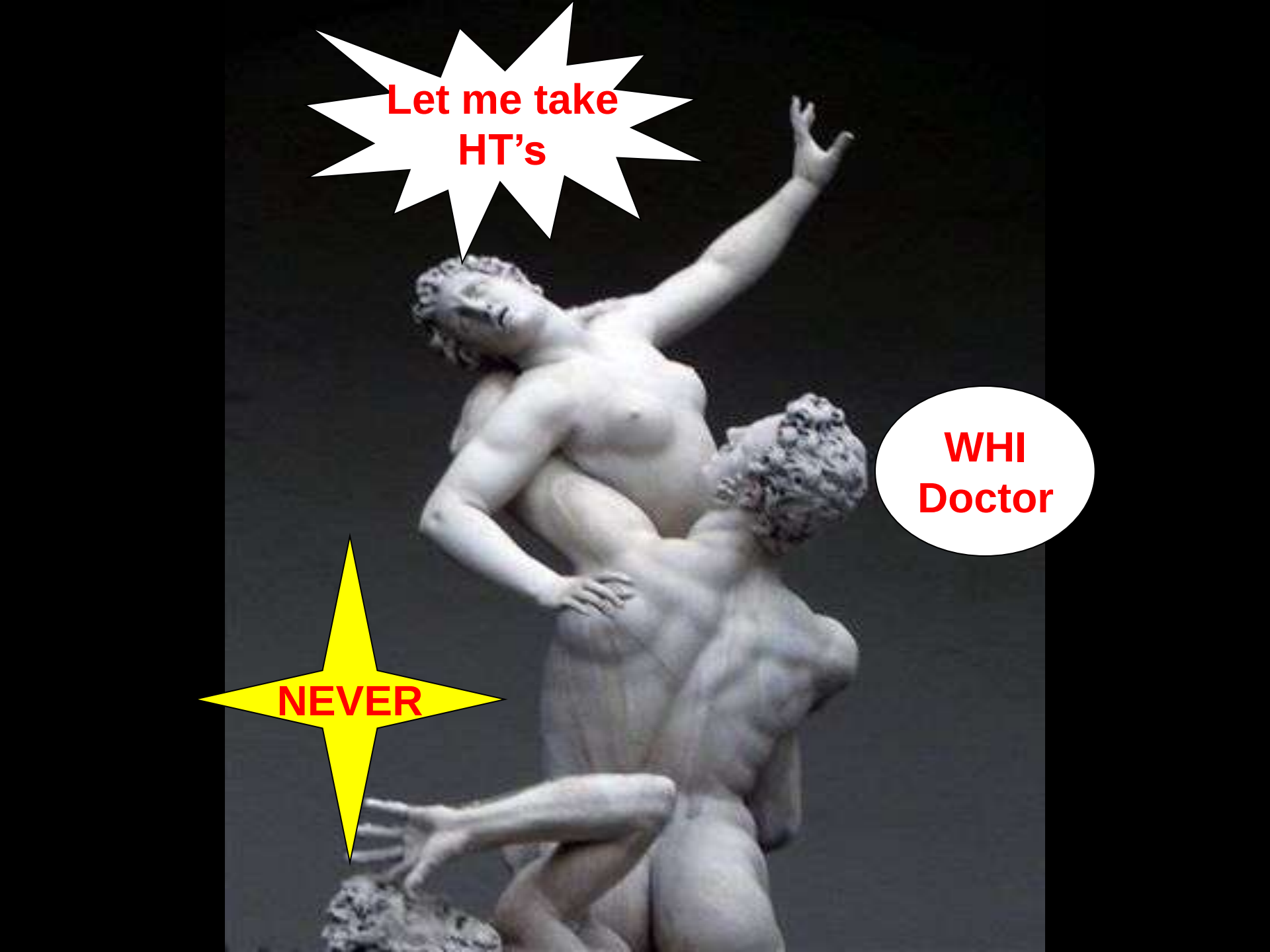
Let me take HT's
WHI Doctor
NEVER

The Risks

White woman's risk of death between the ages of 50 and 94 are:

31.0% from heart disease

2.8% from breast cancer

2.8% from hip fracture

Brinton LA, Schairer C. N Engl J Med.1997;336:1769-1775

WHI

Effect on the risk of breast cancer

WHI ***Nonsignificant*** **increased risk**

RR 1.26 (CI 1.00-1.59); **26%** increased risk

AR 0.38% vs 0.30% (ie, **38** vs **30** events annually per 10.000 women)

HERS ***Nonsignificant*** **increased risk**

RR 1.27 (CI 0.84-1.94); 27% increased risk

AR 0.59% vs 0.47% (ie, 59 vs 47 events annually per 10.000 women)

If Absolute Risks are plotted as percentages,

instead of the additional

8 strokes

7 heart attacks

8 breast cancers ***per 10.000 woman/year***

one would have, respectively

0.08

0.07

0.08 ***cases per 100 woman/year***

a figure that is easier to interpret

WHI results calculated as

	NNT/1 year	NNH/1 year
CHD		1428
Stroke		1250
VTE		588
Breast Cancer		1250
Colon Cancer	1667	
Osteoporotic fractures (totals)	227	

Neves-e-Castro M. Menopause in crisis post-Women's Health Initiative? A view based on personal clinical experience. *Human Reproduction 2003;18:1-7*

"The nurse's study and ones like it could be right and the Women's Health Initiative could be wrong, or vice-versa"

Rossouw J, 2003

”May be each study is wrong. May be estrogen, in pills, is not the chemical to focus on”

Rossouw J, 2003

“If each is right it may be because the women in the two types of studies are different in a way that researchers have not yet figured out”.

Rossouw J, 2003

“It is quite possible that both are correct. The different results may hinge on the differences between the women who joined the studies”

Grodstein F, 2003

“Women considering taking CEE should be counseled about an *increased risk of stroke* but can be reassured about no excess risk of heart disease or breast cancer for at least 6.8 years of use.”

Effects of conjugated Equine Estrogen in Postmenopausal Women with Hysterectomy.JAMA, 2004;291:1701-1712

Breast Cancer

"The increased risk of breast cancer with longer-term exposure, however, seems to be limited in most studies to lean women (ie, BMI<25kg/m2)."

"ET part of the WHI trial has showed no increased the risk of breast cancer"

EMAS Statement 2004.

MWS

- **Breast cancer diagnosed on average 1.2 years after recruitment**

- **Average time between diagnosis and death was 1.7 years *(thus, advanced disease at time of diagnosis)***

Banks E. J Epidemiol Biostat 2001;6:357-63

DISCORDANCE AMONG STUDIES

- **WHI** – ***delayed increase*** in risk (>2 years)

- **MWS** – ***immediate increase*** in risk

  Risk disappearing > than 1 year after stopping HT

Breast Cancer
Million Women Study

The follow-up for breast cancer diagnosis was just over 2½ years, meaning that these breast cancers were almost certainly pre-existent at the start of the observational period.

Press Release from the *British Menopause Society, 2003*

Million Women Study: On-Off-Phenomenon

Shortly after cessation of treatment, past users had no increase in breast cancer incidence or **mortality**. Given the long latency time between tumour induction and detection, plus the fact that **cancer is**, by definition, **an autonomous process that does not cease by stopping exposure**, how can these findings be explained?

.

J. Dinger: Letter to the editor of Lancet (Oct 2003) – refused -.

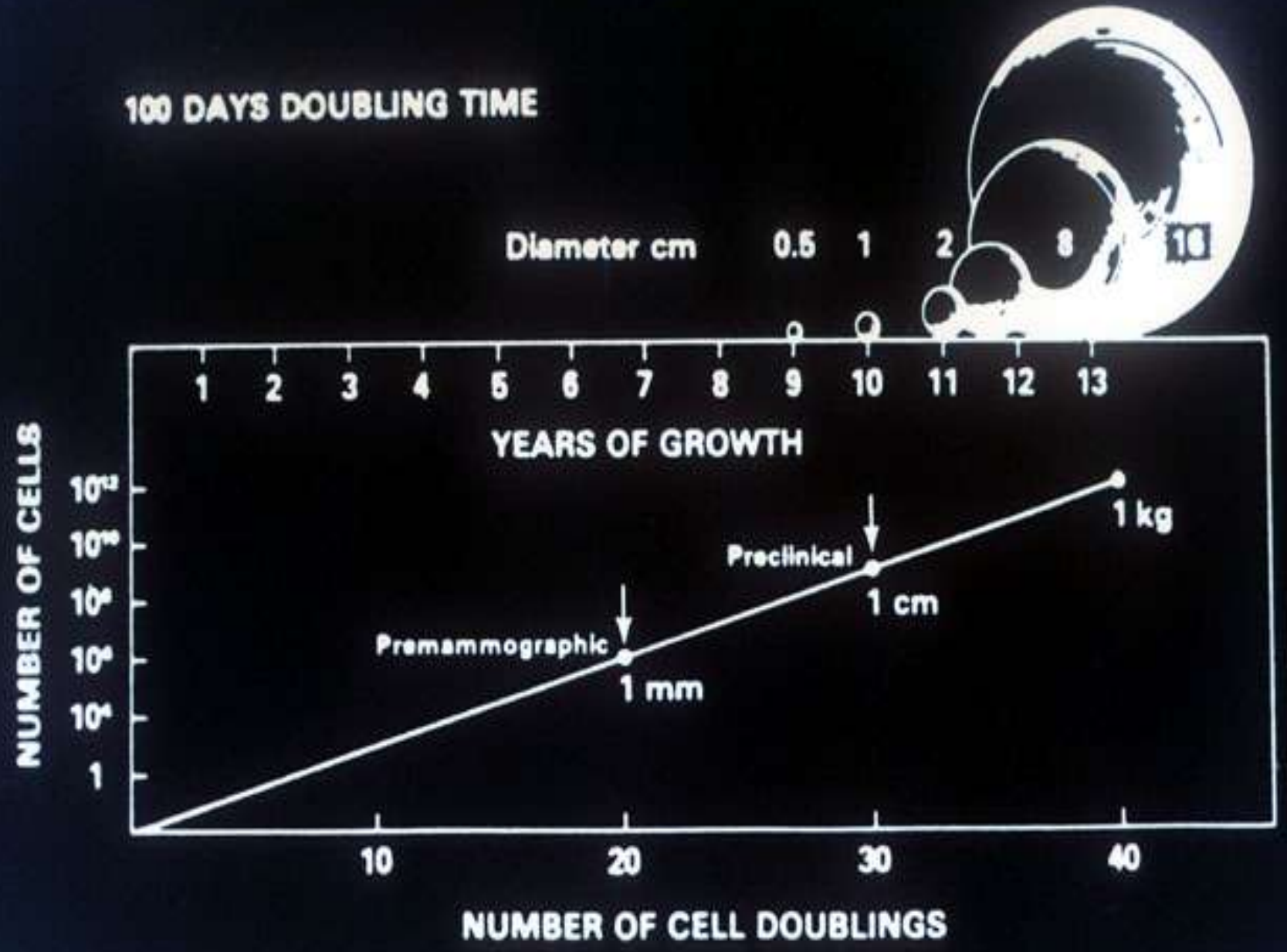

Figure 17–2. The long preclinical existence of breast cancer based on tumor doubling time. (*From Gullino PM: Cancer 1977;39:2697.*)

Breast Cancer

The possibility that contemporary HT causes an increase in breast cancer is not clarified by either the WHI or the MWS and remains to be resolved

Position Statement ***International Menopause Society, 2004***

Occult Breast Cancer

Clinically occult **in situ BC's are frequent in young and middle-aged women.**

Nielsen M *et al*-Br J Cancer 1987;*56*:814-9

Occult Breast Cancer

Breast malignancy was found in 22 women (20%)

Nielsen M *et al*-Br J Cancer 1987;*56*:814-9

Occult Breast Cancer

Malignancy was significantly more frequent among women

. aged more than 40 years

. with late age at first full-term pregnancy

. with alcohol abuse

. with steatosis or cirrhosis of the liver

Nielsen M *et al*-Br J Cancer 1987;*56*:814-9

“Each time we learn something new, the astonishment comes from the recognition that we were wrong before.

In truth, whenever we discover a new fact, it involves the elimination of old ones.

WE ARE ALWAYS, as it turns out, fundamentally IN ERROR.”

Lewis Thomas

English Biologist (1913-1993)

The conclusions of these studies suggest that the *"safe " woman* (NNH between 600-1000 women) to initiate HT is

- between 50-59 years of age
- with vasomotor symptoms
- less than 10 years after the menopause
- being treated with statins
- with a good lipid profile and
- with a Body Mass Index >25

Neves-e-Castro M. Menopause in crisis post-Women's Health Initiative? A view based on personal clinical experience. *Human Reproduction 2003;18:1-7*

This is precisely the profile of the great majority of women who come for consultation after their menopause.

Therefore *it seems that what most gynecologists are doing to their predominant population of patients is not unsafe and contributes not only to a good quality of life but to prevention, as well.*

Neves-e-Castro M*. Menopause in crisis post-Women's Health Initiative? A view based on personal clinical experience. *Human Reproduction 2003;18:1-7

HRT and Breast Cancer link still unclear

Bush TL et al -*Hormone replacement therapy and breast cancer: a qualitative review.* Obstet Gynecol 2001;98:498-508

"The evidence did not support the hypotheses that estrogen use increases the risk of breast cancer and that combined hormone therapy increases the risk more than estrogen only. Aditional observational studies are unlikely to alter this conclusion".

BREAST CANCER

Risk factor	*Relative risk*	*Increase incidence*
Body weight-normal weight : obesity	1 : 2.5	+ 150%
Age at menopause - 42yrs : 52 yrs	1 : 2.0	+ 100%
Age at menarche – 14 yrs: 11 yrs	1 : 1.3	+ 30%
Parity – multiparous : nulliparous	1 : 1.3	+ 30%
Age at first birth – 20 yrs : 35 yrs	1 : 1.4	+ 40%
Oral contraceptives – never user:ever user	1 : 1.1	+ 10%
Hormone replacement-never:5 or more yrs	**1 : 1.3**	***+ 30%***
Alcohol consumption-none:≥20 g daily	1 : 1.3	+ 30%
Serum lipids – normal : raised	1 : 1.6	+ 60%
Physical activity – activate : inactive	1 : 1.2	+ 20%

R. Santen, 2004

RELATIVE RISK OF BREAST CANCER BY BODY WEIGHT

Age at Diagnosis	Weight (Kg)		
	<60	60-69	70+
35-49	1.00	0.54	1.16
50-59	1.00	1.22	1.43
60-69	1.00	1.61	1.81

from deWaard et al ,1964,1978

How to decrease potential risks?

How to decrease potential risks

- Age at begining *(window of opportunity)*
- BMI
- Parenteral estradiol (transdermal, subcutaneous)
- Parenteral progesterone (vaginal, IUD)
- Addition of testosterone or dihidrotestosterone
- Tibolone
- Raloxifene
- Aspirin
- Statins
- hCG ? (Russo, Bo Schoultz)

The Benefits

The Benefits

- Osteoporosis
- Colon Cancer
- CHD *(Nurses Health Study, primate models)*
- Alzheimer
- Quality of life (physical, mental, sexual)

The Truth?

"The objective of both basic and clinical science is to know the truth".

"Every epidemiologic study, no matter how good or how large, gives only one view of the truth".

"It takes many views to come close to seeing the truth"

Bush TL. *Int J Fertil*.2001;46:56-59

“Not everything that can be counted *counts*;

and not everything that *counts* can be counted”

Albert Einstein

“He who learns, but does not think is lost.

He who thinks, but does not learn is dangerous”.

Confucius

If we both *learn* and *think* we will

neither be *lost*

nor *dangerous*

to our postmenopausal women patients”

Wenger NK. ***Am J Geriatr Cardiol 2000 ; 9: 204 - 9***

The Encyclicals…

"What is especially worrying about the statements and prescribing encyclicals is the apparent blinkered belief in the infallibility of the WHI and the MWS"

Sturdee D and MacLennan A –(Editorial) Should epidemiology,the media and quangos determine clinical practice? *Climacteric 2004;7:1-2*

***Biased opinions*,**

be they *pro* or *con*,

dishonor the profession

and

harm our patients.

Sacket DL. The arrogance of preventive medicine. *Can Med Assoc J 2002;167:363-364*

The menopausal hormone therapy

The blind men see an elephant…

Menopausal hormone therapy aptly fits the metaphor of the blind men describing the elephant: ***each touches a part****, ear, trunk, tail, body,* ***and draws a different conclusion.***

We are the blind men. The elephant is the data published in a half-century of medical literature that now includes the report from the Women's Health Initiative (WHI)

Sacket DL*. The arrogance of preventive medicine. *Can Med Assoc J 2002;167:363-364

“There are no really “safe” biological active drugs.

There are only “safe” physicians”

Kaminetzy HA 1993

The take-home message is: (1)

Prescribe postmenopausal hormonal treatments

when clinically indicated,

***if not contraindicated*!**

The take-home message is: (2)

- The prescription of long-term hormonal treatments must depend always on a benefit/risk analysis *in comparison with other non-hormonal medications and strategies*.

MNC/02

The take-home message is: (3)

- ***No answers*** **from ongoing clinical trials** ***are indispensable*** **to practice today a good Medicine !**

MNC/02

Preventing a woman from the benefits of a

sound postmenopausal hormone therapy

because of the fear of rare side effects

does not seem to be satisfactory Medicine...

M.Neves-e-Castro, 2000

Science is the search for truth.

It is not a game in which one tries to beat his opponent, to do harm to others

Linus Carl Pauling, 1958