sismec Società Italiana di Statistica Medica ed Epidemiologia Clinica

Biostatistica per la ricerca e la pratica clinica

Roma - 20 Novembre 2008

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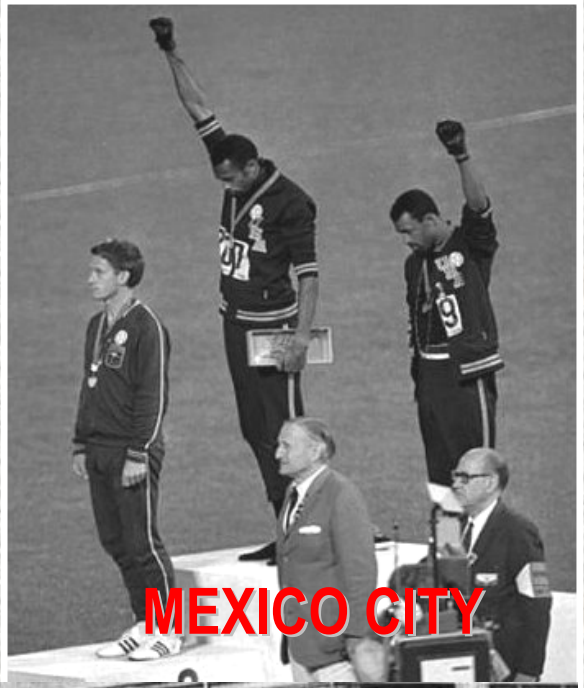
FROM NORMAL VALUES TO REFERENCE VALUES

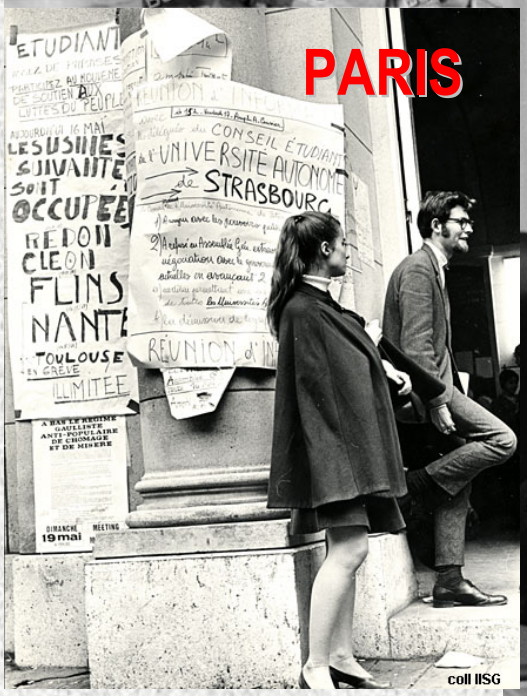
Silvano Milani

Università degli Studi di Milano
Istituto di Statistica Medica
e Biometria "GA Maccacaro"

1968

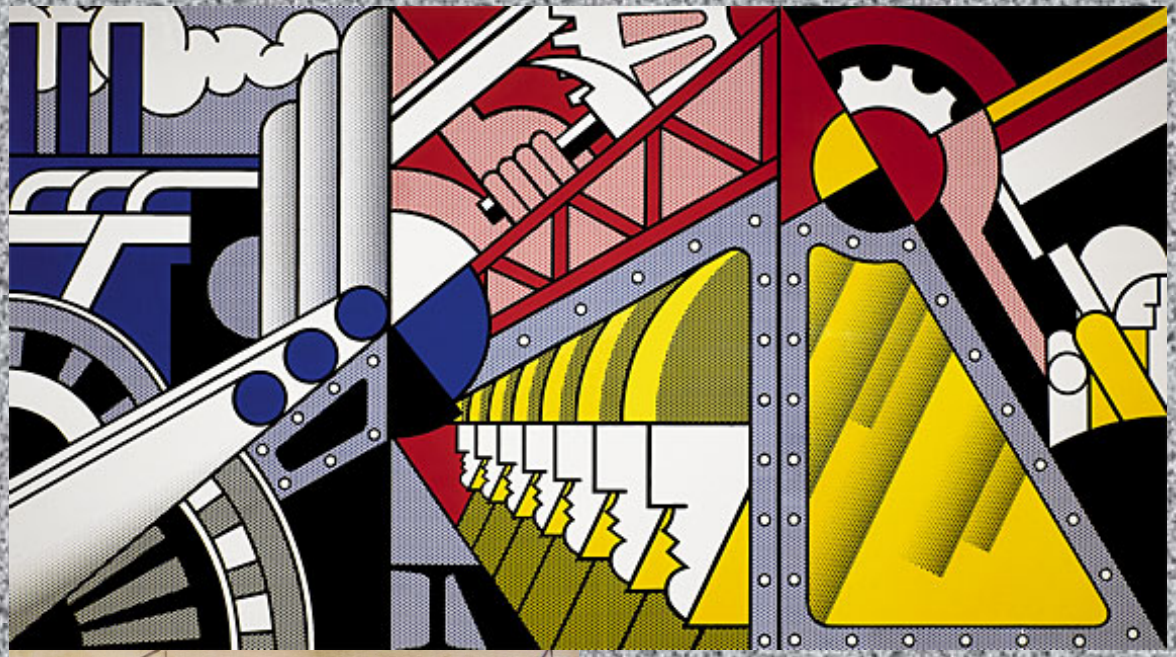

ITALY
LIBERTÀ AGLI STUDENTI E OPERAI ARRESTATI
BASTA CON I MORTI
VOGLIAMO LA LIBERTÀ E LA DEMOCRAZIA PROMESSE
NO ALL
TAVOLA
Bologna Anni 1967-1969


MEXICO CITY

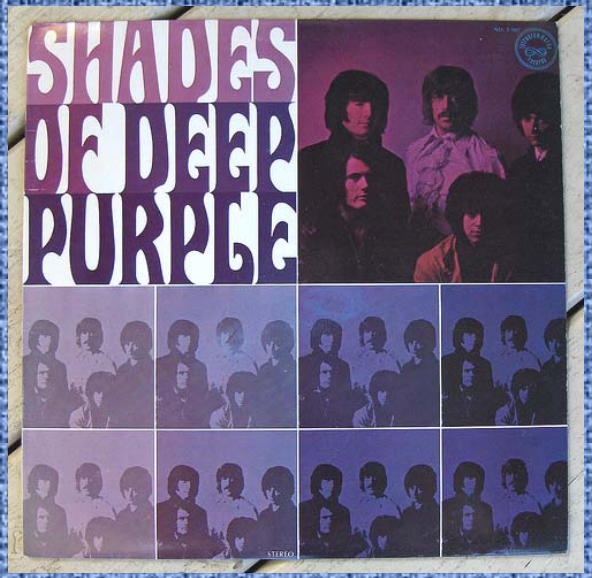

PARIS
ETUDIANT
LES USINES SUIVANTES SONT OCCUPÉES
RENAULT CLEON FLINS NANTES TOULOUSE EN GRÈVE ILLIMITÉE
CONSEIL ÉTUDIANT
UNIVERSITÉ AUTONOME de STRASBOURG
RÉUNION d'INFORMATION
A BAS LE RÉGIME GAULLISTE ANTI-POPULAIRE DE CHÔMAGE ET DE MISÈRE
DIMANCHE 19 mai
MEETING
coll IISG


USA


027
PRAGUE



1968


SHADES OF DEEP PURPLE


pinkfloyd


miles davis
MILES IN THE SKY


Electric Ladyland
the Jimi Hendrix EXPERIENCE
THE JIMI HENDRIX EXPERIENCE • ELECTRIC LADYLAND
AND THE GODS MADE LOVE
HAVE YOU EVER BEEN (TO ELECTRIC LADYLAND)
CROSSTOWN TRAFFIC
VOODOO CHILE
LITTLE MISS STRANGE
LONG HOT SUMMER NIGHT
COME ON (LET THE GOOD TIMES ROLL)
GYPSY EYES
BURNING OF THE MIDNIGHT LAMP
RAINY DAY, DREAM AWAY
1983... (A MERMAN I SHOULD TURN TO BE)
MOON, TURN THE TIDES...gently gently away
STILL RAINING, STILL DREAMING
HOUSE BURNING DOWN
ALL ALONG THE WATCHTOWER
VOODOO CHILD (SLIGHT RETURN)
MCA


The BEATLES


STEREO
ZAPPA
LUMPY GRAVY
ABNUCEALS EMUUKHA ELECTRIC SYMPHONY ORCHESTRA & CHORUS
PIPCO

1968

NINETEEN SIXTYEIGHT

was a knife blade that severed past from future

was an extraordinary year
both in political history and in the history of art

NOT ONLY, BUT ALSO

In the autumn of **1968**, in a Finnish sauna on a little island west of Helsinki, Ralph Gräsbeck and Nils-Erik Saris, sitting at the side of a woodfire and talking about the meaning of normal values, suddenly saw in the glow a shower of sparks emitting a new concept:

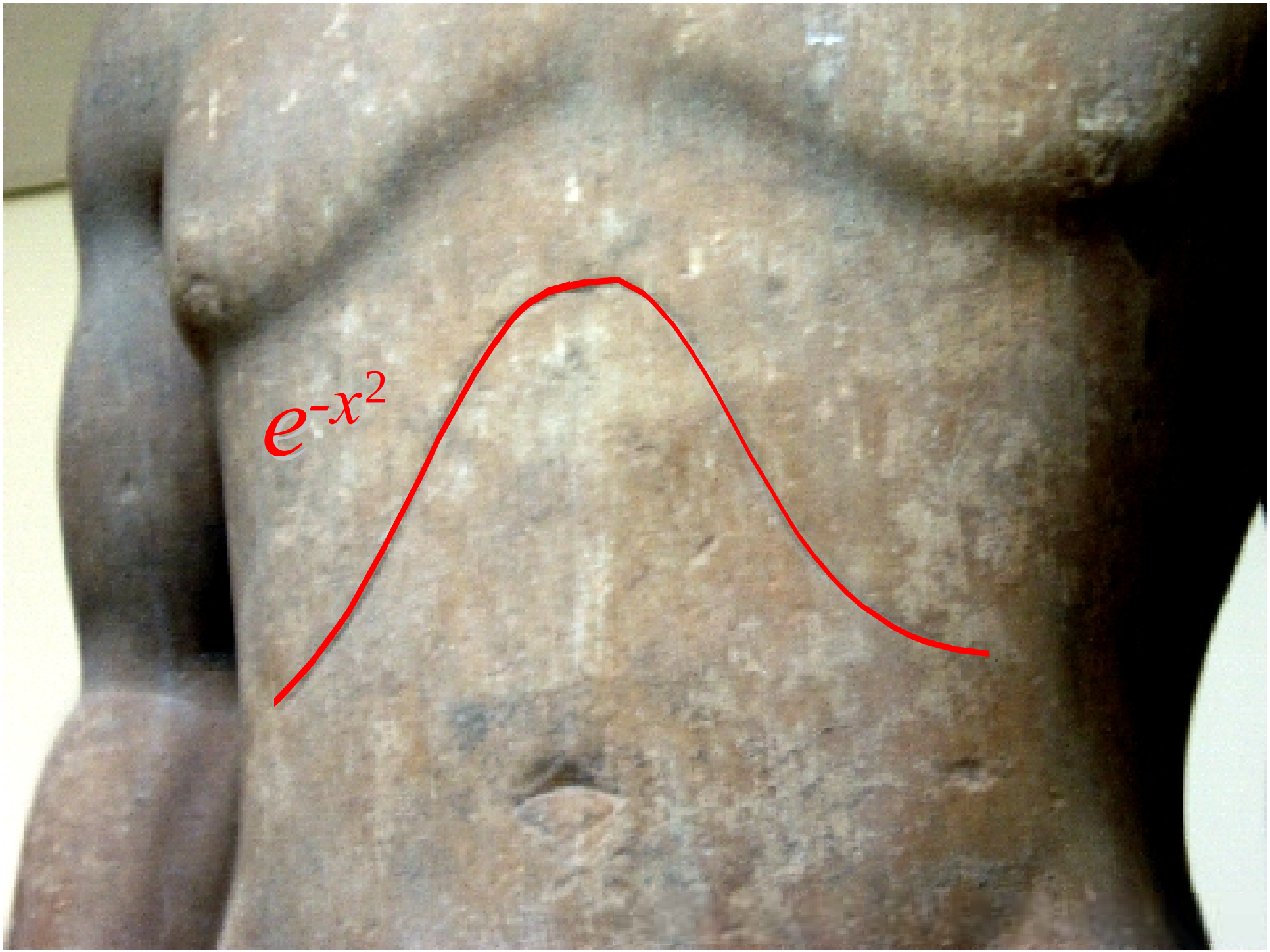
REFERENCE VALUES

1968: DON'T TRUST ANYONE OVER 30

…and the concept of normal values was older, by far older

580 BC: κλεοβις και βιτον

Delphi: (Archaeological Museum)
two κουροι


e^{-x^2}

ADOLPHE QUÉTELET (1796 – 1874)

In "*Sur l'homme et le développement de ses facultés, ou Essai de physique sociale*" (1835) Quetelet describes his concept of ***homme moyen***, who is characterized by the mean values of measured variables that follow a ***normal distribution***. He collected data about many such variables.

THE METAPHYSICS OF NORMALITY

Quetelet applied the law of error universally, not only to physical but also to moral and intellectual laws. The *average man* is an *ideal* that should be approached as closely as possible.

But it is also an empirical result, reached by averaging quantities observed in certain groups, thereby characterizing those groups with certain average physical and moral features or propensities.

Quetelet did not use the average man as a **model** to explain individual behaviour, but as a **yardstick** to measure deviations from this presupposed ideal.

CLAUDE BERNARD (1813-1878)

INTRODUCTION

A L'ÉTUDE DE LA

MÉDECINE EXPÉRIMENTALE

PAR

M. CLAUDE BERNARD

Membre de l'Institut de France (Académie des sciences),
et de l'Académie impériale de médecine,

Professeur de médecine au Collége de France,
Professeur de physiologie générale à la Faculté des sciences,

Membre de la Société royale de Londres,
de l'Académie des sciences de Saint-Pétersbourg
et de l'Académie des sciences de Berlin.

PARIS

J. B. BAILLIÈRE ET FILS,

LIBRAIRES DE L'ACADÉMIE IMPÉRIALE DE MÉDECINE,
Rue Hautefeuille, 19.

Londres	Madrid	New-York
HIPPOLYTE BAILLIÈRE	C. BAILLY-BAILLIÈRE	BAILLIÈRE-BROTHERS

LEIPZIG, E. JUNG-TREUTTEL, QUERSTRASSE, 10

1865

EUROPEAN AVERAGE URINE (1865)

Si l'on recueille l'urine d'un homme pendant vingt-quatre heures et qu'on mélange toutes les urines pour avoir l'analyse de l'urine moyenne, on a précisément l'analyse d'une urine qui n'existe pas; car à jeun l'urine diffère de celle de la digestion, et ces différences disparaissent dans le mélange.

Le sublime du genre a été imaginé par un physiologiste qui, ayant pris de l'urine dans un urinoir de la gare d'un chemin de fer où passaient des gens de toutes les nations, crut pouvoir donner ainsi l'analyse de l'urine moyenne européenne!

CARL WUNDERLICH (1815-1877)

ON THE

TEMPERATURE IN DISEASES:

A MANUAL OF

MEDICAL THERMOMETRY.

BY

DR. C. A. WUNDERLICH,

PROFESSOR DER KLINIK AN DER UNIVERSITÄT LEIPZIG, K. SÄCHS GEHEIMEN MEDICINALRATH, COMTHUR UND RITTER, ETC.

TRANSLATED FROM THE SECOND GERMAN EDITION

BY

W. BATHURST WOODMAN, M.D.,

ASSISTANT-PHYSICIAN TO THE LONDON HOSPITAL, AND PHYSICIAN TO THE NORTH-EASTERN HOSPITAL FOR CHILDREN.

WITH FORTY WOODCUTS AND SEVEN LITHOGRAPHS.

THE NEW SYDENHAM SOCIETY,
LONDON.
MDCCCLXXI.

ANOTHER SIXTYEIGHT

In 1868 Carl Wunderlich published temperature recordings from over 1 million readings in over 25,000 patients made with a foot-long thermometer used in

He established a range of normal temperature from 36.3 to 37.5 °C.

A normal temperature does not necessarily indicate health, but all those whose temperature exceeds or falls short of the normal range are unhealthy.

BEYOND NORMALITY

NORMAL: WHAT DOES IT MEAN?

having gaussian distribution	**gaussian**
most representative of its class	**average**
commonly encountered in its class	**habitual**
most suited to survival	**fittest**
carrying no penalty	**harmless**
commonly aspired to	**conventional**
most perfect in its class	**ideal**

reference individual

an individual defined with ad-hoc criteria

reference population

all possible reference individuals

it has an undetermined number of interchangeable members

it is a hypothetical entity

reference sample group

is a set of reference individuals

reference value

the value obtained by observation or measurement of a quantity on a reference individual

reference values are obtained from a reference sample group

reference distribution

is the distribution of reference values in the reference population
the parameters of the reference distribution may be estimated
on the basis of the reference sample group

reference limits

are derived from the reference distribution for descriptive purposes
by definition a given fraction of the reference values is within the limits
are **not decision limits**, which are used for interpretative purposes

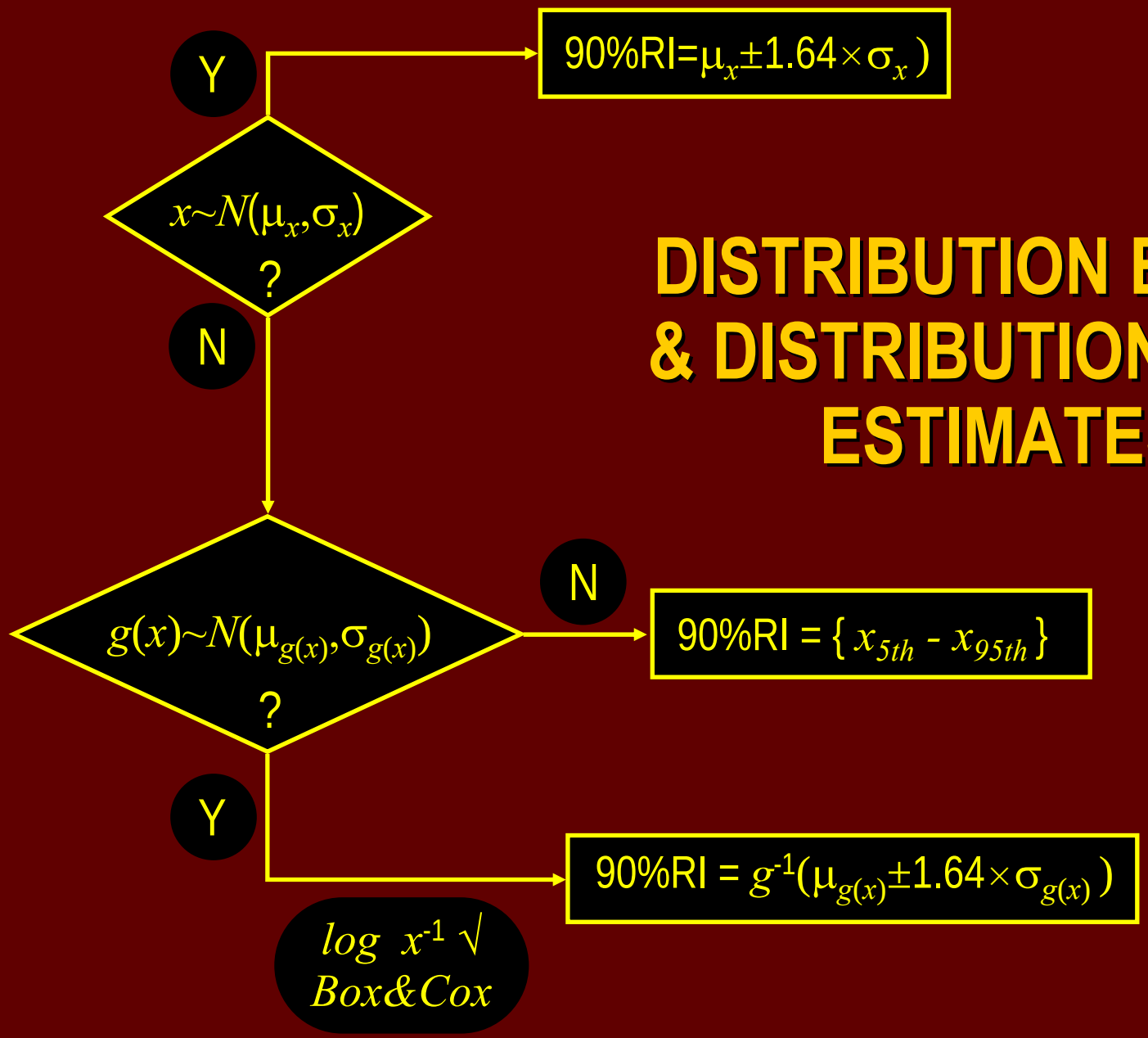
a reference interval

is the interval below (or above) a reference limit
or between two reference limits

90% REFERENCE INTERVALS

90% of the reference individuals are included
between the 5th and 95th centile of the reference distribution
i.e. a 90% reference interval has a 90% specificity

this means that
5% of reference individuals show values unusually low
5% of reference individuals show values unusually high



DISTRIBUTION BASED & DISTRIBUTION FREE ESTIMATES

distribution based

$$V(\tilde{x}_{100p}) = \frac{\sigma^2}{n} \times \left(1 + \frac{z_p^2}{2}\right)$$

$$V(\tilde{x}_{100p}) = \frac{\sigma^2}{n} \times \left(\frac{p(1-p)}{f^2_{\tilde{x}_{100p}}}\right)$$

$V(\tilde{x}_{100p})$	$SE(\tilde{x}_{100p})$	p
1.00	1.00	**0.50**
1.35	1.16	**0.80**
1.82	1.35	**0.90**
2.35	1.53	**0.95**
2.77	1.66	**0.97**

TOLERANCE LIMITS ARE AN ALTERNATIVE

Tolerance limits are limits within which we have a prefixed confidence 1-α (e.g 1- α =95%) that a stated proportion p of the population (e.g. p=90%) lie.

$$95\%TL_{90\%} = \bar{x} \pm_{0.95} k_{0.90} s \qquad k = \sqrt{\frac{(n-1)\left(\frac{1}{1+n}\right) z^2_{(1-p)/2}}{\chi^2_{\alpha,n-1}}}$$

TOLERANCE LIMITS ARE AN ALTERNATIVE

A tolerance interval tend towards the probability interval as the sample size increases.

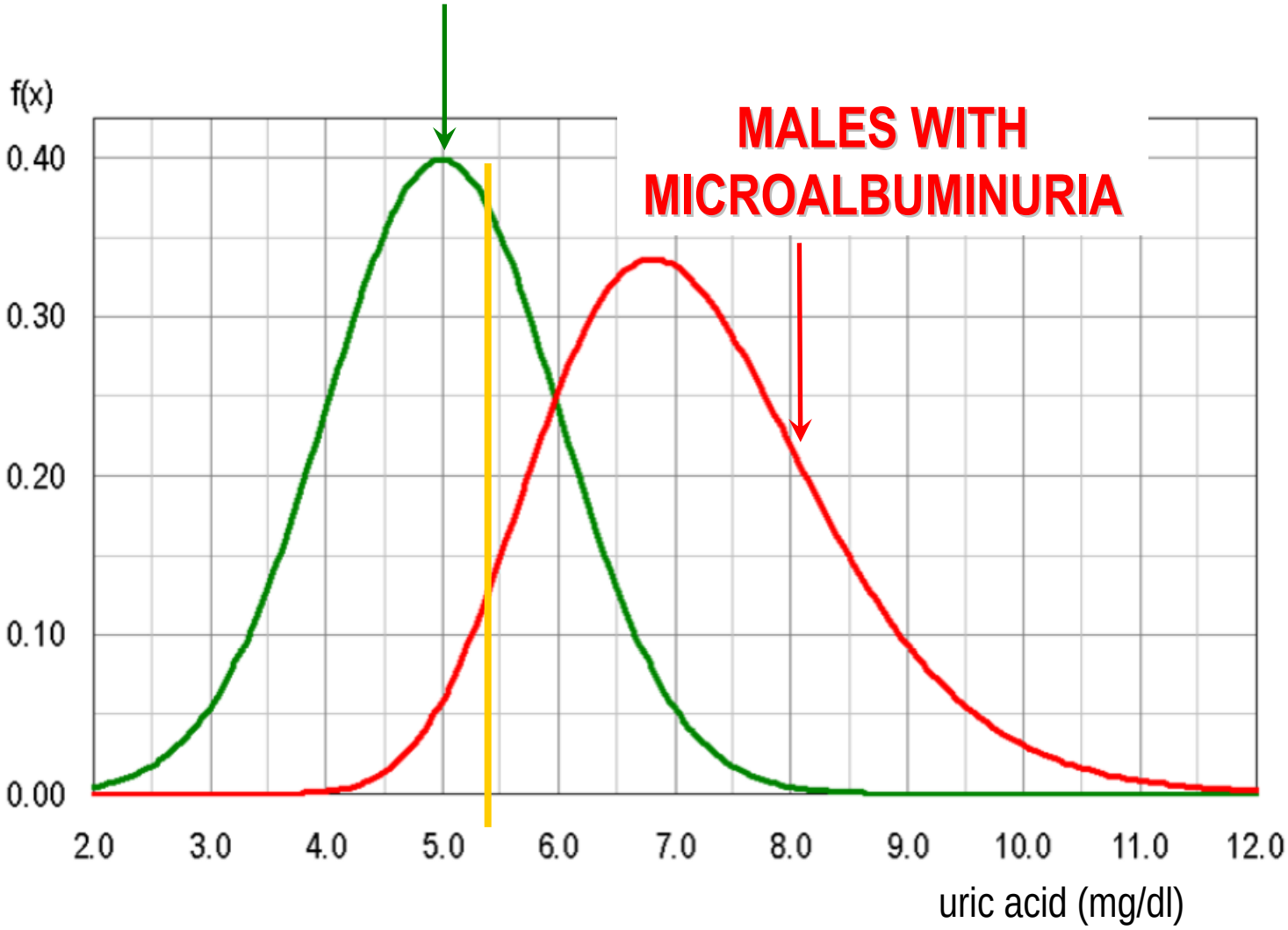
$$95\%TL_{90\%} = \bar{x} \pm_{0.95} k_{0.90} s \xrightarrow[n \to +\infty]{} PL_{90\%} = \mu \pm z_{0.10}\sigma$$

n	k
60	1.958
125	1.846
250	1.780
500	1.737
1000	1.709
$+\infty$	1.645

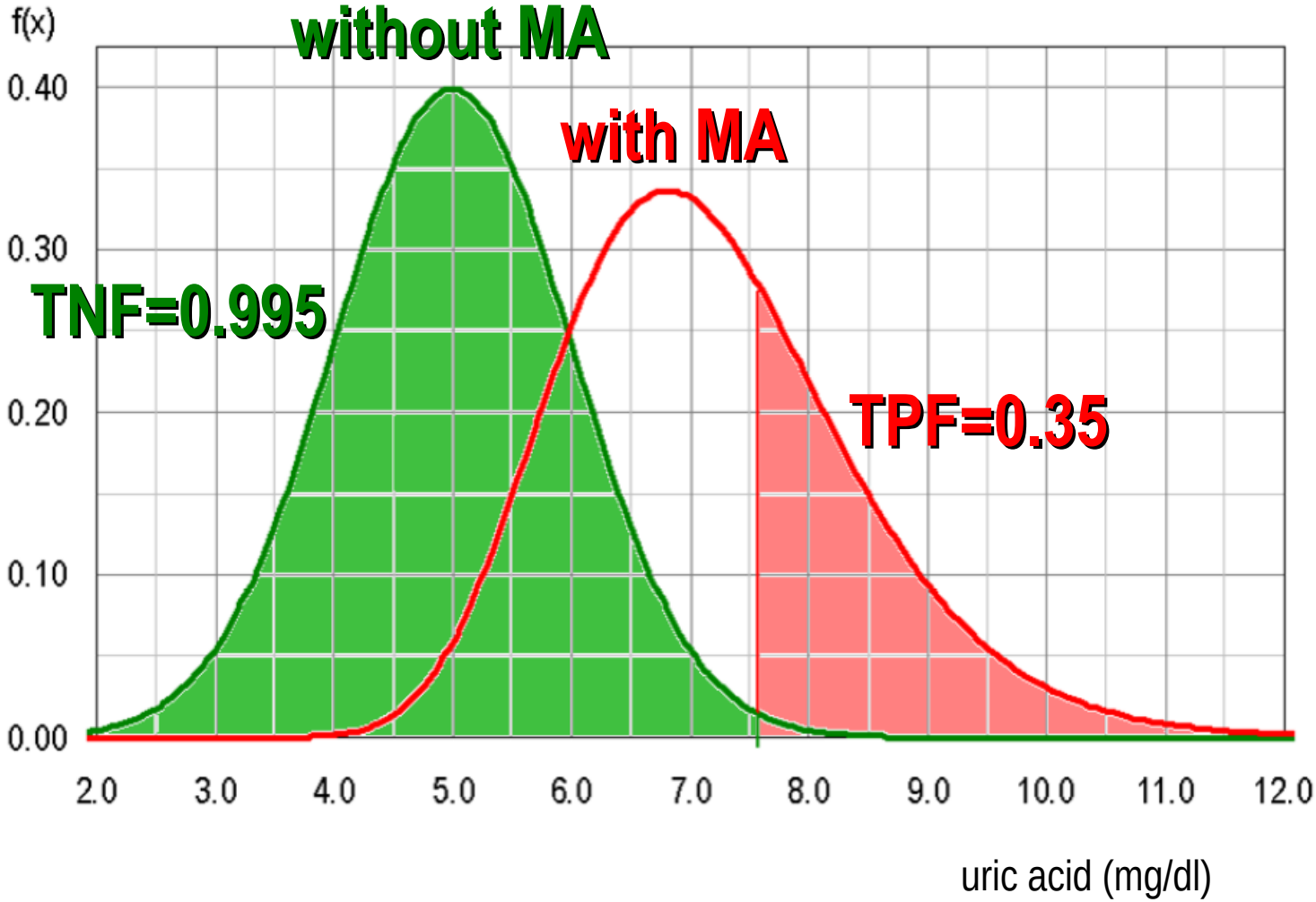
AN EXAMPLE

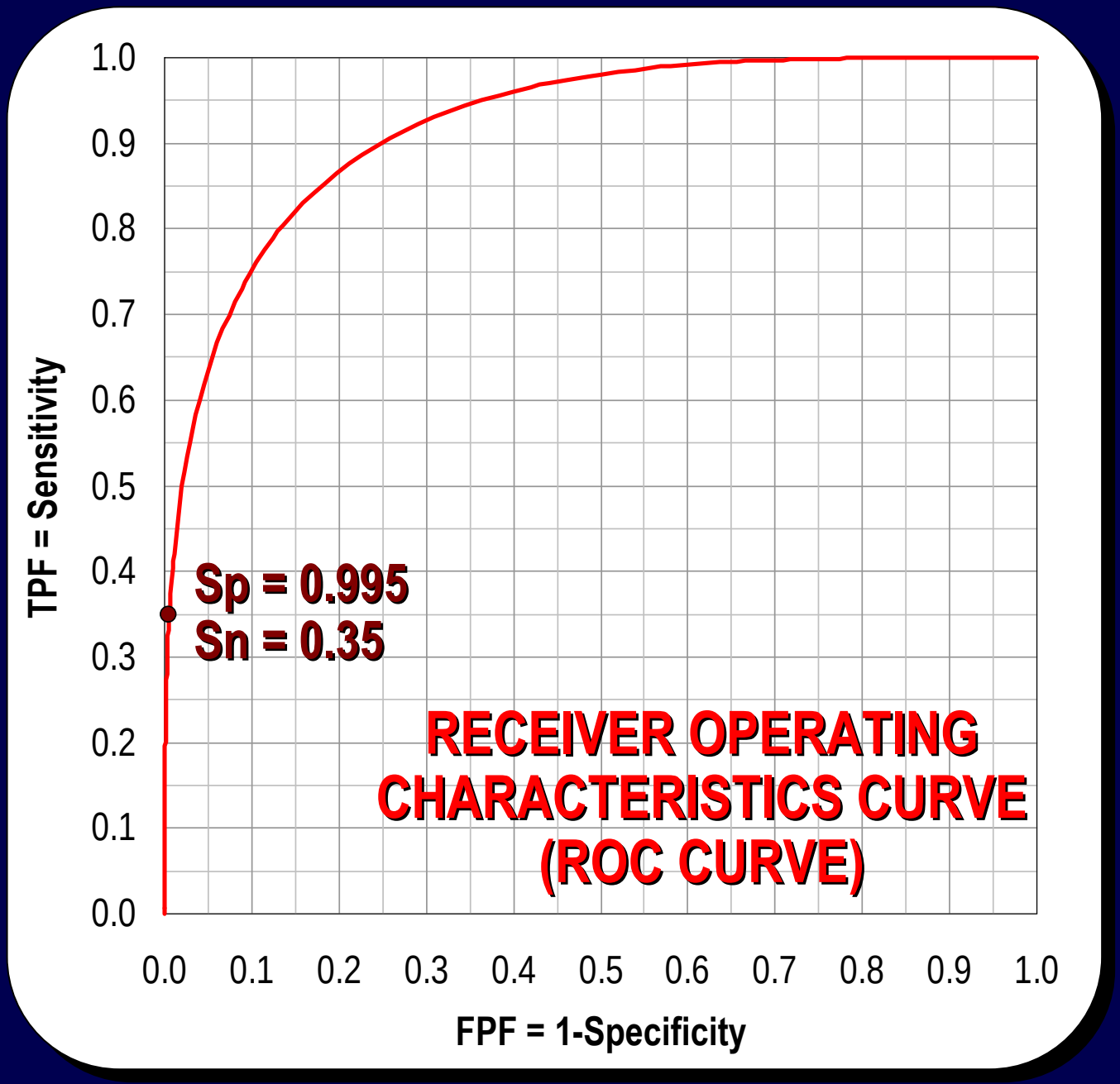
REFERENCE POPULATION

MALES WITHOUT MICROALBUMINURIA

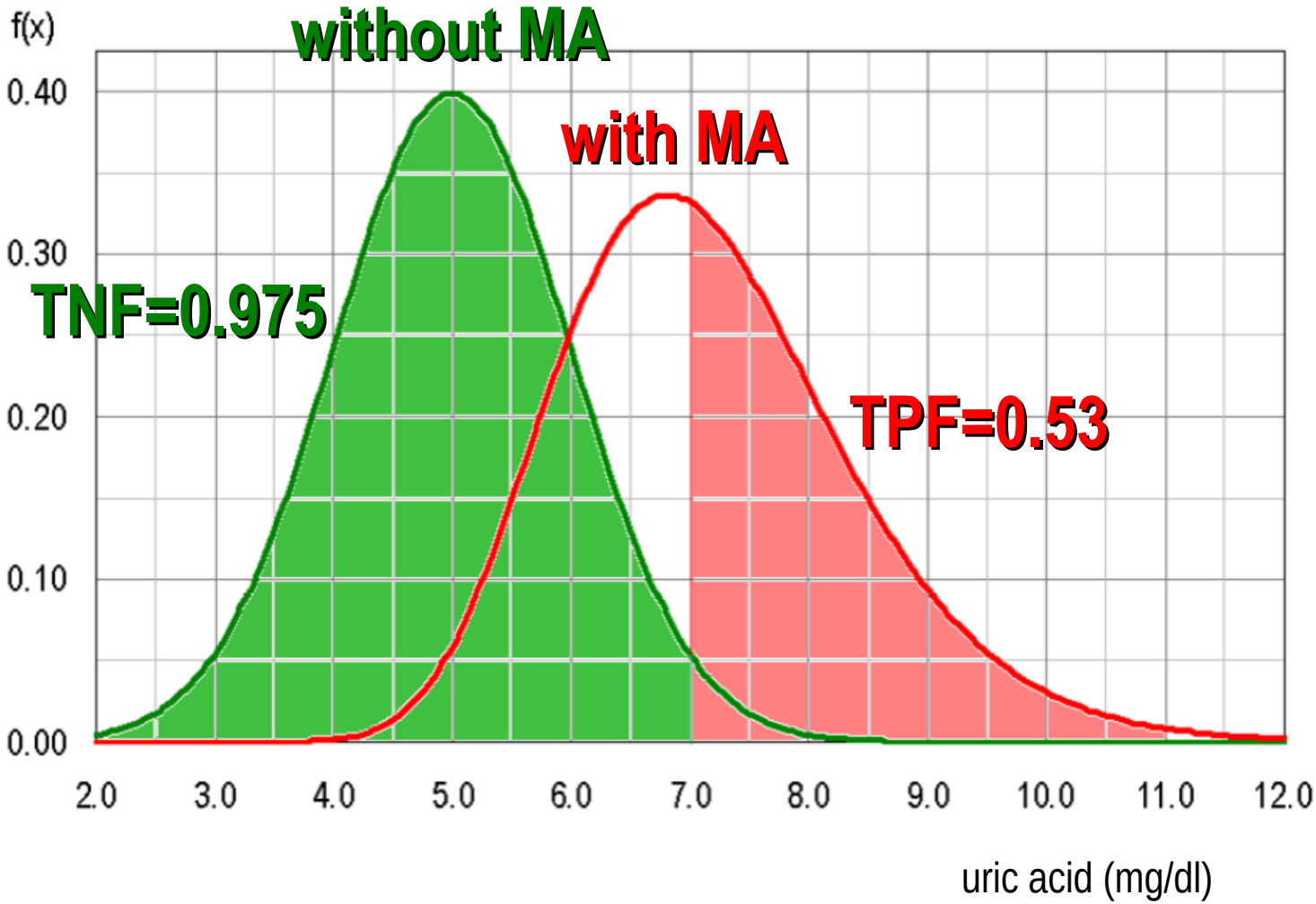


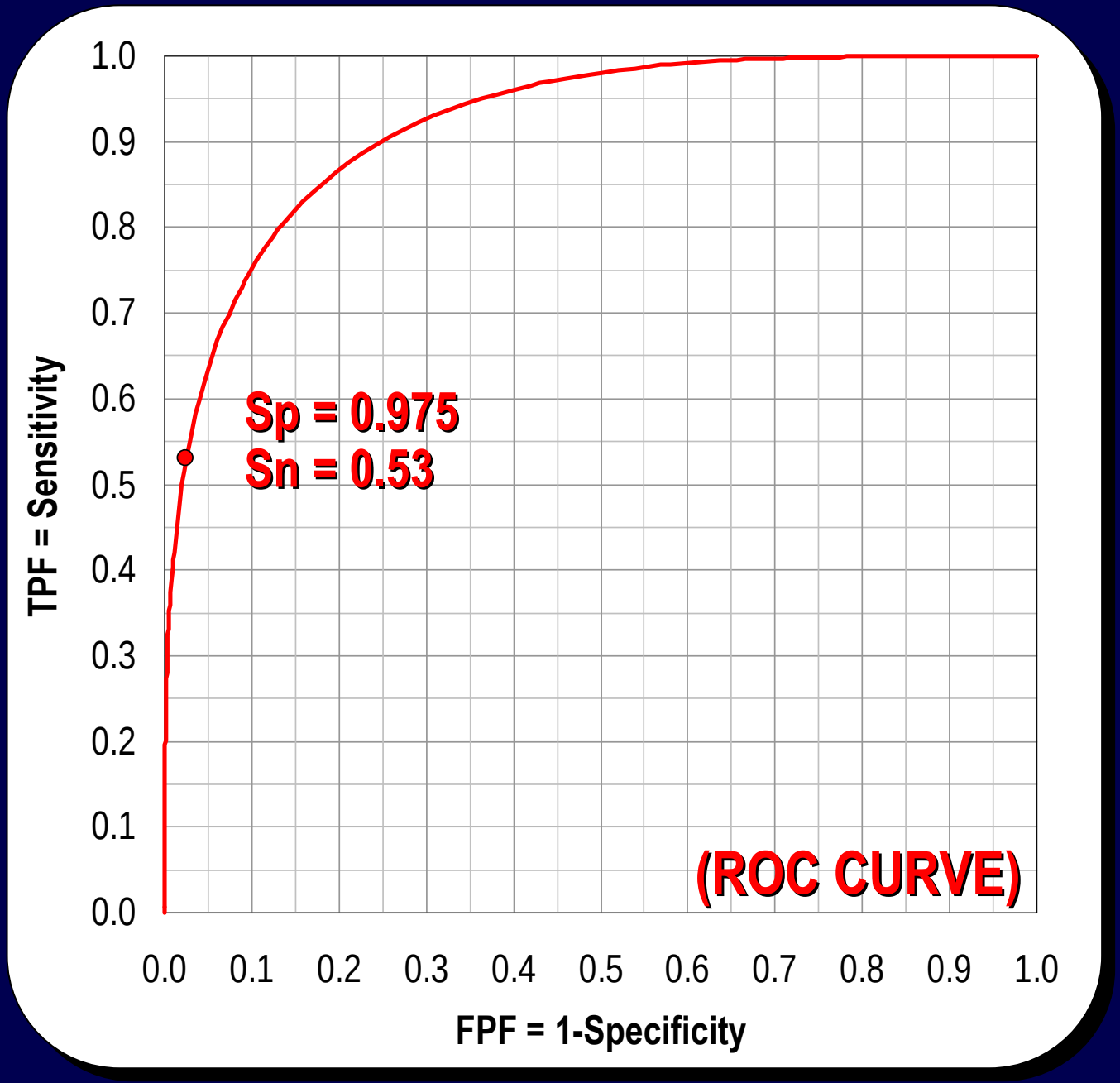
VERY HIGH SPECIFICITY



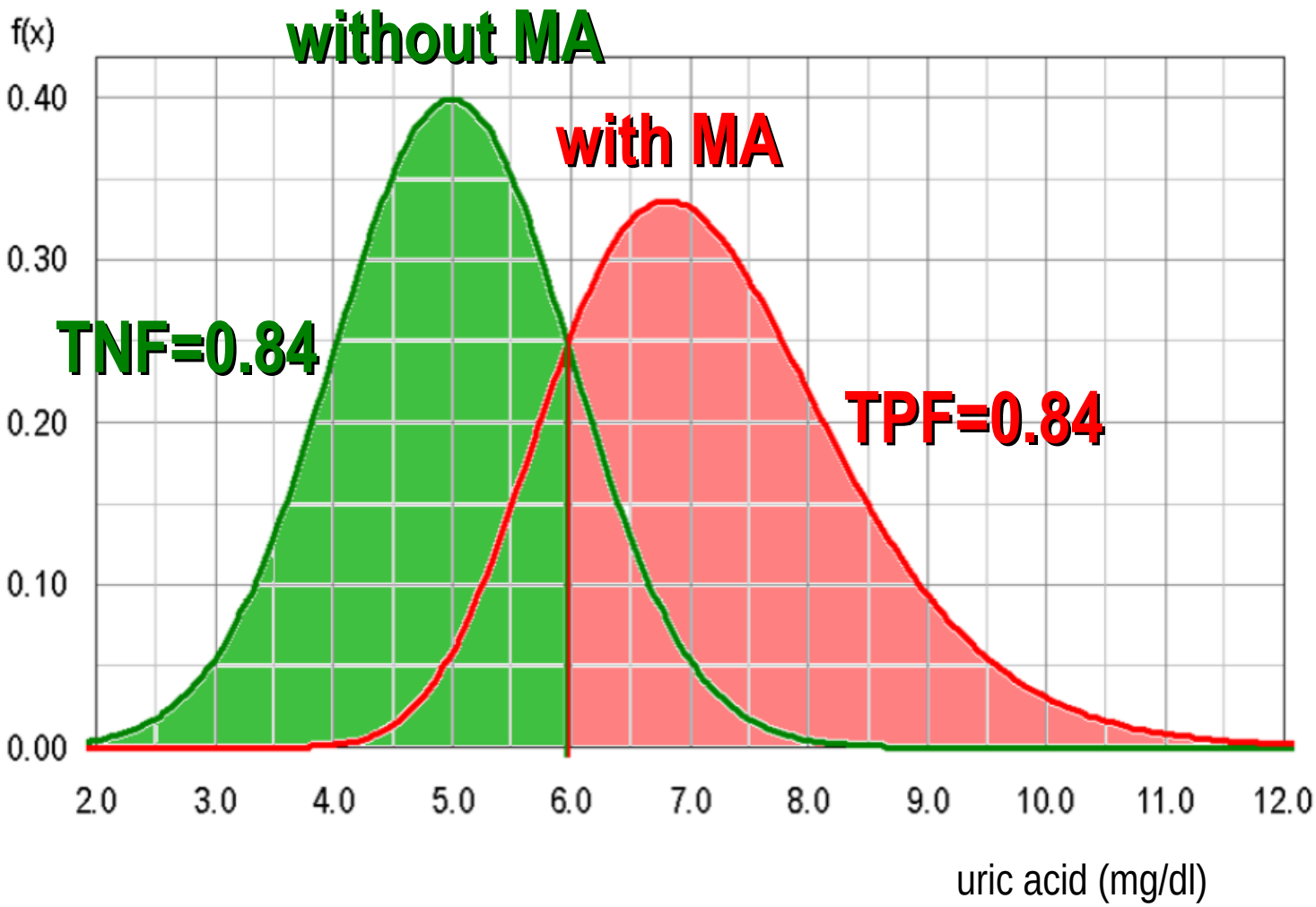

1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
TPF = Sensitivity
Sp = 0.995
Sn = 0.35
RECEIVER OPERATING CHARACTERISTICS CURVE (ROC CURVE)
0.0 0.1 0.2 0.3 0.4 0.5 0.6 0.7 0.8 0.9 1.0
FPF = 1-Specificity

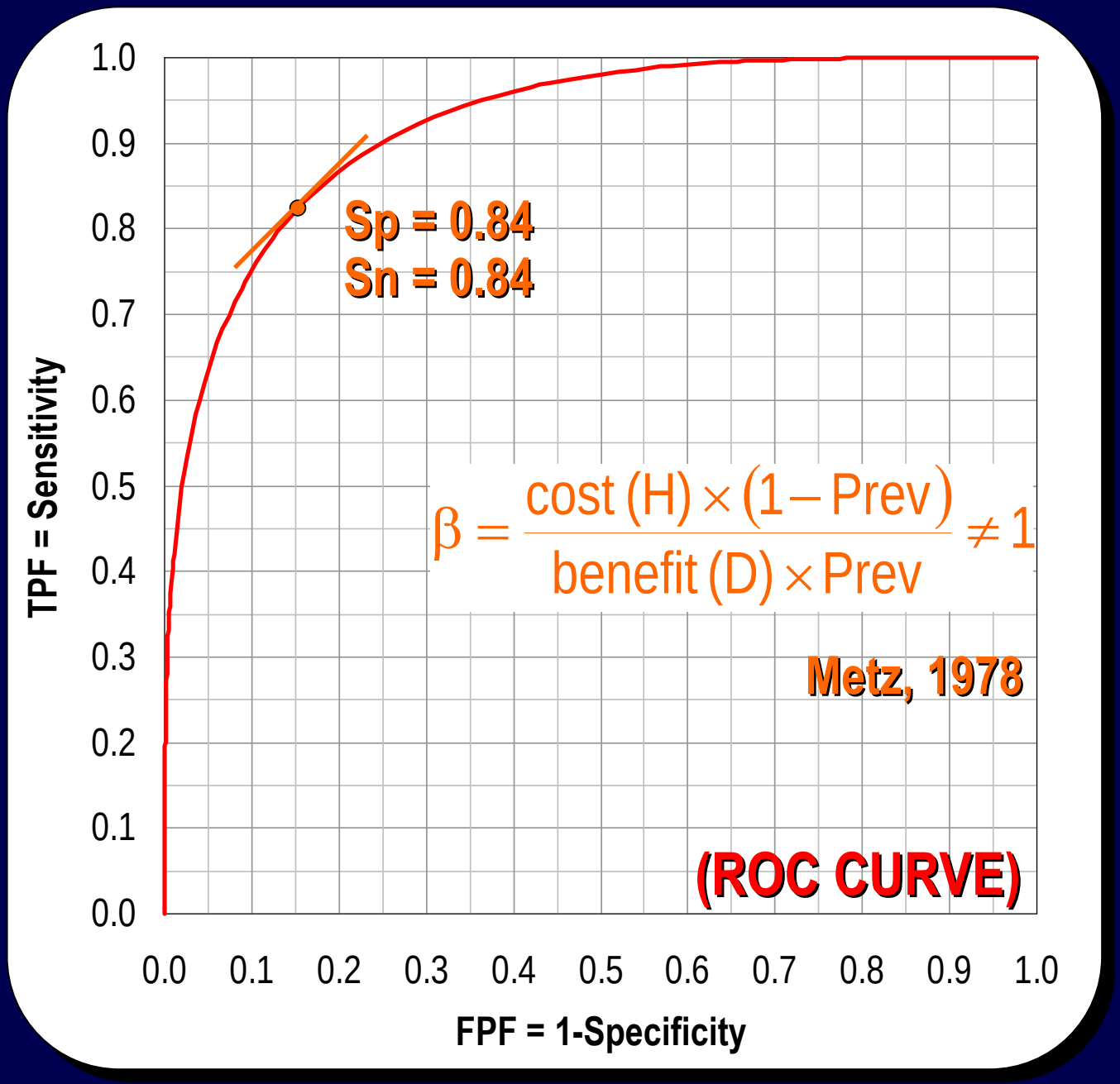
HIGH SPECIFICITY




1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
TPF = Sensitivity
Sp = 0.975
Sn = 0.53
(ROC CURVE)
0.0 0.1 0.2 0.3 0.4 0.5 0.6 0.7 0.8 0.9 1.0
FPF = 1-Specificity

MAXIMUM VALIDITY




1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
TPF = Sensitivity
Sp = 0.84
Sn = 0.84
$\beta = \frac{\text{cost (H)} \times (1 - \text{Prev})}{\text{benefit (D)} \times \text{Prev}} \neq 1$
Metz, 1978
(ROC CURVE)
0.0 0.1 0.2 0.3 0.4 0.5 0.6 0.7 0.8 0.9 1.0
FPF = 1-Specificity

TO SUM UP

As long as the reference limits are determined on the basis of the frequency distribution of the values observed in a reference population, their clinical validity will depend on an external criterion, i.e. on their ability to distinguish subjects at low risk of morbidity or mortality from subjects at high risk.

QUOTH THE RAVEN

$$\lim_{\Delta t \to +\infty} \{Pr(\text{death between } t_0 \text{ and } (t_0 + \Delta t) \mid \text{SBP} > 0)\} = 1$$

$$Pr(\text{death between } t_0 \text{ and } (t_0 + \Delta t) \mid \text{SBP} = 0) = 0 \quad \forall \Delta t$$

Respite - respite and nepenthe from thy memories of Lenore!
Quaff, oh quaff this kind nepenthe, and forget this lost Lenore!'
Quoth the raven, “Nevermore.”

E.A.P.

THANK YOU VERY MUCH FOR YOUR KIND ATTENTION