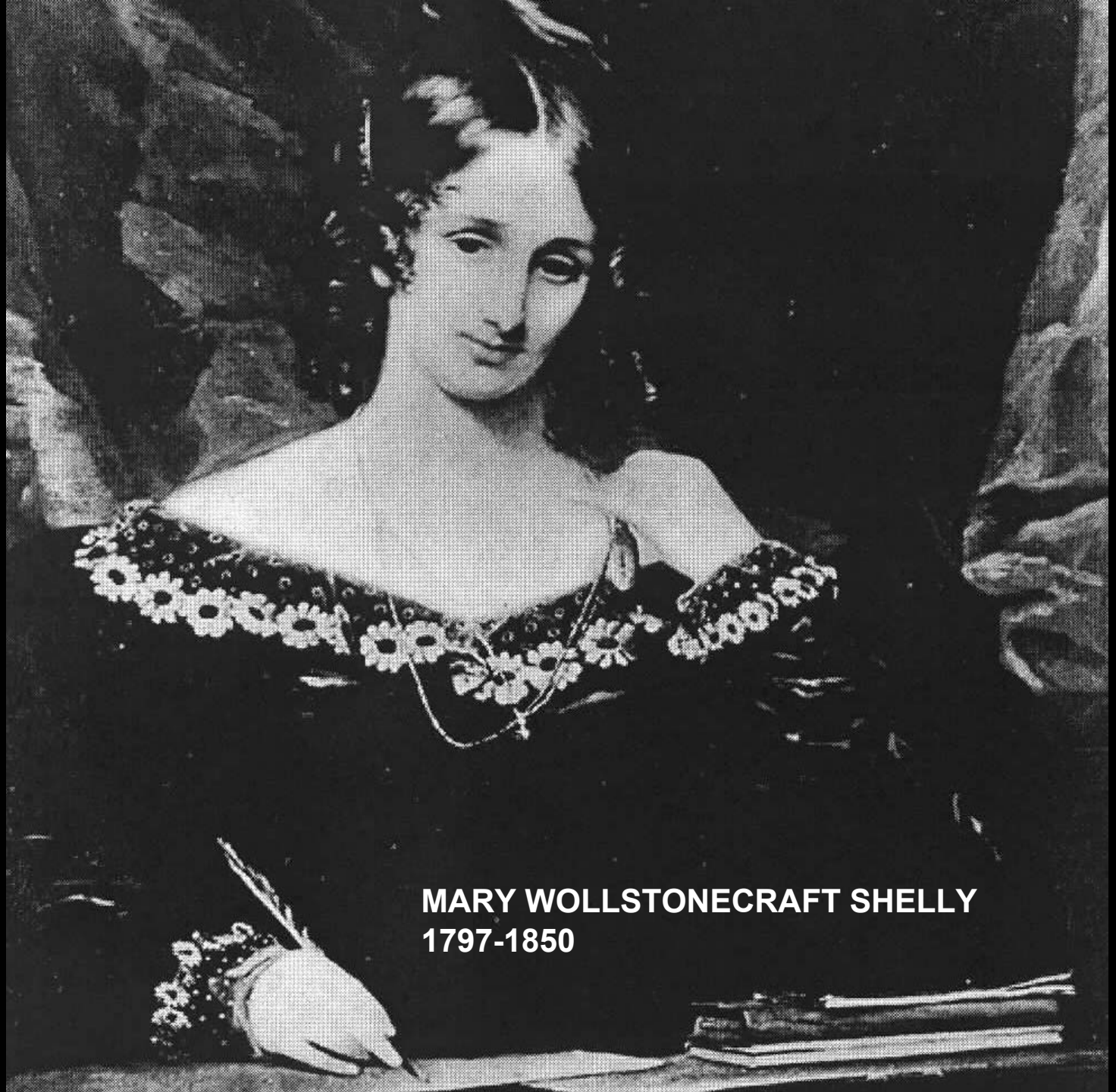
THE LEGACY OF FRANKENSTEIN

REGENERATIVE BIOLOGY AND MEDICINE

DAVID L. STOCUM
SCHOOL OF SCIENCE, IUPUI
and
INDIANA UNIVERSITY CENTER FOR REGENERATIVE BIOLOGY AND MEDICINE



MARY WOLLSTONECRAFT SHELLY
1797-1850

FRANKENSTEIN, or
A MODERN PROMETHEUS

American Association for the Advancement of Science

SCIENCE

4 April 1997
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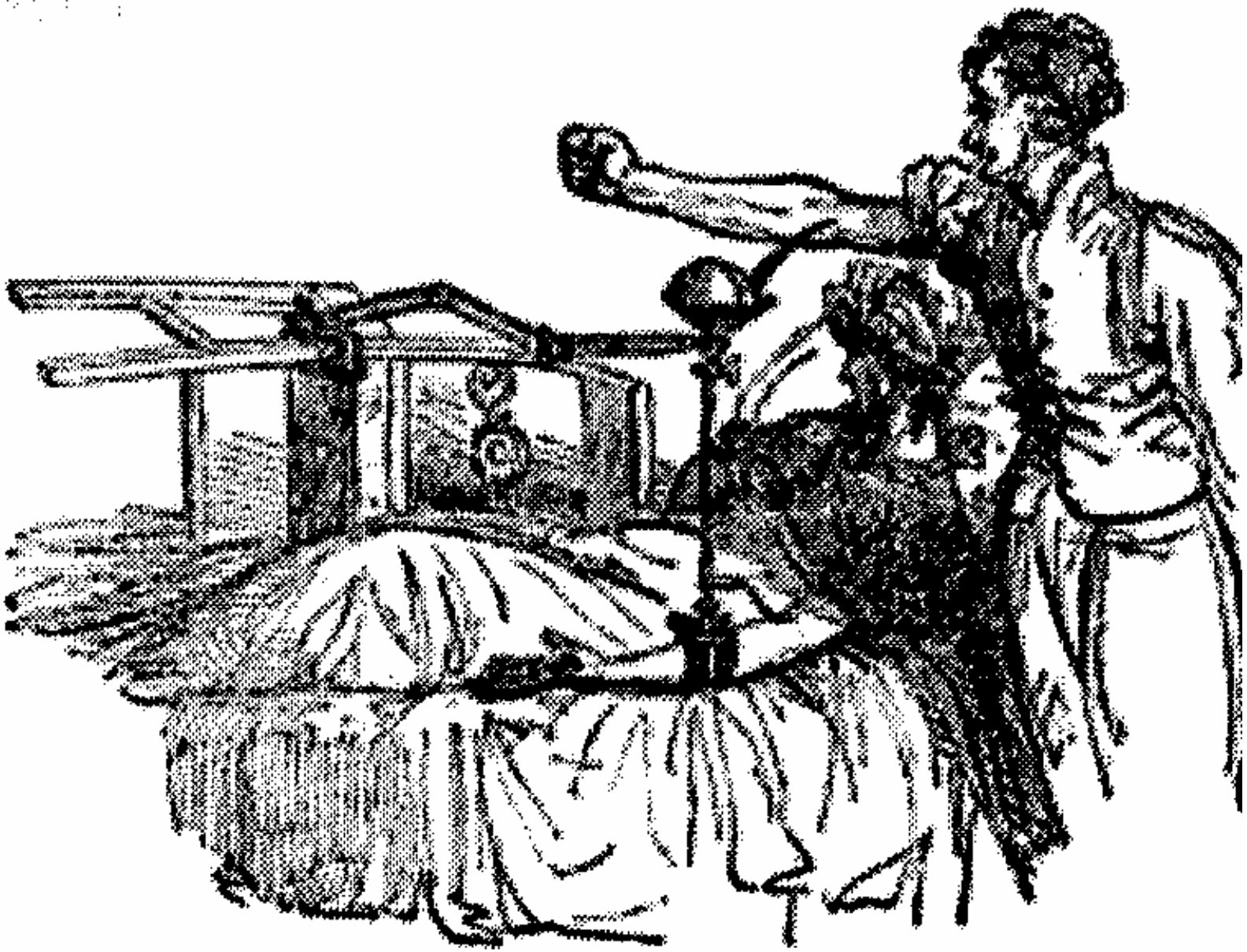
Frontiers in Medicine
Regeneration

FRANKENSTEIN IN THE 20TH CENTURY

TISSUE AND ORGAN TRANSPLANTS

ALLOGENEIC TRANSPLANT

A TRANSPLANT BETWEEN TWO DIFFERENT INDIVIDUALS OF THE SAME SPECIES

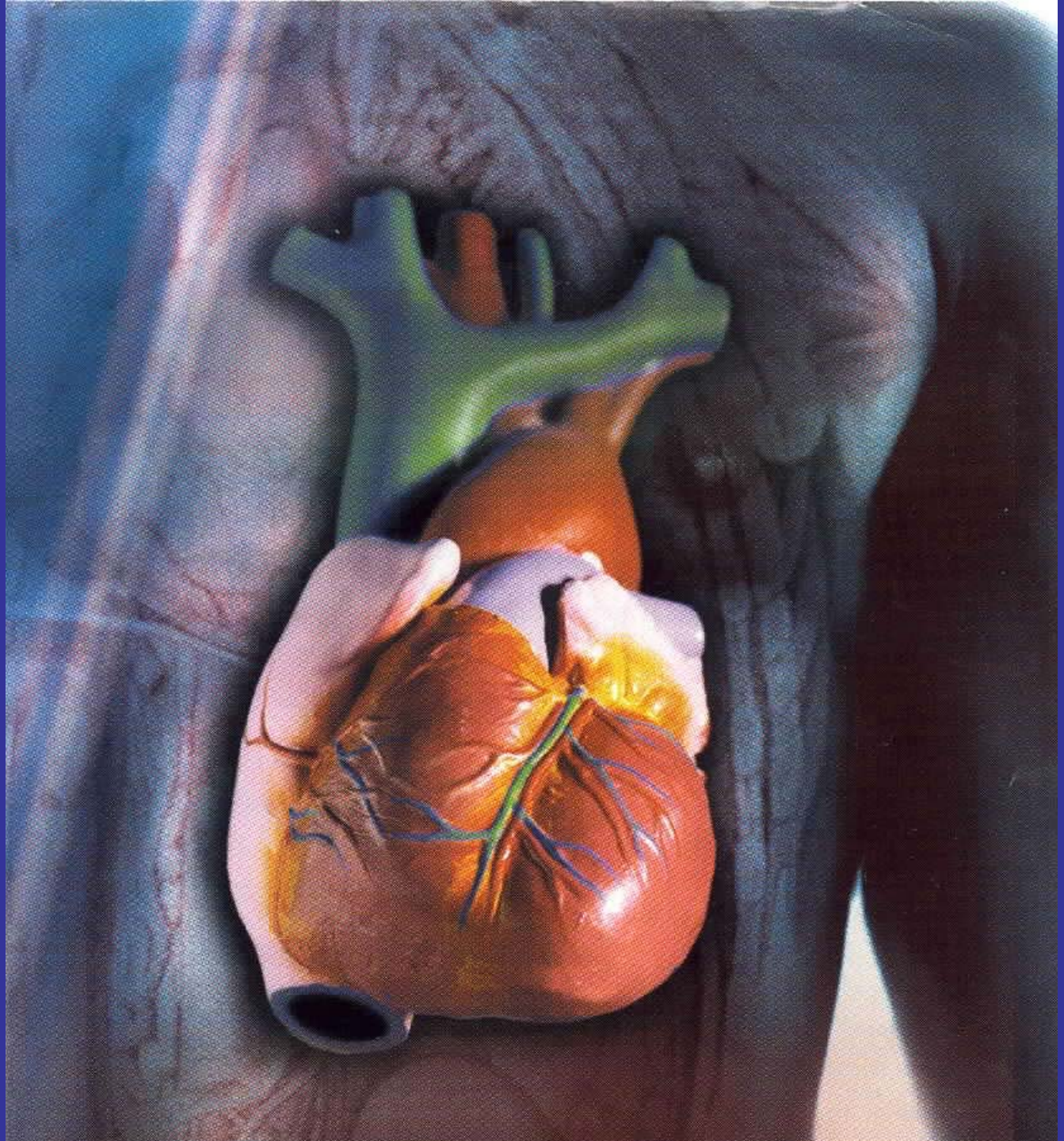


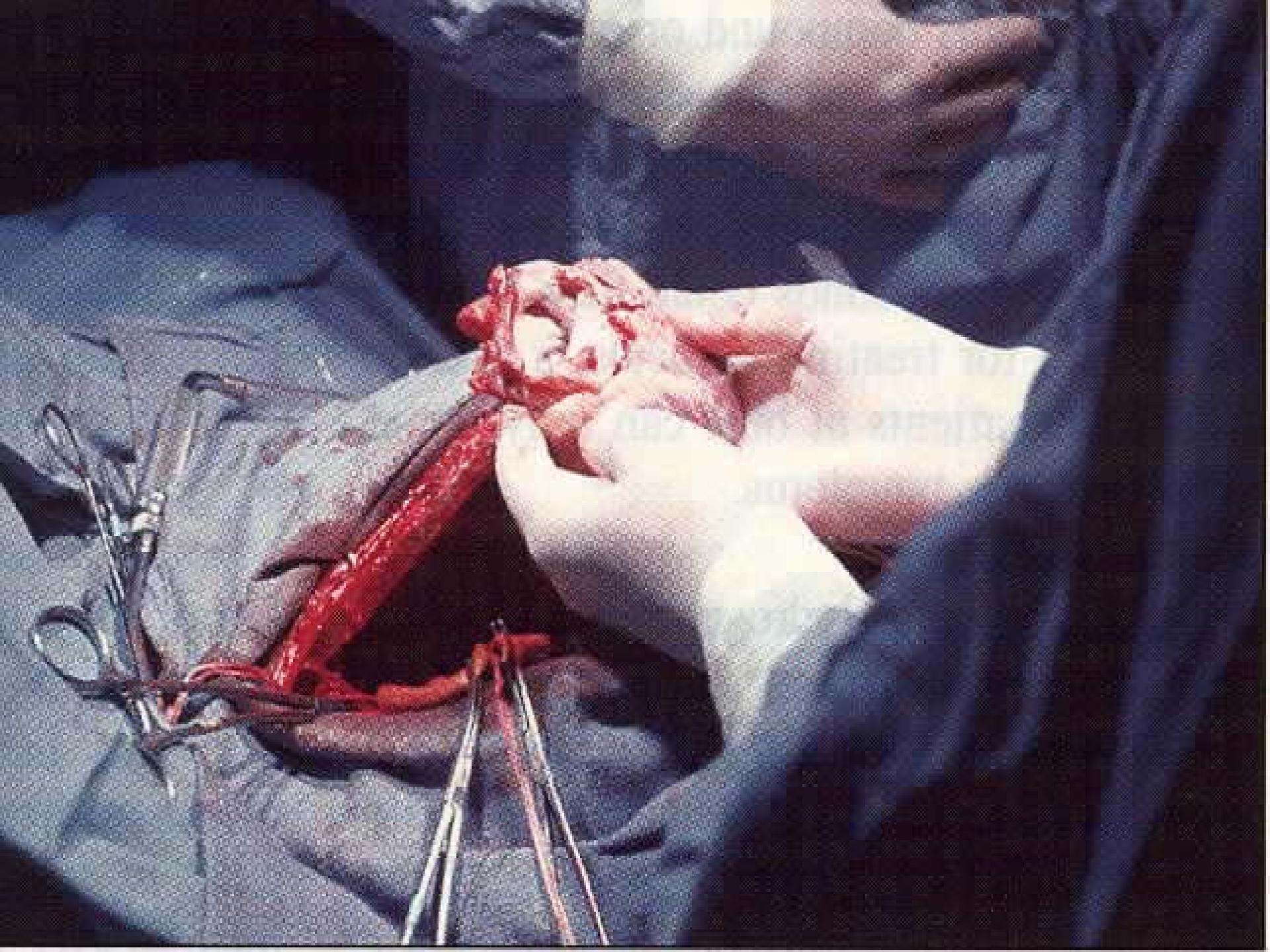
BLUNDELL'S GRAVITATOR, 1828

KARL LANDSTEINER

1900

A, B, O, AB BLOOD GROUPS





HEART TRANSPLANT HISTORY

- 1964--JAMES HARDY, UNIVERSITY OF MISSISSIPPI (CHIMPANZEE DONOR)
- 1967--CHRISTIAN BARNARD, CAPE TOWN, SOUTH AFRICA; ADRIAN KANTROWITZ, COLUMBIA UNIVERSITY
- 1968--MORE THAN 100 TRANSPLANTS PERFORMED
- 1980S--SIGNIFICANT CLINICAL SUCCESS WITH INTRODUCTION OF CYCLOSPORINE AS IMMUNOSUPPRESSANT

SURVIVAL RATES OF HEART RECIPIENTS

- 1 YEAR---78.3%
- 5 YEAR--66.8%
- 10 YEAR--52.5%

XENOTRANSPLANT

A TRANSPLANT FROM ONE SPECIES TO ANOTHER
(E.G., PIG TO HUMAN)


ORGAN DONORS

Xenotransplant experts express caution over knockout piglets

Declan Butler

The safe transplantation of pig organs into human patients remains several steps from realization, experts say. Two announcements that research teams have cloned pigs lacking a gene involved in graft rejection still leave several obstacles to xenotransplantation intact, according to most specialists in the field.

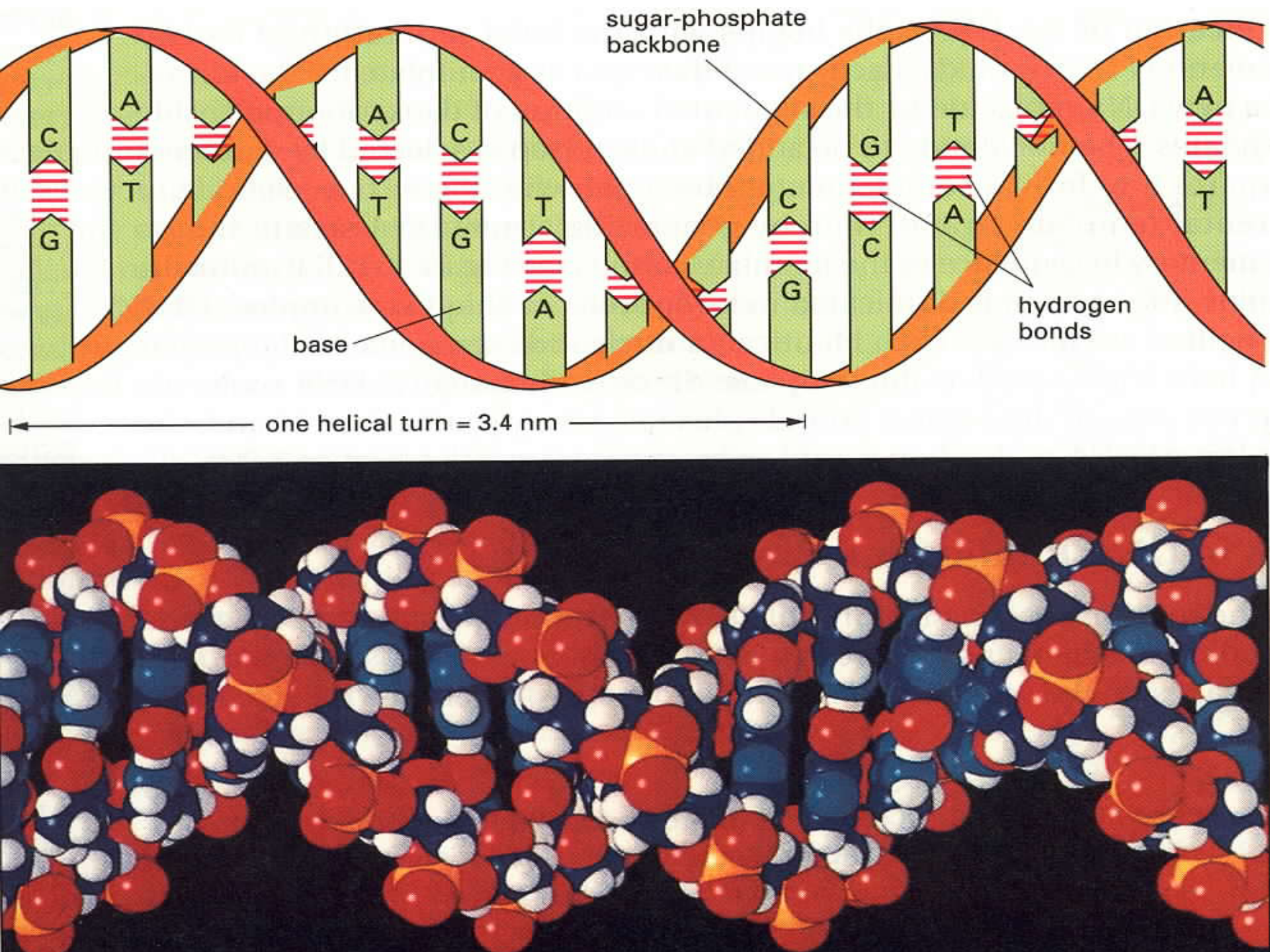
On 2 January, PPL Therapeutics, the Scottish company that cloned Dolly the sheep, announced the birth on Christmas Day of five cloned knockout female piglets. Each had an inactivated gene for α-1,3-galactosyl transferase, an enzyme that adds the sugar α-1,3-galactosyl, or alpha-gal, to the surface of pig cells. The immune systems of humans and Old World primates, who lost this enzyme in evolution, recognize the sugar as foreign and kill transplanted pig organs in minutes.

The timing of PPL's statement was widely interpreted as an attempt to steal the thunder

Porker potential: but the effects of fully deleting a gene that blocks xenotransplants are not known.

NATURE 415:103, 2002

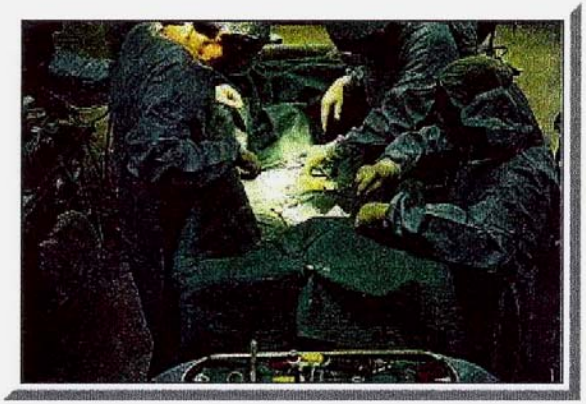
RECOMBINANT DNA


sugar-phosphate backbone
C
A
T
G
A
T
C
G
T
A
base
G
C
T
A
C
G
T
A
hydrogen bonds
one helical turn = 3.4 nm

RESURRECTION: CRYOGENIC PRESERVATION

POPULAR SCIENCE

Can Science Raise the Dead?



BioPreservation, Inc.

The best equipment
The most highly qualified personnel
A serious commitment to suspended animation research

BPI Personnel

Cryopreservation Protocol for BioPreservation Clients (42 KBytes)

BPI Tech Briefs

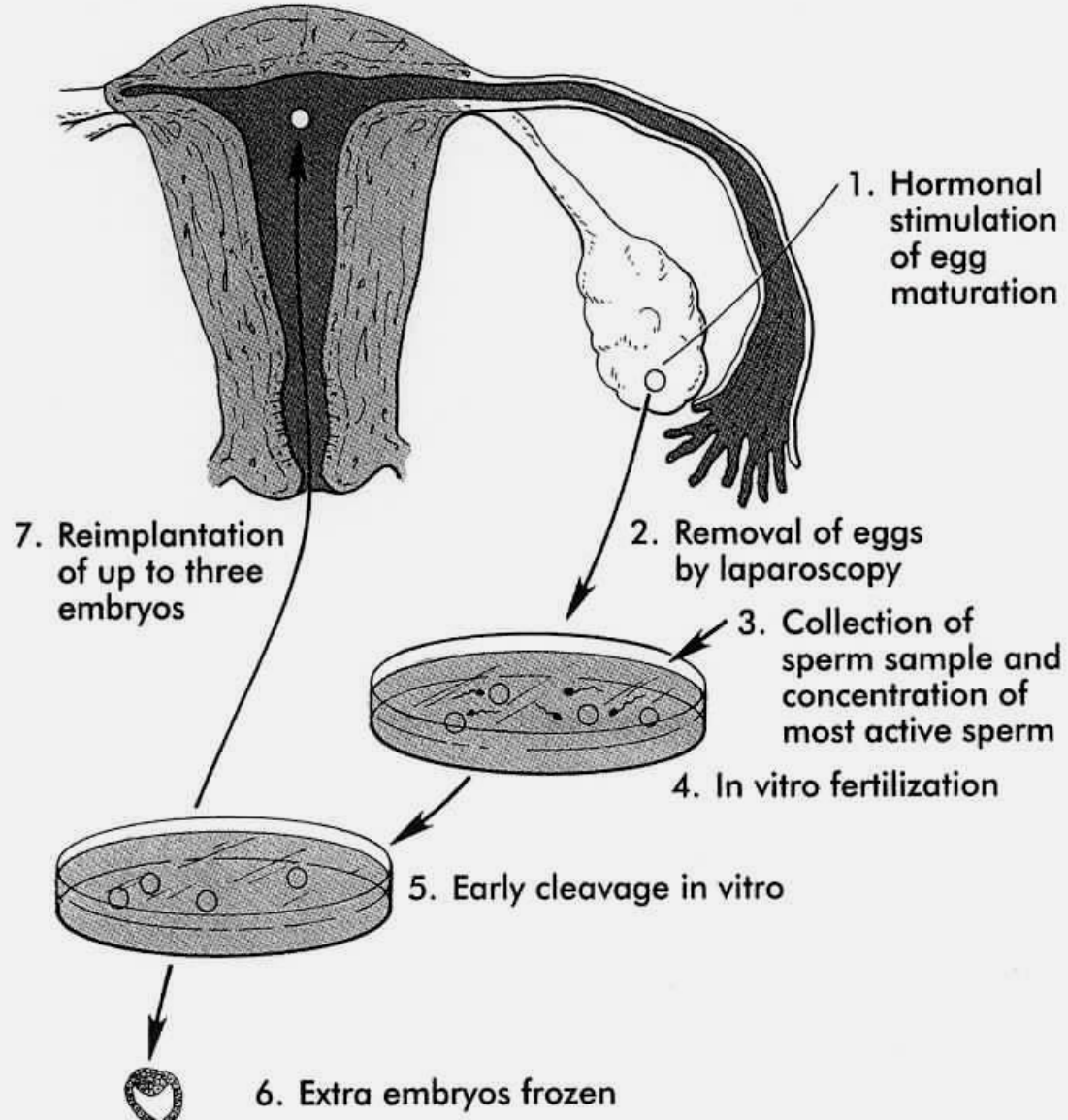
1. Introducing BioPreservation, Inc. (BPI) (19 KBytes)
2. BPI Protocol for Brain Cryopreservation Research (48 KBytes)
3. A Possible Origin for the Burr Hole Drainage Problem (19 KBytes)
4. The Pathophysiology of Cerebral Ischemia (56 KBytes)
5. Air Emboli During Perfusion of the Cryopreservation Patient (20 KBytes)
6. Identification & Assessment of BPI Cryopreservation Patients (31 KBytes)
7. Infection Control in the Standby and Transport Settings (69 KBytes)
8. BioPreservation: Suspension Technology Report (21 KBytes)
9. Case History of ACS Patient 9577 (J. White) Part I (19 KBytes), Part II (18 KBytes), Part III (27 KBytes)
   Case Report Conclusions for J. White (17 KBytes)
10. Standby and Transport (14 KBytes)
11. Perspectives on Death and Dying Today (23 KBytes)
12. Meeting the Needs of Patients and Family (31 KBytes)
13. Dealing with the Patient's Health Care Providers (36 KBytes)
14. Home Hospice (21 KBytes)
15. Standby and Transport Logistics (44 KBytes)
16. Summary of BPI's Canine Brain Cryopreservation Results (48 KBytes)
17. The Flu and You (9 Kbytes)
18. Cryopreservation of CryoCare Patient #C-2150: Part I (26 Kbytes) and Part II (33 Kbytes)
19. Liquid Ventilation: A Bypass on the Way to Bypass (21 KBytes)
20. Premedication of Human Cryopreservation Patients (70 KBytes)
21. Anesthesia in Cryopatients (7 KBytes)
22. Temperature Monitoring of Cryopatients (17 KBytes)
23. Hemostasis in Cryopatients (14 KBytes)

Services

ASSISTED REPRODUCTIVE TECHNOLOGY

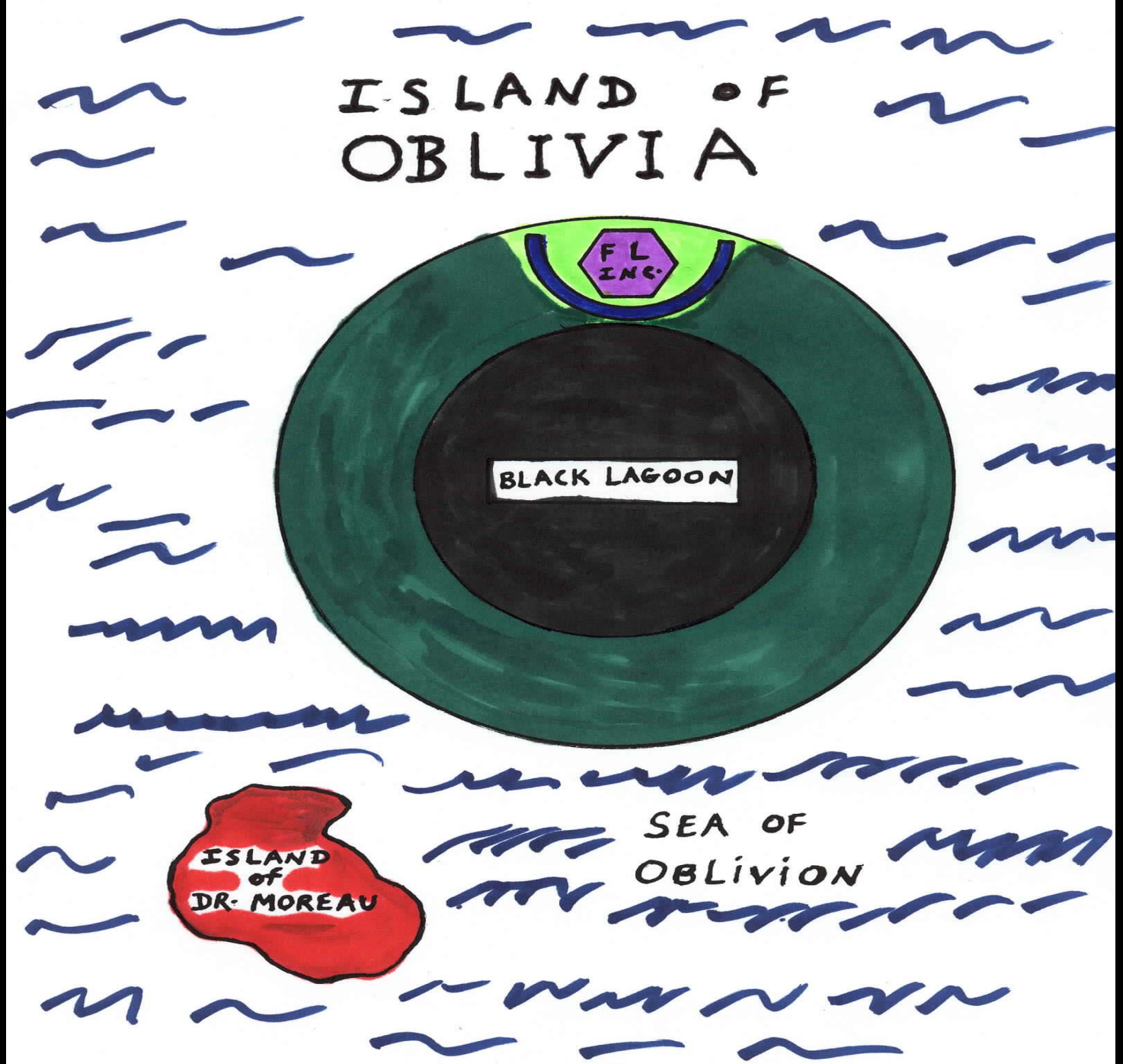
IN VITRO FERTILIZATION

FROM B.M. CARLSON (1994) HUMAN EMBRYOLOGY AND DEVELOPMENTAL BIOLOGY




G A T T A C A

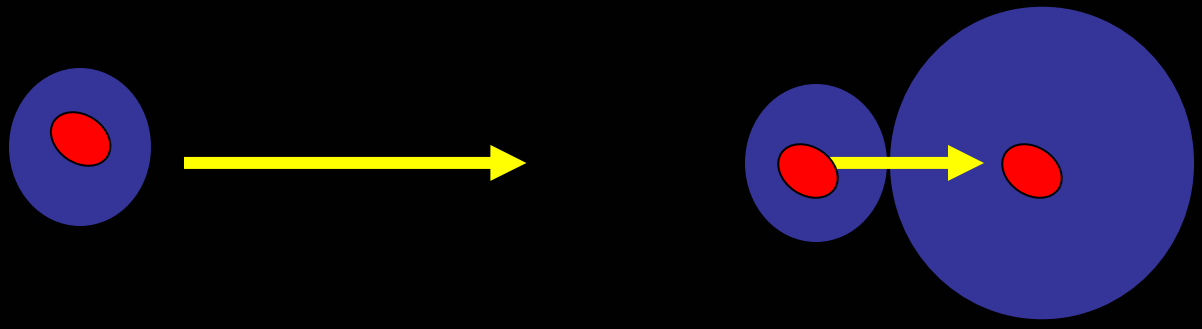
FRANKENSTEIN IN THE 21ST CENTURY


ISLAND OF
OBLIVIA
F L
INC.
BLACK LAGOON
ISLAND
of
DR. MOREAU
SEA OF
OBLIVION

REPRODUCTIVE CLONING

NUCLEAR TRANSFER

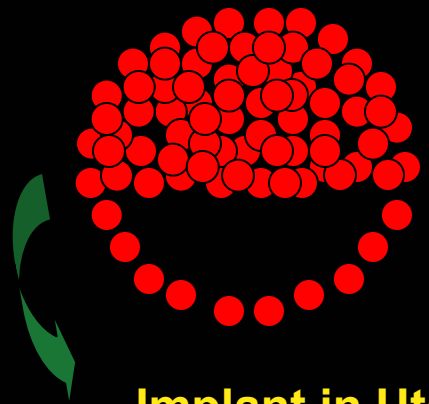
SOMATIC CELL NUCLEUS TRANSFERRED INTO ENUCLEATED EGG



Somatic cell

Enucleated egg

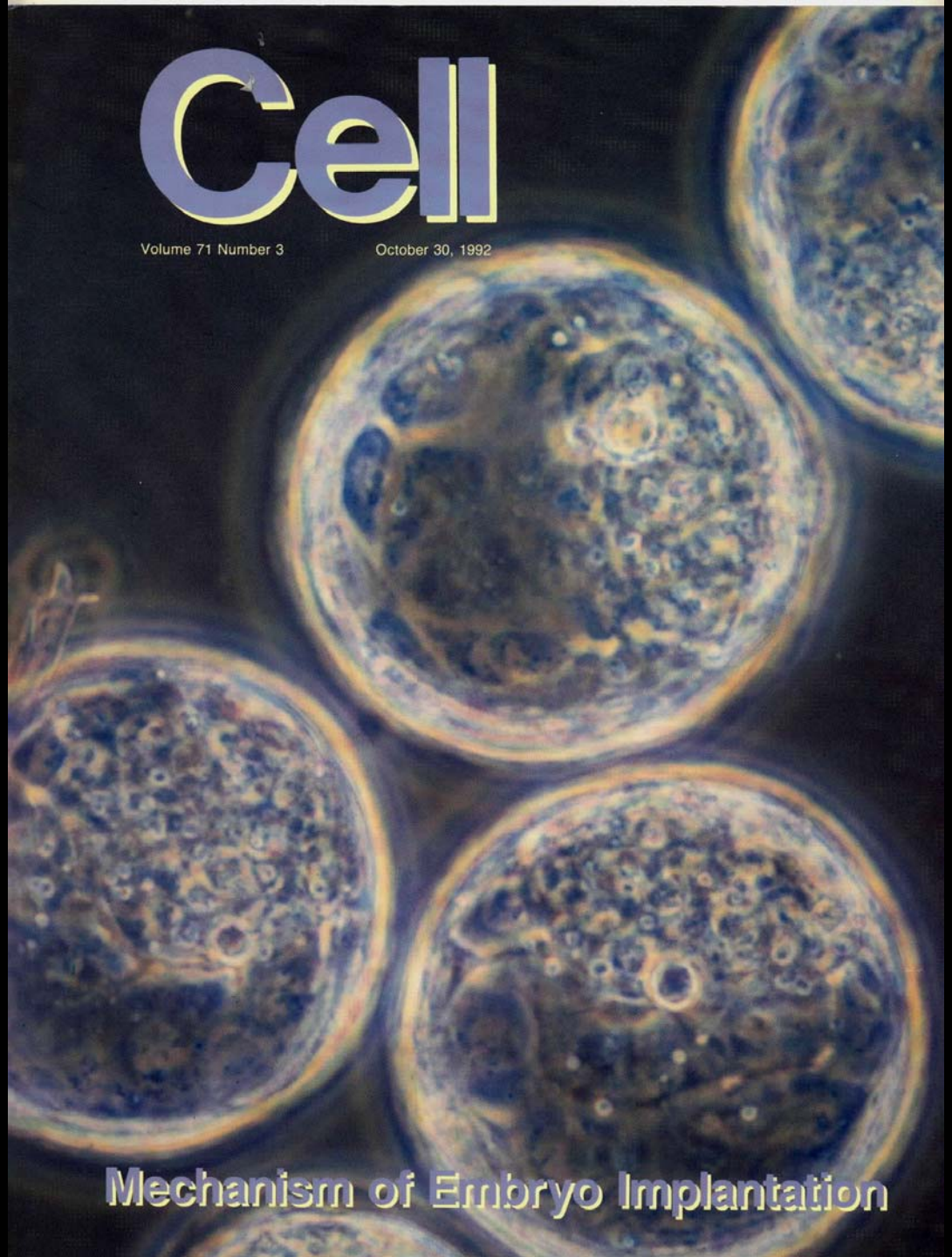
Divide to Blastocyst



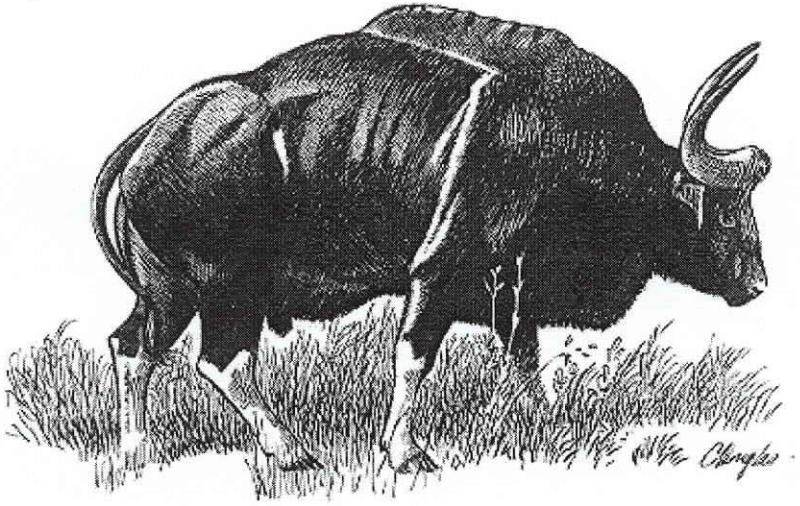
Implant in Uterus

8-CELL STAGE

BLASTOCYSTS



Gaur



Bos gaurus
Endangered

Most people know that cows are a domesticated version of the wild cattle that ranged through the Old World thousands of years ago. Wild cattle still run in small herds in the hilly forests of India, Burma, and the Malay peninsula, and these are the gaurs. Each herd is led by a huge old bull, with the finest horns, a sleek, dark brown coat, and white "stockings." One of this animal's distinguishing features is the saddlelike-hump on their back.

Gaurs are huge animals; they can measure 2 m at the shoulder and can weigh 900 kg. They were once hunted by sportsmen in India as "big game" as was the American bison. Because of their size and strength, and since the Indian tiger is now almost extinct, they have few predators other than man.

WHY NOT CLONE PEOPLE?

- CLONING DOES NOT PROVIDE GENETIC VARIATION
- LESS THAN 3% OF ANIMAL CLONES DEVELOP TO LIVE BIRTH (PRIMATES = 0%)
- MANY, IF NOT MOST, CLONES THAT ARE BORN HAVE ABNORMALITIES.
- EVEN MORE EVIL EXPERIMENTS ARE POSSIBLE

REGENERATION: THE ABILITY TO REPRODUCE THE ORIGNAL STRUCTURE OF A TISSUE, ORGAN OR APPENDAGE

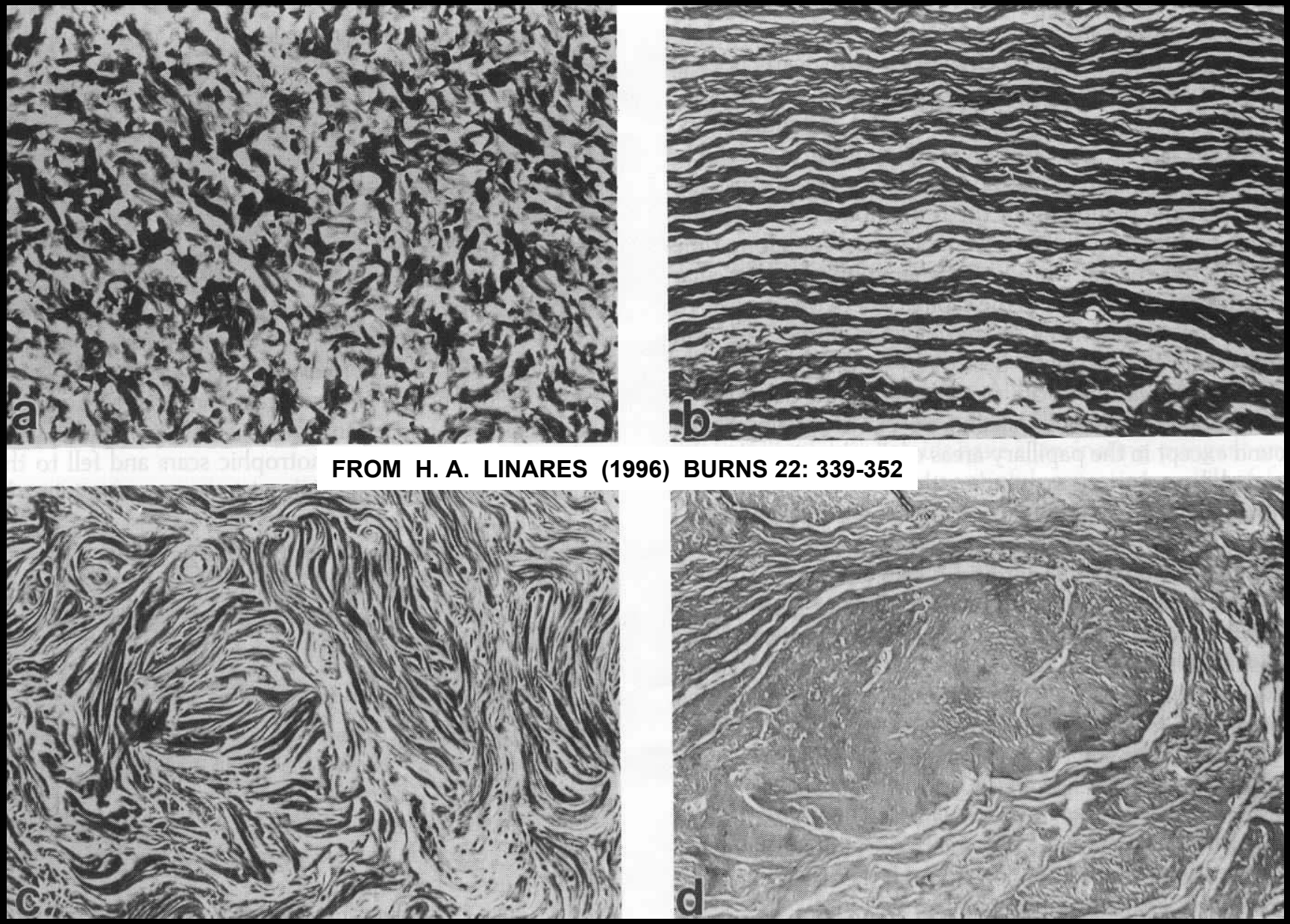
HUMAN TISSUES THAT REGENERATE VIA STEM CELLS

- BLOOD
- EPITHELIA (SKIN, DIGESTIVE SYSTEM, RESPIRATORY SYSTEM, SMALL BLOOD VESSELS)
- PERIPHERAL NERVES
- OLFACTORY NERVE AND BULB
- BONE
- MUSCLE
- HAIR
- FINGERTIPS


a
a
b
b

HUMAN TISSUES THAT SCAR

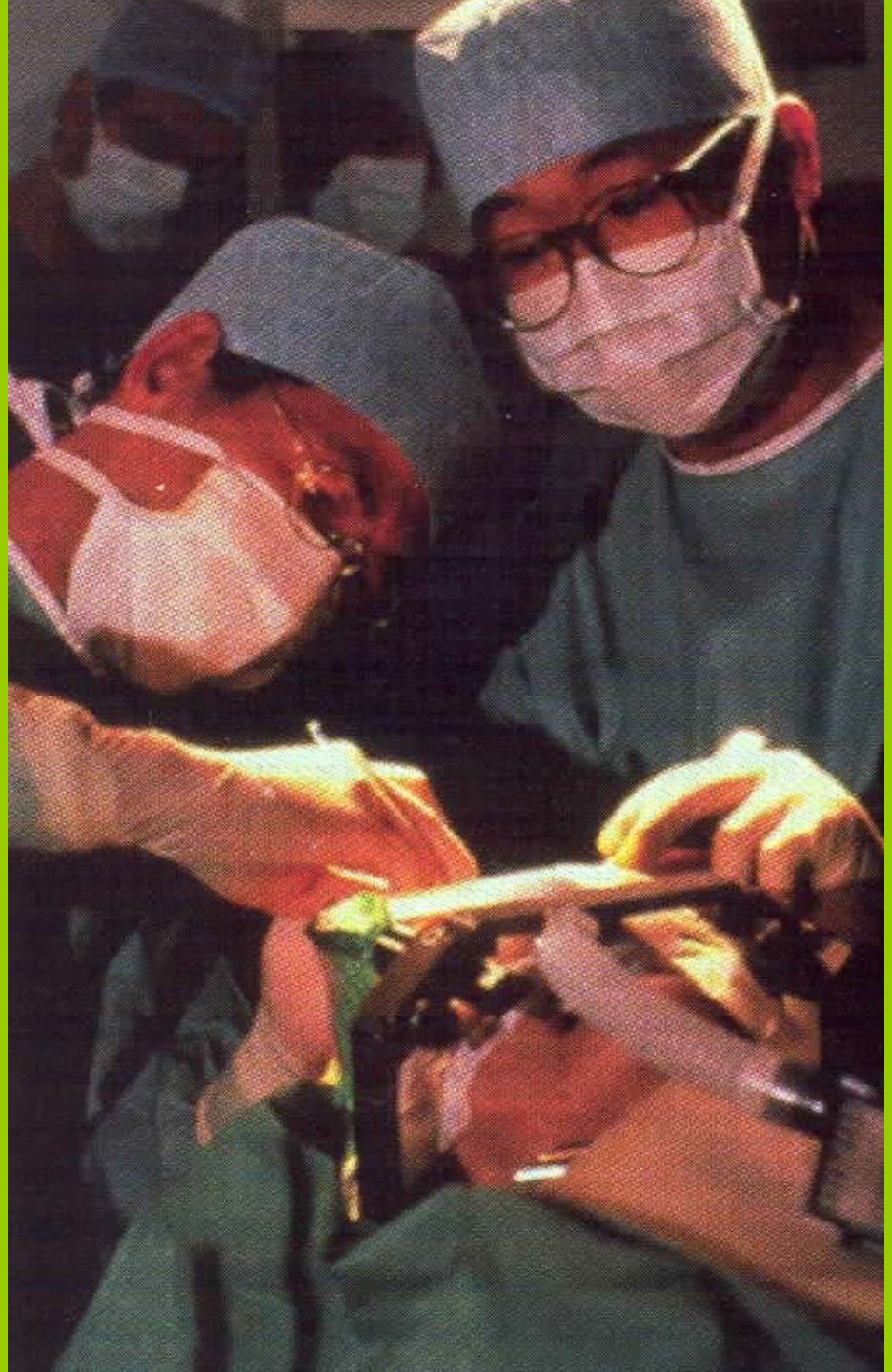
- BRAIN
- SPINAL CORD
- DERMIS OF THE SKIN
- ARTICULAR CARTILAGE
- LIGAMENTS
- MENISCUS OF KNEE
- LUNG TISSUE
- HEART MUSCLE
- KIDNEY TISSUE
- PANCREAS
- LENS AND RETINA OF EYE
- APPENDAGES
- ENDOCRINE TISSUES
- TENDON
- INTESTINE
- LARGE BLOOD VESSELS
- INNER EAR TISSUE
- REPRODUCTIVE TISSUES
- STOMACH
- ESOPHAGUS



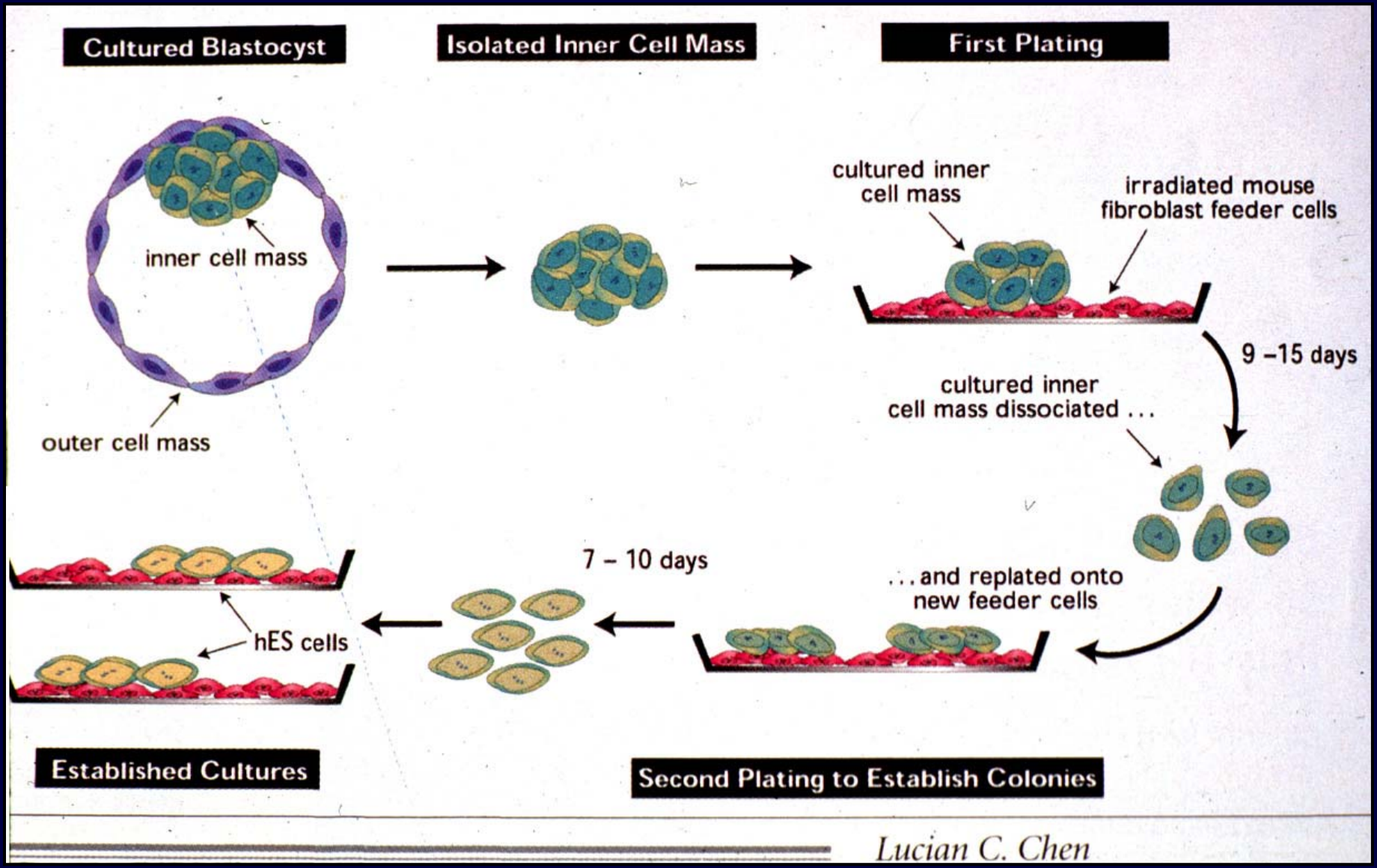
FROM H. A. LINARES (1996) BURNS 22: 339-352

STEM CELL TRANSPLANTS

FETAL CELL TRANSPLANTS FOR PARKINSON'S DISEASE



EMBRYONIC STEM CELLS

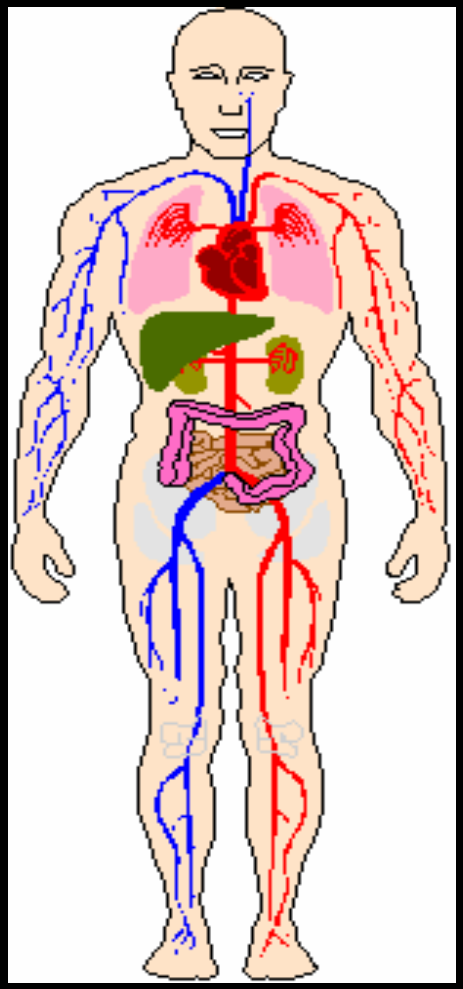

Cultured Blastocyst
Isolated Inner Cell Mass
First Plating
inner cell mass
outer cell mass
cultured inner cell mass
irradiated mouse fibroblast feeder cells
9 –15 days
cultured inner cell mass dissociated . . .
. . . and replated onto new feeder cells
7 – 10 days
hES cells
Established Cultures
Second Plating to Establish Colonies
Lucian C. Chen

EMBRYONIC STEM CELL DERIVATIVES

→

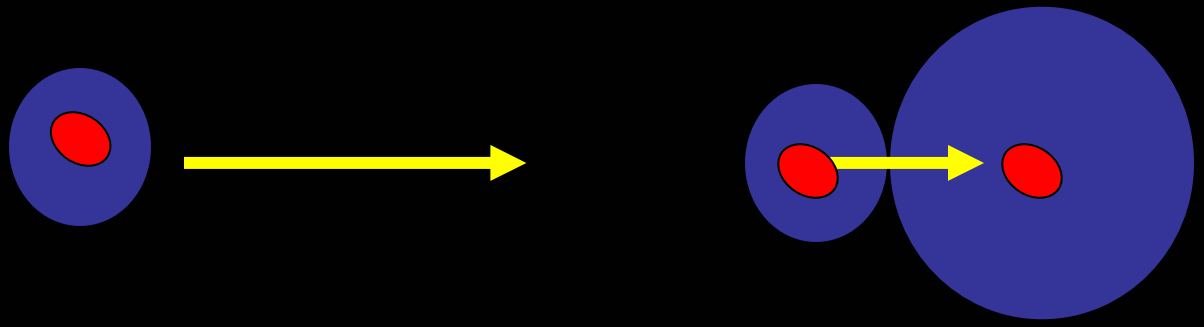
TRANSPLANT

→



THERAPEUTIC CLONING

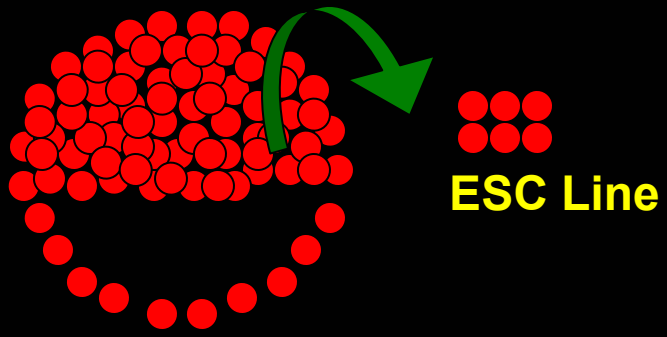
SOMATIC CELL NUCLEUS TRANFERRED INTO ENUCLEATED EGG



Somatic cell

Enucleated egg

Divide



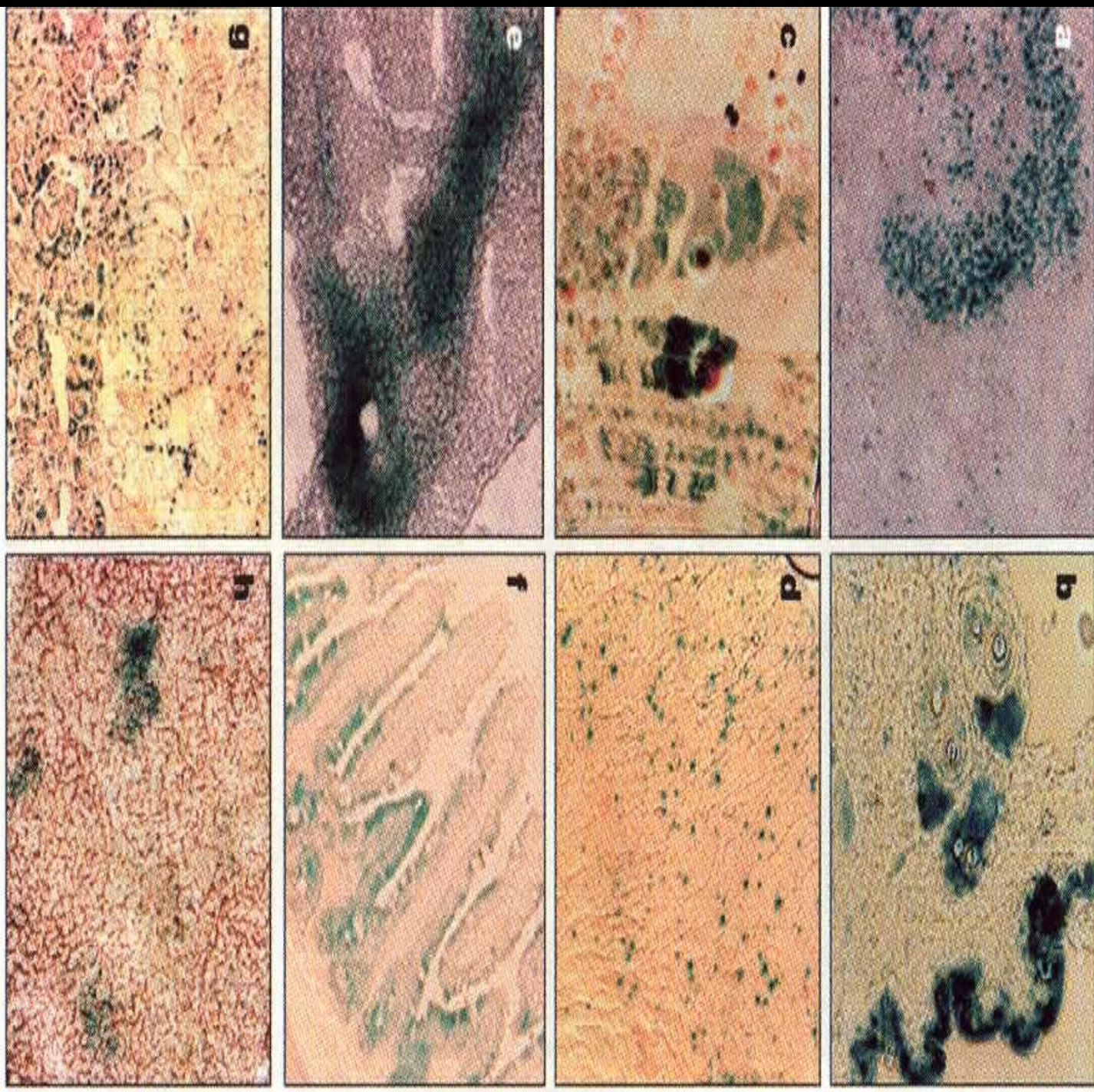
NO IMMUNOREJECTION!

ADULT BONE MARROW STEM CELLS

- PLURIPOTENT
- NO IMMUNOREJECTION
- NO BIOETHICAL CONCERNS

CHIMERIC EMBRYO ASSAY

CHIMERIC EMBRYO ASSAY MAPCs
JIANG ET AL, 2002, NATURE 418:41

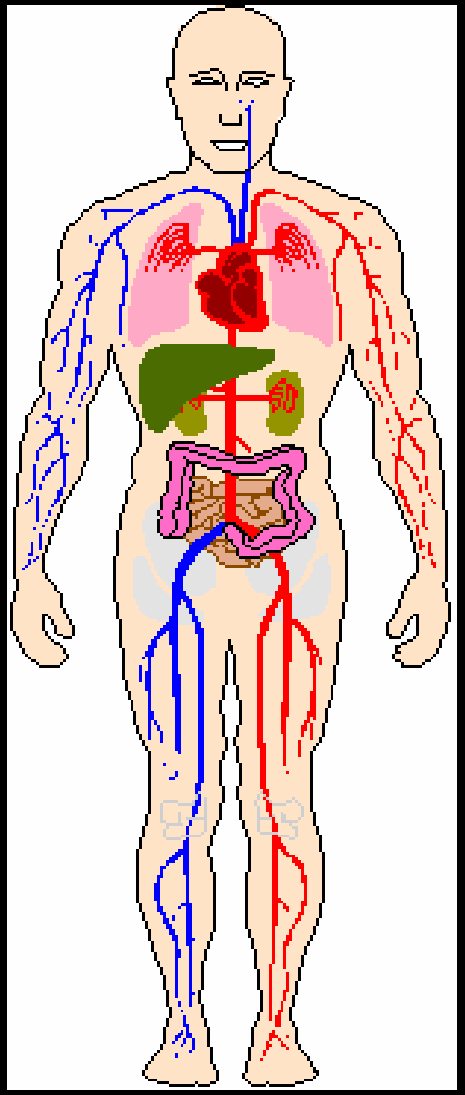


ISSUES ON USE OF BONE MARROW STEM CELLS IN REGENERATIVE MEDICINE

- PAINFUL TO HARVEST
- PLURIPOTENCY EXHIBITED ONLY AFTER MANY DOUBLINGS IN VITRO
- FREQUENCY OF CONVERSION TO OTHER CELL TYPES IS VARIABLE AND RELATIVELY LOW
- NOT TESTED IN A VARIETY OF INJURY ENVIRONMENTS
- DON'T KNOW HOW LONG THEY REMAIN FUNCTIONAL
- RESULTS NOT REPRODUCIBLE
- EXPENSIVE!

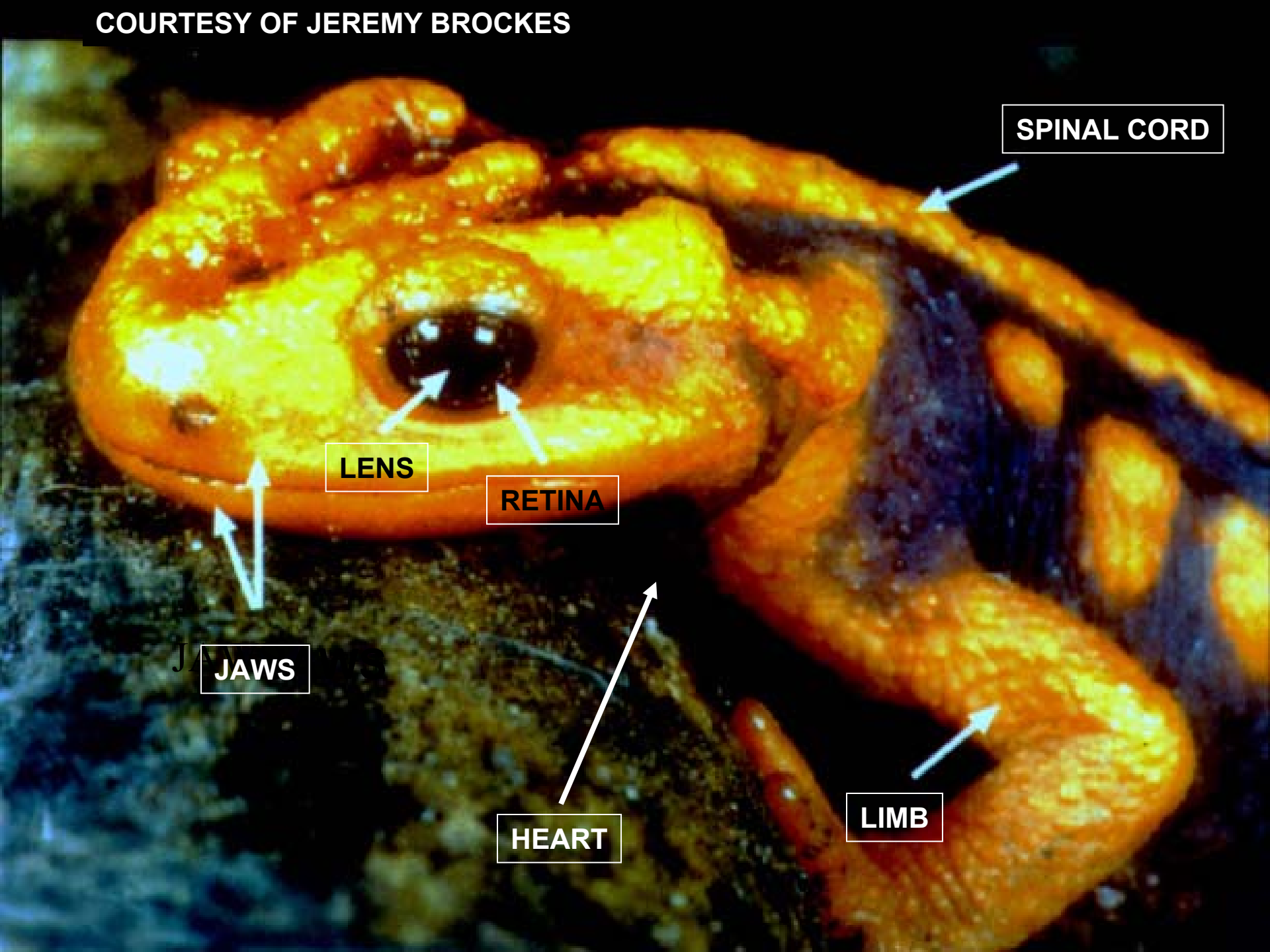
THE FUTURE OF REGENERATIVE MEDICINE

CHEMICAL INDUCTION OF REGENERATION FROM THE BODY'S OWN CELLS



- NO CELL TRANSPLANTATION REQUIRED
- NO CELL CULTURING REQUIRED
- SIMPLE INJECTION OF REGENERATION-PROMOTING / SCAR INHIBITING MOLECULES
- INEXPENSIVE!

THE AMPHIBIANS: STRONG REGENERATORS


COURTESY OF JEREMY BROCKES
SPINAL CORD
LENS
RETINA
JAWS
HEART
LIMB

FROM R.J. GOSS (1969) PRINCIPLES OF REGENERATION

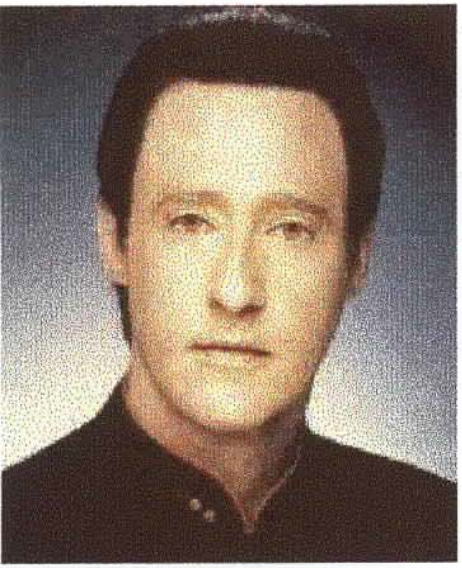

David Stocum


David Stocum


David Stocum

FRANKENSTEIN'S STRATEGY

1. IDENTIFY ALL THE GENES AND PROTEINS RESPONSIBLE FOR REGENERATION IN SPECIFIC AMPHIBIAN TISSUES
2. IDENTIFY THE HUMAN COUNTERPARTS
3. USE THE GENES AS GENE THERAPY OR THE PROTEINS AS MOLECULAR COCKTAILS TO STIMULATE REGENERATION IN NON-REGENERATING HUMAN TISSUES



NFN NMI Data

Lieutenant Commander
DOB: February 2, 2338
LOB: Omicron Theta (Kiron III)

THE LEGACY (AND LESSON) OF FRANKENSTEIN

- THE HUMAN DRIVE TO KNOW PITS ADVANCE VS. THE STATUS QUO
- THE UNACCEPTABLE BECOMES THE STATUS QUO OR GENERATES AN ALTERNATIVE
- THIS CYCLE NEVER ENDS
- FRANKENSTEIN IS A SYMBOL OF BOTH FEAR *AND* HOPE

SELECTED CAST OF FRANKENSTEINS

JOHN BLUNDELL
KARL LANDSTEINER
CHRISTIAN BARNARD
DAVID WHITE
JAMES WILSON
PATRICK STEPTOE
IAN WILMUT
MICHAEL WEST
JAMES THOMSON
AKIRA ONISHI
TERUHIKO WAKAYAMA

EVERYONE AT THIS WORKSHOP