

**Genes, environment and  
individual risk: an incoherent  
question with misleading  
“answers”**

George Davey Smith

Centre for Causal Analyses in Translational Epidemiology  
(CAiTE) / Avon Longitudinal Study of Parents and Children  
(ALSPAC)

University of Bristol

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IEA JOHN SNOW LECTURE 2011

# Epidemiology, epigenetics and the 'Gloomy Prospect': embracing randomness in population health research and practice

George Davey Smith

MRC Centre for Causal Analyses in Translational Epidemiology, School of Social and Community Medicine, University of Bristol, Oakfield House, Oakfield Grove, Bristol BS8 2BN, UK

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Epidemiologists aim to identify modifiable causes of disease, this often being a prerequisite for the application of epidemiological findings in public health programmes, health service planning and clinical medicine. Despite successes in identifying causes, it is often claimed that there are missing additional causes for even reasonably well-understood conditions such as lung cancer and coronary heart disease. Several lines of evidence suggest that largely chance events, from the biomolecular down to the sub-cellular, contribute an important stochastic

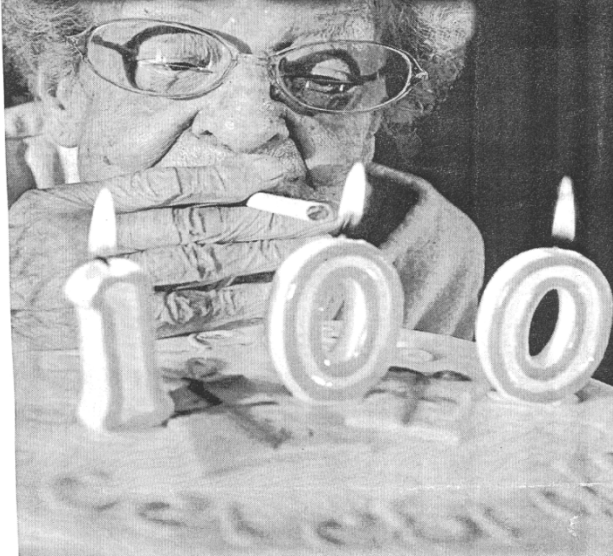
## The Gloomy Prospect

# Mis-specifying individual risk of IHD: what to do?

“.. within any risk group, prediction is poor; it is not at present possible to express individual risk more precisely than as about a 1 in 6 chance of a hitherto healthy man developing clinical IHD in the next 5 years if he is at high risk” .... “There is a pressing need for prospective observational studies in which new risk factors are identified”

Meade TW, Chakrabarti R. Arterial disease research: observation or intervention? *Lancet* 1972;ii:913-6

# LIFE'S A DRAG



**Winnie, 100  
smokes for  
93 YEARS  
and she ain't  
quitting now**



Wartime memories... Winnie had her first cigarette in 1914

By GARETH DORRIAN

**DEFIANT smoker Winnie Langley celebrates reaching 100 yesterday — by lighting her 170,000th cigarette from a candle on her birthday cake.**

She started having a puff an incredible 93 years ago aged seven — just after the First World War broke out in June 1914. She has got through five a day ever since.

Winnie has no plans to quit — even after the nationwide ban forcing smokers outside — and reckons tobacco has never made her ill.

She gets her 100th birthday telegram from the Queen after outliving a husband, Robert, and son, Donald, who died two years ago aged 72.

### Nerves

The former launderette worker said she started smoking weeks after the assassination of Archduke Franz Ferdinand in Sarajevo sparked the First World War.

Winnie, of Croydon, Surrey, said smoking helped "steady the nerves" during two World Wars.

And the reason why Winnie has never suffered of the habit? She said: "I never inhaled."



### STINK'S ON THE HOUSE

**A PUB is squirting round cigarette-scented spray — after drinkers moaned the smoking ban had ruined the atmosphere.**

Landlady Sarah Thornton, 34, below, found the special effects product called Fag Ash on the internet.

She said at the Graven Arms in Birmingham: "Punters love it. Some sit there with unlit ciggies in their mouths."

"Without smoke it stinks of sweaty bodies."

Heaven scent... Sarah with spray

# Why are children in the same family so different from one another?



- Genetics apart, siblings are no more similar than two randomly selected individuals from the population they are from
- They share many of the things that lifecourse epidemiologists have been interested in!

Plomin and Daniels, Behavioral and Brain Sciences, 1987 (IJE 2011)

# Shared environment: a meaningful concept?

- Shared environment in childhood: declining effects on outcomes such as obesity
- Shared environment in adulthood – extended pedigree studies; spousal studies
- Face validity of estimates – e.g. music lessons vs playing in adulthood; child being read to but not reading on their own (Vinkhuyzen et al 2010)

## Effects of heritable and environmental factors in cancers at various sites. Proportion of variance (95% CI)

Site or type	Heritable factors	Shared environment	Non-shared environment
Stomach	0.28 (0-0.51)	0.10 (0-0.34)	0.62 (0.49-0.76)
Colorectum	0.35 (0.10-0.48)	0.05 (0-0.23)	0.60 (0.52-0.70)
Pancreas	0.36 (0-0.53)	0 (0-0.35)	0.64 (0.47-0.86)
Lung	0.26 (0-0.49)	0.12 (0-0.34)	0.62 (0.51-0.73)
Breast	0.27 (0.04-0.41)	0.06 (0-0.22)	0.67 (0.59-0.76)
Cervix uteri	0 (0-0.42)	0.20 (0-0.35)	0.80 (0.57-0.97)
Corpus uteri	0(0-0.35)	0.17 (0-0.31)	0.82 (0.64-0.98)
Ovary	0.22 (0-0.41)	0 (0-0.24)	0.78 (0.59-0.99)
Prostate	0.42 (0.29-0.50)	0 (0-0.09)	0.58 (0.50-0.67)
Bladder	0.31 (0-0.45)	0 (0-0.28)	0.69 (0.53-0.86)
Leukemia	0.21 (0-0.54)	0.12 (0-0.41)	0.66 (0.45-0.88)

Lichtenstein P, Holm MV, Verkasalo OK et al. Environmental and heritable factors in the causation of cancer. *N Engl J Med* 2000;**343**:78-85.

## **Categories of “environmental” factors that cause children in same family to differ**

- Measurement error (non-shared environment is from subtraction)
- “Non-systematic non-shared environment” – stochastic processes during development and beyond
- Systematic differences – birth order, sib-sib interactions, peer effects etc

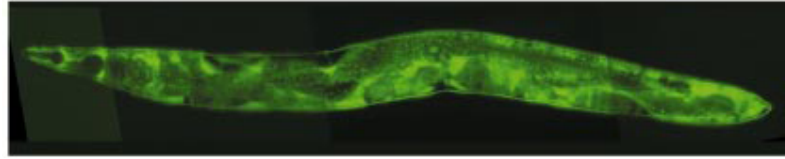


# V

“life’s single lesson: that there is more accident to it than a man can ever admit to in a lifetime and stay sane”

*V, Thomas Pynchon, 1964*

## Lifecourse epidemiology of *C. elegans*



Although factors in the microenvironment or life histories of individuals (for example, the amount of time spent in food as opposed to near it) could profoundly affect ageing rates, we repeatedly observed a stochastic occurrence of cellular demise within the same cell types of individual animals.

*Herndon et al. Stochastic and genetic factors influence tissue-specific decline in ageing C. elegans Nature, 2002*

## Variation of growth of genetically identical marbelled crayfish in an aquarium



How well would epidemiologists be able to predict outcome?

Vogt et al. J Exp Biol 2008;211:510-23

# **A third component causing random variability beside environment and genotype. A reason for the limited success of a 30 year long effort to standardize laboratory animals?**

**KLAUS GÄRTNER**

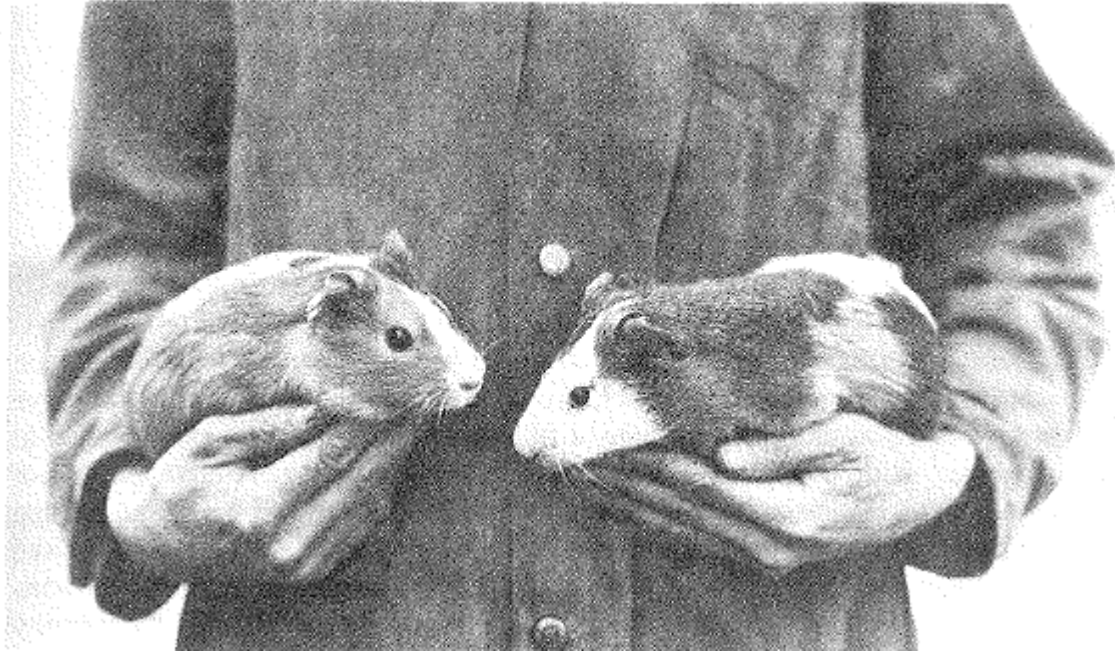
*Medizinische Hochschule Hannover, Abt. Versuchstierkunde Konstanty-Gutschow-Str. 8, D-3000 Hannover, Federal Republic of Germany*

## **Summary**

**This paper is a review of experiments, performed in our laboratory during the past 20 years, designed to analyse the significance of different components of random variability in quantitative traits in laboratory rats and mice. Reduction of genetic variability by using inbred strains and**

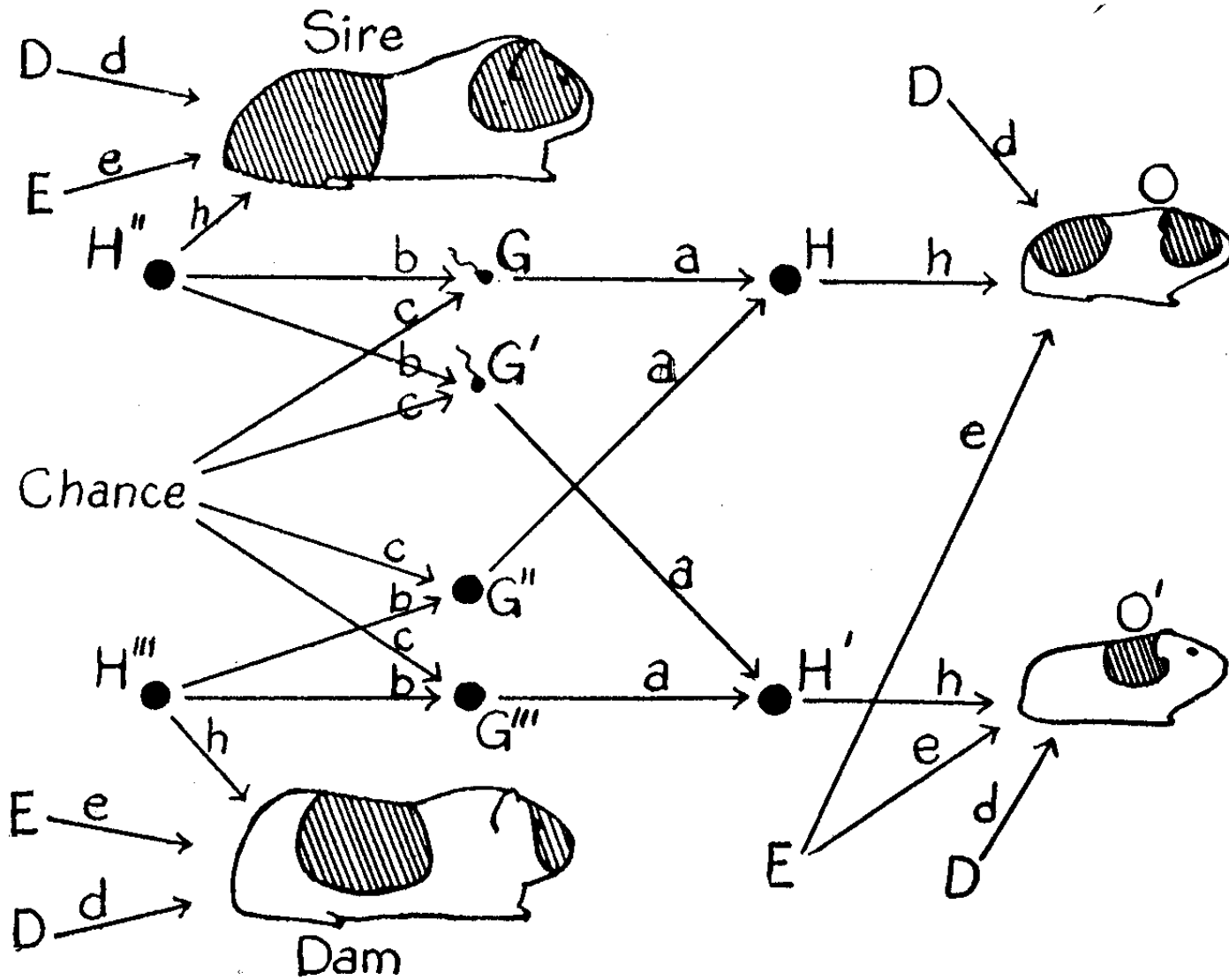
**than the consequence of heterogeneous environmental influences. In a group of inbred rats, the males with the highest chance of parenting the next generation were gathered in the central classes of the distribution of the body weight.**

*Keywords: Components of variance of body*



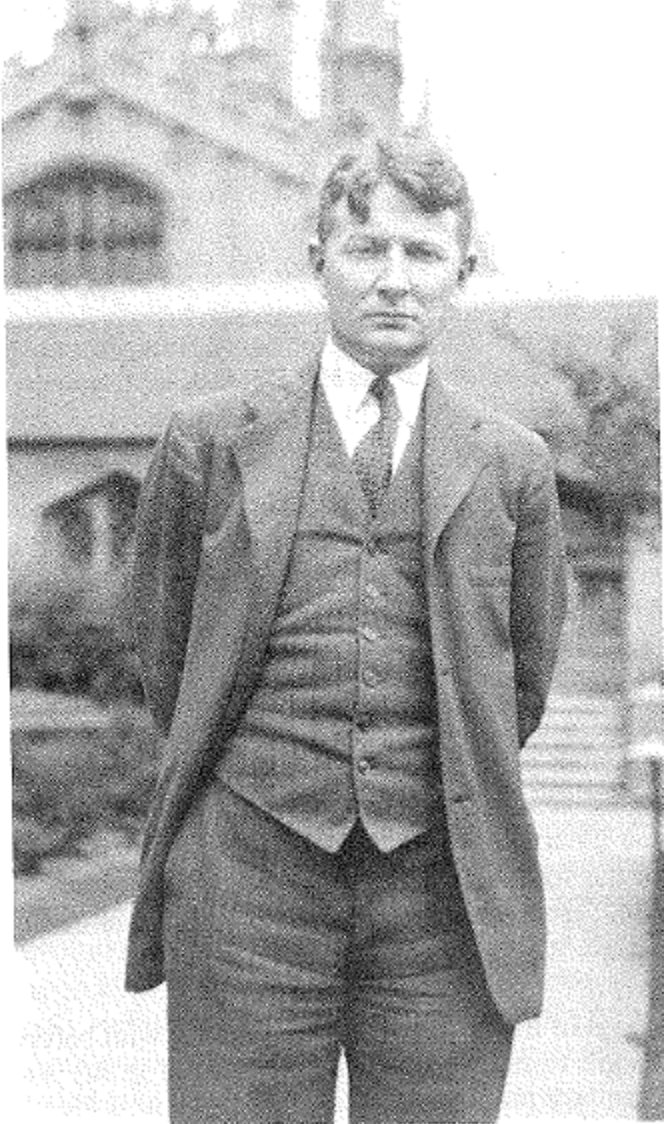
Sewall Wright holding a guinea pig in each hand  
circa 1920.

# Random phenotypic variance? Piebald pattern in guinea pigs



Sewall Wright 1921

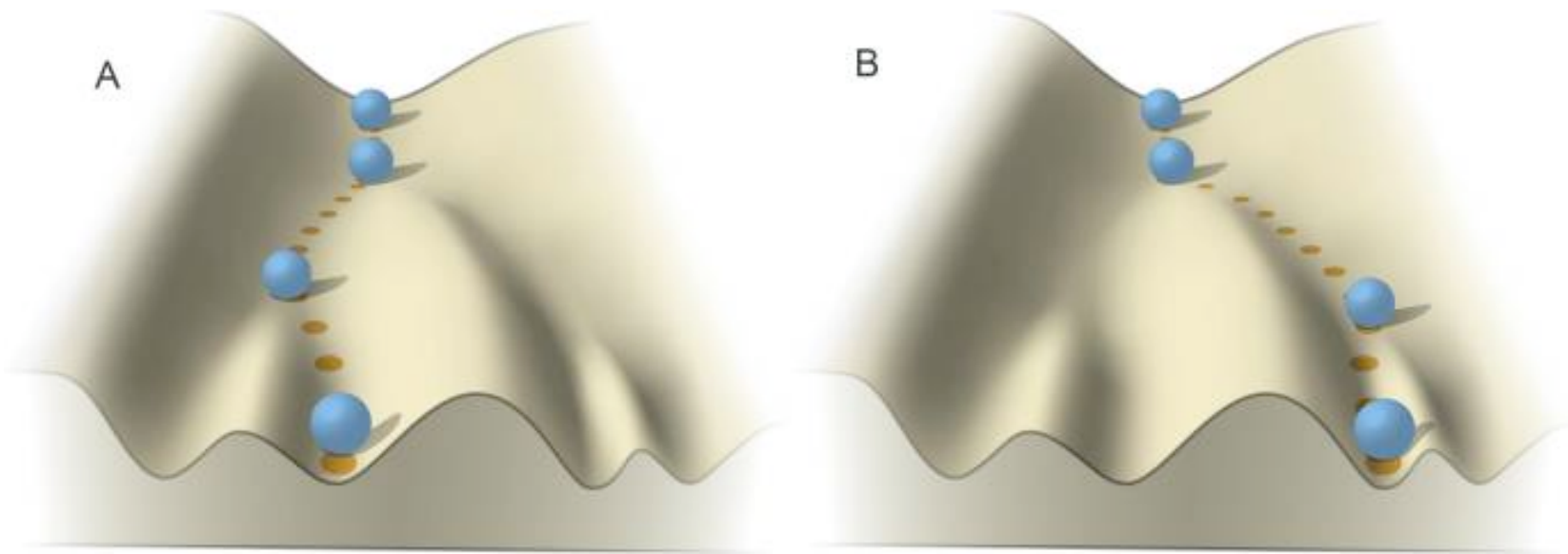
58% of the variance intangible ..



“differences .. must be due to irregularities in development due to the intangible sort of causes to which the word chance is applied”

Sewall Wright 1921

## Stochastic events at the level of gene expression and epigenetic processes



Waddington's epigenetic landscape

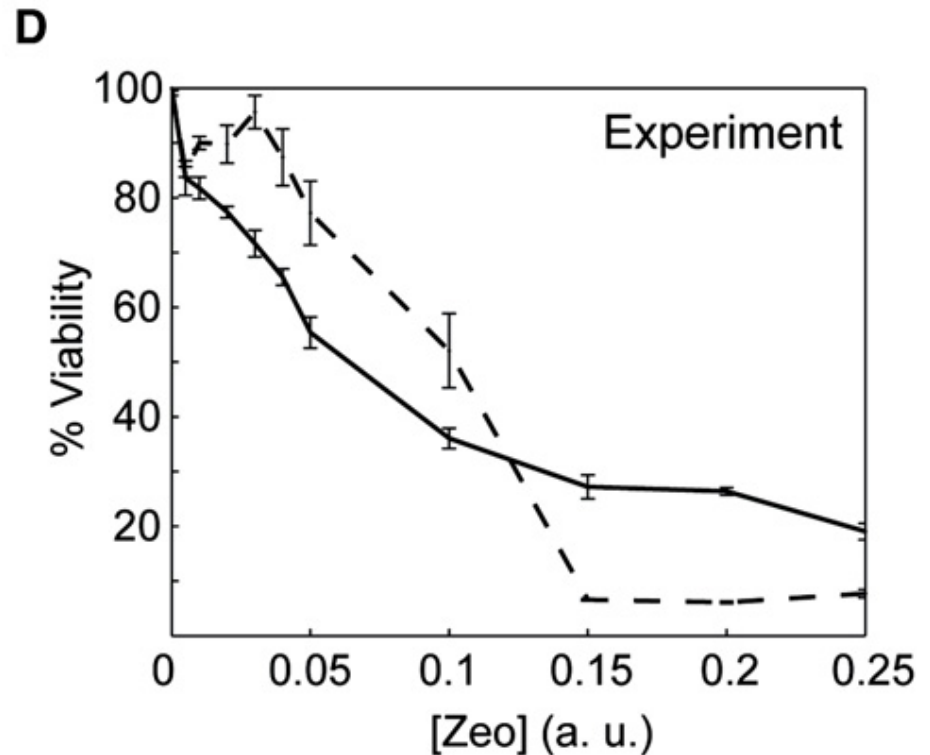
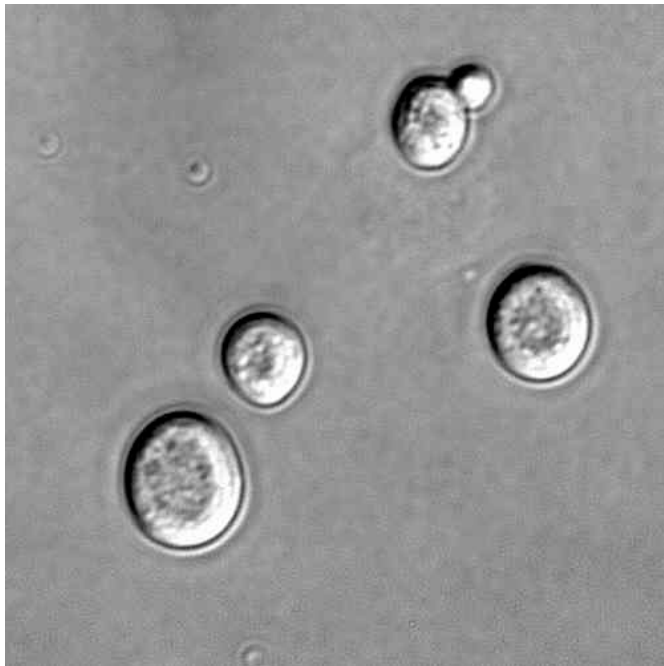




**If they ask you anything you don't know,  
just say it's due to epigenetics.**

# The advantages of being random?

## Saccharomyces cerevisiae



Blake WJ et al. Phenotypic consequences of promoter-mediated transcriptional noise. *Molecular Cell* 2006; 24: 853-65.

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Heaven scent . . . Sarah with spray

Chance from the subcellular to the biographical level

Chance at the ontological or epistemological level

Consider contralateral breast cancer

# Smoking and lung cancer

- lung cancer in cohort studies, pseudo-variance explained 5-10% at best
- lung cancer trends in US, 93% of variance (Whittmore 1989)
- geographical differences within US virtually all variance (Weinberg 1982)
- between-country differences ditto

# Lung cancer

- Heritable: 26%
- Shared environment 12%
- Non-shared environment 62%

Lichtenstein P, Holm MV, Verkasalo OK et al. Environmental and heritable factors in the causation of cancer. *N Engl J Med* 2000;**343**:78-85.

- Most traits have a non-trivial heritable component – good news in that genetic variants can tell us about modifiable causes
- Exposures with apparently small contributions in terms of variance explained can account for most cases of disease in a population
- Unstable aspects of non-shared environment may account for high proportions of the variance but are intractable; luckily they will often not be confounders
- Modifiable exposures that the genetic and shared environmental components are informative about are likely to be the appropriate group-level public health targets

# Mis-specifying individual risk of IHD: what to do?

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