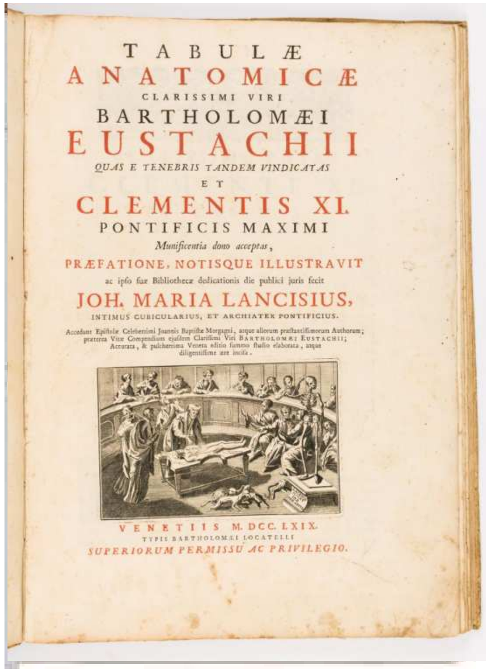
Alberto Falorni
Dipartimento di Medicina
Università di Perugia

Uno sguardo alla storia

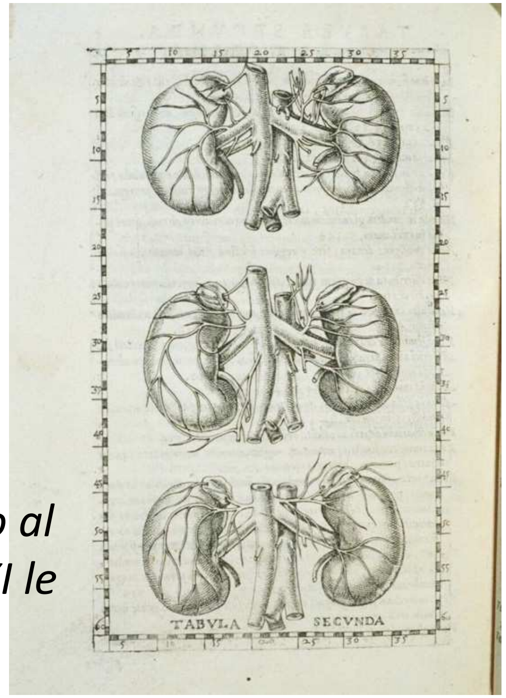
La nostra storia ha inizio a…

San Severino Marche (MC)

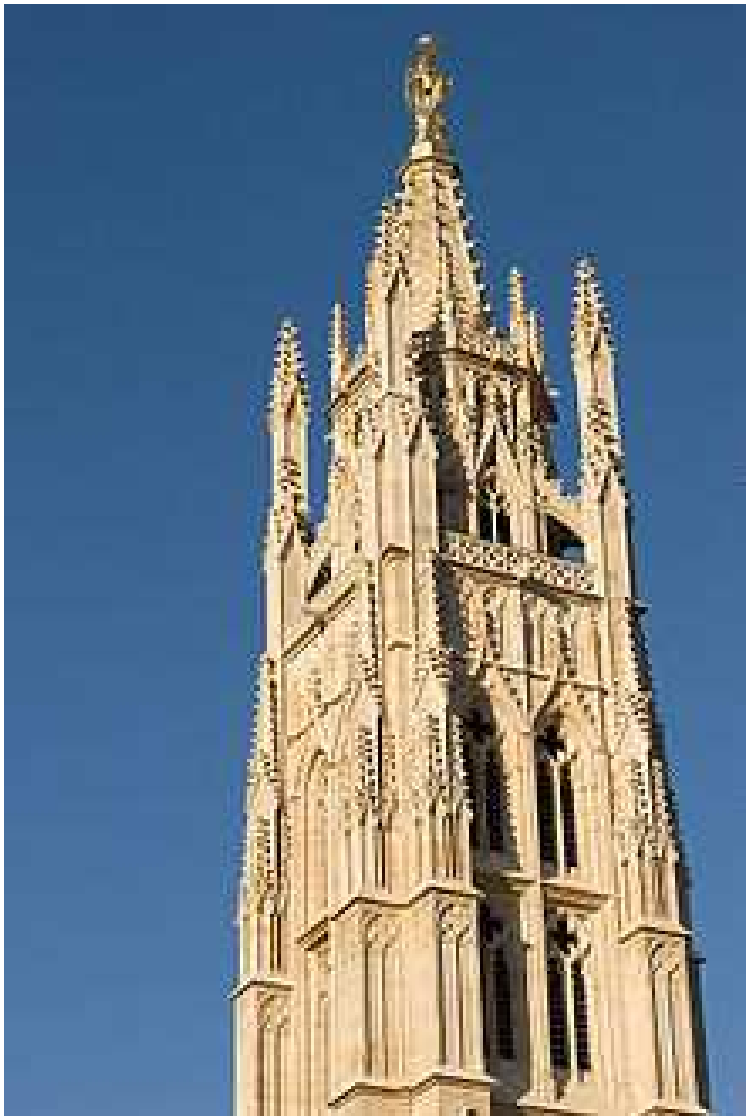
Tra il 1500 e il 1510 nasce Bartolomeo Eustachi



TABULÆ
ANATOMICÆ
CLARISSIMI VIRI
BARTHOLOMÆI
EUSTACHII
QUAS E TENEBRIS TANDEM VINDICATAS
ET
CLEMENTIS XI.
PONTIFICIS MAXIMI
Munificentia dono acceptas,
PRÆFATIONE, NOTISQUE ILLUSTRAVIT
ac ipso suæ Bibliothecæ dedicationis die publici juris fecit
JOH. MARIA LANCISIUS,
INTIMUS CUBICULARIUS, ET ARCHIATER PONTIFICIUS.
Accedunt Epistolæ Celeberrimi Joannis Baptistæ Morgagni, atque aliorum præstantissimorum Authorum; præterea Vitæ Compendium ejusdem Clarissimi Viri BARTHOLOMÆI EUSTACHII; Accurata, & pulcherrima Veneta editio summo studio elaborata, atque diligentissime ære incisa.
VENETIIS M.DCC.LXIX.
TYPIS BARTHOLOMÆI LOCATELLI
SUPERIORUM PERMISSU AC PRIVILEGIO.



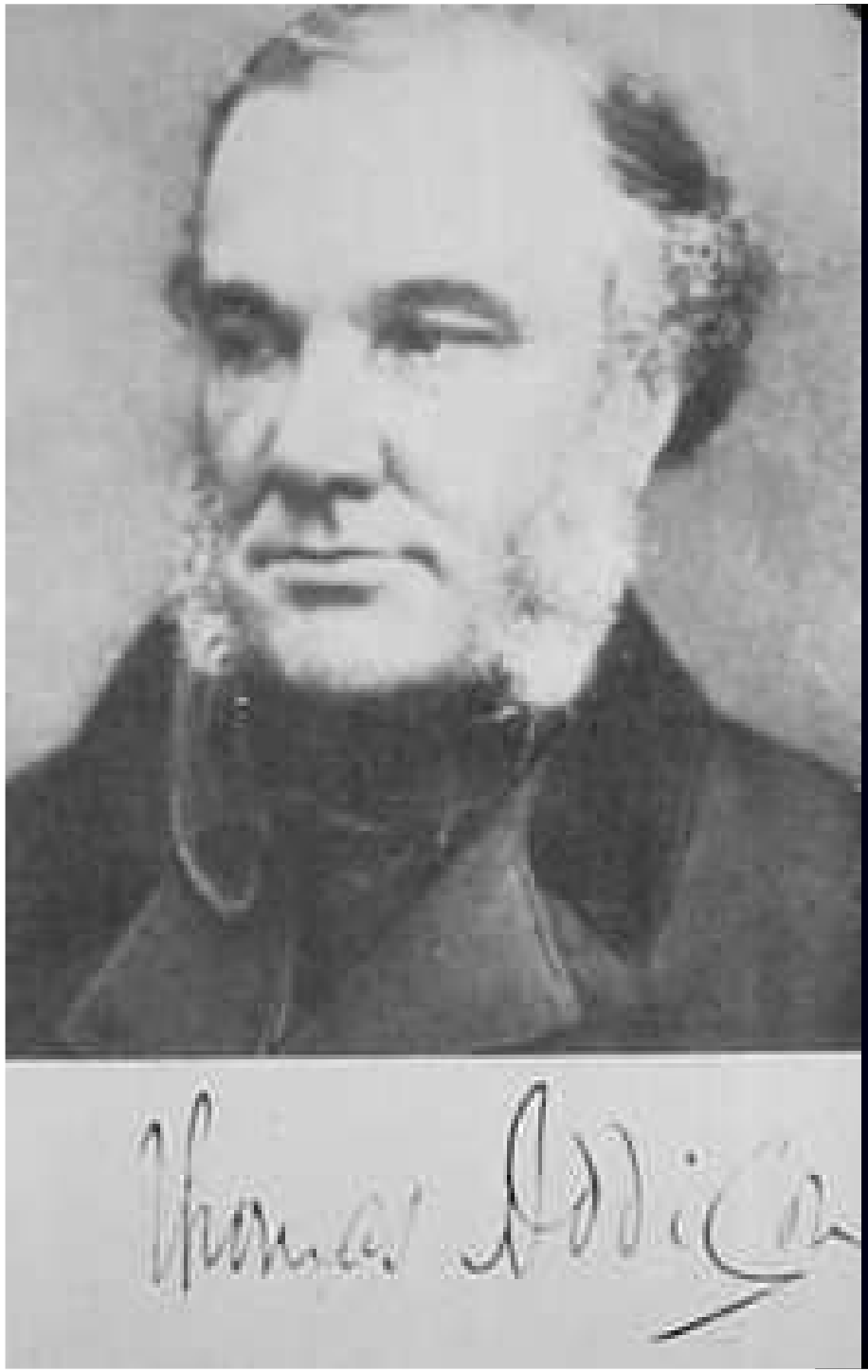
La serie di 47 tavole anatomiche non furono pubblicate fino al 1714 quando Giovanni Maria Lancisi, medico di Clemente XI le trovò da un erede di Matteo Pini e le diede alle stampe



Accademia delle Scienze di Bordeaux (1712)

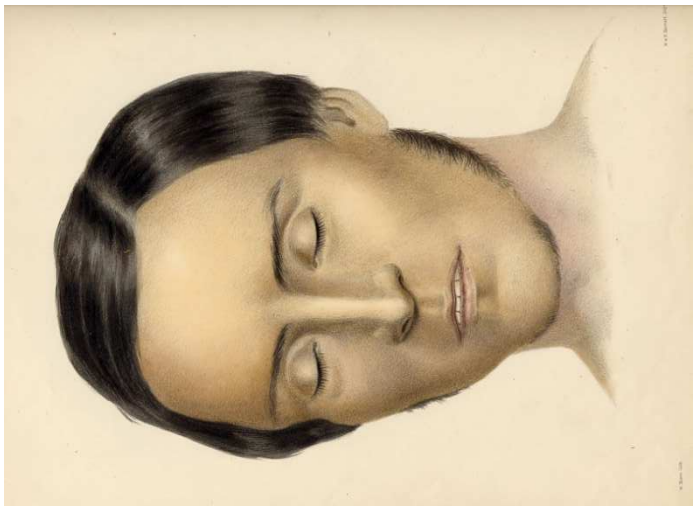
1716
Competizione con premio finale
“Qual è l’importanza delle capsule surrenaliche?”

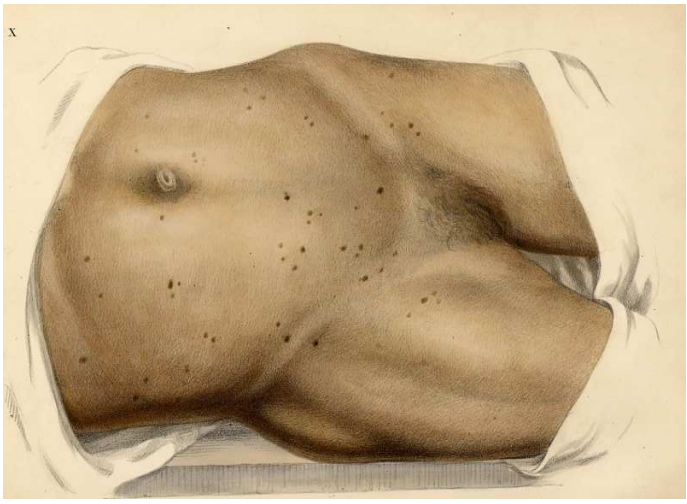
Nessuno si presentò

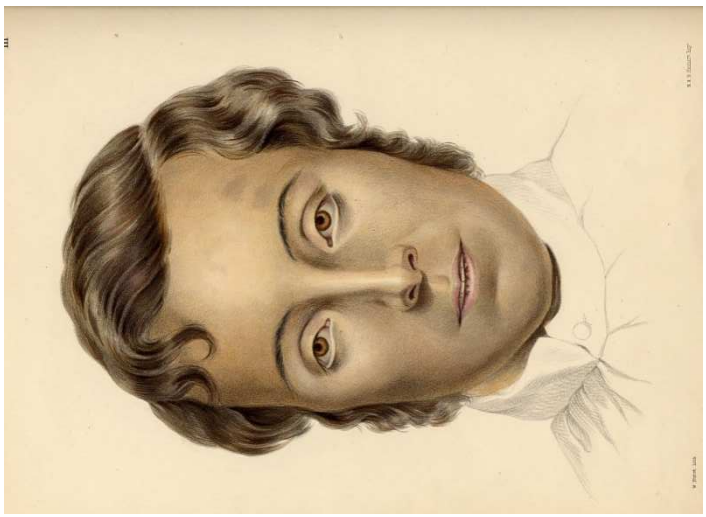


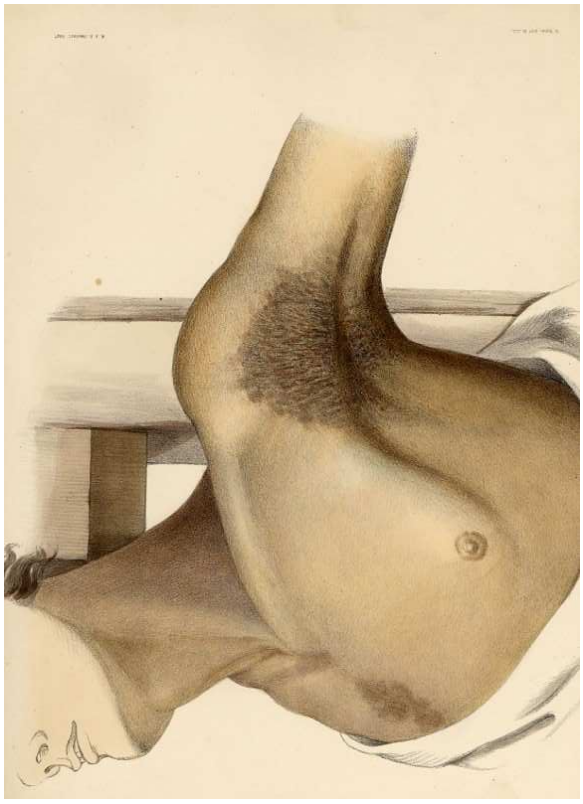
In 1855, Thomas Addison descrive una nuova malattia che ha studiato in 11 pazienti:

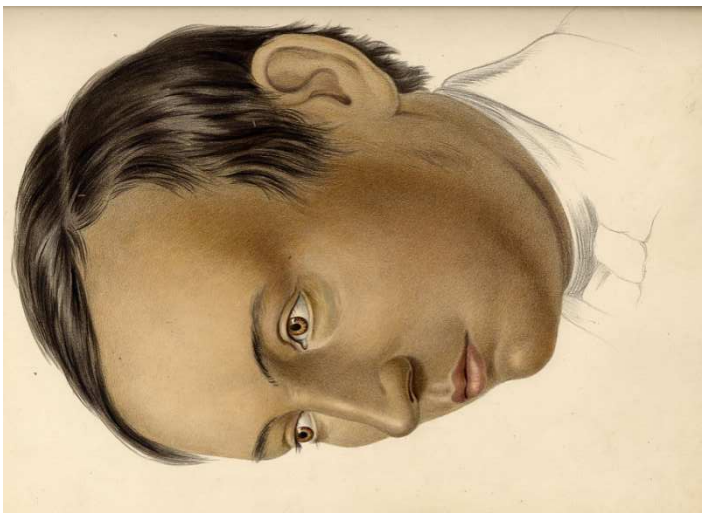
"The leading and characteristic features of the morbid state to which I would direct attention are anaemia, general languor and debility, remarkable feebleness of the heart's action, irritability of the stomach and a peculiar change of colour in the skin, occurring in connexion with a diseased condition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

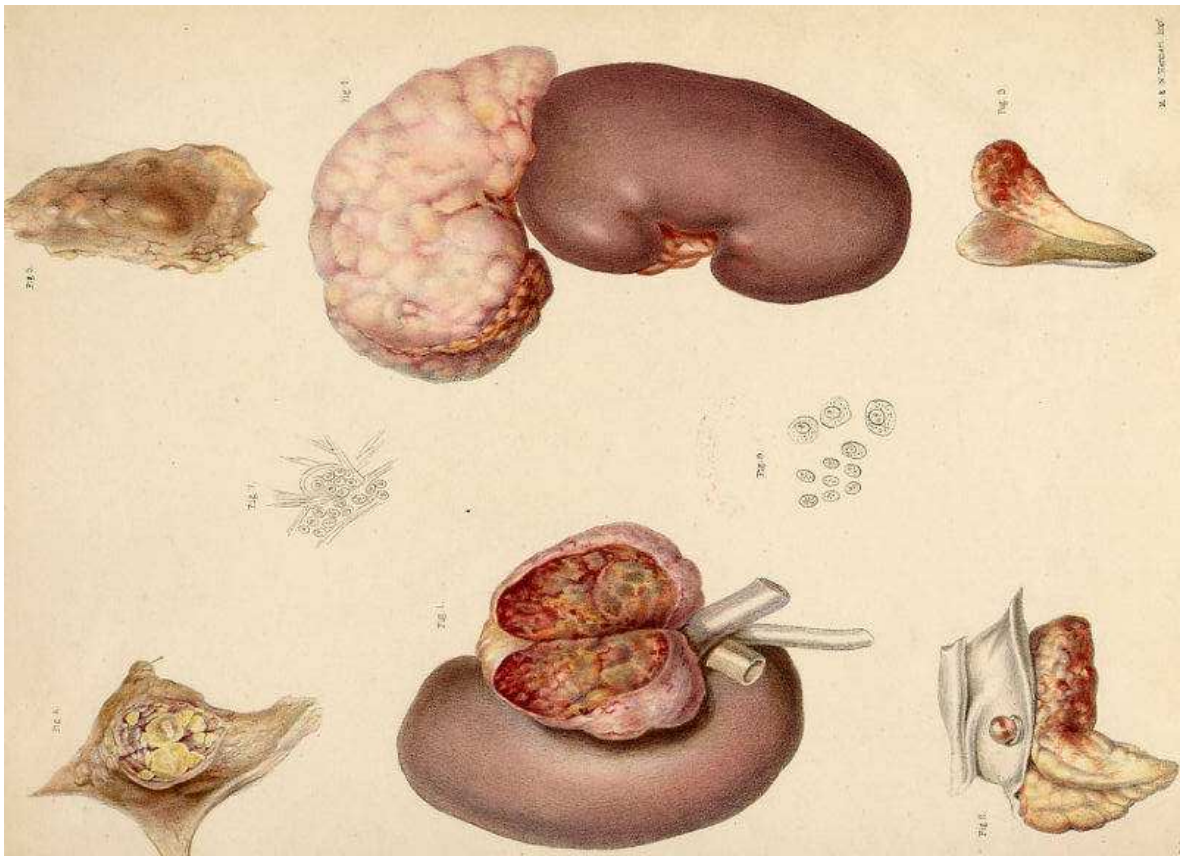


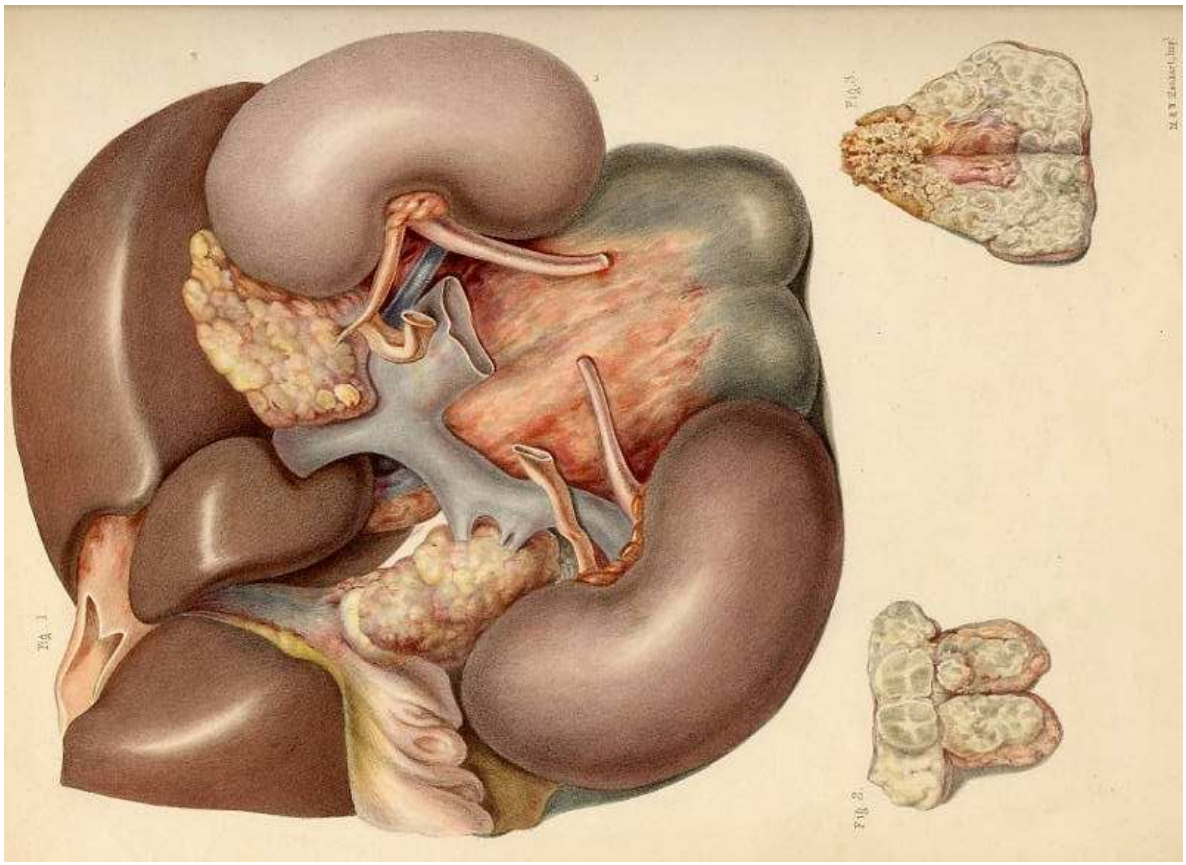












Il primo caso di malattia di Addison autoimmune

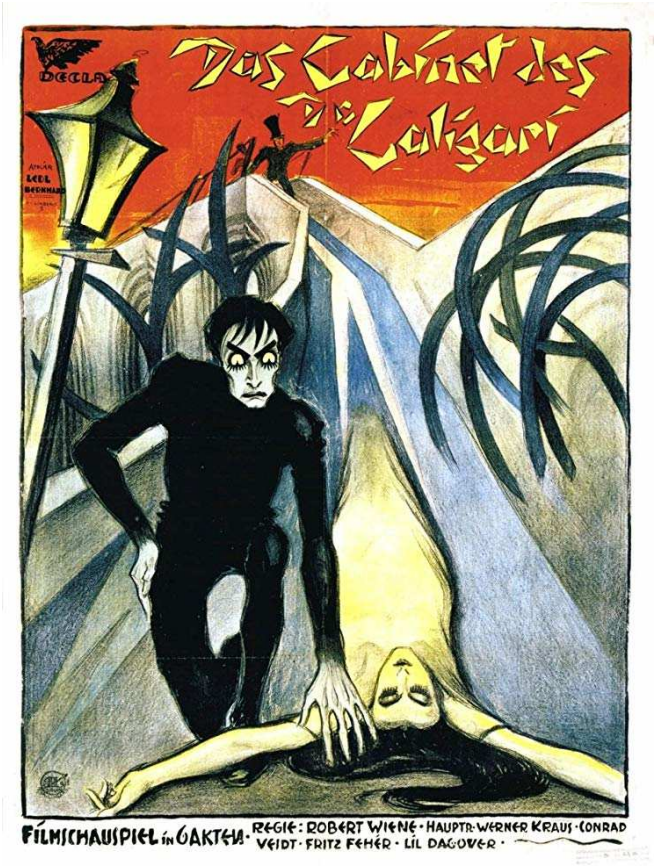
Jane Austen (1775-1817)

"I certainly have not been very well for many weeks, and about a week ago I was very poorly, I have had a good deal of fever at times and indifferent nights, but am considerably better now and recovering my looks a little, which have been bad enough, black and white and every wrong colour. I must not depend upon ever being blooming again. Sickness is a dangerous indulgence at my time of life." 23 marzo 1817

Santa Elisabetta della Trinità (Elizabeth Catez) (1880-1906)

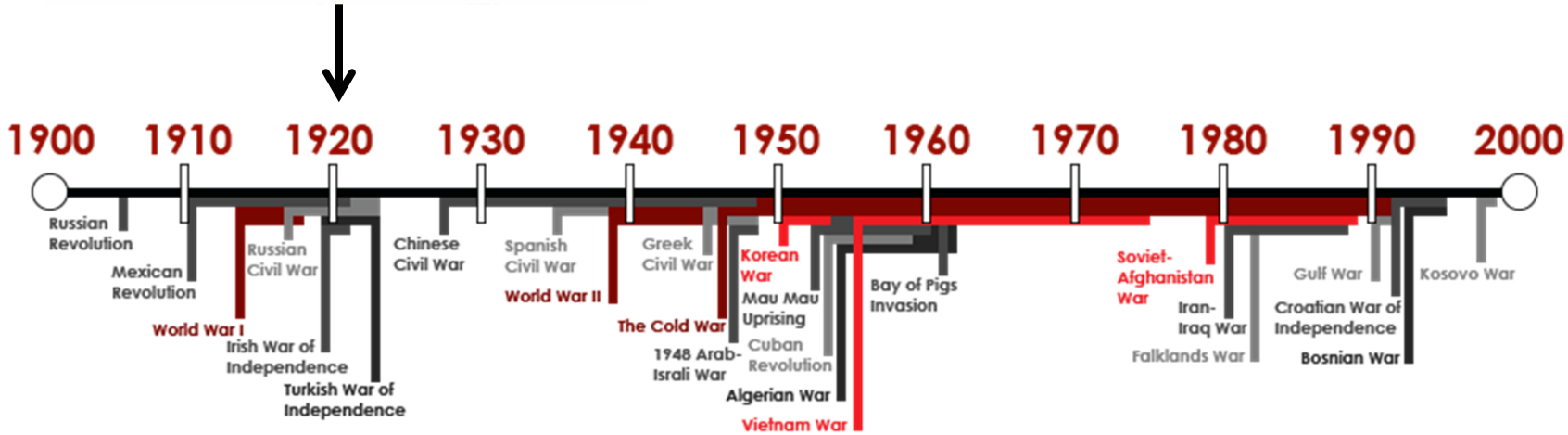
Nel 1895 ***Oliver e Schaefer*** *avevano già descritto i notevoli effetti sulla pressione di estratti surrenalici suggerendo che questi potessero essere utilizzati per trattare la malattia di Addison*

John F.Kennedy (1917-1963)



Nel 1920 (9a Edizione)
The Principles and Practice of Medicine
riporta ***:***

"The relation of Addison' s disease to the adrenals is not the same as that of myxoedema to the thyroid gland, in which the insufficiency is promptly relieved by the administration of thyroid preparation"



Untreated primary adrenal insufficiency associated with poor life expectancy[1]

- Before the availability of glucocorticoids, 2-year mortality rates were >85%

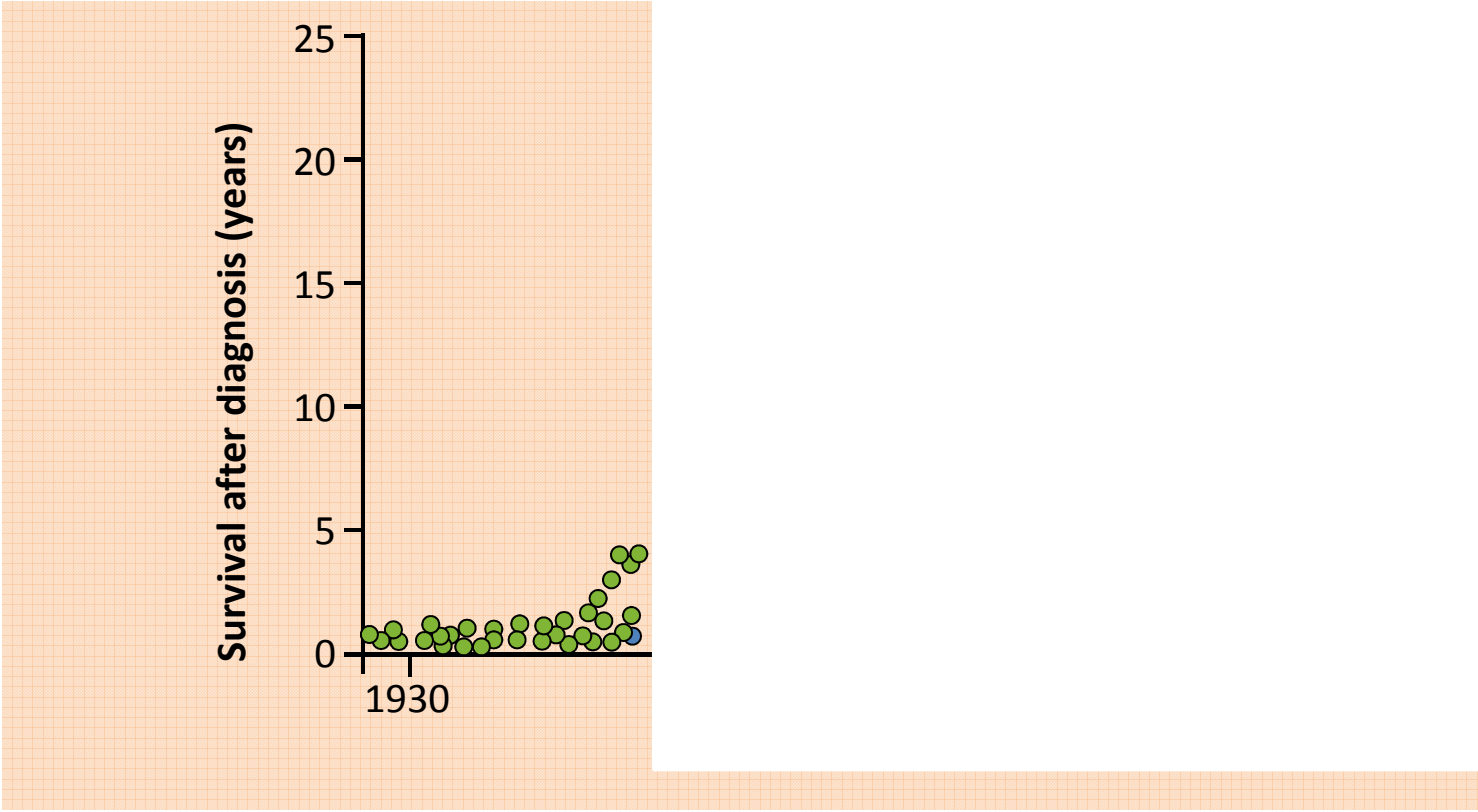
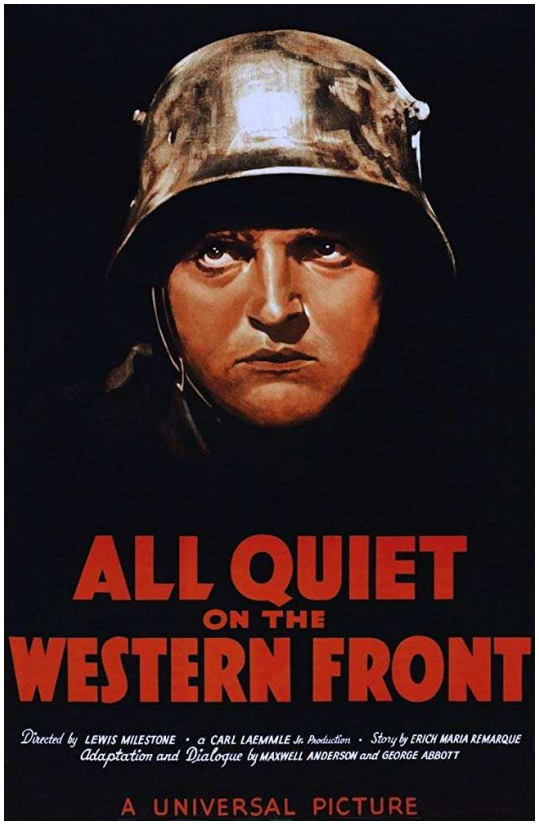


Figure adapted from Dunlop

1. Dunlop D. Br Med J 1963;5362:887–891

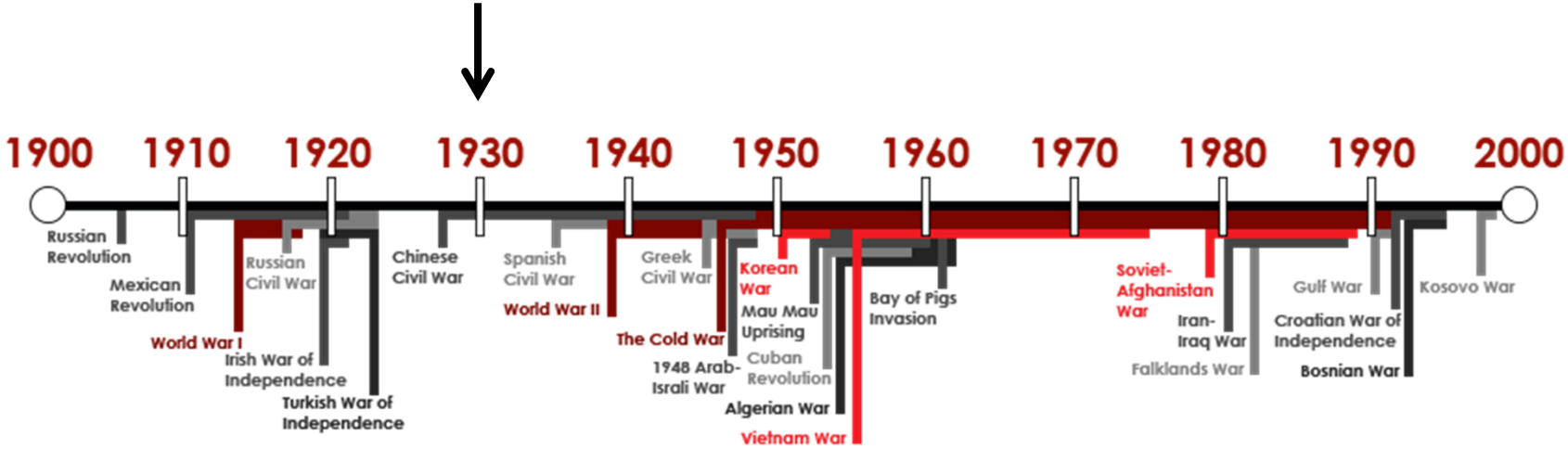


In 1930, Wilbur W. Swingle and Joseph J. Pfiffner, biochemists at Princeton University, succeeded in preparing enough of an adreno-cortical substance for clinical trials.

The trials were conducted at the Mayo Clinic by Leonard G. Rowntree. Twenty cases of Addison's disease and 20 other (nonrheumatologic) patients were treated.

Replacement therapy in the cases of adrenal failure usually was transiently successful.

JAMA, 1931; 97: 1446-53.



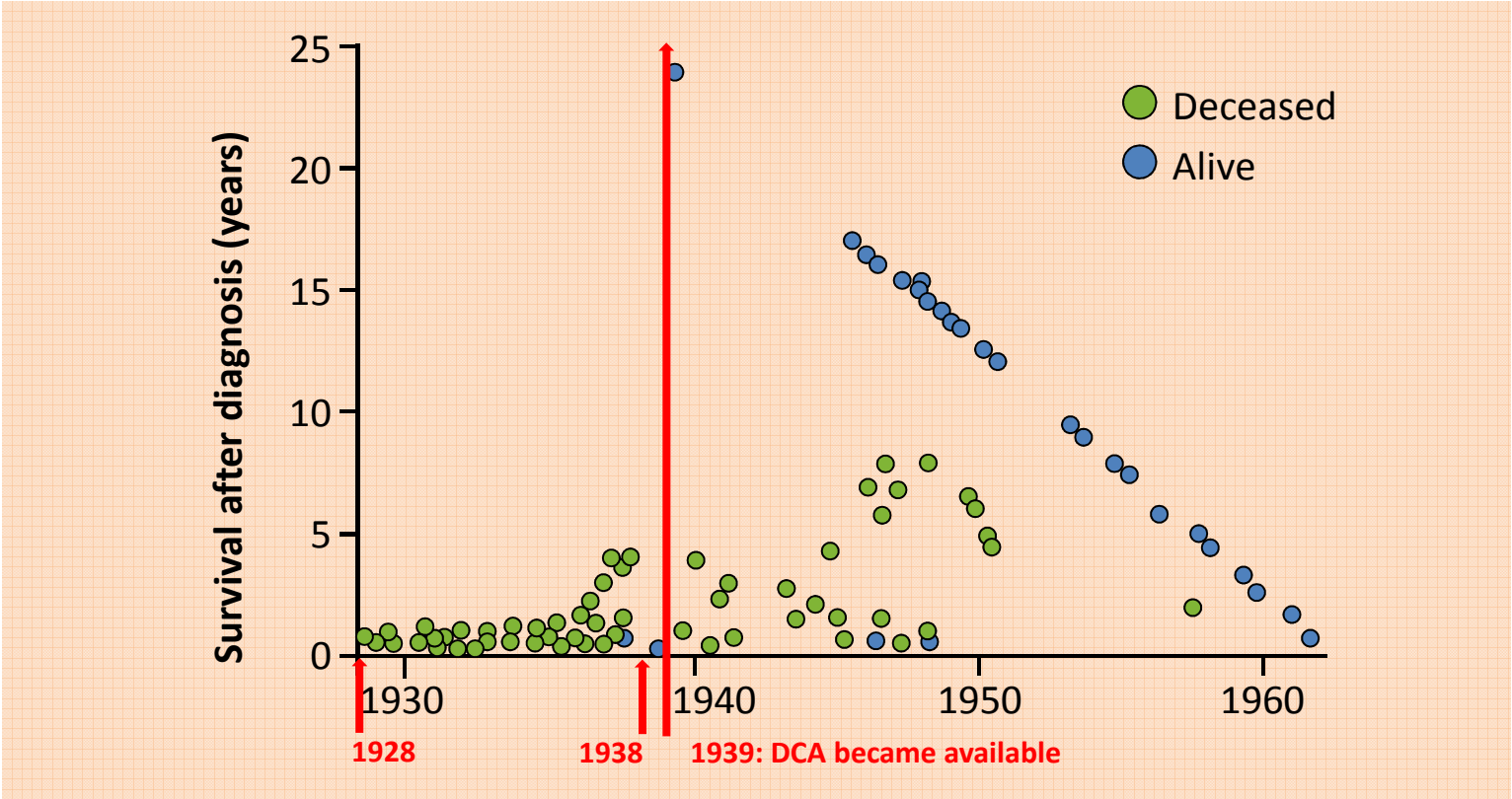
COMPOUND E AND COMPOUND Q

Between 1936 and 1938 E.Kendall's group isolated and purified 20 chemical adrenal compounds including **Compound E (cortisone)**. By the same time T.Reichstein's group in Basel isolated and purified 28 compounds including **Compound Q (deoxycorticosterone)**.

By 1940 their work had allowed isolation of 28 adrenal steroids including also **cortisol** (Kendall's compound F, Reichstein's compound M) and **corticosterone** (Kendall's compound B, Reichstein's compound H)

	Kendall	**Reichstein**
Corticosterone	B	H
Deoxycorticosterone	deoxyB	Q
Tetrahydrocortisone	D	G
Cortisone	E	F
Cortisol	F	M
Dehydrocortisone		A
Tetrahydrocortisol		C
11-deoxycortisol		S

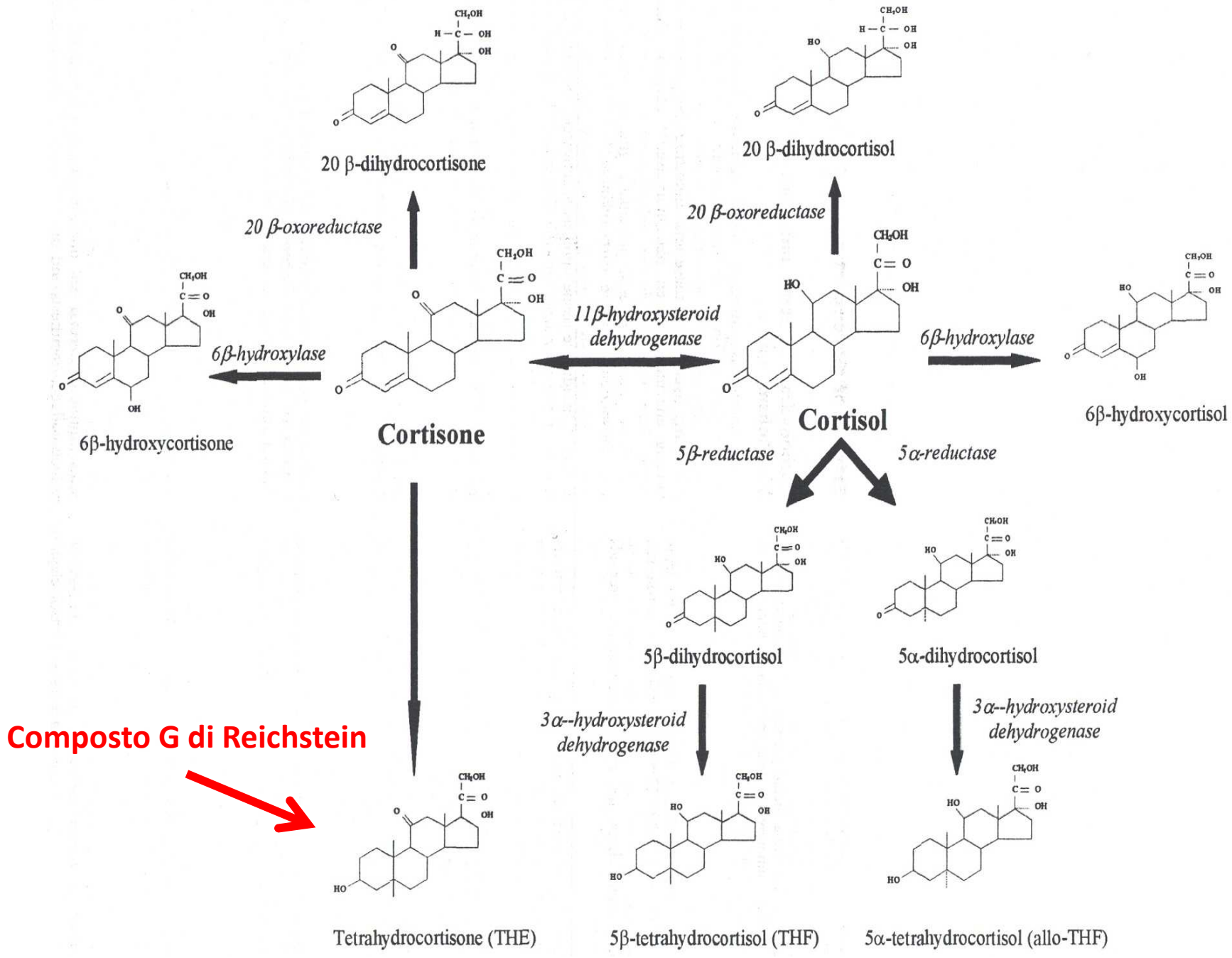
Life expectancy in primary adrenal insufficiency improved after DCA became available



DCA = deoxycorticosterone acetate

Figure adapted from Dunlop

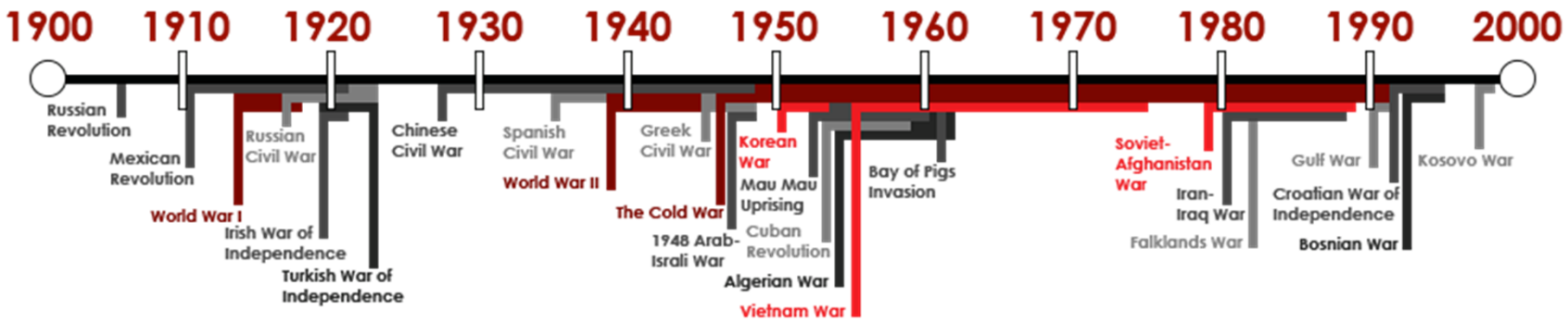
1. Dunlop D. Br Med J 1963;5362:887–891


20 β-dihydrocortisone
20 β-dihydrocortisol
20 β-oxoreductase
20 β-oxoreductase
6β-hydroxylase
11β-hydroxysteroid dehydrogenase
6β-hydroxylase
6β-hydroxycortisone
Cortisone
Cortisol
6β-hydroxycortisol
5β-reductase
5α-reductase
5β-dihydrocortisol
5α-dihydrocortisol
3α--hydroxysteroid dehydrogenase
3α--hydroxysteroid dehydrogenase
Composto G di Reichstein
Tetrahydrocortisone (THE)
5β-tetrahydrocortisol (THF)
5α-tetrahydrocortisol (allo-THF)

Nel 1947, ai laboratori Merck, Sarett sviluppò il primo procedimento pratico per la produzione su larga scala del composto E, che Kendall e Sarett denominarono **cortisone** per differenziarlo dalla Vitamina E.

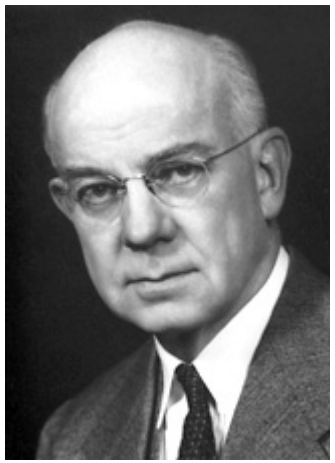
P.Showalter Hench selezionò i primi pazienti trattati con il cortisone (una serie di 33 tra il 1948 e 1949), con risultati in alcuni casi straordinari, in altri più lievi e transitori e registrò i primi effetti indesiderati

"L'artritico che va in bicicletta"



The Nobel Prize in Physiology or Medicine 1950
Edward C. Kendall, Tadeus Reichstein, Philip S. Hench

The Nobel Prize in Physiology or Medicine 1950



Edward C. Kendall
Prize share: 1/3

Tadeus Reichstein
Prize share: 1/3

Philip Showalter Hench
Prize share: 1/3

The Nobel Prize in Physiology or Medicine 1950 was awarded jointly to Edward Calvin Kendall, Tadeus Reichstein and Philip Showalter Hench ***"for their discoveries relating to the hormones of the adrenal cortex, their structure and biological effects".***

1951

CONN JW, LOUIS LH, FAJANS SS: The probability that compound F (17-hydroxycorticosterone) is the hormone produced by the normal human adrenal cortex. *Science 1951;* 113: 713-4.

1955

JW Conn

Primary aldosteronism,

a new clinical syndrome.

J Lab Clin Med 1955

PRIMO USO CLINICO DI CORTICOSTEROIDI

Cortisone	**1948**
Idrocortisone	**1950**
Prednisone	**1954**
Prednisolone	**1954**
Flurocortisone	**1954**
Triamcinolone	**1956**
Metilprednisolone	**1957**
Desametasone	**1958**

CRONOLOGIA DEL RICONOSCIMENTO DEGLI EFFETTI INDESIDERATI DEI CORTICOSTEROIDI

1950

faccia a luna piena, acne, irsutismo, strie cutanee, debolezza muscolare, edema, aumento dell'appetito, irregolarità mestruali, euforia, depressione

1951

ipertensione, iperglicemia, porpora, teleangectasie

1953

infezioni, pseudoreumatismo

1954

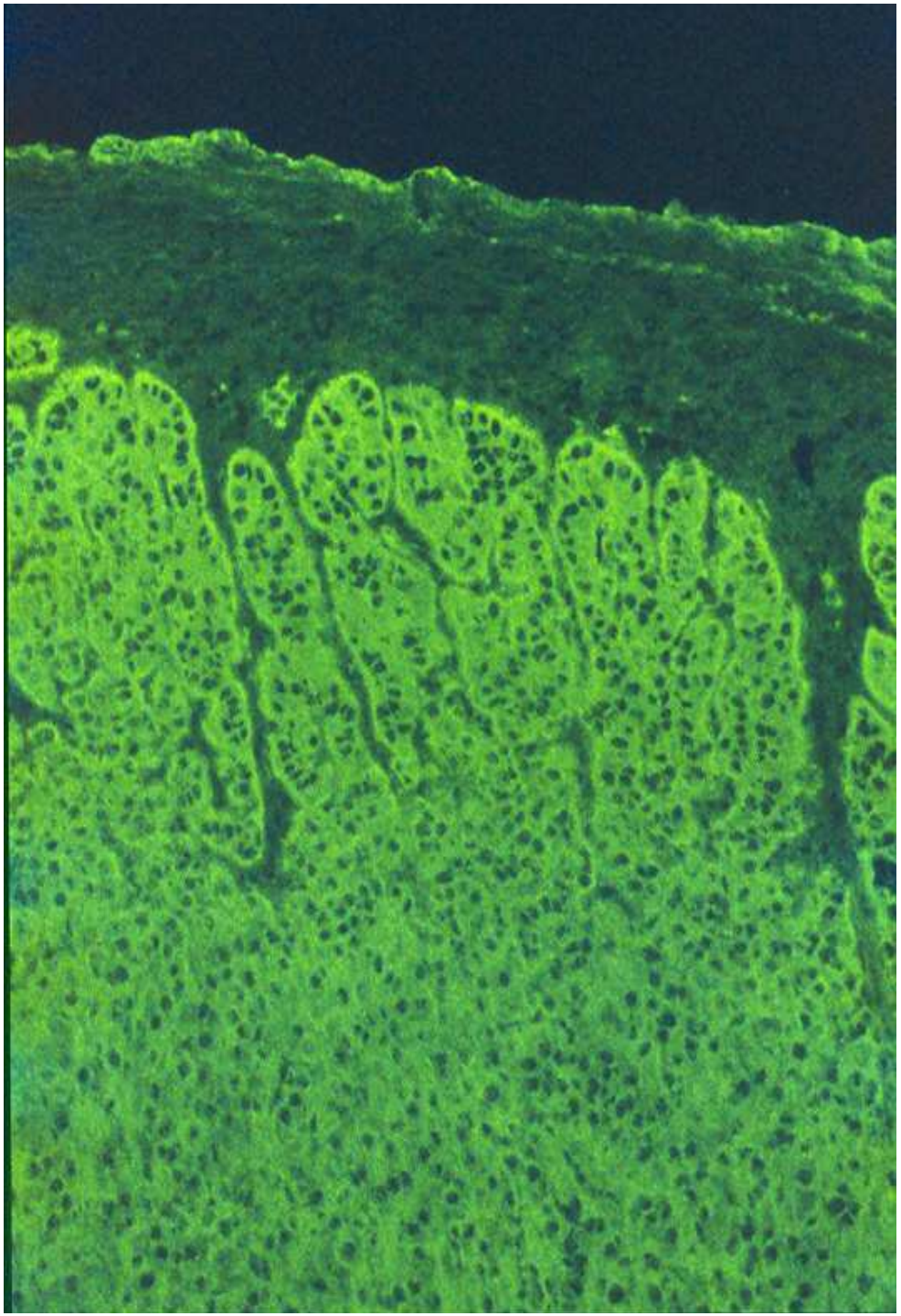
ulcera peptica, osteoporosi, fratture ossee

1960

necrosi ossea asettica, cataratta subcapsulare

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

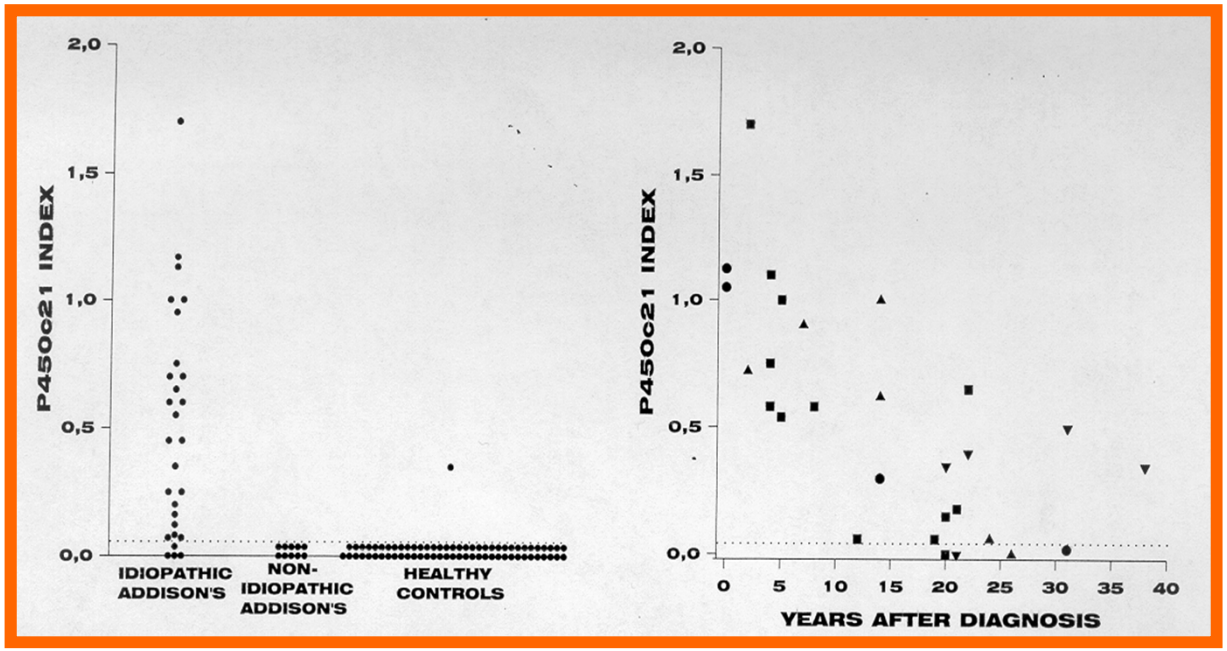
Blizzard RM, Kyle M.
Studies of the adrenal antigens and autoantibodies in Addison's disease.
***J Clin Invest* 42:1653–1660 (1963).**



MALATTIA DI ADDISON AUTOIMMUNE

L’enzima 21-idrossilasi è il principale autoantigene surrenalico

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

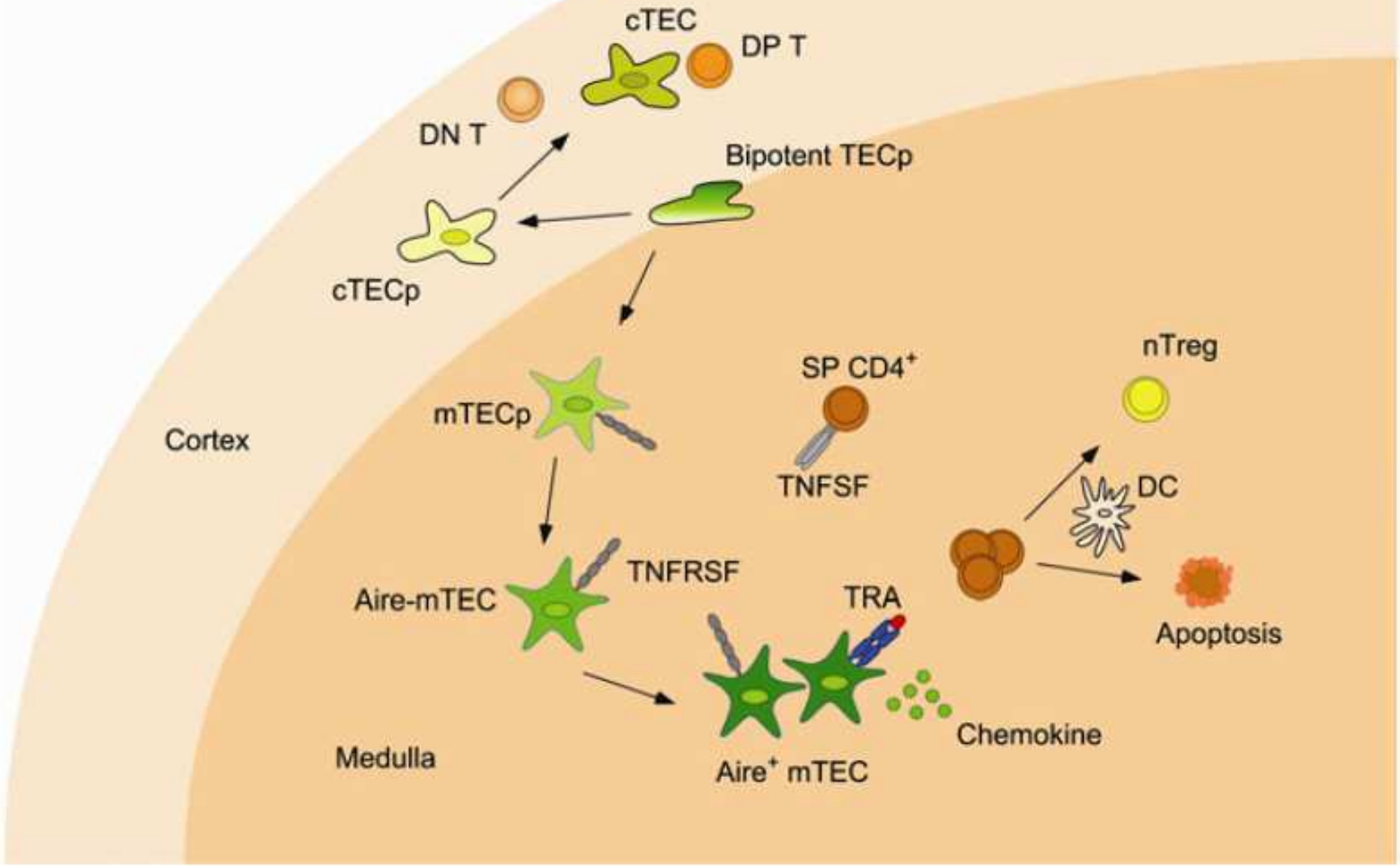


Falorni A. et al, JCEM 1995

Mutations of AIRE causes APS 1/APECED (Addison-Hypoparathyroidism-Candidiasis)

An autoimmune disease, APECED, caused by mutations in a novel gene featuring two PHD-type zinc-finger domains
Johanna Aaltonen et al.
Nature Genetics **17**, 399–403 (1997)

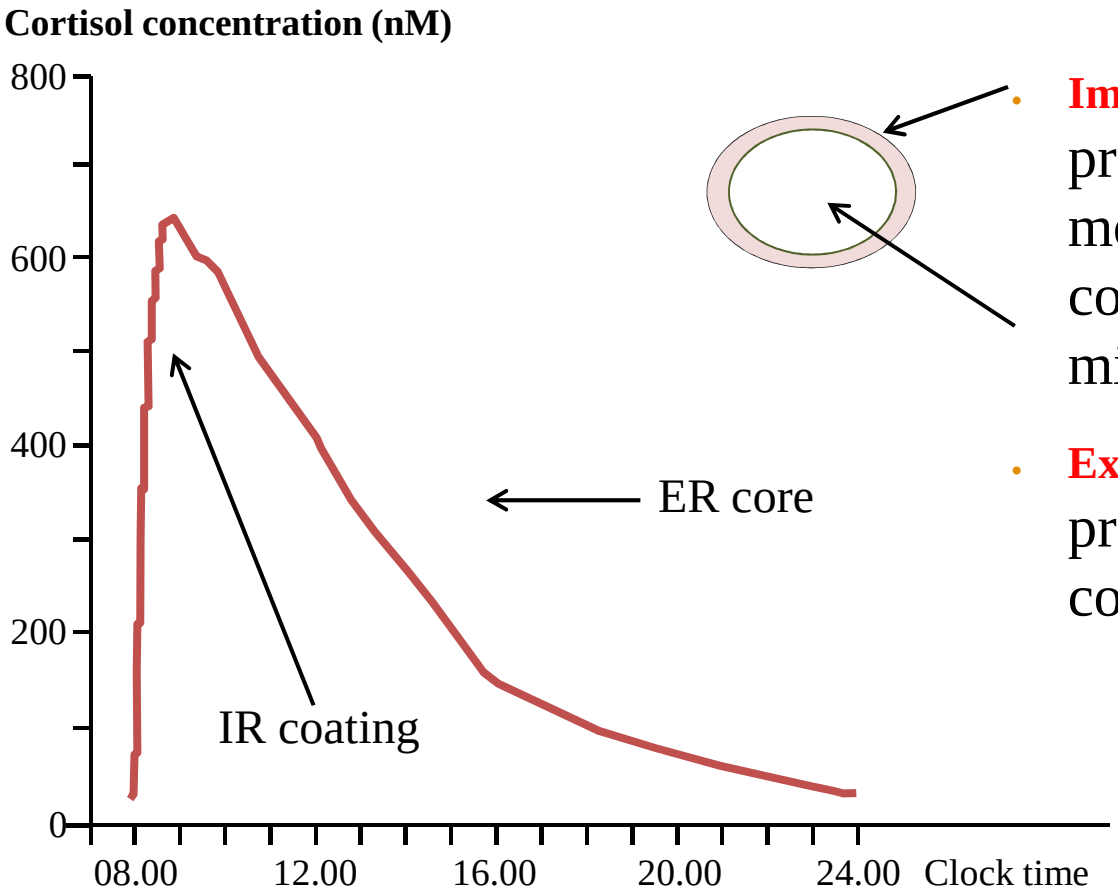
Development and function of medullary thymic epitelial cells (mTEC)



GENETICS OF AUTOIMMUNE ADDISON'S (1990-2018)

Gene	Chromosome
HLA-DRB1	6p21.3
HLA-DQA1	6p21.3
HLA-DQB1	6p21.3
HLA-B	6p21.3
MICA	6p21.33
MICB	6p21.3
CIITA	16p13
CTLA4	2q33
PTPN22	1p13.3-p13.1
VDR	12q13.11
CYP27B1	12q14.1
STAT4	2q32.2-q32.3
GATA3	10p15
NFKB1	4q24
IL23A	12q13.3
CD274/PD-L1	9p24
NLRP1	17p13.2
FCRL3	1q21-q22
GPR174	Xq21.1
NFATC1	18q23

A dual-release hydrocortisone preparation
Hydrocortisone Release Profile

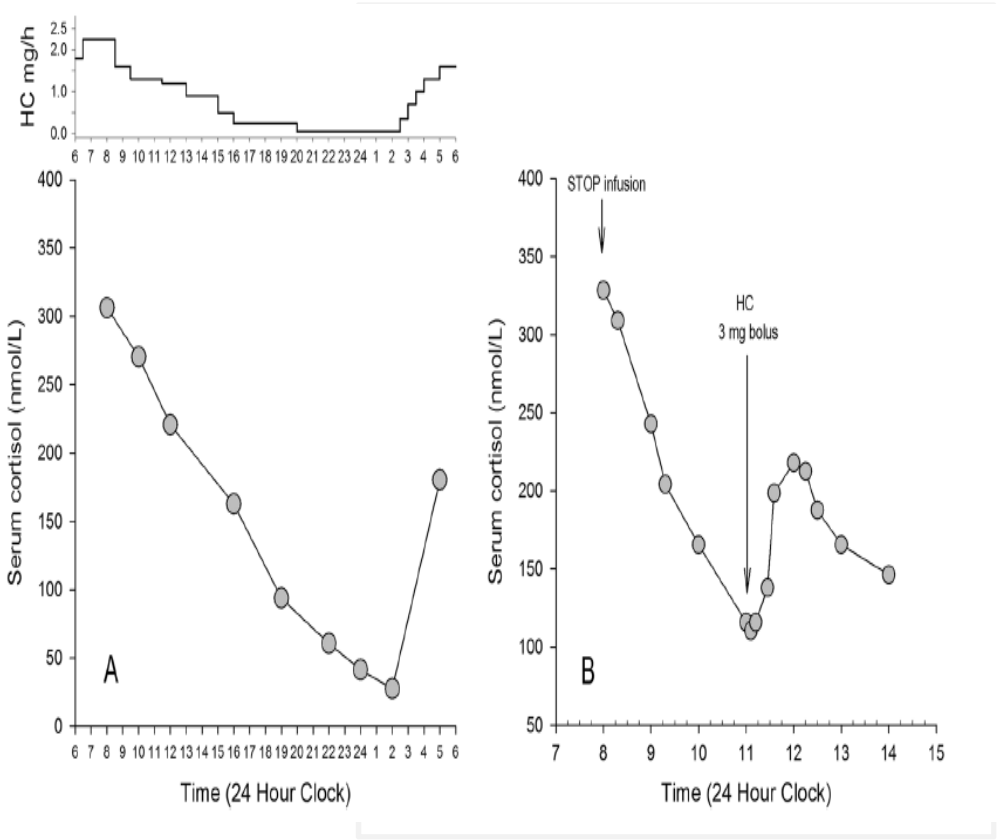


- **Immediate release (IR) coating** provides physiological morning cortisol concentrations within 20 minutes after intake
- **Extended release (ER) core** provides a smooth serum cortisol profile over the day

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

Continuous subcutaneous hydrocortisone infusion in a woman with secondary adrenal insufficiency

Francesca Cardini[1] · Elisabetta Torlone[2] · Vittorio Bini[1] · Alberto Falorni[1]



Endocrine 2019