Nouvelles causes d'hypercorticisme

17 mai 2013

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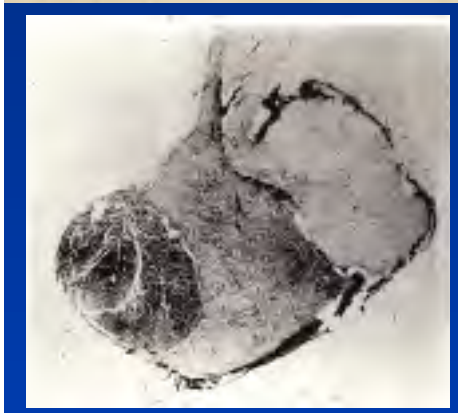
Hôpital Cochin
& INSERM 1016, CNRS 8104

Harvey Cushing

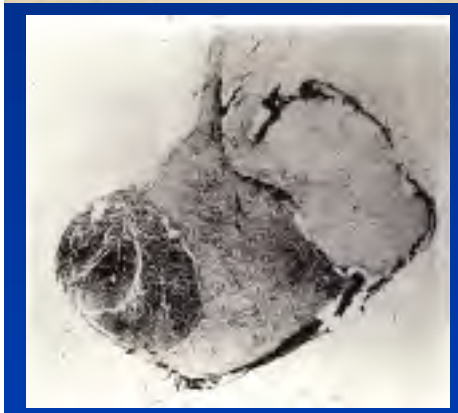
The basophils adenomas of the pituitary gland and their clinical manifestations
1912 & 1932



11/12 patients died within 3 to 7 years
but
patient # 1, “Minnie G” died
in 1958 at age 66

Harvey Cushing

The basophils adenomas of the pituitary gland and their clinical manifestations
1912 & 1932



11/12 patients died within 3 to 7 years
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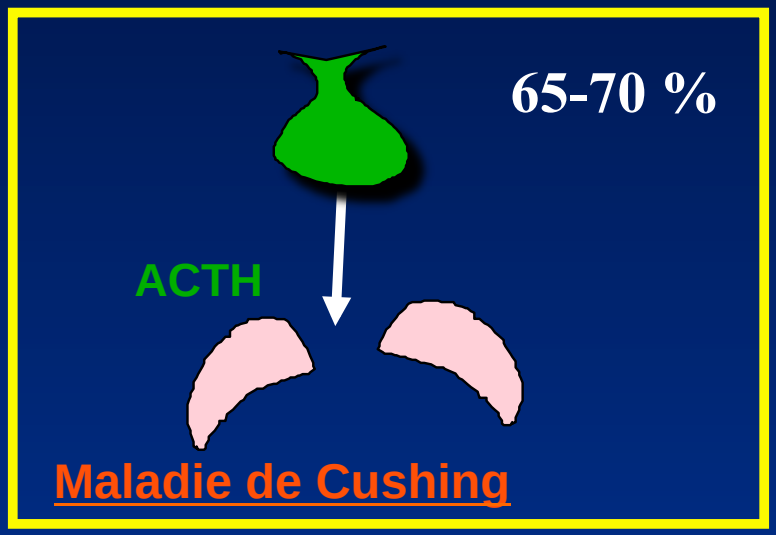
patient # 1, "Minnie G" died
in 1958 at age 66

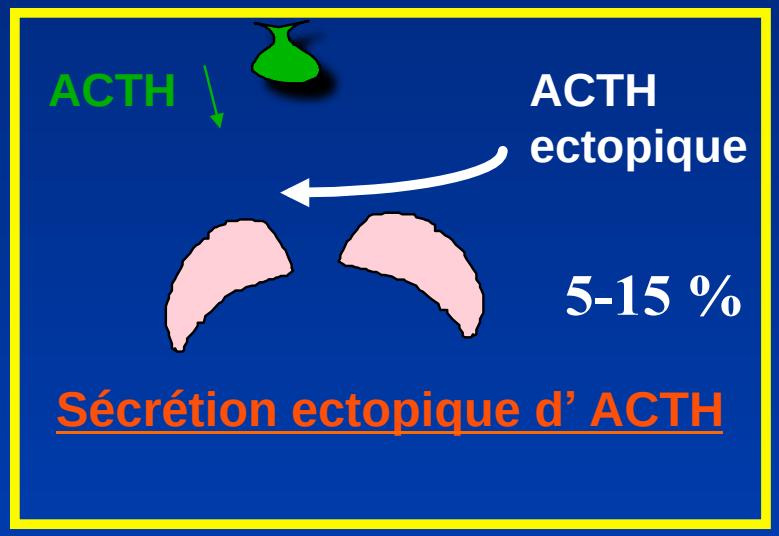
The search for Harvey Cushing's patient, Minnie G., and the cause of her hypercortisolism

- 1910: Craniotomy: negative exploration
- 1922: "no worse than in 1913", cranial X ray: osteoporosis
-1932: "in reasonably good health, though some of the stigmata of her malady still persist
- "the lack of autopsy appeared to be final; the cause of Minnie G.'s Cushing's syndrome and an explanation of its regression seemed to have been put beyond my reach." J A Carney, Am J Surg Pathol, 1995

Causes d'hypercorticisme

1. ACTH-dépendant





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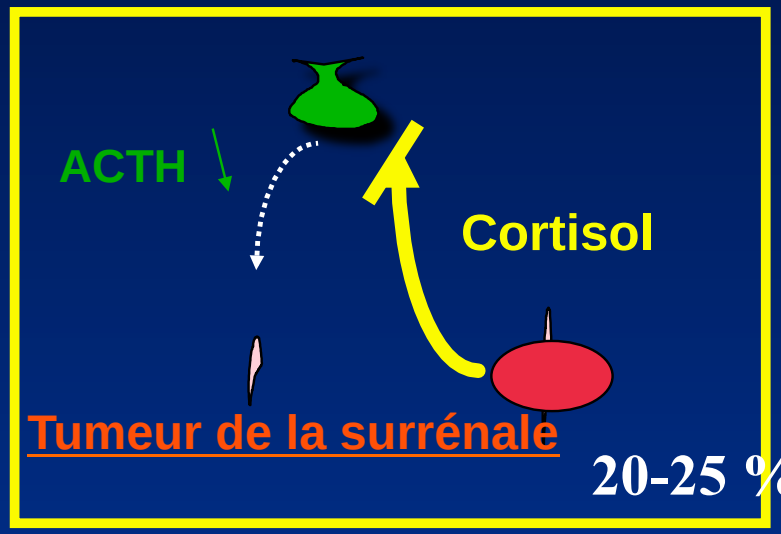
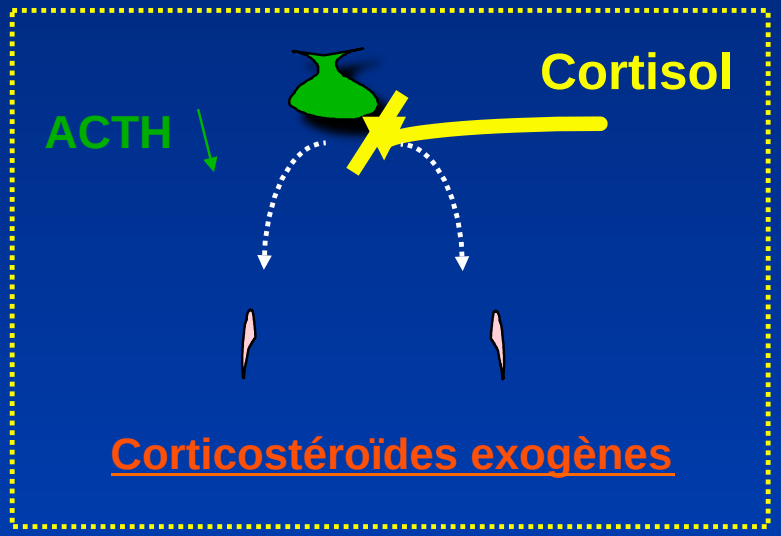




Cas clinique 1

Depuis 1 an :

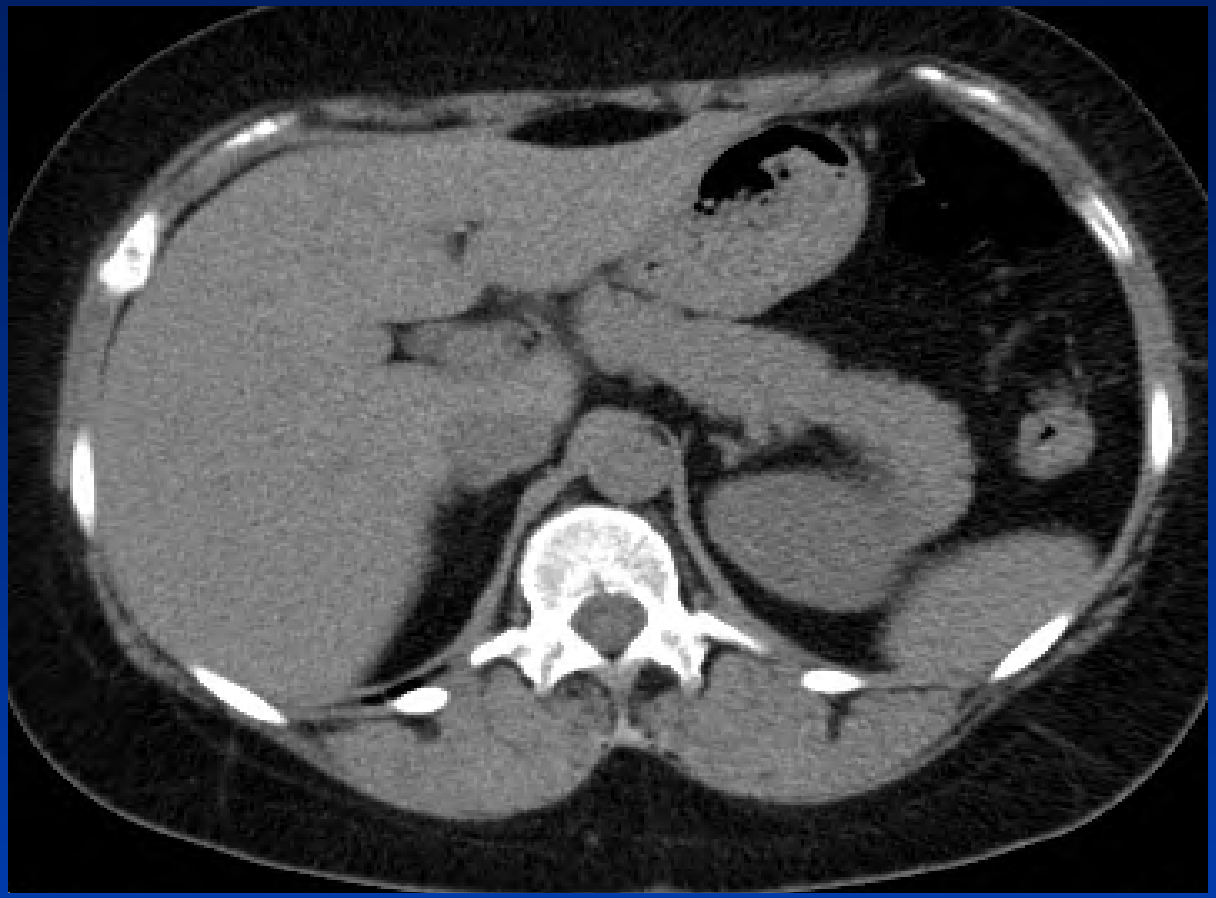
- Chute de cheveux
- aménorrhée
- obésité abdominale
- HTA

Biologie

- K+ : 3.1 mmol/l

Cas clinique 1

ACTH < 2 pg/ml

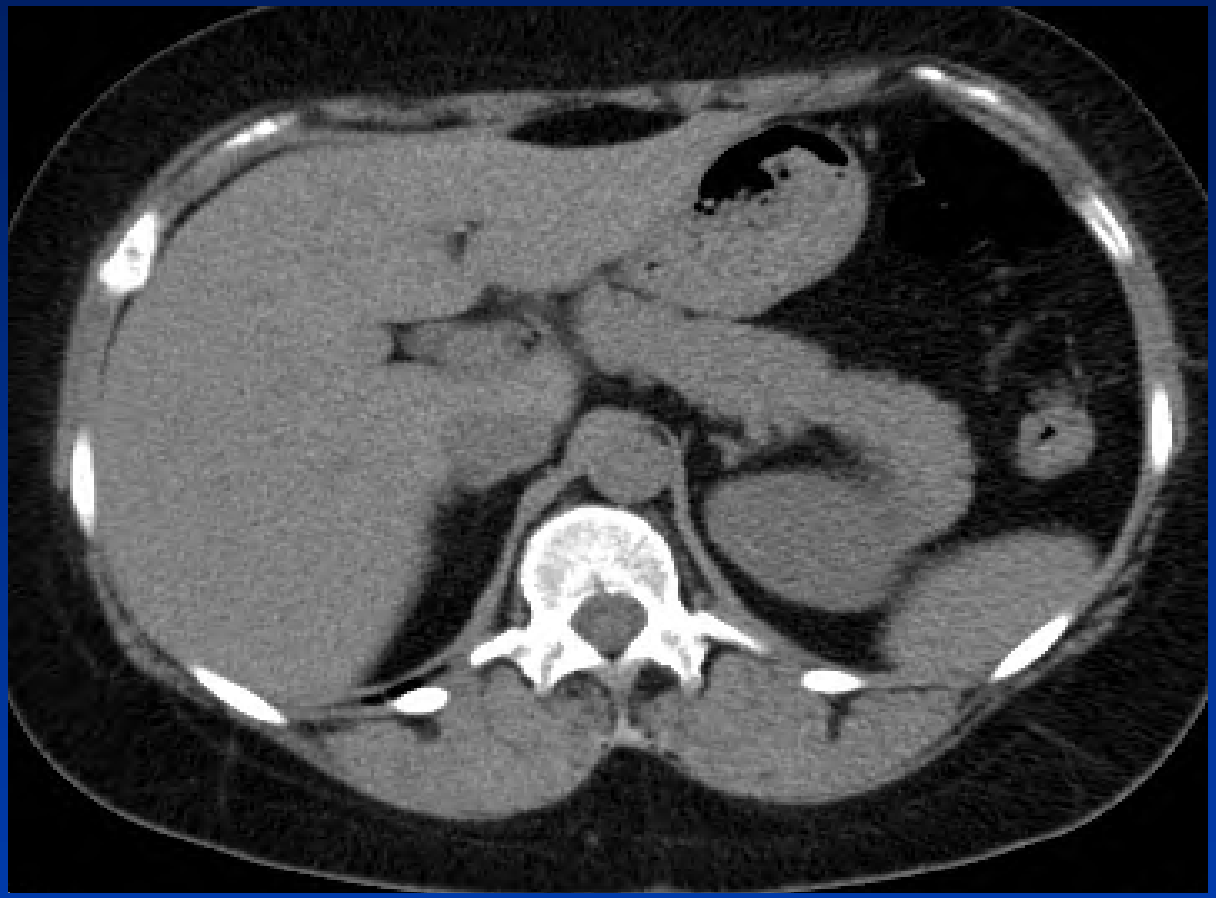


Cas clinique 1

ACTH < 2 pg/ml

Cortisol sérique 8h : < 2 ng/ml,

Cortisolurie: 3 µg/24 hrs



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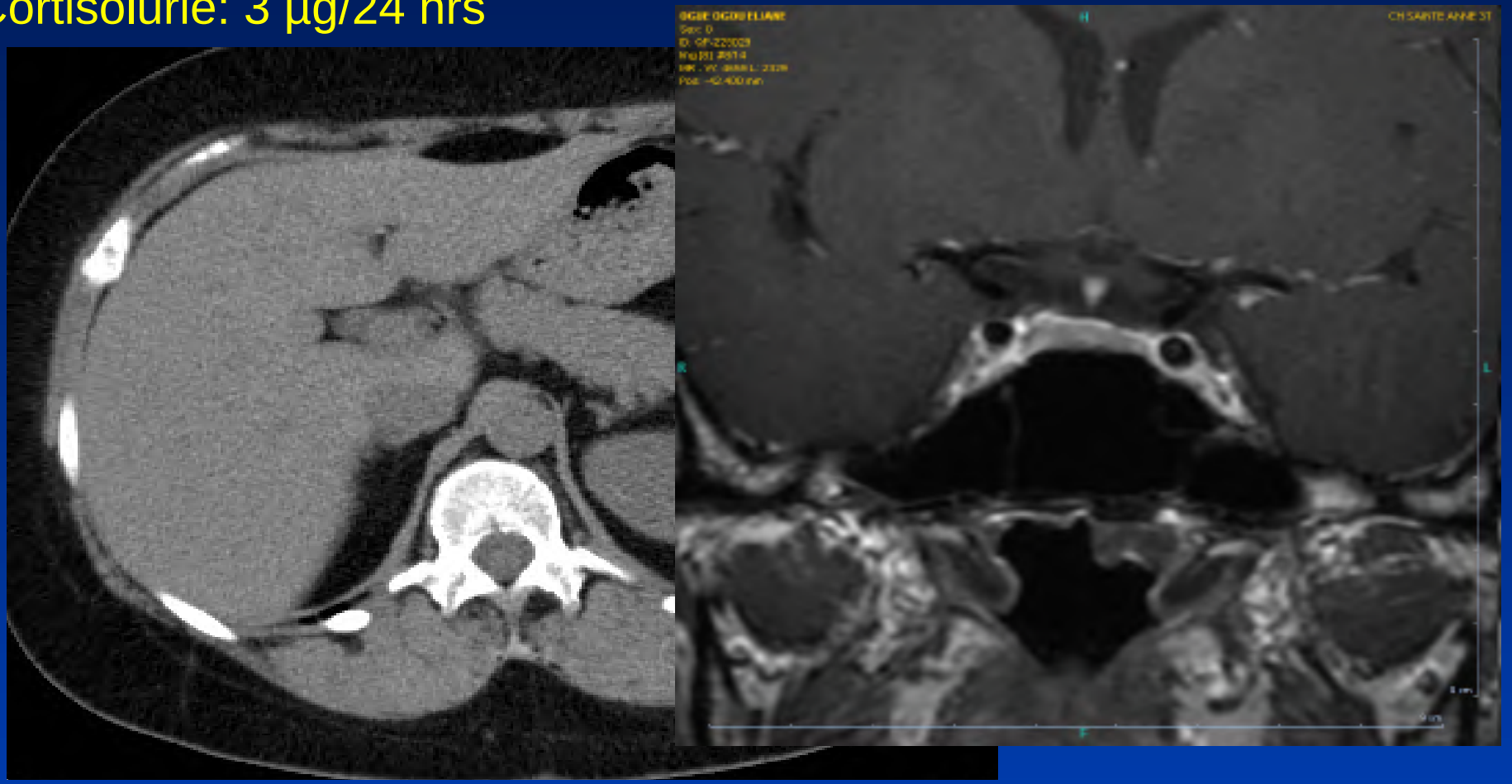
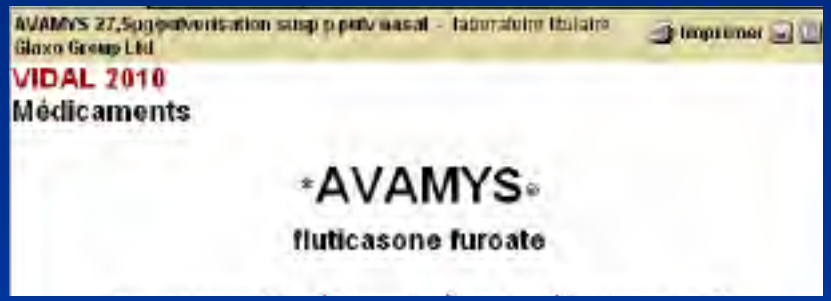


Cas clinique 1

- Avamys spray nasal 2/j

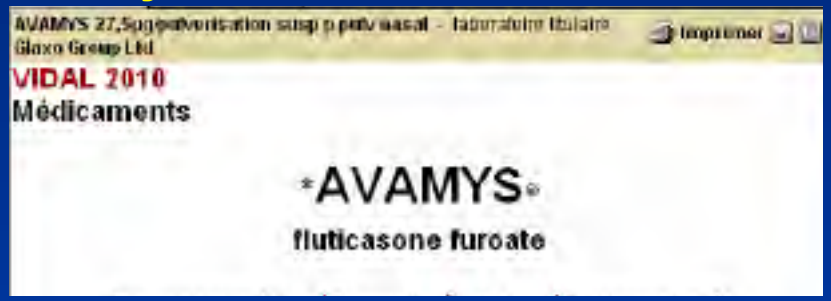
Cas clinique 1

- Avamys spray nasal 2/j



Cas clinique 1

- Norvir 0-0-1
- Prezista 0-0-2
- Aerius 2-0-0
- Loxen 50 1-0-1
- Avamys spray nasal 2/j
- Crestor 5 0-0-1



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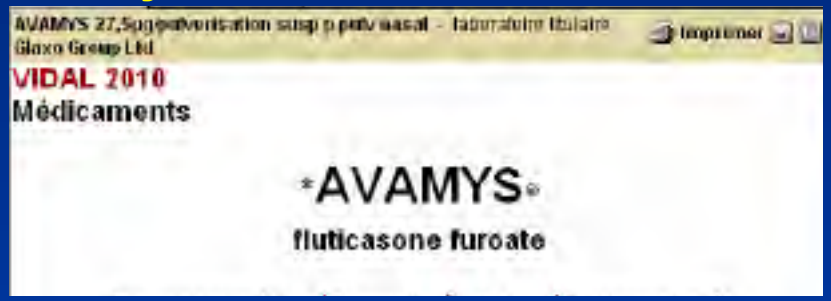


NORVIR 100mg caps molle - laboratoire titulaire:
Abbott France - PIH

Imprimer

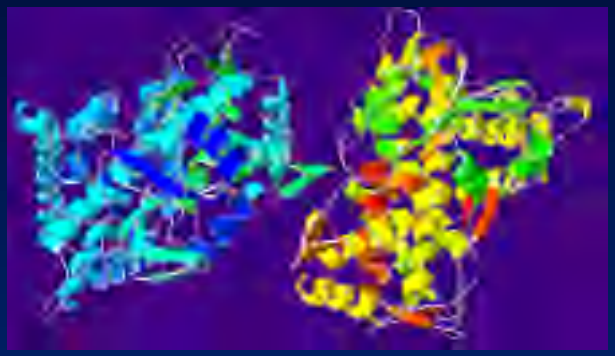
Ritonavir administré comme potentialisateur pharmacocinétique ou comme agent antirétroviral :

Le ritonavir présente une forte affinité pour plusieurs isoformes du cytochrome P450 (CYP), dans l'ordre décroissant suivant : CYP3A4 > CYP2D6. La coadministration de Norvir avec un médicament métabolisé essentiellement par le CYP3A peut augmenter les concentrations plasmatiques du médicament coadministré, ce qui peut augmenter ou prolonger son effet thérapeutique et ses effets indésirables. Pour certains

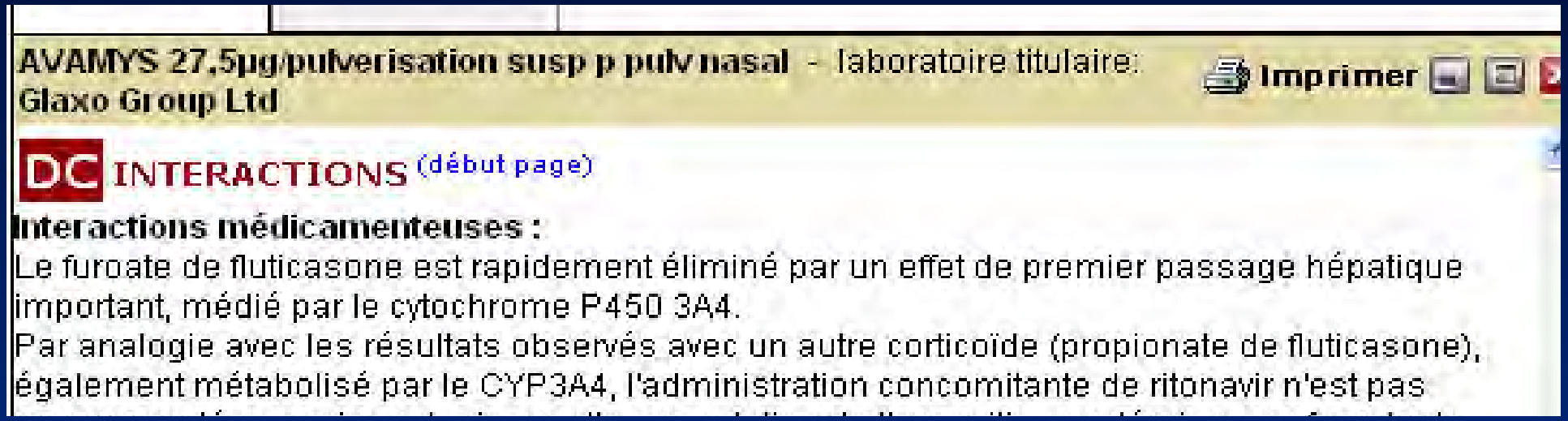
RITONAVIR

inhibiteur puissant du cytochrome P450, isoforme 3A4 +++

Cytochrome P450 (CYP)



- Enzyme membranaire
- Membrane interne mitochondrie, RE
- Ubiquitaire
- 57 gènes codant pour de nombreuses isoformes
- Métabolisme de centaines de substances endogènes ou exogènes (75% du métabolisme)
- Dans foie : Métabolisme des substances toxiques
- Rôle ++ dans stéroïdogénèse (CYP21, aromatase)



FLUTICASONE

Elimination hépatique (premier passage) médiée par l'isoforme 3A4 du cytochrome P450

Demi-vie 15h

Drug interactions between inhaled corticosteroids and enzymatic inhibitors

Amélie Daveluy · Cécile Raignoux · Ghada Miremont-Salamé · Pierre-Olivier Girodet · Nicholas Moore · Françoise Haramburu · Mathieu Molimard

Eur J Clin Pharmacol (2009) 65:743–745

inhibitor

	Gender	Age (years)	Type of effect	Inhaled corticosteroid	Dose µg/day (BE µg/day)	Associated enzymatic inhibitor	Other drugs
1	F	9	CS	Fluticasone	250 (500)	Ritonavir, lopinavir	Abacavir, didanosine
2	F	10	CS	Fluticasone	1,000 (2,000)	Ritonavir, lopinavir	Abacavir, topical beclomethasone
3	F	13	CS	Fluticasone	1,000 (2,000)	Itraconazole	Mycophenolate, tacrolimus, cotrimoxazole
4	M	14	AI	Budesonide	1,000 (1,250)	Itraconazole	–
5	M	16	CS	Fluticasone	500 (1,000)	Ritonavir, fosamprenavir	Zidovudine, tenofovir
6	F	26	AI	Budesonide	1,600 (2,000)	Itraconazole	–
7	F	27	AI	Fluticasone	1,000 (2,000)	Itraconazole	Dornase alpha
8	F	30	CS	Fluticasone	500 (1,000)	Itraconazole	Salmeterol, formoterol
9	F	31	CS	Fluticasone	1,000 (2,000)	Ritonavir, lopinavir	Lamivudine, tenofovir
10	F	36	CS	Fluticasone	1,500 (3,000)	Verapamil	Sertraline, omeprazole, zolpidem
11	M	42	CS	Fluticasone	2,000 (4,000)	Ritonavir, lopinavir	Lamivudine, stavudine
12	F	69	AI	Budesonide	1,600 (2,000)	Diltiazem	Theophylline, terbutaline, insulin, metoprolol, molsidomine, ranitidine, enalapril, atorvastatin, diclofenac, cloonipramine, flecainide
13	F	58	AI	Fluticasone	1,000 (2,000)	Itraconazole	–
14	M	72	AI	Budesonide	2,000 (2,500)	Diltiazem	Atorvastatin, molsidomine, aspirin
15	F	75	AI	Fluticasone	NA	Verapamil	Salmeterol, molsidomine, aspirin

Inhibiteur de protéase et Cushing iatrogène: possible aussi avec d'autres corticothérapies « locales »

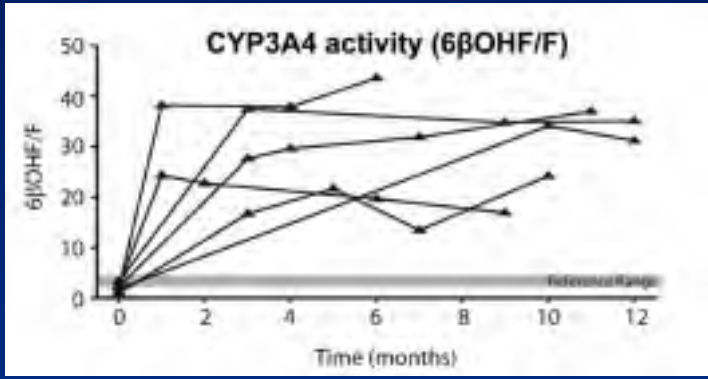
Ritonavir and epidural triamcinolone as a cause of iatrogenic Cushing's syndrome. Albert NE, Kazi S, Santoro J, Dougherty R. Am J Med Sci. 2012 Jul;344(1):72-4

Iatrogenic Cushing syndrome after a single intramuscular corticosteroid injection and concomitant protease inhibitor therapy. Levine D, Ananthakrishnan S, Garg A. J Am Acad Dermatol. 2011 Oct;65(4): 877-8.

Cushing's syndrome and adrenal axis suppression in a patient treated with ritonavir and corticosteroid eye drops.
Molloy A, Matheson NJ, Meyer PA, Chaterjee K, Gkrania-Klotsas E. AIDS. 2011 Jun 19;25(10):1337-9. doi: 10.1097/QAD.

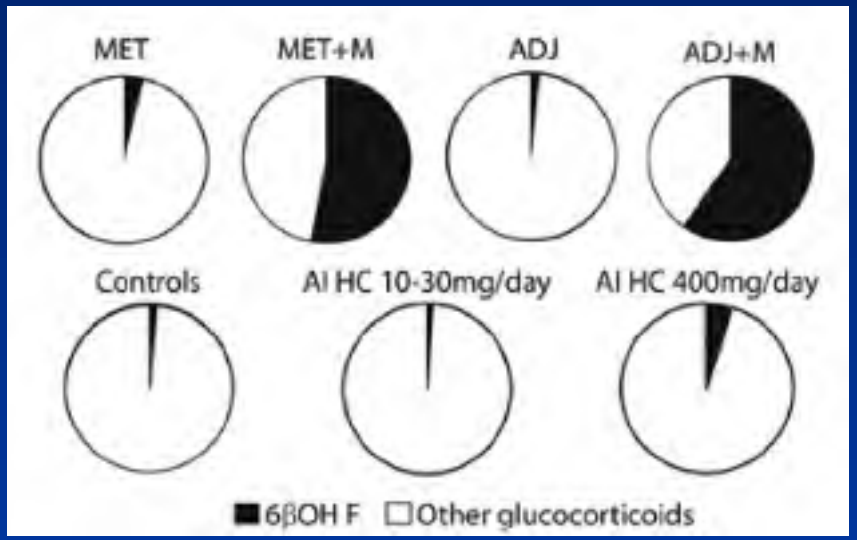
Mitotane: exemple d'inducteur enzymatique du Cytochrome P450 3A4:

Analyse par par spectrométrie de masse des stéroïdes urinaires



ACC

Controls & Adr Ins



V Chortis, JCE&M 2013

Catabolisme de l'hydrocortisone

Cas clinique 2

Femme, 39 ans

Syndrome de Cushing

- Prise de 40 kg en 2 ans 1/2, 94kg, 1m64, IMC 35
- Syndrome dépressif

Cortisolurie x 38 à 65 N

Cortisol salive minuit x 8 N

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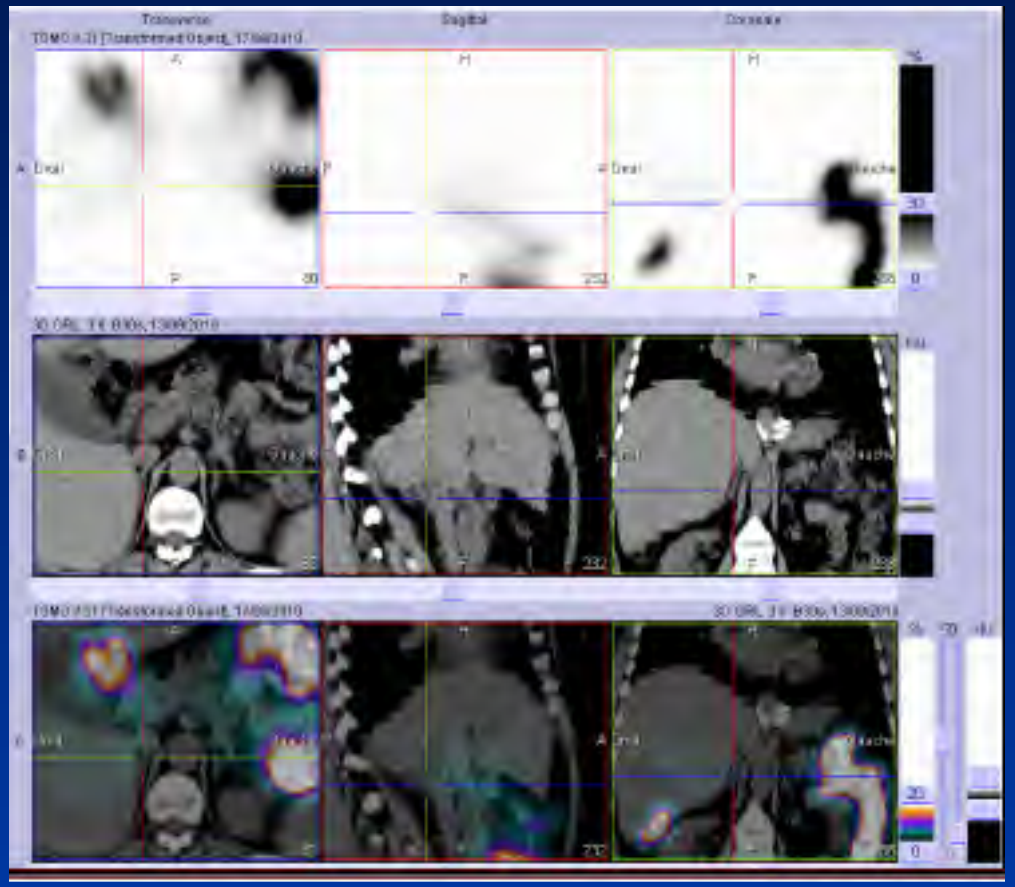
Cortisol salive minuit x 8 N

Cortisolémie après 1 mg Dectancyl 45 nmol/l (N < 50)

ACTH < 2 pmol/l

Cas clinique 2

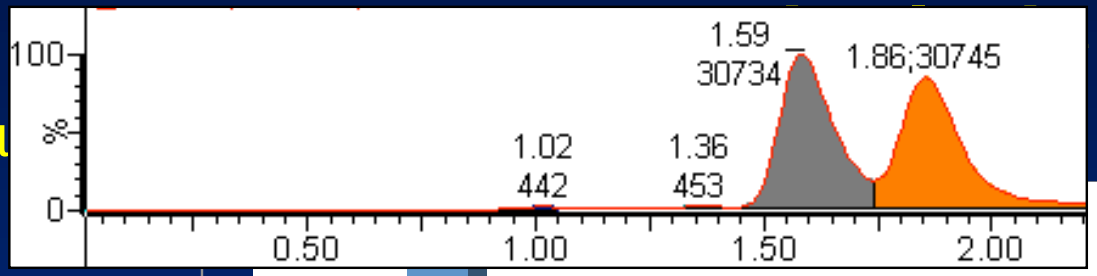


Scintigraphie iodocholestérol

Cas clinique 2

µ

/24h



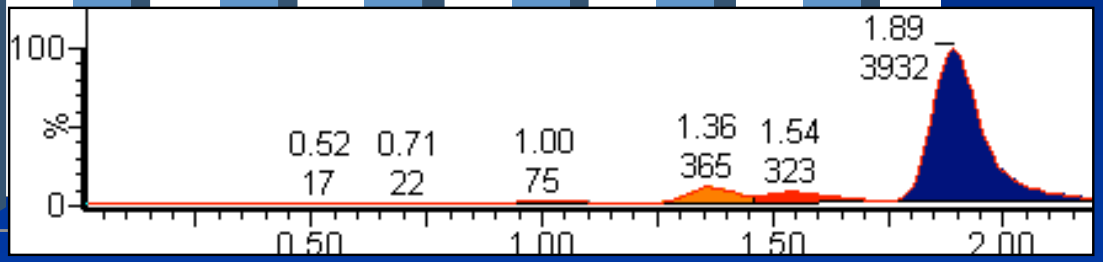
1000

100

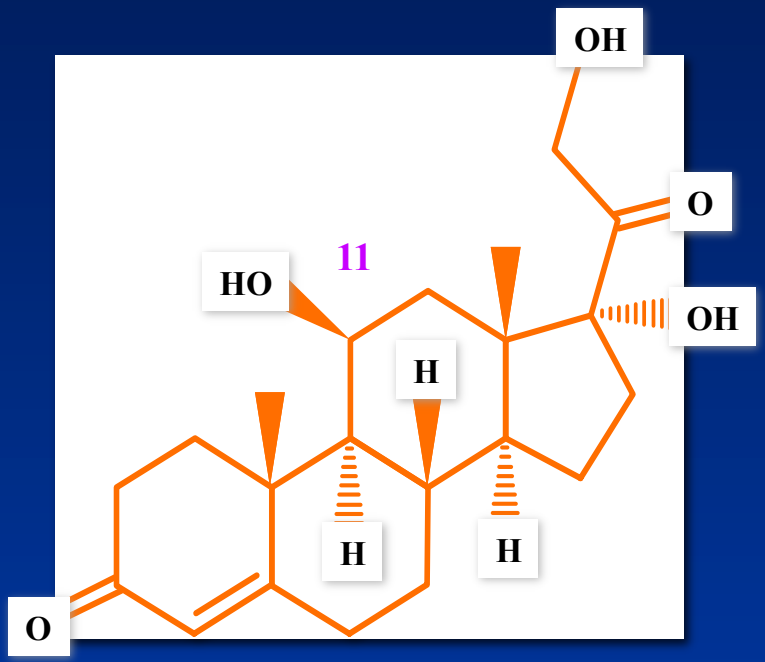
10

1

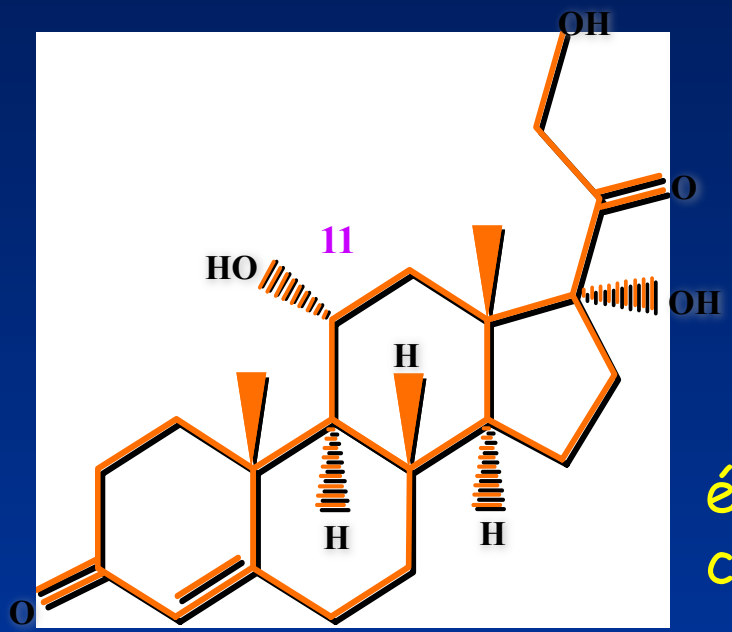
J1 J2 J3 J4 J5 J6 J7 J8 J9 J10



Cas clinique 2:
étude des stéroïdes en spectrométrie de masse



Cortisol

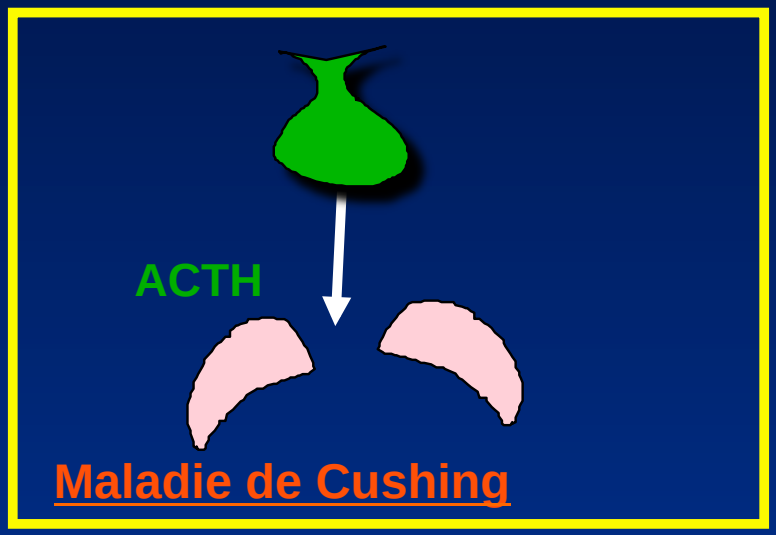


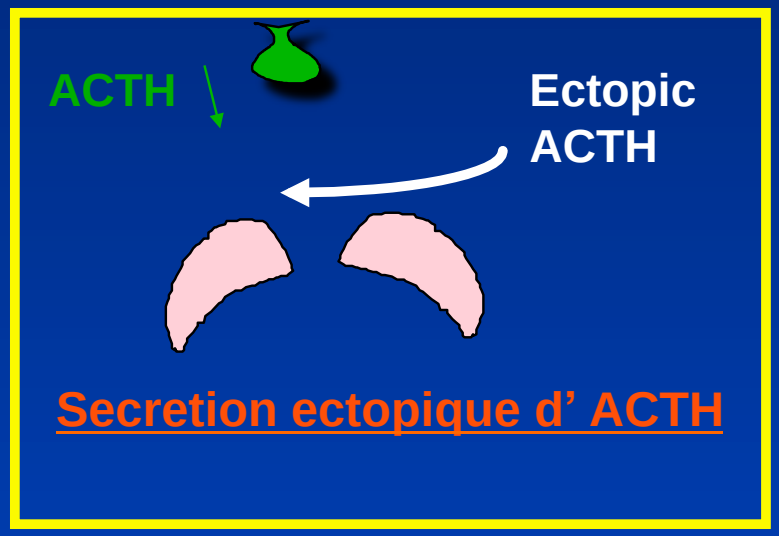
Epicortisol

épimère du cortisol en 11

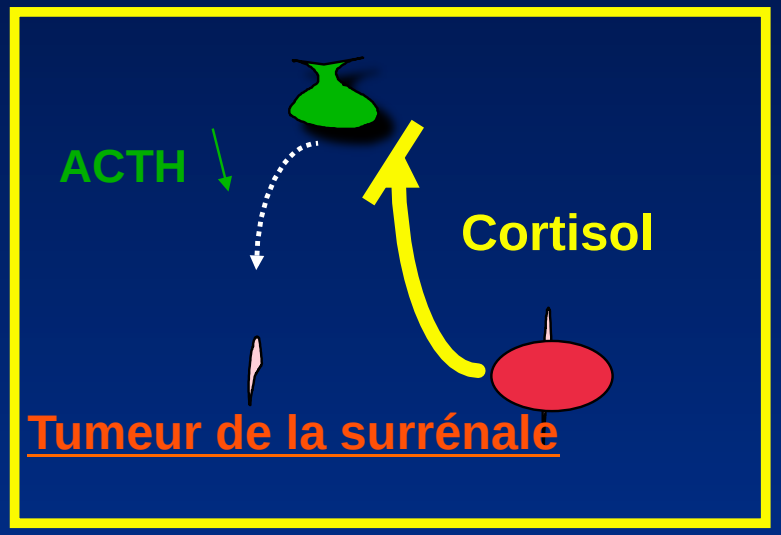
Causes d'hypercorticisme endogène: « Cushing »

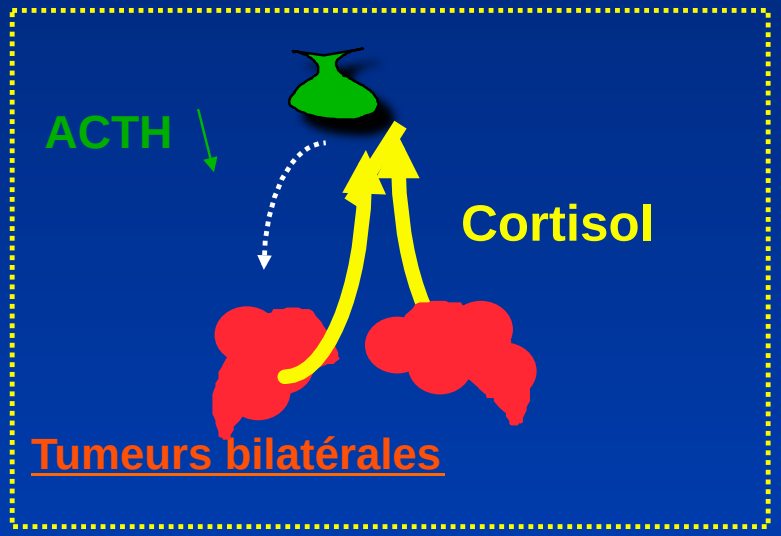
1. ACTH-dépendant





2. ACTH-indépendant





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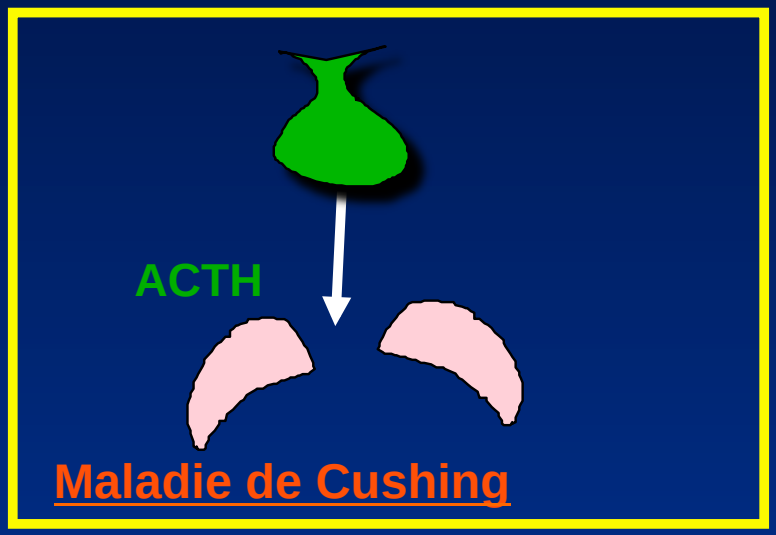
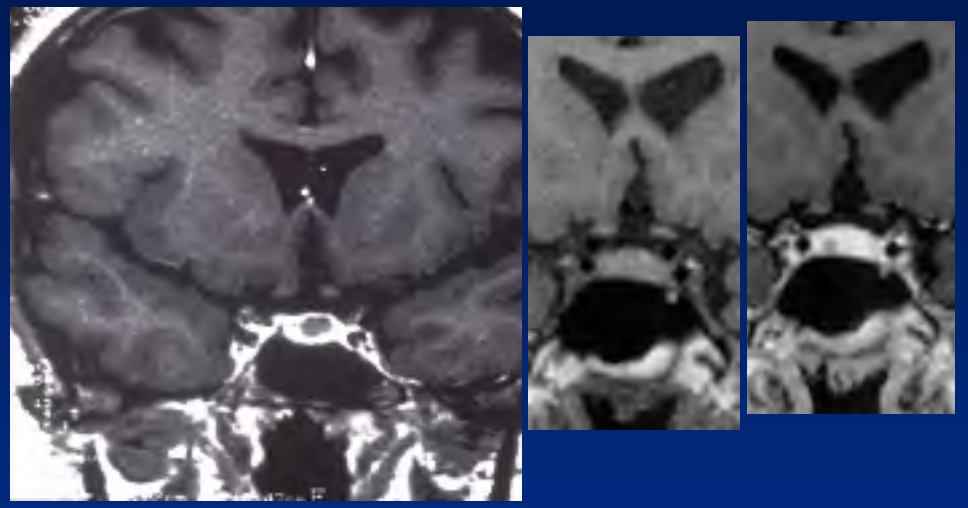
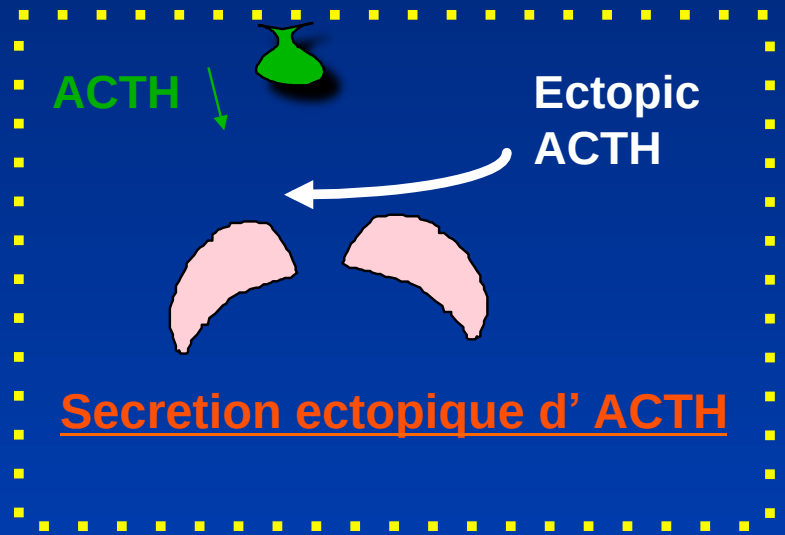
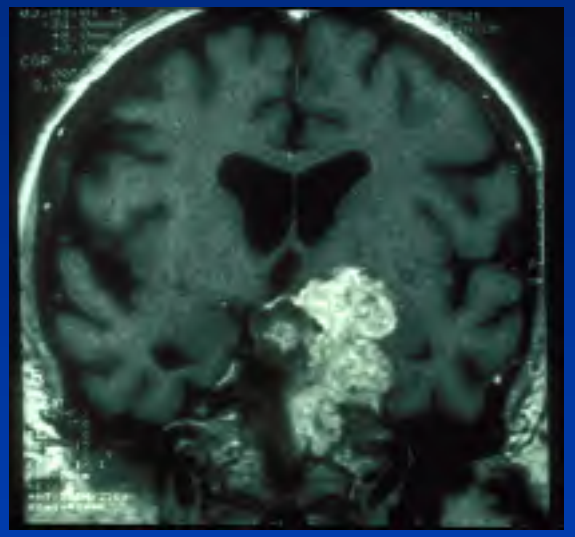
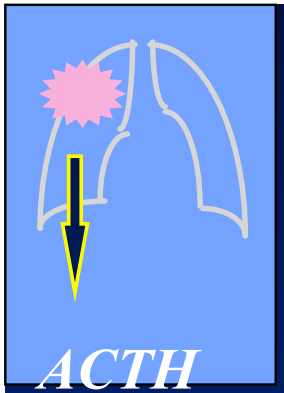


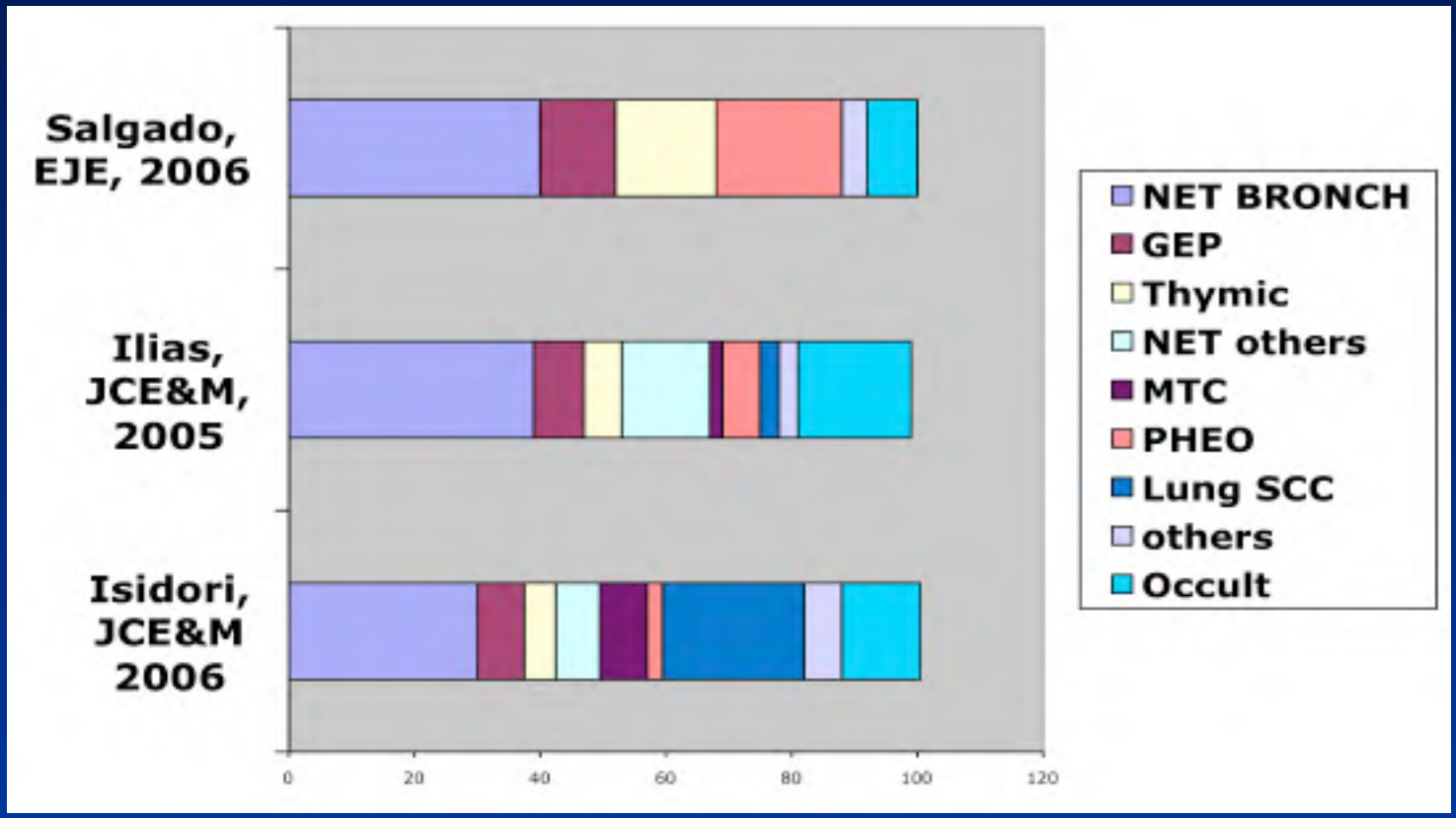






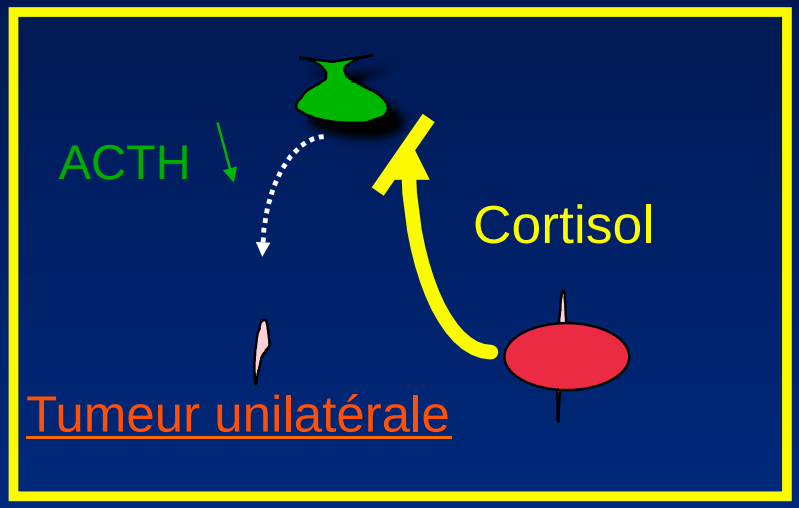


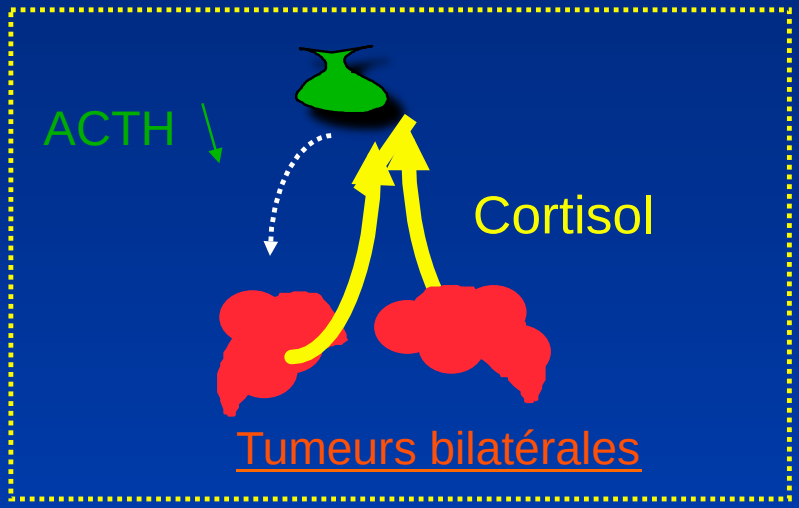
Sécrétion ectopique d'ACTH

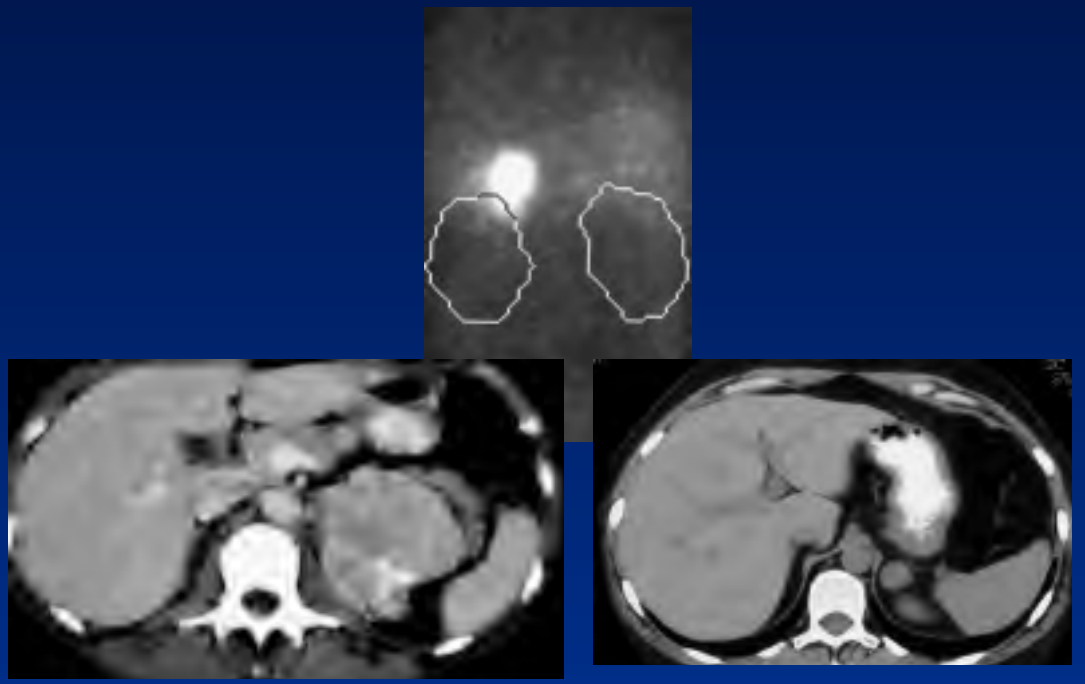


Tumor identified at first investigation in 50-70 % of patients and during follow-up in 15-20 %

Causes surrénaliennes d'hypercorticisme endogène (ACTH-indépendant)



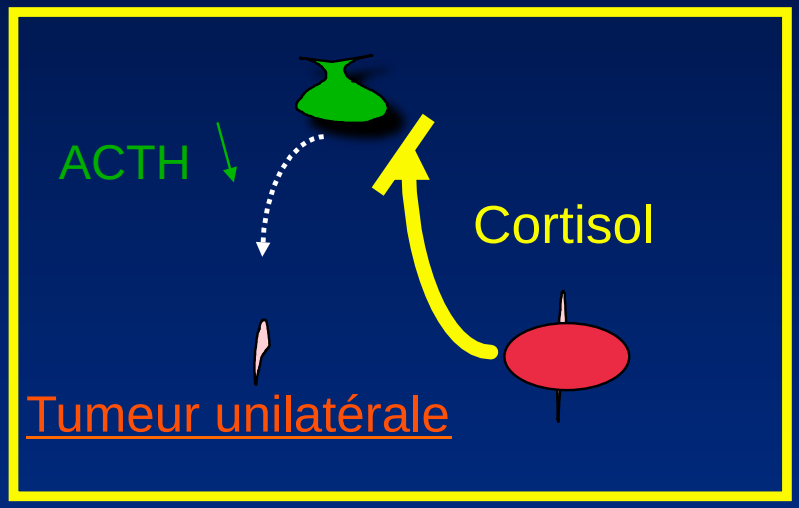


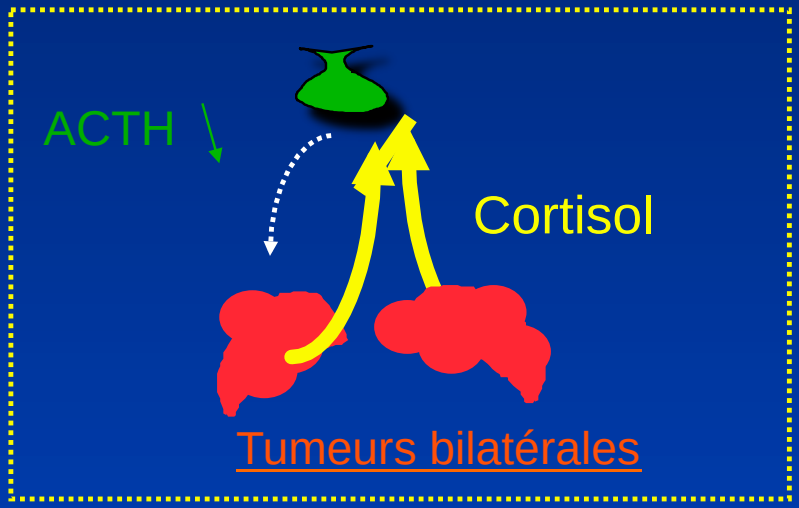


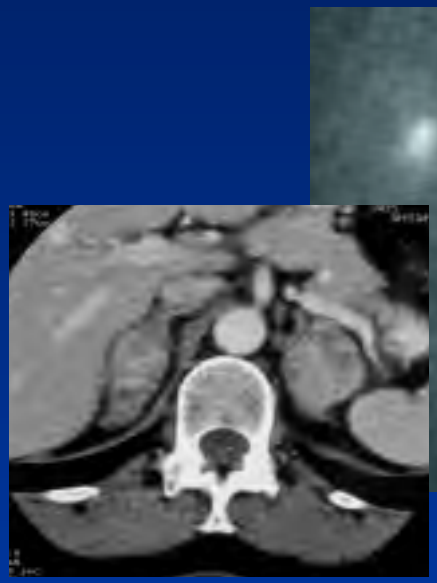
Corticosurrénalome

Adénome

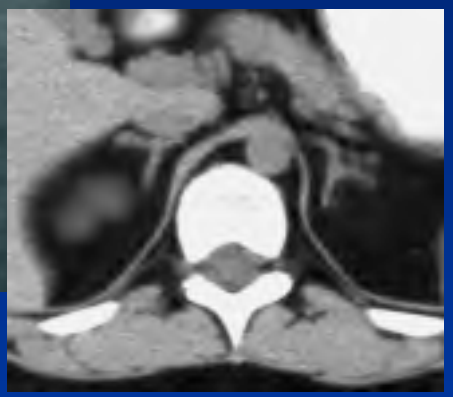
Causes surrénaliennes d'hypercorticisme endogène (ACTH-indépendant)







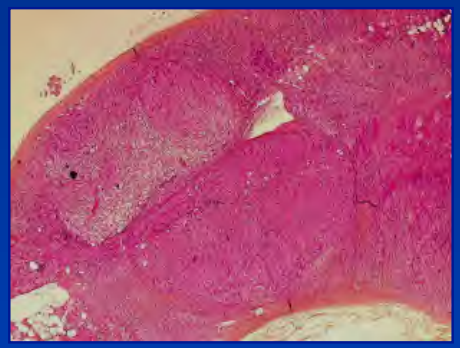
Hyperplasie Macronodulaire



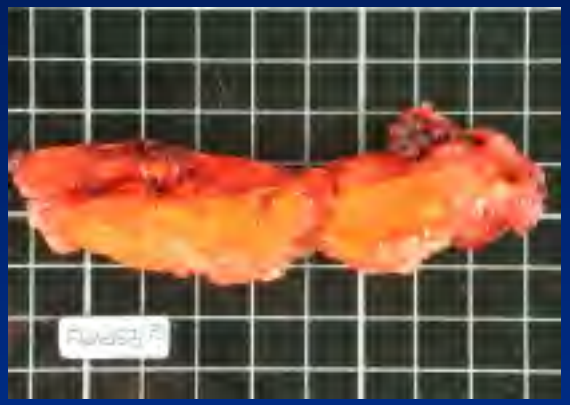
Dysplasie micronodulaire pigmentée

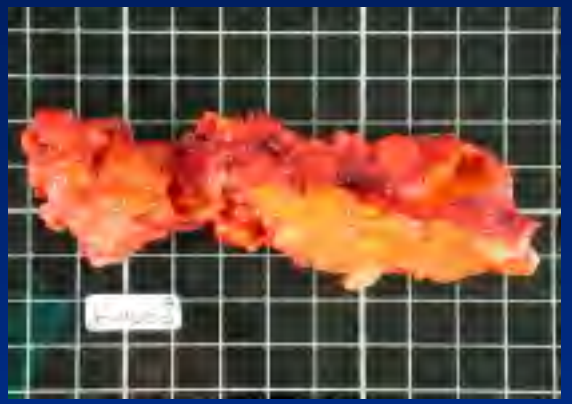
Tumeurs bilatérales

MICRO



MACRO





Cas Clinique 3

12 ans:

acne, hirsutisme, prise de poids

14 ans

déficit enzymatique ???

----> Dexamethasone 6 mois

+ 10 Kg, hypertension

15 ans Cortisolurie = 36 µg/24h

Test au synacthène:

Cortisol 149 ➔183 ng/ml

ACTH: < 5 pg/ml

21 ans: infarctus du myocarde

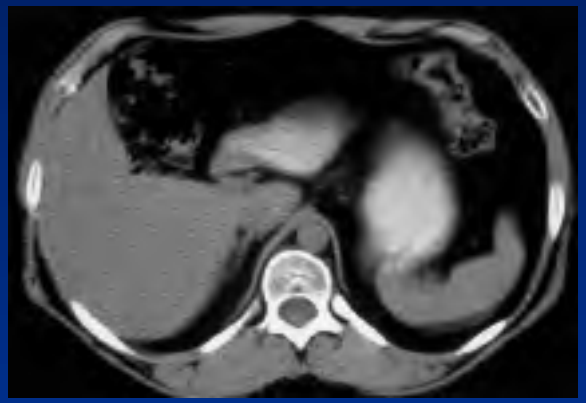
23 ans:

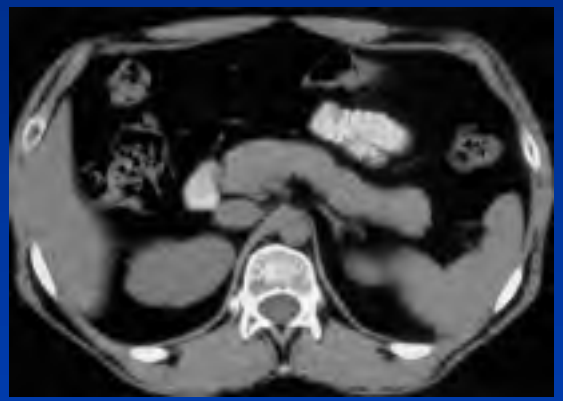
* Cortisolurie= 212 µg/24h(N < 90)

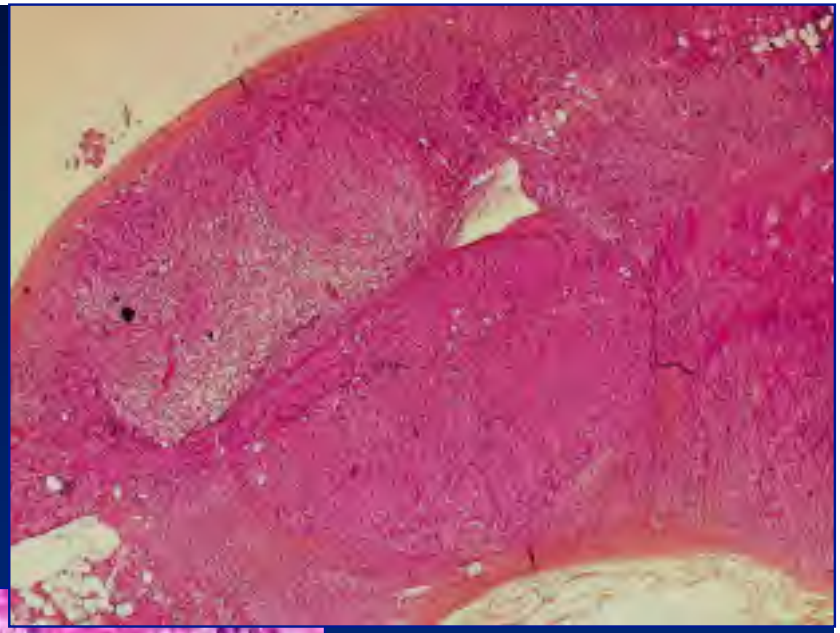
* Cortisolémie:

8h : 218 ng/ml 24h: 193 ng/ml

* ACTH < 2 pg/ml







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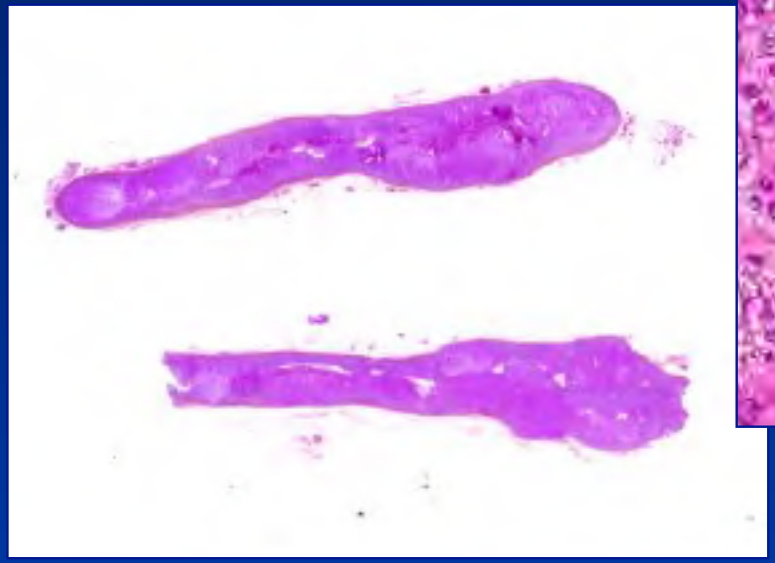
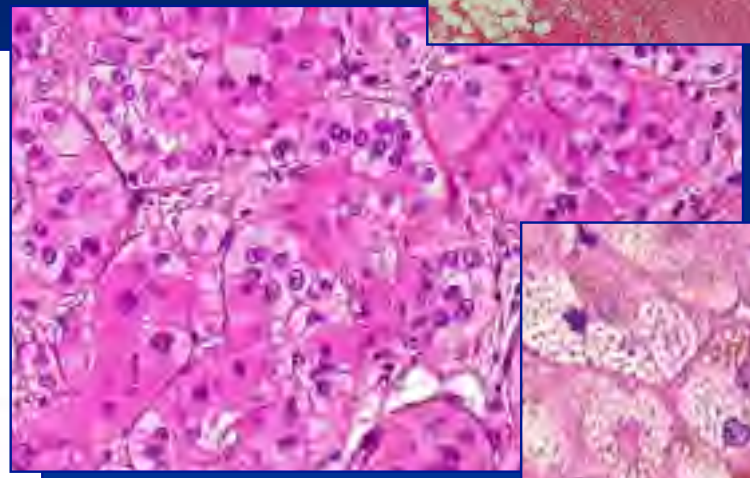
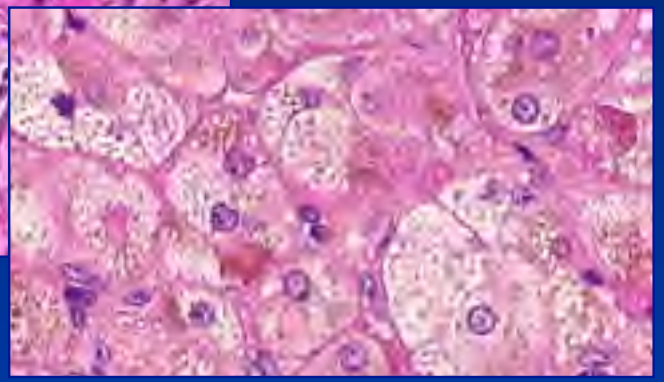
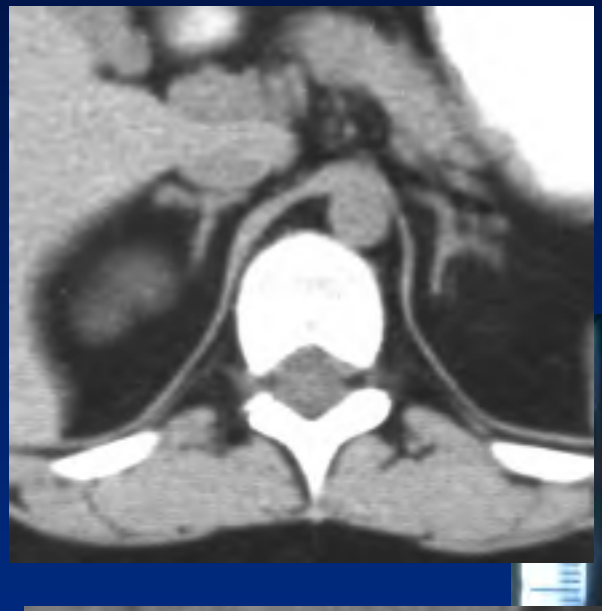


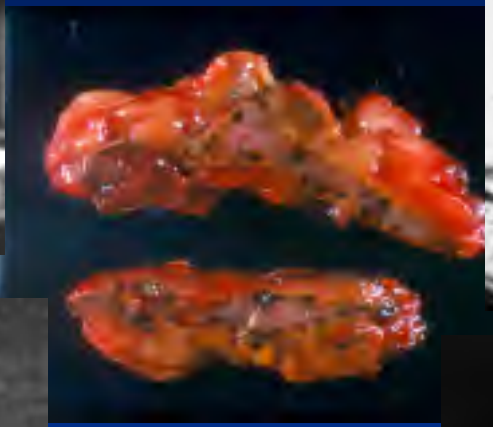


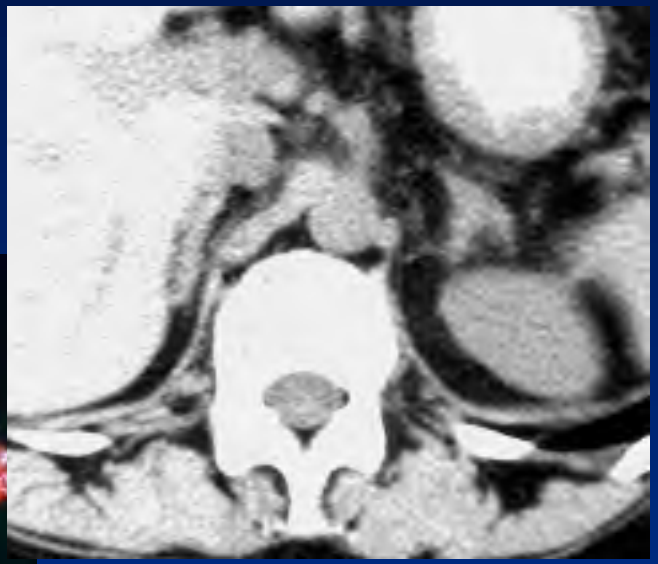


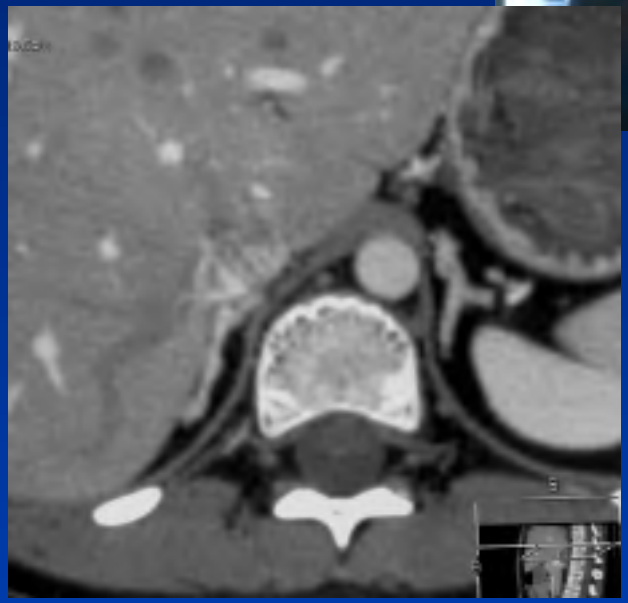
Dysplasie micronodulaire pigmentée des surrénales
Primary Pigmented Nodular Adrenocortical Disease (PPNAD)

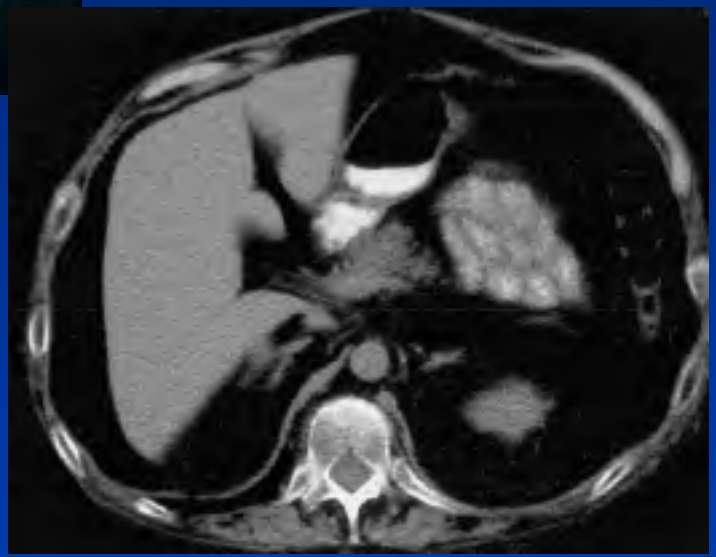
PPNAD











Carney complex

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The Complex of Myxomas, Spotty Pigmentation, and Endocrine Overactivity

J. AIDAN CARNEY, M.D., PH.D., F.R.C.P.I., HYMIE GORDON, M.D., F.R.C.P.,
PAUL C. CARPENTER, M.D., B. VITTAL SHENOY, M.D., AND VAY LIANG W. GO, M.D.

In 1984, we reported four Mayo Clinic patients with Cushing syndrome and an unusual bilateral adrenal disorder to which we gave the descriptive title "primary pigmented nodular adrenocortical disease" (31). A search of the literature had revealed 24 similar cases; in 3 of these, the disorder was familial. In one family, initially reported in 1980 by Schweizer-Cagianut et al., two siblings were affected: one sibling, who also had an eyelid "fibroma," became hemiparetic 4 years after adrenalectomy; the other was thought to have neurofibromatosis because of skin "fibromas." A third sibling did not have the adrenal disorder but died at age 5 years of a cardiac myxoma (29).

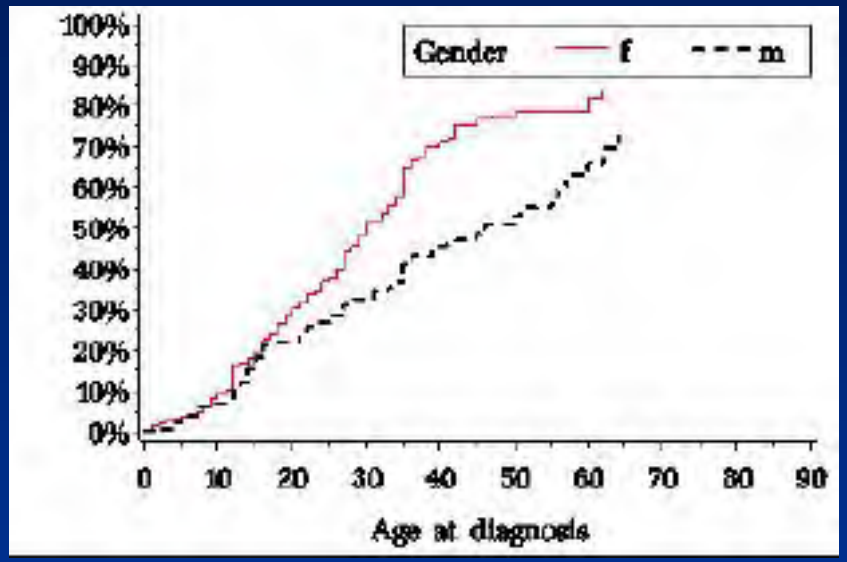
to the clinical records, the patient
lized, but predominantly centrofa-
wn-black pigmentation of the skin
eral myxoid mammary fibroadeno-

veizer-Cagianut and associates re-
t their patient (29) with primary
ular adrenocortical disease and
died. At autopsy a cardiac myxoma
fibroma on her eyelid was reinter-
coma"; both breasts contained mul-
ign fibroadenomas with an unusual
d vascularized stroma"; and she also
eckled pigmentation around the
ne lips." Meanwhile, we had learned
3) with combinations of Cushing
ac myxomas, other myxoid tumors,

Medicine 64:270-283, 1985

Age at diagnosis of Primary Pigmented Nodular Adrenocortical Disease Disease (PPNAD): *according to gender*

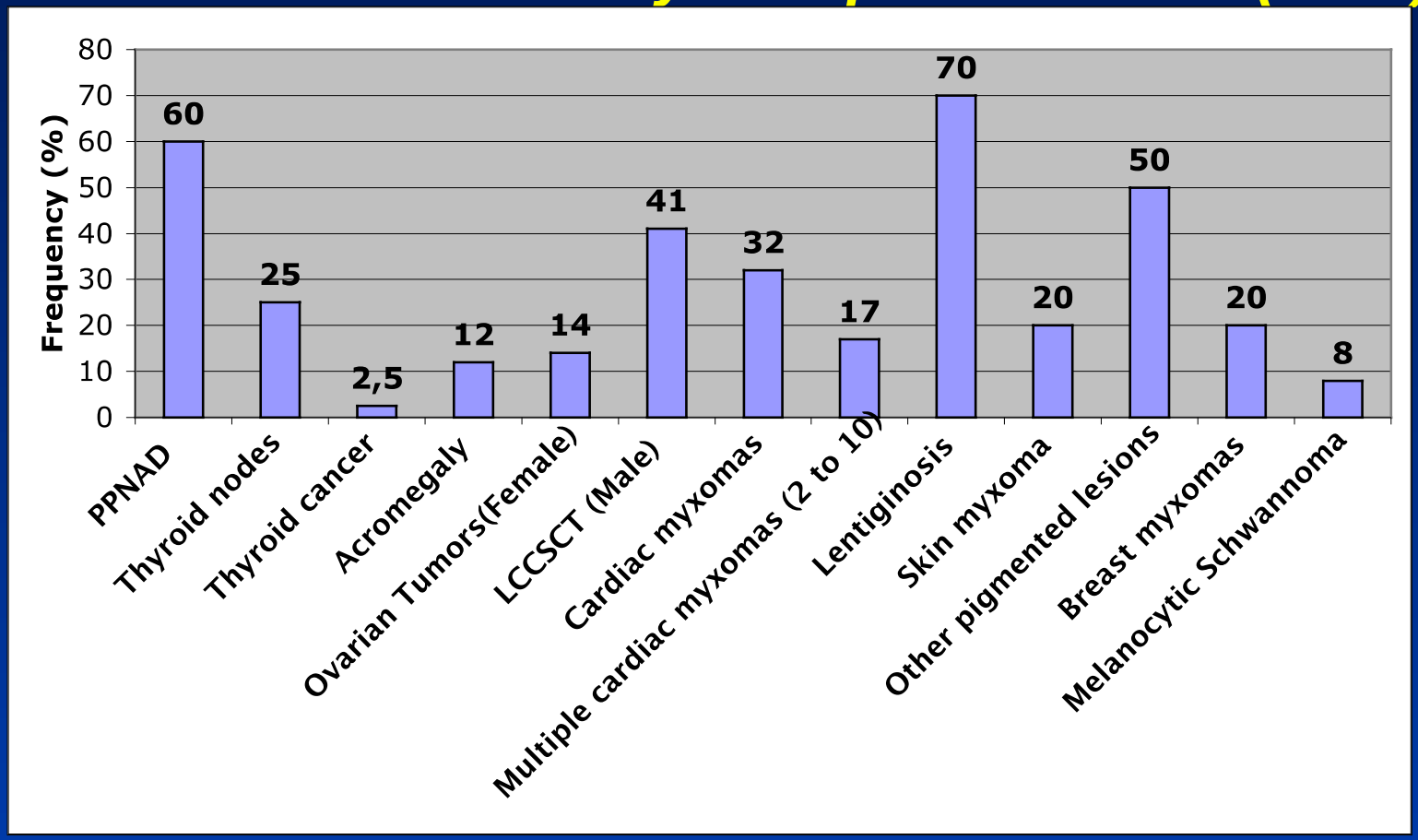
212 patients with PPNAD from the 353 (60 %) patients with CNC and/or PPNAD of the CNC Network (CCN) *(J Bertherat, JA Carney, C Stratakis)*



Age at diagnosis according to gender
Sex ratio F/M: 2,42
p: 0.0004

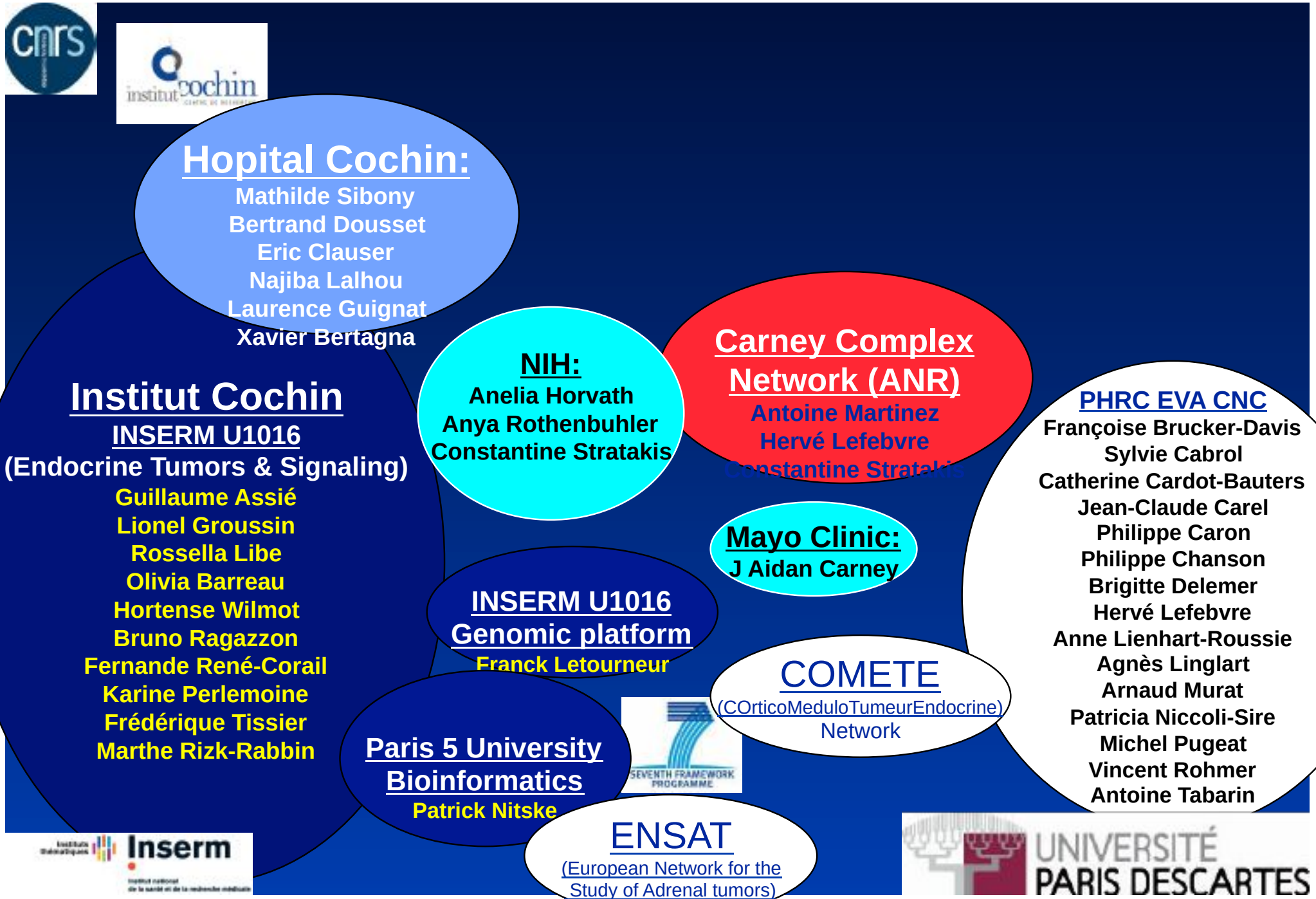
J Bertherat, JCE&M, 2009

Frequency of the various clinical manifestations of CNC in 353 patients from 185 families : *results from the Carney Complex Network (CCN)*



J Bertherat, et al, J Clin Endocrinol metab, 2009

CNC: lentiginosis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Bertrand Dousset
Eric Clauser
Najiba Lalhou
Laurence Guignat
Xavier Bertagna
Institut Cochin
INSERM U1016
(Endocrine Tumors & Signaling)
Guillaume Assié
Lionel Groussin
Rossella Libe
Olivia Barreau
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Karine Perlemoine
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