

# Pancreatic islet isolation in the UK

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Dr Martin Press,  
Director, Islet Transplant Unit,  
Royal Free Hospital,  
London, UK.

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# UK Islet Transplant Consortium: 2000

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- Bristol
- Cambridge
- Edinburgh
- King's
- Leicester
- Newcastle
- Oxford
- Royal Free
- Worcester

# Number of patients transplanted 2000-2007

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- Bristol
- Cambridge
- Edinburgh
- King's (5)
- Leicester
- Newcastle
- Oxford (3)
- Royal Free (4)
- Worcester



# Proposed rationalisation

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Phase 1: select 2 best isolating centres:

- King's
- Oxford
- Royal Free

Phase 2: satellite transplanting centres:



# NCG funded consortium (from 1 April 2008)

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## Isolating centres

- London
  - King's
  - Royal Free
- Oxford

## Transplanting centres

- Bristol, Manchester, Newcastle
- (Edinburgh)

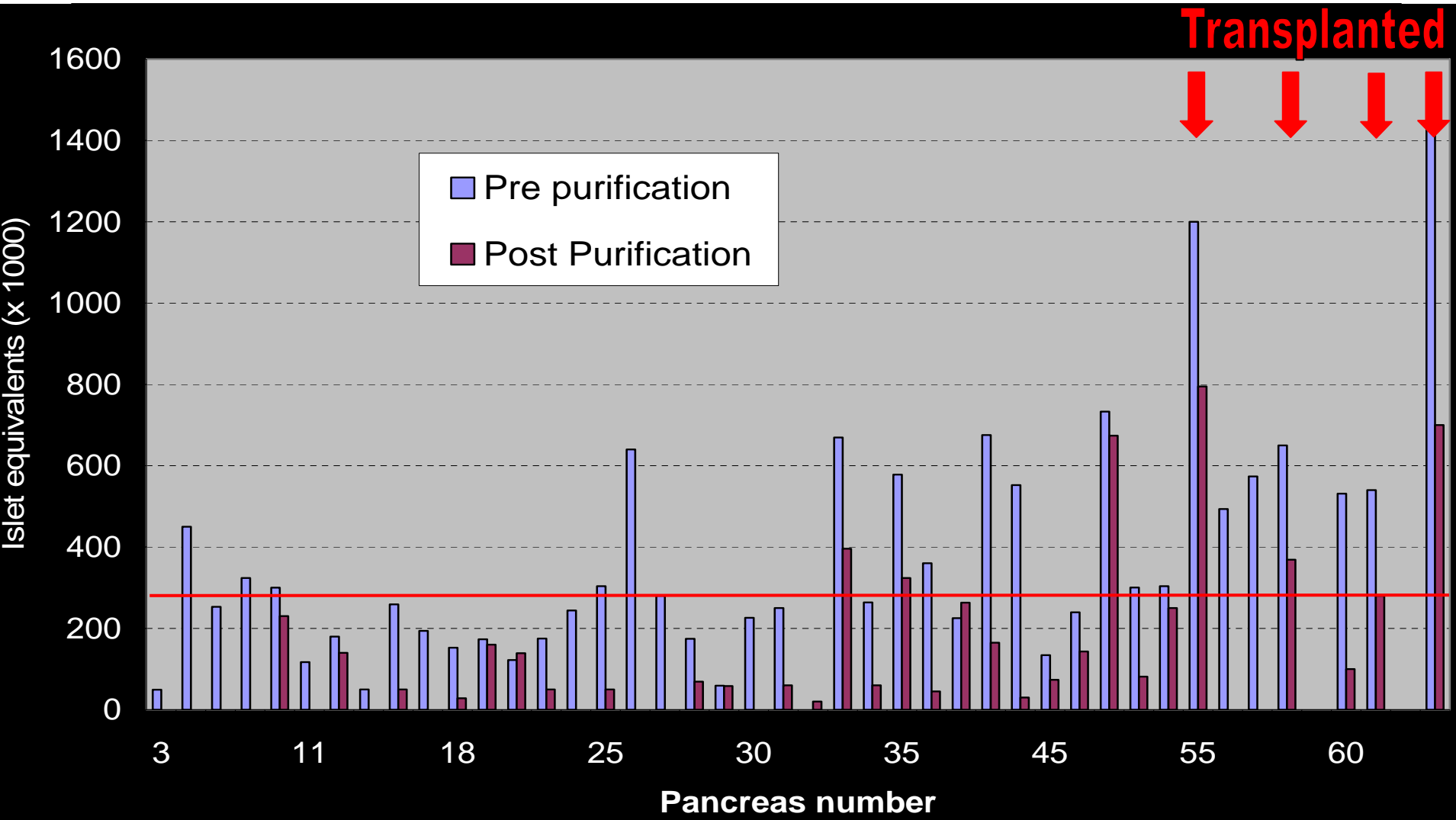


# Current situation

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- Rota of isolating centres
- National prioritised waiting list

# Isolations to September 05 (RFH)





# The Kooner gambit

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- Distend pancreas to 80mmHg with collagenase alone
- When you realise you've forgotten the NPase, add it before the pressure is increased

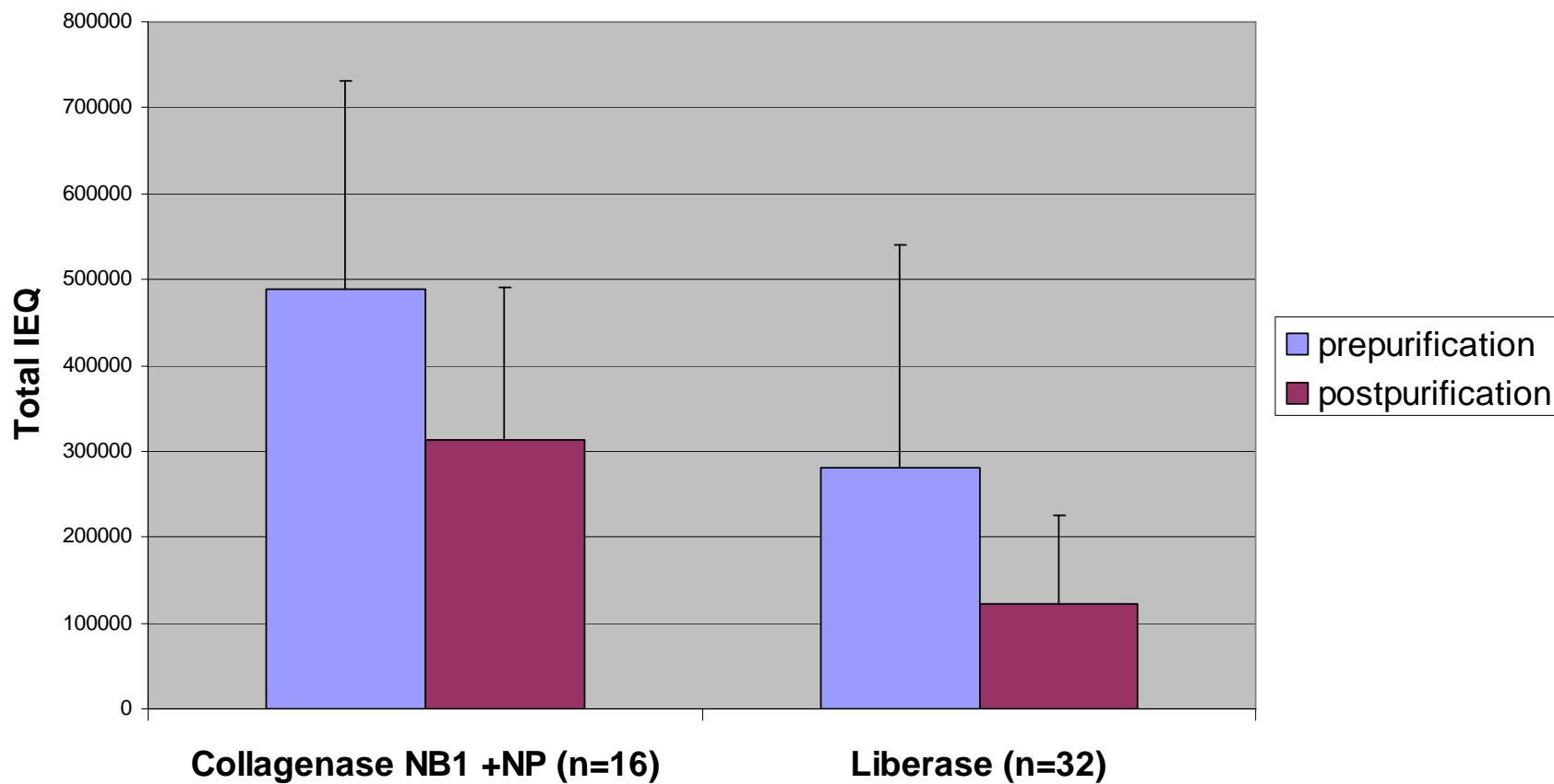


# Royal Free protocol

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1. Collagenase: 2000u NB1 in 10ml HBSS.
2. NPase: 50u in 5ml sterile water.
3. Add collagenase to 350 ml perfusion solution (HBSS + Ca<sup>++</sup>) and pour into cold block
4. Infuse collagenase solution into cannulated pancreas to pressure of 60-100mmHg
5. Add 15-25u NPase to cold block sump and raise perfusion pressure to 160-200mmHg
6. Digestion time typically 18-25min

# Islet Isolation



# Sequential enzyme infusion

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- Results just as good as using them together
- Could one do even better with different protocols?
- Ability to vary both ratio of enzymes and timing
- ?differences from other centres related to characteristics of pancreases

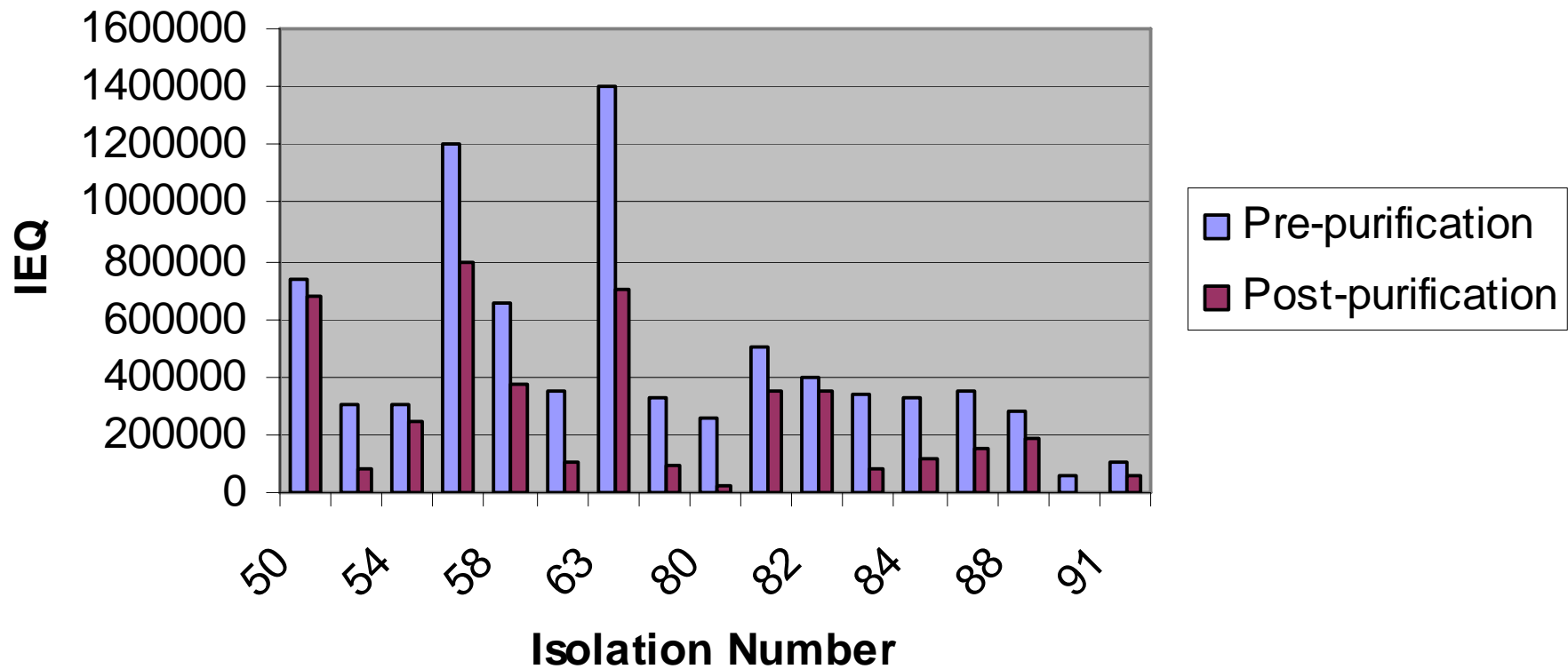
# Differences between 3 UK centres

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	K	RF	O
NPase (U)	50	<25	50
Enzymes	simul	seq	simul
Gradient	UW	Biocoll	Biocoll
COBE	cooled	not cooled	cooled
Speed	3000	2000	2000
Culture	no	<24h	<4h

# Isolations 50-93

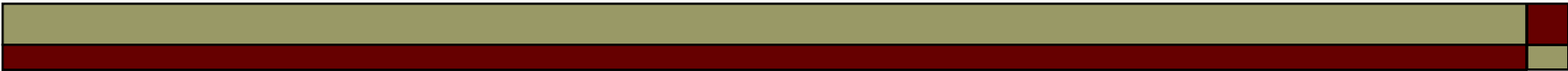
**ISLET ISOLATIONS: Pre & Post Purification IEQs**



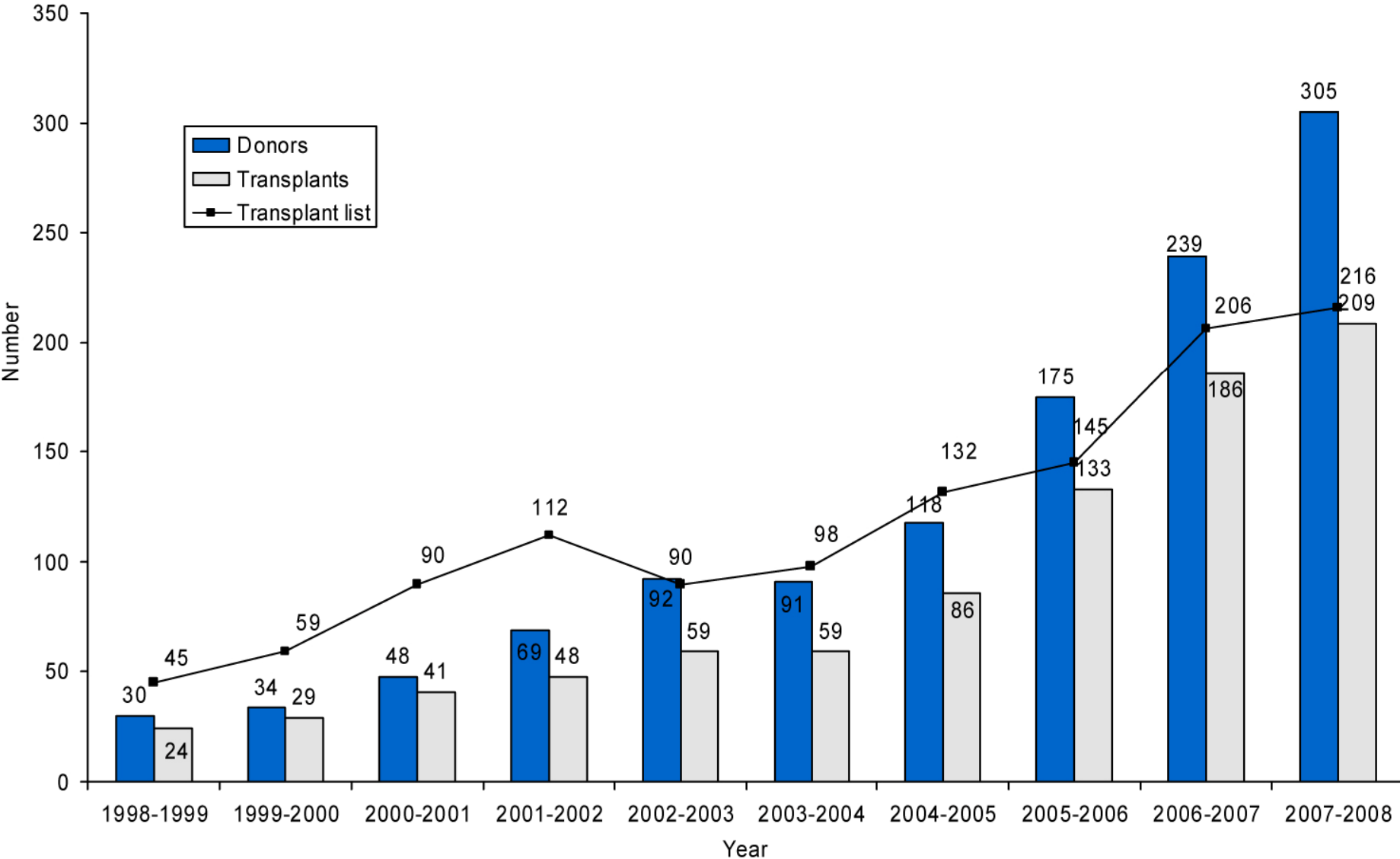
# Variables in islet isolation

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- The staff +
- The enzymes ++
  - Interbatch variation
  - Enzyme concentrations
  - Timing of enzymes
- The pancreases ++++



**Figure 4.1** Deceased heartbeating pancreas programme in the UK, 1 April 1998 - 31 March 2008  
Number of donors, transplants and patients on the active transplant list at 31 March



# Whole pancreas transplants. Apr 05

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- Whole pancreas transplantation centres
  - Cambridge
  - Cardiff
  - Edinburgh
  - Guy's
  - Hammersmith
  - Manchester
  - Newcastle
  - Oxford



# Number of transplants 2007-08

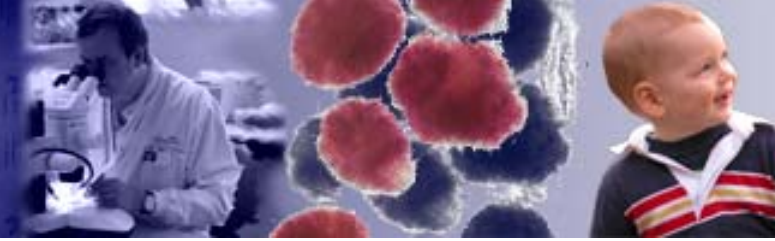
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- Whole pancreas transplantation centres
  - Cambridge 20
  - Cardiff 26
  - Edinburgh 21
  - Guy's 26
  - Hammersmith 14
  - Manchester 36
  - Newcastle 11
  - Oxford 88

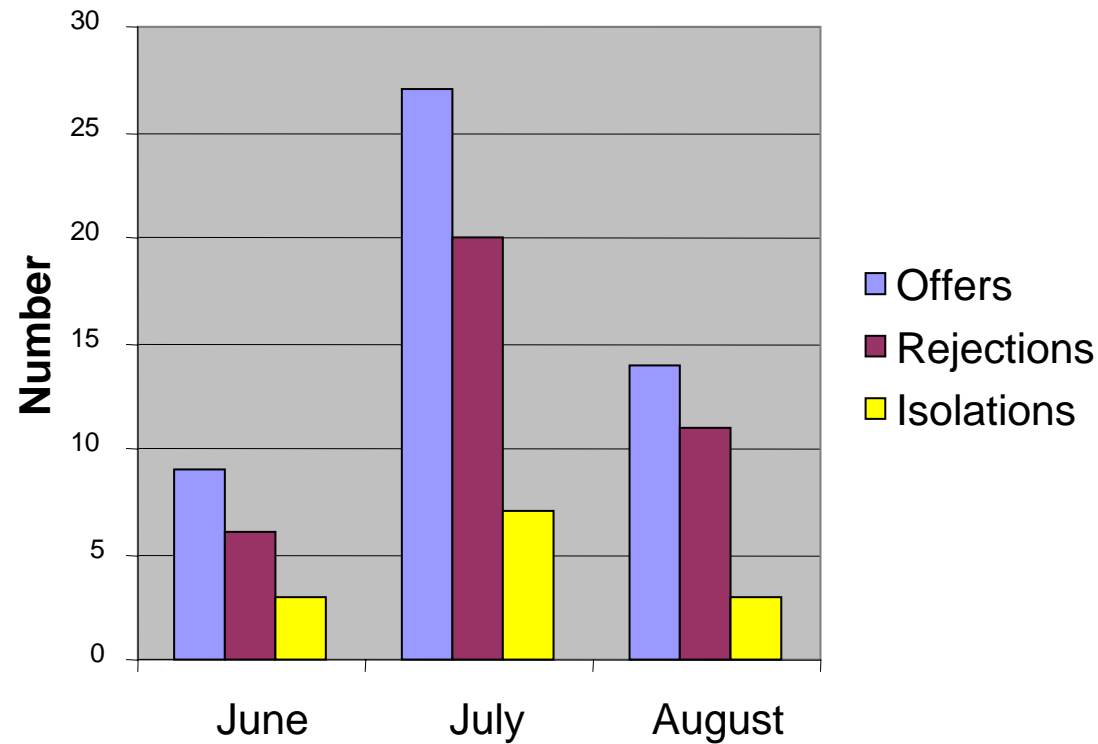
# Pancreas allocation

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- From 1<sup>st</sup> April 2005 until 1<sup>st</sup> August 2008, islet transplant programme got
  - Donors rejected by whole organ programme
- Since 1<sup>st</sup> August 2008, islet programme gets:
  - Donors rejected by whole organ programme
  - Donors with BMI>30



## NCG joint centres activity

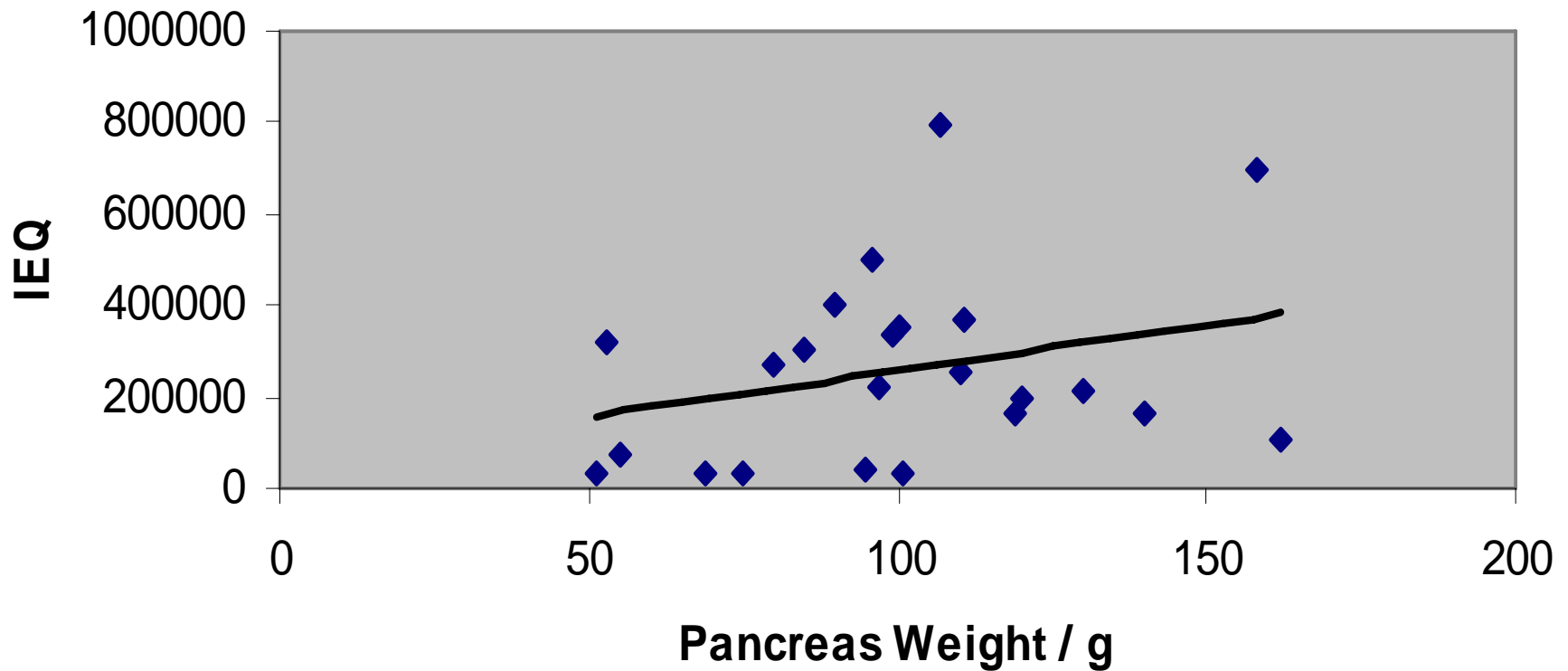


# Pancreases isolated since 1<sup>st</sup> August

	<b>Age</b>	<b>CIT</b>	<b>panc wt</b>	<b>BMI</b>	<b>IEq pre</b>	<b>IEq post</b>
<b>Tx (mean) 2005</b>	46	5.2	118	31	762,500	535,500
<b>Since 1<sup>st</sup> Aug 08</b>	42	6	78	34	20,000	
	65	7	72	24	180,000	60,000
	27	5	68	20	120,000	80,000
	43	8	32	34	170,000	60,000
	38	7	31	30		
	28	6.5	155	24		
	34	11	95	25	320,000	250,000
	53	12		36		
<b>Mean</b>	44	8.0	71	29	162,000	112,500

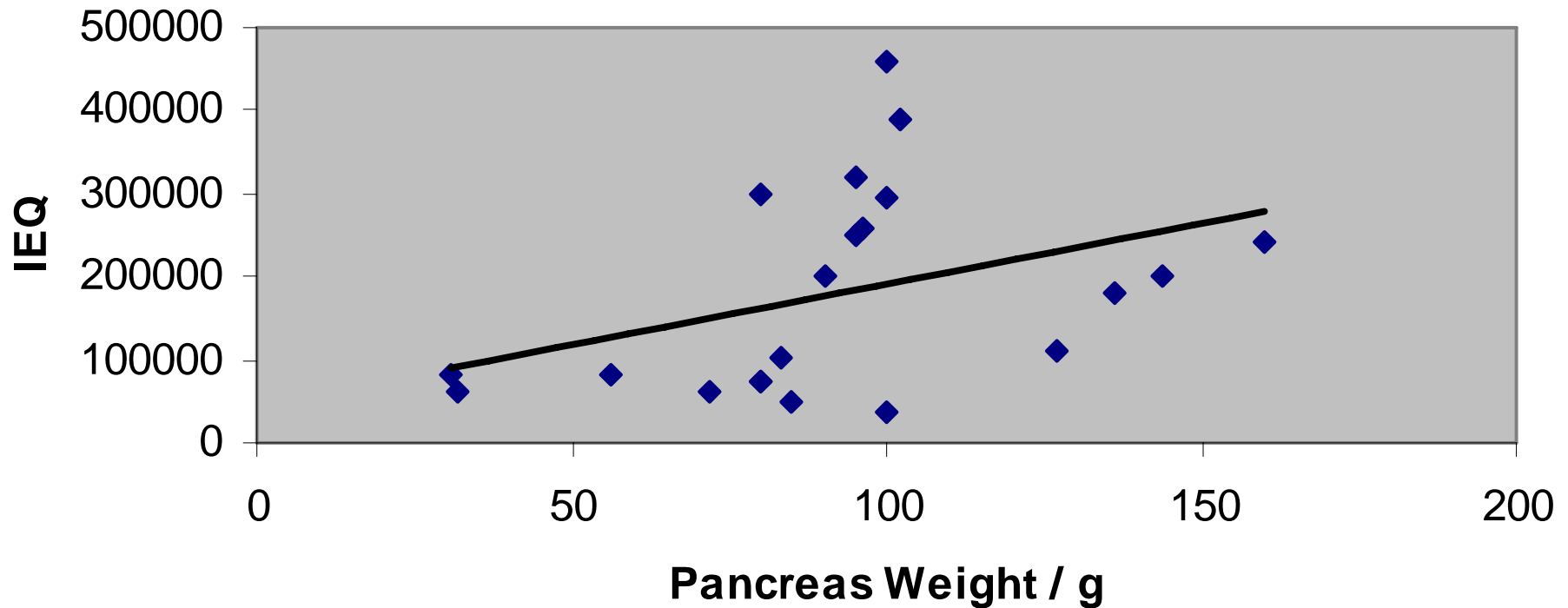
# UK pancreases 2003-07

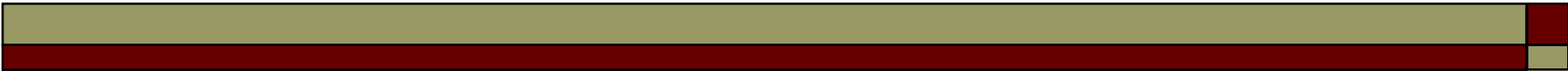
Graph showing the relationship between Pancreas Weight and IEQ (2003-2007)



# UK pancreases since 1<sup>st</sup> August

**Graph showing the relationship between Pancreas Weight and IEQ (2008)**



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- Transplantable numbers not seen in pancreases <75g
  - How can we modify digestion protocols to match pancreas characteristics?
  - Are the current release criteria appropriate for small pancreases?

# Neutral protease

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- Low dose <50u
  - Geneva, Lille, Royal Free
- Medium dose 50-150u
  - Uppsala, (Leicester)
- High dose 200+u
  - San Francisco, Miami





# Need for multi-centre trial

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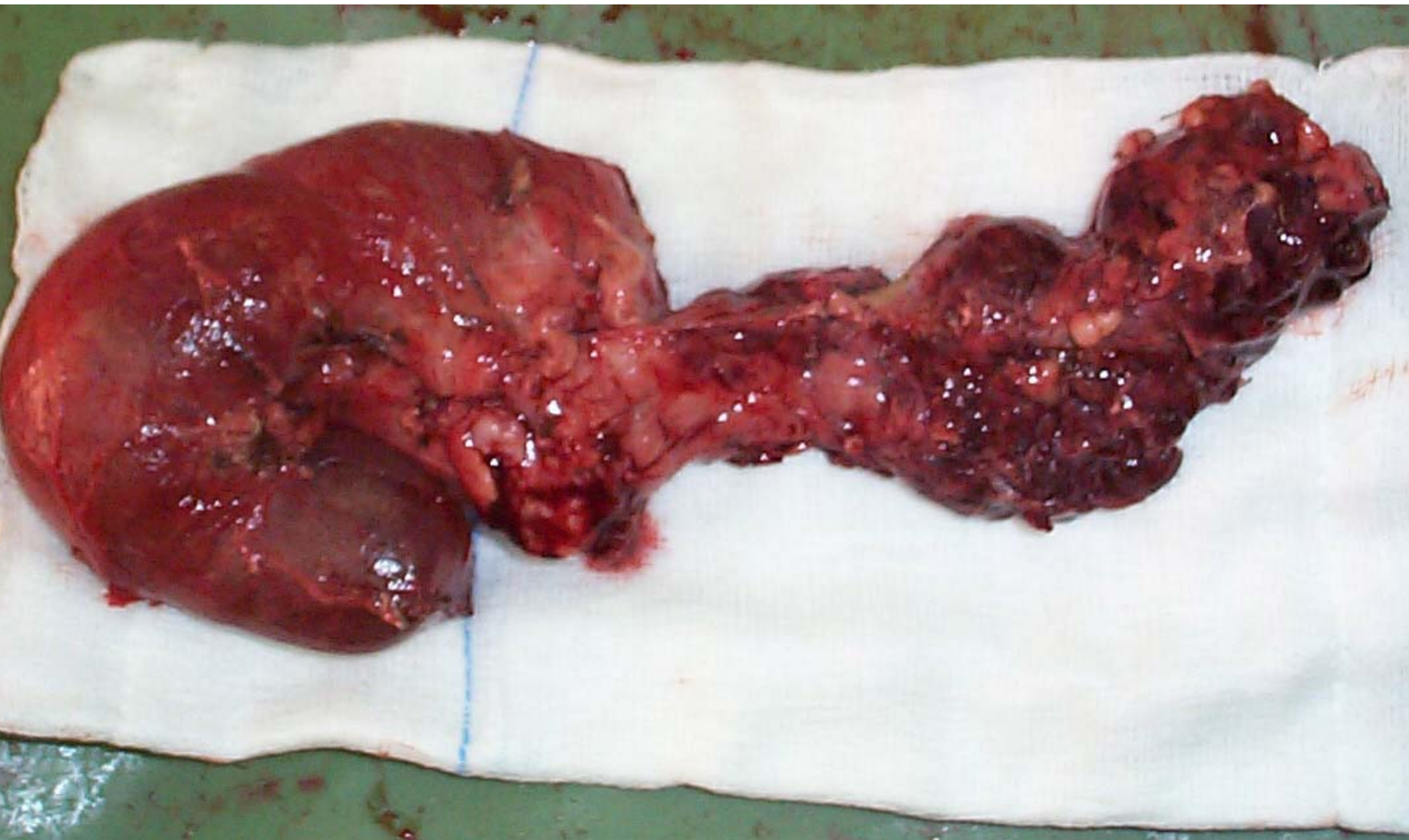
- to compare different enzyme ratios
- individualised protocol for given pancreas
  - pancreas weight
  - donor age
  - donor BMI
  - preservation method
  - ?pancreas density
  - ?collagen type

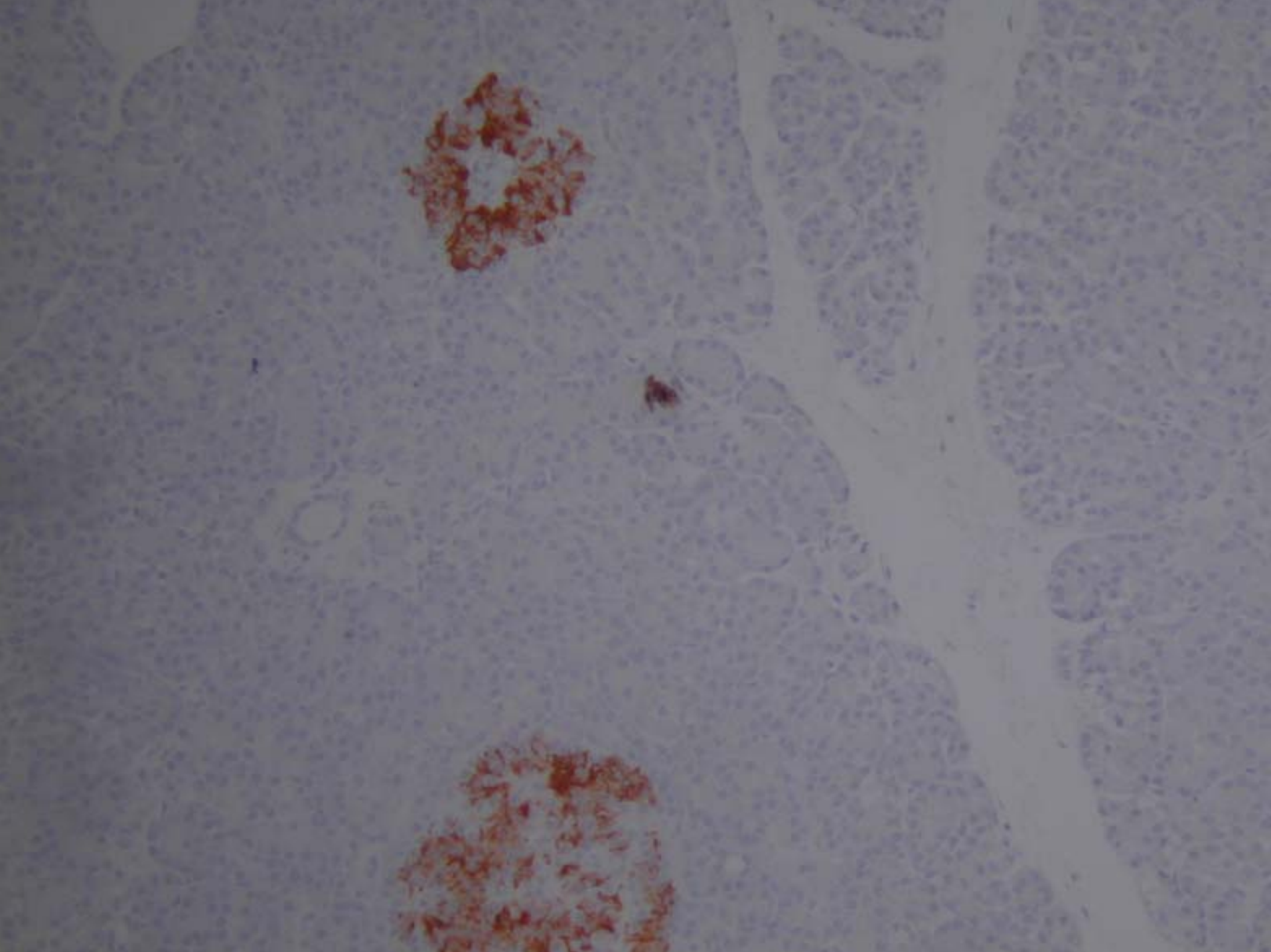


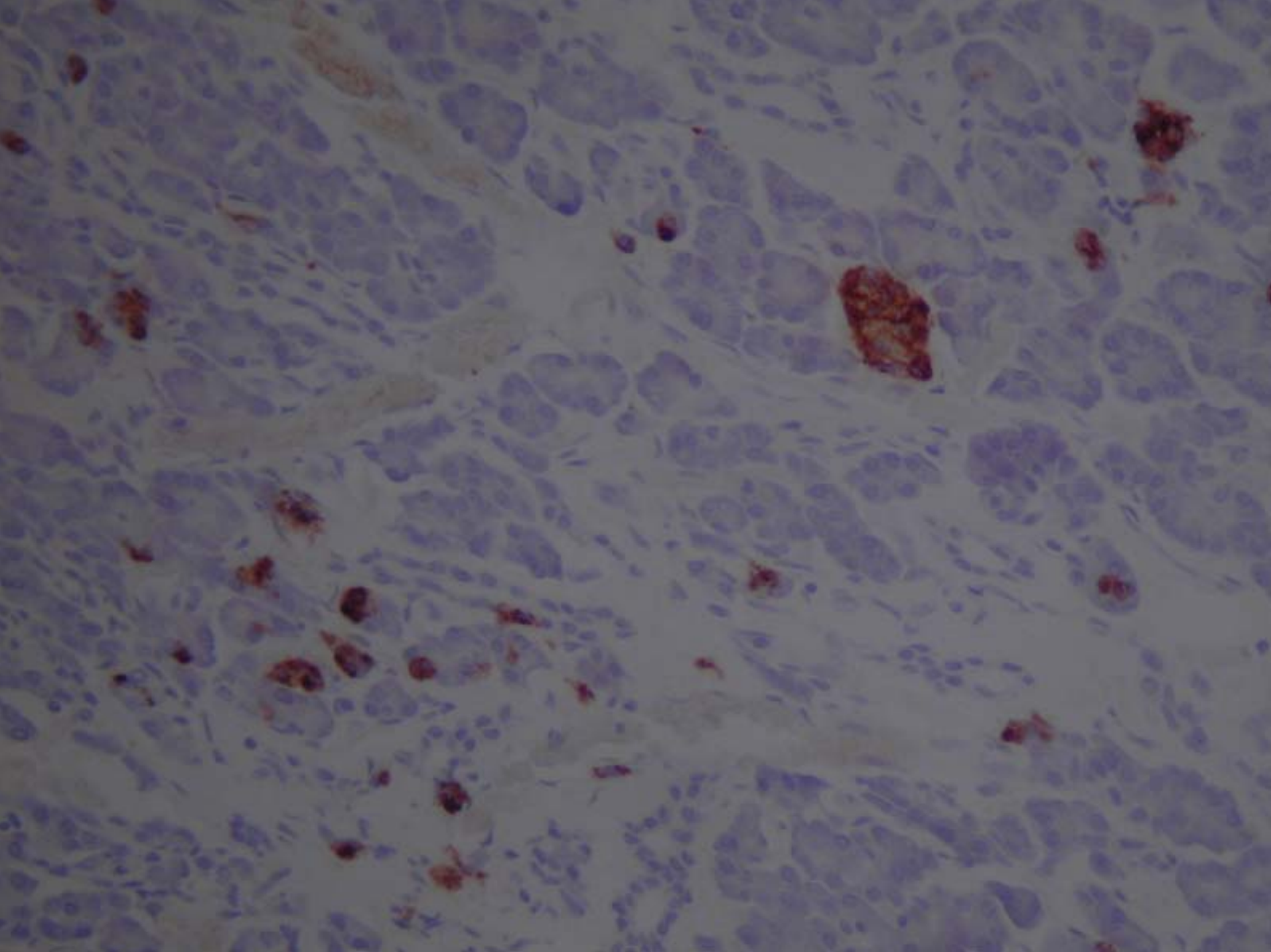
# Autotransplantation: Leicester

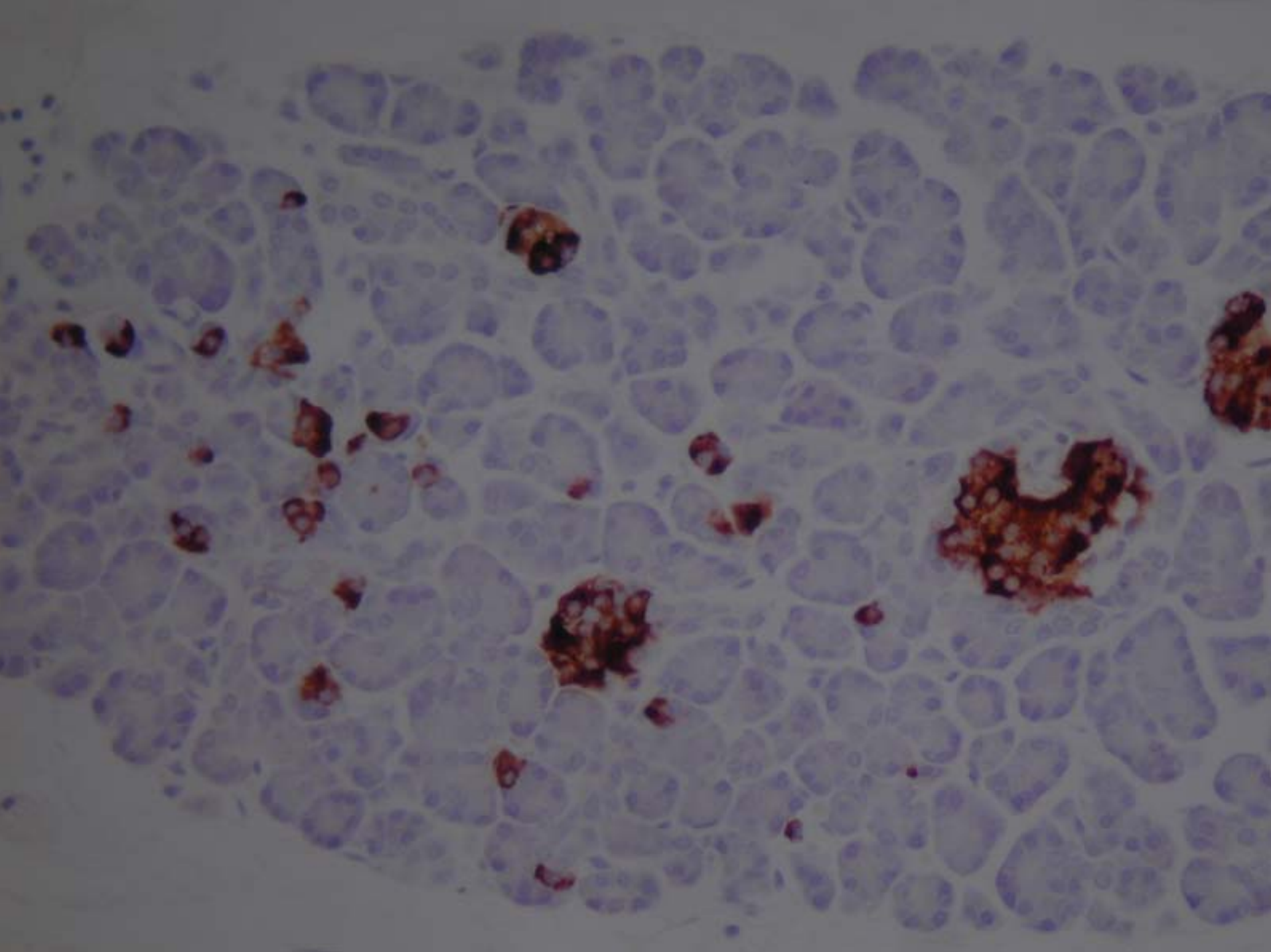
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- Mr Ashley Dennison
- Dr Roger James









# Autotransplantation: Leicester

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- Just done 50<sup>th</sup>. 10 year follow-up
- 1 in 4 insulin indep, median 16 mos
- 1 in 10 long term insulin independence
- All single transplants
- Even 2000 IEq/kg → little or no insulin reqt
- 100% C-peptide positive
- No diabetic complications seen

# Auto-transplantation

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- Fiercer digestion
- Digest to completion
- No attempt at purification
- Median tissue volume 13ml
- Median rise in portal pressure 8mmHg
- Single 5,000u heparin injection
- Thrombosis almost unknown





# FDA Product Release Criteria

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- $>4,000$  IEq/kg recipient body weight
- Transplanted tissue volume  $<10$ g

# Summary

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- Until 2005, we were obtaining excellent islet preparations with low doses of NPase, given sequentially. This may reflect the pancreases we were digesting in 2004-5
- We have no logical way of allowing for pancreas variables
- A multi-centre trial of different protocols may be necessary to move forward
- It may be appropriate to re-examine product release criteria



# Conclusion

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- The fault, dear Brutus, lies not in our stars but in ourselves that we are underlings.

William Shakespeare, Julius Caesar, Act 1, Scene 2.



# Pancreas offers for islet transplants

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- Reciprocal relationship to whole pancreas transplants
- Whole pancreas programme funded from 1<sup>st</sup> April 2005.
- Islet programme funded from 1<sup>st</sup> Apr 2008
- Agreement for islet programme to use pancreases from donors with BMI>30 from 1<sup>st</sup> August 2008.

# Enzyme ratios

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- Brandhorst 2.6-4.5% (50-90u) NPase
- Bucher 1.2-6.25% (25-125u)NPase
- Juszczak 50u severe over digestion
- Ricordi 200u ‘because if I use any less it doesn’t work’

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	AGE CIT/h	WEIGHT/g	BMI	IEQ(pre)	IEQ(post)
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**TRANSPLANTED ISLETS**

<b>MEAN</b>	<b>46.5</b>	<b>5.25</b>	<b>118</b>	<b>31.5</b>	<b>170,000</b>	<b>9625000</b>	<b>553500</b>
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**UK ISOLATIONS FROM 1ST AUGUST 2008**

42	6	78	34	20000	-
65	7	72	24	180000	60000
27	5	68	20	120000	80000
43	8	32	34	170000	60000
38	7	31	30		
28	6.5	155	24		
34	11	95	25	320000	250000
53	12		36		
53	8		32		
63	9	37	28		

<b>MEAN</b>	<b>44.6</b>	<b>7.95</b>	<b>71</b>	<b>28.7</b>	<b>162000</b>	<b>112500</b>
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# Variables in islet isolation

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