FDA/NIH Joint Symposium on Diabetes

May, 2004

Insulin Pumps: Hopes and Expectations

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How to “Cure” Diabetes?

Biologic Approaches

- Organ Transplant
- Islet Cell Transplant
- Embryonic Stem Cells
- Adult Stem Cells

Mechanical Approaches

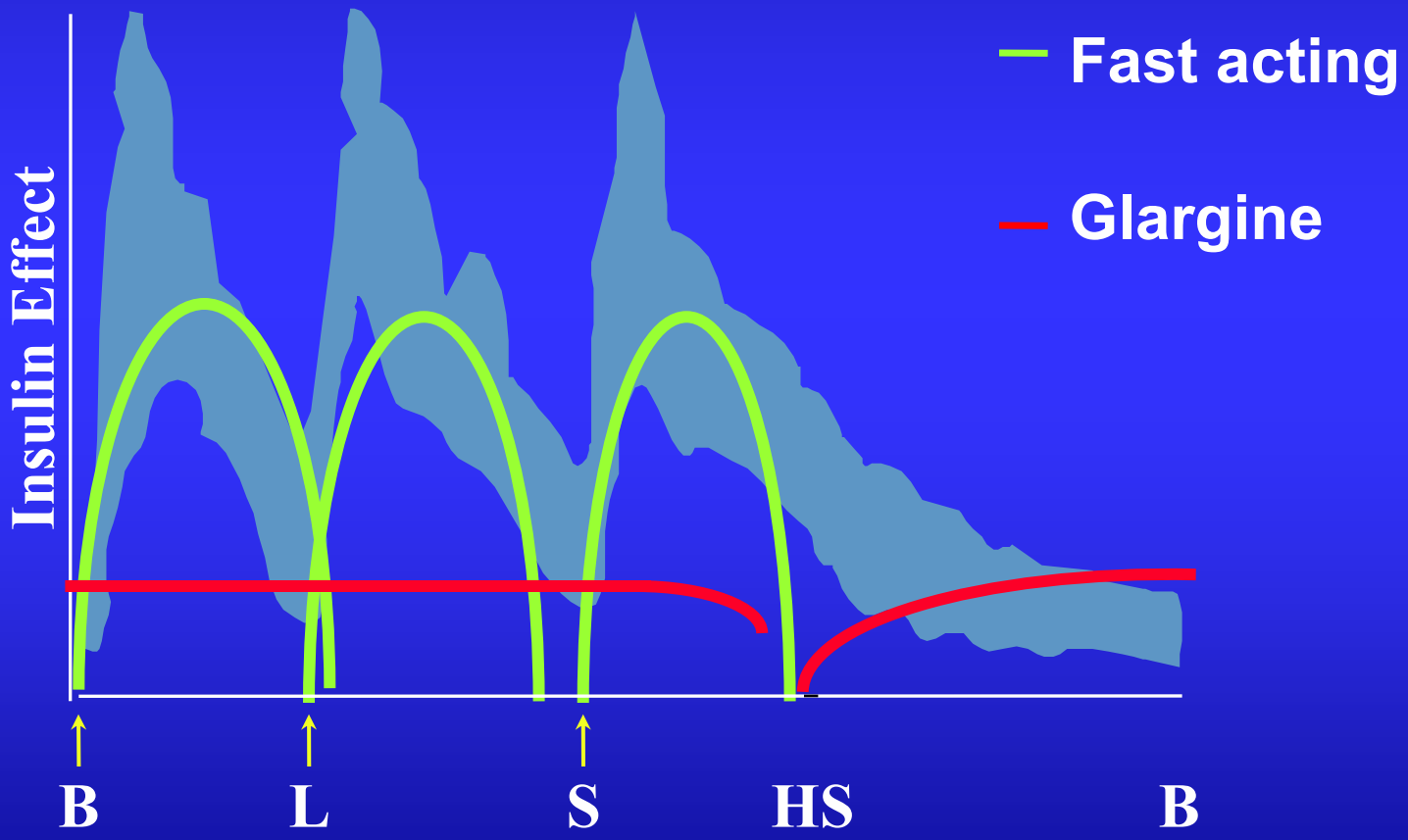
- External, open loop pumps
- Implantable open loop pumps
- Continuous glucose sensing
- Closed loop pumps, external or implanted

How to “Cure” Diabetes?

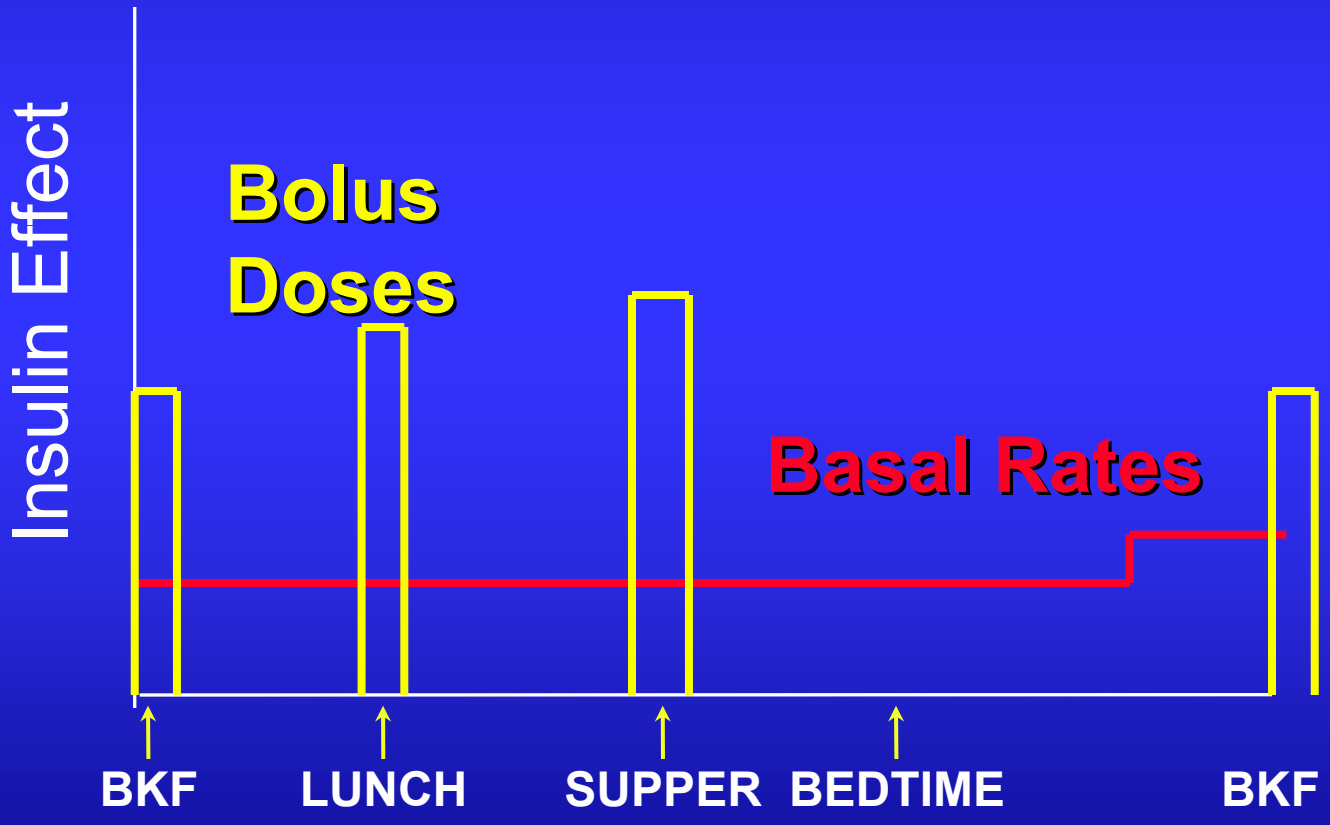
Mechanical Approaches

- **External, open loop pumps**
- Implantable open loop pumps
- Closed loop pumps, external or implanted

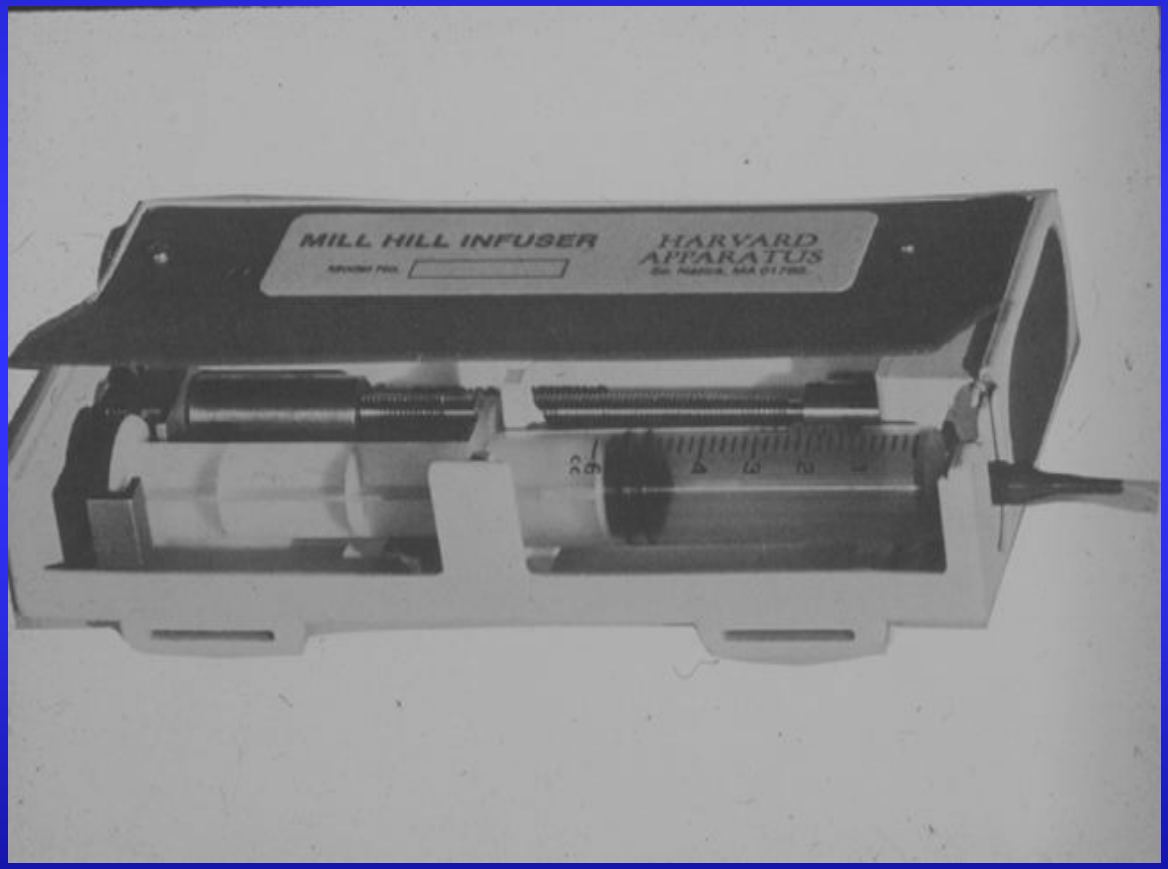
Multiple Daily Injections (MDI): with Glargine Insulin



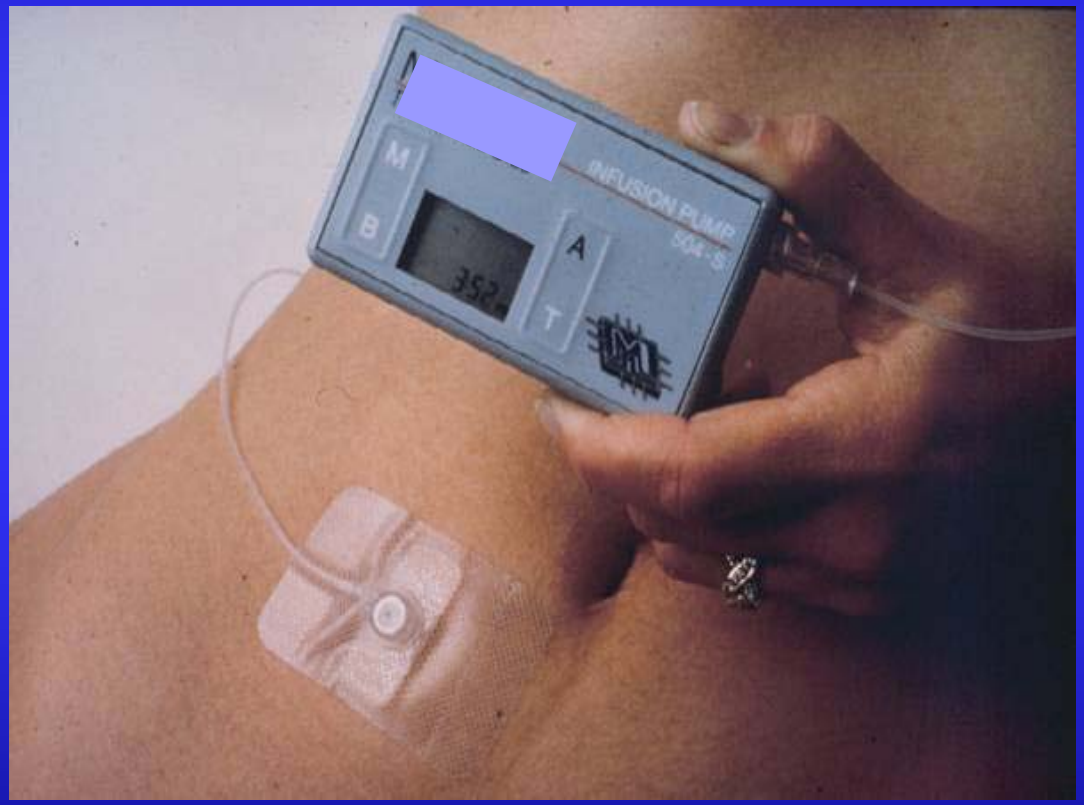
External Insulin Pump: Basal/Bolus Therapy



External Pumps, CSII: The Mill Hill Infuser



External Pumps, CSII: A Recent Model



Telemetry: Glucose Monitor to External Pump

Medtronic MiniMed's "Paradigm System"

Finger-stick Glucose Meter telemeters result to pump, displayed to patient

Telemetry: Glucose Sensor to Alarm

Medtronic MiniMed's "Guardian System"

Continuous sensor triggers alarm

External Pumps (CSII): Current Status:

- Available therapy since 1980s for type 1 diabetes or unstable type 2
- Well over 100,000 pumps sold
- At least 4 Manufacturers:
  - Medtronic MiniMed,
  - Deltec,
  - Animas
  - Disetronic (+/-)

External Pumps, CSII: Advantages

- Flexibility of meal, activity timing
- Freedom from multiple daily injections
- More precise insulin delivery patterns:
  - True Basal/Bolus
- Most evidence suggests improved glycemic control

External Pumps (CSII): Limitations

- Always “wearing” a device
- Change the set every three days
- Skin irritation/infection
- Some poor skin insert sites
- Peripheral insulin delivery

Insulin Pumps: Hopes and Expectations

So implantable insulin pumps were invented

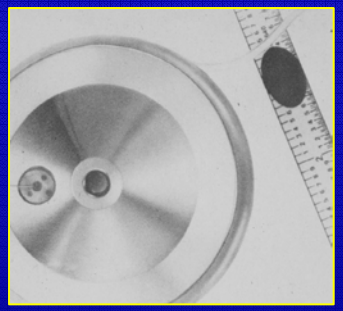
Implantable Insulin Pumps (IIP): Potential Advantages

- No “externality”
- Refills (“maintenance”) only every 3 months
- More physiologic, hepatic Portal insulin delivery
  - With its potential advantages for hepatic glucose handling, lipids, etc.

Implanted Insulin Pump Therapy

Buchwald et al., Continuous Rate IIP

1970 1975 1980 1985 1990 2000



Implanted Insulin Pump Therapy

NASA in its Hayday

1970 1975 1980 1985 1990 2000

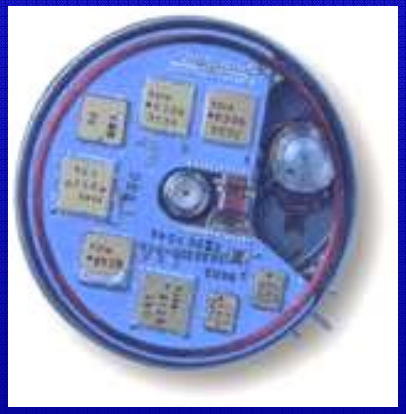
The Pump that Landed on Mars

Implanted Insulin Pump Therapy

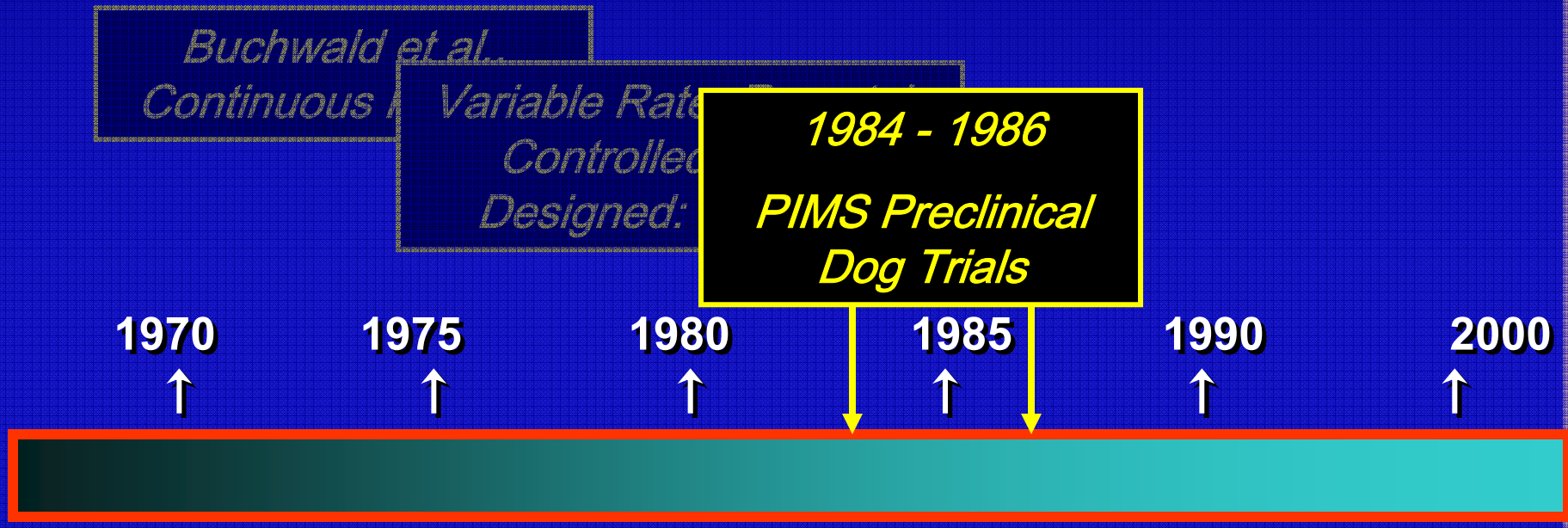
Buchwald et al.
Continuous

Variable Rate, Remotely Controlled Pumps Designed: JHU/APL

1970 1975 1980 1985 1990 2000

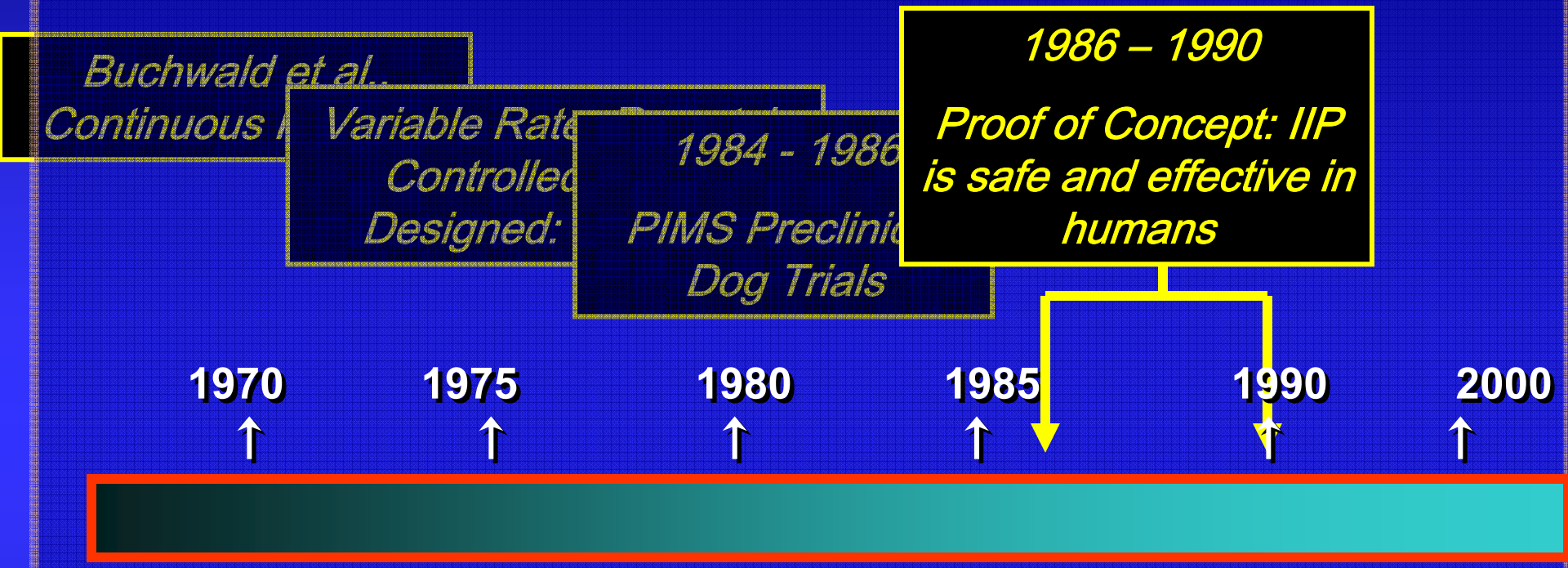


Implanted Insulin Pump Therapy




MEDICATION PROGRAMMING SYSTEM (MPS)
What happened to this guy's brown hair?

Implanted Insulin Pump Therapy



Saudek et al. A preliminary trial of the Programmable Implantable Medication System for insulin delivery. NEJM 321:574-79, 1989.

Implanted Insulin Pump Therapy

Buchwald et al.,
Continuous I

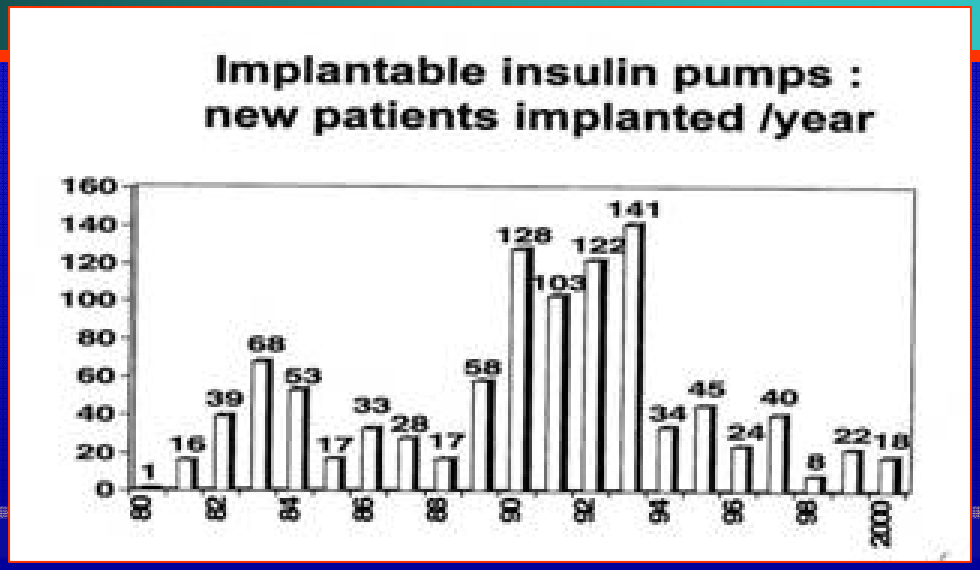
Variable Rate
Controlled
Designed:

1984 - 1986
PIMS Preclinic
Dog Trials

1986 – 1990
Proof of Concept: IIP
is safe and effective in

1990 -2000
IIP Trials Expand

1975 1980 1985 1990 2000



1990 – 2000: What was Learned?

- IIP is safe and effective on a relatively large-scale
- Refills are practical, safe
- Metabolic control can be improved with IIP
- Hypoglycemia can be lessened
- Lipid metabolism can be improved

BUT…

1990 – 2000: What was Learned?

BUT…

- Catheters and Insulin are a vulnerable point
- Autoimmunity, pocket complications and refills/flushes are manageable
- Batteries, programming can be improved

1990 – 2000: What was Learned?

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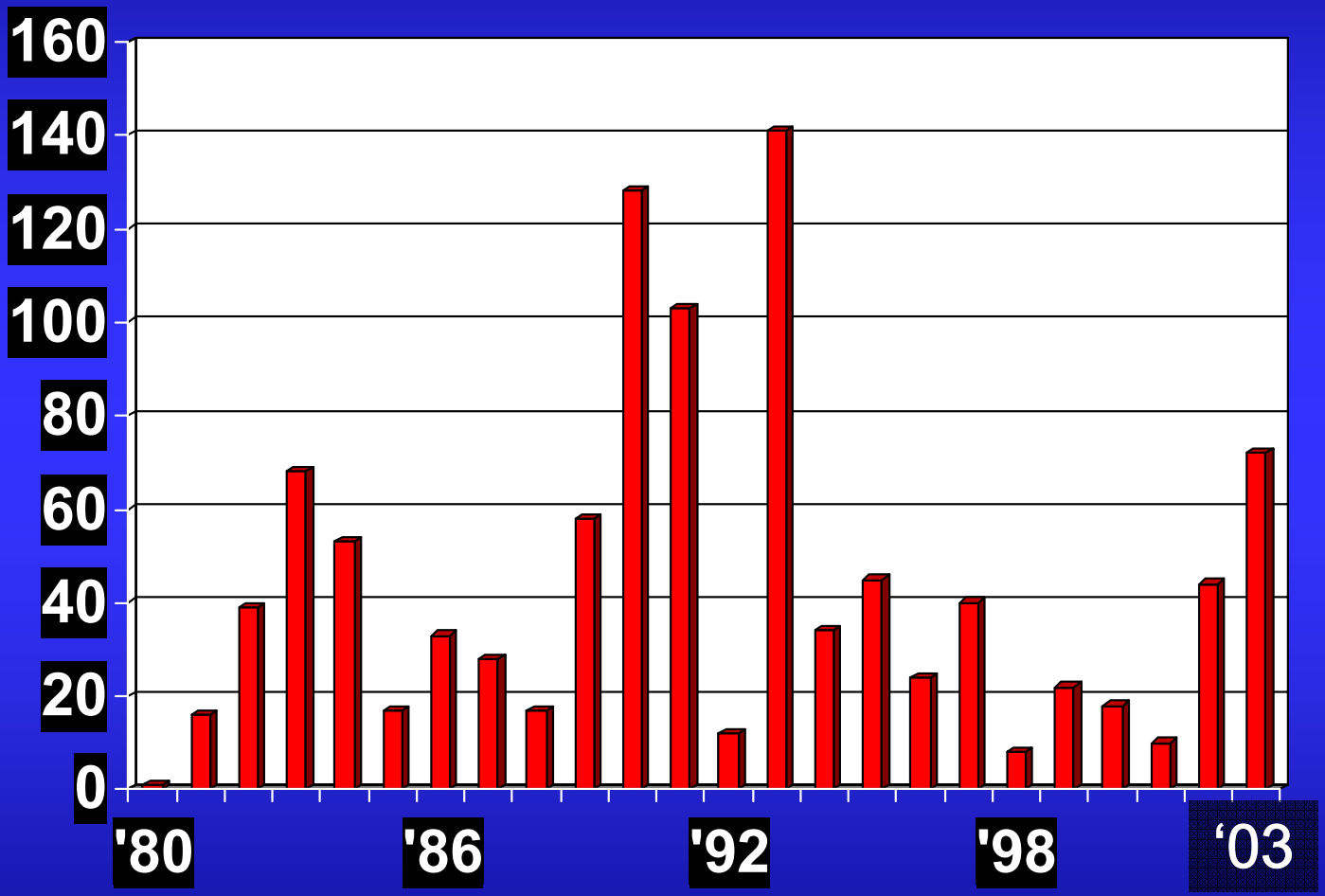
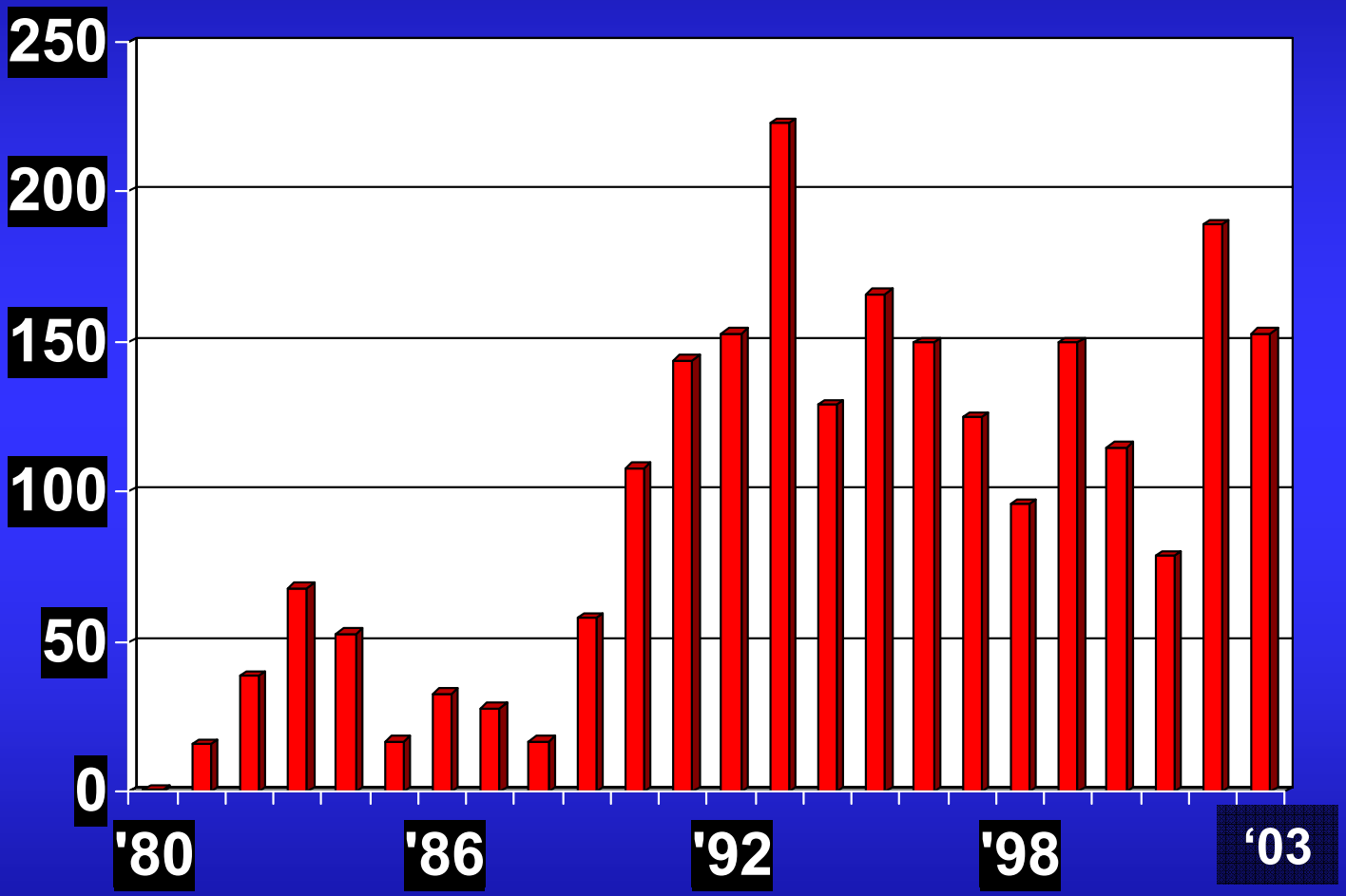
Implants per Year, Worldwide



ISGIID 2000 and Lassman-Vague, ISGIID 2003

Pumps Implanted, by Year, Worldwide



ISGIID 2000 and Lassman-Vague, ISGIID 2003, updated by Kolopp, 2004

Number of active centers and patients (2000-2003)

	2000	2004
Active Patients	340	424#
Active Centers	31*	28*

365 patients in France, 59 in USA

*Most centers are in France > Elsewhere in Europe > USA

Lassman-Vague, ISGIID 2003,

Updated by Kolopp, 2004

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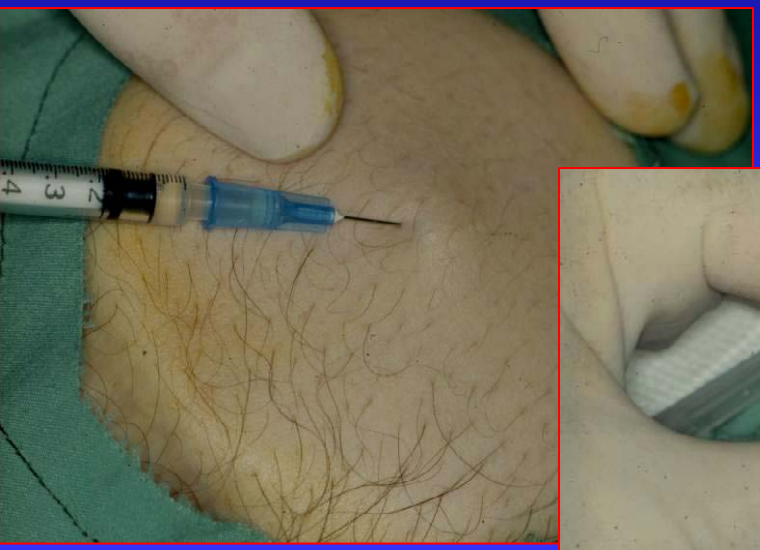
Pump Refill Procedure



Every 3 months, 6,000 units of insulin, in office, 10-15 min.

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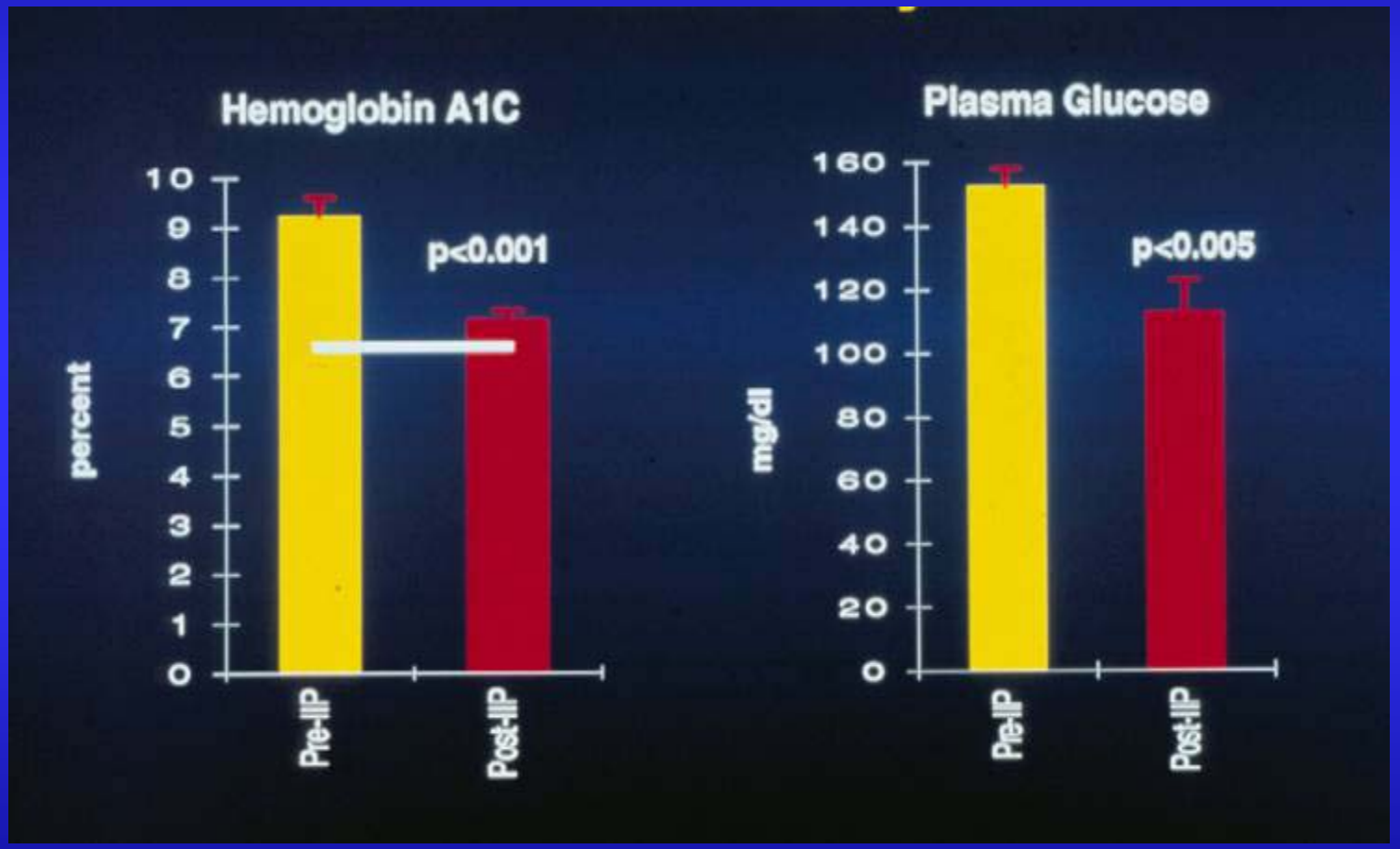
JHU IIP Glycemic Results



Strassbourg IIP Glycemic Results

	CSII with LP	IP	*p*
BG (mg/ml)			
– Mean BG	153.3 ± 17.3	145.4 ± 18.3	< 0.01
– Preprandial BG	147.5 ± 21.8	139.9 ± 20.0	< 0.05
– Postprandial BG	157.5 ± 15.7	148.8 ± 20.3	0.07
– SD of BG values	78.8 ± 17.3	69.2 ± 2.4	< 0.01
HbA_{1c} (%)	7.8 ± 0.9	7.3 ± 0.8	< 0.05

Catargi,Diabetes Metab 28:133-7, 2002

EVADIAC: French Consortium

Treatment	Cum F/U, pt.yrs	HbA1c ± SEM	Severe Hypo % per pt yr
Subcutaneous	51	8.1 ± 0.1	69
MDI	20	8.2 ± 0.1	69
CSII	28	7.9 ± 0.1	99
Implantable Pump	214	7.7 ± 0.1	11

Jeandidier et al. Diab Care 19:780,1996

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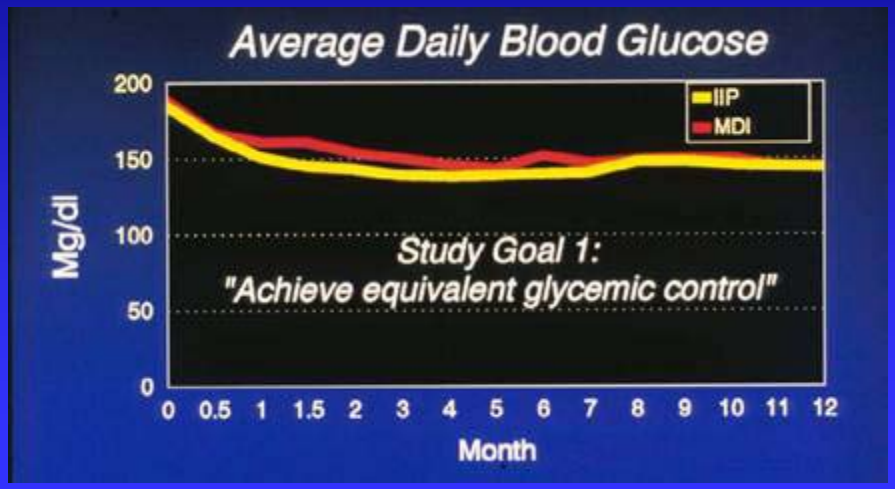
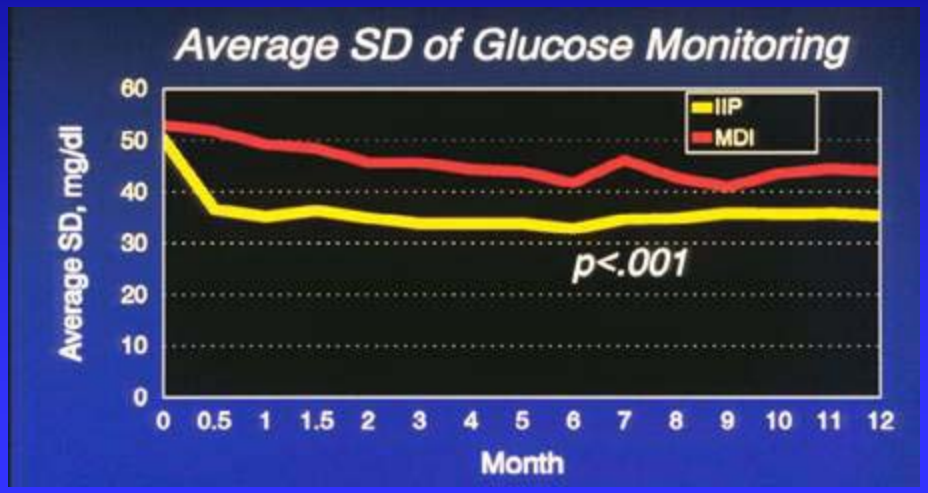
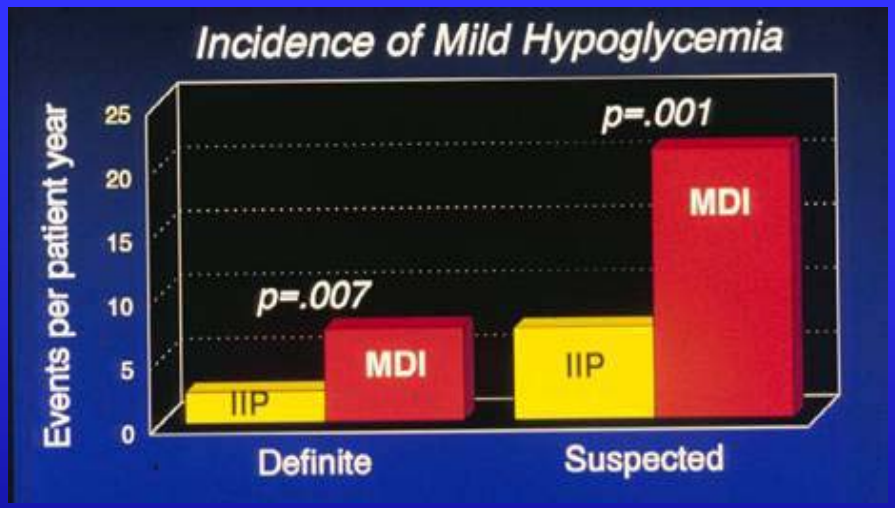
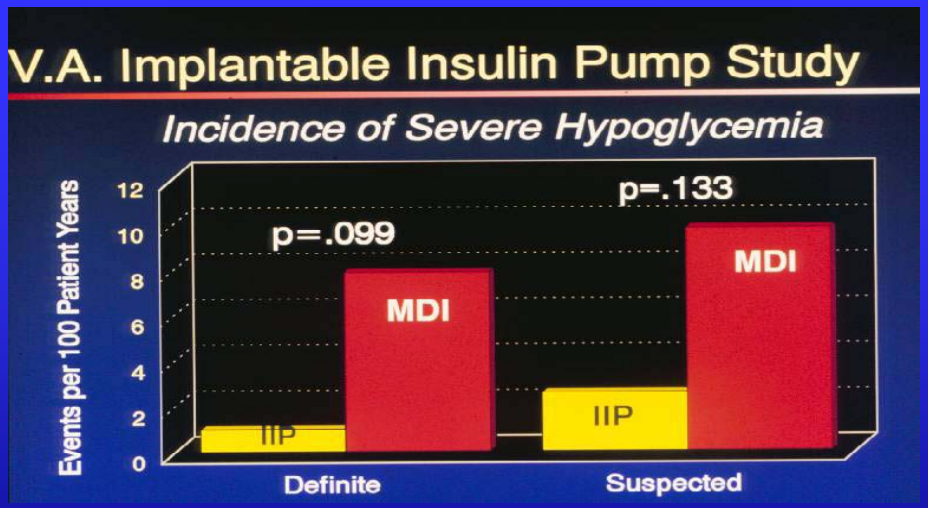
- Hypoglycemia can be lessened

Evidence of Benefit of IIP: The V.A. Trial



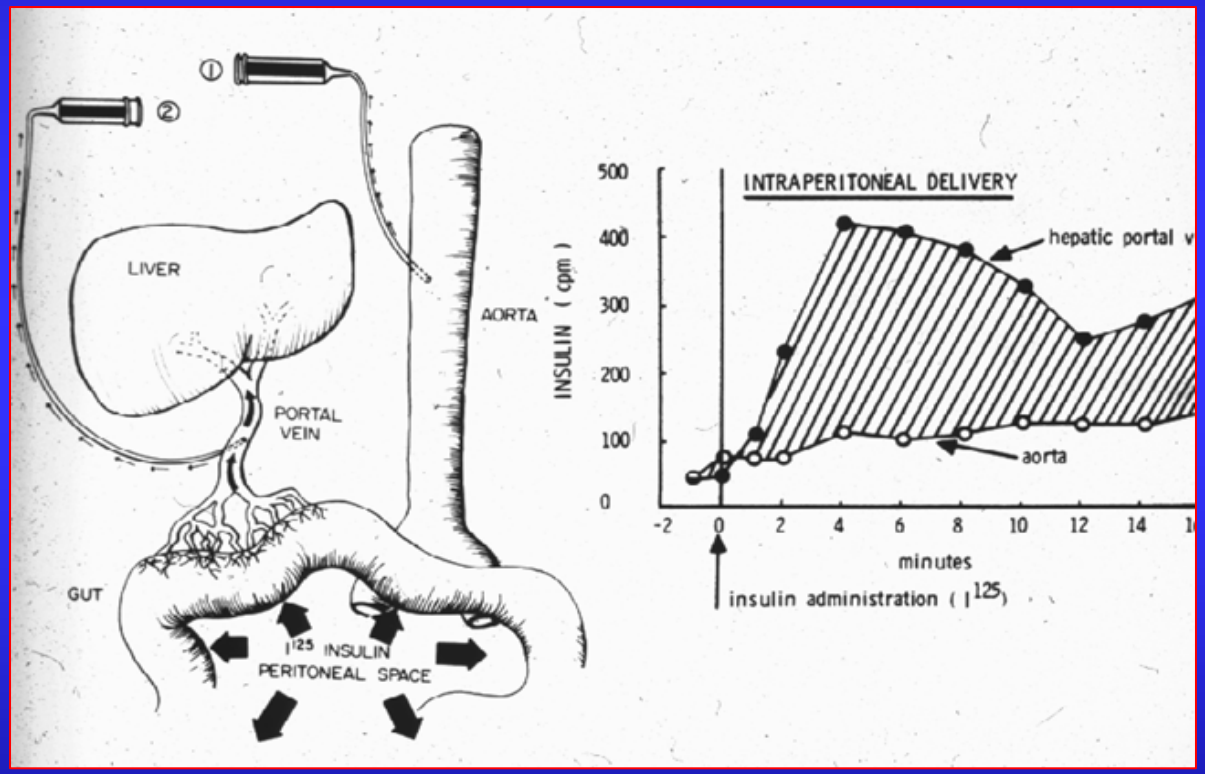






J Amer Med Assoc, 276:1322-1327, 1996.

Potential Effects of Peritoneal Delivery



Peripheral vs. Portal Insulin with

Plasma Insulin after insulin delivery at various sites

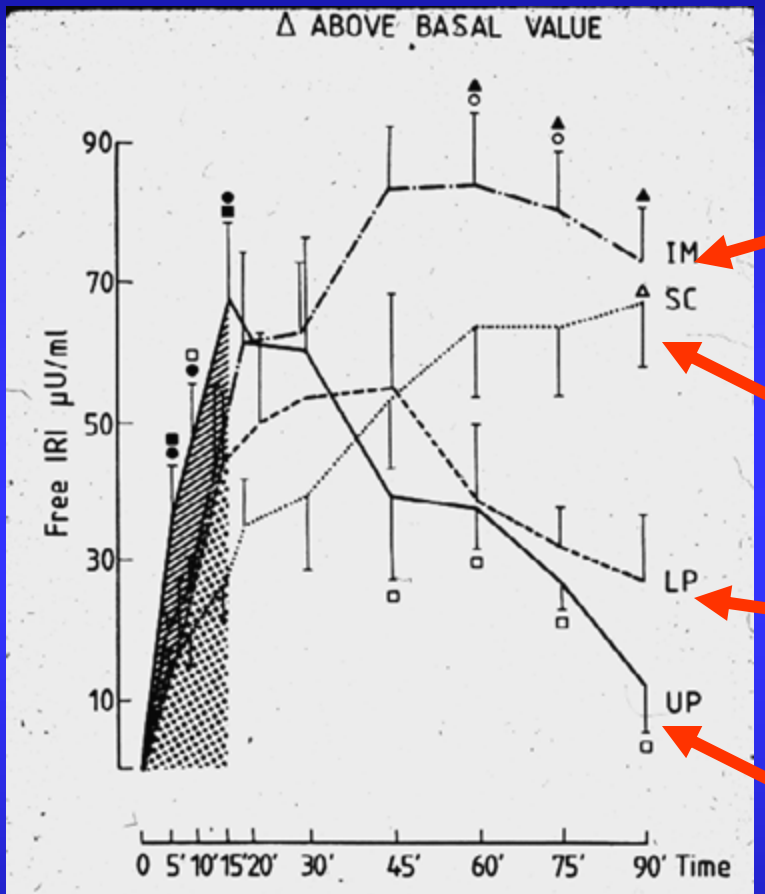


FIG. 2. Plasma free insulin after subcutaneous (SC), intramuscular (IM), and intraperitoneal insulin administration above (UP) and below (LP) transverse mesocolon. $P < .05$: ●, SC vs. UP; ■, UP vs. LP; □, UP vs. IM; ○, SC vs. IM; ▲, IM vs. LP; △, SC vs. LP. *Shaded area* represents first 15 min after intraperitoneal injection (area UP > area LP; $P < .05$).

Micossi et al., Diab Care 1986

Intramuscular

Subcutaneous

Lower Peritoneu

Upper Peritoneu

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- Refills are practical
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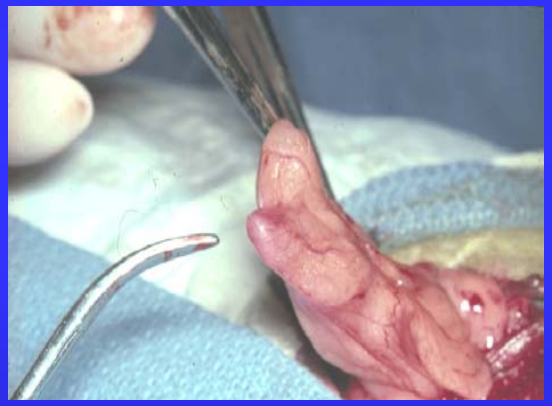
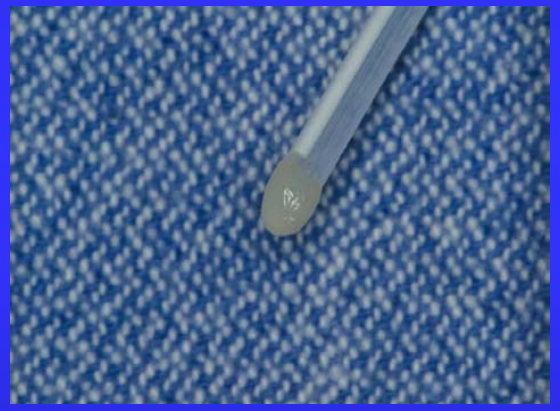
BUT…

Catheter Tip Obstruction

1st Dog Implantation



In Humans



~ 10 – 15% per pt year

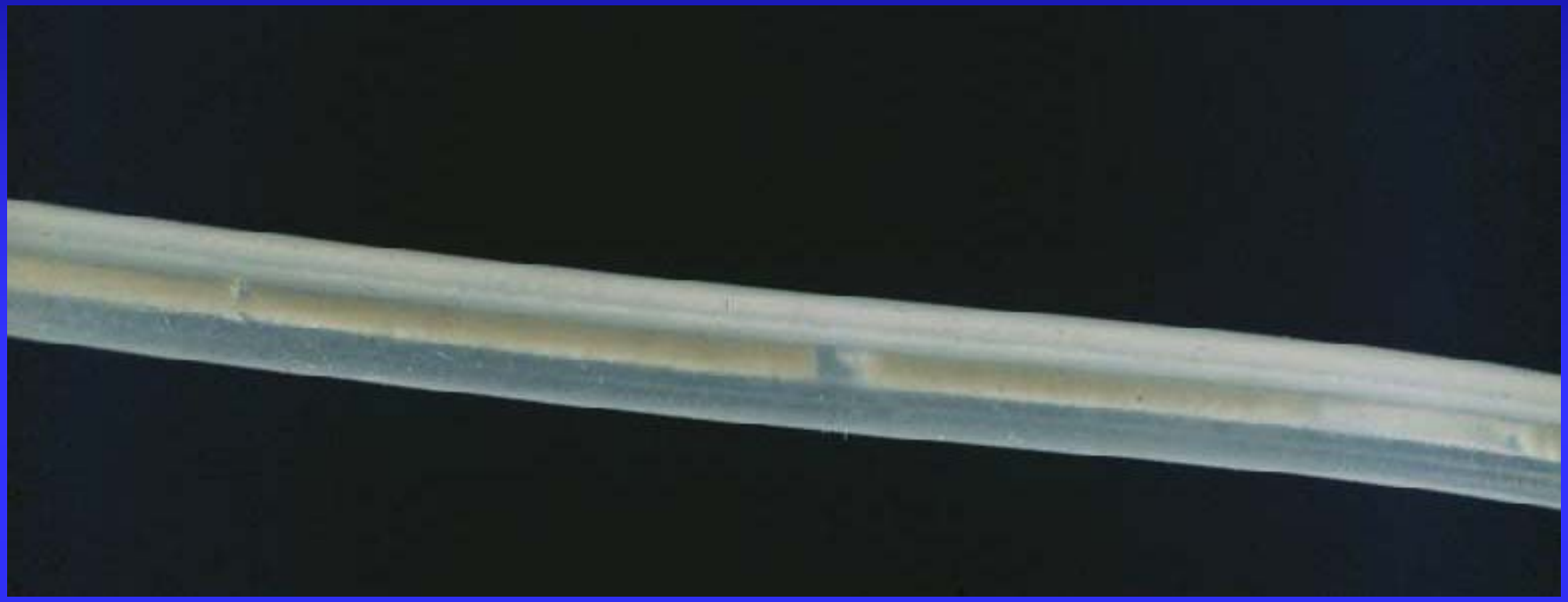
Can be corrected with Side Port Flush

Pump Pocket Infections, Pain

- Incidence varies by center
- 0 – 28% per patient-year
- Mean 7.1% per patient-year

Belicar, Lassmann-Vague.
Diabetes Care 1998; 21:325-6

Insulin Precipitation in Catheter

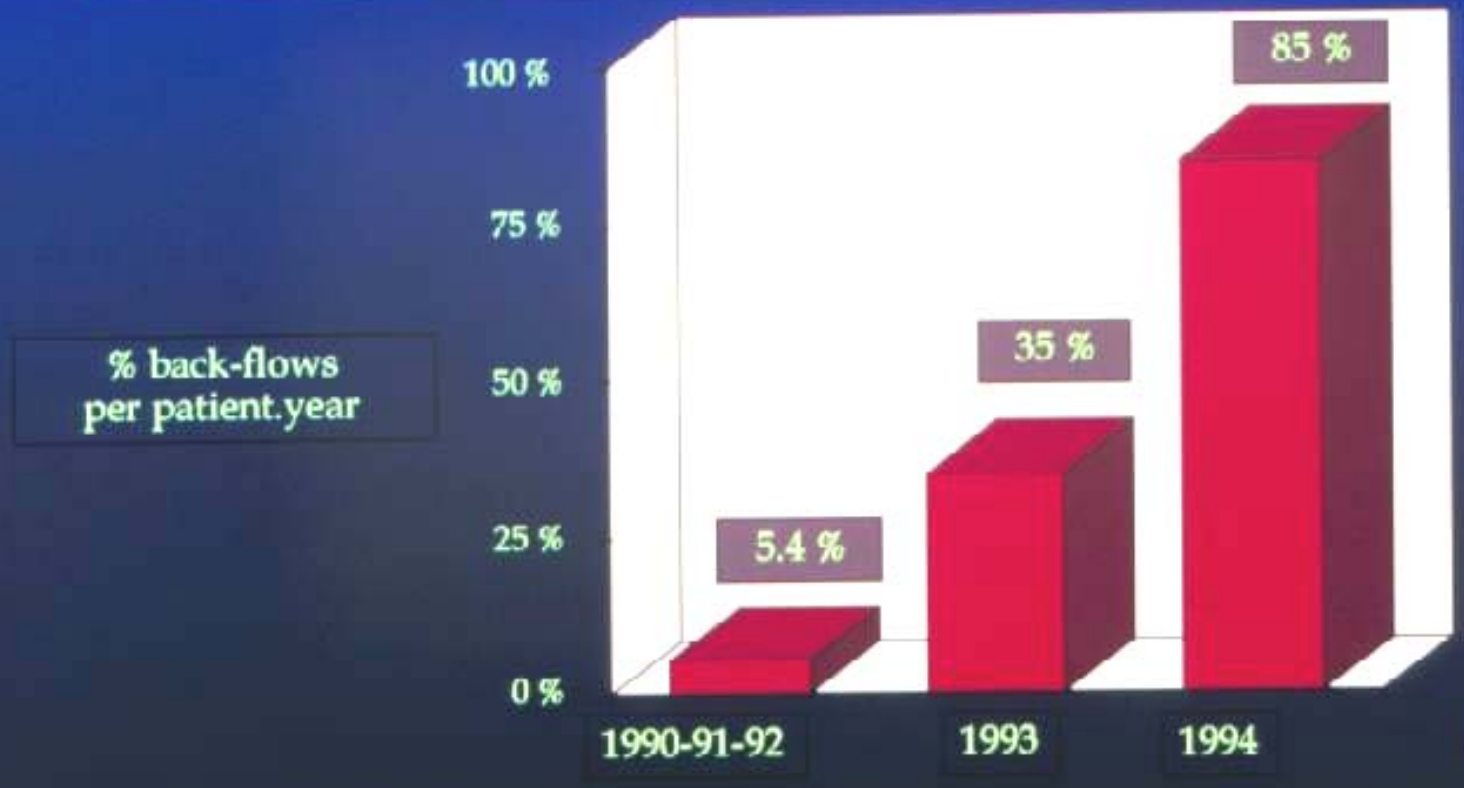


Insulin with Polyethylene Polyproylene Glycol ("Genapol", HOE 21 PH)

- Insulin stabilized with additive*
- Demonstrated in vitro insulin stabilization
- No evidence of insulin aggregation for about 8 years of PIMS and MIP trials (1986 – 1994)

*Grau, Saudek. Stable insulin preparation for implanted insulin pump: laboratory and animal trials. Diabetes 36:1453-59, 1987.

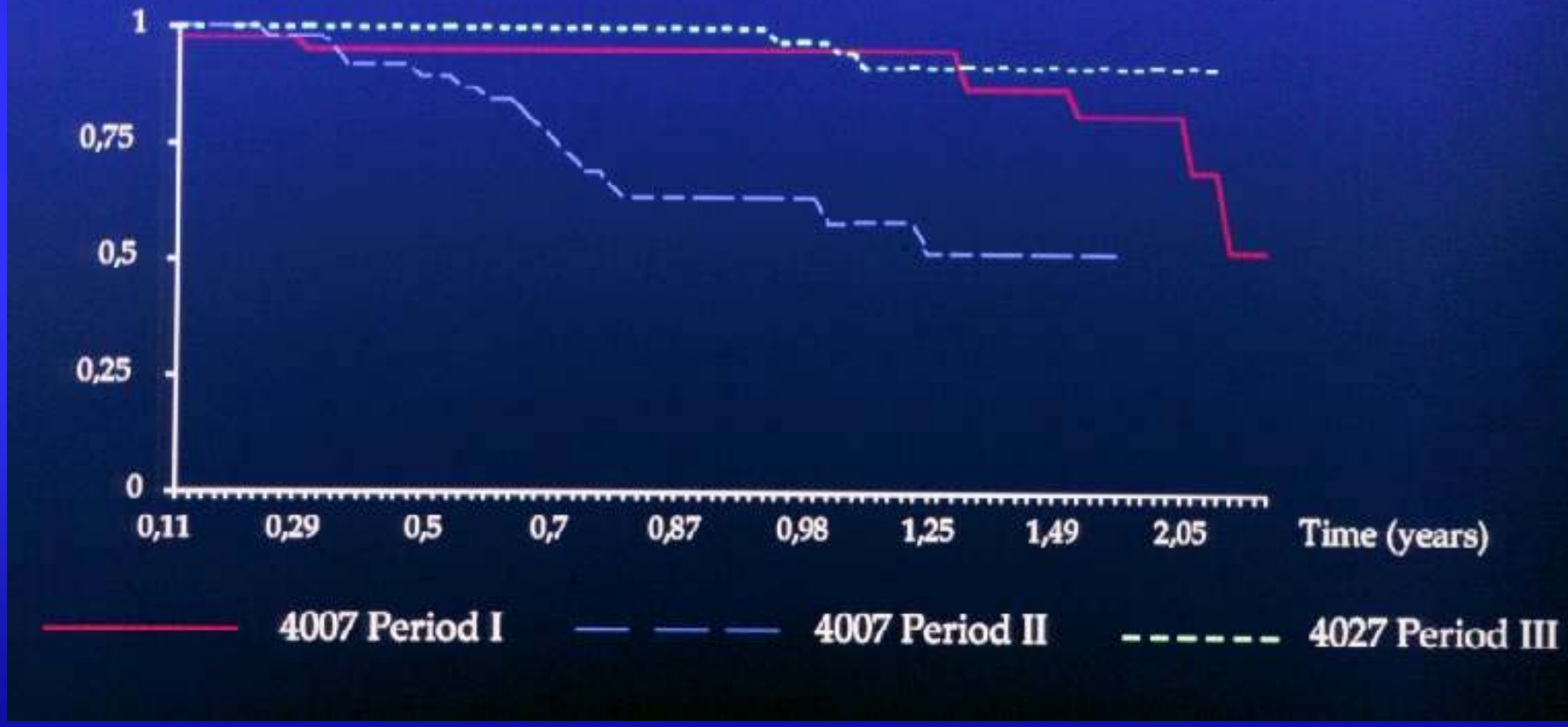
Underdelivery phenomenons



EVADIAC 96

Number of pumps	284	340	459
Mean follow-up (months)	7.4	10.1	11.3

Catheter survival rate



Insulin Problems in IIP: 1994 - 98

- In mid-1990's, Hoechst changed the manufacturing technique of insulin in minor respects.
- Caused serious problem:
  - Insulin aggregating and precipitating in the catheter causing under-delivery
  - Insulin on the valves causing backflow, under-delivery
- Catheter flush and pump rinse approaches were developed to tide us through

Insulin Aggregation

- Method developed for rapid assessment of insulin stability, Van Entwerp et al*
- Insulin preparation improved and methods to evaluate insulin batches established
- Aventis HOE 21 PH now appears to be stable

*Horm Metab Res 1997; 29: Abstr P2

1990 – 2000: What was Learned?

BUT…

- Catheters and Insulin are the vulnerable points
- Autoimmunity, pocket complications and refills/flushes are manageable
- Batteries, programming can be improved

Anti-Insulin Antibodies in IIP

- Concern about whether a new insulin formulation would be antigenic.
- Some subjects were developing “fasting lows”, despite little-to-no insulin given after supper.

Insulin Antibody Responses After Long-Term Intraperitoneal Insulin Administration via Implantable Programmable Insulin Delivery Systems

Craig L. Olsen, MD
Eve Chan, MS
Dee S. Turner, MSN
Mohamed Iravani, BS
Maria Nagy, PHD
Jean-Louis Selam, MD
Nathan D. Wong, PHD
Ken Waxman, MD
M. Arthur Charles, MD, PHD

Mean Antibody Response over Time Post-Implant, Split into "Responders" and "Non-responders"

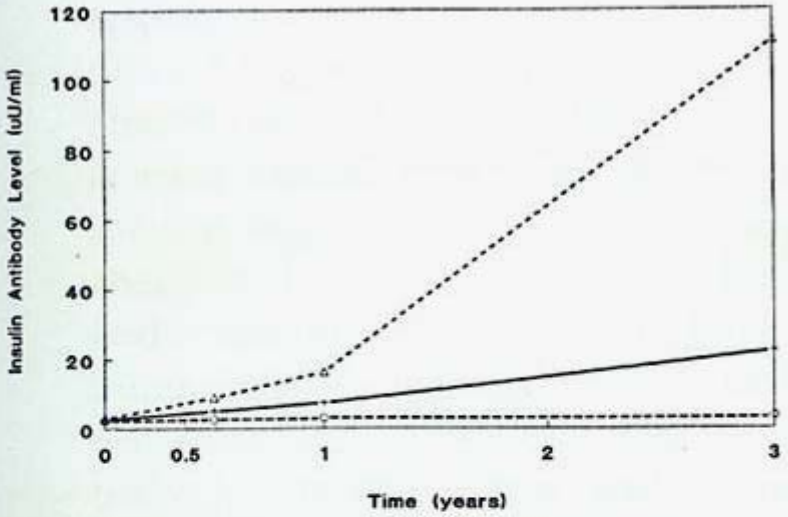


Figure 1—*Mean insulin antibody levels in all 15 patients (+), nonresponder patients (○), and responder patients (△) before and during 3 years of follow-up. Repeated-measures ANOVA showed highly significant within-group antibody elevations in the total group and responder group compared with preimplantation ($P < 0.0001$), whereas the nonresponder group showed no changes ($P = 0.8$). Repeated-measures ANOVA also showed between group differences in the responder and nonresponder groups ($P < 0.001$).*

Olsen t al, DCare

Mean Antibody Response over Time Post-Implant, Indicating those with Fasting Low Syndrome

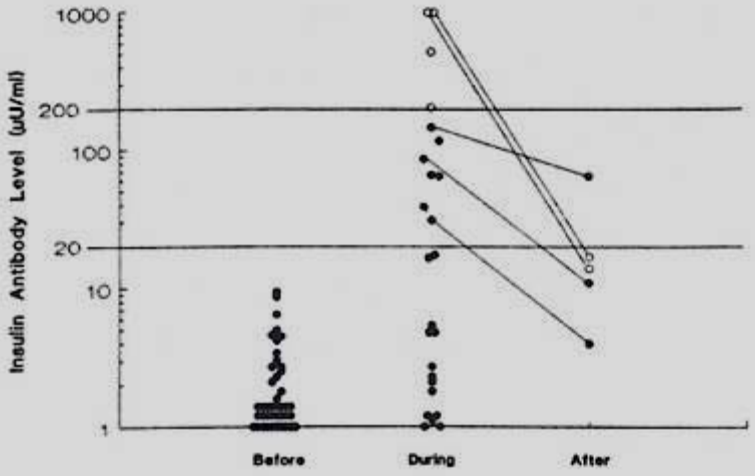
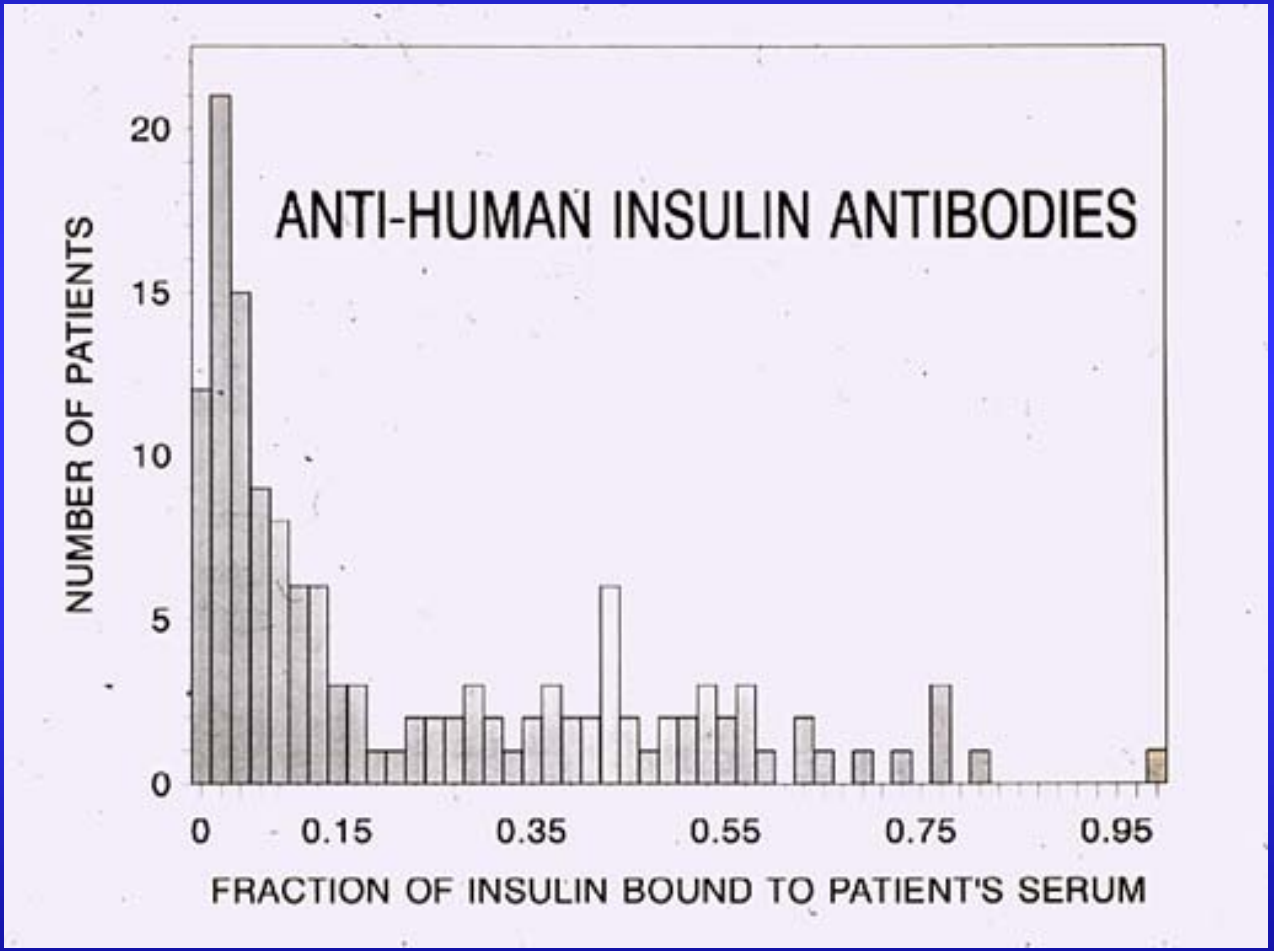
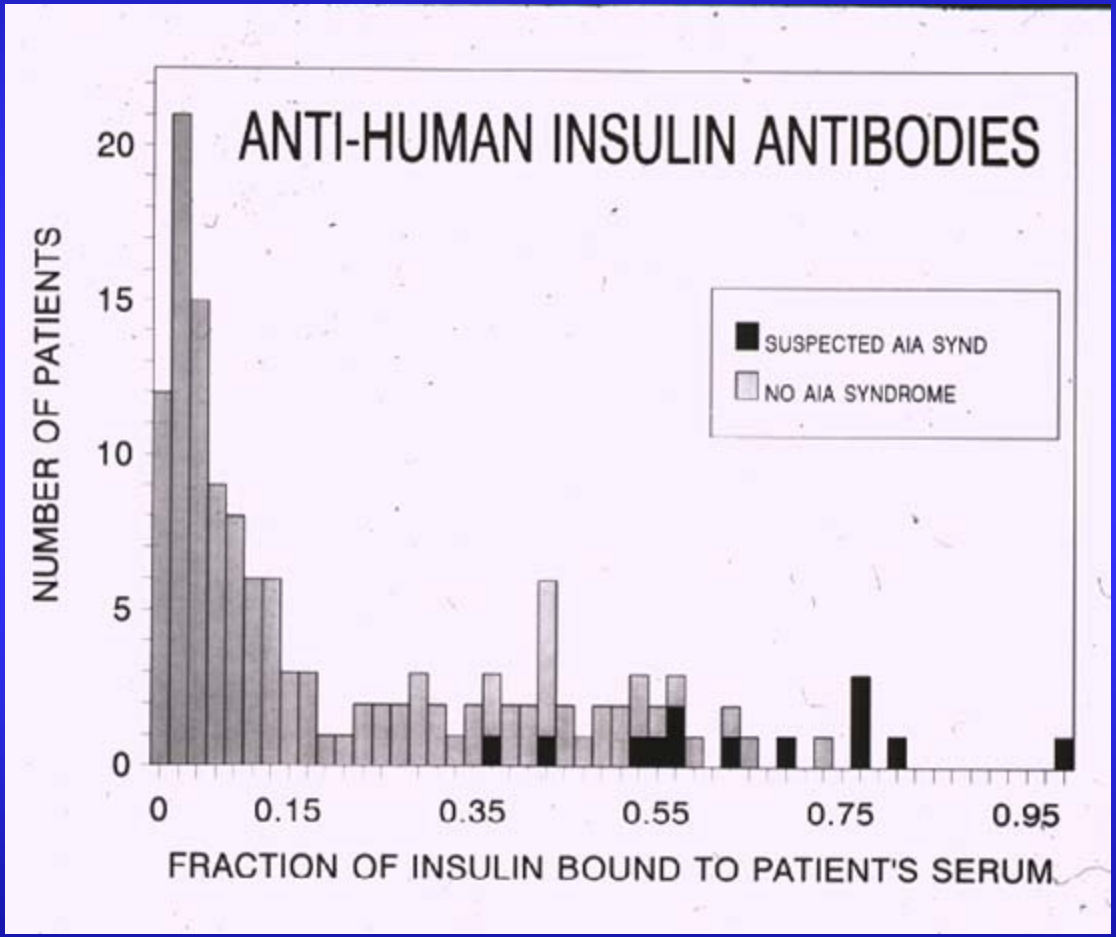


Figure 2—*Individual insulin antibody levels before, peak values during, and levels after discontinuing implantable pump use. (○), Patients experiencing the clinical syndrome of nocturnal hypoglycemia despite decreased nighttime basal rates and/or increased total daily insulin needs. (●), Patients not experiencing such symptoms. The logarithmic scale is to the base 10; however, 20 and 200 are used to illustrate the normal and critically high levels for the associated clinical syndrome.*

Distribution of Anti-Insulin Antibody Titres, JHH Subjects



Distribution of Anti-Insulin Antibody Titres and Those with Clinically Prolonged Insulin Action



Anti Insulin Antibodies

- AIA induced by IIP are high affinity antibodies
- No metabolic consequences were noted

Lassmann-Vague, et al.
Immunogenicity of long-term intraperitoneal insulin administration with implantable insulin pumps.
DCare 1995;18:498.

Anti-InsuliIn Antibodies on IIP

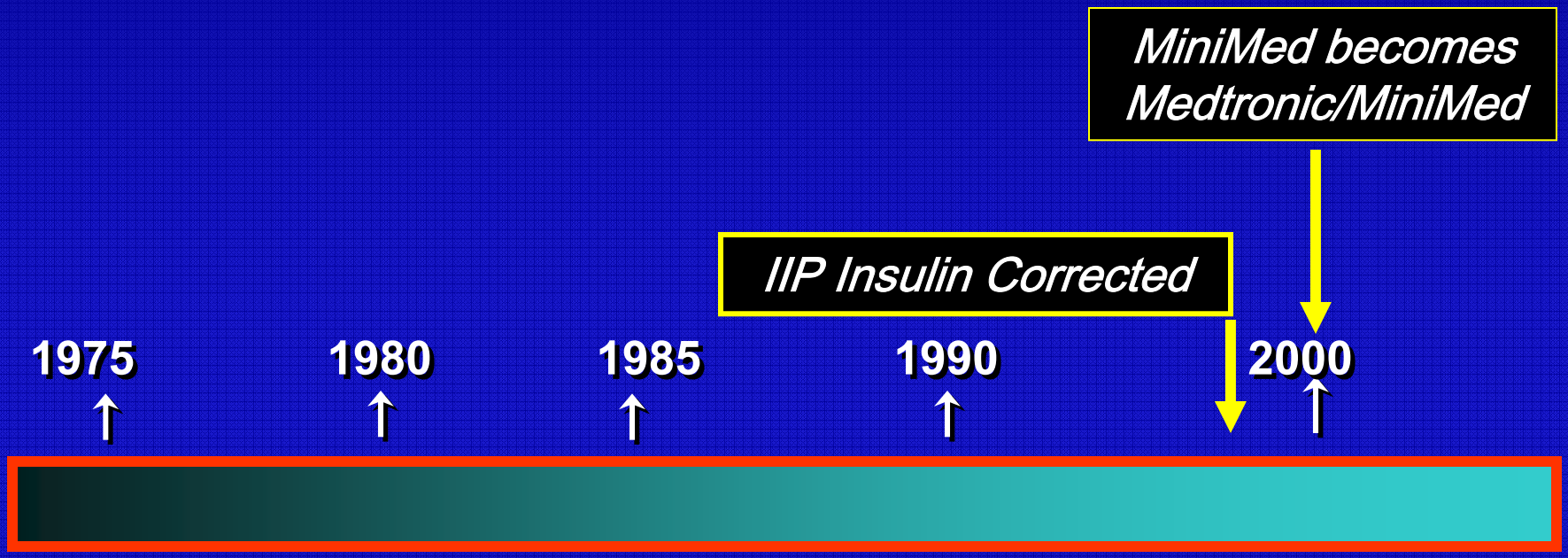
- HOE 21 PH did not induce consistent antibody response when delivered SQ
- Intraperitoneal insulin did induce antibody, but this was not specific to HOE 21 PH

Conclude:

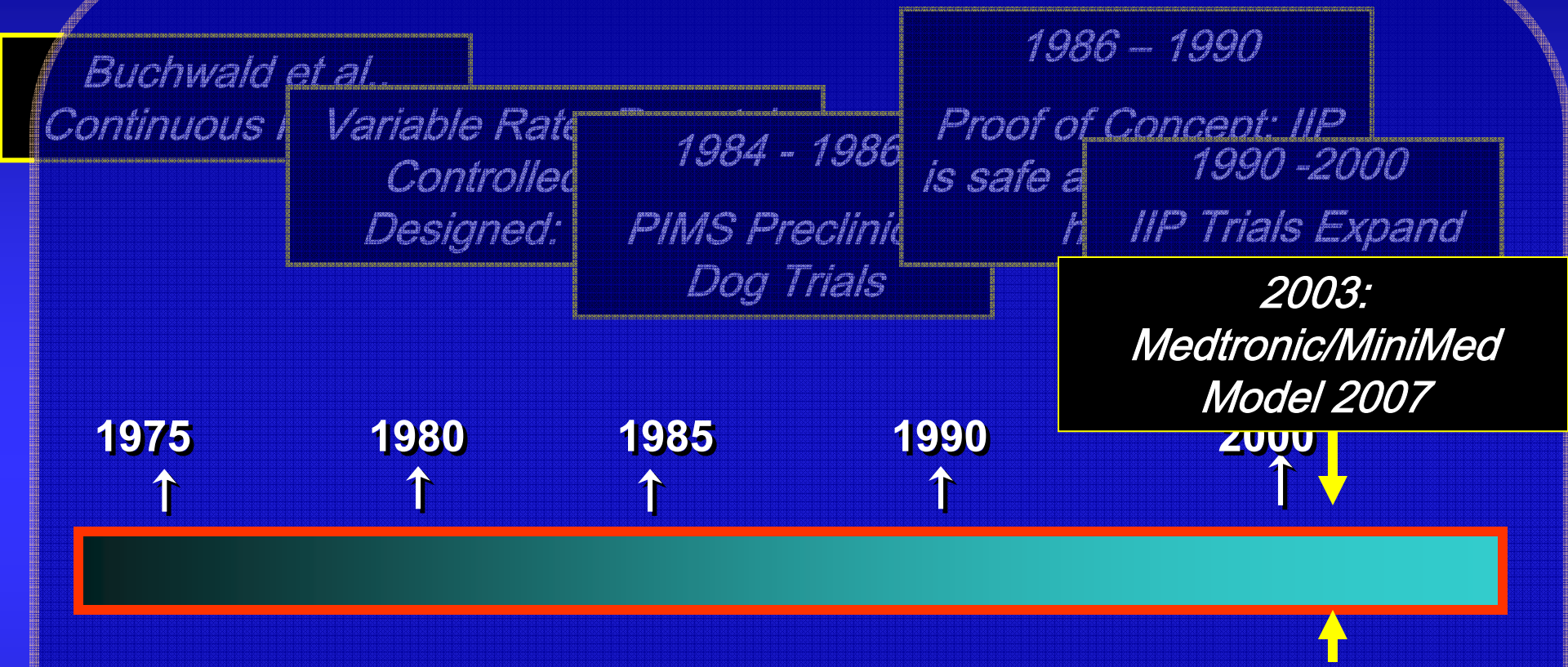
New routes of insulin delivery do occasionally induce anti-insulin antibody, which is rarely clinically significant

Jeandidier, et al.
Comparison of antigenicity of Hoechst 21 PH insulin using either implantable intraperitoneal pump or subcutaneous enxternal pump infusion in type 1 diabetic patients.
Diabetes Care 2002; 25:84-88.

Implanted Insulin Pump Therapy



Implanted Insulin Pump Therapy



Medtronic Implantable Insulin Pump Model 2007

External pump communicator

Titanium disk:
diameter – 8.1 cm
thickness – 2.0 cm
weight – 131 gm (empty reservoir)

Refill port

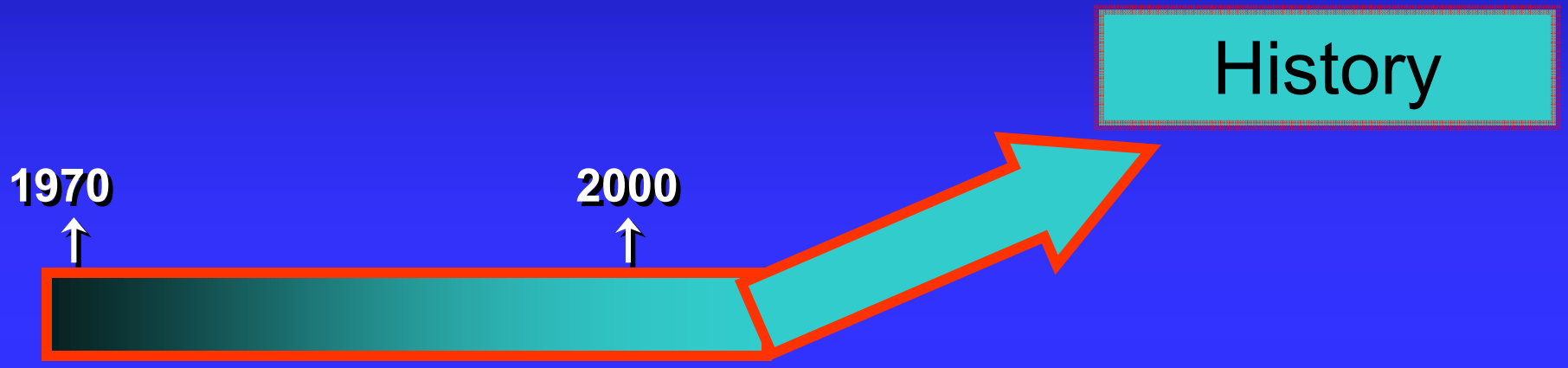
Intraperitoneal catheter

Implantable Insulin Pumps
Medtronic MiniMed 2007

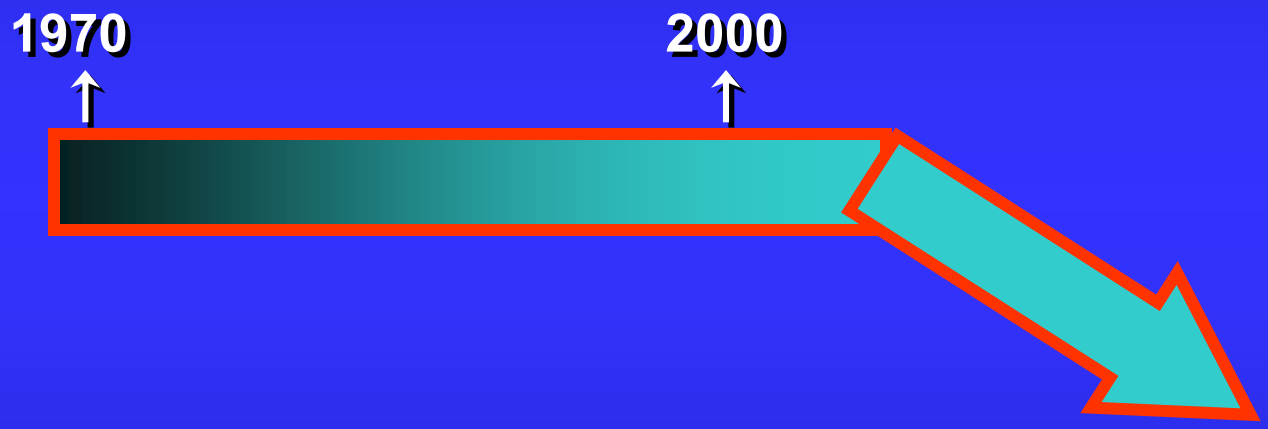
- 8 year battery life,
  up from 3 years
- Faster, better communicator
- Surgery improved

Implantations started at JHH February 3, 2004

Implanted Insulin Pump Therapy: Where to?



Implanted Insulin Pump Therapy: Where to?



Someday, hopfully, part of closed loop system

Implanted Insulin Pump Therapy: Where to?

A product, an option for regular diabetes care

Implanted Insulin Pump Therapy: Where to?

A product, an option for regular diabetes care

The world needs better diabetes care– easier, safer, more successful.

Because <u>the cost of diabetes is in the complications</u>

"Closing the Loop"

Could be accomplished in a number of ways:

External Sensor to External Pump

External Sensor to Implanted Pump

Implanted Sensor to External Pump

Implanted Sensor to Implanted Pump

The Long Range Plan: Fully Implanted, Closed Loop Insulin Delivery

- Mate the Implanted Pump,
- With an intravenous Glucose Sensor
- Develop the Linking Software

Easy!

Collaborators at Johns Hopkins:

Michael Boyne, M.D.

Chee Chia, M.D.

Kim Loman, R.N., CDE

Alicia Greene

Surgeons: Anthony Imbembo, Henry Pitt, Robert Udelsman Mark Talamini

The Founding Fathers:

Pr. E. Pfeiffer

Pr. J. Mirouze

Pr. G. Pozza

Pr. G. Slama

Karl Irsigler

Ulrich Grau

and others

Contemporaries (more or less):

Jean-Louis Selam

Philipe Vague

Michel Pinget

Ian Campbell

Gerard Reach

Piero Micossi

Uwe Fischer

Fred Dunn

David Nathan

Perry Blackshear

Michael Albisser

Harold Kritz

Jean Pierre Taubert

and others

Younger Generation: The Children

Nathalie Jeandidier

Veronique Lasman-Vague

Sophie Boivin

Kristin Rebrin

Maria Librenti

Denis Raccah

Michael Boyne

Eric Renard

Pauline Belicar

Maryanne Kolopp

Marina Scavini

Christiane Brousolle

V. Kessler

Chee Chia

and others