Roadmap

- Administration:
  - Corrected version of lecture 14 notes is on website
  - Hand out homework!
- Correcting F_{ST} for allele frequency?
- h^2 and the response to selection
- Long-term breeding experiments
- "Missing heritability"

Can F_{ST} be normalized to its maximum?

- I was not able to find a paper doing this explicitly
- Touched on in: Alcala and Rosenberg (2017) Genetics
  - They showed that max(F_{ST}) depends on number of subpopulations as well as allele frequencies
  - Estimates of between-population variation using all continents at once higher than pairwise estimates
  - They note “paradoxical” F_{ST} values in many studies
- Work remains to be done here!

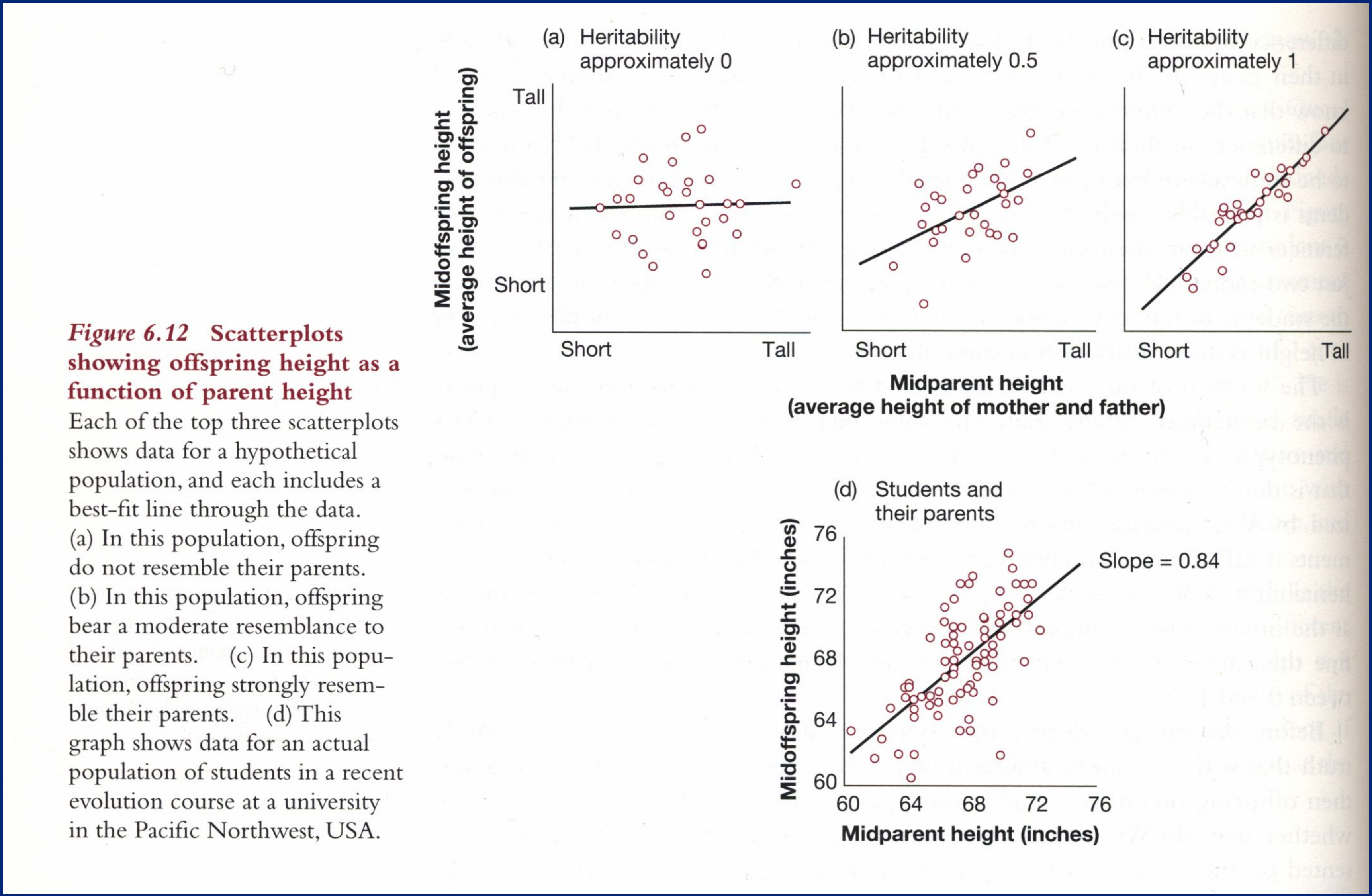
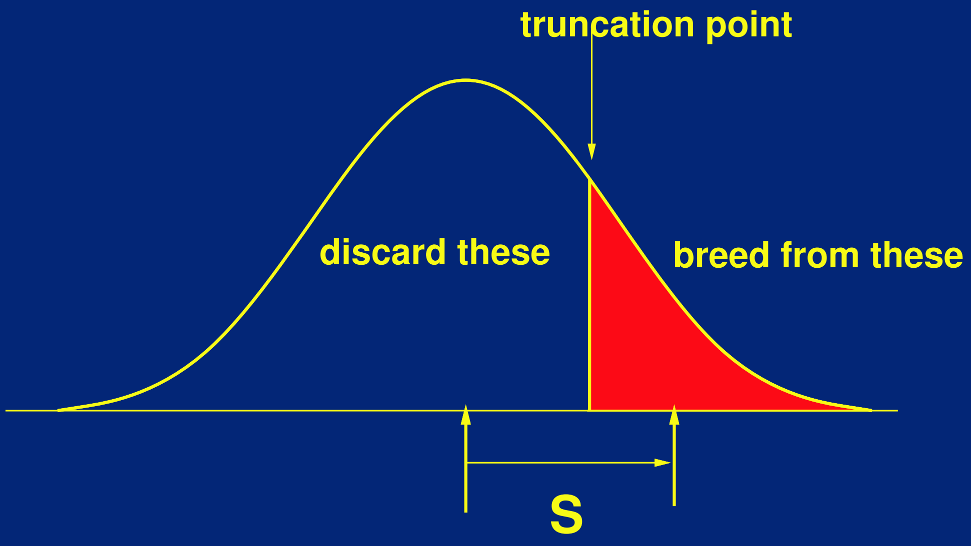


Figure 6.12 **Scatterplots showing offspring height as a function of parent height** Each of the top three scatterplots shows data for a hypothetical population, and each includes a best-fit line through the data. (a) In this population, offspring do not resemble their parents. (b) In this population, offspring bear a moderate resemblance to their parents. (c) In this population, offspring strongly resemble their parents. (d) This graph shows data for an actual population of students in a recent evolution course at a university in the Pacific Northwest, USA.

What is h^2 actually good for?

- Predict one-generation phenotype response to selection on the trait
- "Breeder's Equation": $R = h^2 S$
- R is the response (the change in offspring relative to parents)
- S is the selection, measured as the difference between mean trait of breeding stock and mean trait of population

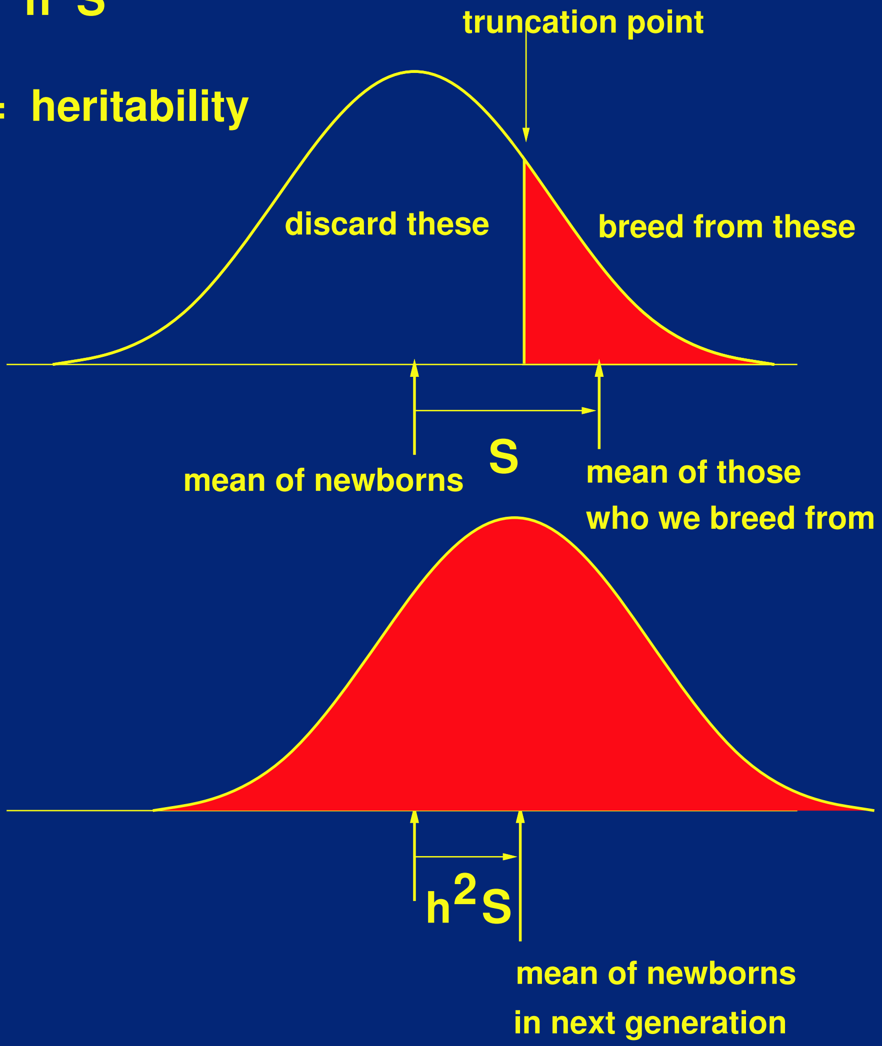
Selection differential S



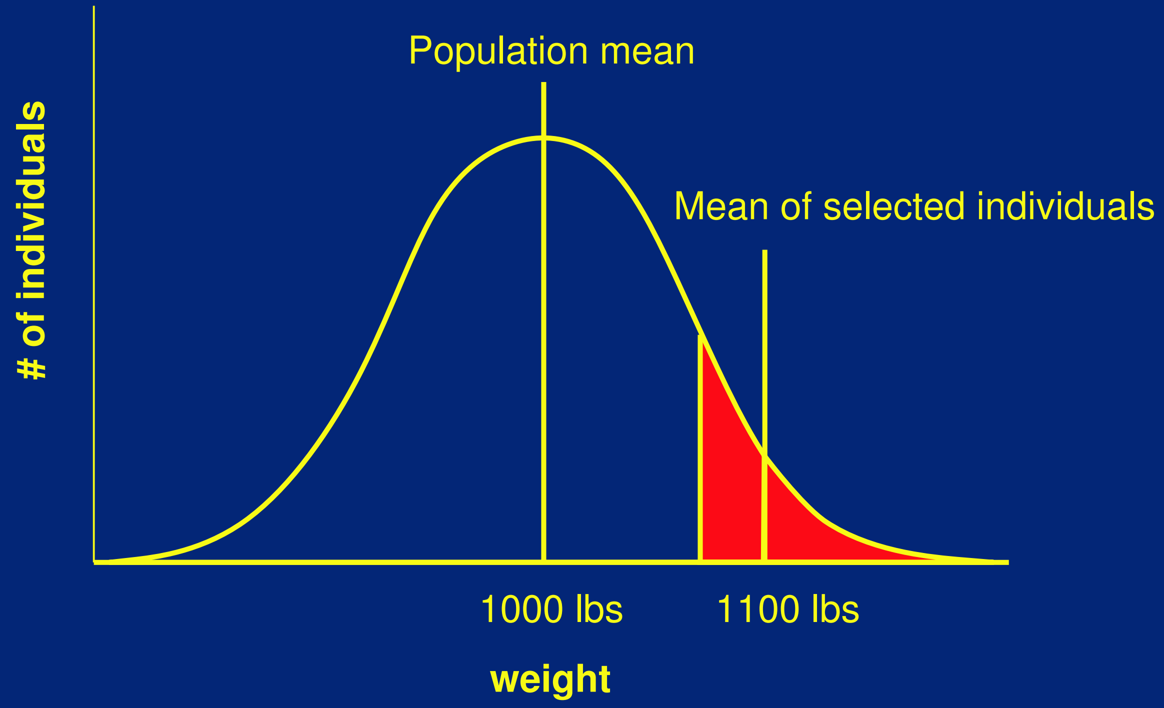
Response to artificial selection

$R = h^2 S$

h^2 = heritability



Possible gain per generation



If heritability = 0.4

S = selection differential

= mean of selected individuals - population mean = 100 lbs

R = gain

= h^2S = 40 lbs

This is the expected gain in one generation

Practice problem

- Sample wild corn with a mean of 100 kernals/ear and considerable variation
- Breed from ears with a mean of 150 kernals/ear
- Heritability of kernals/ear is 75%
- How many kernals/ear do I expect in 1 generation?

Practice problem

- We gain 37.5 kernals in 1 generation
- In 100 generations will we have corn with 3850 kernals/ear?
- Is there something wrong with our reasoning?

Long-term selection experiments

- Goal: find the limits of selection on a trait
- Strategies:
  - Continued directional selection
  - Relaxed selection (stop applying pressure)
  - Reversed selection (select in the opposite direction)
  - Replicate lines (assess impact of stochastic mutation)

University of Illinois corn [started in 1896] (OIL)

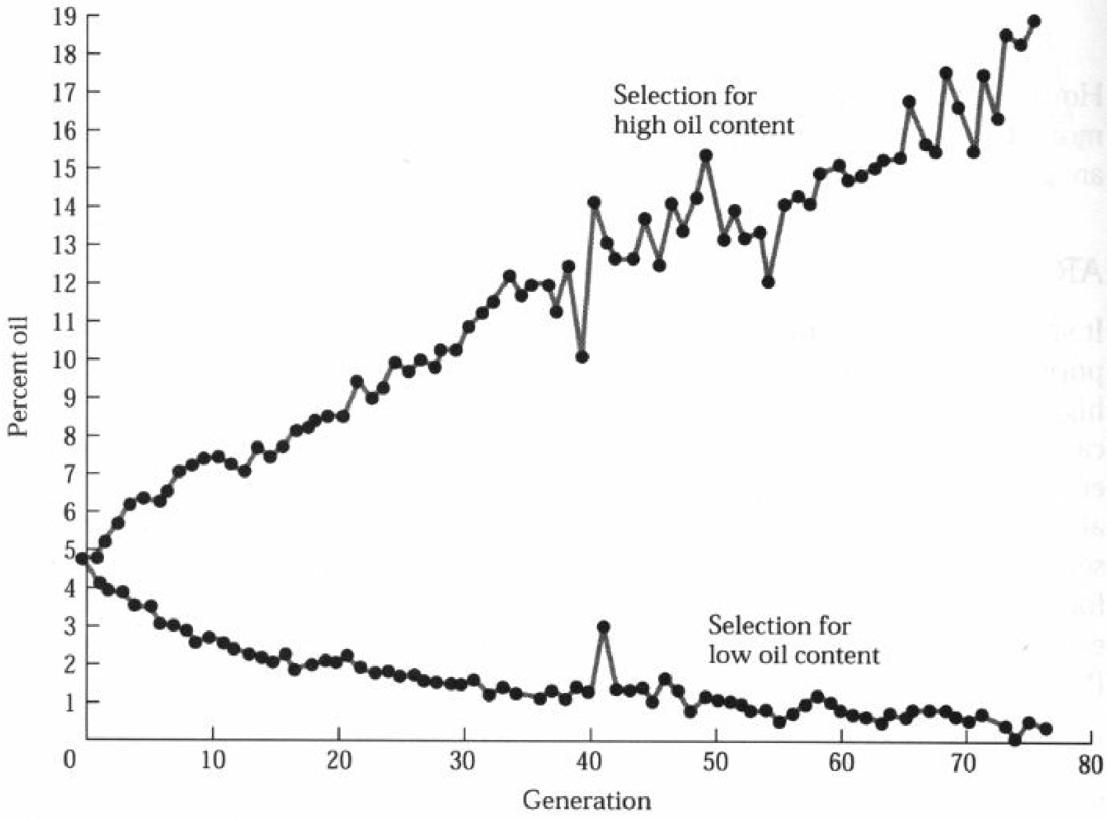
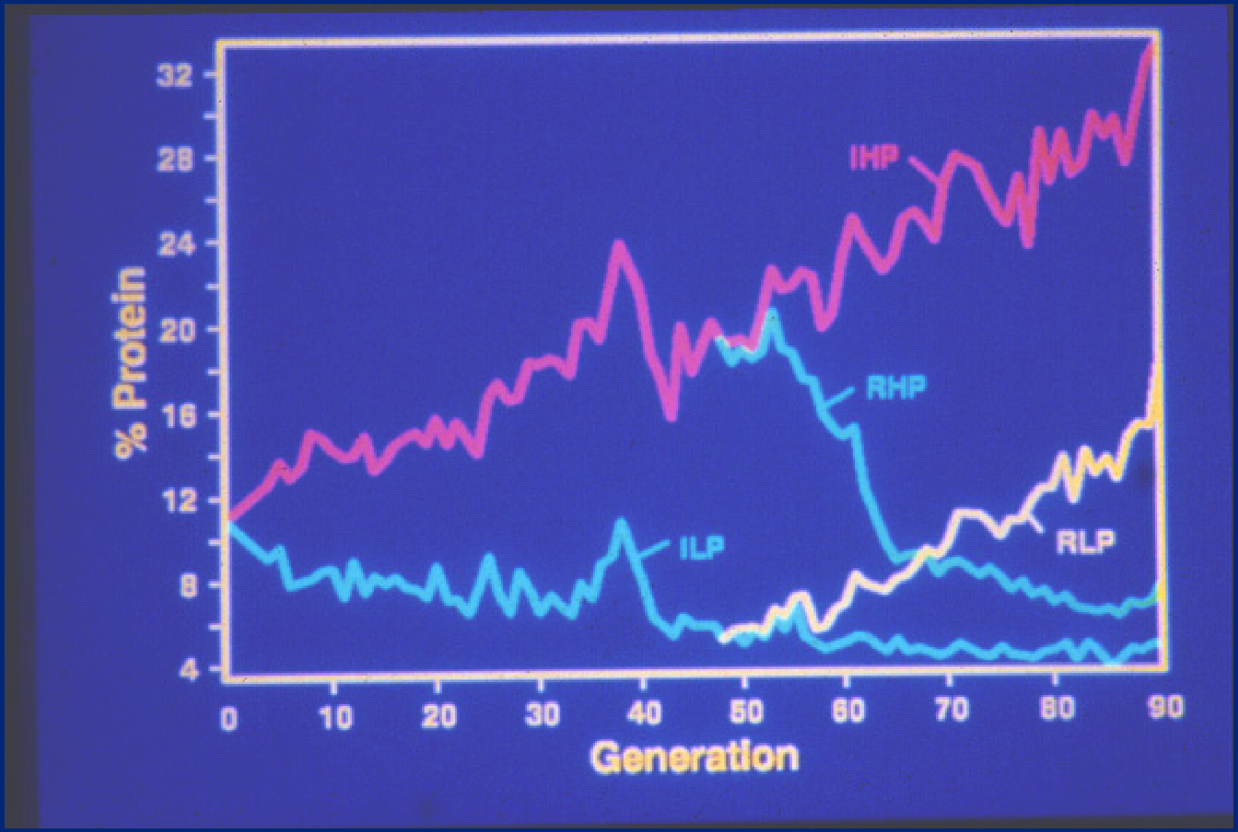


Figure 4.6 Results of a long-term experiment selecting for high and low oil content in corn seeds. Begun in 1896, the experiment has the longest duration of any on record and still continues at the University of Illinois. (After Dudley 1977.)

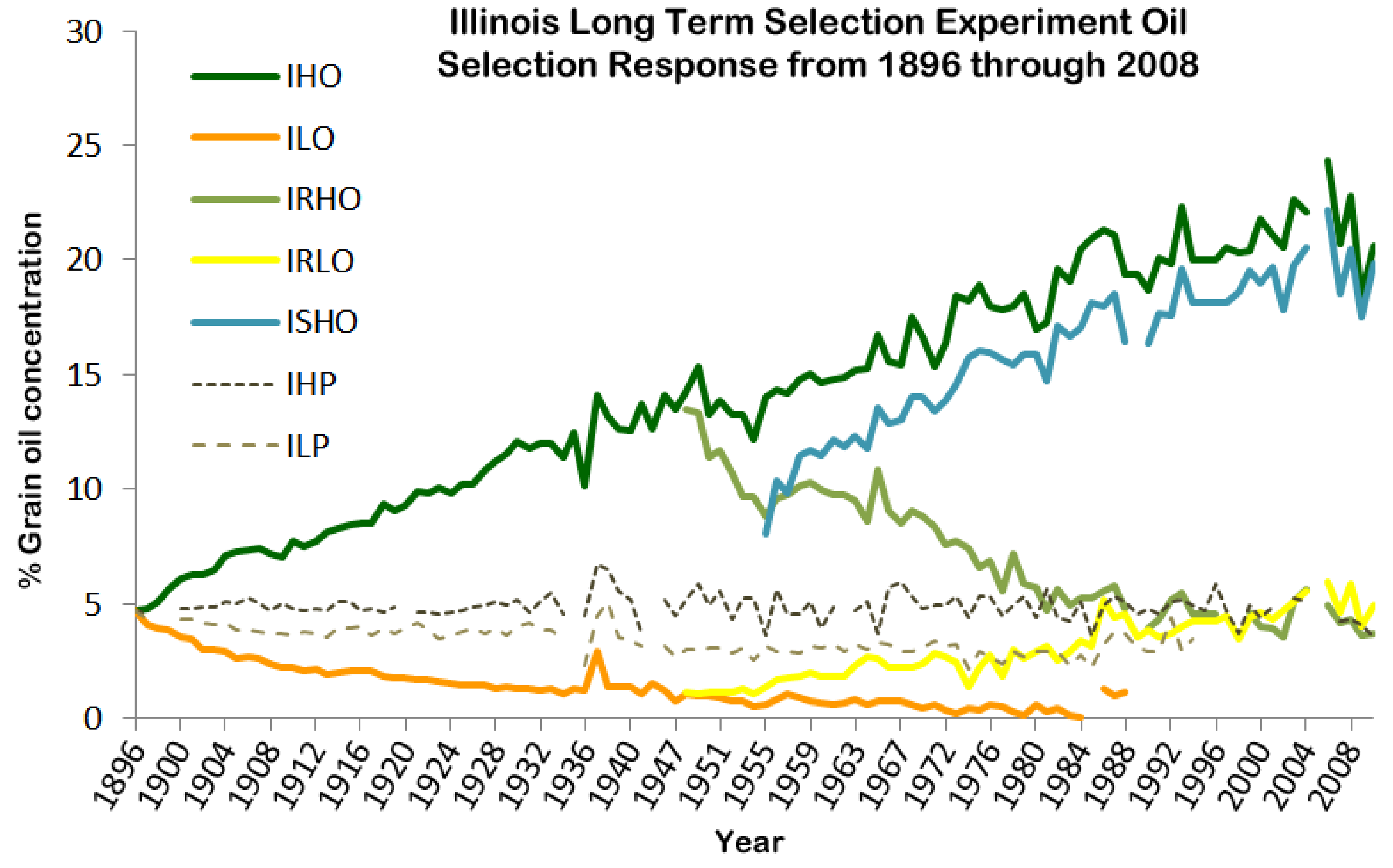
University of Illinois corn (PROTEIN)



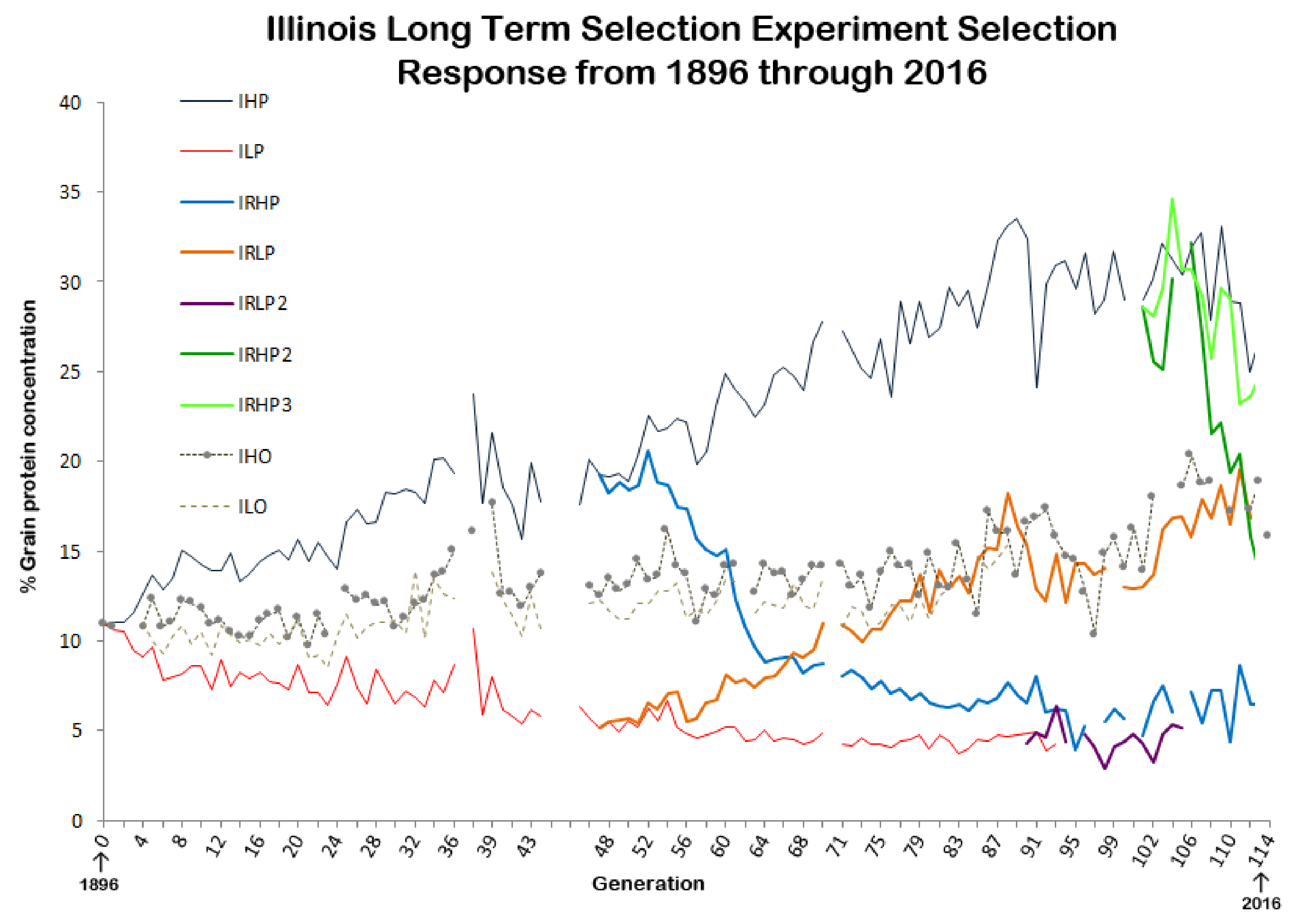
When selection falters

- Genetic variation exhausted
- Natural selection opposing artificial selection
- Remaining variation generates mainly V_D:
  - Dominance and (especially) overdominance
  - Unhelpful linkage disequilibrium
  - Unhelpful epistasis
- Environmental variation swamping V_A

Illinois Oil revisted



Illinois Protein revisited



Bristle number in Drosophila

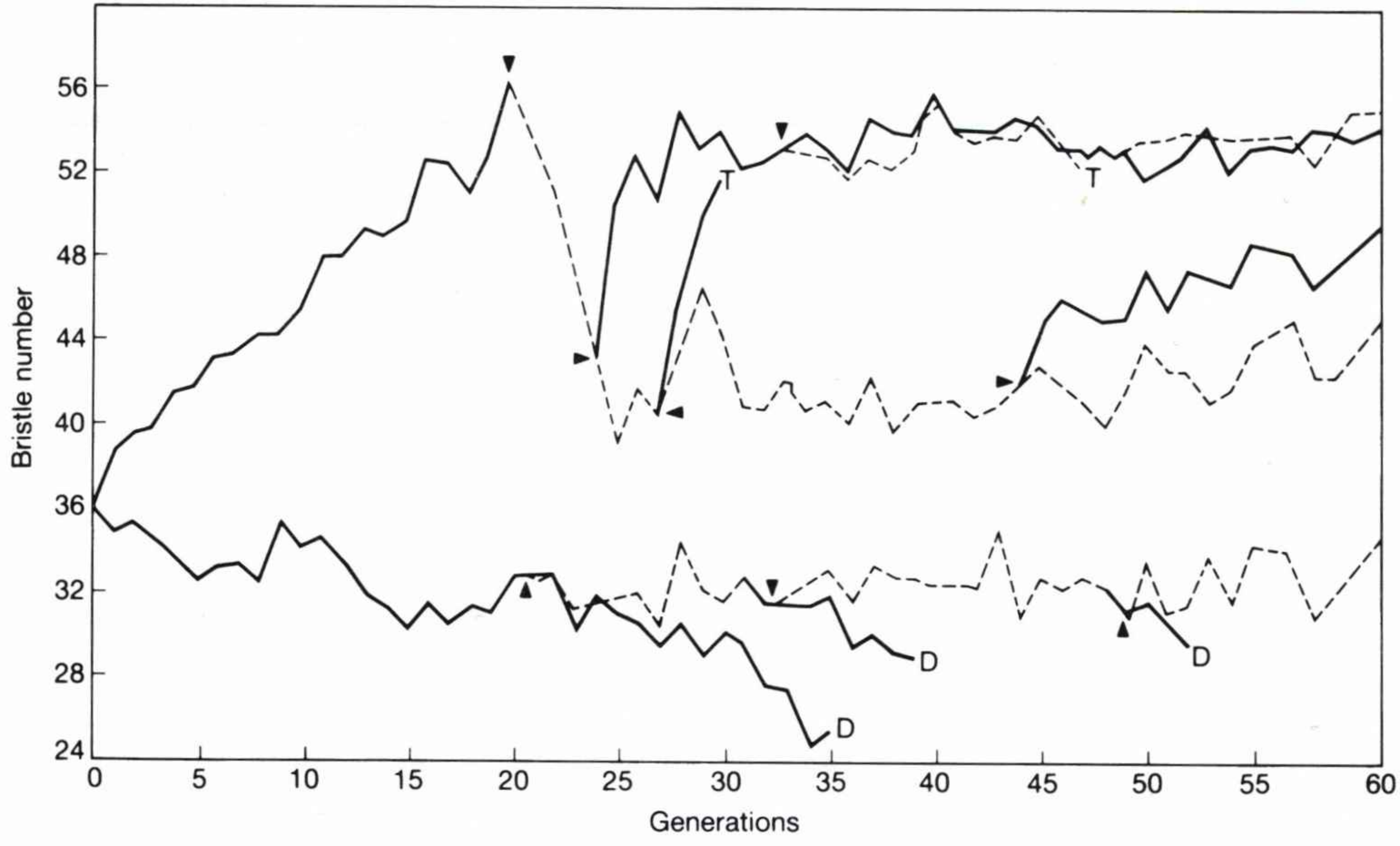


Figure 6.11 Response to selection for abdominal bristle number in *Drosophila melanogaster* (after Mather and Harrison 1949). Full lines, selected populations; broken lines, populations in which selection was relaxed; T, line terminated deliberately; D, line died out through infertility.

What strategies can show us

- Reverse selection: checks for exhaustion of variability
- Relax selection: checks for variability, opposing natural selection
- Replicate lines: separates stochastic from deterministic effects

You're never selecting just one trait

Estany et al. 2002

- Pigs selected for increased litter size:
  - Grew more rapidly at young ages
  - Slowed growth more with increasing age
  - Ate less frequently
  - Spent more time eating per "meal"
- These findings may represent:
  - Genetic correlations among traits (linkage)
  - Biological correlations (constraints)
  - Genetic drift in small populations

Missing heritability?

- Heritability of height in humans around 0.8
- Multiple family studies in different contexts
- GWAS hits explain only about 5% of height variance
- Where is the rest?

Visscher (2008)

- Three GWAS on human height
- 14K-34K initial survey, 6K-20K validation studies
- 54 SNPs robustly associated with height variation
- Mean effect size 0.4 cm per “increasing” allele (near the lower limit of detection)
- Poor agreement between studies–underpowered?
- “It remains a challenge to reconcile the findings of GWAS and linkage studies, because the former suggest individual variants with small effects, whereas the latter suggest genomic regions with large effects within pedigrees.”

Estimates of heritability and number of loci for complex traits

Adapted from Maniolo et al. (2010) Nature 461.

Trait	Known loci	Heritability explained
Age-related macular degeneration	5	50%
Crohn's disease	32	20%
Lupus	6	15%
Type 2 diabetes	18	6%
HDL cholesterol	7	5.2%
Height	40	5%
Early onset myocardial infarction	9	2.8%
Fasting glucose	4	1.5%

Brainstorm: where is the missing heritability?

Some possibilities

- Lurking places:
  - Many variants of very small effect
  - Variants of large effect, but extremely rare
  - Structural variants and other hard-to-type variation
  - Epigenetics
  - Epistasis/gene interactions
- Issues with GWAS approach:
  - Sample size
  - Reliance on LD
  - V_{GE}
  - Chip design (common SNPs only)

Monday

- Sex linkage
- Sex ratio
- Sex determination

One-minute responses

- Please:
  - Tear off a slip of paper
  - Give me one comment or question on something that worked, didn't work, needs elaboration, etc.