

# A not-well-known Lionel Penrose - Ronald Fisher collaboration

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UCC Mathematical Sciences Seminar Series

# OUTLINE

- ▶ Down Syndrome: what it is; epidemiology
- ▶ 1933 (Mother's age? Father's Age?) **CHANCE 2025**
  - ▶ Penrose J Gen., 1933: Relative Effects of Parental Ages
    - data, two analyses, no mention of input from Fisher
  - ▶ Sudoku 2014-2023: Reconstructing  $42 \times 31 \times 2$  Table
    - Initial surprises
    - What does/does not vary across multiple solutions
    - Sufficiency, various fits
- ▶ 1934 (Mother's age? Birth Order?) **Biometrika 2024**
  - ▶ Penrose Proc. R. Soc. Lond. B, 1934 results
  - ▶ Penrose Ann. Eugen, 1934 Fisher / cond'nal logistic regn.
  - ▶ Archives UCL/Adelaide Penrose-Fisher collaboration

[\[ Go to my other webpage on Penrose & the first conditional logistic regression \]](#)

## 'Statistical Sudoku' Challenge: splitting the Penrose frequency table

This table is from the 1933 article *'The relative effects of paternal and maternal age' in Down's syndrome* by the geneticist Lionel Penrose.

The row totals at the right of the table contain the paternal-age-specific frequencies for the 'Normal' (N) and Down's children (D) separately. Likewise, the columns totals at the bottom contain separate maternal-age-specific frequencies for the 'Normal' and Down's children.

However, the frequencies in the body of the table are the **sums** of the frequencies of Normal and Down's cases.

The **CHALLENGE** is to split each row-column-specific sum into the frequency of N and the frequency of D cases.

Summary of data

150 Families

Maternal Age (q)

N = Normal; D = Down's

	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40	41	42	43	44	45	46	47	N	D
17	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
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2023

Prob[Down Syndrome | Parents' Ages]:

Statistical Sudoku and Analyses of Penrose's Data (J. Genetics 1933)

[2023.11.22 Presentation by J. Hanley And S. Roy, McGill Biostatistics Seminar Series](#)

[ .mp4 video : \*Penrose's daughter Shirley, born in London, Ontario, appears from London, England in last few frames ]

2025

[R code to read in Penrose's data and generate 'Sudoku' solution sets](#)

Article in CHANCE magazine: [Lionel Penrose's statistical consultant: and lessons from the statistical 'sudoku' they left us](#)

[Appendices to manuscript](#)

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[\[ Go to my other webpage on Penrose & the first conditional logistic regression \]](#)

**Material related to [Biometrika 2024 article](#) on the conditional logistic regression fitted by Lionel Penrose and Ronald Fisher in 1934.**

**1934 Articles**

- \* [The relative aetiological importance of birth order and maternal age in mongolism.](#)

Penrose LS. Proceedings of the Royal Society B 115 431-450.

- \* [A method of separating the relative aetiological effects of birth order and maternal age, with specific reference to mongolian imbecility.](#)

Penrose LS. Annals of Eugenics 6 108-132.

**Data set**

- \* [Penrose's 1934 Data: 217 sibships with at least one child with DS \(.csv\)](#)

The dataset was reconstructed from the appendices to the two 1934 articles.

It has information on 224 affected children (the no. reported in the articles), but on 806 unaffected children (rather than the 807 reported)

**Archives**

- \* [Birth Order and Down's syndrome Correspondence](#) at Wellcome Library

- \* [Penrose Papers](#) at UCL Digital Collections

- \* [R A Fisher Correspondence Files](#) at University of Adelaide

- \* [Penrose's diary account of the family tour of North America in 1958](#)

before the 10th International Congress of Genetics at McGill University, and the [conferring of an honorary doctorate](#) (last few slides)

- \* [Penrose's diary account of his 1964 visit to the USA](#), where (in NYC) he received the [Joseph P. Kennedy Jr. Foundation's International Award from LBJ](#)

- \* First [Awards ceremony \(1962\)](#), where the awards were presented by [JFK](#).

**Material related to**

**"The first conditional logistic regression and the first nested case-control study"**

McGill Biostatistics Seminar Series, 2024.11.27

**Presentation**

[video](#) | ['slides'](#) [lyrics](#) (these include some material not in video/audio)

**Background:**

- \* Reviews: [Cole-1979](#) [Liddell-1988](#) [Breslow-1996](#) [Doll-2001](#) [Breslow-2007](#)

- \* Articles:

**Webinar presentation**

**"A not-well-known Lionel Penrose - Ronald Fisher collaboration"**

Sponsored by CHANCE magazine and the ASA History of Statistics Interest Group

September 24, 2025

[video, to be added](#) | ['slides'](#) | [lyrics](#)



# Why we are telling these two stories ...

- ▶ Epidemiology/genetics/statistics/optimization/history
- ▶ Opportunity to reflect on
  - 90 years of growth in statistical methods/computing
  - what we have forgotten along the way
  - sufficient statistics and data privacy/disclosure
  - ‘let the analysis fit the design’
  - ML fitting of a conditional logistic regression in 1934

# Down syndrome

🌐 87 languages ▾

Article [Talk](#)

[Read](#) [View source](#) [View history](#) [Tools ▾](#)

From Wikipedia, the free encyclopedia



**Down syndrome** or **Down's syndrome**, also known as **trisomy 21**, is a [genetic disorder](#) caused by the presence of all or part of a third copy of [chromosome 21](#).<sup>[3]</sup> It is usually associated with [developmental](#) delays, mild to moderate [intellectual disability](#), and characteristic physical features.<sup>[1]</sup><sup>[12]</sup> There are three types of Down syndrome, all with the same features: Trisomy 21, the most common type; Mosaic Down syndrome, and Translocation Down syndrome.<sup>[13]</sup><sup>[14]</sup>

The parents of the affected individual are usually [genetically](#) normal.<sup>[15]</sup> The probability increases from less than 0.1% in 20-year-old mothers to 3% in those of age 45.<sup>[4]</sup> The extra chromosome is provided at conception as the egg and sperm combine.<sup>[16]</sup> A very small percentage of 1-2% gets the additional chromosome in the embryo stage and it only impacts some of the cells in the body; this is known as Mosaic Down syndrome.<sup>[17]</sup><sup>[18]</sup> Usually, babies get 23 chromosomes from each parent for a total of 46, whereas in Down syndrome, a third 21st chromosome is attached.<sup>[18]</sup> It is believed to occur by chance, with no known behavioral activity or environmental factor that changes the probability.<sup>[2]</sup> Down syndrome can be identified during pregnancy by [prenatal screening](#), followed by diagnostic testing, or after birth by direct observation and [genetic testing](#).<sup>[6]</sup> Since the introduction of screening, Down syndrome [pregnancies](#) are often [aborted](#) (rates varying from 50 to 85% depending on maternal age, gestational age, and maternal race/ethnicity).<sup>[19]</sup><sup>[20]</sup><sup>[21]</sup>

There is no cure for Down syndrome.<sup>[22]</sup> Education and proper care have been shown to provide good [quality of life](#).<sup>[7]</sup> Some children with Down syndrome are educated in typical school classes, while others require more [specialized education](#).<sup>[8]</sup> Some individuals with Down syndrome graduate from [high school](#), and a few attend [post-secondary education](#).<sup>[23]</sup> In adulthood, about 20% in the United States do paid work in some capacity,<sup>[24]</sup> with many requiring a sheltered work environment.<sup>[8]</sup> Support in financial and legal matters is often needed.<sup>[10]</sup> Life expectancy is around 50 to 60 years in the [developed world](#), with proper health care.<sup>[9]</sup><sup>[10]</sup> Regular [screening](#) for health issues common in Down syndrome is recommended throughout the person's life.<sup>[9]</sup>

## Down syndrome

**Other names**

Down's syndrome, Down's, trisomy 21



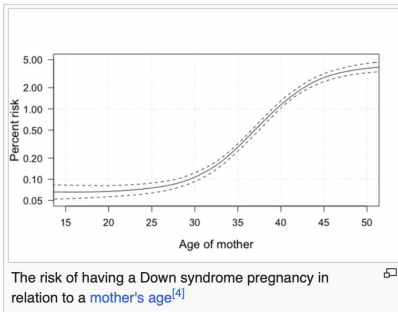
An eight-year-old boy displaying characteristic facial features of Down syndrome

**Specialty** [Medical genetics](#), [pediatrics](#)

# Epidemiology

Down syndrome is the most common chromosomal abnormality in humans.<sup>[9]</sup> Globally, as of 2010, Down syndrome occurs in about 1 per 1,000 births<sup>[1]</sup> and results in about 17,000 deaths.<sup>[132]</sup> More children are born with Down syndrome in countries where abortion is not allowed and in countries where pregnancy more commonly occurs at a later age.<sup>[1]</sup> About 1.4 per 1,000 live births in the United States<sup>[133]</sup> and 1.1 per 1,000 live births in Norway are affected.<sup>[9]</sup> In the 1950s, in the United States, it occurred in 2 per 1,000 live births with the decrease since then due to prenatal screening and abortions.<sup>[92]</sup> The number of pregnancies with Down syndrome is more than two times greater with many spontaneously aborting.<sup>[10]</sup> It is the cause of 8% of all [congenital disorders](#).<sup>[1]</sup>

[Maternal age](#) affects the chances of having a pregnancy with Down syndrome.<sup>[4]</sup> At age 20, the chance is 1 in 1,441; at age 30, it is 1 in 959; at age 40, it is 1 in 84; and at age 50 it is 1 in 44.<sup>[4]</sup> Although the probability increases with maternal age, 70% of children with Down syndrome are born to women 35 years of age and younger, because younger people have more children.<sup>[4]</sup> The [father's older age](#) is also a risk factor in women older than 35, but not in women younger than 35, and may partly explain the increase in risk as women age.<sup>[134]</sup>



## Lionel Penrose



**Born** Lionel Sharples Penrose  
11 June 1898<sup>[1]</sup>  
[London, UK](#)<sup>[3]</sup>

**Died** 12 May 1972 (aged 73)  
London, UK

**Alma mater** [St John's College, Cambridge](#)  
[University of Vienna](#)  
[King's College London](#)

**Known for** [Penrose triangle](#)  
[Penrose method](#)  
[Penrose stairs](#)<sup>[4]</sup>  
[Penrose's Law](#)<sup>[5][6]</sup>  
[Penrose square root law](#)  
[Penrose–Banzhaf index](#)

**Spouse** [Margaret Leathes](#) (m. 1928)

**Children** [Oliver Penrose](#)  
[Roger Penrose](#)  
[Jonathan Penrose](#)  
[Shirley Hodgson](#)

**Awards** [Fellow of the Royal Society](#)<sup>[1]</sup>  
[Lasker Award](#)<sup>[2]</sup>  
[James Spence Medal](#) 1964.

### **Scientific career**

**Fields** [Pediatrics](#), [Psychiatry](#), [Genetics](#)

**Institutions** [University of Cambridge](#)  
[University College London](#)

# Journal of Genetics, 1933

Journal of Genetics, 1933

THE RELATIVE EFFECTS  
OF PATERNAL AND  
MATERNAL AGE IN  
DOWN'S SYNDROME

BY L.S. PENROSE, M.D.\*

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In the human species ages of the parents are so closely correlated that it is difficult to separate the effects of the two elements. Hitherto attempts maternal age is of more aetiological importance than the paternal age. For example, a serious attempt to solve the problem was made in 1927 by Van der Scheer<sup>2</sup>, who compared the relative percentages of 316 Down's syndrome children born at various maternal ages with the percentages of normal children born to mothers of equivalent ages in a very large series of families gathered from the general population. The resulting ratios showed a very marked increase in the incidence of affected children as the age of the mother increased, and also a similar, though not quite so marked, rise of the incidence with increasing paternal age.

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**BACK THEN**, the use of a (Pearson) **CORRELATION** between a **binary (0/1) Y** and a **quantitative X** was **COMMON**.

# Material

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The present writer has attempted a **similar treatment** of 150 families of the human species containing **Down's syndrome among the children.**

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The present writer has attempted a **similar treatment** of 150 families of the human species containing **Down's syndrome among the children**.

Every family included was visited personally and, among other things, the **ages of the parents at the birth of each child** was carefully recorded: miscarriages and all individuals in whom a **diagnosis of normality or Down's syndrome** could not be made with certainty were excluded.

No obvious disparity was observed between the ages of the parental pairs, which were distributed in a manner resembling that found by pooling all married couples in the general population.

		150 Families																														N = Normal; D = Down's				
		Maternal Age (q)																																		
Paternal age (p)		17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40	41	42	43	44	45	46	47	N	D		
17	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	1	.	
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21	.	.	1	2	2	.	.	.	.	.	1	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	6	.	
22	.	.	.	1	4	3	.	1	.	.	.	.	.	.	.	.	.	1	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	8	2	
23	.	.	2	1	1	2	3	1	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	8	2	
24	.	.	.	.	2	3	4	5	2	1	.	.	.	1	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	16	2	
25	.	.	.	1	2	.	4	6	7	4	4	.	2	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	27	3	
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29	1	.	.	.	.	.	2	1	3	1	3	3	6	2	1	2	1	.	.	.	.	.	.	.	1	.	.	.	.	.	.	.	.	25	2	
30	.	1	.	.	.	.	.	2	3	4	2	5	4	5	1	1	1	2	1	.	.	.	.	.	.	1	.	.	.	.	.	.	.	31	2	
31	.	.	1	.	1	.	1	.	4	3	4	3	3	6	7	3	4	1	2	.	.	.	.	.	.	.	.	.	.	.	.	.	.	39	4	
32	.	.	.	1	.	.	.	1	.	1	1	2	1	5	4	6	2	2	1	.	.	.	.	1	.	.	.	.	.	.	.	.	.	26	2	
33	.	.	.	.	1	.	1	1	.	.	2	3	5	4	3	1	5	1	1	2	.	1	.	.	.	.	.	.	.	.	.	.	.	28	3	
34	.	.	.	.	1	.	.	.	.	.	1	.	.	.	5	.	8	5	2	1	1	2	.	.	.	1	.	.	.	.	.	.	.	30	2	
35	.	.	.	.	.	.	.	.	.	.	1	.	.	1	1	3	3	4	6	10	4	3	3	1	.	.	.	.	.	.	.	.	.	33	7	
36	.	.	.	.	.	.	1	2	.	.	.	2	.	.	.	6	2	3	3	4	5	1	3	.	2	.	.	.	.	.	.	.	.	32	2	
37	.	.	.	.	.	.	.	1	.	.	.	.	1	.	1	2	6	2	5	2	9	2	2	1	1	1	.	.	.	.	.	.	.	27	9	
38	.	.	.	.	.	.	.	.	1	1	.	.	2	.	.	1	2	2	2	4	5	4	1	2	2	.	.	.	.	.	.	.	.	21	8	
39	.	.	.	.	.	.	.	1	.	2	1	.	.	.	.	1	.	2	4	6	2	2	2	7	1	.	1	1	.	.	.	.	.	25	8	
40	.	.	.	.	.	.	.	.	.	.	.	.	1	.	1	1	.	1	3	1	.	2	3	4	3	2	1	1	.	.	.	.	.	17	7	
41	.	.	.	.	.	.	.	.	.	.	.	.	.	.	1	1	.	.	.	1	2	.	.	3	4	4	1	1	.	.	.	.	.	10	8	
42	.	.	.	.	.	.	.	.	.	.	.	.	.	1	1	.	.	2	.	.	2	6	2	3	3	2	.	1	.	1	.	.	.	9	15	
43	.	.	.	.	.	.	.	.	.	.	.	.	1	.	.	.	.	.	1	.	1	3	1	3	3	4	3	2	.	.	.	.	.	11	11	
44	.	.	.	.	.	.	.	.	.	.	.	.	.	.	1	.	.	.	1	.	1	2	3	5	1	3	1	2	.	.	.	.	.	11	9	
45	.	.	.	.	.	.	.	.	.	.	.	.	.	1	.	2	1	.	1	1	2	.	1	1	1	.	3	3	3	2	.	.	15	7		
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47	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	2	2	.	.	.	.	.	.	1	5	.	.	2	1	.	.	7	6	
48	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	1	.	1	1	.	.	2	1	1	1	1	.	.	2	1	6	6			
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N	1	2	5	8	13	11	22	31	25	31	31	22	30	36	32	32	35	27	35	21	21	22	21	16	10	9	6	5	8	4	3	573				
D	.	.	2	1	3	2	3	1	.	3	4	2	1	.	2	2	6	7	9	5	9	11	10	13	15	16	8	7	4	5	1		154			



**Correlations** obtained from data summarised in Table I:

D = Indicator (0/1) of Down's syndrome

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D = Indicator (0/1) of Down's syndrome

$r(D, \text{Father'sAge})$

**+0.294**  $\pm$  0.034

$r(D, \text{Mother'sAge})$

**+0.362**  $\pm$  0.032

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$r(D, \text{Mother'sAge})$

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$r(\text{Father'sAge}, \text{Mother'sAge})$

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$r(\text{Father'sAge}, \text{Mother'sAge})$

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**PARTIAL Correlations** ( $r_p$ )

**Correlations** obtained from data summarised in Table I:

D = Indicator (0/1) of Down's syndrome

$$r(D, \text{Father's Age})$$
$$+0.294 \pm 0.034$$

$$r(D, \text{Mother's Age})$$
$$+0.362 \pm 0.032$$

$$r(\text{Father's Age}, \text{Mother's Age})$$
$$+0.829 \pm 0.012$$

**PARTIAL Correlations** ( $r_p$ )

$$r_p(D, \text{Father's Age})$$

eliminating Mother's Age

$$-0.011 \pm 0.04$$

$$r_p(D, \text{Mother's Age})$$

eliminating Father's Age

$$+0.221 \pm 0.04$$

**M = MOTHER'S AGE**

150 Families

Maternal Age (q)

N = Normal; D = Down's

**D**  
0 1

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**F = FATHER'S AGE**

$$r(F, M) = 0.829$$

**r(D, F)**

$$= 0.294$$

$$r(D, M) = 0.362$$

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It is not, however, necessary to use this technique to demonstrate the various points,

and the **following method is at once clearer and more precise.**”

Observed (& 'expected') mean parental ages  
of Down's vs Normal children

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	Father			Mother	
	Obs.	Exp.		Obs.	Exp.
Down's	39.383	39.471		37.253	35.712
<u>Normal</u>	<u>33.830</u>	<u>33.803</u>		<u>31.249</u>	<u>31.680</u>
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"There can be little doubt, judging from these results, which confirm those obtained by the partial correlation technique, that the father's age is an insignificant factor in the aetiology of Down's syndrome, the emphasis being entirely on the age of the mother."

Penrose consults Fisher: 1932



# Penrose consults Fisher: 1932



Royal Eastern Counties' Institution  
for the Mentally Defective,  
Colchester.

29th October 1932

Dear Dr Fisher,

I have been working out some statistical results in connection with maternal and paternal age and their relative effects in [REDACTED]. Taking the first 50 families available I have obtained the following results :-

---

$r_1$ , Maternal age and incidence of [REDACTED], = .44

$r_2$ , Paternal age and incidence of [REDACTED], = .34

$r_3$ , Maternal age & paternal age (for every child in each family) = .73

Partial correlation  $r_1$  (eliminating paternal age) = .30

Partial correlation  $r_2$  (eliminating maternal age) = .03

There are in all 237 children, among whom there are 52 [REDACTED], in these families, and [REDACTED] is correlated with maternal and paternal age in  $r_1$  and  $r_2$

There are in all 237 children, among whom there are 52 [REDACTED], in these families, and simply  $r_1$  and  $r_2$  correlated with maternal and paternal age in  $r_1$  and  $r_2$ .

The question I want to ask you is, how many families will be required to give significance to these results, which appear to show that maternal age is of importance but paternal age insignificant? I have available nearly 200 families and have every reason to suppose that similar figures will be obtained from the whole group to those I have found in the first 50 families. The question of significance is rather troublesome because I am not sure what the effect is of having several of the children in the same family and am doubtful whether the ordinary methods of finding the standard deviations of these coefficients are applicable here. If you think that about 180 families would give a significant result, it seems to me that it is an elegant method of demonstrating what has been rather a vexed question for some time.

Please excuse my bothering you in this way, but technical points of this kind frequently arise in my work and it is a very great help to have your advice on such matters.

Yours sincerely

31 October 1932.

Dr. L. Penrose,  
Royal Eastern Counties' Institution,  
Colchester.

Dear Dr. Penrose:

I do not understand what is the variate you call incidence of [REDACTED]. As far as I can see you have two observed two-way distributions of Mothers' age ( $x$ ) and Fathers' age ( $y$ ), one for [REDACTED] and one for normals.

These supply a common value (based on pooled products) of the regression of Fathers' age on Mothers' age, i.e. of  $y$  on  $x$ :

$$Y = bx + c.$$

— { You wish to compare  $\bar{x}$  for [REDACTED] with  $\bar{x}$  for normals, and this is a straight  $t$  test.

— { Equally you can compare  $\bar{y} - b\bar{x}$  for [REDACTED] v. normals, with a known standard error.

2014

# Regression-type models for 'imaginary' response variates: 1933-

[ \* Fisher's derogatory term for BINARY variates used in a Pearson correlation ]

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[ \* Fisher's derogatory term for BINARY variates used in a Pearson correlation ]

1936	Fisher	The Use of Multiple Measurements in Taxonomic Problems. (LDA) Ann. Eugenics.
1952	Duncan, Rhodes	Multiple [Probit] Regression with a Quantal Response (Meeting Abstract)
1955	Berkson	Max. likelihood and min. $\chi^2$ estimates of the logistic function (JASA)
1958	Cox	The regression analysis of binary sequences (JRSS-B)
1962	Cornfield	Joint dependence of risk of CHD on ... : a discriminant function analysis (Fed. Proc)
1966	Cox	Some procedures connected with the logistic qualitative response curve. (Essays)
1967	Cornfield, Kannel	Multivariate Analysis of Risk of Coronary Heart Disease in Framingham (JChronicDis)
1967	Walker, Duncan	Estimation of Probability of an Event as Function of Several Independent Variables (B'ka)
1972	Nelder, Wedderburn	Generalized Linear Models (JRSS-A)
1973	McFadden	Conditional logit analysis of qualitative choice behavior (Book Chapter, Economics)

Wed 2014-12-31 2:37 PM

Dear Dr Hanley,

Thank you for your interesting message.

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I have also written a paper commenting on this work of my father's. When I wrote it\* I was not aware of my father's correspondence with R A Fisher, and my paper may have other flaws as well — it was not refereed. It was published as A beautiful method of analysis in "Fifty years of human genetics: A Festschrift and liber amicorum to celebrate the life and work of George Robert Fraser", \*2007.

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Your "sudoku" problem appears to have **multiple solutions** in general. For example, suppose the **matrix** were

N    D            then the 6 solutions are

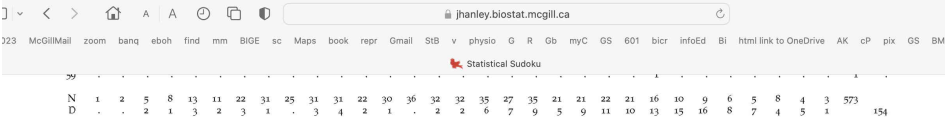
5	5	5	5	5,0	0,5	4,1	1,4	...	0,5	5,0
5	5	5	5	0,5	5,0	1,4	4,1	...	5,0	0,5

N	5	5
D	5	5

With best wishes for the new year

Oliver Penrose





It is easy to split a few of the small ( $N + D$ ) counts into their separate  $N$  and  $D$  components. e.g.  $N[18,18] = 1$ ;  $D[18,18] = 0$ . But for larger ( $N + D$ ) counts closer to the centre of the table, the task of splitting them into  $N$  and  $D$  becomes progressively more difficult.

Background

Down syndrome or Down's syndrome, also known as trisomy 21, is now known to be a genetic disorder caused by the presence of all or part of a third copy of chromosome 21. It is typically associated with physical growth delays, characteristic facial features, and mild to moderate intellectual disability.

Screenshot } [The relative effects of paternal and maternal age in Down's syndrome](#) by [Lionel Penrose](#), was published in the Journal of Genetics, May 1933, Volume 27, Issue 2, pp 219-224. This was before its genetic nature was known. Penrose was one of the first to establish that its frequency rate was a stronger function of maternal than paternal age, and (in a separate article in 1934) of [maternal age than birth order](#)

JH became aware of Penrose's work through the Wellcome Library's recent digitization of [The Lionel Penrose papers](#). These papers also contain extensive correspondence with statistician Ronald Fisher, a pioneer in statistical genetics.

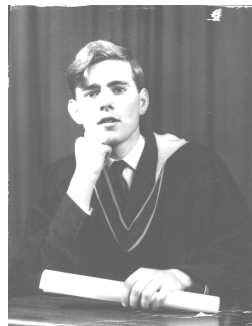
Lionel Penrose was the father of mathematician [Roger Penrose](#), chess Grandmaster [Jonathan Penrose](#), mathematician [Oliver Penrose](#) (who graciously provided JH with this [reconsideration of his father's 1933 work](#). [It appears as the chapter 'A beautiful method of analysis': O. Penrose, pp 443-451 in "Fifty years of human genetics: A Festschrift and liber amicorum to celebrate the life and work of George Robert Fraser", edited by Oliver Mayo and Carolyn Leach, ISBN 9781862547537, Wakefield Press, Adelaide, 2007]), and geneticist [Shirley Victoria Hodgson](#) (who graciously sent JH a copy of her father's book "Clinical and Genetic Study of 1280 Cases of Mental Defect: Colchester Survey").

James Hanley,  
Dept of Epidemiology, Biostatistics and Occupational Health,  
McGill University

[jhanley.biostat.mcgill.ca](#)



UNIVERSITY COLLEGE CORK  
Coláiste na hOllscoile Corcaigh



**BSc (Mathematics/Statistics) 1968**  
**MSc (Mathematics/Statistics) 1969**



# STATISTICAL SUDOKU

2023

Supratik Roy



15



15

19:21

57:18



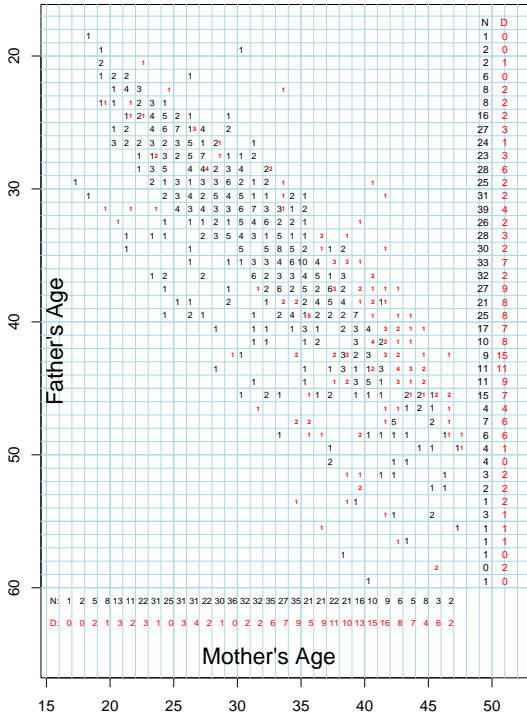
# SUDOKU !

# SUDOKU !

For each of the 325 cells,  
shown are the number of children

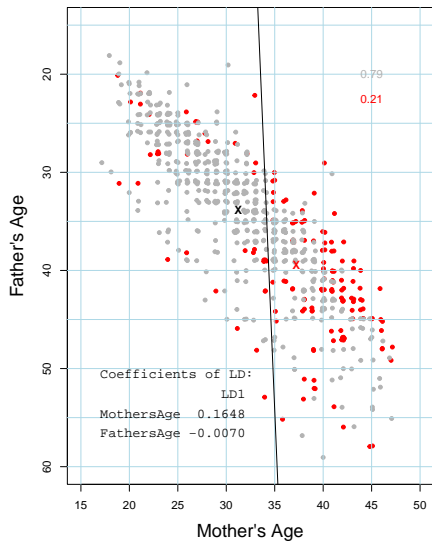
unaffected    affected

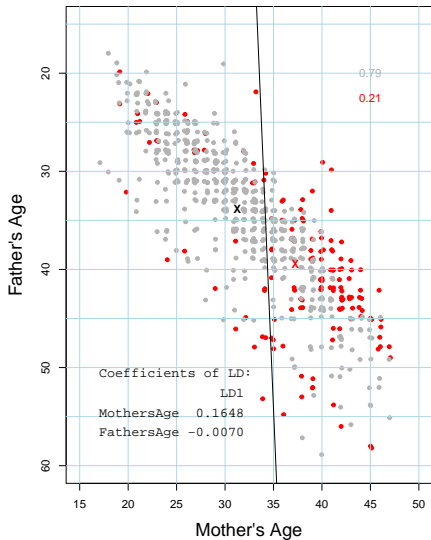
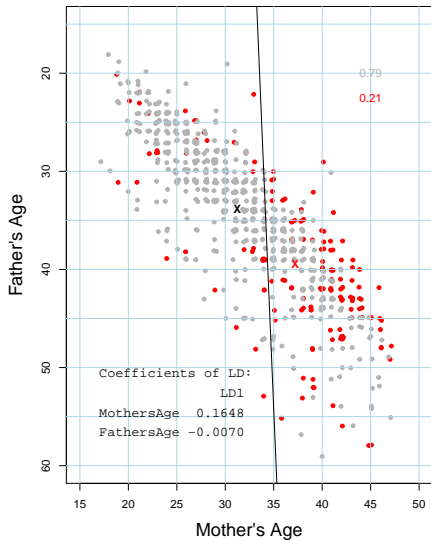


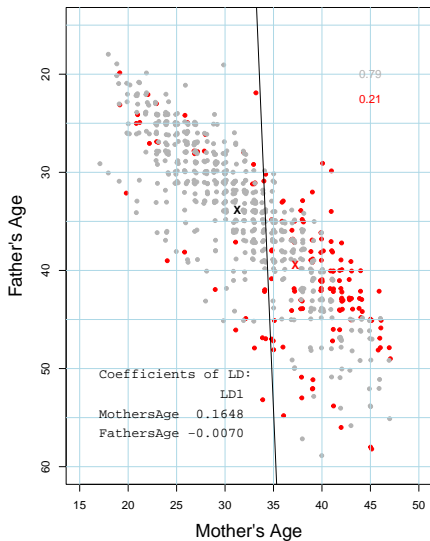
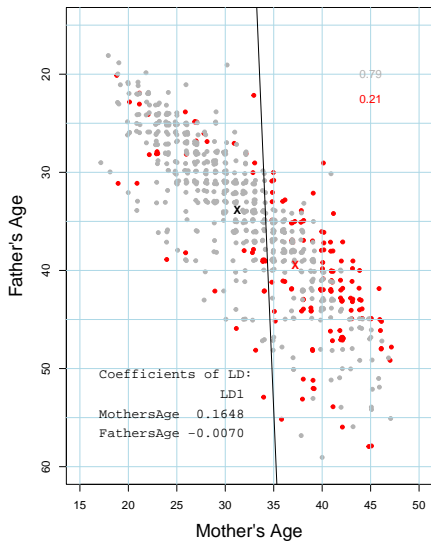


# JH's first analyses of 3-D datasets

- ▶ Linear Discriminant Analysis
- ▶ Logistic regression
- ▶ And the surprises he got!







LDA: Same fit no matter the solution !

# Logistic regression

```
glm(formula = Downs ~ ... , family = binomial)
```

Coefficients:

Estimate Std.Error z.value Pr(>|z|)

(Intercept)	-4.796	0.489	-9.80	< 2e-16	***
FathersAge	0.095	0.012	7.51	5.62e-14	***

(Intercept)	-6.526	0.610	-10.69	<2e-16	***
MothersAge	0.151	0.016	9.04	<2e-16	***

(Intercept)	-6.491	0.614	-10.57	< 2e-16	***
MothersAge	0.162	0.027	5.94	2.8e-09	***
FathersAge	-0.011	0.022	-0.51	0.604	

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- ▶ The three 2-D marginal tables that Penrose published were sufficient to derive his statistics.
- ▶ Recall Fisher on sufficiency and what use can be made of the remainder of the data.
- ▶ The 'Goodness of Fit' statistics DO vary from solution to solution; Penrose did not supply any G.o.F measure for his dataset. See webpage for SR's explorations of 11 solution sets.

What summary statistics are needed to fit a logistic regression?

# What summary statistics are needed to fit a logistic regression?

Example with 2 predictors,  $x$  (age of mother) and  $z$  (age of father)

$$P[D = 1] = \frac{e^{q_1(x) + q_2(z)}}{1 + e^{q_1(x) + q_2(z)}}, \quad P[D = 0] = \frac{1}{1 + e^{q_1(x) + q_2(z)}}.$$

$$L(\{d_{ijk}, x_i, z_j\}) = \prod_{i,j,k} \left( \frac{e^{q_1(x_i) + q_2(z_j)}}{1 + e^{q_1(x_i) + q_2(z_j)}} \right)^{d_{ijk}} \left( \frac{1}{1 + e^{q_1(x_i) + q_2(z_j)}} \right)^{1 - d_{ijk}}.$$

$$\begin{aligned} \log L &= \sum_{i,j} \left[ \sum_k d_{ijk} q_1(x_i) + \sum_k d_{ijk} q_2(z_j) - \sum_k \ln(1 + e^{q_1(x_i) + q_2(z_j)}) \right] \\ &= \sum_{i,j} \left[ d_{ij\bullet} q_1(x_i) + d_{ij\bullet} q_2(z_j) - f_{ij} \ln(1 + e^{q_1(x_i) + q_2(z_j)}) \right] \end{aligned}$$

where  $f_{ij}$  is the total number of observations in the  $(i, j)$ -th cell, and  $q_1$  and  $q_2$  are unknown functions of  $x$  and  $z$ .

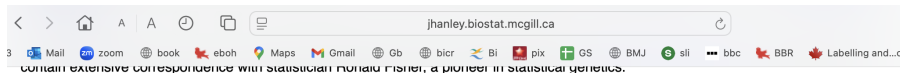
$$= \underbrace{\sum_i d_{i\bullet\bullet} q_1(x_i)} + \underbrace{\sum_j d_{\bullet j\bullet} q_2(y_j)} - \sum_{i,j} f_{ij} \sum_k \ln \left( 1 + e^{q_1(x_i) + q_2(y_j)} \right).$$

- ▶ For the Penrose data set, we have the marginals  $d_{i\bullet\bullet}$ ,  $d_{\bullet j\bullet}$  and  $f_{ij}$  are the sum of Downs and non-Downs.
- ▶ Therefore the log likelihood remains invariant over all possible distributions of Downs as long as the marginals and the distribution of sums remain the same.
- ▶ Therefore maximum likelihood estimates for usual logistic regression or even spline logistic regression will be unique and independent of the actual distribution of Downs.
- ▶ However, the **fit** of each solution to the estimated likelihood will **differ**. From a model based approach we can consider the distribution of Downs that gives the best fit to a given model.

In *simplest* case, where  $q_1(a) = \underline{\beta_1 a}$  and  $q_2(a) = \underline{\beta_2 a}$ , the 3 sufficient statistics for  $\{\beta_0, \beta_1, \beta_2\}$  are the number of **cases**: 154; the sum of the ages of their 154 mothers: 5736 years; and their 154 fathers 6065 years.



# EXPLORING SOLUTION SETS / co-au. Roy



Lionel Penrose was the father of mathematician [Roger Penrose](#), chess Grandmaster [Jonathan Penrose](#), mathematician [Oliver Penrose](#) (who graciously provided JH with this [reconsideration of his father's 1933 work](#). [It appears as the chapter 'A beautiful method of analysis': O. Penrose, pp 443-451 in "Fifty years of human genetics: A Festschrift and liber amicorum to celebrate the life and work of George Robert Fraser", edited by Oliver Mayo and Carolyn Leach, ISBN 9781862547537, Wakefield Press, Adelaide, 2007]), and geneticist [Shirley Victoria Hodgson\\*](#) (who graciously sent JH a copy of her father's book "Clinical and Genetic Study of 1280 Cases of Mental Defect: Colchester Survey").

2023

Prob[Down Syndrome | Parents' Ages]:

Statistical Sudoku and Analyses of Penrose's Data (J. Genetics 1933)

[2023.11.22 Presentation by J. Hanley And S. Roy, McGill Biostatistics Seminar Series](#)

[.mp4 video : \*Penrose's daughter Shirley, born in London, Ontario, appears from London, England in last few frames ]

2025

[R code to read in Penrose's data and generate 'Sudoku' solution sets](#)

[Appendices to manuscript, now-accepted by CHANCE\\*\\*. These were shared with reviewers](#)

\*\*The accepted article

"Lionel Penrose's statistical consultant: and lessons from the statistical 'sudoku' they left us"  
is planned to be published in the next issue.

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# Lionel Penrose's Statistical Consultant and Lessons from the Statistical "Sudoku" They Left Us

*James A. Hanley and Supratik Roy*

Lionel Penrose's 1933 study was one of the first to establish that "the father's age is not a significant factor in the risk of Down's syndrome, while the mother's age is to be regarded as very important." We identify the statistical consultant who helped Penrose improve on the prevailing regression methods for handling binary responses. Using a form of "statistical sudoku," we explain how to create complete data sets from the summary data Penrose worked with and shared, and we describe the

[...] 150 families of the human species containing Down's syndrome among the children. Every family included was visited personally and, among other things, the ages of the parents at the birth of each child was [sic] carefully recorded: miscarriages and all individuals in whom a diagnosis of normality or Down's syndrome could not be made with certainty were excluded. No obvious disparity was observed between the ages

the three (2-D) marginal distributions but stopped short of giving the full 3-D distribution. Penrose omitted the cell-specific distributions of  $N$  and  $D$ 's.

Penrose's challenge was how to deal with the tricky statistical issue that today we call confounding. The strong correlation of the parent's ages means that when the father's age or the mother's age is considered on its own, the probability that a child is affected by Down's syndrome will seem to be strongly related to that parent's age.

**CHANCE 2025, to appear**



**The Relative Aetiological Importance of Birth  
Order and Maternal Age in [REDACTED]**

L. S. Penrose

*Proc. R. Soc. Lond. B* 1934 **115**, doi: 10.1098/rspb.1934.0051, published 1  
August 1934

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A METHOD OF SEPARATING THE RELATIVE AETIOLOGI-  
CAL EFFECTS OF BIRTH ORDER AND MATERNAL AGE,  
WITH SPECIAL REFERENCE TO [REDACTED]

Annals of Eugenics [REDACTED]

Vol 6, Issue 1 Oct 1934

By L. S. PENROSE, M.D.

pp 108-131

*From the Research Department, Royal Eastern Counties' Institution*

“Proc. Roy. Soc. paper has 2 methods of analysis.. ”

- ▶ Wright's method of partial correlation  
– but it cannot easily handle families of varying sizes,  
and the **mode of their selection.**
- ▶ These complications are avoided by using the  
**second method, suggested by Prof R. A. Fisher.**

**PURPOSE:** describe Fisher's method in detail.

# **Studies in the history of probability and statistics, LI: the first conditional logistic regression**

By J. A. HANLEY

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## **SUMMARY**

Statisticians and epidemiologists generally cite the publications of [Prentice & Breslow \(1978\)](#) and [Breslow et al. \(1978\)](#) as the first description and use of conditional logistic regression, while economists cite the book chapter by Nobel laureate McFadden ([McFadden, 1973](#)). We describe the until-now-unrecognized use of, and way of fitting, this model in 1934 by Lionel Penrose and Ronald Fisher.

*Some key words:* Birth order; Down's syndrome; Estimating equation; Family-based selection; Maternal age; Peer review; Relative odds; Standard error.

<https://jhanley.biostat.mcgill.ca/Penrose/>

## e.g. Applying discrete choice models to predict Academy Award winners

*J. R. Statist. Soc. A* (2008)  
171, Part 2, pp. 375–394

Iain Pardoe

His Oscar Predictions <http://iainpardoe.com/oscars/>

*University of Oregon, Eugene, USA*

and Dean K. Simonton

*University of California at Davis, USA*

[Received September 2005. Revised June 2007]

**Summary.** Every year since 1928, the Academy of Motion Picture Arts and Sciences has recognized outstanding achievement in film with their prestigious Academy Award, or Oscar. Before the winners in various categories are announced, there is intense media and public interest in predicting who will come away from the awards ceremony with an Oscar statuette. There are no end of theories about which nominees are most likely to win, yet despite this there continue to be major surprises when the winners are announced. The paper frames the question of predicting the four major awards—picture, director, actor in a leading role and actress in a leading role—as a discrete choice problem. It is then possible to predict the winners in these four categories with a reasonable degree of success. The analysis also reveals which past results might be considered truly surprising—nominees with low estimated probability of winning who have overcome nominees who were strongly favoured to win.

**Keywords:** Bayesian; Conditional logit; Films; Forecasting; Mixed logit; Motion pictures; Movies; Multinomial logit

Reference to (Nobel Laureate) McFadden, D. (1974) Conditional logit analysis of qualitative choice behavior.

Table 4: Explanatory variables for Best Actress in a Leading Role

1. Indicator for Best Picture Oscar nomination [1939–2004]. Only 25 actresses have won the Best Actress in a Leading Role Oscar for a movie that did not receive a Best Picture nomination (most recently, Charlize Theron for *Monster* in 2003).
2. Natural logarithm of the number of previous Best Actress in a Leading Role Oscar wins [1938–2004]. 24 percent of Best Actress Oscar nominees with no previous lead actress wins have won the Oscar, whereas 13 percent of Best Actress Oscar nominees with one or more previous lead actress wins have won. This variable has been log-transformed because it is highly skewed.
3. Indicator for winning a Golden Globe for Best Actress in a Leading Role (Drama) [1944–2004]. Of the 62 Best Actress Oscar winners from 1943 to 2004, 31 had won a Golden Globe for Best Actress (Drama) a few weeks earlier.
4. Indicator for winning a Golden Globe for Best Actress in a Leading Role (Musical or Comedy) [1952–2004]. Of the 55 Best Actress Oscar winners from 1950 to 2004, 11 had won a Golden Globe for Best Actress (Musical or Comedy) a few weeks earlier.
5. Indicator for winning a Screen Actor's Guild award [1996–2004]. Of the 11 Best Actress Oscar winners since 1994, eight had already won a SAG award. *Chance* 2005, vol 18(4), 32-39



Why not regular (unconditional) logistic regression?

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- ▶ Data are organized by competition & year ('set')

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# Why not regular (unconditional) logistic regression?

- ▶ Data are organized by competition & year ('set')
- ▶ There's a winner in each competition [ indep. Bernoulli r.v.s ]
- ▶ Some elements of profile did not exist in earlier years

Data, (relative & scaled-to-sum-to-1, modelled) Win Probabilities, LogLikelihood Contributions

Data, (relative & scaled-to-sum-to-1, modelled) Win Probabilities, LogLikelihood Contributions

Year	Nominee	Profile				Rel. Prob $e^{\mathbf{X}\beta}$	Prob. Win ( $P$ )	Winner? ( $Y$ )	LogLik ( $Y \log P$ )
		$X_1$	$X_2$	...	$X_K$				
2025	Nominee <sub>1</sub>	✓	✓	✓	✓	$\omega_1$	$\omega_1 / \sum \omega$	0	-
2025	Nominee <sub>2</sub>	✓	✓	✓	✓	$\omega_2$	$\omega_2 / \sum \omega$	0	-
2025	Nominee <sub>3</sub>	✓	✓	✓	✓	$\omega_3$	$\omega_3 / \sum \omega$	0	-
2025	Nominee <sub>4</sub>	✓	✓	✓	✓	$\omega_4$	$\omega_4 / \sum \omega$	1	$\log P_4$
2025	Nominee <sub>5</sub>	✓	✓	✓	✓	$\omega_5$	$\omega_5 / \sum \omega$	0	-

Data, (relative & scaled-to-sum-to-1, modelled) Win Probabilities, LogLikelihood Contributions

Year	Nominee	Profile				Rel. Prob $e^{X\beta}$	Prob. Win ( $P$ )	Winner? ( $Y$ )	LogLik ( $Y \log P$ )
		$X_1$	$X_2$	...	$X_K$				
2025	Nominee <sub>1</sub>	✓	✓	✓	✓	$\omega_1$	$\omega_1 / \sum \omega$	0	-
2025	Nominee <sub>2</sub>	✓	✓	✓	✓	$\omega_2$	$\omega_2 / \sum \omega$	0	-
2025	Nominee <sub>3</sub>	✓	✓	✓	✓	$\omega_3$	$\omega_3 / \sum \omega$	0	-
2025	Nominee <sub>4</sub>	✓	✓	✓	✓	$\omega_4$	$\omega_4 / \sum \omega$	1	$\log P_4$
2025	Nominee <sub>5</sub>	✓	✓	✓	✓	$\omega_5$	$\omega_5 / \sum \omega$	0	-
						$\sum \omega$	1		
2024	Nominee <sub>1</sub>	✓	✓	✓	✓	etc	etc	0	-
2024	Nominee <sub>2</sub>	✓	✓	✓	✓			1	$\log P_2$
2024	Nominee <sub>3</sub>	✓	✓	✓	✓			0	-

Data, (relative & scaled-to-sum-to-1, modelled) Win Probabilities, LogLikelihood Contributions

Year	Nominee	$X_1$	Profile			Rel. Prob $e^{X\beta}$	Prob. Win ( $P$ )	Winner? ( $Y$ )	LogLik ( $Y \log P$ )
2025	Nominee <sub>1</sub>	✓	✓	✓	✓	$\omega_1$	$\omega_1 / \sum \omega$	0	-
2025	Nominee <sub>2</sub>	✓	✓	✓	✓	$\omega_2$	$\omega_2 / \sum \omega$	0	-
2025	Nominee <sub>3</sub>	✓	✓	✓	✓	$\omega_3$	$\omega_3 / \sum \omega$	0	-
2025	Nominee <sub>4</sub>	✓	✓	✓	✓	$\omega_4$	$\omega_4 / \sum \omega$	1	$\log P_4$
2025	Nominee <sub>5</sub>	✓	✓	✓	✓	$\omega_5$	$\omega_5 / \sum \omega$	0	-
						$\sum \omega$	1		
2024	Nominee <sub>1</sub>	✓	✓	✓	✓	etc	etc	0	-
2024	Nominee <sub>2</sub>	✓	✓	✓	✓			1	$\log P_2$
2024	Nominee <sub>3</sub>	✓	✓	✓	✓			0	-
etc									
1938	Nominee <sub>1</sub>	✓	✓		✓	etc	etc	0	-
1938	Nominee <sub>2</sub>	✓	✓		✓			0	-
1938	Nominee <sub>3</sub>	✓	✓		✓			1	$\log P_3$
1938	Nominee <sub>4</sub>	✓	✓		✓			0	-



Data, (relative & scaled-to-sum-to-1, modelled) Win Probabilities, LogLikelihood Contributions

Year	Nominee	$X_1$	Profile			Rel. Prob $e^{X\beta}$	Prob. Win ( $P$ )	Winner? ( $Y$ )	LogLik ( $Y \log P$ )
2025	Nominee <sub>1</sub>	✓	✓	✓	✓	$\omega_1$	$\omega_1 / \sum \omega$	0	-
2025	Nominee <sub>2</sub>	✓	✓	✓	✓	$\omega_2$	$\omega_2 / \sum \omega$	0	-
2025	Nominee <sub>3</sub>	✓	✓	✓	✓	$\omega_3$	$\omega_3 / \sum \omega$	0	-
2025	Nominee <sub>4</sub>	✓	✓	✓	✓	$\omega_4$	$\omega_4 / \sum \omega$	1	$\log P_4$
2025	Nominee <sub>5</sub>	✓	✓	✓	✓	$\omega_5$	$\omega_5 / \sum \omega$	0	-
						$\sum \omega$	1		
2024	Nominee <sub>1</sub>	✓	✓	✓	✓			0	-
2024	Nominee <sub>2</sub>	✓	✓	✓	✓	etc	etc	1	$\log P_2$
2024	Nominee <sub>3</sub>	✓	✓	✓	✓			0	-
etc									
1938	Nominee <sub>1</sub>	✓	✓		✓			0	-
1938	Nominee <sub>2</sub>	✓	✓		✓	etc	etc	0	-
1938	Nominee <sub>3</sub>	✓	✓		✓			1	$\log P_3$
1938	Nominee <sub>4</sub>	✓	✓		✓			0	-
DATA in Black									$\sum \text{LogLik}$

Data, (relative & scaled-to-sum-to-1, modelled) Win Probabilities, LogLikelihood Contributions

Year	Nominee	$X_1$	Profile $X_2 \quad \dots \quad X_K$			Rel. Prob $e^{X\beta}$	Prob. Win ( $P$ )	Winner? ( $Y$ )	LogLik ( $Y \log P$ )
2025	Nominee <sub>1</sub>	✓	✓	✓	✓	$\omega_1$	$\omega_1 / \sum \omega$	0	-
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2025	Nominee <sub>3</sub>	✓	✓	✓	✓	$\omega_3$	$\omega_3 / \sum \omega$	0	-
2025	Nominee <sub>4</sub>	✓	✓	✓	✓	$\omega_4$	$\omega_4 / \sum \omega$	1	$\log P_4$
2025	Nominee <sub>5</sub>	✓	✓	✓	✓	$\omega_5$	$\omega_5 / \sum \omega$	0	-
						$\sum \omega$	1		
2024	Nominee <sub>1</sub>	✓	✓	✓	✓			0	-
2024	Nominee <sub>2</sub>	✓	✓	✓	✓	etc	etc	1	$\log P_2$
2024	Nominee <sub>3</sub>	✓	✓	✓	✓			0	-
etc									
1938	Nominee <sub>1</sub>	✓	✓		✓			0	-
1938	Nominee <sub>2</sub>	✓	✓		✓	etc	etc	0	-
1938	Nominee <sub>3</sub>	✓	✓		✓			1	$\log P_3$
1938	Nominee <sub>4</sub>	✓	✓		✓			0	-
DATA in Black									$\sum \text{LogLik}$

FITTING in Red

$$\hat{\beta} = \underset{\beta}{\operatorname{argmax}} \sum \text{LogLik}$$

# Data, (relative & scaled-to-sum-to-1, modelled) Win Probabilities, LogLikelihood Contributions

Year	Nominee	$X_1$	Profile			$X_K$	Rel. Prob $e^{\mathbf{X}\beta}$	Prob. Win ( $P$ )	Winner? ( $Y$ )	LogLik ( $Y \log P$ )
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2025	Nominee <sub>2</sub>	✓	✓	✓	✓	✓	$\omega_2$	$\omega_2 / \sum \omega$	0	-
2025	Nominee <sub>3</sub>	✓	✓	✓	✓	✓	$\omega_3$	$\omega_3 / \sum \omega$	0	-
2025	Nominee <sub>4</sub>	✓	✓	✓	✓	✓	$\omega_4$	$\omega_4 / \sum \omega$	1	$\log P_4$
2025	Nominee <sub>5</sub>	✓	✓	✓	✓	✓	$\omega_5$	$\omega_5 / \sum \omega$	0	-
							$\sum \omega$	1		
2024	Nominee <sub>1</sub>	✓	✓	✓	✓	✓			0	-
2024	Nominee <sub>2</sub>	✓	✓	✓	✓	✓	etc	etc	1	$\log P_2$
2024	Nominee <sub>3</sub>	✓	✓	✓	✓	✓			0	-
etc										
1938	Nominee <sub>1</sub>	✓	✓			✓			0	-
1938	Nominee <sub>2</sub>	✓	✓			✓	etc	etc	0	-
1938	Nominee <sub>3</sub>	✓	✓			✓			1	$\log P_3$
1938	Nominee <sub>4</sub>	✓	✓			✓			0	-
DATA in Black										$\sum \text{LogLik}$

FITTING in Red

$$\hat{\beta} = \underset{\beta}{\operatorname{argmax}} \sum \text{LogLik}$$

**Predictions for 2026:** compute  $e^{X\hat{\beta}}$  for each 2026 nominee, and rescale to  $P$ 's

**The Relative Aetiological Importance of Birth Order and Maternal Age in [REDACTED]**

L. S. Penrose

*Proc. R. Soc. Lond. B* 1934 **115**, doi: 10.1098/rspb.1934.0051, published 1 August 1934

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First submission received by the Royal Society on November 25, 1933.

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First submission received by the Royal Society on November 25, 1933.

217 families  
(210 had 1 affected child, 7 had 2: → 224 'Cases')

# Peer Review: 1933

# Peer Review: 1933

8th December 1933.

Dr. Penrose,  
Royal Eastern Counties Institution,  
Essex Hall,  
Colchester.

Dear Dr. Penrose,

I have had your paper on age and birth order among [REDACTED] sent to me as referee by the Royal Society, and as I have a good deal to say, I am writing directly to you, instead of letting it trickle through anonymously as extracts from the referee's report. Either way I am afraid you will find it a confounded nuisance.



The whole difficulty turns on the point made in section three, but that section makes it far from clear. You do not mention the essential point, that choosing families only containing [REDACTED], the proportion of [REDACTED] must be highest in the smallest families, which generally contain early, but not late children by birth rank.

Now it seems to me that your family data are much too important for you to be satisfied with an unconvincing statistical analysis.

I mean, that no one reading your paper critically will feel sure that a more exact treatment would not have yielded a different result.

I may add that I entirely expect your actual conclusions to be the right ones, but that is no sufficient reason why they should not be adequately established.

$$\text{or } \frac{1}{4} \frac{p}{q} : \frac{1}{2} \frac{p'}{q'}$$

or say,  $x : x'$

where ~~it~~ is proportional to  $\frac{1}{q}$ .

For families containing one [REDACTED]

but more than one normal, the expectations are

clearly  $\frac{x}{S(x)}$

$$\frac{x}{S(x)}, \frac{x'}{S(x')}, \frac{x''}{S(x'')}$$

where  $S(x)$  is the sum of the values  $x$  for the different maternal ages in the family.

For families containing two [REDACTED] the expectations of [REDACTED] at each place will be

$$\frac{x S'(x)}{SS(x, x')}$$

adding up to two.

When  $S'(x)$  is the sum of the other values, and  $SS(x, x')$  stands for the sum of all the products  $xx'$  at a time.



B

# Revised Manuscript

“To avoid these sources of ambiguity the data have been subjected to analysis by an **entirely different method which was suggested by Professor R. A. Fisher**. By use of this new process we are able, after a single complex reconstruction, **[JH 2024: conditional logistic model]**

# Revised Manuscript

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**to compare the observed number of Down's syndrome cases in any given birth rank with the number which is to be expected on the hypothesis that the probability of a Down's syndrome child depends upon maternal age (in some manner unknown prior to the data) but not, given age, upon birth rank.**”

# Revised Manuscript

“To avoid these sources of ambiguity the data have been subjected to analysis by an **entirely different method which was suggested by Professor R. A. Fisher**. By use of this new process we are able, after a single complex reconstruction, **[JH 2024: conditional logistic model]**

**to compare the observed number of Down's syndrome cases in any given birth rank with the number which is to be expected on the hypothesis that the probability of a Down's syndrome child depends upon maternal age (in some manner unknown prior to the data) but not, given age, upon birth rank.**"

**i.e., they didn't fit a model with both age and birth order; they fitted one based just on age, and then (effectively) grouped the predictions by birth order.**

*Table 2. Test of theory that birth order is not an aetiological factor: observed (O) and expected (E) numbers of Down's syndrome children, and standard errors*

Birth rank	O	E	Difference	Standard Error	
				1934	2024
1st	26	23.97	+2.03	2.68	2.9
2nd or 3rd	55	57.56	-2.56	3.85	3.9
4th, 5th or 6th	59	61.98	-2.98	4.07	4.1
7th to 10th	61	58.37	+ 2.63	3.41	3.3
11th to 17th	23	22.14	+0.86	1.84	1.8
Total	224	224.02			

Source: Table X page 122 of Penrose (1934a). E's computed from fitted  $x$  function in Table 1. 2024 Standard errors estimated by simulation (see text).

Their fitting of their age-only model, where they categorized age as 7 age-bins, each 5 years wide. So their model had 6 free age-effect parameters.



Table 1. Trial  $\omega$  values, and age-specific fitted (‘calculated’) frequencies of Down’s syndrome (DS) children

Data	Maternal age group	15–19	20–24	25–29	30–34	35–39	40–44	45–49
	Observed no. of normal children	10	114	199	228	170	67	15
	Observed no. of DS children	3	13	14	27	64	81	22
Fitting Trial no. ↘								
1	$\omega$ values	83[4]	31[2]	19[1]	33[2]	104[5]	321[15]	407[20]
	Calculated no. of DS children	3.69	16.87	19.50	29.11	59.48	76.99	18.35
⋮	(fitted)							
7	$\omega$ values	22[4]	10[2]	6[1]	19[3]	88[15]	296[50]	558[90]
	Calculated no. of DS children	2.98	12.87	13.82	26.58	64.14	81.46	22.17
⋮								
clogit	Scaled $\omega$ values	[3.47]	[1.59]	[1]	[2.96]	[13.19]	[43.62]	[81.53]

Source: Page 440 of [Penrose \(1934a\)](#).  
Since the  $\omega$  values are relative odds, values in brackets have been scaled so that the lowest risk age group (25–29) serves as the reference category, with a scaled odds of 1:1. See [Penrose \(1934b\)](#) for how he chose the  $\omega$ ’s for each trial. The scaled  $\omega$  values fitted in five iterations by the clogit function in the R survival package ([R Development Core Team, 2024](#)) yielded calculated frequencies that were, in absolute terms, within  $10^{-9}$  of the observed ones.

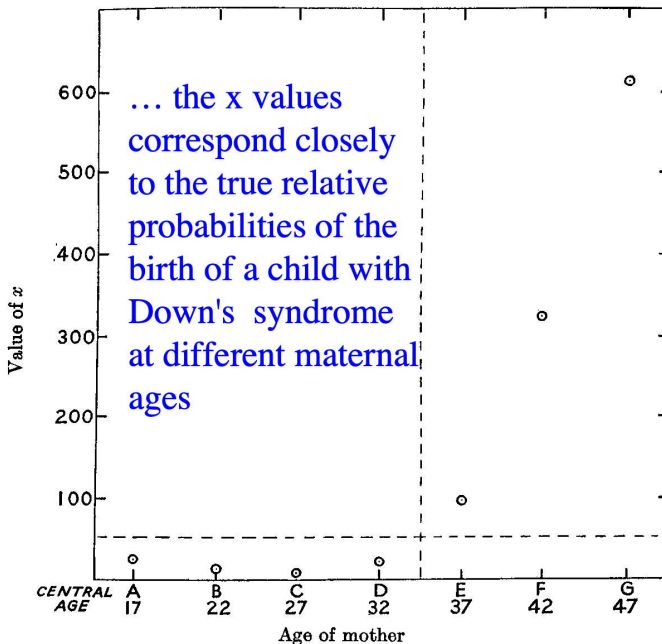


Fig. 1. Final estimate of values of  $x$  for maternal age groups

### Maternal Age.

[illegible]

Maternal Age—(continued)

Serial number	Sex	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40	41	42	43	44	45	46	47	48						
196	m						1			3			7				9																						
197	m					1		2	3		4		5		6							7																	
198	m, f															3			4				5																
199	f								1		2															7													
200	f																					1				2			3										
201	m															1		2				4																	
202	f												1															3											
203	m						1																																
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205	f												1				3	4				5				6							8						
206	m			1																																			
207	f																																1						
208	f															1					4		6	7				8											
209	f																								2														
210	m										1		2									3			4														
211	m																9	10					13					14					15						
212	f													1			2	3																					
213	m											4					5		6																				
214	m																																						
215	m					1		2			3											8	3	9	10		11		6	12			13	14					
216	f																5	6	7			10						14	15										
217	m, m																						2											{ 3 3					
		1	3	6		14	17	16	26	42		39	41	40	38	41		51	42	48	45	42		49	34	28	32	27		21	18	12	11	8	8	6	1	—	
		—	—	3		1	3	4	4	1		—	3	6	3	2		2	4	6	6	9		13	8	15	14	14		18	16	23	12	12		7	8	6	1

# Maternal Age—(continued)

Serial number	Sex	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40	41	42	43	44	45	46	47	48
196	m						1			3			7				9																
197	m					1		2	3		4		5		6							7		5									
198	m, f															3			4	5				5					6				
199	f								1		2															7							
200	f																					1				2			3				
201	m															1		2		3		4											
202	f												1						2									3					
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204	m													1								3											
205	f												1				3	4				5				6							8
206	m			1																													
207	f																																1
208	f																1				4		6	7				8					
209	f																									2							
210	m										1		2									3			4								
211	m																9	10					13					14				15	
212	f													1			2	3															
213	m											4					5		6														
214	m																																
215	m				1		2			3											8	3	9	10			11		6	12		13	14
216	f																5	6	7			10						14	15				
217	m, m																																<div>33</div>
		1	3	6	14	17	16	26	42	39	41	40	38	41	51	42	48	45	42	49	34	28	32	27	21	18	12	11	8	8	6	1	—
		—	—	3	1	3	4	4	1	—	3	6	3	2	2	4	6	6	9	13	8	15	14	14	18	16	23	12	12	7	8	6	1

JH has assembled these data into a 'long' .csv file that is available on his website <https://jhanley.biostat.mcgill.ca/Penrose/>



**CONFIDENTIAL.**

NOTE.—It is the invariable practice of the Society's Officers, in correspondence with the communicator, and through him with the author of a paper, to preserve the anonymity of a referee. In order, however, to enable an author to consider suggested modifications, or to enable a communicator to consider the desirability of withdrawing a paper, it is frequently desirable to acquaint the communicator with the substance of a referee's criticisms. The referee is requested to *enclose within square brackets* any section of or phrase in his report, which he would wish to be withheld from the communicator in any correspondence of this kind.

**REFeree's REPORT.**

To the Sectional Committee for Physiology.

Paper by L. S. Penrose.

On The relative aetiological importance of birth order and maternal age in Mongolism.

1. Should the paper be read before the Society? ☒

2. Should it be published by the Society? ☒

3. Should it be published in the "Philosophical Transactions" or the "Proceedings"?  
(See Standing Orders on opposite page.) Proceedings

4. Should it be published in full or only in part? Full

5. Are any material modifications necessary? ☒

The paper has been reworked so as to meet quite fully the criticism previously made

**SCIENCE IN THE MAKING**

Title:

**Referee's report by Ronald Aylmer Fisher, on a paper 'The relative aetiological importance of birth order and maternal age in [mongolism]' by Lionel Sharples Penrose**

Author:

Ronald Aylmer Fisher

Reference Number:

RR/50/84

Date:

May 1934

URL:

[https://making-science.royalsociety.org/items/rv\\_50\\_84/referees-report-by-ronald-aylmer-fisher-on-a-paper-the-relative-aetiological-importance-of-birth-order-and-maternal-age-in-mongolism-by-lionel-sharples-penrose](https://making-science.royalsociety.org/items/rv_50_84/referees-report-by-ronald-aylmer-fisher-on-a-paper-the-relative-aetiological-importance-of-birth-order-and-maternal-age-in-mongolism-by-lionel-sharples-penrose)

6. Which illustrations, if any, accompanying the paper should be reproduced?

**This paper has been reworked so as to meet quite fully the criticism previously made**

Signature R. A. Fisher

It is requested that any further remarks may be written on foolscap paper.

# RECORDS OF SPECIAL CONVOCATIONS DURING THE CONGRESS

10th International Congress of Genetics, McGill University, Aug 20-27, 1958

A SPECIAL CONVOCATION of McGill University was held in the Percival Molson Memorial Stadium on Wednesday, August 20. Degrees of Doctor of Science, *honoris causa*, were conferred upon Professor Hitoshi Kihara, Professor Lionel S. Penrose, and Professor Curt Stern. The remarks of the Principal and Vice-Chancellor, Dr. F. Cyril James, are included below together with the citation of the recipients prepared by Dr. Lloyd G. Stevenson, Dean of the Faculty of Medicine, and the response of Professor Curt Stern for the recipients.

## REMARKS OF THE PRINCIPAL AND VICE-CHANCELLOR

It is my privilege this morning, from this Convocation platform, to offer to each of you a warm welcome to Montreal, and especially to McGill University. I hope that the arrangements made for your comfort by the Committee headed by my colleague Professor J. W. Boyes will make your stay pleasant, and that the scientific discussions during this X International Congress of Genetics will be intellectually rewarding. When you meet again, at some other place, for the eleventh Congress, I hope that the tenth will be a pleasant memory to evoke nostalgic talk during the intervals between more serious discussion.

Genetics is a comparatively new science, but we at McGill were early indoctrinated by the enthusiasm and skill of a master. Although Leonard Huskins—whom the Genetics Society of Canada commemorates in its annual Memorial Lecture—came to McGill as Associate Professor of Botany in 1930, his enthusiasm





Special Convocation, McGill University: *left to right*—Professor Sewall Wright, Professor L. S. Penrose, Professor Curt Stern, Professor H. Kihara, Professor F. Cyril James (Principal and Vice-Chancellor)

New York Times, Feb. 9, 1964

# Kennedy Foundation

## Its Efforts Set an Example for U. S. In Fight Against Mental Retardation

Last Wednesday evening a distinguished group of citizens headed by President Johnson met in New York to pay tribute to three physicians and three civic leaders for their contributions to the fight against mental retardation.

The occasion was the presentation of the Second Annual International Awards of the Joseph P. Kennedy Jr. Foundation.

Those honored were:

Dr. Grover Francis Powers, professor emeritus of pediatrics, Yale University.

Dr. Robert P. L. Lafon, professor of neuropsychiatry, University of Montpellier, France.

Dr. Lionell S. Penrose, professor of genetics, University College, London.

Senator Lister Hill of Alabama.

Bert T. Combs, former Governor of Kentucky.

Representative John E. Fogarty of Rhode Island.

In many ways the dinner, which was preceded by a day-long scientific program, was a tribute to President Kennedy.

It was during Mr. Kennedy's Presidency that the spotlight was focused for the first time on mental retardation nationally through the President's Panel on Mental Retardation.

**\$631 Million Provided**

As a result of two major waves of legislation passed last

### Joseph P. Kennedy, Jr. Foundation Annual International Awards Dinner New York, N.Y. Program

Sargent Shriver  
Executive Director, Joseph P. Kennedy, Jr. Foundation

The Honorable Edward M. Kennedy  
President, Joseph P. Kennedy, Jr. Foundation

The Honorable Lyndon B. Johnson  
President of the United States

The Right Honourable Lester Bowles Pearson  
Prime Minister of Canada

TO SOLVE A HUMAN PUZZLE

Film of the achievements of the International Award Winners  
Produced by the Joseph P. Kennedy, Jr. Foundation  
in cooperation with the Warner-Lambert Pharmaceutical Co.

Guest Master of Ceremonies: Jack Benny  
Special Guest Stars: Ethel Merman, Nat "King" Cole  
Music by Count Basie

The problem of mental retardation was once obscured by ignorance and superstition. Today it is heightened by a new spirit of hope. Much of this new hope stems from the studies and writings of Dr. Lionell S. Penrose. Galton Professor of Eugenics at the University of London. For more than thirty years, Dr. Penrose has been investigating the genetic factors in mental retardation. His "Colchester Survey" was the first large-scale systematic attempt to identify specific causal factors in a large group of retardates. All of his many books and papers are a provocative blend of terse fact and stimulating theoretical speculation. His work has been—and will continue to be—an inspiration to other dedicated men to attack the problem of mental retardation until, hopefully, it is solved.



LYNDON B. JOHNSON

36th President of the United States: 1963 - 1969

## Remarks in New York City at the Joseph P. Kennedy, Jr., Foundation Awards Dinner

February 05, 1964

Mr. Chairman, Mr. Prime Minister, Your Eminence, Mrs. Kennedy, members of the Kennedy family, award winners, distinguished guests and friends:

Earlier generations of Americans were fortunate to have known the Adamsses, the Lees, the Randolphs, the Lafalettes, and the Roosevelts.

Our generation is proud and blessed to have known the Kennedys. They are an extraordinary family, fierce competitors in life, they are a closely knit team, for they are all genuine friends as well as relatives—united in prayer, devoted to their parents and maintaining a community of purpose and practice which makes them the world's second most powerful Common Market.

Unlike many who have their opportunities, they prefer labor to leisure. They place the public good ahead of private gain. They both preach excellence and pursue it. They have been granted more than their share of greatness, but they have also been dealt more than their share of grief. The senseless, mindless murder of their martyred brother and son brought endless, timeless grief to every American home.

John Kennedy was to have been here tonight. No cause was closer to his heart. Millions of people, at home and abroad the world, will reap the harvest of his pioneering work in this field—a field which has been so greatly misunderstood and so greatly neglected so many years.

Humbly, I shall carry on for him here, as I intend to carry on the great efforts that he started for lasting peace. With his memory and his spirit to inspire us, and his words and his works to guide us, we shall live up to that trust. We shall finish his fight; and we shall conquer mental retardation and mental illness and poverty and every other foe of the land that he loved, and every other foe of the people he served.



FEBRUARY 15, 1964

THE ILLUSTRATED LONDON NEWS

A WINDOW ON THE WORLD.

NEW YORK, PRESIDENT JOHNSON PRESENTS ONE OF SIX INTERNATIONAL AWARDS OF THE JOSEPH KENNEDY JR. FOUNDATION TO DR. LIONELL PENROSE (LEFT), PROFESSOR OF EUGENICS AT UNIVERSITY COLLEGE, LONDON, FOR HIS CONTRIBUTION IN THE FIGHT AGAINST MENTAL ILLNESS. THIS FOUNDATION WAS ESTABLISHED IN 1946 IN MEMORY OF THE LATE PRESIDENT'S BROTHER, KILLED DURING THE WAR. (Wire photograph.)

Three Trains, Three Planes, a Ship  
and an Etched Piece of Glass with a Silver Stand

1964



"We can say with some assurance that, although children may be the victims of fate, they will not be the victims of our neglect."

Sponsored by John F. Kennedy, October 24, 1963, upon signing the Child Health and Mental Retardation Planning Amendment.



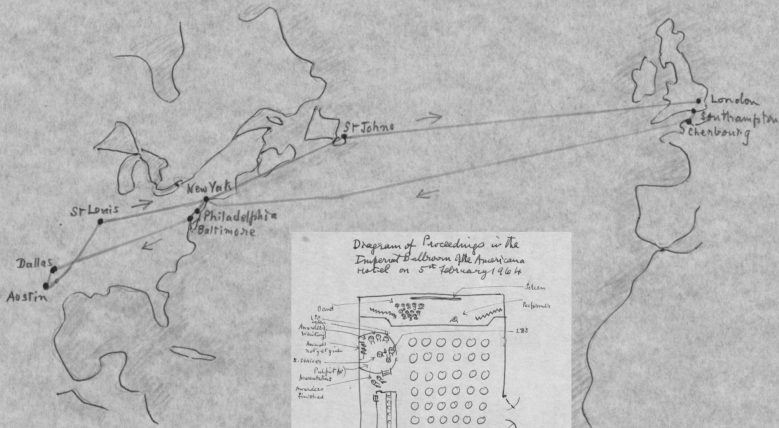
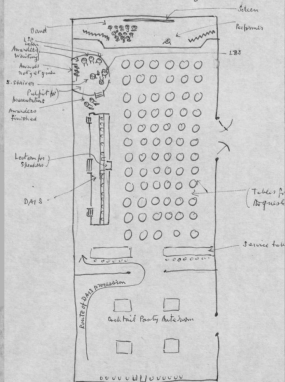


Diagram of Proceedings in the  
Imperial Ballroom of the Americana  
Hotel on 5<sup>th</sup> February 1964



18 pp.

Three Trains, Three Planes, a Ship  
and an Etched Piece of Glass with a Silver Stand

1964

29th January  
to 2nd February

First of all, about the ship : in my opinion the Queen Elizabeth is a quite remarkable object. Since she is 1031 feet



8



December 6, 1962 - President John F. Kennedy, Awards Dinner of the Joseph P. Kennedy Jr. Foundation

[LINK](#)

**Material related to [Biometrika 2024 article](#) on the conditional logistic regression fitted by Lionel Penrose and Ronald Fisher in 1934.**

**1934 Articles**

- \* [The relative aetiological importance of birth order and maternal age in mongolism.](#)

Penrose LS. Proceedings of the Royal Society B 115 431-450.

- \* [A method of separating the relative aetiological effects of birth order and maternal age, with specific reference to mongolian imbecility.](#)

Penrose LS. Annals of Eugenics 6 108-132.

**Data set**

- \* [Penrose's 1934 Data: 217 sibships with at least one child with DS \(.csv\)](#)

The dataset was reconstructed from the appendices to the two 1934 articles.

It has information on 224 affected children (the no. reported in the articles), but on 806 unaffected children (rather than the 807 reported)

**Archives**

- \* [Birth Order and Down's syndrome Correspondence](#) at Wellcome Library

- \* [Penrose Papers](#) at UCL Digital Collections

- \* [R A Fisher Correspondence Files](#) at University of Adelaide

- \* [Penrose's diary account of the family tour of North America in 1958](#)

before the 10th International Congress of Genetics at McGill University, and the [conferring of an honorary doctorate](#) (last few slides)

- \* [Penrose's diary account of his 1964 visit to the USA](#), where (in NYC) he received the [Joseph P. Kennedy Jr. Foundation's International Award from LBJ](#)

- \* First [Awards ceremony \(1962\)](#), where the awards were presented by [JFK](#).

**Material related to**

**"The first conditional logistic regression and the first nested case-control study"**

McGill Biostatistics Seminar Series, 2024.11.27

**Presentation**

[video](#) | ['slides'](#) [lyrics](#) (these include some material not in video/audio)

**Background:**

- \* Reviews: [Cole-1979](#) [Liddell-1988](#) [Breslow-1996](#) [Doll-2001](#) [Breslow-2007](#)

- \* Articles:

**Webinar presentation**

**"A not-well-known Lionel Penrose - Ronald Fisher collaboration"**

Sponsored by CHANCE magazine and the ASA History of Statistics Interest Group

September 24, 2025

[video, to be added](#) | ['slides'](#) | [lyrics](#)



WRAP-UP

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- ▶ Statistical '**Archaeology**' can be fun – and instructive and inspiring!

Thanks to:

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*"You are still too young but 'one day' I will let you see the statistics journals where Fisher and Pearson were so nasty to each other."*