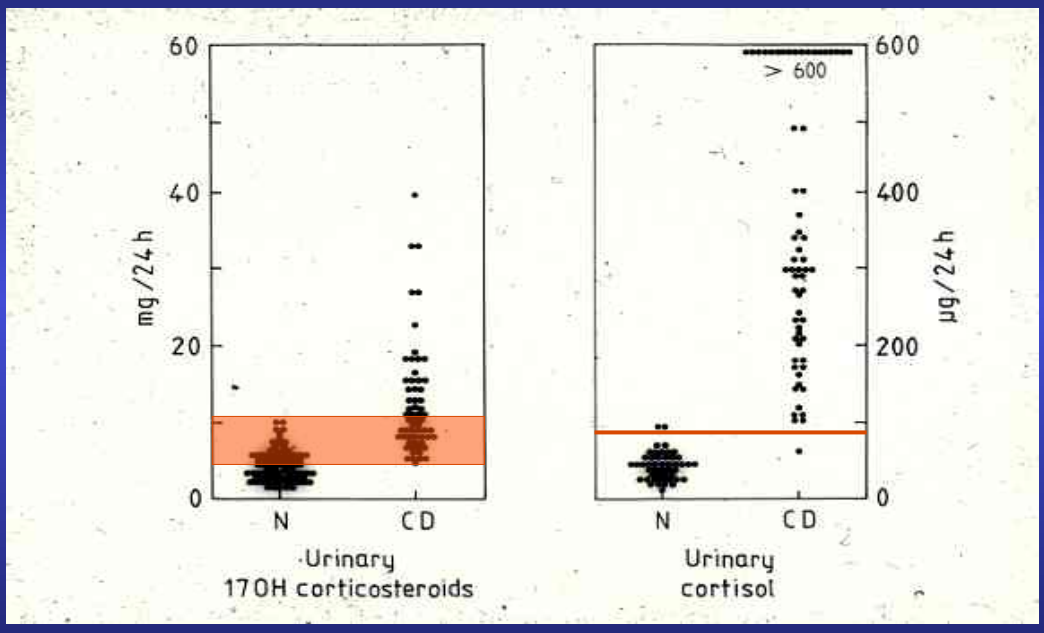
CUSHING'S SYNDROME

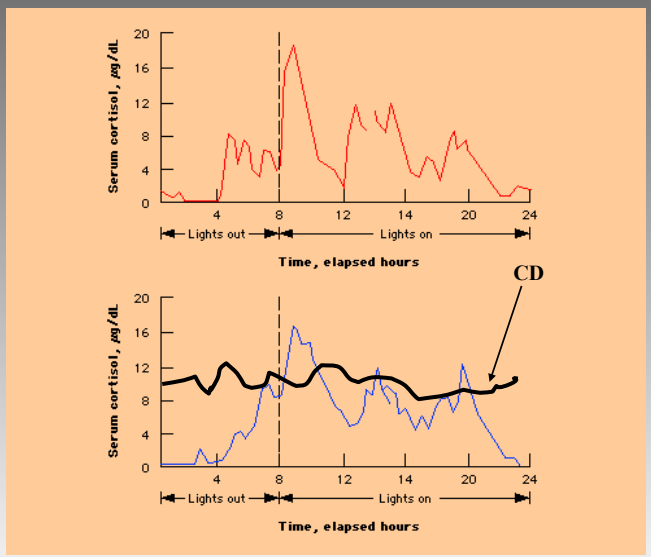
- Chronic hypercortisolism -

-!Cortisol secretion is not normally suppressible.

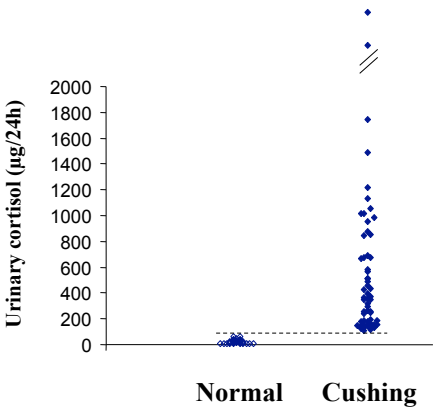
Suppression tests

- classic low dose dex suppression test (2 mg/day x 2 days)
- 1-mg overnight dex suppression test (1 mg dex at midnight)

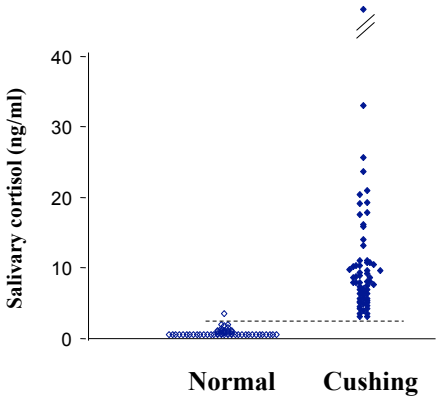




24h-urinary cortisol



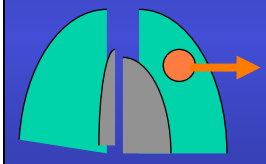
Midnight salivary cortisol



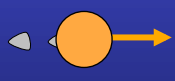
Syndrome de Cushing
=
Tumeur Endocrine

CUSHING'S SYNDROME

ACTH — Cushing's Disease



ACTH — Ectopic ACTH Syndrome



CORTISOL — « Adrenal » Cushing's Syndrome

CHRONIC HYPERCORTISOLISM

Etiology of 809 Cushing!'s syndrome

(Hôpital Cochin, 1992)

	n= (%)	sex ratio (F/M)
Cushing!'s Disease	548 (68 %)	2.8
Ectopic ACTH syndrome*	58 (7%)	1.4
Primary adrenocortical tumor	199 (25 %)	4.2
Benign adenoma	*111 (14 %)*	*5*
Adrenocortical carcinoma	*88 (11 %)*	*3.6*
PPNAD/AIMAH	4 (0.4 %)	-

* Bronchial neuroendocrine tumor (BNT) well differentiated («!carcinoid!»): 30 %, undifferentiated BNT: 15 %, thymoma: 15%, pancreatic endocrine tumor: 15%, medullary cancer of the thyroid: 10%, pheochromocytoma: 5%, others 10%

CUSHING'S SYNDROME

- Establish its cause -

ACTH-Dependent ?

YES (Non suppressed plasma ACTH)

NO (Suppressed plasma ACTH)

Pituitary-Dependent

-!HDD +
-!CRH +
- Cathé +

Non-Pituitary-Dependent

-!HDD -
-!CRH -
- Cathé -

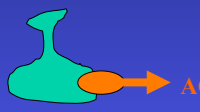
Adrenal Cushing's syndrome

CUSHING'S DISEASE

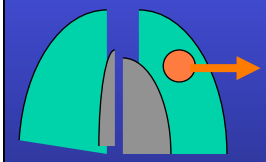
ECTOPIC ACTH SECRETION

ADRENAL « TUMOR »

ACTH-dependent Cushing's syndrome

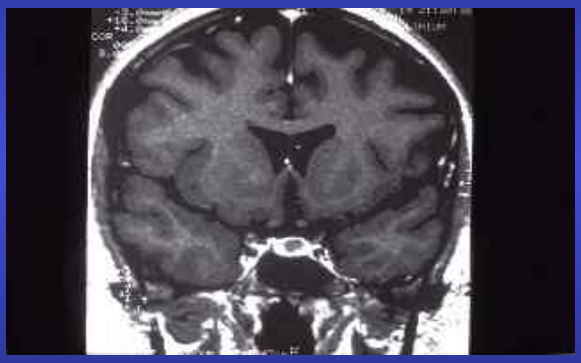


CLINICAL	ANATOMICAL	MOLECULAR
Typical	Micro adenoma	- ?
« Silent »	Macro adenoma (cancer)	- ?

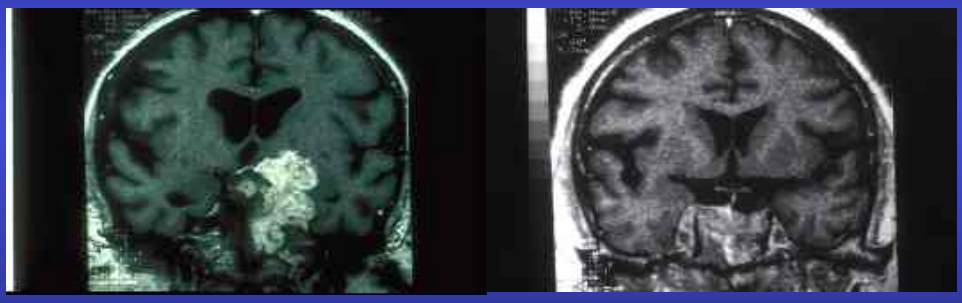


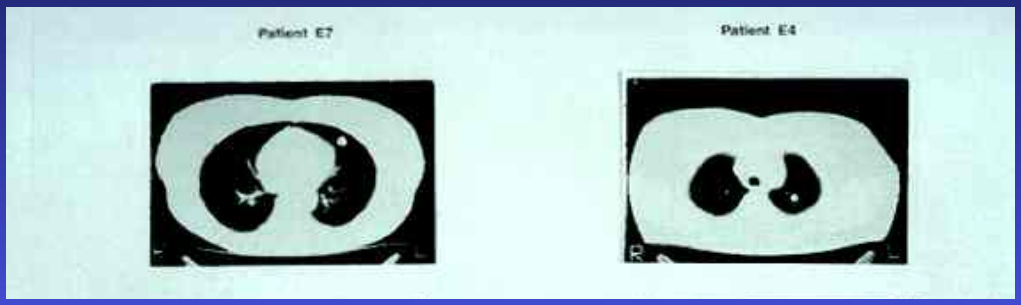
Occult	Carcinoid	- V3-R (legitimate !)
Aggressive	SCCL	- E2F

Micro adénome



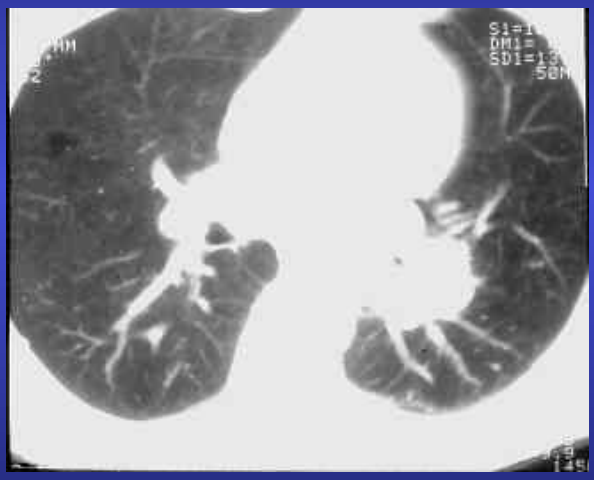
Macro adénomes





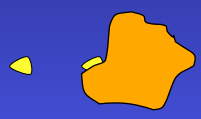
Sécrétion Ectopique d'ACTH
Carcinoides bronchiques « occultes »

Cancer anaplasique du poumon avec Sécrétion ectopique d'ACTH



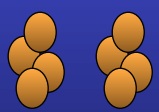
« ADRENAL » CUSHING'S SYNDROME

Adenoma — - Sporadic, Isolated



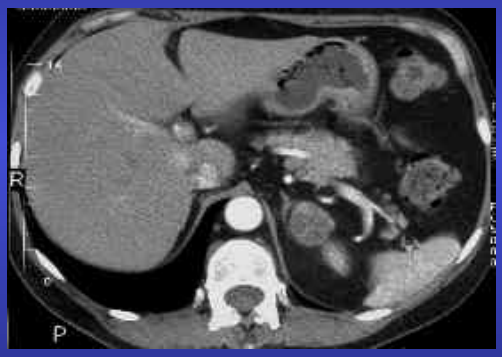
Carcinoma — - Sporadic, Isolated
- Syndromic (BWS, LF)

PPNAD
(Primary Pigmented Nodular Adrenal Disease) — - Isolated
- Familial,Syndromic (Carney Complex)

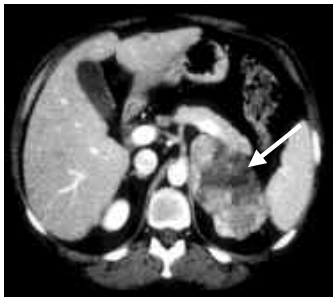


AIMAH
(ACTH Independent-Macronodular Adrenal Hyperplasia) — - Isolated
- Familial
- Syndromic (Mc Cune-Albright)

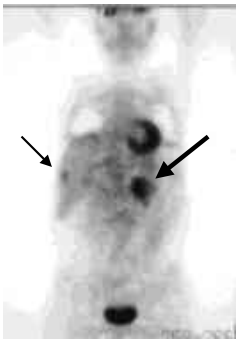
Adénome cortico surrénal



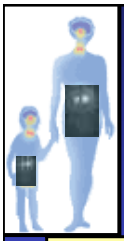
Adrenal cortical carcinoma



CT Scan
spontaneous density 27UH



PET Scan
18-FDG uptake



Carney complex"

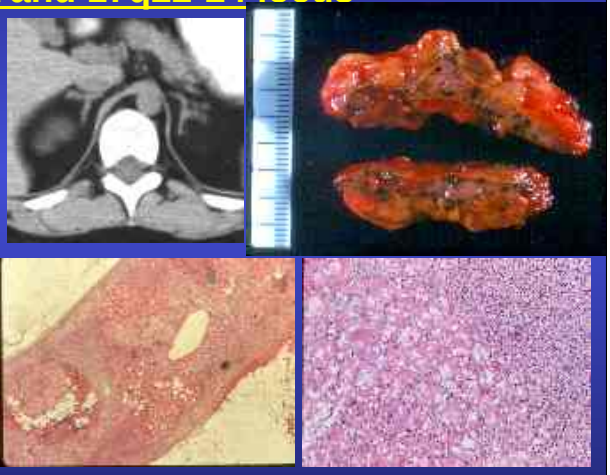
The complex of myxomas, spotty pigmentation, and endocrine overactivity.

Medicine, 1985, J Aidan Carney"

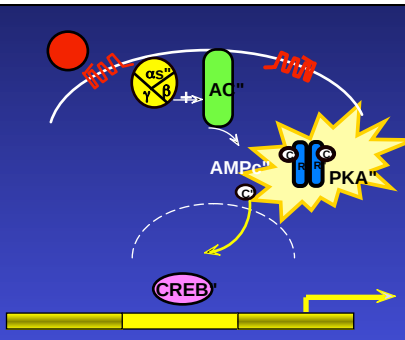
PRKAR1A and 17q22-24 locus"

	Frequency
Spotty skin pigmentation	77 %
Skin Myxoma	33%
Cardiac Myxoma	53 %
PPNAD	**26 %**
Breast ductal adenoma	3 %
LCCST	33 % (male)
Thyroid tumor	5 %
Acromegaly	10 %
Melanocytic schwannoma	10 %

CA Stratakis, L Kirschner, J A Carney, JCEM, 2001 (n= 338)



Primary Pigmented Nodular Adrenocortical Disease"

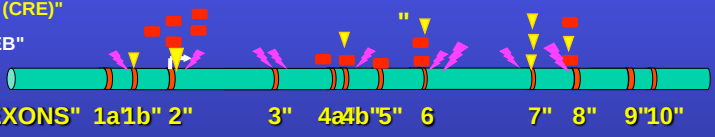


TGAC:GTCA"
cAMP Response Element (CRE)"

CRE-Binding Protein: CREB"

Germ line inactivating heterozygous mutation of PRKAR1A in 40 % of the kindreds: "

L Kirshner, et al, Nat Genet, 2000
Hum Mol Genet, 2000"



The "CCC" (Carney-Cushing-Cochin) hypothesis:"

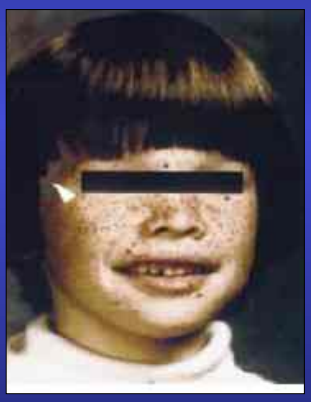
In patients referred for Cushing's syndrome due to PPNAD, *PRKAR1A* mutations might be more frequent: 15/19 index cases with CCN (78 %) & 15/23 index cases with isolated PPNAD (65 %). "

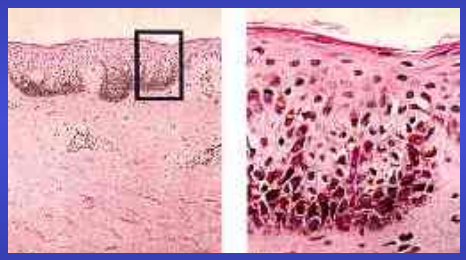
L Groussin, et al, JCEM, & Am J Hum Genet 2002"

Introduction
Manifestations

•!Lentiginose 77 %

+ fréquente
période péripubertaire
péri-orificielle





Lentiginose

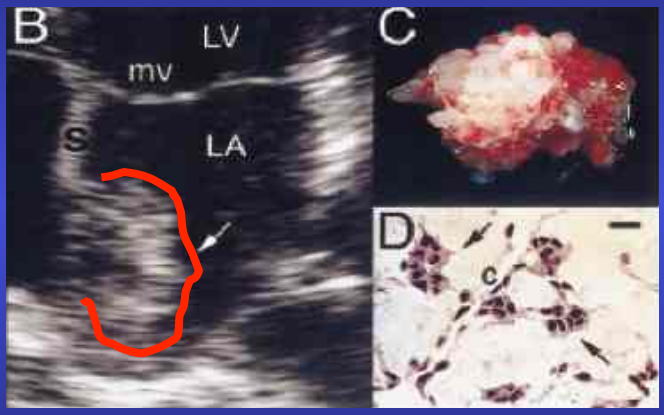
Hyperplasie
des mélanocytes

•!Lentiginose 77 %
•!Myxome cardiaque 53 %

pronostic vital
accident embolique

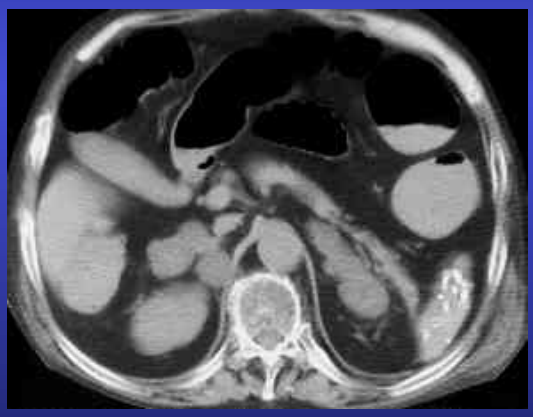
Cellule souche
mesenchymateuse
pluripotente

•!sujet jeune
•!toutes les cavités
•!récurrent

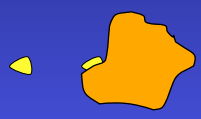
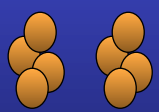


Matrice extracellulaire
abondante

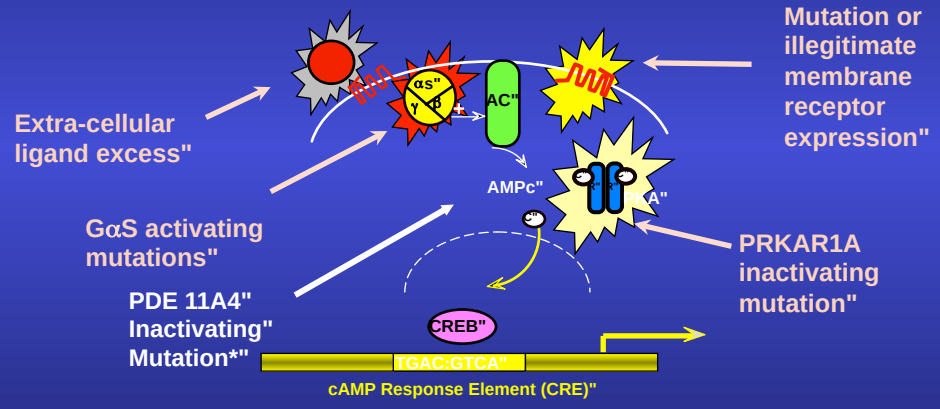
AI-MAH
(ACTH Independent- Macronodular Adrenal Hyperplasia)



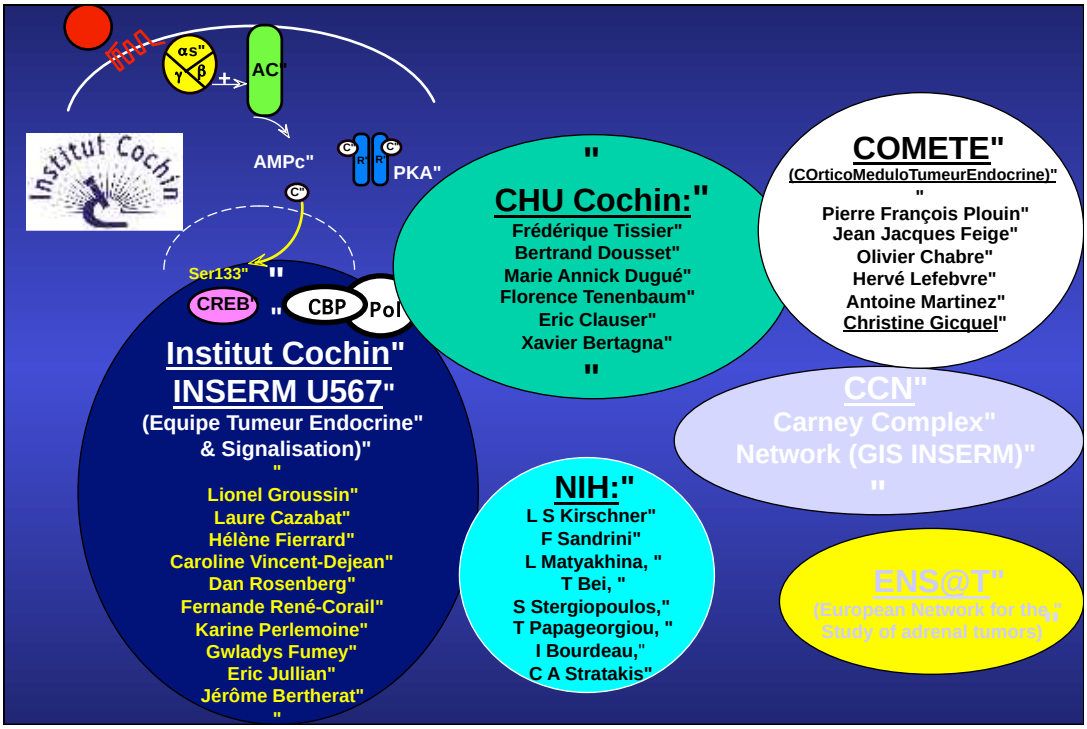
« ADRENAL » CUSHING' S SYNDROME

		MOLECULAR
 **Adenoma**	- Sporadic, Isolated	-!β-caténine -!APC
 **Carcinoma**	- Sporadic, Isolated - Syndromic (BWS, LF)	- IGFII, 17p13, … - IGFII, p53
 **PPNAD** (Primary Pigmented Nodular Adrenal Disease)	- Isolated - Familial,Syndromic (Carney Complex)	- PRKARIA - PDE11A4
 **AIMAH** (ACTH Independent-Macronodular Adrenal Hyperplasia)	- Isolated - Familial - Syndromic (Mc Cune-Albright)	- « illegitimate Rs » - Gsa - APC

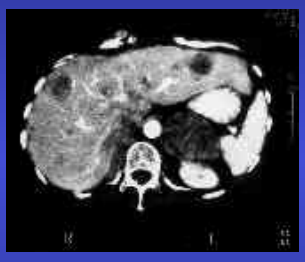
The multiple alterations of the cAMP pathway in endocrine tumors"

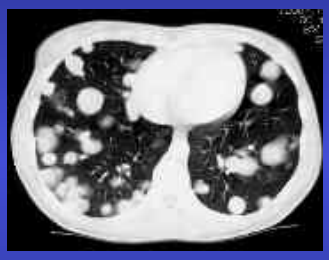


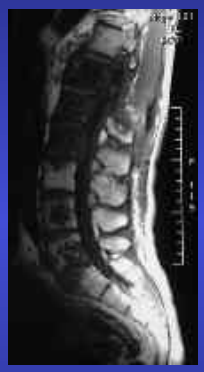
* Horvath et al. (NIH /Cochin) Nature Genetics July 2006



ACC : distant metastases







Liver :
85/202 (42 %)

Lung :
79/202 (39%)

Bone :
20/202 (10 %)

Cochin Series (COMETE Network) : 202 patients, !
mean follow-up 3.4 ± 4.4 years (0.3 to 26 years)!

18FDG Pet scan in « advanced »ACC