

# General principles of development

.... the ontogenic origin of form

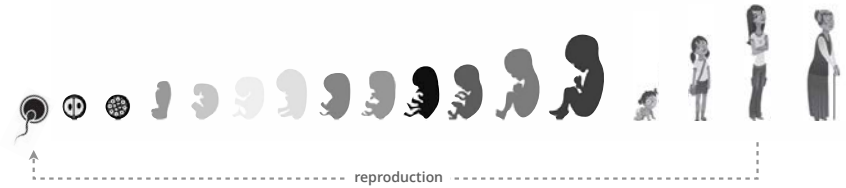


LEO Miguel Concha M.D. Ph.D.  
 Laboratory of Experimental Ontogeny  
 Biomedical Neuroscience Institute  
 ICBM, Faculty of Medicine  
 Universidad de Chile

BNI

UNIVERSIDAD DE CHILE

## Some key questions in developmental biology



**When does development start?**

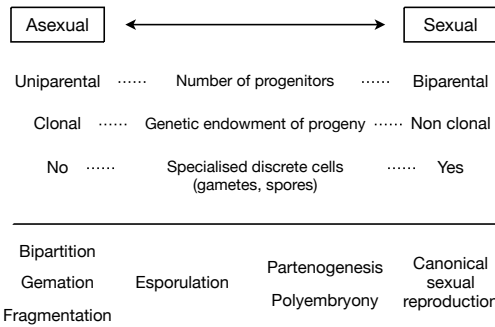
How do cells know what to do?

## Some key questions in developmental biology



*When does development start? — reproduction*

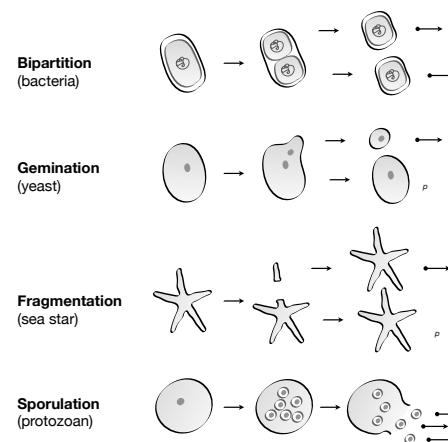
Generation of **new individuals** (demographic aspect) and **younger** (with longer life expectancy)



## Some key questions in developmental biology



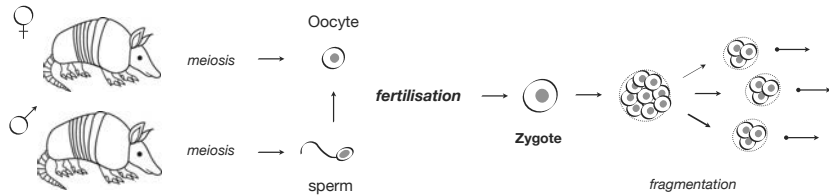
*When does development start? — asexual reproduction*



Some key questions in developmental biology



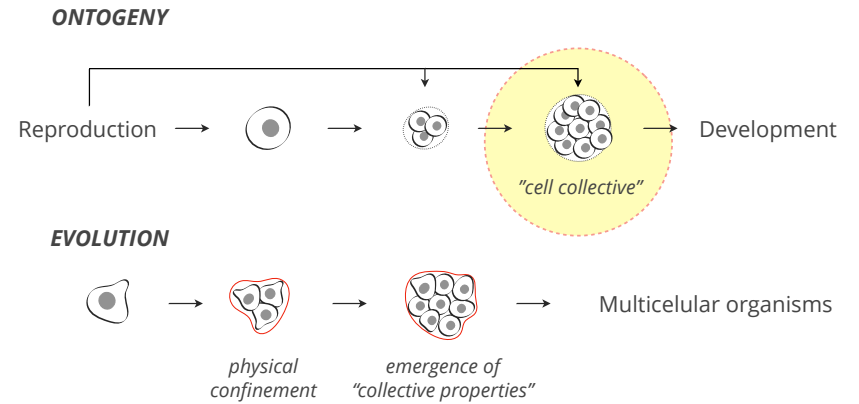
When does development start? — sexual reproduction



Some key questions in developmental biology



When does development start?



Some key questions in developmental biology



When does development start?

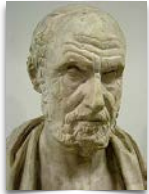
How do cells know what to do?

The notion of how cells know what to do, or how cells generate form in the embryo, has changed throughout history

Origin of embryo form · deterministic vs regulative views



The conflicting Ancient Greek views on morphogenesis



Hippocrates of Cos  
(Ἱπποκράτης ὁ Κῶσος, 460 - 370 BC)

The embryo is built under the influence of an "internal fire"

The shape of organs is **predetermined** by properties of tissues.

All parts form at the same time.

VS



Aristotle  
(Ἀριστοτέλης, 384 - 322 BC)

Embryo formation is controlled by a **final cause** (purpose).

The whole is functionally prior to the parts.

Organs appear gradually.

Origin of embryo form · deterministic vs regulative views

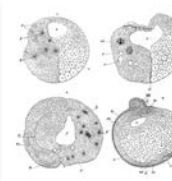


Contrasting visions of development at the dawn of the experimental era



Wilhelm Roux  
(German, 1850 - 1924)

Considered the developing organism's body as **a sum (mosaic) of autonomous parts.**



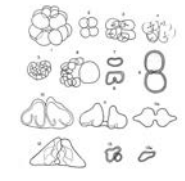
**1888** - pierced one cell of a 2-cell frog embryo with a hot needle, discovered that the survival blastomere formed only a body half.

VS



Hans Driesch  
(Prusian, 1867 - 1941)

Considered the organism's development as **self-differentiation** of equipotent parts.



1: Normal embryo  
2,3,4,5: Embryos from dissociated blastomeres  
7-12: Conjoined twins

**1891** - agitated sea urchin embryos at the 2- & 4-cell stage to disassociate into separate cells. Each cell developed a complete but smaller larval sea urchin.

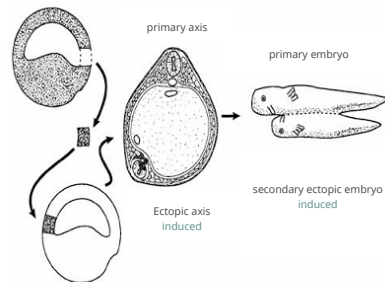
Origin of embryo form · regulative view of development



The **organiser** and the phenomenon of embryonic **induction**



Hans Spemann  
(German, 1869 - 1941)

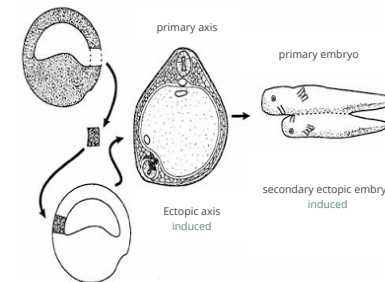
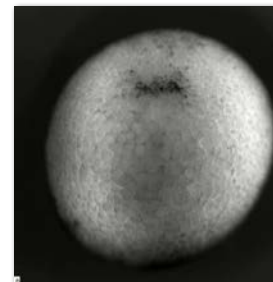


Together with his wife **Hilde Mangold** (1898-1924), they transplanted the dorsal blastopore lip of salamander embryos to the ventral part of another embryo, giving rise to an ectopic embryo that originated from host cells (1924). They recognized the fundamental principle of **embryonic induction** by an **organizer**.

Origin of embryo form · regulative view of development



The **organiser** and the phenomenon of embryonic **induction**



Together with his wife **Hilde Mangold** (1898-1924), they transplanted the dorsal blastopore lip of salamander embryos to the ventral part of another embryo, giving rise to an ectopic embryo that originated from host cells (1924). They recognized the fundamental principle of **embryonic induction** by an **organizer**.

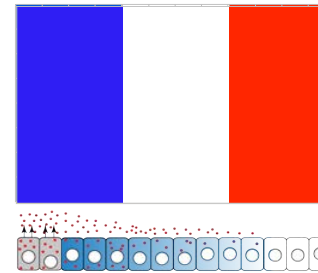
The concept of **morphogen** and **positional information**



Lewis Wolpert  
(British, 1929 - today)

The concept of **morphogen** and **positional information**

The french flag of Lewis Wolpert



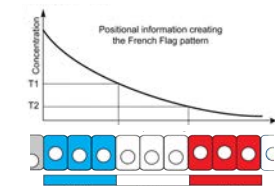
**MORPHOGEN**

**Source**

Localised  
Diffusion

**Response**

Discrete  
According to  
concentration



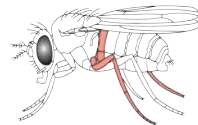
Morphogen concentration across space could be gradual enough such that many different positions could be reliably defined based simply on their differences in concentration (Wolpert, 1969, 1971)

Development is determined by genes and their biochemical products



■ Antennapedia

2nd thorax segment = 2nd leg pairs



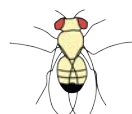
■ Ultrabithorax

3rd thorax segment = last leg pair (halteres - inhibit wing formation)

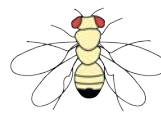


Mutante que expresa el gen Antennapedia en la cabeza

Patas en lugar de antenas  
Pares normales de patas



Mosca normal

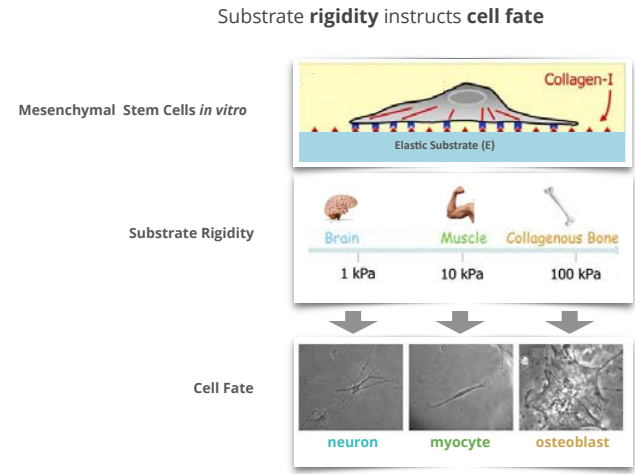
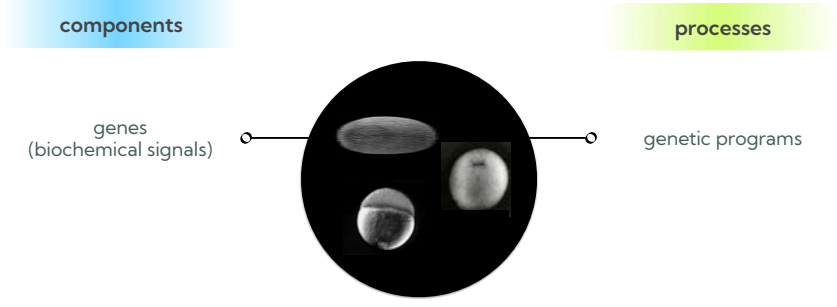


Mutante Ultrabithorax

Development is determined by genes and their (biochemical) products

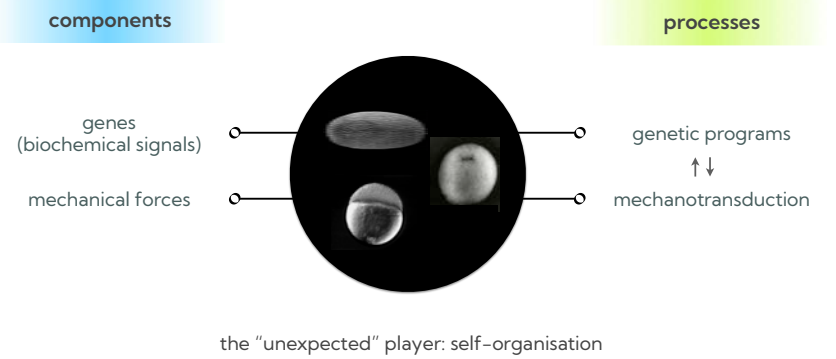
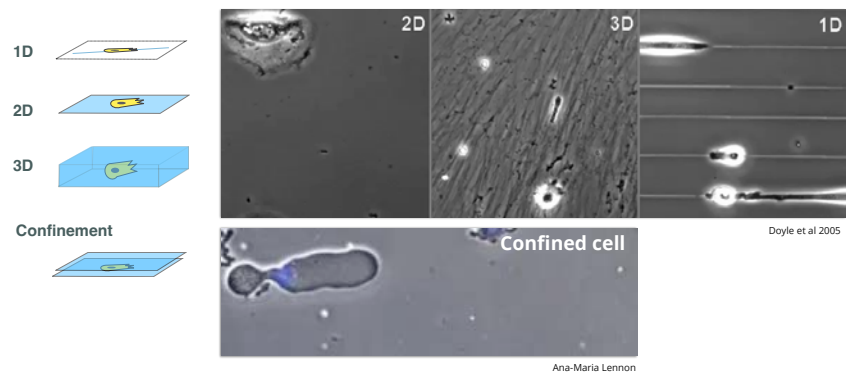


The organism is encoded in informational molecules (GENES under regulatory molecules), and individual development is only the implementation of this information.



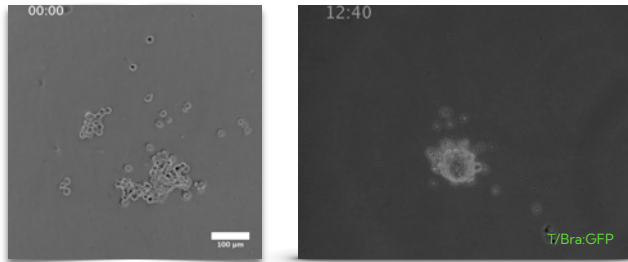
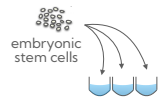
Dennis Discher Group (UPEN): Engler et al (2006) Cell 126:677-689

Substrate **geometry** affects **cell behaviour**




Origin of embryo form · the “unexpected” player: self-organisation 

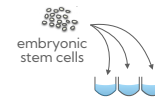
Self-organised collective interactions between ESCs generate molecular patterns



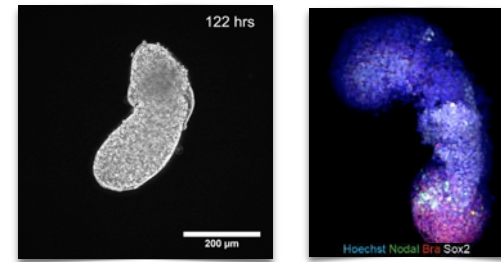
van den Brink et al 2014

Origin of embryo form · the “unexpected” player: self-organisation 

Self-organised collective interactions between ESCs generate molecular patterns



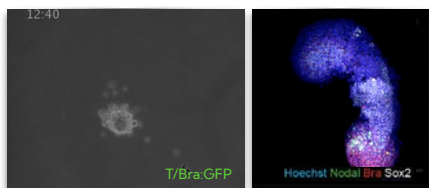
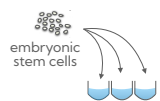
“Gastruloids”



Beccari et al 2018

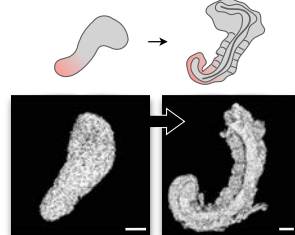
Origin of embryo form · the “unexpected” player: self-organisation 

Self-organisation can generate molecular patterns, but..... mechanics and geometry is required to generate shapes




van den Brink et al 2014

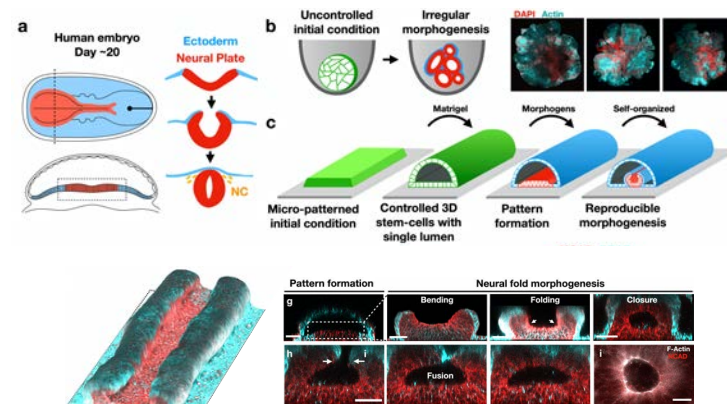
+ Mechanics  
(ECM, engineered devices)  
“border conditions”



Veenvliet et al 2020

Origin of embryo form · geometry guides self-organisation 

Neural tube morphogenesis *in vitro* from stem cells



Karzbrun et al 2021

*Cells (and not genes) are the key elements of development*

*Development can be seen as a guided self-organised process*

*.....in this context, it is fundamental to understand*

*the principles of self-organisation **in vivo***

&

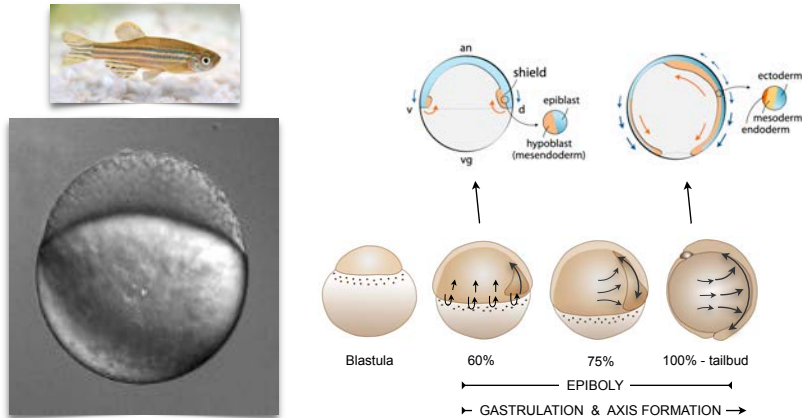
*the nature and function of guidance cues*

*— “border conditions” of self-organisation —*

Gastrulation in zebrafish · a deterministic mode of development



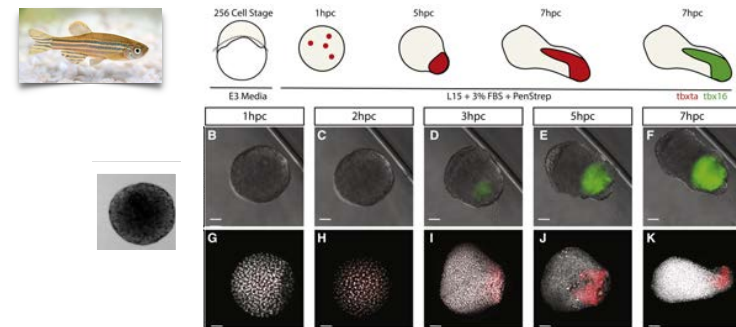
Gastrulation involves massive cell transformations — fate and morphogenesis



Gastrulation in zebrafish · a deterministic mode of development



Explants of zebrafish blastula cells can *in vitro* self-generate a gastruloid (“pescoïd”)

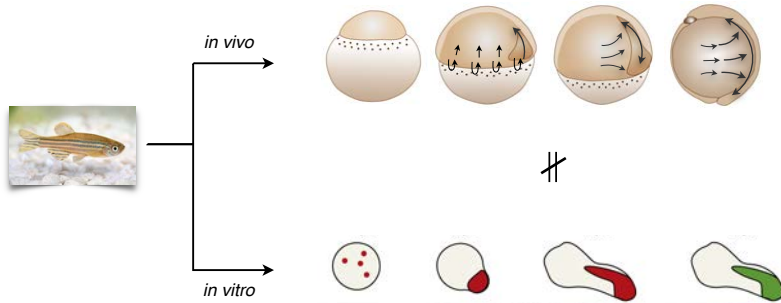


Fulton et al 2020

Gastrulation in zebrafish · a deterministic mode of development



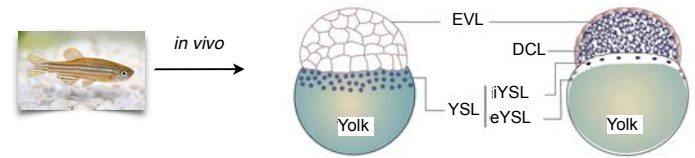
What is different between the *in vivo* and *in vitro* conditions?



Gastrulation in zebrafish · a deterministic mode of development



In vivo, gastrulation occurs in a defined architecture defined by the geometry of a **polarised egg** with **extraembryonic domains**



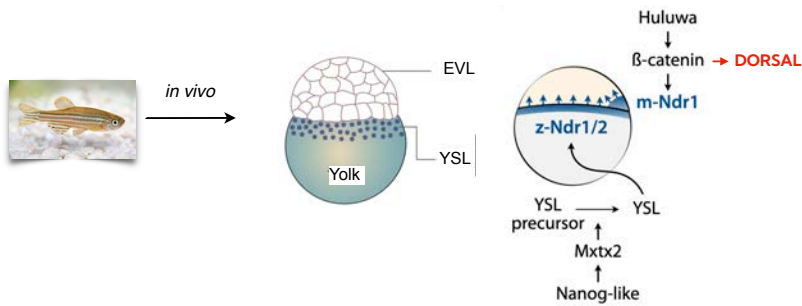
cellular domains of the late blastula (pre-gastrulation)

Concha and Reig 2023

Gastrulation in zebrafish · a deterministic mode of development



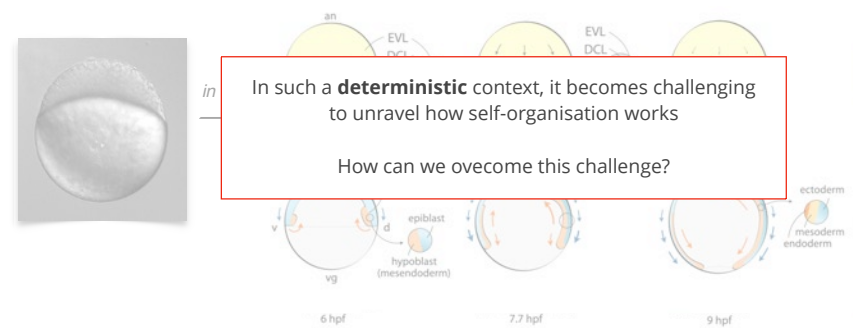
Early **biochemical signals of maternal origin** in the yolk and the specification extraembryonic domains guide gastrulation in a **deterministic** manner



Gastrulation in zebrafish · a deterministic mode of development



Early **maternal deterministic biochemical signals** and the **expanding morphogenesis of extraembryonic tissues** define the architecture of gastrulation

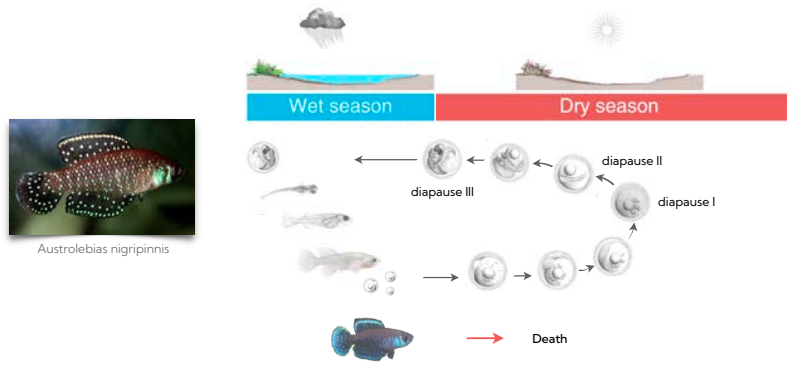


In such a **deterministic** context, it becomes challenging to unravel how self-organisation works

How can we overcome this challenge?



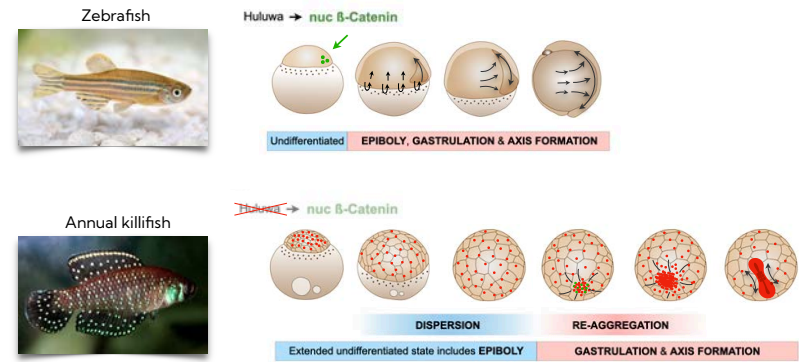
Extreme ecology led to drastic evolutionary developmental adaptations



*Austrolebias nigripinnis*

Adapted from Valenzano et al. 2015; Platzer and Englert 2016

Developmental adaptations made tissue self-organisation accessible



Zebrafish



Annual killifish

