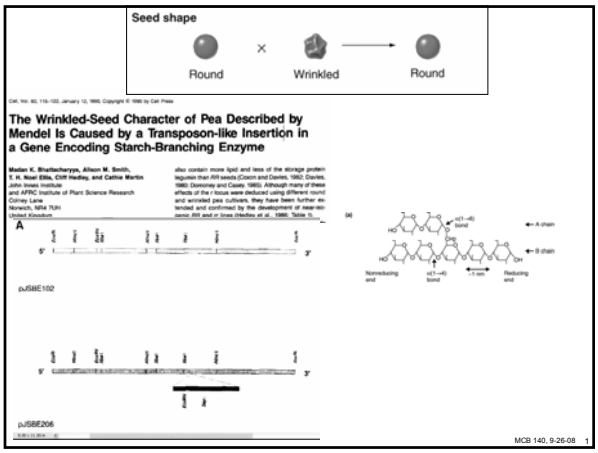


Gene → phenotype

Other genes → epistasis → variable expressivity (sickle-cell anemia)

The environment → "norm of reaction" → variable penetrance (BRCA1-induced breast cancer)

Epigenetic effects

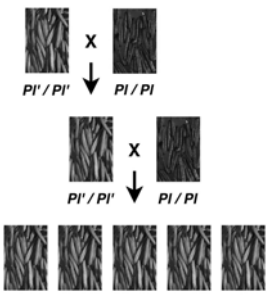
Epigenetics

Mitotically **and/or** meiotically resistant inheritance of a phenotypic difference that occurs without a change in the DNA sequence.

Maize (corn) – *Zea mays*

Courtesy of Prof. Jay Hollick, MCB Department

?!!!



R. Alexander Brink, 1950
Vicky Chandler, Jay Hollick

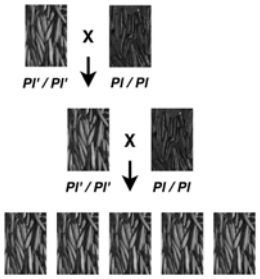
What is going on

This is paramutation:

a **meiotically** heritable change in the phenotype of a plant that results not from the physical alteration of the primary DNA sequence of the underlying genes, but from an effect on their expression.

Recall Mendel's "compromise that the two alleles of a gene reach in a heterozygous organism for the life of a plant."

In this case, the compromise is not reached. The PI' allele somehow causes the epigenetic silencing of the PI allele – silencing that persists through meiosis.



A critical aspect of the paramutation process – one that is shared by many epigenetic processes

It is sensitive to the environment:

paramutation can be variably expressive (in other words, the extent of paramutation can vary, and how variable it is can be specified by the environment).

Environmental Programming of Heritable Epigenetic Changes in Paramutant *r*-gene Expression Using Temperature and Light at a Specific Stage of Early Development in Maize Seedlings

Bernard C. Mikula

Defiance College, Defiance, Ohio 43512

Manuscript received April 21, 1994
Accepted for publication May 12, 1995

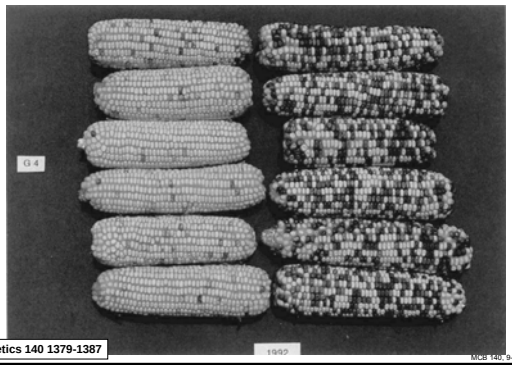
ABSTRACT

Different heritable expression-states were programmed into *R* alleles from *R/R-lst* heterozygotes under different temperature conditions applied during a developmental period in which flowering is induced. At maturity, *R*-allele expressions in test crosses of male gametes derived from *R/R-lst* seedlings raised 15 days in 32° and continuous light conditions differed significantly from those of sib seedlings raised for 15 days in 22° and continuous light conditions and shifted to six 12-hr light-dark cycles, days 16–21. This experiment provides the first evidence in higher organisms that environmental conditions, applied at a specific stage of development cause a heritable change in a specific allele expression. My earlier evidence required a statistical analysis for demonstrating heritable change; I present photographic evidence of this environmental effect on four *R* alleles.

Genetics 140 1379-1387

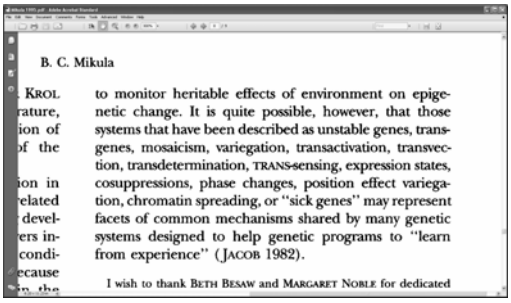
Grandpaternal seedling conditions

32C LL 22C LL



Genetics 140 1379-1387

An evolutionary perspective



B. C. Mikula

KROL ... to monitor heritable effects of environment on epigenetic change. It is quite possible, however, that those systems that have been described as unstable genes, transgenes, mosaicism, variegation, transactivation, transvection, transdetermination, TRANS-sensing, expression states, cosuppressions, phase changes, position effect variegation, chromatin spreading, or "sick genes" may represent facets of common mechanisms shared by many genetic systems designed to help genetic programs to "learn from experience" (JACOB 1982).

I wish to thank BETH BESAW and MARGARET NOBLE for dedicated

Mikula (1995) Genetics 140 1379-1387

Persephone, the Greek goddess of Spring

A bit of plant biology – the seeming paradox of vernalization

"Vernalization is the process by which prolonged exposure to cold temperatures promotes flowering.

Monocarpic species senesce after flowering and setting seed. … Plants that require vernalization to flower thus typically require two seasons to complete the life cycle and are usually classified as biennials or winter annuals.

Many winter annuals and biennials become established in the fall, taking advantage of the cool and moist conditions optimal for their growth. The vernalization requirement of such plants prevents flowering until spring has actually arrived. "

R. Amasino *The Plant Cell* 16:2553-2559 (2004)

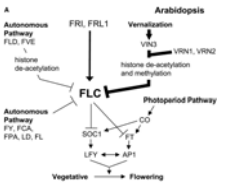
Vernalization

A) A biennial cabbage (*Brassica oleracea*) variety with an obligate vernalization requirement that had been growing for five years without cold exposure. The small plant in my daughter's hands is a summer-annual variety of *B. oleracea* that flowers rapidly without vernalization. **(B)** and **(C)** Summer annual and vernalization-requiring types of henbane **(B)** and Arabidopsis **(C)**. In both examples, a single-dominant gene is responsible for the vernalization-requiring habit. All plants were grown in long days (inductive photoperiods) without vernalization. The rapid-flowering summer annuals (which have initiated flowering) are at left and the winter-annual types at right.

R. Amasino *The Plant Cell* 16:2553-2559 (2004)

"I think it is reasonable to refer to the vernalization-induced, mitotically stable acquisition of the competence to flower as **an epigenetic switch** because it is a change that can be propagated through cell divisions in the absence of the inducing signal."

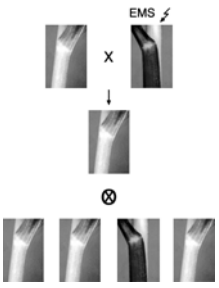
R. Amasino *The Plant Cell* 16:2553-2559 (2004)



"The vernalization-mediated repression of *FLC* is epigenetic in the sense discussed above: The repressed state of *FLC* is maintained after vernalized plants are returned to warm growing conditions. Thus, in Arabidopsis, vernalization provides competence to flower by repressing the expression of a flowering repressor. As expected, *FLC* expression is on again in the next generation. This resetting of the epigenetic switch during passage to the next generation is reminiscent of genomic imprinting in animals. But the unique aspect of this switch is that the on-to-off direction of the switch is set by perception of the environment, whereas the off-to-on direction is set by passage to the next generation."

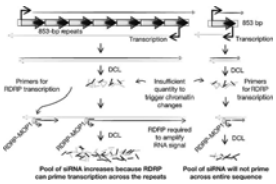
R. Amasino *The Plant Cell* 16:2553-2559 (2004)

From screen …



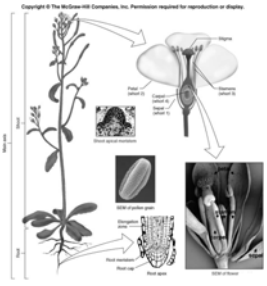
Hollick and Chandler
Genetics, Vol. 157, 369-378

To mechanism:

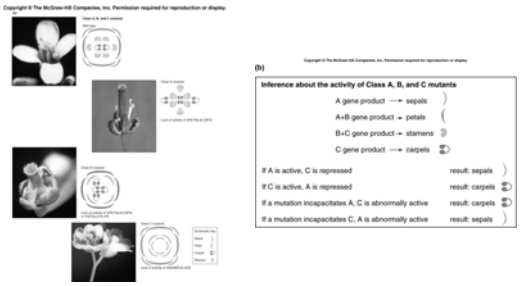


Alleman et al.
Nature 442, 295-298

Arabidopsis thaliana



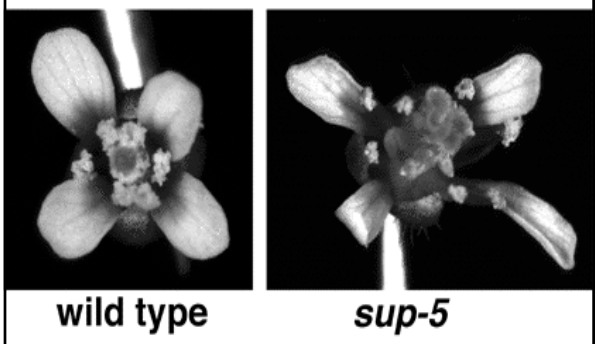
Some mutations that affect flower structure



S. Jacobsen and E. Meyerowitz

"Superman"

Wild-type flower: 6 stamens (♂).
superman null mutations: 12 stamens.



S. Jacobsen, UCLA

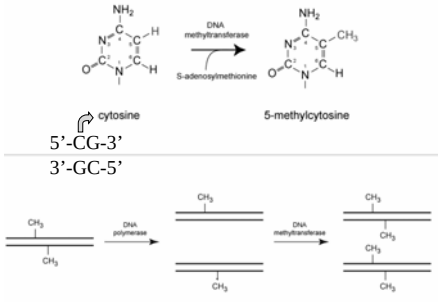
No comment on the nomenclature

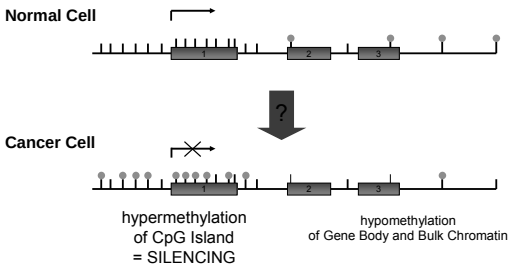
There are two ways to mutate the *SUPERMAN* gene and get the same phenotype (12 stamens):

1. Just delete the gene.
2. Keep the gene as it and METHYLATE it!

The methylated form is an "epi-allele" of *SUPERMAN* and is called *clark kent*.

S. Jacobsen, UCLA





Jones and Baylin *Nat Rev Genet.* 2002 Jun;3(6):415-28

S. Jacobsen, UCLA

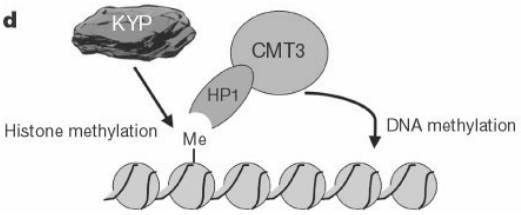
Suppressors of *clark kent*

clk-st

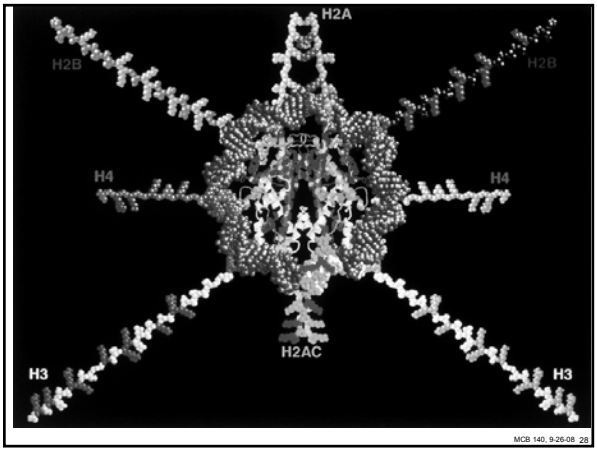
Suppressor mutants:
Cmt3 (the DNMT)
or
kyp (kryptonite)

S. Jacobsen, UCLA

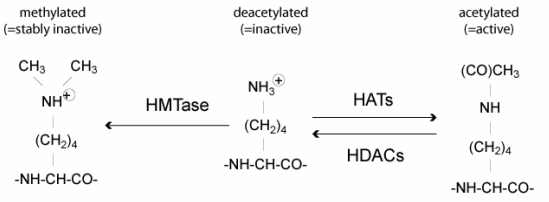
kyp (kryptonite) codes for an H3K9 histone methyltransferase!



Jackson et al. (Jacobsen) *Nature* **416:** 556-560 (2002).



Histone methylation

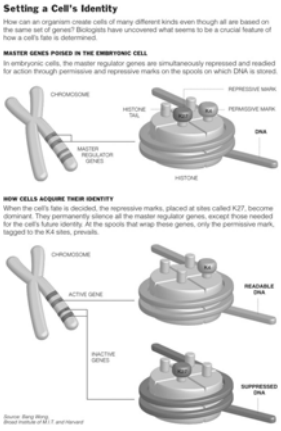


2007:

Young, Jaenisch – Nature, Cell

Bernstein – Cell

Wade – New York Times



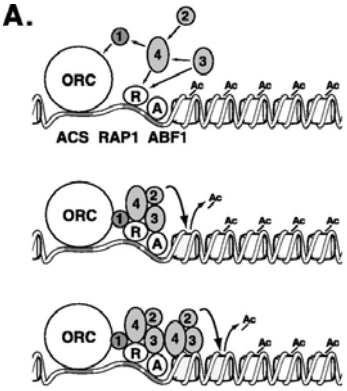
The molecular basis of epigenetic inheritance …

… is the deposition, and subsequent maintenance through mitosis (plants and animals) and meiosis (plants) of covalent marks (such as methylation) on the DNA, and on the histones.

These marks do NOT change the DNA sequence, but they change how the DNA sequence is read.

The machinery that deposits these marks, the (dys)regulation of this machinery, and how the marks are read out – are, without a doubt, the #1 field of study in genetics today.

Resveratrol



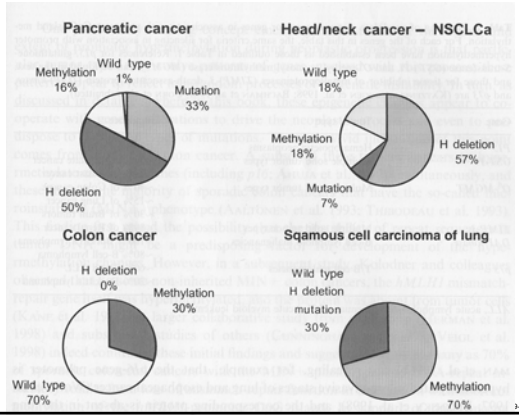
Rusche L, Kirchmaier A, Rine J (2002) *Mol. Biol. Cell* **13:** 2207.

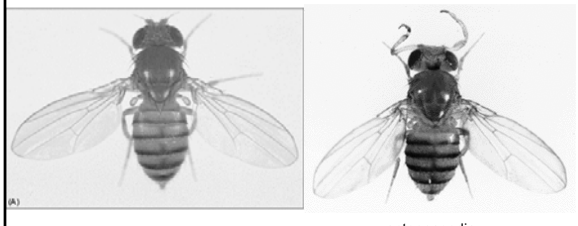
Gene Inactivation Associated With CpG Island Methylation In Cancer

Gene	Locus	Function	Cancer
• Rb	13q14.2	Cell cycle regulation	Retinoblastoma
• VHL	3p25	RNA elongation	Renal carcinoma
• P16	9p21	CDK inhibitor	Carcinomas
• P15	9p21	CDK inhibitor, TGF-β-induced	Leukemia, glioma
• E-cadherin	16q22.1	Invasion/metastasis suppressor	Breast, prostate, gastric
• Estrogen Rec	6q25	Hormone receptor	Breast, colon
• GST-π	11q13	Detoxifying enzyme	Prostate
• O⁶MGMT	10q24-qter	DNA repair	Cell lines
• Calcitonin	11p15	Hormone	Leukemia, lung, colon

Jones and Baylin *Nat Rev Genet.* 2002 Jun;3(6):415-28

S. Baylin: p16 (INK4A) loss of function in different types of human cancer





wt antennapedia

Homeotic mutations (W. Bateson)

Genetics

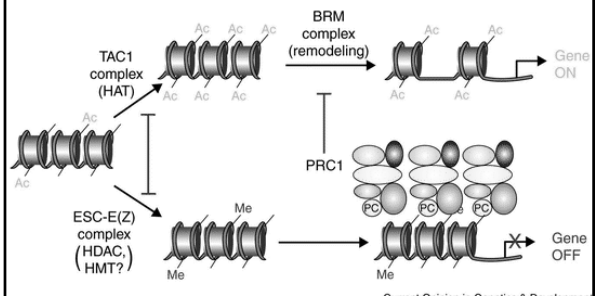
Allele

Heterozygous

Homozygous

"… Not that there has merely been a change, but that something has been changed into the likeness of something else."

How Polycomb and Trithorax work



Current Opinion in Genetics & Development

extra sex combs

enhancer of zeste

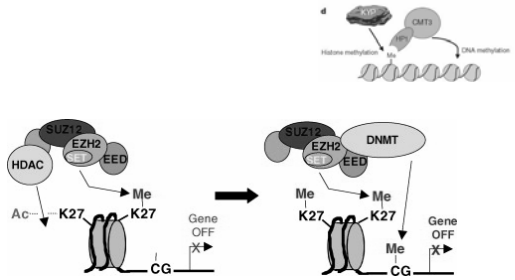
E(z) = HMTase!

PubMed on "ezh2": 207 refs, e.g. …

Cancer Res. 2006 Apr 15;66(8):4095-9.

Identification of EZH2 as a molecular marker for a precancerous state in morphologically normal breast tissues.

Ding L, Erdmann C, Chinnaiyan AM, Merajver SD, Kleer CG. Department of Pathology, University of Michigan Medical School, Ann Arbor 48109, USA. The discovery of molecular markers to detect the precancerous state would have profound implications in the prevention of breast cancer. We report that the expression of the Polycomb group protein EZH2 increases in histologically normal breast epithelium with higher risk of developing cancer. We identify EZH2 as a potential marker for detecting preneoplastic lesions of the breast in vivo and as a possible target for preventative intervention.



Mutat Res. 2008 Aug 3.
Roles of the EZH2 histone methyltransferase in cancer epigenetics.
Simon JA, Lange CA.

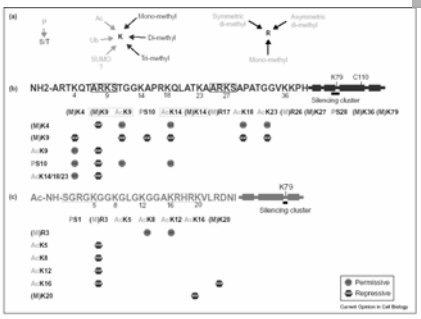
Nothing in Biology Makes Sense Except in the Light of Evolution
Theodosius Dobzhansky, 1973

Why is it called the "theory" of evolution?

After all, the origin of species by means of natural selection as proposed by Darwin is a "theory" in the same category with the following "theories":

1. That the Earth is a slightly compressed sphere.
2. That light is both a wave and a particle.
3. That the ratio of the circumference of a circle to its diameter is π (~3.14159...)

David Allis: "the histone code"



Fischle, Wang, Allis *COCB* 2003

Genes and the environment

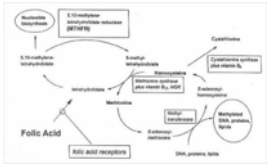


Table 1: Selected Food Sources of Folate and Folic Acid [1]

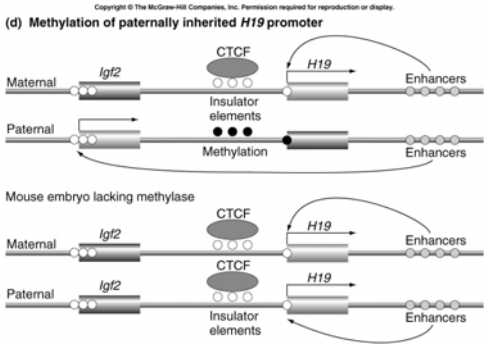
Food	Micrograms (µg)	% DV*
*Breakfast cereals fortified with 100% of the DV, ½ cup	400	100
Beef liver, cooked, braised, 3 ounces	185	45
Cowpeas (blackeyes), immature, cooked, boiled, ½ cup	105	25
*Breakfast cereals, fortified with 25% of the DV, ½ cup	100	25
Spinach, frozen, cooked, boiled, ½ cup	100	25
Great Northern beans, boiled, ½ cup	90	20
Asparagus, boiled, 4 spears	85	20
*Rice, white, long-grain, parboiled, enriched, cooked, ½ cup	65	15
Vegetarian baked beans, canned, 1 cup	60	15
Spinach, raw, 1 cup	60	15
Green peas, frozen, boiled, ½ cup	50	15
Broccoli, chopped, frozen, cooked, ½ cup	50	15
*Egg noodles, cooked, enriched, ½ cup	50	15
Broccoli, raw, 2 spears (each 5 inches long)	45	10
Avocado, raw, all varieties, sliced, ½ cup sliced	45	10
Peanuts, all types, dry roasted, 1 ounce	40	10

Solter and Surani

Gynogenetic embryos – very small.

Androgenetic embryos – very large.

Imprinting



The Haig hypothesis

Imprinting evolved as a manifestation of parental conflict over the allocation of maternal resources to the developing fetus: “intrauterine tug of war” over how big the fetus will be.

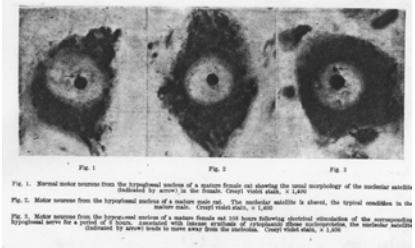
Paternally expressed genes increase embryo size.

Maternally expressed genes decrease embryo size.

Peromyscus polionotus
(the monogamous mouse)

Vrana et al. Nature Genetics 20: 362 (1998).

The Barr body

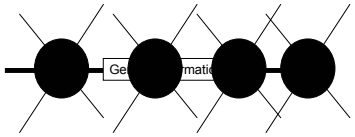


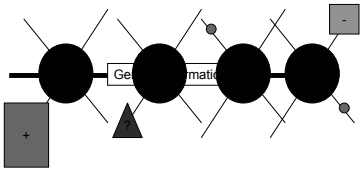
X-chromosome inactivation

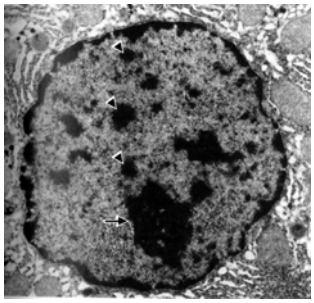
In brief, early in the development of female mammals, the nucleus inactivates – transcriptionally – one of its X chromosomes. Then, remarkably, expression off the other X is doubled.

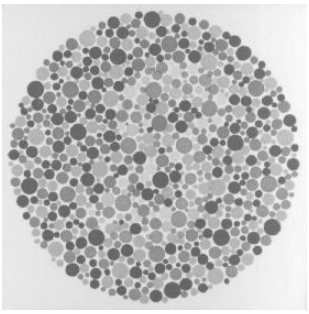
This is somewhat illogical (why not just leave both Xs active?), and is a phenomenon known as “dosage compensation.”

Its molecular basis is the physical coating of the entire X chromosome by a noncoding RNA called XIST.









"**It's All in the Genes**"
New York Times, 5/2/04

S.J. Gould – keep Darwin out of it

"Those who recruit Darwin to support a particular moral or political line should remember that, at best, evolutionary biology may give us some insight into the anthropology of morals -- why some (or most) peoples practice certain values, perhaps for their Darwinian advantage. **But science can never decide the morality of morals.** Suppose we discovered that aggression, xenophobia, selective infanticide and the subjugation of women offered Darwinian advantages to our hunter-gatherer ancestors a million years ago on the African savannahs. **Such a conclusion could not validate the moral worth of these or any other behaviors, either then or now."**

New York Times 5-29-98