

# Past, Present and Future of Diabetes

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Norfolk and Norwich University Hospital NHS Trust

# To Begin With, Some History

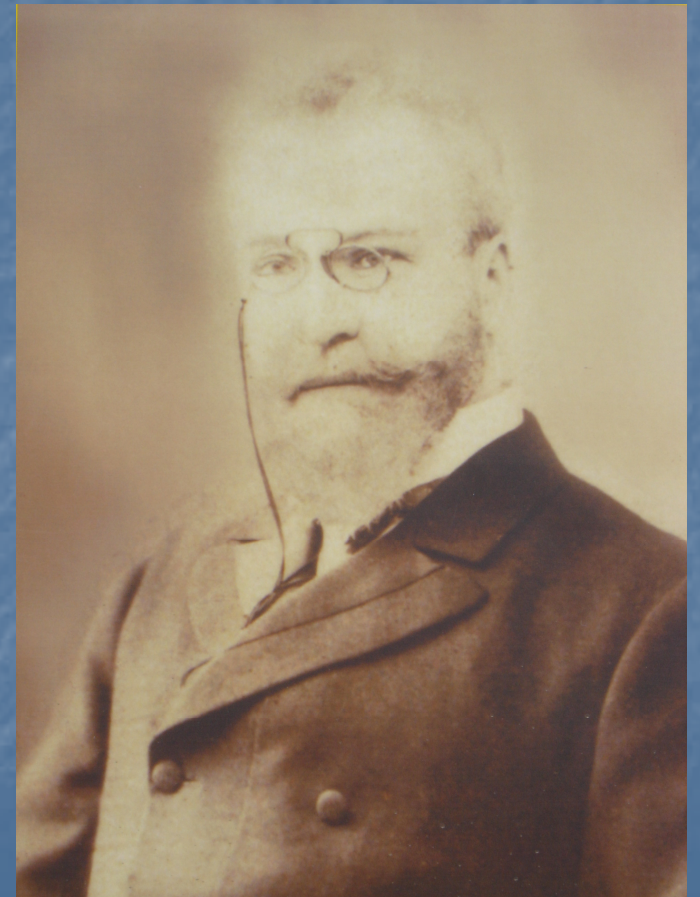
- διαβήτης – ‘to stand apart’ or ‘a siphon’ first described by Aretaeus of Cappadocia commenting on the passing of lots of urine
- First recorded in English in about 1425 as ‘diabete’

# Some History

- The sweet taste had been noticed in urine by the ancient Greeks, Chinese, Egyptians, and Indians but it was only in 1675 that Thomas Willis added the word 'mellitus'
- It was in 1776 that Matthew Dobson confirmed that the sweet taste was because of an excess of sugar in the urine and blood of people with diabetes

# Some History

- Nothing much happened for the next few centuries...
- In the late 19<sup>th</sup> Century, Oskar Minkowski and others discovered the role of the pancreas in diabetes by taking them out of dogs and realising that they died of the condition

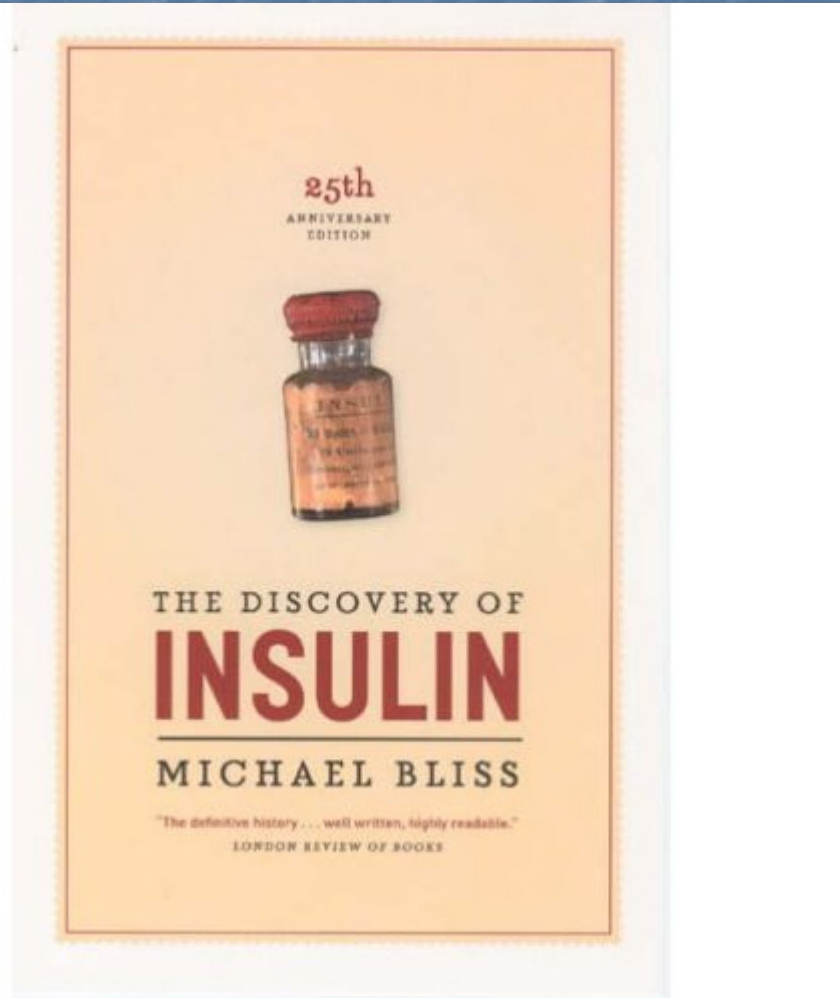
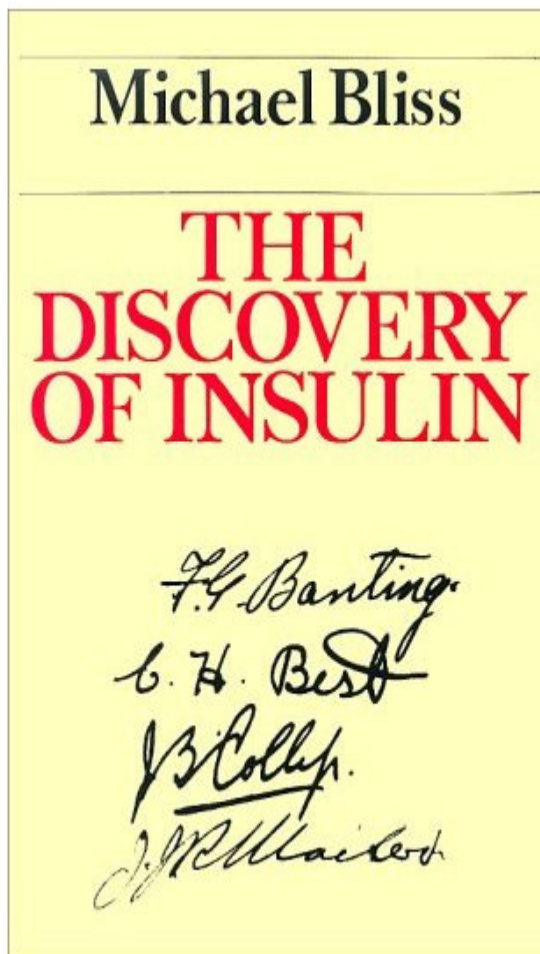


# 1921 and All That.....

- Banting, Best, Collip, and McLeod at the University of Toronto



# Credit Where it is Due





**MICHAEL BLISS**

**THE  
DISCOVERY  
OF INSULIN**

"A gripping piece of historical detection." – *Canadian Historical Review*

**Michael Bliss**

**THE  
DISCOVERY  
OF INSULIN**



# Some History

- It was 'ignorant' junior surgeon Fred Banting who took the germ of an idea to JRR McLeod – the renowned physiologist
- McLeod – who knew of the unsuccessful work of others over the preceding 30 years – gave Banting a tiny room, a few dogs, and a medical student – Charles Best



# Toronto

- Banting and Best managed to get through dozens of dogs trying different methods to get the pancreas to fail and then to replace it
- Despite their poor science, and poor records, they eventually 'stumbled' on something promising

# Marjorie?

- They had lots of dogs – often obtained from dubious sources



# The Problems

- Their pancreatic extract was impure and lacked consistency
- Banting felt that McLeod was trying to steal their thunder by taking credit for their work
- Apparent lack of progress

# The Solution

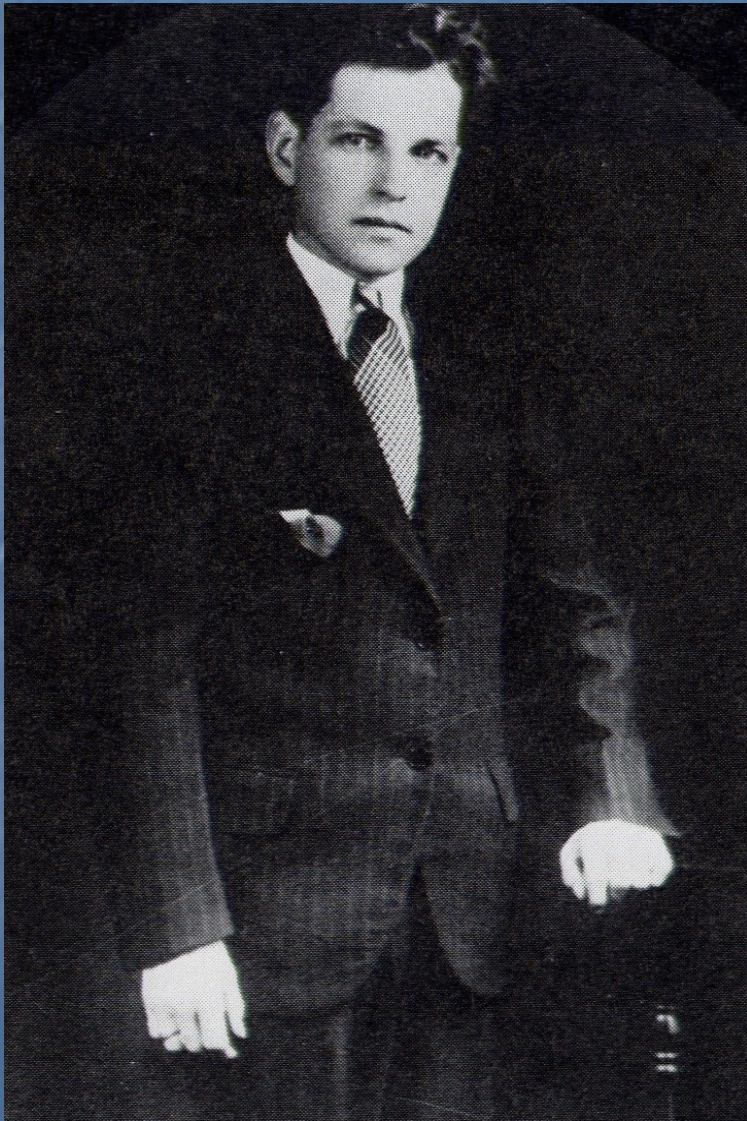
- McLeod brought in a leading biochemist to help with purification – James Bertram Collip
- Collip was working on calcium but agreed to work with McLeod during a 1 year sabbatical



# Success!

- Collip developed an alcohol extraction technique
- This led to better quality, and purer extract
- The results were presented (by McLeod) to the American Physiological Society in late 1922 to great fanfare

# Leonard Thompson



- Regarded as the first person to ever receive insulin on 11<sup>th</sup> January 1922 aged 14
- He lived for 13 years before dying in a car accident

Grams  
of  
sugar

220  
200  
180  
160  
140  
120  
100  
80  
60  
40  
20

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January February

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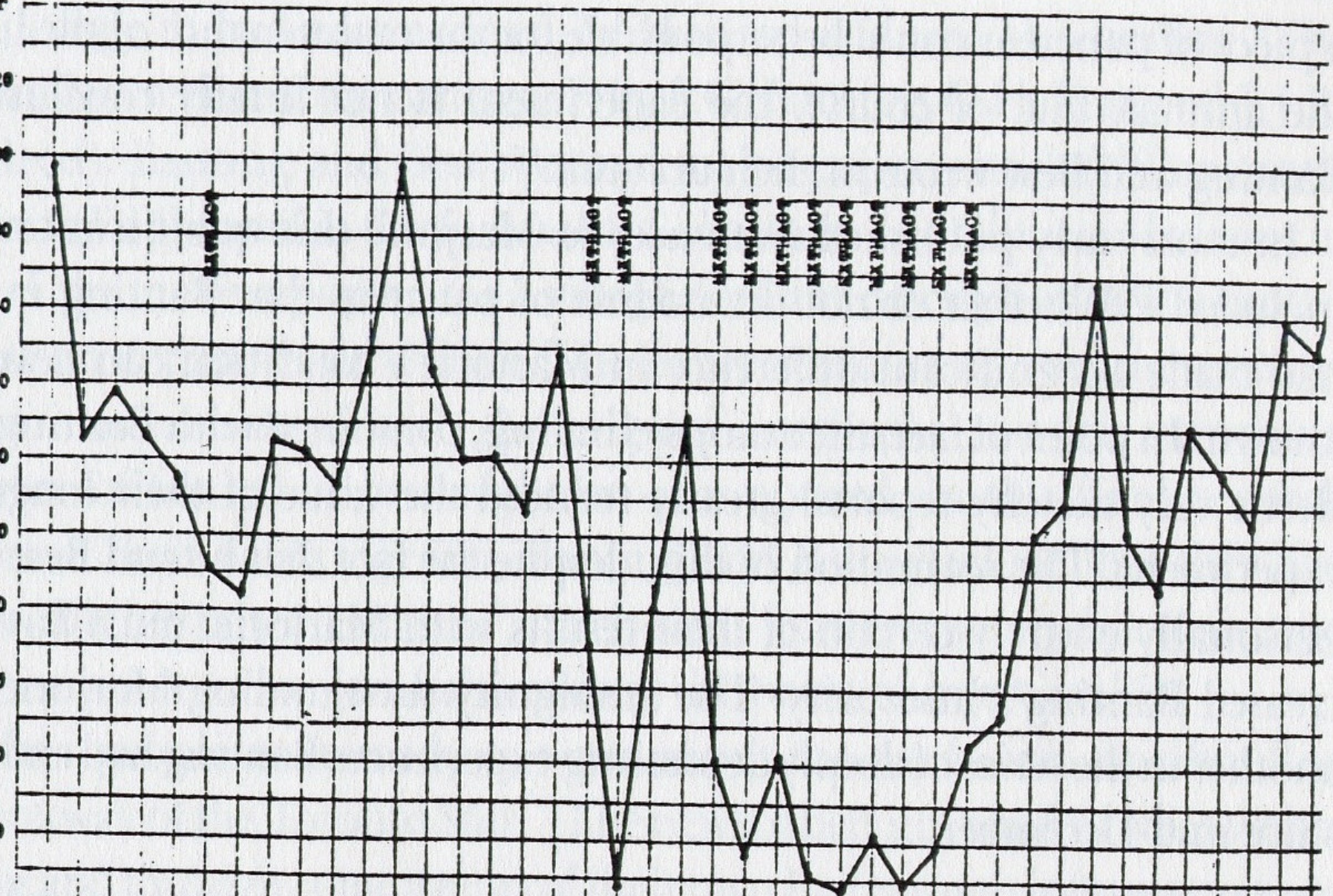
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# Success!

- Insulin was in immediate demand, but production was very limited
- In the APS audience was the man from Eli Lilly – who agreed to develop large scale production



# Recognition

- In 1923, Banting and McLeod were awarded the Nobel Prize for Medicine
- Banting gave half his prize immediately to Best, and McLeod gave half of his to Collip

# What Has Happened Since Then?

- The Diabetic Association, was set up in 1934 by novelist HG Wells and Dr RD Lawrence
- “To promote the study, the diffusion of knowledge, and the proper treatment of diabetes in this country.”



1923 - “I’ve got some insulin. It works. Come back quick.”

# What Has Happened Since Then?

- The first oral agents were launched in 1942 – the sulphonylureas
- The British Diabetic Association was formed in 1954 – the Norwich branch launched in 1958
- Biguanides were launched in the 1950's – with metformin being launched in 1979
- The amino acid sequence of insulin was reported in 1955 by Fred Sanger (another Nobel Prize)

# What Has Happened Since Then?

**The British Diabetic Association**  
NORWICH, NORFOLK BRANCH

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**10th ANNIVERSARY  
MEETING**

FOR ALL DIABETICS, FRIENDS AND RELATIONS  
WILL BE HELD ON

Wednesday, June 19th, 1968  
at 7.30 p.m.

IN THE  
Assembly House, Theatre Street  
NORWICH

---

**THE LORD MAYOR OF NORWICH**  
Councillor E. A. Gambling, J.P. will preside

**GUEST SPEAKERS :**

DR. J. CAMPBELL, F.R.C.P.  
MISS P. COOPER, Matron,  
Norfolk & Norwich Hospital  
M. IRELAND, Esq., Chairman of Branch  
J. G. L. JACKSON, Secretary General, B.D.A.

The Film  
**“DIAGNOSIS DIABETES ”**  
will be shown at 8.30 p.m.

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Local enquiries may be made to Hon. Secretary : A. M. Falconer,  
64, Onley Street, Norwich, NOR 95E

# What Has Happened Since Then?

- In 1988 Gerald Reaven described the constellation of conditions making up the Metabolic Syndrome
- In the mid 1990's acarbose and metaglinides became available
- Troglitazone was launched in the UK in March 1997 and withdrawn in May 1997

# What Has Happened Since Then?

- In 1997 Richard Greenwood and others form ABCD
- BDA becomes Diabetes UK in 2000
- By 2008 there are over 400 local branches across the UK



# A Brief History of Insulin

- 1922 Banting, Best, Collip use bovine insulin extract in human
- 1923 Eli Lilly produces commercial quantities of much purer bovine insulin than Banting et al had used
- 1923 Farbwerke Hoechst, one of the forerunner's of today's Sanofi Aventis, produces commercial quantities of bovine insulin in Germany
- 1923 Hagedorn founds the Nordisk Insulinlaboratorium in Denmark – forerunner of today's Novo Nordisk
- 1926 Nordisk receives a Danish charter to produce insulin as a non-profit
- 1936 Canadians D.M. Scott, A.M. Fisher formulate a zinc insulin mixture and license it to Novo
- 1936 Hagedorn discovers that adding protamine to insulin prolongs the duration of action of insulin
- 1946 Nordisk formulates Isophane porcine insulin aka Neutral Protamine Hagedorn or NPH insulin
- 1946 Nordisk crystallizes a protamine and insulin mixture
- 1950 Nordisk markets NPH insulin
- 1953 Novo formulates Lente porcine and bovine insulins by adding zinc for longer lasting insulin
- 1955 Frederick Sanger determines the amino acid sequence of insulin
- 1965 Synthesized by total synthesis by and coworkers
- 1969 Dorothy Crowfoot Hodgkin solves the crystal structure of insulin by x-ray crystallography
- 1973 Purified monocomponent (MC) insulin is introduced
- 1978 Genentech produces synthetic 'human' insulin in *Escheria coli* bacteria using recombinant DNA techniques, licenses to Eli Lilly
- 1981 Novo Nordisk chemically and enzymatically converts porcine to human insulin
- 1982 Genentech synthetic 'human' insulin (above) approved
- 1983 Eli Lilly and Company produces synthetic 'human' insulin with recombinant DNA technology, Humulin
- 1985 Axel Ullrich sequences a human cell membrane insulin receptor.
- 1988 Novo Nordisk produces recombinant human insulin
- 1996 Lilly Humalog "lispro" insulin analogue approved.
- 2000 Sanofi Aventis Lantus "glargine" insulin analogue approved for clinical use in the US and Europe.
- 2004 Sanofi Aventis insulin glulisine insulin analogue approved for clinical use in the US.
- 2006 Novo Nordisk Levemir "detemir" insulin analogue approved for clinical use in the US.

## 2 BIG Trials

- Type 1 diabetes - Diabetes Control and Complications Study (DCCT)
  - NEJM 1993 329(14):977-86
- Type 2 diabetes - United Kingdom Prospective Diabetes Study (UKPDS)
  - Lancet 1998 352:837-853 & BMJ 1998 317:703-713
- Both asking the same question – does good diabetes control make a difference in diabetes related outcomes?



The Answer

**YES!!**

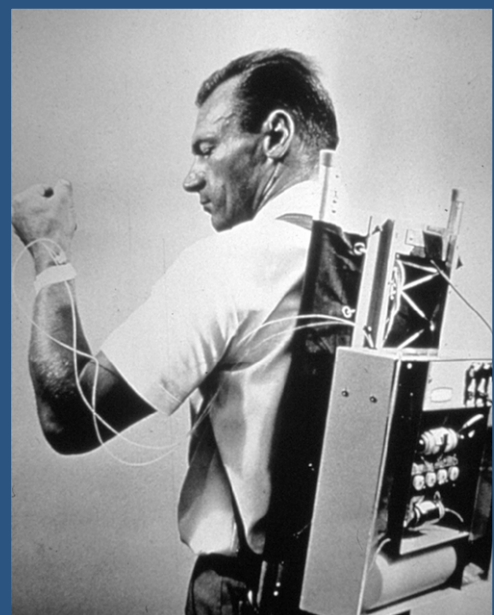
# New Agents

- GLP-1 analogues
- DPP-IV inhibitors
- Amylin
- AGE inhibitors

# Since Then

- Looking more at prevention
  - Diabetes Prevention Program (USA)
  - Da Qing (China)
  - Diabetes Prevention Study (Finland)

# New Technologies



# Where Are We Now?

*The* NEW ENGLAND  
JOURNAL *of* MEDICINE

ESTABLISHED IN 1812

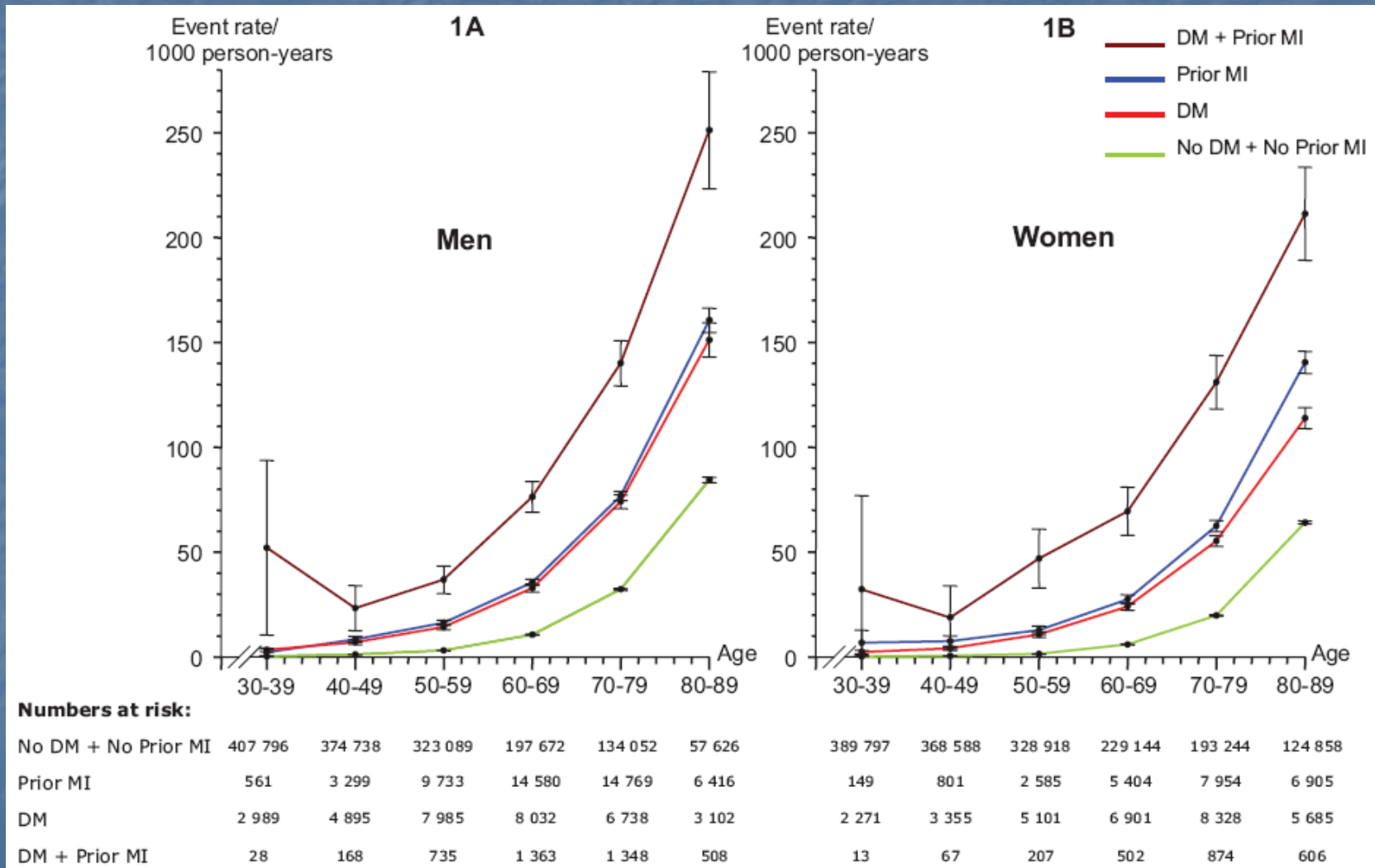
JUNE 14, 2007

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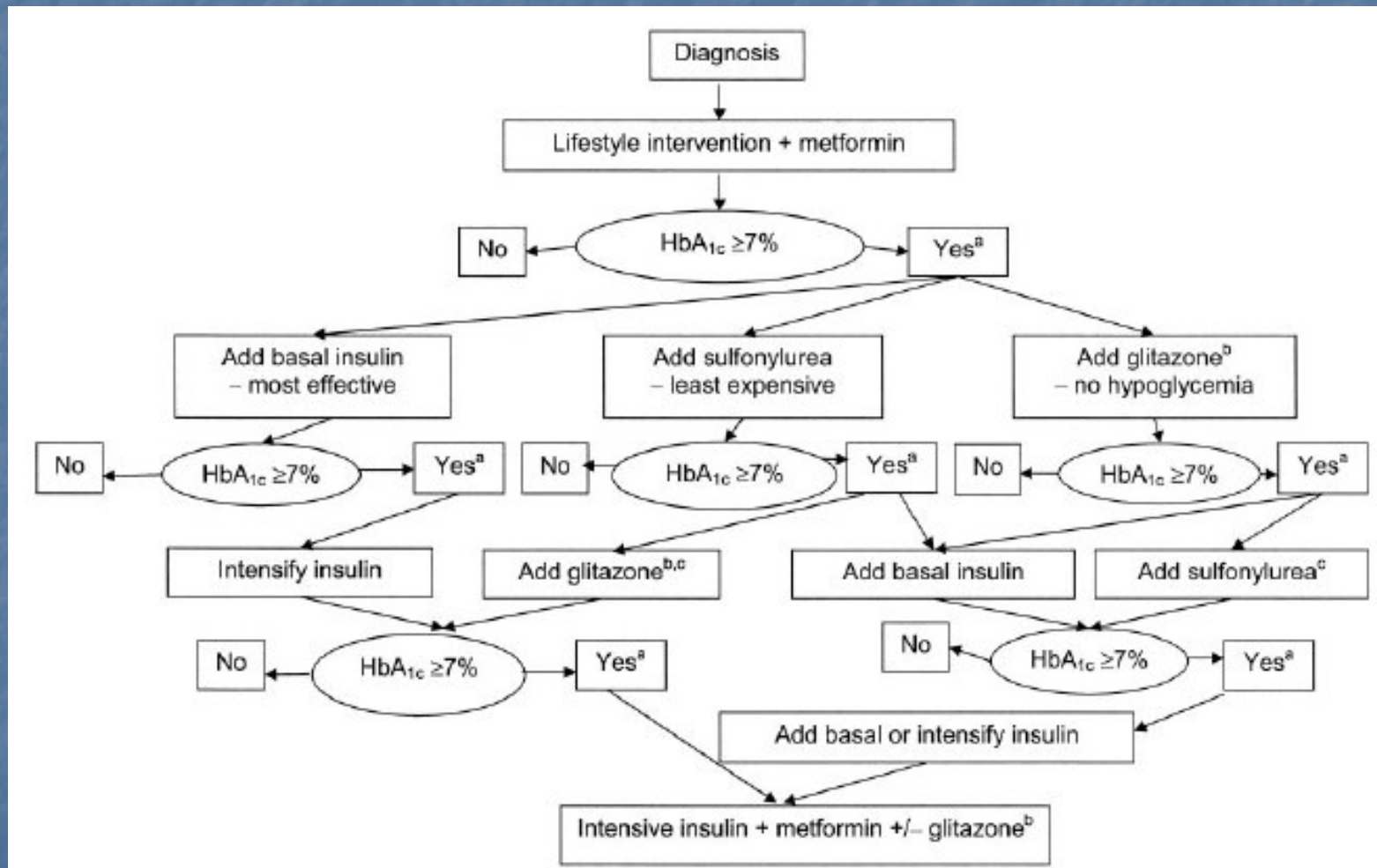
## Effect of Rosiglitazone on the Risk of Myocardial Infarction and Death from Cardiovascular Causes

Steven E. Nissen, M.D., and Kathy Wolski, M.P.H.

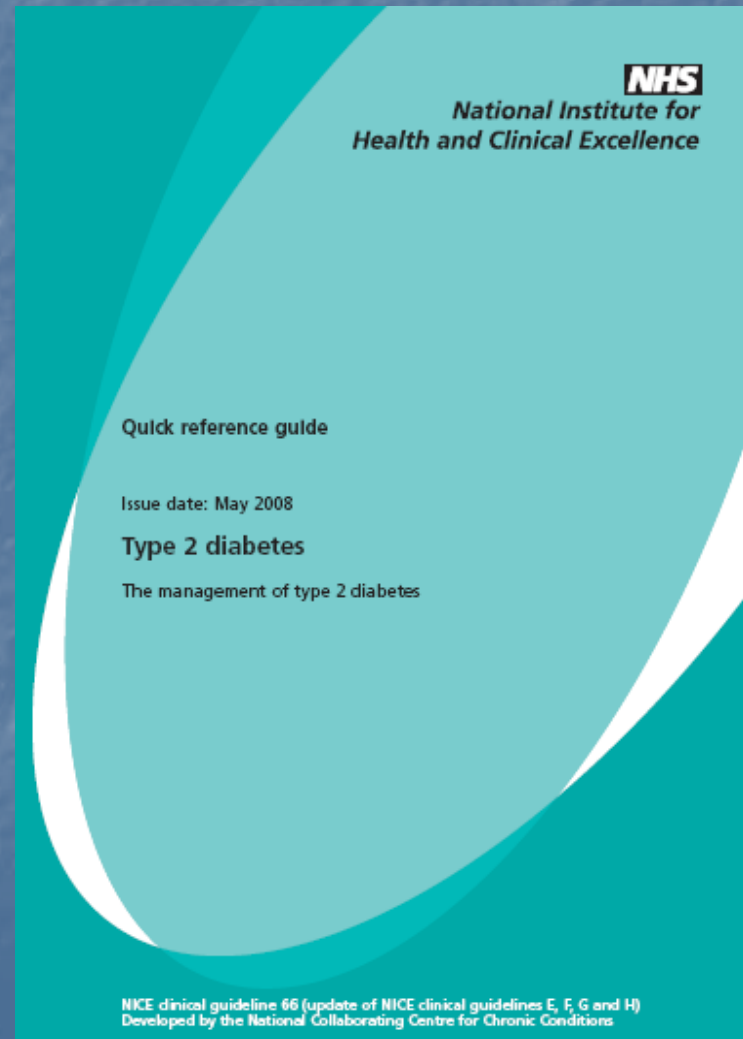
# Data From 3.3M Danes



# EASD / ADA Guidelines



# The Law Unto NICE... May 2008





# The Future?

- Islet cell transplants
- Closed loop systems
- Stem cell therapy
- Gene therapy

## 20 page EDP2 today

We're almost there...

Approaching the 10th anniversary of the EDP We Care Appeal, we're in sight of the £1m goal set at the very start



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# CHOCOLATE WILL SAVE

Women volunteers wanted to help with medical research

22 News

THE TIMES Monday April 28 2008

Norwich Evening News Monday, April 28, 2008

www.eveningnews24.co.uk

pinkun.com

Join the debate on the ultimate fans' website

## Chocolate fans wanted for new study into diabetes

Not many people need an excuse to eat chocolate every day - but now a group of women are being asked to do just that.

Researchers at the University of East Anglia are today launching a unique study of how chocolate can reduce the risk of heart disease in post-menopausal women with type 2 diabetes.

It has been shown that cocoa, the main ingredient of chocolate, is a rich source of compounds called flavonoids, which have been shown to reduce risk factors for heart disease.

And now, with the help of a Belgian chocolatier, a specially-made chocolate bar has been developed for the study, giving a higher dose of these protective compounds and maximising potential benefits.

The UEA is calling out for 150 women who meet the criteria to take part in the study, the first of its kind, where they will be asked to eat this specially formulated chocolate every

give added protection against heart disease on top of that provided by prescription drugs.

This is particularly important for the women who are the focus of this research, as deaths due to heart disease increase rapidly after the menopause and having type 2 diabetes increases this risk by a further three-and-a-half times.

Peter Curtis, clinical trial co-ordinator, said: "We think this study is going to be important for this group of women and will tell us how to design effective intervention in the future."

"They are at such a high risk compared with non-diabetic and pre-menopausal women that any improvement in their risk can only be beneficial."

At just of the study, participants will have their risk of heart disease tested on five occasions during the year to see whether change occurs. These tests will take place at UEA or the Norfolk and Norwich University



Research: A study is being carried out in Norwich into the benefits of eating flavonoids, found in chocolate, on the health of post-menopausal women with type 2 diabetes.

who have type 2 diabetes and have not had a period for at least one year and are not taking HRT. Volunteers also need to have been

### Raise your concern

Families in Hethersett have been invited to attend the next Safer Neighbourhood Action Panel (SNAP) meeting to raise any concerns they have about crime or anti-social behaviour in the area.

The Hethersett and Milbourn Safer Neighbourhood Team will meet on Tuesday, May 20, at Hethersett Junior School. Doors open at 7pm.

All SNAP meetings are open to the public and provide an opportunity for the public to voice their concerns about issues in their neighbourhood before a panel of representatives from local agencies.

→ To speak to a member of the safe neighbourhood team in any area call Norfolk police on 0845 456 4562.

### Ballet school success

A Norfolk schoolboy is celebrating at being accepted to the Royal Ballet School.

John Robinson, of Old Buckenham, has been successful in gaining a place at the prestigious school as a mid-associate. He will be appearing at the Theatre Royal in Norwich in Coppelia on Friday, July 4 and Saturday, July 5.

→ For more details about the show or tickets call 0693 630000.

### Public meeting

Members of the public are invited to Broadland District Council's overview and scrutiny committee meeting.

The meeting will be held on Tuesday, May 6, at 10am at the Old Office, Prebenk, Yarmouth Road.

→ To see the agenda, go to www.broadland.gov.uk

Nigel Hawkes Health Editor

Researchers in Norwich have set themselves an easy challenge: finding 150 women prepared to eat a bar of chocolate a day.

The chocolate is free, and made specially for the trial by a Belgian chocolatier. The intention is to see whether it improves the women's health.

The volunteers must be past the menopause, must suffer from type 2 diabetes, and must already be taking statins to reduce their cholesterol levels. They will also need the approval of their GPs.

Postmenopausal women with type 2 diabetes are usually advised to avoid choc-

olate. Rich in sugar and fat, it is definitely not part of their recommended diet.

Chocolate is also rich in flavonoids, compounds that have been linked with a reduced risk of heart disease. Chocolate companies have seized on the research - some of which they have funded themselves - to encourage the belief that chocolate can be good for you.

Until now, few of the trials have met the highest standards of scientific rigour. A team from the University of East Anglia plans to put that right.

The volunteers, all postmenopausal women who are not taking HRT, will be divided into two groups. Half will eat the special chocolate, the other half a normal

bar as a placebo. The women will be checked at the start of the one-year trial, and five times during it.

Ultrasound scans will measure the thickness of the wall of the carotid artery, and the total volume of plaque, the material that blocks the arteries in heart disease. Peter Curtis, who is co-ordinating the study, said:

"The chocolate has three times the amounts of flavonoids you would find in a normal high cocoa chocolate. This has been achieved by a special extraction process that retains the chemicals we think are the important ones."

It tastes, he says, "quite nice" with a flavour of caramel. Soy has been added to provide an even greater dose of flavonoids.

Aedin Cassidy, Professor of Diet and Health at the university, who is heading the project, said: "We hope to show that adding flavonoids to their diets will provide additional protection from heart disease and give women the opportunity to take more control over reducing their risk of heart disease in the future."

Ketan Dhataraya, consultant in diabetes at the Norfolk and Norwich University Hospital, added: "If the trial confirms that flavonoids improve the level of protection against heart disease, it could have a far-reaching impact on the advice we give."

Iain Frame, director of research at Diabetes UK, which is funding the trial, said:

"We certainly don't advise people to start eating a lot of chocolate as it's very high in sugar and fat. We would always recommend that people with diabetes eat a diet low in fat, salt and sugar with plenty of fruit and vegetables."

He said that older women with diabetes were five times more likely to develop heart disease.

→ To find out more or to volunteer, please telephone 01693 285710 and ask for Andrea Brown (study nurse) or Dr Peter Curtis (study co-ordinator) or e-mail FLAVO@uea.ac.uk



The special chocolate bar created by a Belgian chocolatier for the clinical diabetes trial

## Wanted: women to eat chocolate

Researchers in Norwich have set themselves an easy challenge: finding 150 women prepared to eat a bar of chocolate a day. The chocolate is free, and made specially for the trial by a Belgian chocolatier. The intention is to see whether it improves the women's health. The volunteers must be past the menopause, must suffer from type 2 diabetes, and must already be taking statins to reduce their cholesterol levels. They will also need the approval of their GPs. Postmenopausal women with type 2 diabetes are usually advised to avoid chocolate. Rich in sugar and fat, it is definitely not part of their recommended diet. Chocolate is also rich in flavonoids, compounds that have been linked with a reduced risk of heart disease. Chocolate companies have seized on the research - some of which they have funded themselves - to encourage the belief that chocolate can be good for you. Until now, few of the trials have met the highest standards of scientific rigour. A team from the University of East Anglia plans to put that right. The volunteers, all postmenopausal women who are not taking HRT, will be divided into two groups. Half will eat the special chocolate, the other half a normal bar as a placebo. The women will be checked at the start of the one-year trial, and five times during it. Ultrasound scans will measure the thickness of the wall of the carotid artery, and the total volume of plaque, the material that blocks the arteries in heart disease. Peter Curtis, who is co-ordinating the study, said: "The chocolate has three times the amounts of flavonoids you would find in a normal high cocoa chocolate. This has been achieved by a special extraction process that retains the chemicals we think are the important ones." It tastes, he says, "quite nice" with a flavour of caramel. Soy has been added to provide an even greater dose of flavonoids. Aedin Cassidy, Professor of Diet and Health at the university, who is heading the project, said: "We hope to show that adding flavonoids to their diets will provide additional protection from heart disease and give women the opportunity to take more control over reducing their risk of heart disease in the future." Ketan Dhataraya, consultant in diabetes at the Norfolk and Norwich University Hospital, added: "If the trial confirms that flavonoids improve the level of protection against heart disease, it could have a far-reaching impact on the advice we give." Iain Frame, director of research at Diabetes UK, which is funding the trial, said:

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### Nurses are engulfed by tide of paperwork

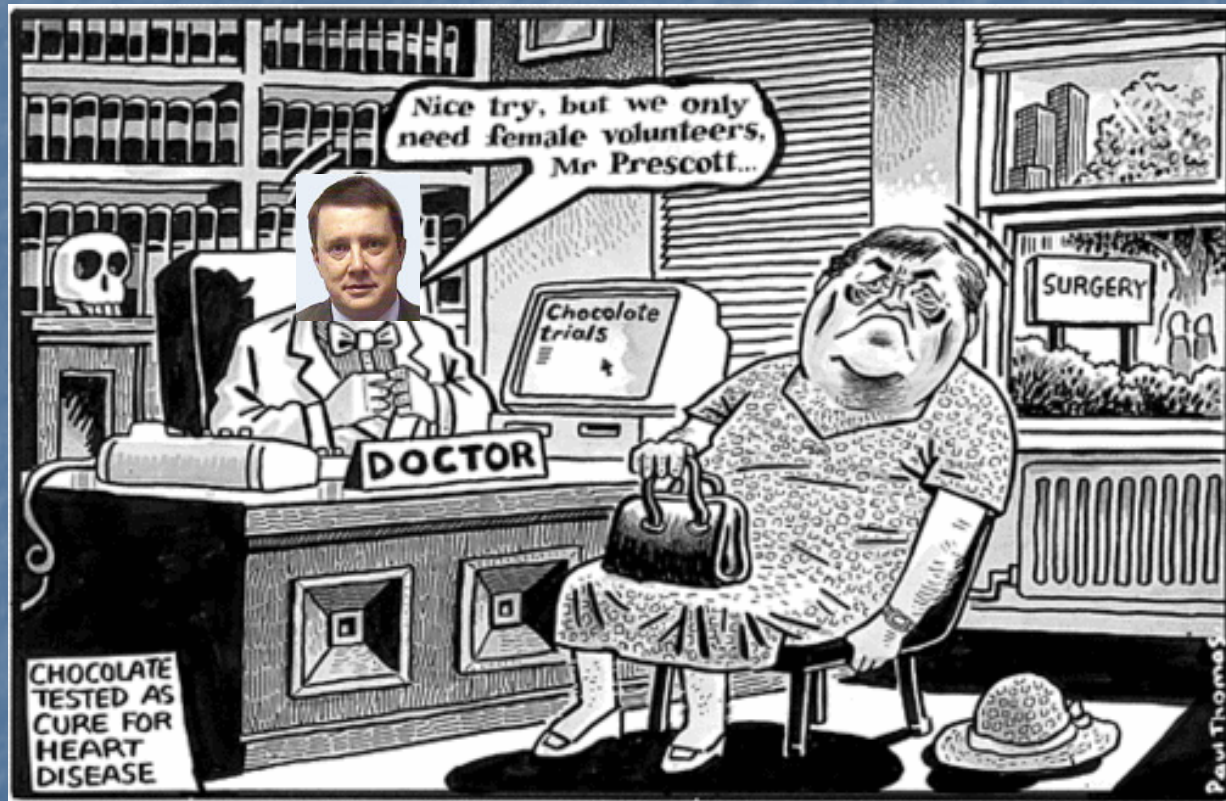
David Rose

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### MONACO GRAND PRIX SUNDAY 25TH MAY 2008

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# A Little Local News.....



Daily Express April 29<sup>th</sup> 2008

Thank you for your attention