Topping and tailing:

A not-very-progressive professional life in neurological research

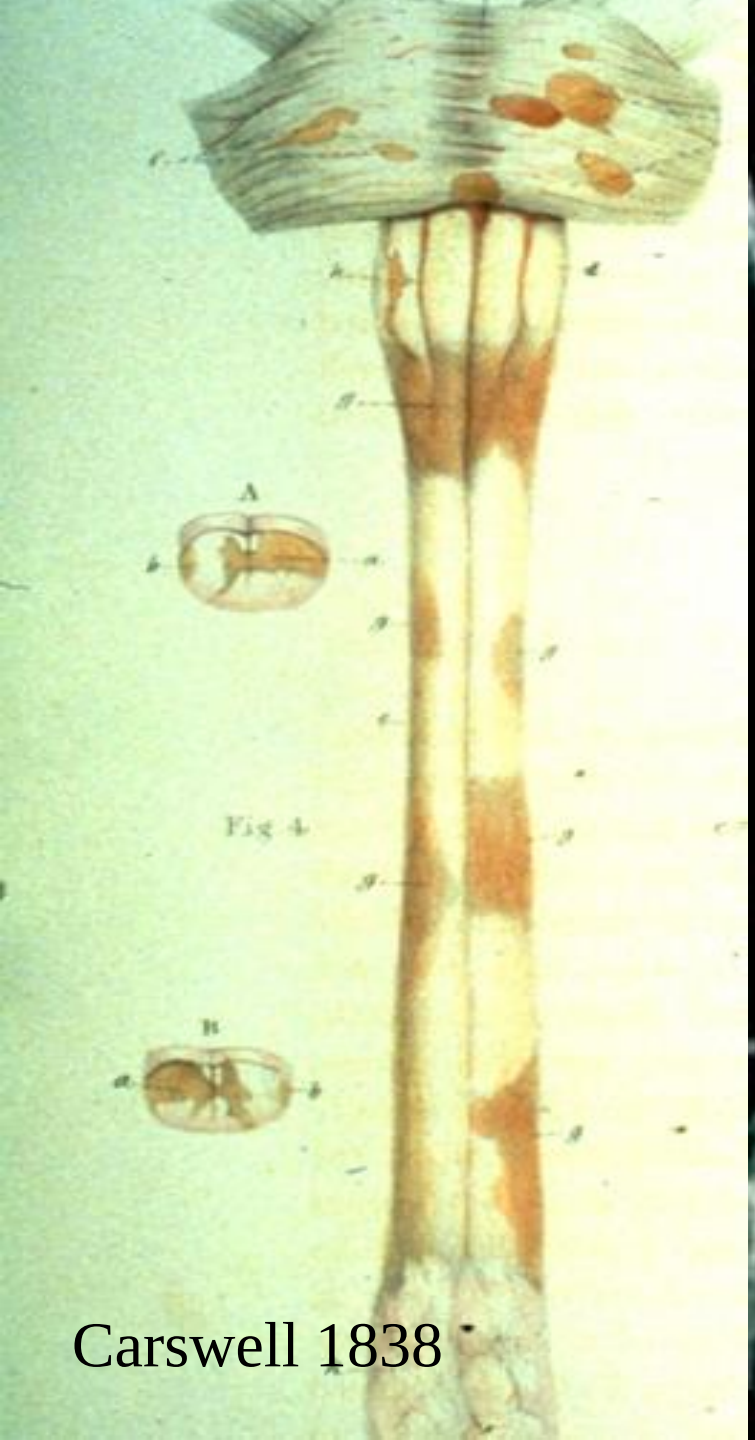
Neil Scolding

Emeritus Professor of Clinical Neuroscience, Consultant Neurologist

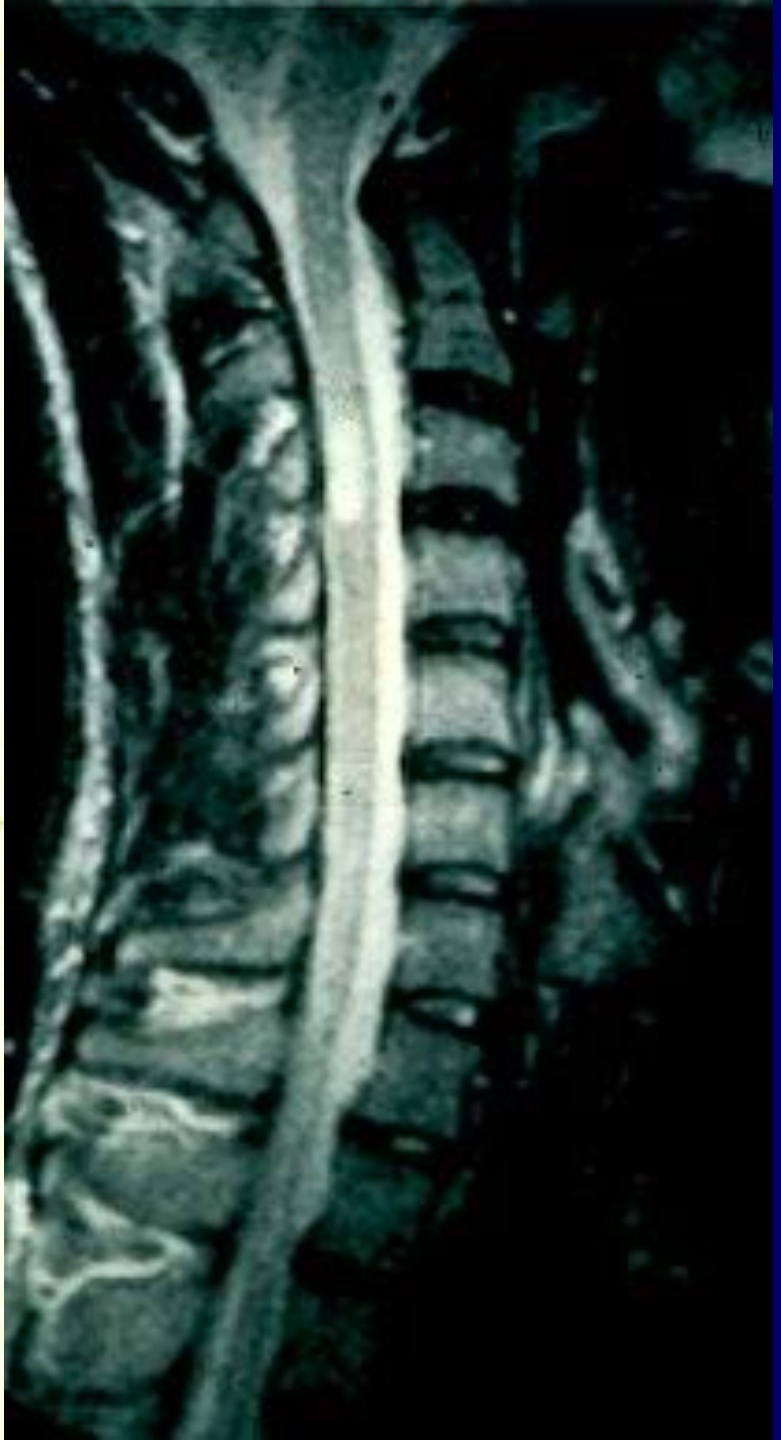
University of BRISTOL

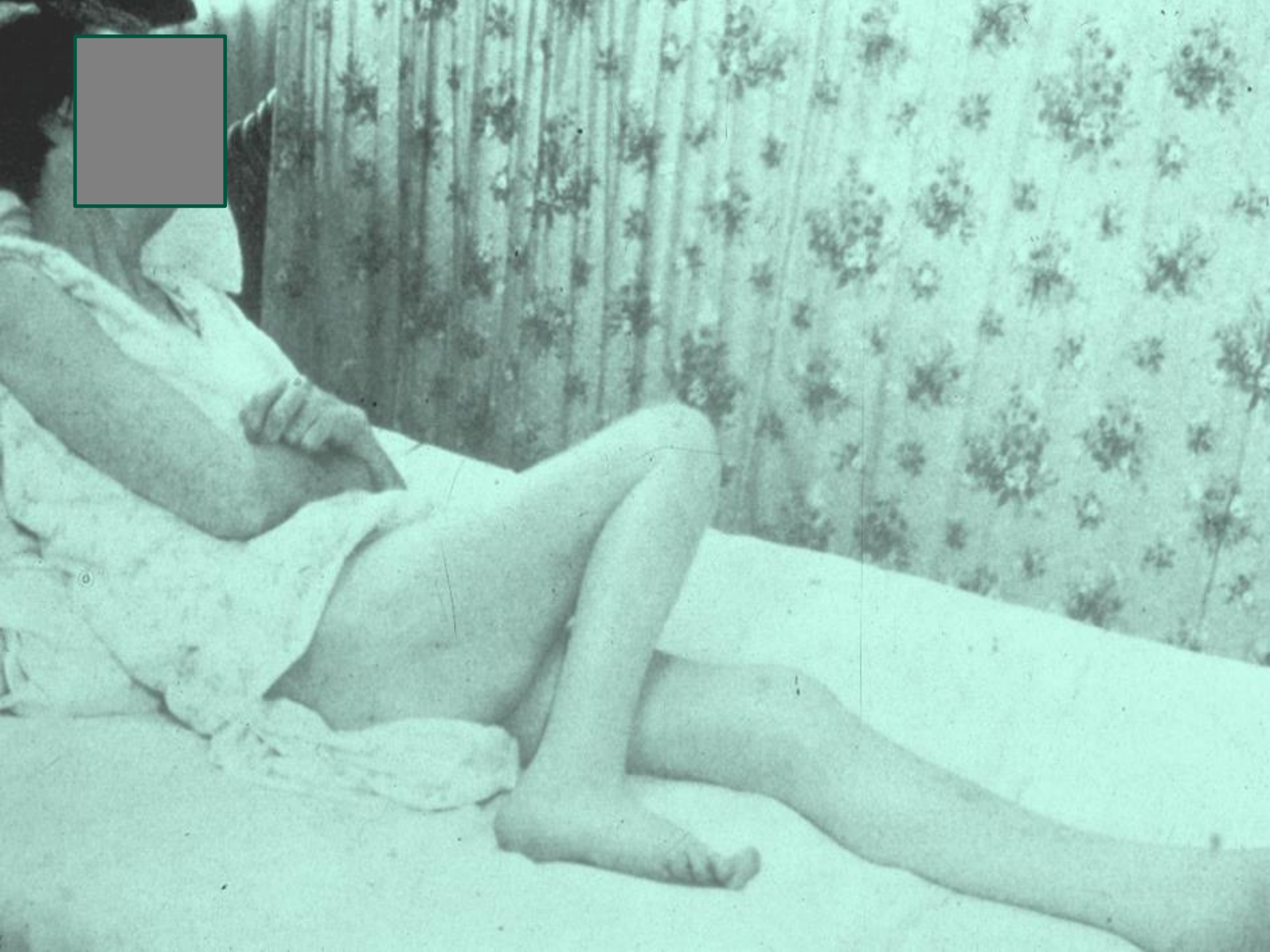
North Bristol NHS NHS Trust

Bristol Institute of Clinical Neurosciences



Carswell 1838






Assisted Dying


DAILY EXPRESS
INFLATION PLUNGES
It's beginning to look a lot like... bounce back
'OUR HOUSE FEELS EMPTY WITHOUT HER LAUGHTER'
WE MUST GIVE DAME ESTHER HER FINAL CAMPAIGN VICTORY


Mirror
GET YOUR Mirror Mirror 70P A DAY FOR SIX MONTHS
John Pilger dies at 84
With the power of words he fought for truth & justice
FREE INSIDE
Slimming World
yes you can
RECIPE SPECIAL
PLUS JOIN Slimming World FOR FREE
ASSISTED DYING DEBATE
GIVE US THE CHOICE
71% back call for law change as Esther Rantzen steps up 'free vote' bid

THE TIMES

Thursday August 23, 2012

My Las Vegas pool party

By Abigail Radnor News, page 5

Bonkbuster sex v Mummy Porn

By Jilly Cooper Times2

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In the end, "natural causes" intervened where the High Court would not. Within days of the verdict, he began having difficulty breathing. Over the weekend, his condition grew worse, prompting doctors to suspect an infection or a collapsed lung. By Monday evening, two GPs had visited the family home in Melksham. In the small, cramped bedroom that had become his world, Mr Nicklinson lay dribbling, refusing everything but the water his wife held to his lips.

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Continued on page 14, col 1

Fugitive tycoon guilty of £29m theft

Fiona Hamilton Crime Correspondent

Anil Nadir, one of Britain's most notorious fugitives, is facing a lengthy jail term for plundering his Polly Peck empire of almost £29 million.

The two decades that Nadir spent evading justice came to an abrupt end at the Old Bailey yesterday when he was convicted of ten charges of theft.

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How The Times brokered Asil Nadir's return

News, pages 8, 9

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Continued on page 9, col 5

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Why not?

PRINCIPLES

- ***Autonomy***
- ***Prevent indignity***
- ***Prevent suffering***

PRACTICE [REASONS TO BE CAUTIOUS]

- ***Slippery slope***
- ***Unintended consequences***
- ***Who else supports?***

Arguments for euthanasia/assisted dying

Autonomy

"right to die" [?]

= a **right to suicide**

- (Dignity in Dying do NOT support a general right to suicide)

- Rather, a right restricted disabled/sick/frail/elderly

Autonomy/personal freedom/choice

but choice is not an absolute

- buying/taking cocaine
- selling cocaine
- committing incest with a consenting adult
- wearing a seatbelt
- killing another individual even if consenting

Autonomy/personal freedom/choice

1994 UK Select Committee

"the interests of the individual cannot be separated from the interests of society...

....*dying is not only a personal or individual affair"*

Why not?

PRINCIPLES

- *Autonomy*
- ***Prevent indignity***
- *Prevent suffering*

PRACTICE [REASONS TO BE CAUTIOUS]

- *Slippery slope*
- *Unintended consequences*
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Prevent indignity?

all human beings have a basic worth or fundamental dignity

any other approach – 'quality of life' - *must* be **arbitrary**

Dignity is best protected by NOT putting the terminally ill, disabled, etc in

Why not?

PRINCIPLES

- *Autonomy*
- *Prevent indignity*
- ***Prevent suffering***

PRACTICE [REASONS TO BE CAUTIOUS]

- *Slippery slope*
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Prevent suffering?

- is killing the individual an appropriate response to suffering?
- *palliative care works*

(Belgium, 2002-7 : palliative care physician was consulted in only 12% of all cases of euthanasia)

The quality of death

Grim reapings

An attempt to rank end-of-life care in different countries

Jul 15th 2010 | from the print edition

CUSTOMER-SATISFACTION surveys are commonly used to improve the service in hotels and shops. Alas, they are unsuitable for rating the quality of death. So the Lien Foundation, a charity, commissioned the Economist Intelligence Unit, our sister company, to devise a ranking of end-of-life care. The report, published on July 14th, rates 40 mostly rich countries by how well they care for the dying.

Britain tops the table. For all the health-care [illegible], British doctors tend to be honest about prognoses. The mortally ill get plentiful pain killers. A well-established hospice movement cares for

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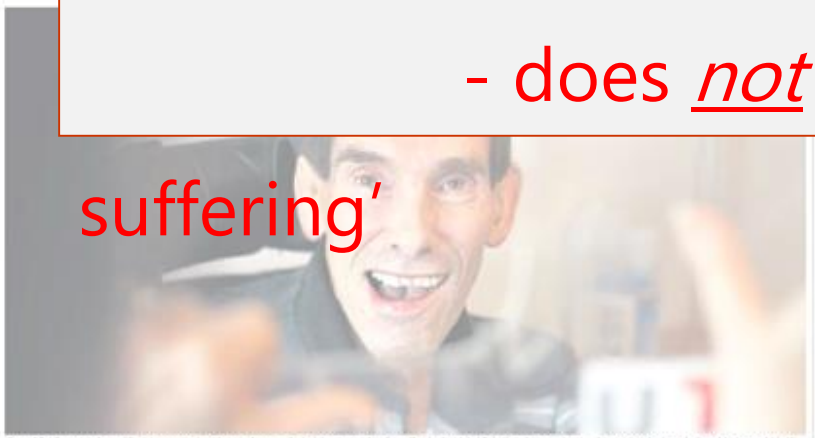
Thursday August 23, 2012

palliative care - works

- does *not* involve 'prolongation of suffering'



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Up to half a million home owners who have

Inside today

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A set to win over the

Prevent suffering

Sanctity/Inviolability of life

'KEEP ALIVE AT ALL COSTS'

- Not good medicine
- No origin in medical ethics or law

The right not to be intentionally, purposefully killed

Ethical and legal framework

Sanctity/Inviolability of life

While respecting the inviolability of life, it is perfectly licit to give painkillers to the terminally ill, or withhold life-prolonging treatment **if** :-

- the treatment is futile : cannot restore health
- the treatment is excessively burdensome

Why not?

PRINCIPLES

- *Autonomy*
- *Prevent indignity*
- *Prevent suffering*

PRACTICE [REASONS TO BE CAUTIOUS]

- ***Slippery slope***
- *Unintended consequences*
- *Who else supports?*

Slippery slope

Not just likely; not merely that it has occurred in EVERY legislature where assisted suicide has been permitted – but absolutely inevitable

Why?

Principle is that an individual is 'better off dead'

- *is it reasonable to deprive people of this 'benefit' simply because they are incapable of being asked to be killed?*
- *is it reasonable (or possible?) to confine this benefit to*

Slippery slope

2005 survey of deaths in Netherlands

9,965 deaths

The NEW ENGLAND JOURNAL of MEDICINE

SPECIAL ARTICLE

End-of-Life Practices in the Netherlands under the Euthanasia Act

Agnes van der Heide, M.D., Ph.D., Bregje D. Onwuteaka-Philipsen, Ph.D., Mette L. Rurup, Ph.D., Hilde M. Buiting, M.Sc., Johannes J.M. van Delden, M.D., Ph.D., Johanna E. Hanssen-de Wolf, M.Sc., Anke G.J.M. Janssen, M.A., H. Roeline W. Pasman, Ph.D., Judith A.C. Rietjens, Ph.D., Cornelis J.M. Prins, M.Sc., Ingeborg M. Deerenberg, M.Sc., Joseph K.M. Gevers, Ph.D., Paul J. van der Maas, M.D., Ph.D., and Gerrit van der Wal, M.D., Ph.D.

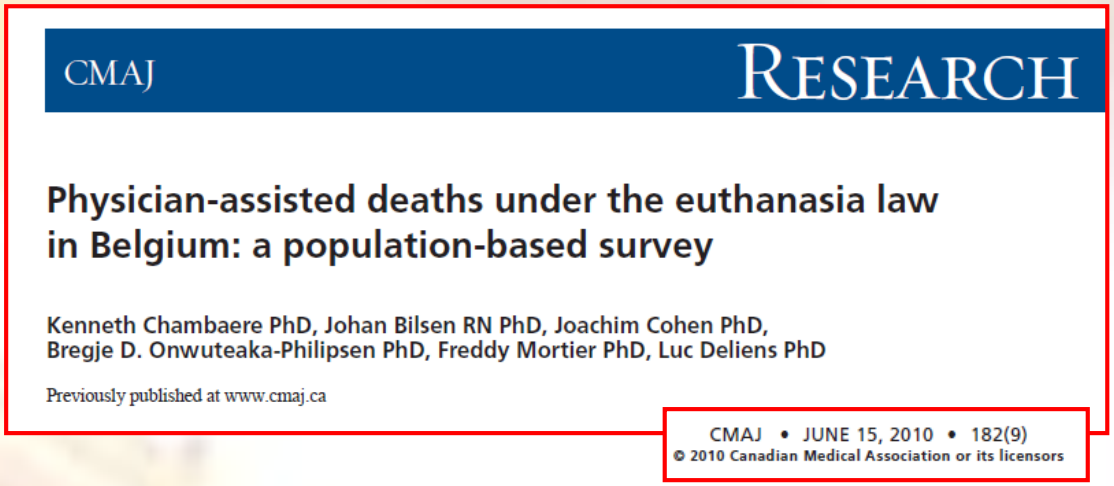
N Engl J Med 2007;356:1957-65.

- 400 deaths [*p.a.*] "the result of the ending of life without an explicit request by the patient"
- 1.8% of all deaths were the result of euthanasia or PAS
  - in **every jurisdiction numbers have increased over time** and continue to do so; there has also been a shift from permitting assisted suicide for cancer victims to include other diseases.
- "80.2% of all cases of euthanasia or PAS were reported"

Slippery slope

2007 survey of deaths in Belgium

208 euthanasia/PAS deaths, 6 month period



CMAJ RESEARCH

Physician-assisted deaths under the euthanasia law in Belgium: a population-based survey

Kenneth Chambaere PhD, Johan Bilsen RN PhD, Joachim Cohen PhD, Bregje D. Onwuteaka-Philipsen PhD, Freddy Mortier PhD, Luc Deliens PhD

Previously published at www.cmaj.ca

CMAJ • JUNE 15, 2010 • 182(9)

- 32% "*without explicit request by the patient*"
  - 78% of these "*the decision was not discussed with the patient*"

Slippery slope

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Last Updated: Sunday, 23 January, 2005, 01:03 GMT

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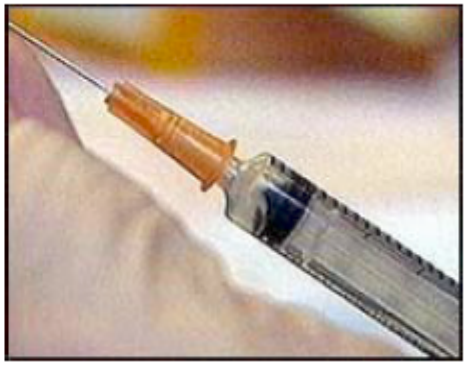
Dutch told of child euthanasia

Dutch doctors have reported 22 mercy killings of terminally ill babies since 1997, according to a new study.



The report authors want to encourage reporting of child euthanasia cases

None of the doctors involved were charged, although euthanasia for children is illegal in the Netherlands.

The report, in the Dutch Journal of Medicine, is the first detailed examination of child euthanasia.

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Slippery slope

The NEW ENGLAND JOURNAL of MEDICINE

PERSPECTIVE

The Groningen Protocol — Euthanasia in Severely Ill Newborns

Eduard Verhagen, M.D., J.D., and Pieter J.J. Sauer, M.D., Ph.D.

"After the decision has been made and the child has died, an outside legal body should determine whether the decision was justified"

NEJM 352:959-962

N ENGL J MED 352;10 WWW.NEJM.ORG MARCH 10, 2005

Why not?

PRINCIPLES

- *Autonomy*
- *Prevent indignity*
- *Prevent suffering*

PRACTICE [REASONS TO BE CAUTIOUS]

- *Slippery slope*
- ***Unintended consequences***
- *Who else supports?*

Unintended consequences

- pressure on elderly/vulnerable/disabled

Unintended consequences

Who favours euthanasia?

34% of 'frail elderly'
60% of their relatives

- *opposed*

  by a clear majority of : -

  - the elderly
  - physically and mentally ill
  - those experiencing pain

- *most likely to support*

  white, male, wealthy, educated, in good health.

EXCEL Omnibus Study # 912, ICR Survey Reasearch Group; Washington Post, 1996
Koenig HG, Wildman-Hanlon D, Schmader K. Attitudes of elderly patients and their families toward physician-assisted suicide. Arch Intern Med. 1996 Oct 28;156(19):2240-8.

Unintended consequences

Practice of medicine

Undermines palliative care

Undermines doctors – medicine

Unintended consequences

"A change in the law to allow physician-assisted dying would have profound implications for the role and responsibilities of doctors and their relationships with patients.

Acting with the primary intention to hasten a patient's death would be difficult to reconcile with the medical ethical principles of beneficence and non-maleficence."

General Medical Council

Aug. 17, 2015

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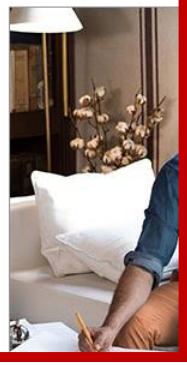
OPINION | COMMENTARY

A Doctor-Assisted Disaster for Medicine

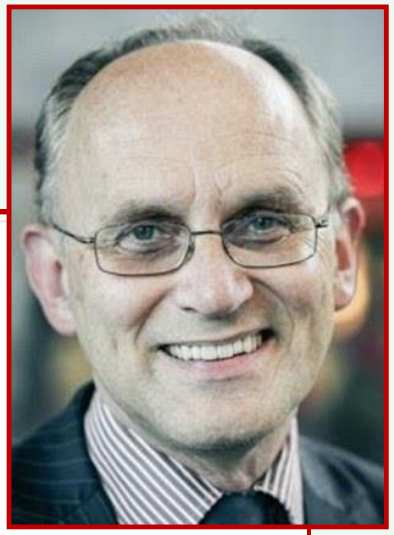
As a physician in Oregon, I have seen the dire effect of assisted-suicide laws on patients and my profession.



Dr William L. Toffler

Professor of Family Medicine at Oregon Health and Science University in Portland and a licenced GP for 35 years

"Since the voters of Oregon narrowly legalized physician-assisted suicide 20 years ago, there has been a profound shift in attitude toward medical care—new fear and secrecy, and a fixation on death. …. Proponents claim the system is working well with no problems. This is not true."



Prof Theo Boer

Professor of Ethics at the Protestant Theological University at Groningen

2007 - advocate of euthanasia law in Holland, then euthanasia regulator;

2014 - opponent

Mail Online

By STEVE DOUGHTY FOR THE DAILY MAIL

PUBLISHED: 23:40, 9 July 2014 | **UPDATED:** 09:44, 10 July 2014

Don't make our mistake: As assisted suicide bill goes to Lords, Dutch watchdog who once backed euthanasia warns UK of 'slippery slope' to mass deaths

- Theo Boer, a European assisted suicide watchdog, said 'don't do it'
- In Netherlands euthanasia has been legal since 2002
- However, in six years the numbers of deaths have doubled
- Peers are preparing to debate the Assisted Dying Bill
- Bill has been promoted by Lord Falconer, a Labour former Lord Chancellor

the very existence of a euthanasia law turns assisted suicide from a last resort into a normal procedure.

Unintended consequences

Medicine cannot be well-practiced unless patients trust doctors.

Doctors cannot inspire that trust unless patients believe that doctors : -

- are for no reason disposed to kill them
- have no inclination, *or legal requirement*, to ask if the patient is the kind of human being who is worth caring for or treating.

Why not?

PRINCIPLES

- *Autonomy*
- *Prevent indignity*
- *Prevent suffering*

PRACTICE [REASONS TO BE CAUTIOUS]

- *Slippery slope*
- *Unintended consequences*
- ***Who else supports?***

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theguardian

Polly Toynbee

"Another bad argument is that the frail will be intimidated into hastening the end of their lives so as not to be a burden on their children. Well, why not? "

jobs dating more UK edition

theguardian

Polly Toynbee

Oregon: Year 1 10% of patients listed concerns about being a "burden on the family" as a motivation for seeking assisted suicide.

2022 - over 50% of cases.

BMJ Supportive & Palliative Care 2023

Baroness Warnock

"If you're demented, you're wasting people's lives – your family's lives – and you're wasting the resources of the National Health Service."

Who favours euthanasia?

Who favours euthanasia?

Economics

'As soon as he gets beyond 60-65 years of age, man lives beyond his capacity to produce, and he costs society a lot of money... *euthanasia will be one of the essential instruments of our future societies*.'

Jacques Attali
ex-President, European Bank for Reconstruction and Development

Who favours euthanasia?

Economics

"the cost-saving from a nation-wide push towards living wills is likely to be enormous".

[*Official Report*, Commons, 14/12/04; Col. 1558.]

The proper practice of medicine, *without resorting to euthanasia*, **can and should** include the following:

1. Terminating or not initiating a medically useless treatment.

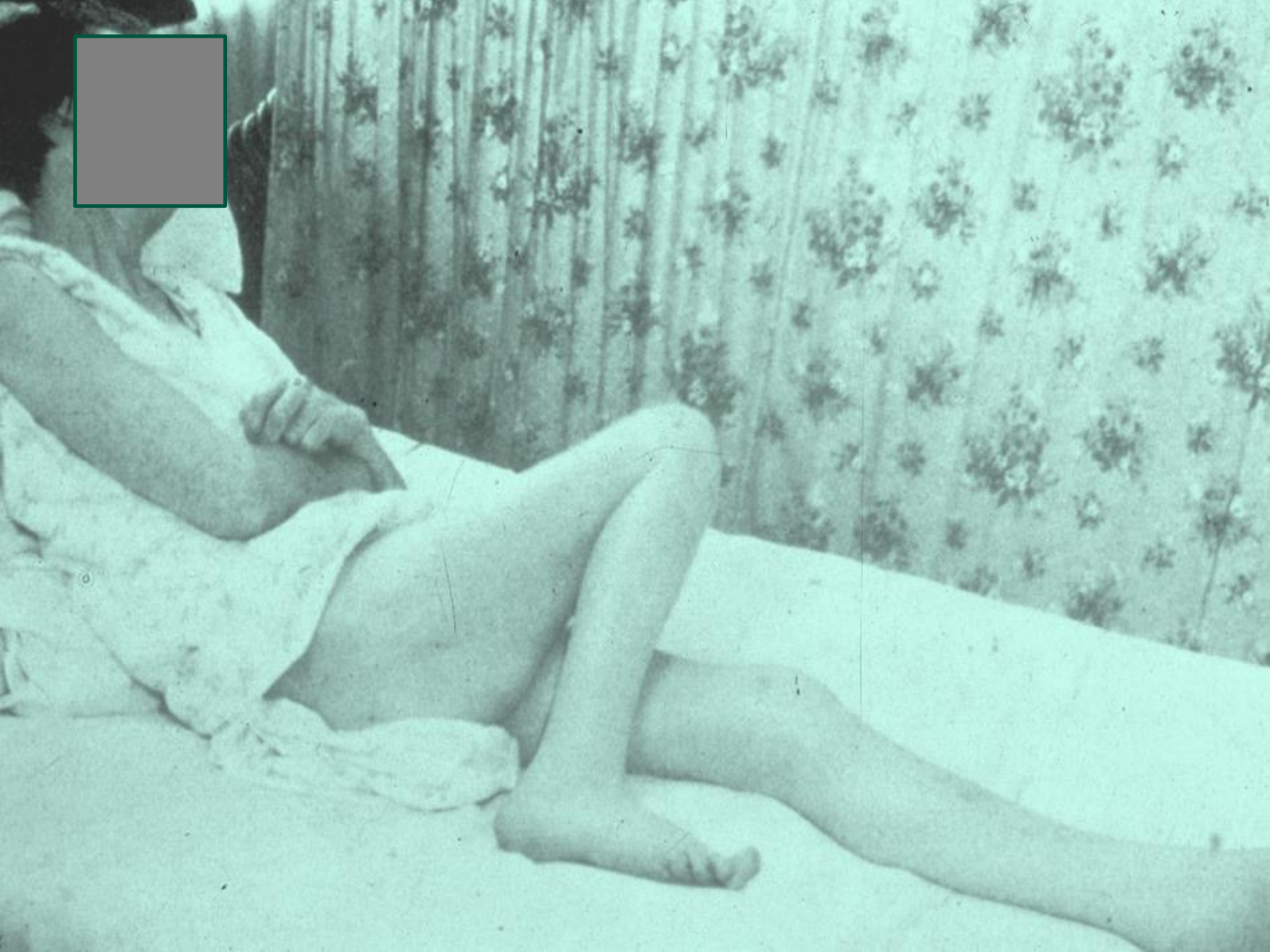
2. Proportionate pain and symptom treatment where the intention is not to kill but to relieve suffering *(principle of 'double effect').*

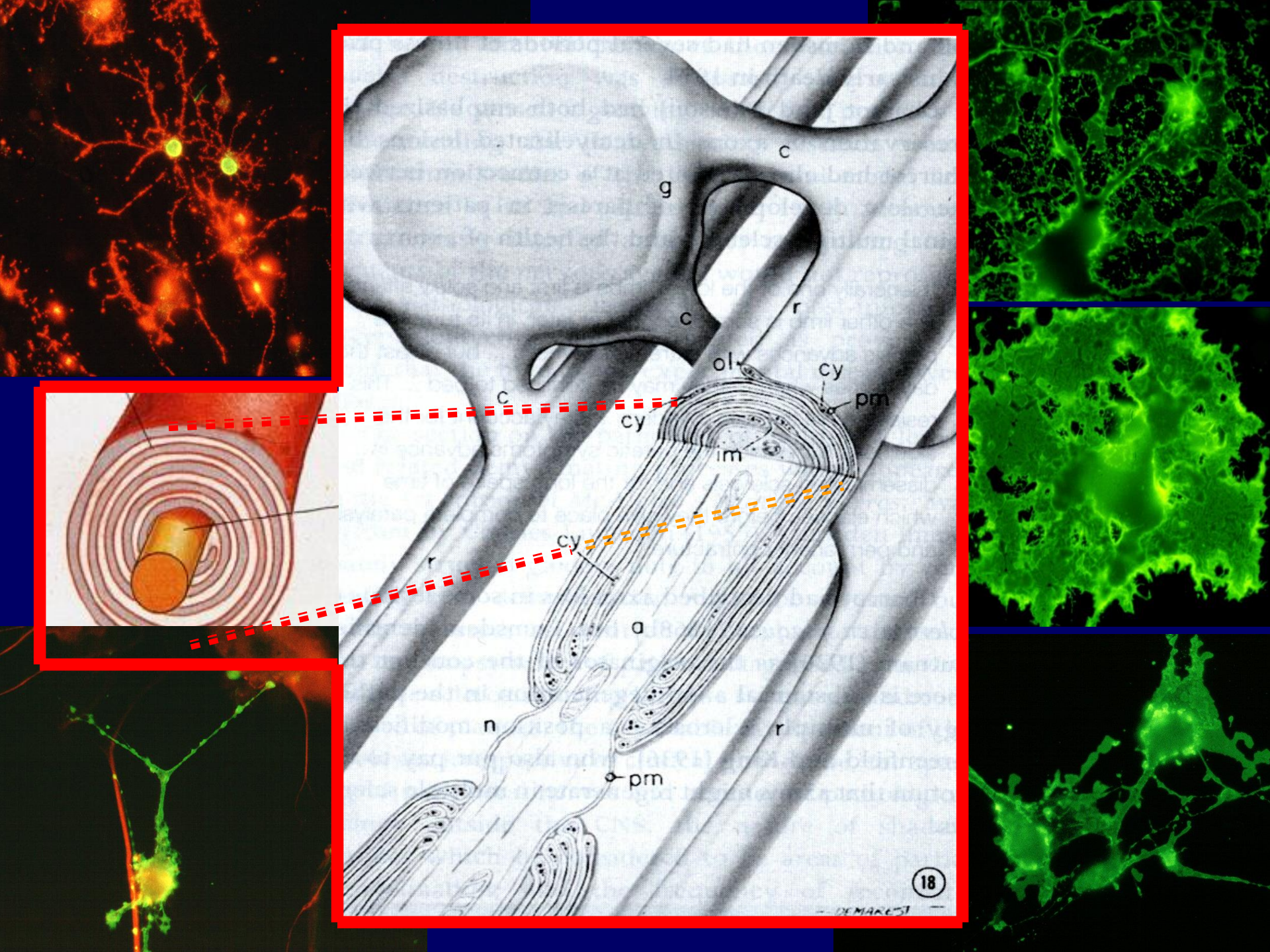
Deliberately / intentionally ending the life of a patient

carries TOO MANY RISKS

"one of the great mistakes is to judge policies and programs by their intentions rather than their results"

Milton Friedman

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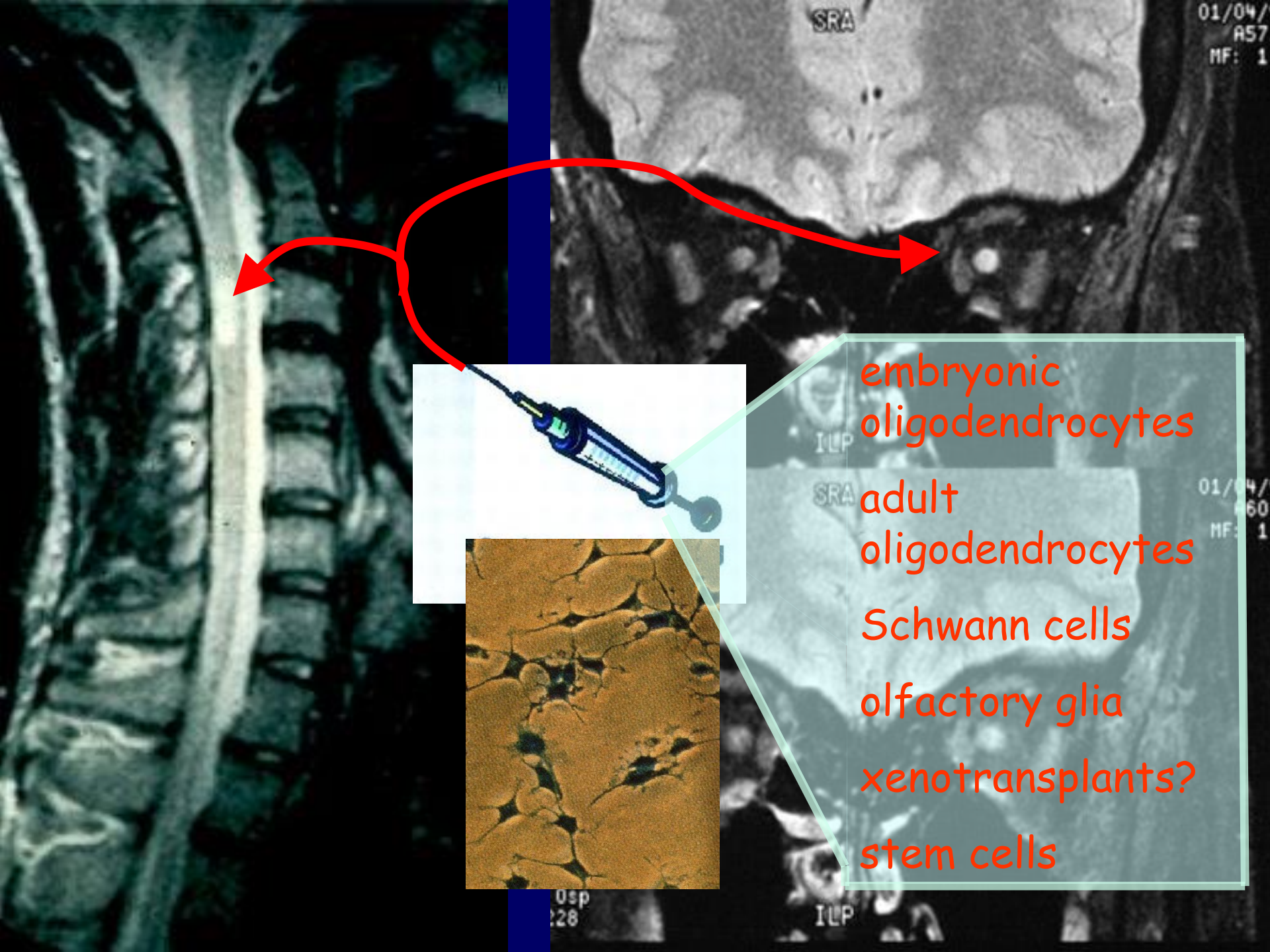


embryonic oligodendrocytes

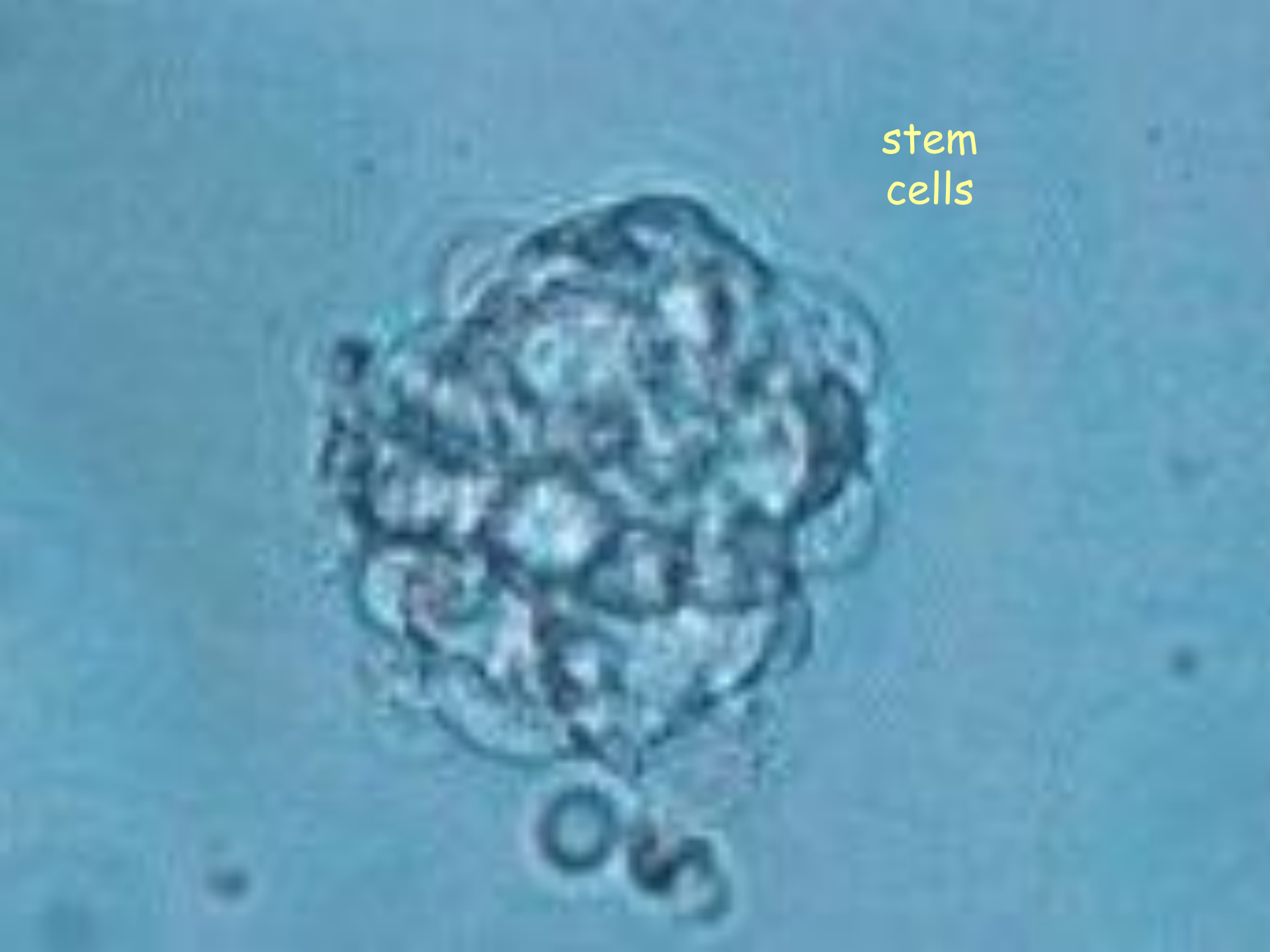
adult oligodendrocytes

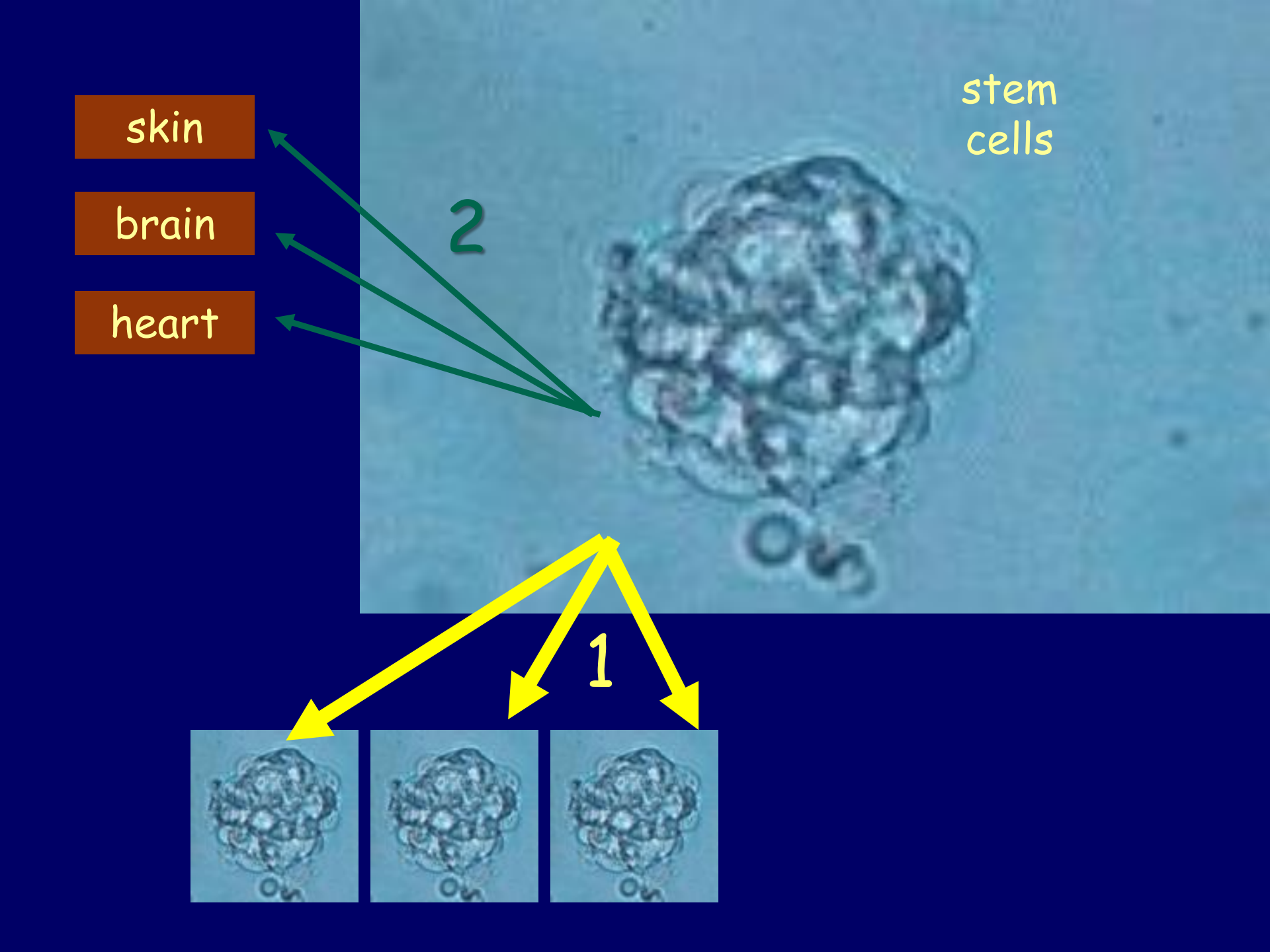
Schwann cells

olfactory glia

xenotransplants?

stem cells


stem
cells


skin
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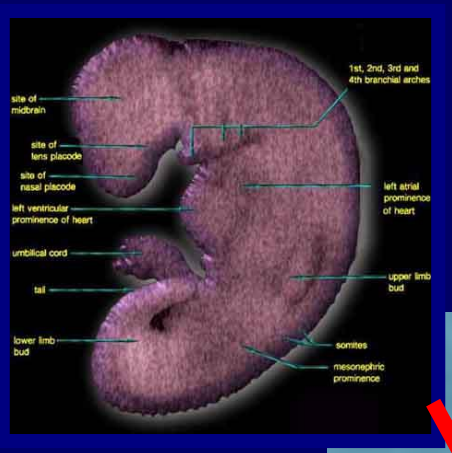
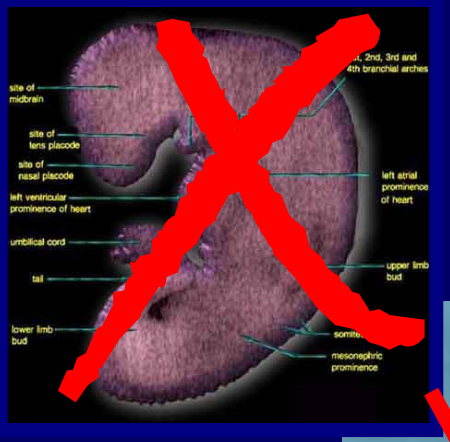
stem
cells
1


1st, 2nd, 3rd and 4th branchial arches
site of midbrain
site of lens placode
site of nasal placode
left atrial prominence of heart
left ventricular prominence of heart
umbilical cord
upper limb bud
tail
lower limb bud
somites
mesonephric prominence

stem cells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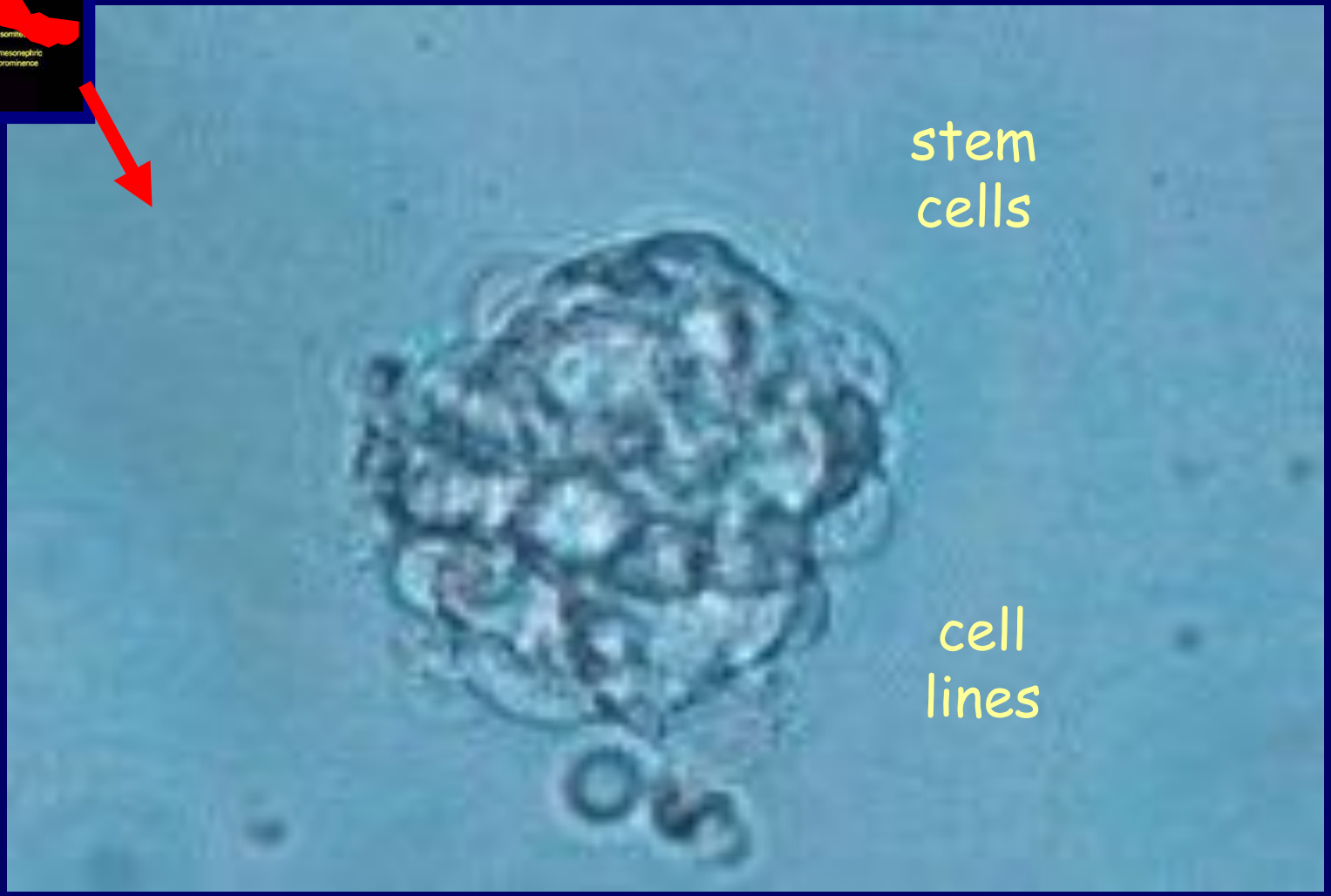
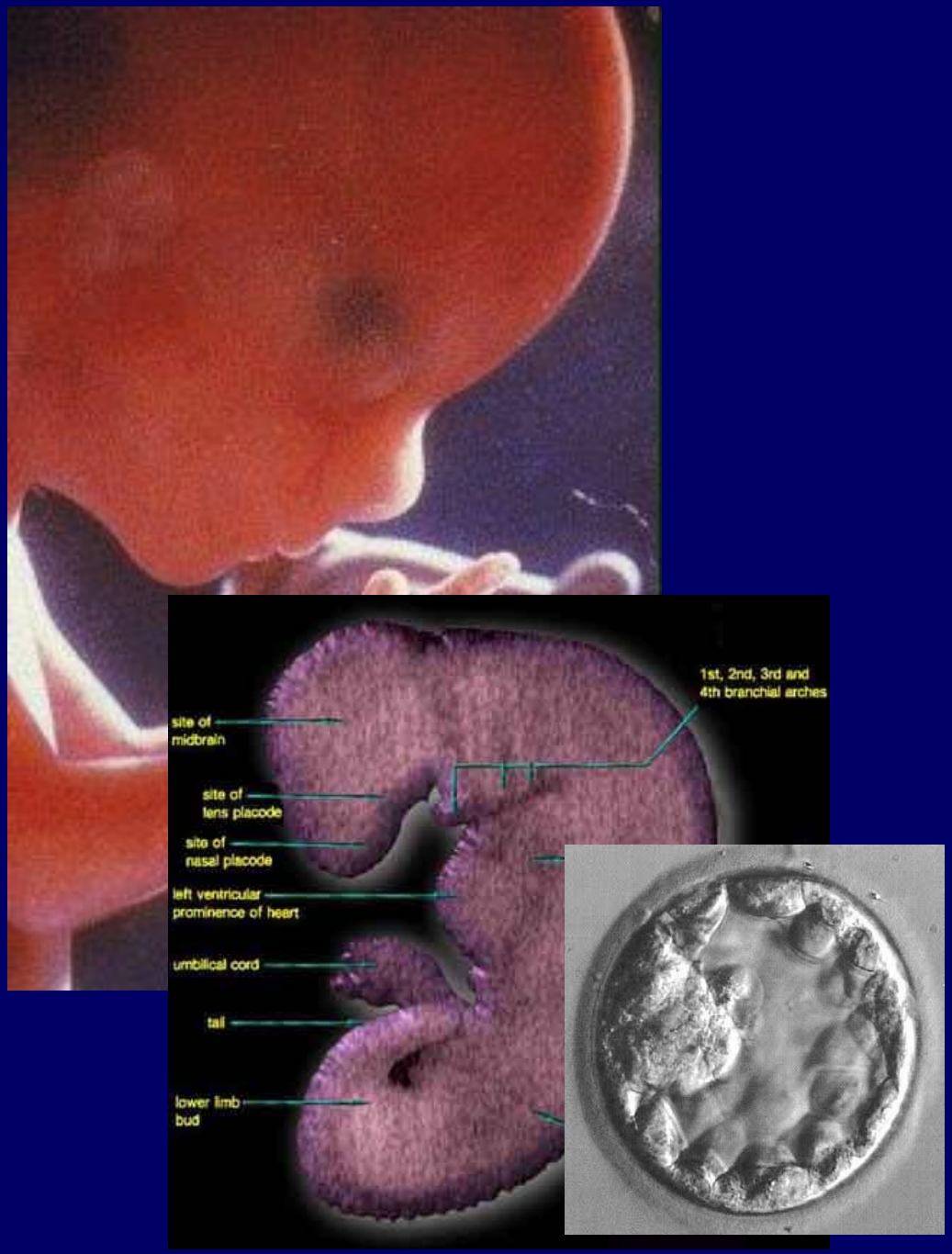

stem cells
cell lines

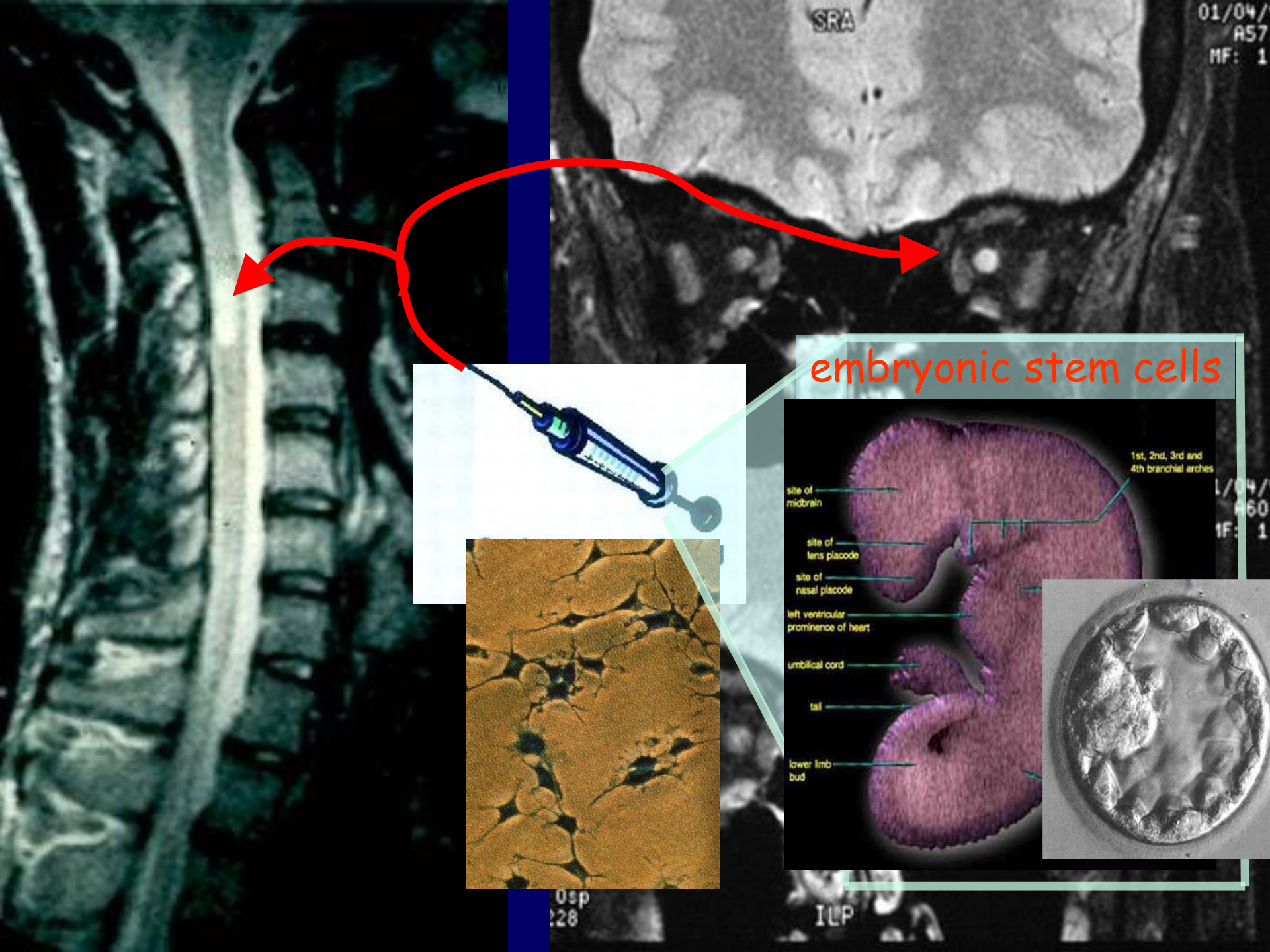


Alive

Human

Individual……

…..a human being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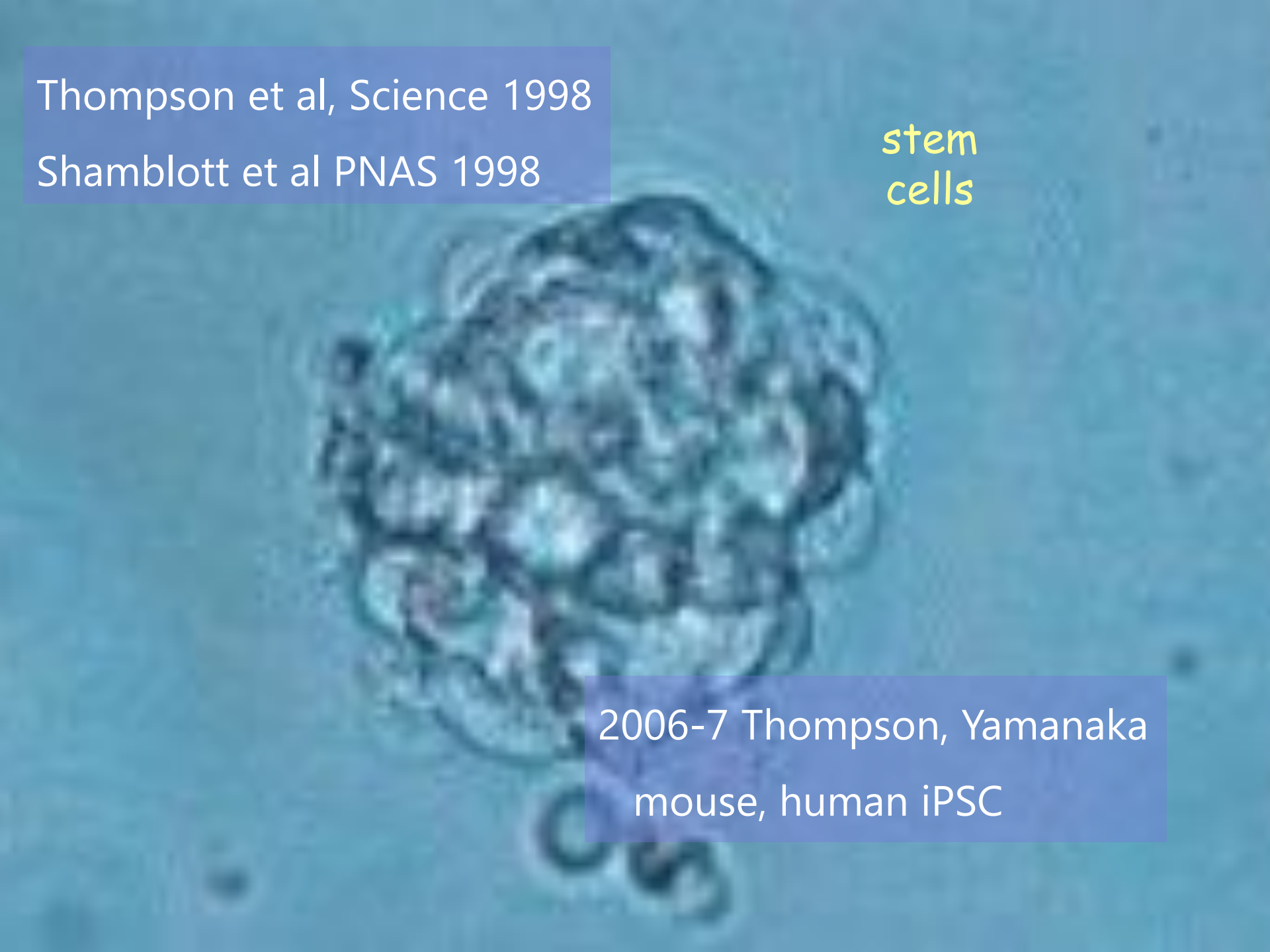
embryonic stem cells
1st, 2nd, 3rd and
4th branchial arches
site of
midbrain
site of
lens placode
site of
nasal placode
left ventricular
prominence of heart
umbilical cord
tail
lower limb
bud
Osp
228
ILP

Thompson et al, Science 1998

Shamblott et al PNAS 1998

stem cells



2006-7 Thompson, Yamanaka

mouse, human iPSC

19 DECEMBER 2008

Breakthrough of the Year

Reprogramming Cells

By inserting genes that turn back a cell's developmental clock, researchers are gaining insights into disease and the biology of how a cell decides its fate

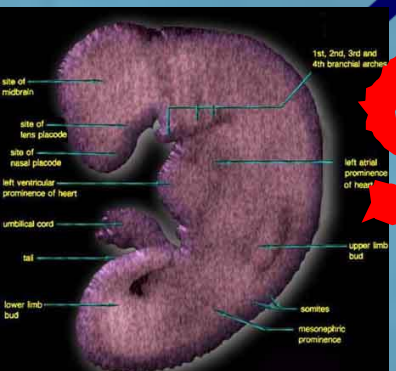
Professor Shinya Yamanaka

"When I saw the embryo, I suddenly realized"—

there was such a small difference between it and my daughters

... I thought, we can't keep destroying embryos for our research. There must be another way".

Adult tissue



IPSCs from ANY adult cell

STANDPOINT.O

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February 2009

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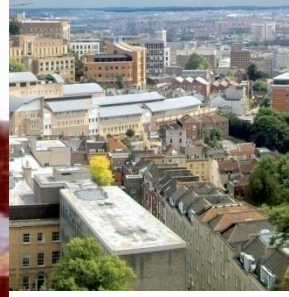
Cosmos

The Stem Cell Wars are Over

NEIL SCOLDING
February 2009

It is now a decade since human embryonic stem cells were discovere
and since the UK legislated to facilitate cloning human embryos for
research. Since then, barely a week has passed without new stem cell
stories appearing. Last November, it was widely reported that the



Series

Stem Cells 1

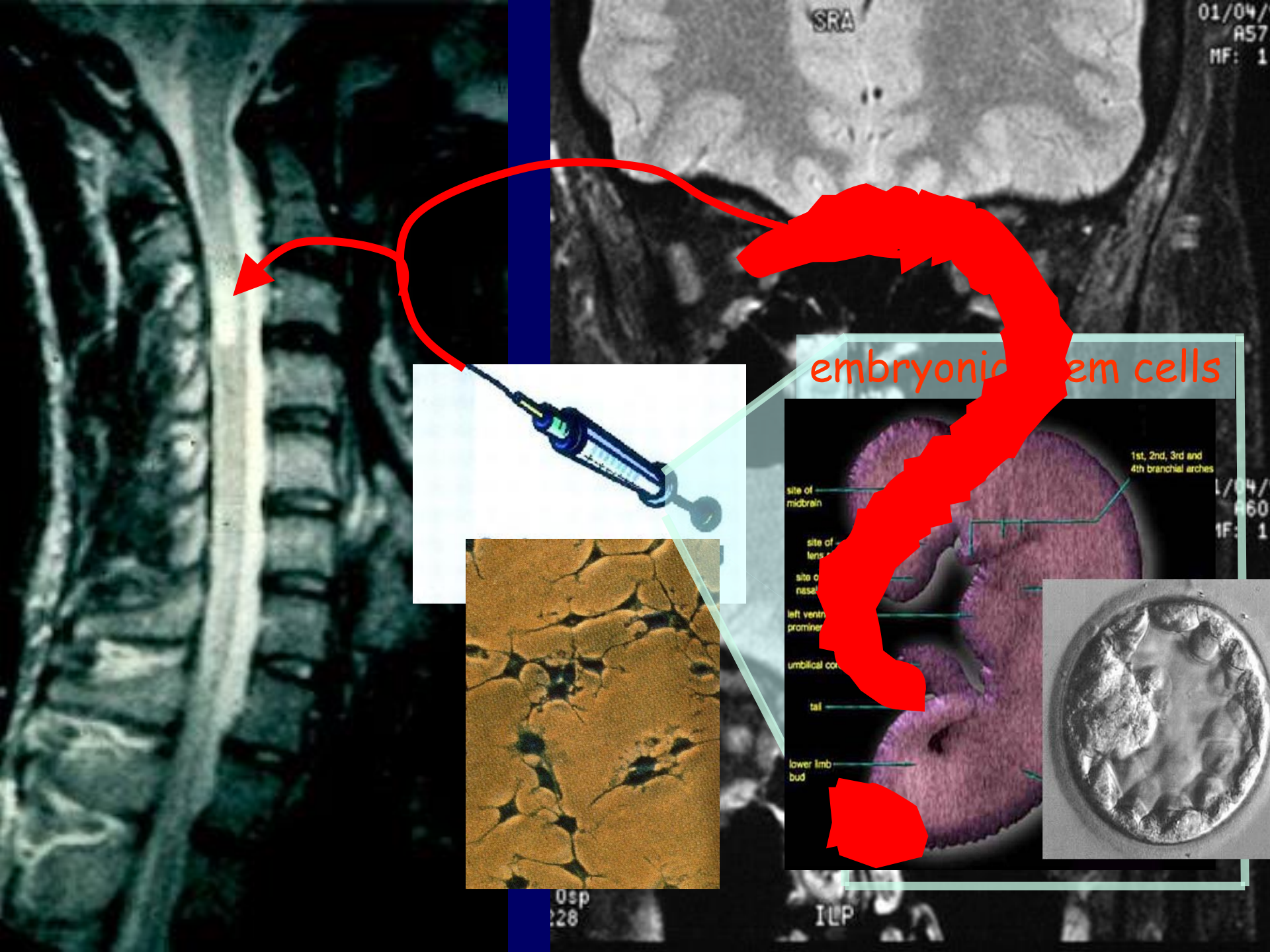
Cell therapy for multiple sclerosis: an evolving concept with implications for other neurodegenerative diseases

Claire M Rice, Kevin Kemp, Alastair Wilkins, Neil J Scolding

Lancet 2013; 382: 1204–13

Multiple sclerosis is a major cause of neurological disability, and particularly occurs in young adults. It is characterised by conspicuous patches of damage throughout the brain and spinal cord, with loss of myelin and myelinating cells (oligodendrocytes), and damage to neurons and axons. Multiple sclerosis is incurable, but stem-cell therapy might offer valuable therapeutic potential. Efforts to develop stem-cell therapies for multiple sclerosis have been conventionally built on the principle of direct implantation of cells to replace oligodendrocytes, and therefore to regenerate myelin. Recent progress in understanding of disease processes in multiple sclerosis include observations that spontaneous myelin repair is far more widespread and successful than was previously believed, that loss of axons and neurons is more closely associated with progressive disability than is myelin loss, and that damage occurs diffusely throughout the CNS in grey and white matter, not just in discrete, isolated patches or lesions. These findings have introduced new and serious challenges that stem-cell therapy needs to overcome; the practical challenges to

Lancet 2013; 382: 1204–13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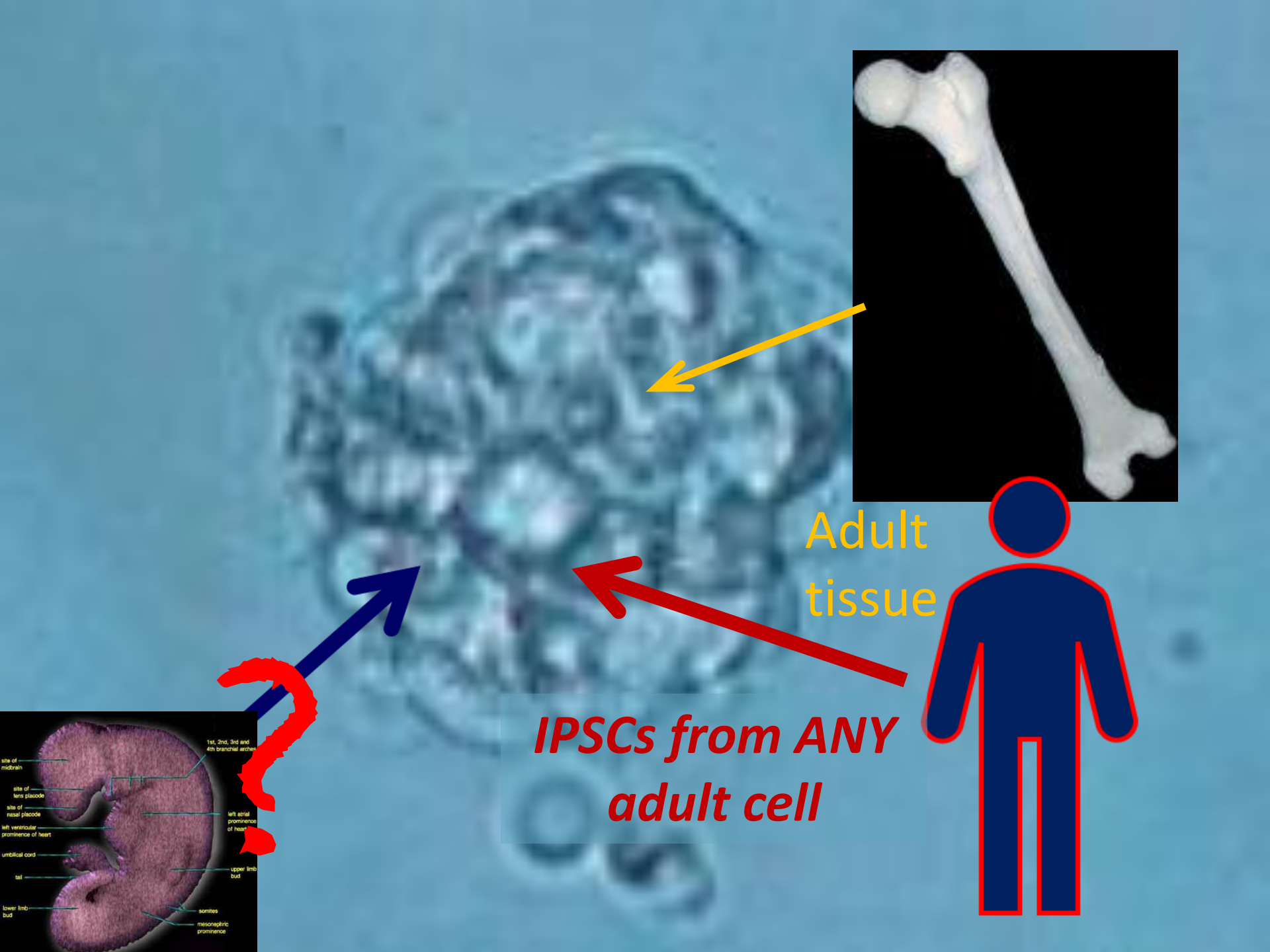
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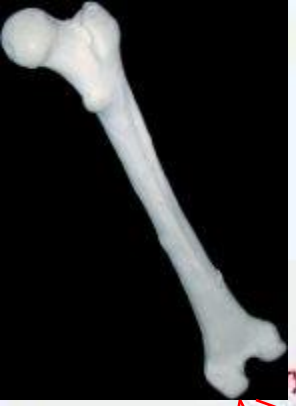
upper limb bud
tail
lower limb bud
somites
mesonephric prominence

Bone marrow cells for tissue repair

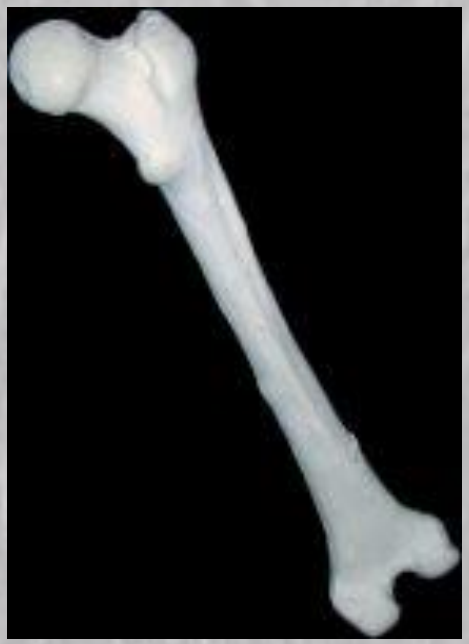


Circulating bone marrow stem cells enter the brain and spinal cord and may contribute to the repair of damaged tissue

University of BRISTOL

adapted from: Korbling & Estrov, NEJM 2003

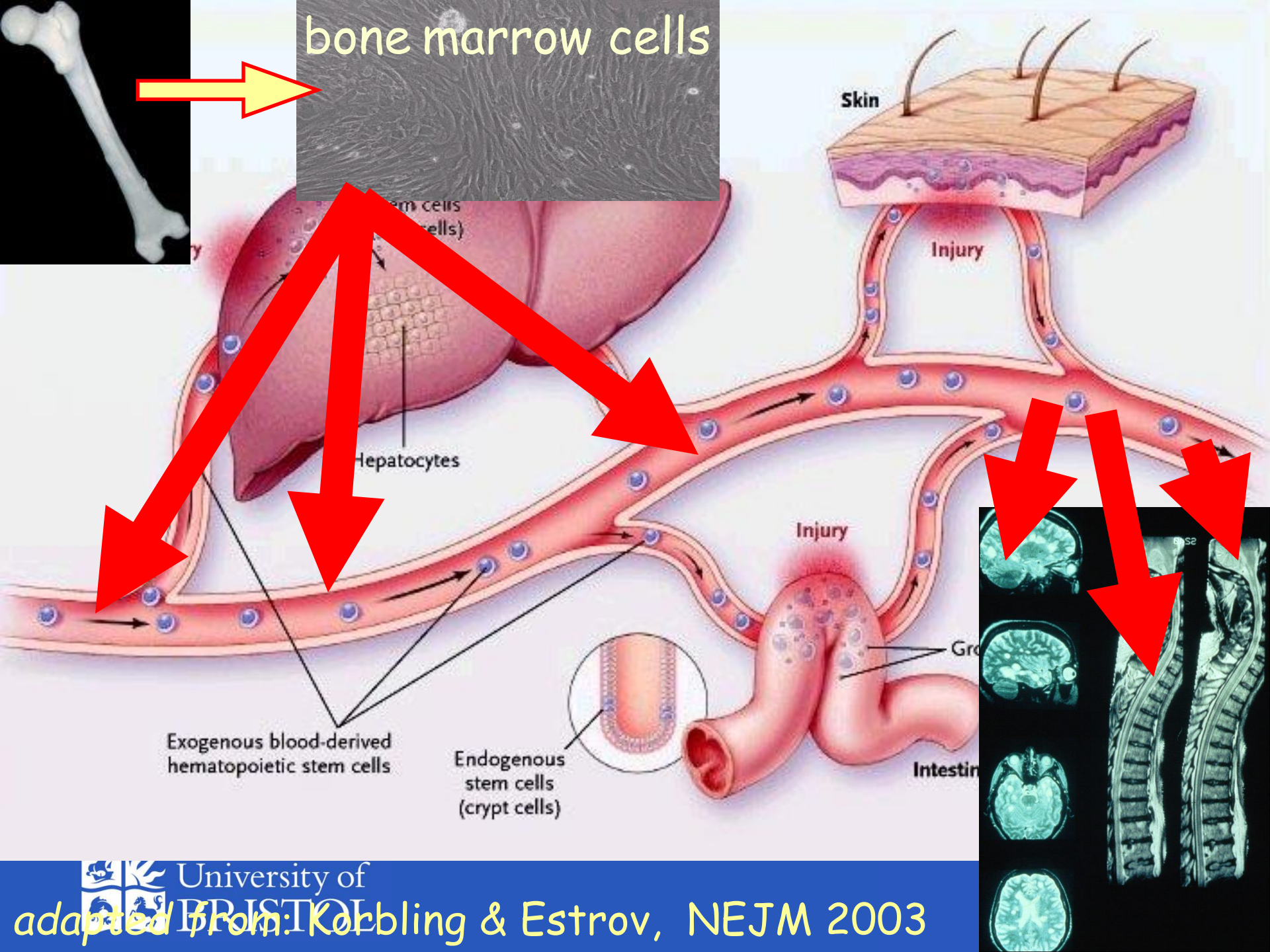
Bone marrow stem cells ***stimulate or re-programme repair*** both directly and through a range of 'non-canonical' mechanisms :-



- fusion
- immune modulation
- neuroprotection
- growth factor production
- reduced scar formation
- new vessel formation
- **REGULATE LOCAL TISSUE STEM CELLS**
- [*transdifferentiation*]

Blau, H. M. Cell fusion: A twist of fate. Nature 419, 437 (2002).

Rice CM, Scolding NJ. Adult stem cells--reprogramming neurological repair? Lancet. 2004; 364:193-199



adapted from: Korbling & Estrov, NEJM 2003

Study of Intravenous Autologous Marrow in Multiple Sclerosis (SIAMMS)

6 participants

Mean age 48 yrs

Disease duration 16 yrs

Median EDSS 6

Intervention:

Daycase procedure

Bone marrow harvest (250-750ml) under general anaesthesia

Bone marrow is filtered

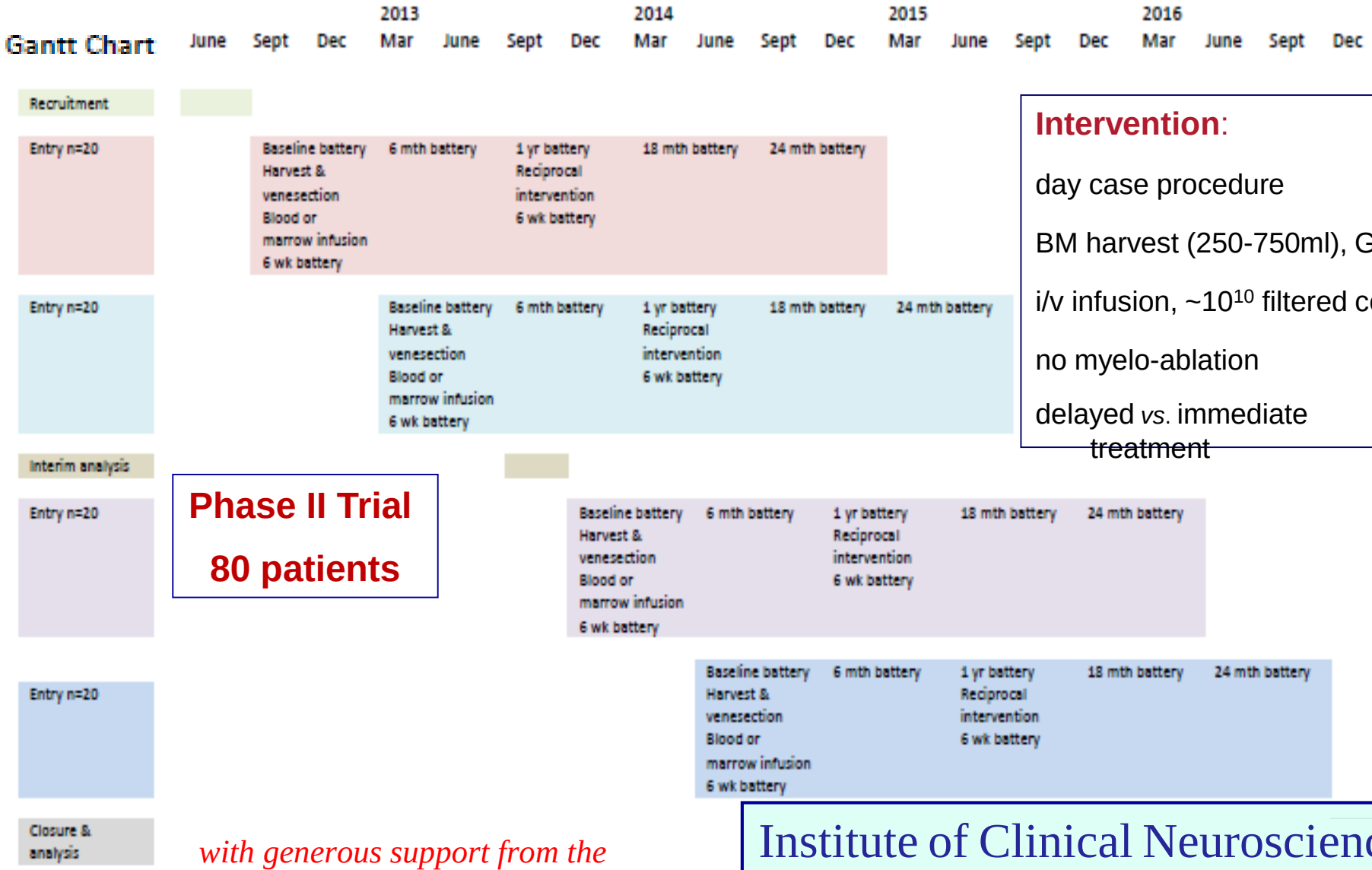
Intravenous infusion of autologous marrow cells

No myelo- or lymphoablation

Cell dose 9 x10^9 TNC

Assessment of Bone Marrow Cell Therapy in Multiple Sclerosis

ACTiMuS



Intervention:

day case procedure

BM harvest (250-750ml), GA

i/v infusion, ~10^{10} filtered cells

no myelo-ablation

delayed *vs.* immediate treatment

Phase II Trial

80 patients

with generous support from the Silverman Family Foundation

Institute of Clinical Neurosciences
BRISTOL

nature publishing group

ARTICLES

[1]Institute of Clinical Neurosciences, University of Bristol, Frenchay Hospital, Bristol, UK; [3]Burden Neurological Institute, Bristol, UK; [4]Adult BMT Unit, Bristol Children's H

Received 14 December 2009; accepted 17 February 2010; advance online publication

CLINICAL PHARMACOLOGY & THERAPEUTICS

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Mohyeddin Bonab M, Yazdan

Hematology-Oncology & BMT Re

Abstract

BACKGROUND: Mesenchy mesodermal lineages have tools in cell and gene thera

OBJECTIVE: To evaluate th manifestations of MS patie

METHODS: Ten patients w disease from 3. neurolo

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CONCL patient

Journal of Neuroimmunology 227 (2010) 185–189

Contents lists available at ScienceDirect

Journal of Neuroimmunology

journal homepage: www.elsevier.com/locate/jneuroim

Bone marrow mesenchymal stem cell transplantation in patients with multiple sclerosis: A pilot study ☆

Bassem Yamout [a,*], Roula Hourani [b], Haytham Salti [c], Wissam Barada [a,1], Taghrid El-Hajj [a,2], Aghiad Al-Kutoubi [b], Aline Herlopian [a], Elizabeth Kfoury Baz [d], Rami Mahfouz [d], Rima Khalil-Hamdan [d], Nabeela M.A. Kreidieh [d], Marwan El-Sabban [e], Ali Bazarbachi [a]

[a] Departments of Internal Medicine, American University of Beirut Medical Center, Beirut, Lebanon
[b] Departments of Radiology, American University of Beirut Medical Center, Beirut, Lebanon

Safety and Immunological Effects of Mesenchymal Stem Cell Transplantation in Patients With Multiple Sclerosis and Amyotrophic Lateral Sclerosis

Dimitrios Karussis, MD, PhD; Clementine Karageorgiou, MD; Adi Vaknin-Dembinsky, MD, PhD;

Autologous mesenchymal stem cells for the treatment of secondary progressive multiple sclerosis: an open-label phase 2a proof-of-concept study

Peter Connick,* Madhan Kolappan,* Charles Crawley, Daniel J Webber, Rickie Patani, Andrew W Michell, Ming-Qing Du, Shi-Lu Luan, Daniel R Altmann, Alan J Thompson, Alastair Compston, Michael A Scott, David H Miller, Siddharthan Chandran

Lancet Neurol 2012; 11: 150–56
Published Online January 10, 2012
DOI:10.1016/S1474-4422(11)70305-2

Summary

Background More than half of patients with multiple sclerosis have progressive disease characterised by accumulating disability. The absence of treatments for progressive multiple sclerosis represents a major unmet clinical need. On the basis of evidence that mesenchymal stem cells have a beneficial effect in acute and chronic animal models of multiple sclerosis, we aimed to assess the safety and efficacy of these cells as a potential neuroprotective treatment for

Intervention: After culture, a mean (SD) of 63.2×10^6 (2.5×10^6) MSCs was injected intrathecally (n=34) and intravenously (n=14). In 9 cases, MSCs were magneti-

sponses of lymphocytes, and the expression of $CD40^+$, $CD83^+$, $CD86^+$, and HLA-DR on myeloid dendritic cells at 24 hours after MSC transplantation.

ORIGINAL ARTICLE

Annals of Neurology
Volume 70, Issue 1, pages
59–69, July 2011

Intravenous Autologous Bone Marrow Mononuclear Cells for Ischemic Stroke

Sean I. Savitz, MD,[1] Vivek Misra, MD,[1] Mallik Kasam, PhD,[1] Harrinder Juneja, MD,[3] Charles S. Cox, Jr, MD,[2] Susan Alderman, RN,[1] Imo Aisiku, MD,[1] Siddhartha Kar, MD,[1] Adrian Gee, PhD,[4] and James C. Grotta, MD[1]

Objective: Cellular therapy is an investigational approach for stroke. Mononuclear cells (MNCs) from the bone marrow reduce neurological deficits in animal stroke models. We determined if autologous MNC infusion was feasible and safe in patients with ischemic stroke.
Methods: We conducted an open-label prospective study of a bone marrow harvest followed by readministration of autologous MNCs in 10 patients, 18 to 80 years old, with acute middle cerebral artery ischemic stroke. Bone marrow was aspirated from the iliac crest, and MNCs were separated at a Good Manufacturing Practices facility and administered intravenously up to a maximum of 10 million cells/kg. The harvest and infusion had to occur between 24 and 72 hours after stroke. Patients were monitored for 6 months.
Results: Bone marrow aspiration was successfully completed in all patients. Eight received 10 million cells/kg, and 2 received ≥7 million cells/kg. There were no significant adverse events related to harvest or infusion. Two patients had infarct expansion between enrollment and harvest and underwent hemicraniectomy after cell infusion. One patient died at 40 days due to a pulmonary embolism related to the stroke. There were no study-related severe adverse events. Median National Institutes of Health Stroke Scale score was 13 before harvest, 8 at 7 days, and 3 at 6 months. At 6 months, all surviving patients had shifted down by at least 1 point on the modified Rankin Scale compared to day 7. Seven of 10 patients achieved a Barthel Index ≥90.
Interpretation: This study suggests that a bone marrow harvest and reinfusion of autologous MNCs were safe and

Department of Neurology, University of Texas Medical School at Houston, Texas, USA

Peter Connick,* Madhan Kolappan,* Charles Crawley, Daniel J Webber, Rickie Patani, Andrew W Michell, Ming-Qing Du, Shi-Lu Luan, Daniel R Altmann, Alan J Thompson, Alastair Compston, Michael A Scott, David H Miller, Siddharthan Chandran

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The Church has a great esteem for scientific and technological research…..it is a service to truth, goodness and beauty

Pope John Paul II May 2000