Designing Matter:

The role of sledgehammers in organ replacement

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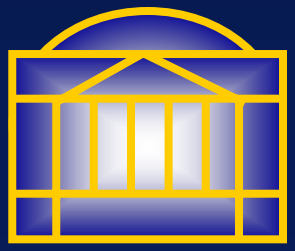
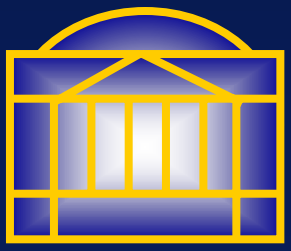




The story of “Ellen”

Ellen and citrullinemia

- 18 y.o. high school honor student
- Older sibling died of the disease at age 3 y.o.
- Diagnosed at birth with citrullinemia (urea cycle defect)
- Controlled with special diet and amino acid supplementation

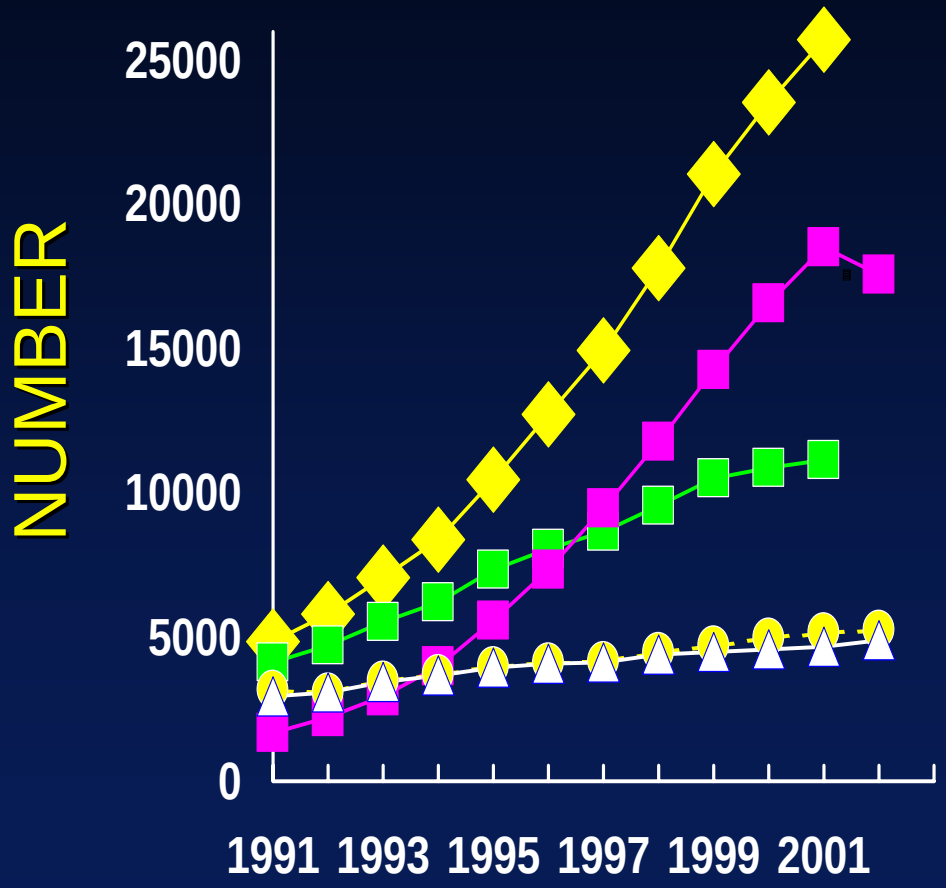
Ellen and citrullinemia (II)

- Hospitalized in 2002 after viral illness with coma but recovered
- Hospitalized 2 weeks ago with markedly elevated ammonia
  - No obvious precipitating event
- Currently in pediatric ICU at UVA in coma awaiting liver transplant

Potential options for Ellen's transplant-Sledgehammer style

- Deceased donor transplant
  - Voluntary v. ?mandatory donation
- Living donor liver transplant
  - Volunteer donor vs. ?purchase organ overseas
- Baboon or pig liver transplant
- Isolated liver cell transplant

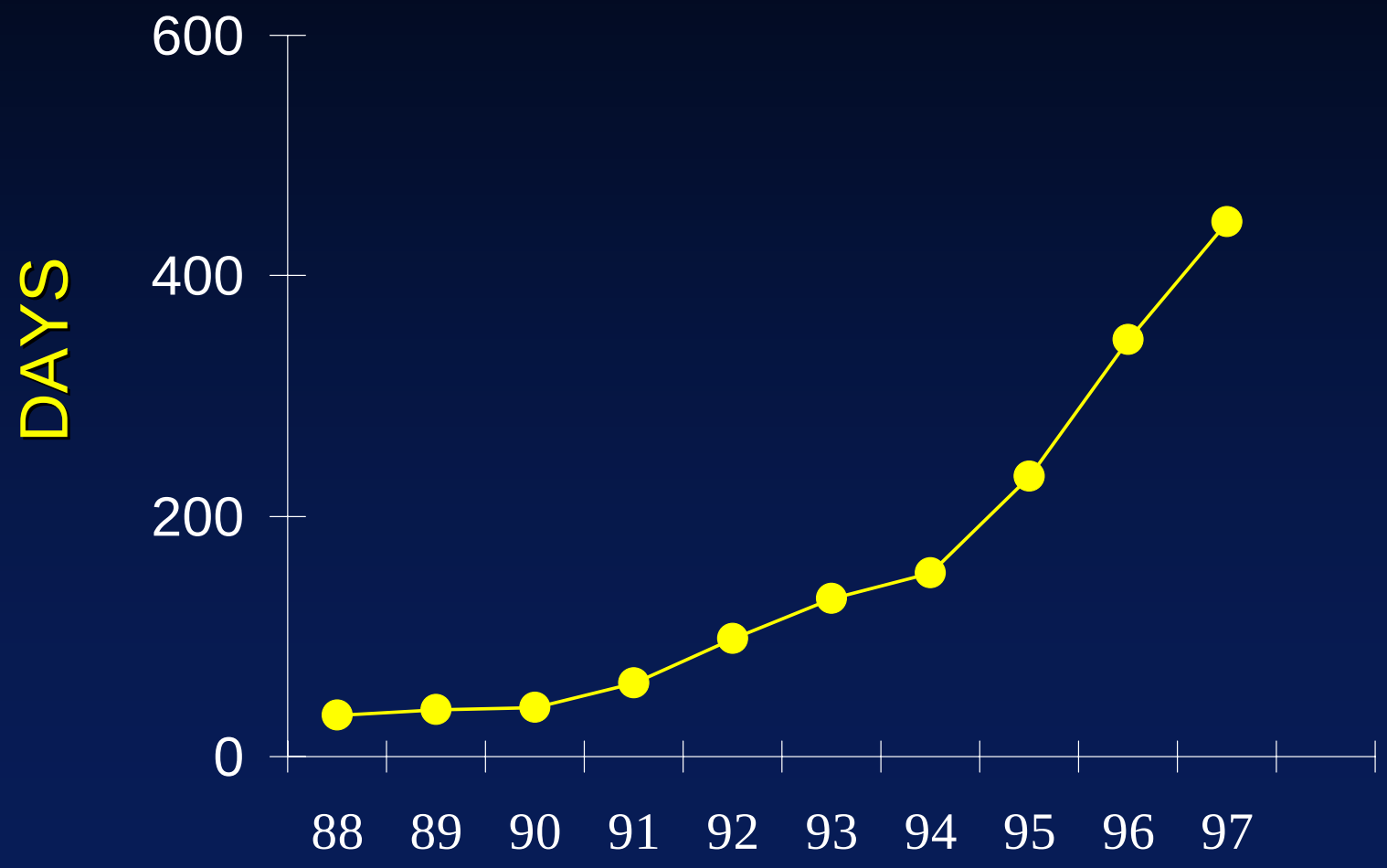
Discrepancy between supply and demand



- Total of all patients listed for OLT in a year
- No. of registrations for waiting list
- No. of candidates on waiting list on Dec. 31
- No. of total liver recipients
- No. of deceased donor liver recipients

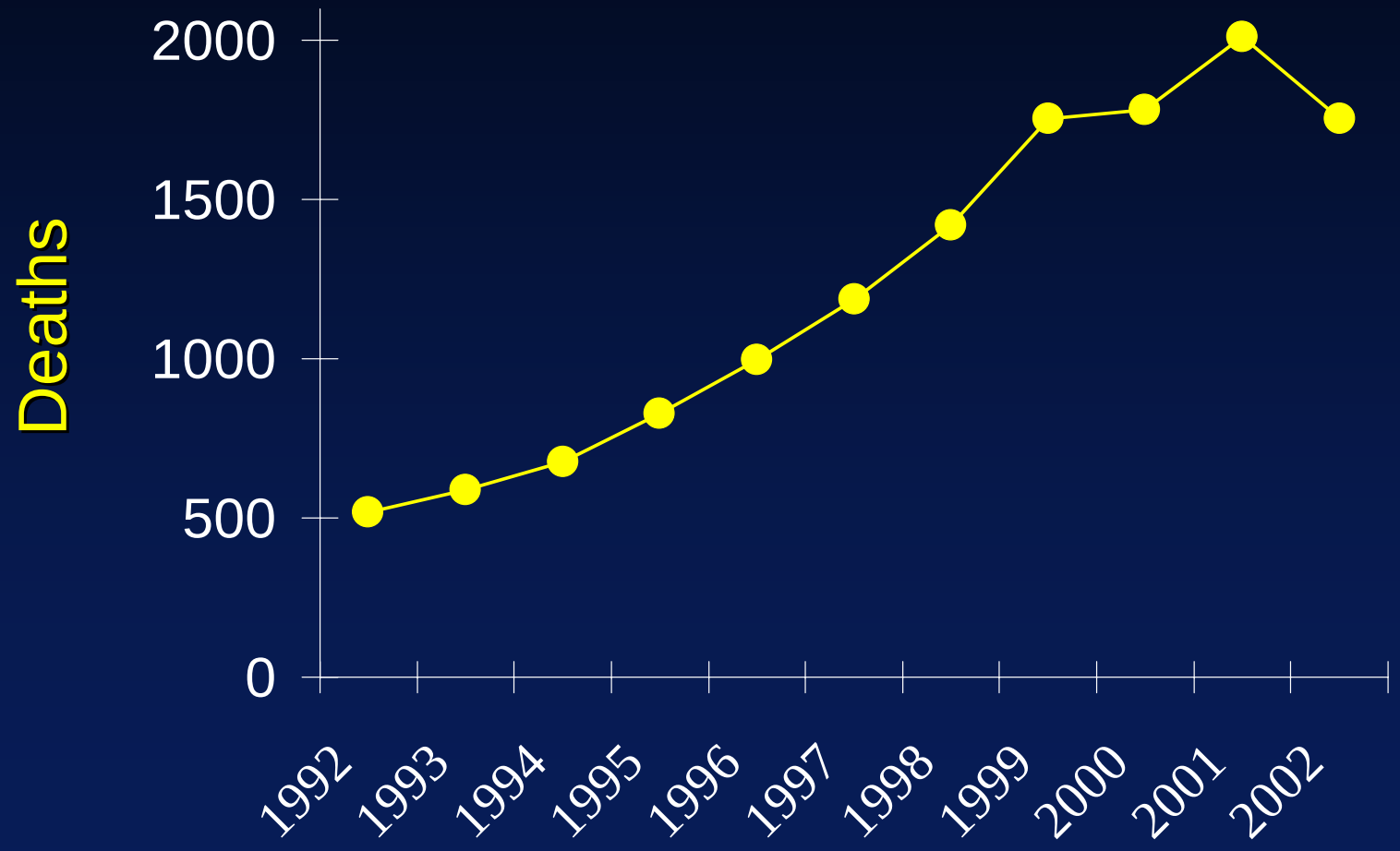
2002 OPTN/SRTR Annual Report 1991-2001

Median waiting time for liver transplantation by year of listing



2002 OPTN/SRTR Annual Report 1991-2001

Reported deaths on liver transplant wait list



2002 OPTN/SRTR Annual Report 1991-2001

Deaths on the Waiting List
1990, 1995, 1999

Organ Type	1990	1995	1999
Kidney	956	1,543	3,073
Liver	382	834	1,756
Pancreas	22	5	18
Kidney-Pancreas*	-	86	169
Heart	654	782	712
Lung	57	348	591
Heart-Lung	67	28	53
Intestine*	-	19	44
Total	2,098	3,498	6,143

* The Kidney-Pancreas waiting list began in 1992; the Intestine waiting list began in 1993.
Source: OPTN waiting list and removal files as of 9/5/00.

Increasing number of patients referred for transplantation

- Increasing awareness of liver transplant
- Improved care of life-threatening complications of liver disease
- Increasing number of patients with hepatitis C infection
- Expanded payor acceptance
  - Medicare, VA Medicaid

Expanding indications for liver transplantation (1)

- Fulminant Hepatic Failure
- Cirrhosis
- Structural problems

  i.e. Sclerosing cholangitis, polycystic liver disease, biliary atresia

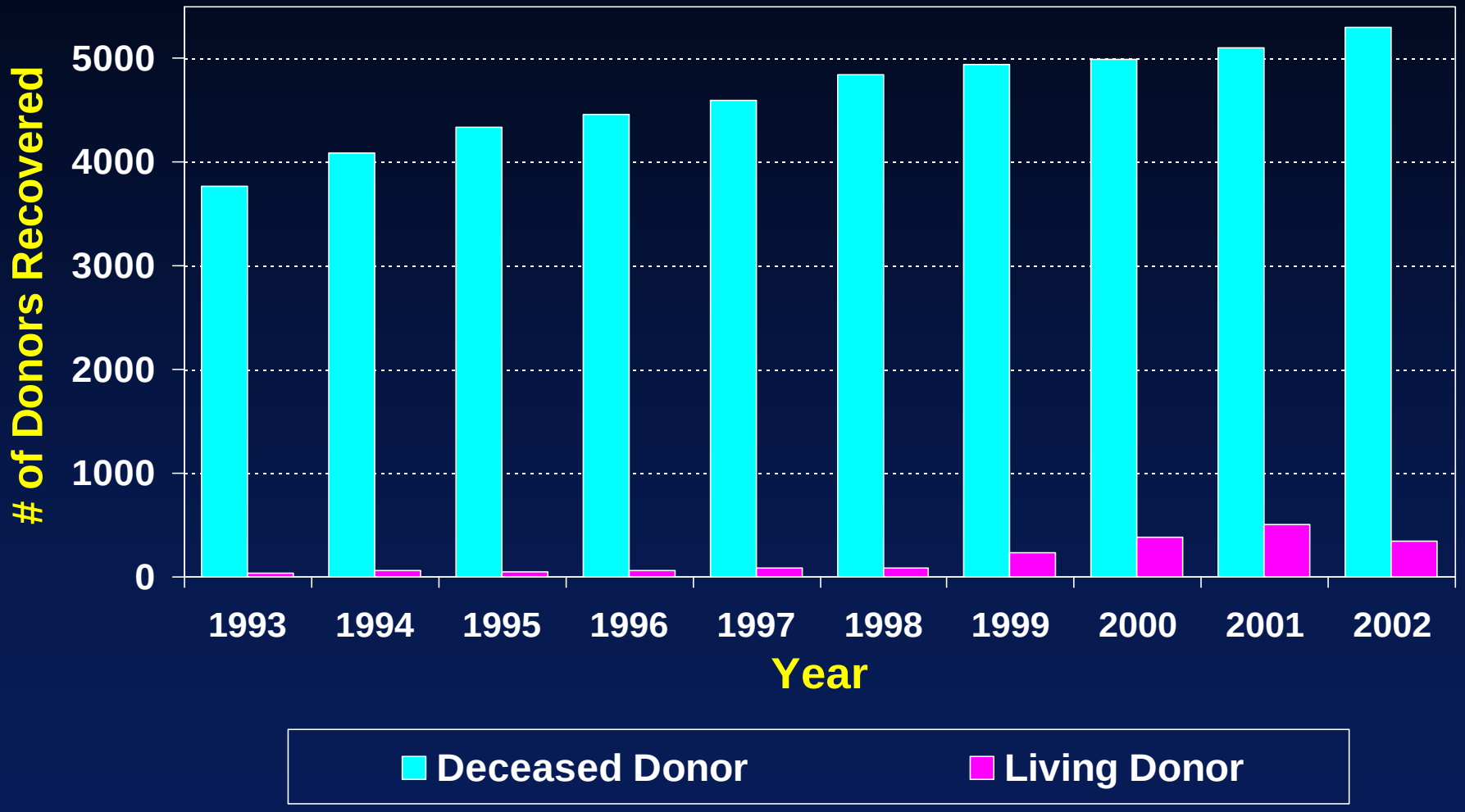
- Inborn errors of metabolism

  i.e. cystic fibrosis, Crigler-Najjar syndome, tyrosinemia, familial amyloidotic polyneuropathy

Expanding indications for liver transplantation (2)

- Hepatitis B
- Hepatocellular carcinoma
- Metastatic neuroendocrine tumor

Liver Donors
1993-2002

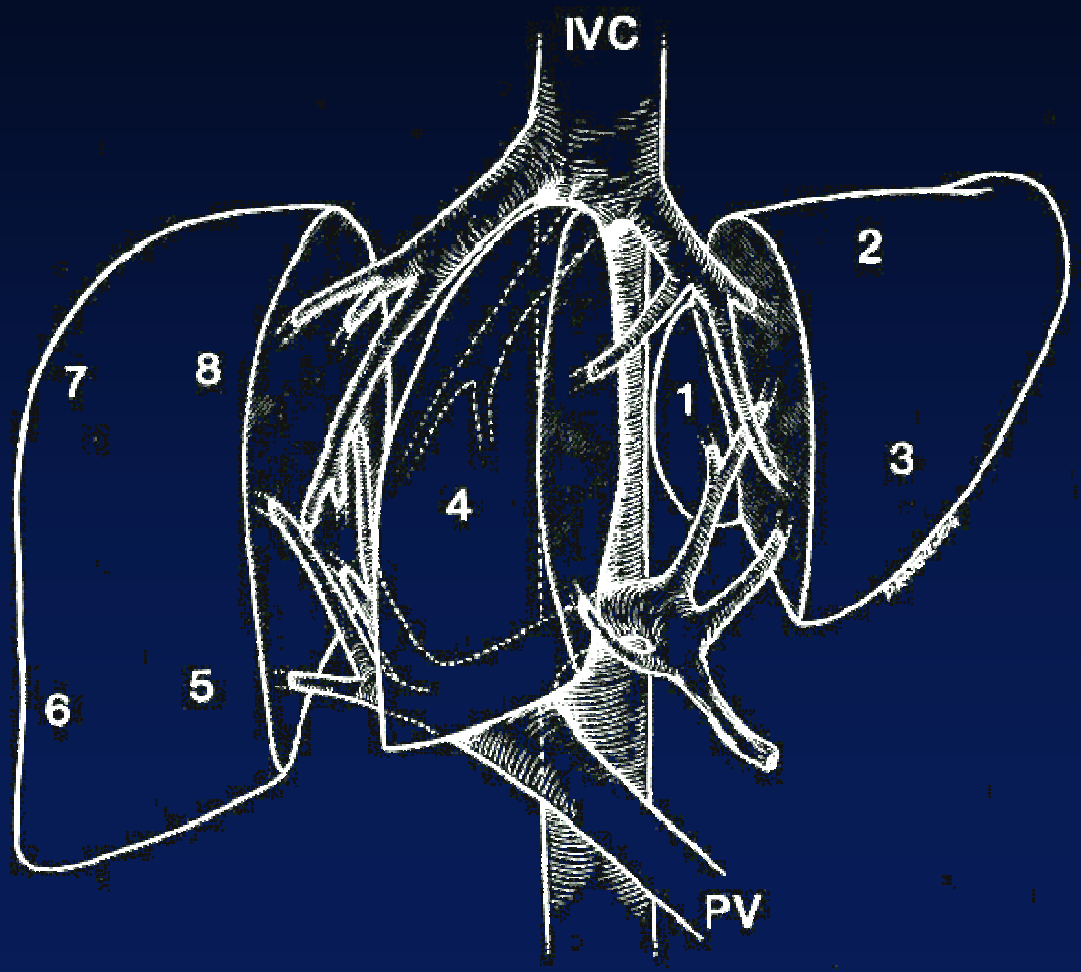


www.optn.org

Adult to adult living donor liver transplant

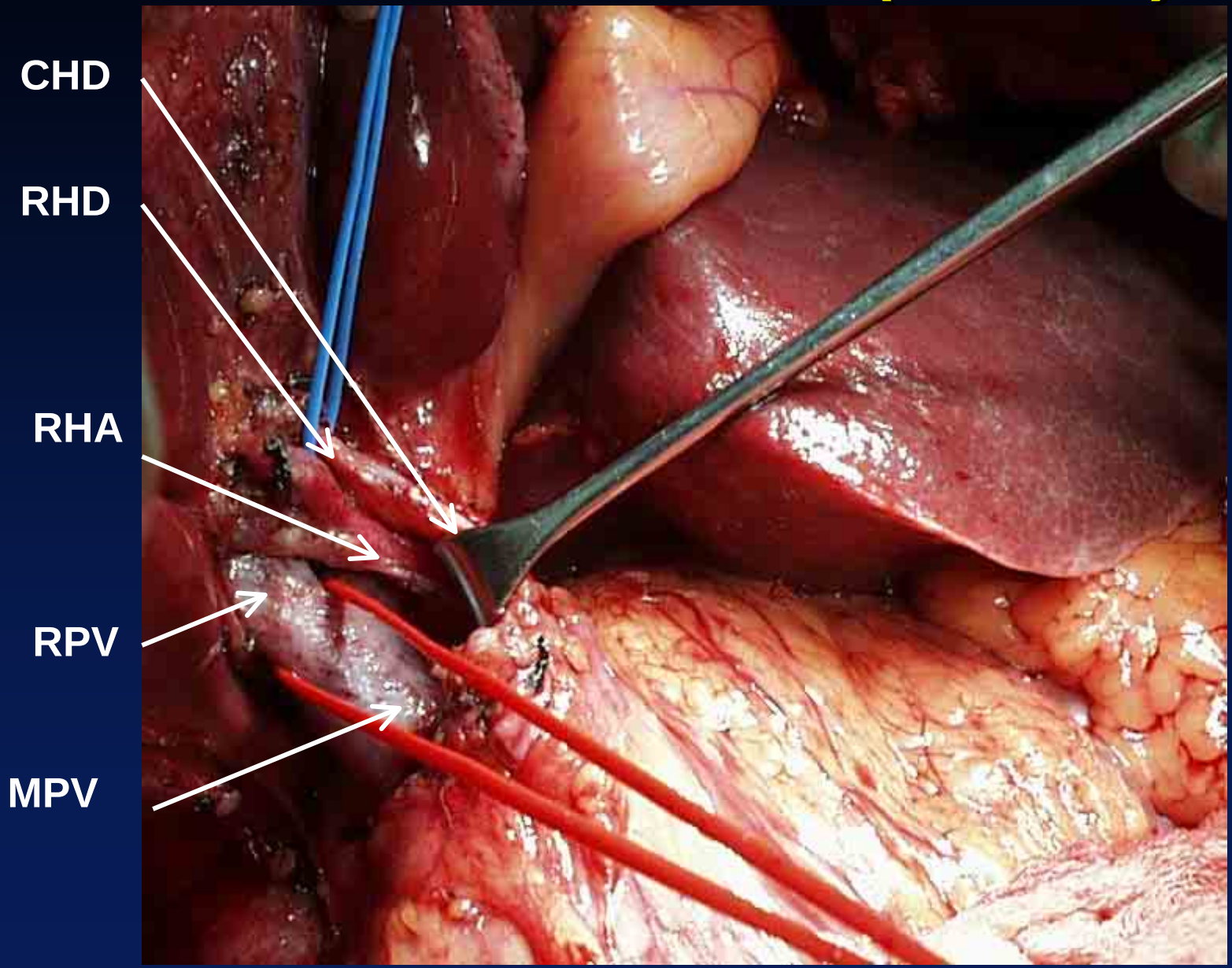
- Benefit to recipient is decreased wait time and thus theoretical decreased risk of mortality
- Benefit to society is increased number of total liver transplants performed
- Risk to recipient is potential increased rate complications after procedure
- Risk to donor is medical, financial and psychological

Potential anatomic resections

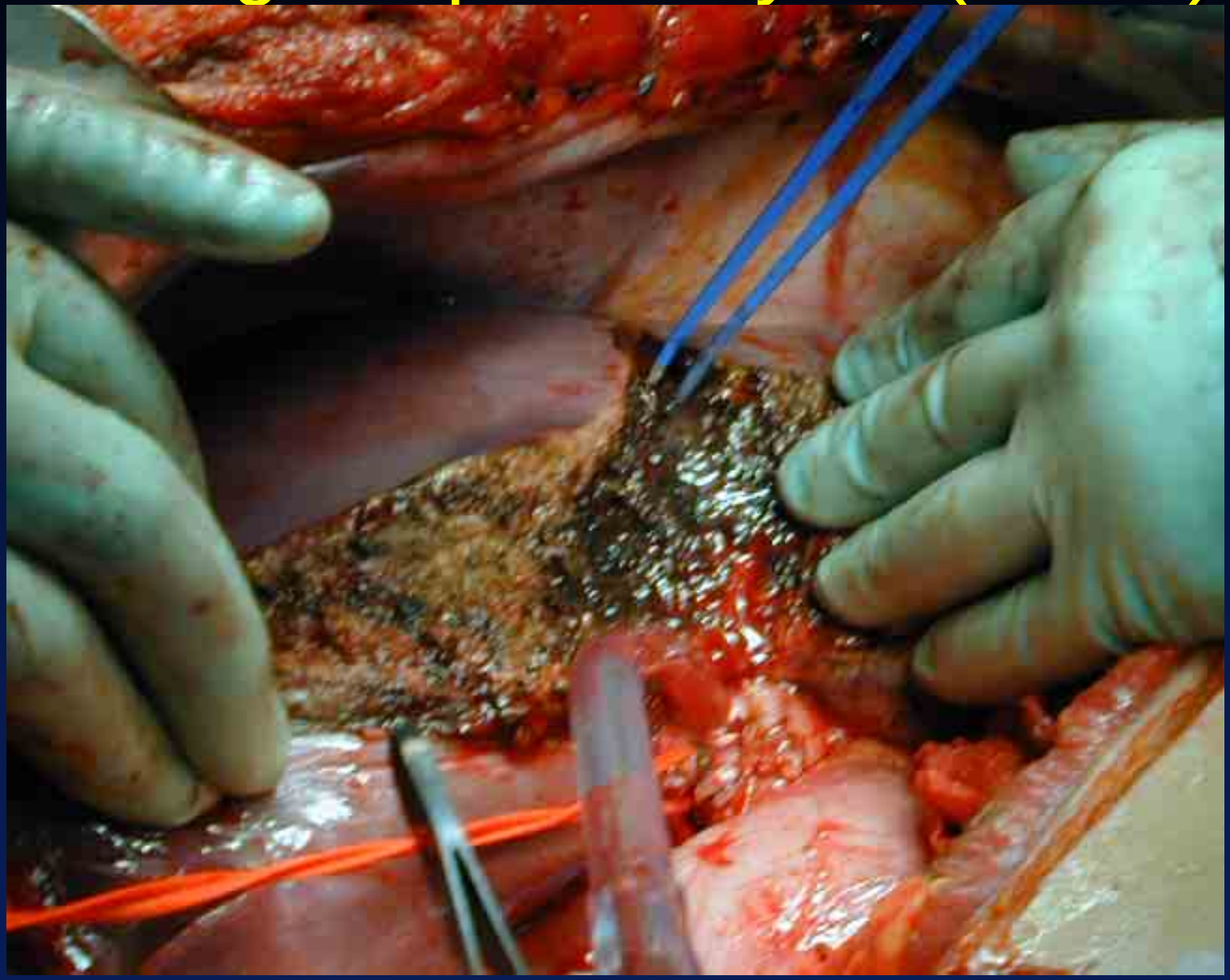


- Right lobectomy
- Left lobectomy
- Extended L lateral segmentectomy

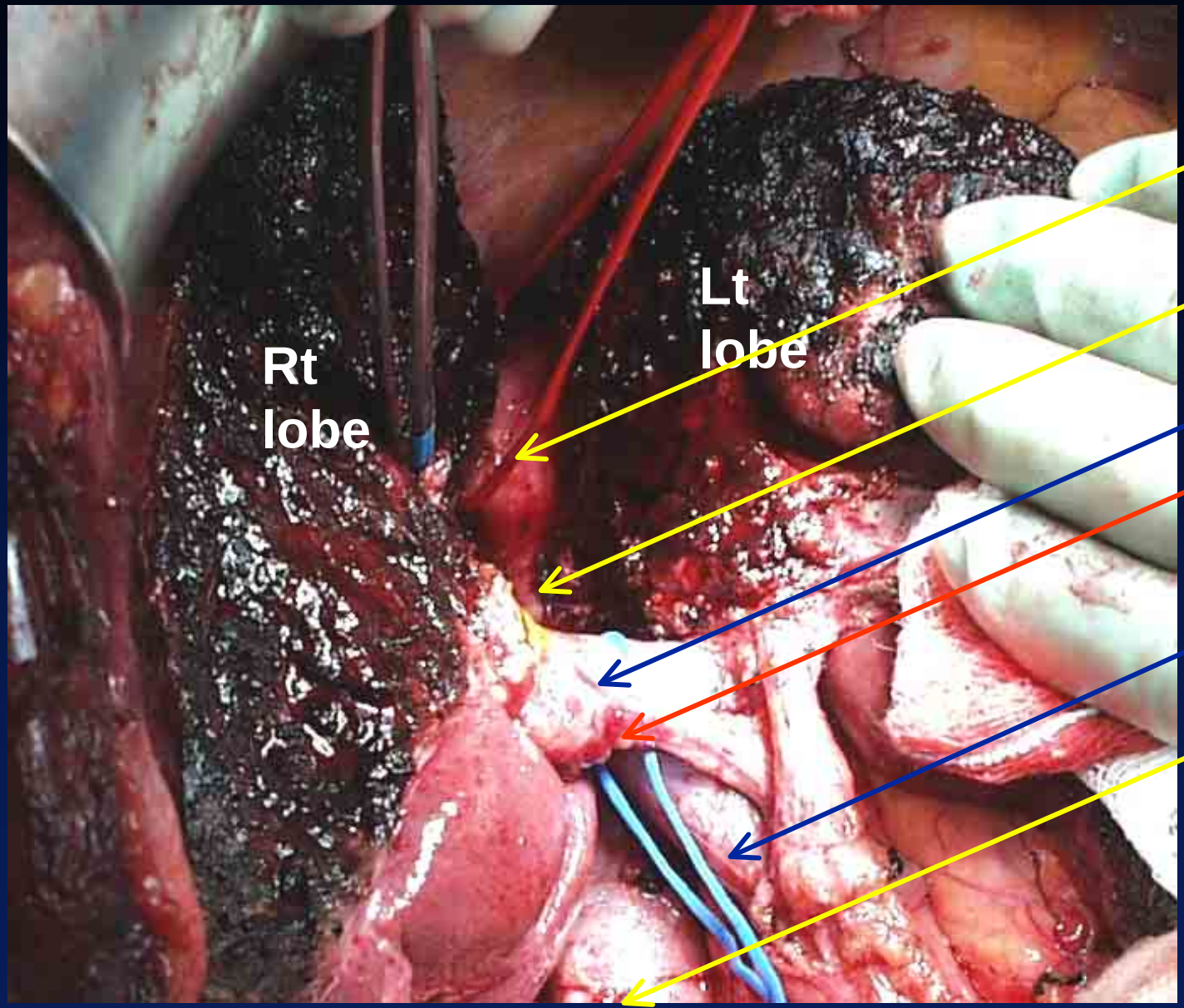
Dissection of hilum (donor)



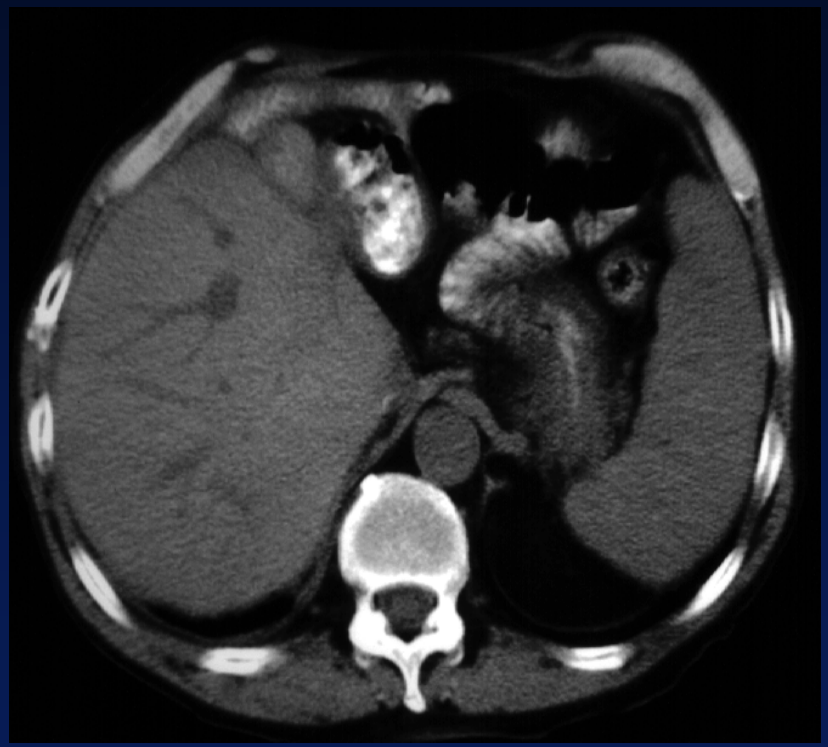
Dividing the parenchyma (donor)



Isolated right lobe of liver (donor)



Postoperative follow-up CT at post-transplant 4 months



Characteristics of living donors

- Age 18-65+

18-34 years old	42.8%
35-49 years old	35.6%
50-64 years old	9.3%
65+ years old	0.4%

- Relationship to recipient

Parent	14.8%
Offspring	26.7%
Full sibling	11.9%
Other relative	9.9%
Spouse	7.0%
Other unrelated	14.6%

2001 LDLT data, from OPTN/SRTR 2002 Annual Report

Duration of adult liver donor hospitalizations

< 1 week	**38.3%**
7-10 days	**55.2%**
10+ days	**6.5%**

Source: A2ALL SRTR data analysis 1998-2002

Adult living donor morbidities

Bleeding requiring transfusion	**8.5%**
Infection	**6.0%**
Pulmonary embolism	**0.5%**
Return to OR	**3.3%**
Bile leak	**0.01%**
Abscess	**0.005%**

SRTR analysis of A2ALL centers 1998-2002

Adult living donor mortality

- Two reported U.S. deaths directly related to donation: total n>1200
- Two donor deaths in Social Security Death Master File (SSDMF) reported as suicide
- One death in SSDMF within two years of donation cause not provided

Source: SRTR, A2ALL

Other approaches to liver replacement, modification and support

Hepatic xenotransplantation

- Chimpanzee to human (4)
- Baboon to human (7)
- Pig to human (1)

Recent auxiliary xenotransplant

- Pig to human
  - Cedars Sinai 1996
  - FHF AIH
  - Failure at 20 hours due to hyperacute vascular rejection
  - High titers of xenoreactive antibodies despite plasmapheresis and pig kidney perfusion

Rydberg *et al*., Xenotransplantation 1996;3:340.

Recent orthotopic xenotransplants

- Baboon to human, Pittsburgh
  - Chronic Hep B/HIV
    - 70 days, chronic vascular rejection, died of infection
  - Chronic Hep B
    - 26 days, poor function, died of infection, evidence of baboon CMV transmission

Fung et al., World J Surg 1997;21:956.

Ex vivo xenoperfusions

- Pig liver perfusion as successful bridge to OLT (4.5-12 hours)
  - reduced hyperacute rejection
  - normal levels of xenoreactive antibodies
  - reduced complement/ complement activation

Tector et al., Liver Transplantation 2001;7:82-29.

Barriers to hepatic xenotransplantation

- Hyperacute rejection
  - xenoreactive antibodies
  - complement activation
- Donor protein and lipid production
- Infectious transmission
  - PERV, CMV…..

Stategies for xenotransplantation

- Genetic engineering
  - Reduce hyperacute vascular rejection
    - Reduce antigenicity
    - Downregulate complement activation
  - Upregulate hepatocyte function

Kanazawa et al. Seminars Liver Dis 2000;20:511.

Hepatocyte transplantation

- Correct metabolic defect
- Bridge to liver transplant
- Bridge to spontaneous recovery
- Cannot reverse portal hypertension !!!!

New approaches to liver replacement therapy: Scorecard

- Living donor liver transplant

  Here today

- Cell transplantation from deceased donor organs

  On the map

- Xenotransplantation

  Over the horizon (way past Blacksburg)

- Bioengineered organs

  ?Clearly the future