

INTRODUCING IDDT

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The Insulin Dependent Diabetes Trust (IDDT) is a registered charity and was formed in 1994. We are concerned with listening to the needs of people who live with diabetes, understanding those needs and doing our utmost to offer help and support. We not only want to help those who actually have diabetes but also their carers – the husbands, wives, partners and parents, indeed, all of us who ‘live with diabetes’. We recognise that when one person in a family has diabetes, all other family members are affected to a greater or lesser extent and they all have views and needs which may be different from the person with diabetes, but nevertheless are important.

The Trust was set up to look at some of the day to day difficulties of living with diabetes, the worries, fears and concerns that perhaps we don't talk about at the hospital clinic – the ones that many of us experience and understand because we actually live with diabetes. As a charity, IDDT has a Board of Trustees and all the Trustees either have diabetes or have family members with diabetes. So we all know first hand that while diabetes doesn't rule our lives, it is an important part of them. It needs care and attention, it can be a nuisance and it is not without its problems!

AIMS OF THE IDDT

- To offer care and support to people with diabetes and their carers, especially those experiencing difficulties with GM (synthetic) insulin.
- To influence appropriate bodies to ensure that a wide range of insulins remain available to ensure that all insulin users have a continued supply of their chosen insulin.
- To ensure that all patients and carers are properly informed of the various treatments available to them, as is their right under *“Your guide to the NHS”*.
- To collect information and experiences from people with diabetes and their carers to help others in the same situation and to pass it to healthcare professionals to create a better understanding of “life with diabetes”.
- Where possible, to represent the direct voice of the patient, as the consumer, in relation to healthcare and research.

The Trust is run entirely by voluntary donations. We do not accept funding from the pharmaceutical industry, so not only are we independent and uninfluenced by funding sources but we are seen to be so.

JOIN IDDT NOW by contacting:
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Membership is free, although we do welcome donations to help us to help you.

THE FORMATION OF IDDT

The Trustees came together because we all had one thing in common – we all experienced adverse effects when using GM (synthetic) insulin but when changed to natural animal insulins many of those adverse effects disappeared. These experiences made us wonder how many more people experience similar problems but have not thought of changing their insulin to see if this removes the problems, as it did for us. In recognising our needs for natural animal insulins, we also recognise the need for the continued availability of natural animal insulins. Continued availability is essential not only for people that have changed to animal insulins and for those who have always used them, but also for those who may be unable to use synthetic GM or analogue insulins in the future. Following its formation, IDDT was contacted by people in many different countries, all experiencing problems with GM (synthetic) insulin and so in 1999 an umbrella organisation, IDDT-International, was formed. This has enabled people with diabetes in different countries to work together and exchange information, to unite to gain recognition of the adverse reactions to GM (synthetic) insulin some people suffer and to campaign for the availability of easily accessible animal insulin. This provides people living with diabetes with an umbrella organisation to protect and represent their interests in response to the global policies of the pharmaceutical industry.

Since 1994 we have widened our interests and concerns to cover many aspects of living with diabetes and this is largely as a result of the expressed wishes of our members and people who contact IDDT. However, ensuring that people with diabetes receive information and choice of treatment, especially the type of insulin, remains our main concern. We hope that IDDT can provide people who live with diabetes with information, support and encouragement to enable them to be involved in decisions about their healthcare and that this will enable them to make informed decisions about their treatment, especially about their choice of insulin.

INSULIN TYPES

Beef insulin is made from insulin extracted from the pancreases of cattle.

Pork insulin is made from the pancreases of pigs, again as the name implies.

Human insulin was introduced in 1982 but the name is very misleading and implies that it is insulin from human beings. It is not. It is made by genetic modification [GM] from yeast or from e-coli.

Insulin analogues - were introduced in the 1990s and are made from so-called GM 'human' insulin by a further GM process.

Note name change - in 2003 Novo Nordisk changed the names of their range of synthetic GM 'human' insulin - the word '*human*' was omitted. So for example, what was '*Human Actrapid*' became simply '*Actrapid*'. Therefore it is even less obvious that the insulins are made by GM technology and there is the potential for confusion. The names of ***Pork Actrapid*** and ***Pork Insulatard*** have NOT changed but as the names are the same as the synthetic insulins, IDDT has concerns that confusion or errors could arise when a prescription for Novo Nordisk pork insulin is dispensed **so**

- **ALWAYS** check that you have the correct insulin BEFORE leaving the pharmacy.
- **ALWAYS** read the Patient Information Leaflet even if you have been using insulin for years, because this is where any changes will be reported.

IDDT's policy when referring to insulins of different types is to use the source of insulin in the name. So in our literature ***beef and pork insulins*** keep the names they have always had and may be referred to jointly as natural animal insulin. However, any insulin made by genetic modification is referred to as ***GM (synthetic) insulin*** to enable people to immediately understand the source of the insulin and it includes 'human' and analogue insulins.

THE SYNTHETIC AND ANIMAL INSULIN DEBATE

Gathering information - evidence from patients and their carers.

When IDDT formed in 1994 an important task was to collect information from people with diabetes and their family carers about their experiences with GM (synthetic) insulin. We sent questionnaires to everyone who contacted us and analysed the first 100 we received, those received subsequently were all very similar to the first 100.

This is what we discovered:

- **Analysis showed that on average the adverse effects did not appear until 13 months after treatment with 'human' insulin began and most people complained of 3 or 4 of the following adverse reactions.**
- **41% - loss of warnings of hypos or 'I function on automatic pilot'.**
- **34% - extreme tiredness or lethargy**
- **9% - sleeping all the time**
- **32% - weight increase of 1.5 stones [21 pounds] and above**
- **28% - feeling unwell all the time**
- **24% - memory loss or confusion**
- **9% - blood glucose levels dipping and peaking erratically**
- **8% - described by their families as 'not the same person'**
- **5% - mood changes, described as difficult to live with**
- **7% - pains, especially in the legs and joints**
- **4% - irregular or late periods**

In addition 24% said that their doctor was unwilling or reluctant to change their insulin to natural animal insulin and 3% told us their doctor didn't listen or said the problems were 'all in the mind'. Other common statements were:

- **'I didn't know that there was such a thing as animal insulin.'**
- **'I was never told there were alternatives'.**
- **'I didn't realise that 'human' insulin was not derived from humans'.**

Sadly so many years later, we are still receiving similar reports.

FACTS

- **After over 20 years there is still no evidence to show that GM (synthetic) insulins have any clinical benefits for patients over animal insulin.**
- **Synthetic insulin is a more aggressive insulin because it has a faster action, a higher peak of action and a shorter duration of action than both beef and pork insulin.**

PATIENT EXPERIENCE

Interview with Beverley Freeman

We recently talked to Beverley Freeman about her diabetes. Bev is 35 years old and has had diabetes since she was 5 years old. She used animal insulin for about eight years and was then changed to synthetic GM 'human' insulin. After several years on synthetic insulin, she became very unwell and so insisted on changing back to animal insulin which she has used ever since.

Question: *Although you were quite young when you first changed to synthetic insulin, were you aware of any changes in your diabetes?*

Bev: No

Question: *So what made you change back to animal insulin?*

Bev: I didn't feel at all well and it was really a last resort. I seemed to be always visiting my GP and had lots of tests but he couldn't find anything wrong with me.

Question: *What do you mean when you say that you weren't very well?*

Bev: I felt constantly tired and depressed. I felt as though I had high blood sugars but they weren't. I had problems remembering things from one minute to the next and felt unable to hold a conversation. I felt inadequate and a sort of numbness and separate from what was going on around me. On top of this I put on a lot of weight very quickly.

Question: *So what happened then?*

Bev: Because I had heard rumours about synthetic insulin affecting people differently, as a last resort I changed back to animal insulin and at this point if it hadn't worked I don't know what I would have done. I was lucky, my GP was happy to change me back to pork insulin.

Question: *How did things change then?*

Bev: I did roughly the same doses of animal insulin and within 3 days felt a completely different person. I was able to get up in the mornings and feel awake for the first time in about 4 years! My depression went away, there was pinkness in my cheeks and I generally felt a lot fitter and healthier. My warnings of hypos came back and it was only then that I realised that they had gradually disappeared while I was on synthetic insulin.

Question: *So what happened over a longer period?*

Bev: I lost weight almost straight away and over 6 months lost nearly 3 stones [42 pounds] without dieting. My memory went back to normal and I became more aware of what was going on around me and I felt able to include myself in this and could hold conversations with confidence again.

Question: *So were there any other changes that happened that you wouldn't have put down to changing your insulin?*

Bev: Yes. When I was on synthetic insulin I regularly got infections, frequent tonsillitis and any cuts always went septic. I had regular stomach upsets and I suffered badly with constipation. I never had regular periods. All this has changed dramatically and I have none of these problems now I am on animal insulin.

Question: *Finally, have you any comments you would like to make?*

Bev: Yes. I'm fully aware that synthetic insulin agrees with some people but for me it was crippling. I lost my teenage years to synthetic insulin. People must have the choice of insulins and be given the benefit of information from the experiences of people who have suffered as a result of treatment with synthetic insulin.

A LITTLE BIT OF HISTORY

- For nearly 60 years people with diabetes who required insulin treatment used animal insulin, originally beef insulin and in the 1970s highly purified pork insulin became available. All insulin is now highly purified whether beef, pork or GM.
- In 1982 genetically modified so-called 'human' insulin received marketing approval. Approval was given in five months, a remarkably short time when one realises that it was the very first genetically produced drug to be licensed and used on people. According to an article published in 1996, the clinical trials that took place used only 300 people for a drug that was to be used in millions of people throughout the world. (Practical Diabetes International, July/August 1996, Vol 13, No 4)
- It was claimed that GM (synthetic) insulin was better than animal insulin because it is an exact copy of the insulin molecule produced by the body. It was also claimed that it would not produce antibodies, that it would be cheaper because it was easier to make and finally that animal insulin supplies were likely to run out. None of these claims proved to be true.
- During the mid-1980s there were widely circulated, but untrue, rumours that animal insulins were being discontinued. This resulted in the over 80% of people in the UK being transferred from animal to synthetic insulin and in the majority of cases for no good clinical reasons.
- Within a year of the changeover people started reporting loss or reduced warning symptoms of hypoglycaemia [now called hypoglycaemia unawareness], more severe hypos and generally, more problems in controlling their diabetes safely. As time progressed other symptoms were reported: extreme tiredness, weight increases, feeling unwell and behavioural changes.
- The majority of people who reported these problems to their doctors were either ignored or not believed and many were even refused their right to change to the beef or pork insulin that had previously suited them. Nearly 3,000 people wrote to the then British Diabetic Association (now Diabetes UK) but little or no action was taken at the time.
- In the early 1990s Diabetes UK commissioned Dr Natasha Posner to carry out a study of only 384 of the 3,000 letters it had received. However, the study was never published because Diabetes UK considered that it was *'too alarmist'*.
- In the early 1990s around 700 people attempted to take a class action against the manufacturers of GM (synthetic) insulin but failed for 'lack of scientific evidence'. IDDT has since discovered that during this period insulin manufacturer, Novo Nordisk employed a PR company to "defend the safety profile of human insulin". The PR company described this as a crisis management programme and rather worryingly, this included media training of UK medical spokespeople.
- The adverse effects to synthetic insulin experienced by some people continue to be reported. It is now evident that some people diagnosed more recently who have never used animal insulin also suffer the well-recognised adverse reactions to synthetic insulin that regress with a change to natural animal insulin.
- In 1998 the first insulin analogue was introduced with little proven benefit for patients and no evidence of long-term safety, which is of special concern because of the potential for carcinogenic effects.
- In 2005 Novo Nordisk began the systematic discontinuation of some of their human insulin range so further reducing the choice for patients and their doctors. Their recommendations are that people are transferred to GM (synthetic) insulin analogues despite their long-term safety being unknown. In 2006, Eli Lilly is making similar discontinuations.

THE BATTLE CONTINUES

Over 20 years after its introduction, people are still battling with their doctors and/or healthcare professionals for recognition of the adverse effects of synthetic insulins. However, as a result of a long lobbying campaign by IDDT this should no longer be the case as the UK Dept of Health has now recognised that not everyone is suited to GM (synthetic) insulins. They are also supported by a Position Statement entitled '*Animal, Human and Analogue Insulins*' from the International Diabetes Federation. For people who have difficulty convincing their doctors and healthcare professionals of their wishes to continue to use, or to change to animal insulins, IDDT has included these statements in this leaflet or we will supply copies. Call IDDT on 01604 622837 or e-mail enquiries@iddtinternational.org

THE RESPONSE TO PATIENTS' EXPERIENCES

The evidence from patients and their carers was not, and often still is not listened to even though it is clear that for some people a change to animal insulin makes their symptoms disappear. It is, however, now widely accepted, and supported by evidence, that synthetic insulins have no clinical advantages over animal insulin for the majority of patients. Many of the medical and nursing professionals, researchers, diabetes associations and the insulin manufacturers maintain that there is no scientific evidence to support the experiences of people who cannot tolerate synthetic insulin. It is still claimed that synthetic insulins are better than animal insulin but no evidence is provided to justify this statement and long-term randomised trials to compare animal and synthetic insulins have never been carried out. This is a surprising claim when even the manufacturers themselves have made the following statements:

- **Research carried out by Eli Lilly in 1981** showed an increased risk of hypoglycaemia with synthetic insulin and the product information for marketing approval for prescribers states that physicians and patients should be warned of this.
- **Press Release, Sept 9th 1999, Novo Nordisk stated** “.....Historically improving glycaemic control with soluble human insulin has been associated with an increased risk of hypoglycaemia.”
- **Aventis Pharmaceuticals, April 24th 2000 Press Release stated:** “Human insulin therapy may be associated with hypoglycaemia, worsening of diabetic retinopathy, lipodystrophy, skin reactions (such as injection-site reaction, pruritus, and rash), allergic reactions, sodium retention and oedema.”

The following statements support the concerns of patients:

British National Formulary [BNF] No 30, September 1995 page 280 (and also in the current edition) states:

Preparations of human sequence of insulin should theoretically be less immunogenic, but in trials no real advantage has been shownSome patients have reported loss of warnings of hypoglycaemia after transfer to human insulin. Patients should be warned of this possibility and if they believe that human insulin is responsible for their loss of warnings it is reasonable to transfer them back to porcine insulins. When prescribing insulin great care should be taken to specify whether a human or an animal insulin is required. Indications for changing from animal to human preparations must be carefully considered in the light of these reported problems. Beef insulins are still available for patients who specifically request them.

- **Drug and Therapeutics Bulletin, March 1989,**

This government sponsored safety bulletin, reported that 'human' insulin is no better than conventional insulin treatment and may hold dangers for people with diabetes. The Bulletin also said that 'human' insulin may cause loss of early warning symptoms of hypoglycaemia. (The Bulletin has continued to maintain this stance.)

- **US Report of Post Market Adverse Drug Effects,1995, FDA**

The 1995 table for reported post-market adverse drug effects in the US shows the top 10 suspect drugs. Humulin, 'human' insulin produced by Eli Lilly, is ranked number eight and is one of only three non-prescription drugs to be on this list. The Medicines Control Agency in the UK does not make public their reported adverse drug reactions.

- **Committee on Safety of Medicines (CSM), August 19th 1998**

A letter from Baroness Hayman, Parliamentary Under Secretary of State at the Dept of Health said:

"The CSM concluded that some patients did experience problems with human insulins, particularly when initially transferred from animal insulins and were better suited to continuing their treatment with animal insulins. However, the CSM sees no evidence of a safety problem specific to human insulin. Indeed most patients respond well on it.... To ensure that patients continue to have a choice of treatment both animal and human insulin will remain available."

- **The Lancet, 1998; Vol 352: 502-3**

Professor Stephanie Amiel "Severe confusional hypoglycaemia in its extreme forms can destroy confidence, relationships and livelihoods, if not lives.....The newer more purified insulins* probably compound the problem [of night hypos] by being just that little bit shorter acting than their predecessors."

*The reference to this statement is dated 1983 when the newer insulins referred to could only be synthetic.

- **The Lancet, 1998; Vol 352: 1549 Response to Professor Amiel**

F Wolff, responded to this by pointing out that when insulin is extracted from the beta cells of the pancreas of pigs or cattle, small amounts of glucagon are also extracted from the alpha cells by the process itself and are therefore present in animal insulins. The author points out that the newer insulins ['human'] do not contain glucagon. The significance of this is that glucagon is a counter-regulatory hormone and these hormones provide protection from hypoglycaemia by triggering the warning signs of an impending hypo.

IDDT believes that a wide range of insulin should be available to suit differing needs of people with diabetes. This includes both GM (synthetic) human insulins, (synthetic) insulin analogues and natural animal insulins to give doctors and patients the choices they need.

Cochrane Reviews

Cochrane reviews are the 'gold standard' method of assessing research to provide evidence to help doctors and patients make informed decisions about treatments. Reviews are important not just to show what research has been carried out and how well, but also what research has never been done which can result in a lack of evidence. They are regularly updated to take into account research carried out after the original review.

Cochrane Reviews can be found by visiting the Cochrane Library www.cochranelibrary.com

'Human' versus animal insulin in people with diabetes mellitus

By B Richter, G Neises

[First published July 2002, most recent amendment November 2004]

This review looked at research carried out from 1966 onwards and over this period 2156 participants took part in 45 randomised-controlled studies. The reviewers concluded that there were no significant differences between the two insulins in terms of metabolic control, hypoglycaemic episodes, insulin dose or insulin antibodies. But it also concluded that the majority of research carried out was of 'methodologically poor quality' and that there has been *no* research to compare mortality and diabetic complications rates or quality of life - vital issues to consider by people with diabetes when making choices about insulin treatment.

So the Review provided high quality evidence that GM (synthetic) insulin is *not* superior to animal insulin and that research to compare mortality and complication rates and quality of life on synthetic and animal insulins has never been carried out.

The Review gives hope to people with diabetes

It highlights that the introduction of GM (synthetic) insulin took place without sufficient proof of its advantages or safety and as it is not superior to animal insulin, that there is no evidence to support the policy of synthetic insulin being first line treatment for people requiring insulin. Healthcare professionals have no evidence to claim that synthetic insulin is superior to animal insulin or to deny that it causes adverse effects in some people. So for people who want to remain in animal insulin or to change to animal insulin, the Review provides evidence to support them and gives them the 'courage' to put their case for treatment with animal insulin.

Short acting insulin analogues versus regular human insulin in patients with diabetes mellitus.

Siebenhofer A, Plank J, Berghold A, Narath M, Gfrerer R, Pieber T.

[First published April 2004, most recent amendment August 2004]

Short-acting insulin analogues act more quickly and so more nearly match insulin release in non-diabetic people but despite this theoretical superiority over regular human insulin, the risk-benefit ratio of short acting insulin analogues in the treatment of diabetic patients is still unclear. This review compared short-acting insulin analogues [Humalog and NovoRapid] with regular short-acting human insulin and altogether 7933 participants took part in 42 randomised controlled studies. 25 studies were carried out in people with Type 1 diabetes, 5 in people with Type 2 diabetes, 5 with a combination people with Type 1 and Type 2 diabetes and one in women with gestational diabetes. The authors concluded that short-acting insulin analogues showed only minor benefit in the majority of people. Short-acting insulin analogues were almost identically effective to regular human insulin in long-term glycaemic control and were associated with similar episodes of low blood sugar [hypoglycaemia]. There is no information available on comparisons of late complications such as problems with the eyes, kidneys or feet, in other words, this research has not been done. Equally due to fears of potentially carcinogenic and proliferative effects, most studies to date have excluded patients with advanced diabetic complications.

They also found that 83% of the studies were of poor methodological quality and 81% of them were sponsored by the analogue manufacturers themselves, with sponsors of the remaining studies not being declared.

The authors recommend:

- for safety purposes, there needs to be a long-term follow-up of large numbers of patients who use short acting insulin analogues. Furthermore, there needs to be well-designed studies in pregnant women to determine the safety profile for both the mother and the unborn child.
- Until the long-term safety and efficacy of analogue insulins have been established, there should be a cautious response to the vigorous promotion of insulin analogues.

THE SAFETY OF INSULIN ANALOGUES – SHOULD PATIENTS BE CONCERNED?

This is the title of an IDDT Supplement containing a paper by Professor Ernst Chantelau and Jenny Hirst raising questions about the use of insulin analogues in view of their carcinogenic potential and the fact that their long-term safety is unknown. IDDT has no wish to be alarmist but these facts are in the public domain and as IDDT has a responsibility to provide people with information to inform their treatment choices, we cannot, and should not, avoid this discussion.

Insulin analogues are new biotechnology products and as such, are likely to have different patterns of toxicity with unknown consequences. The clinical benefits of insulin analogues have been extensively studied and have proved to be negligible in terms of glycaemic control but the biological effects have *not* been systematically studied despite their carcinogenic potential being recognised by the scientific community.

Human insulin has a weak mitogenic effect. Mitogenicity is the promotion of the division and proliferation of any cell including malignant and non-malignant tumour cells. The mitogenic potential with insulin analogues is thought to be due to their structural similarity to insulin-like-growth-factor-1 [IGF-1] and/or faulty signalling through the insulin receptor. The similarity to IGF-1 could also affect the progression of retinopathy.

The first example of this mitogenic effect was in the AspB10 insulin analogue, developed by Novo Nordisk. Trials were stopped because it was found to induce mammary tumours in rats. Therefore the European Agency for the Evaluation of Medicinal Products [EMA] states that a thorough assessment of the carcinogenic potential is indicated for all new insulin analogues. More information can be found by visiting

<http://www.emea.eu.int/pdfs/human/swp/037201eu.pdf> and we will be happy to send copies of this to people without internet access. It is also worth looking at the EMA approval documents for each analogue insulin on their website www.emea.eu

Copies of IDDT's Supplement 'The Safety of Insulin Analogues' can be obtained from IDDT, PO Box 294, Northampton NN1 4XS, tel 01604 622837, e-mail enquiries@iddtinternational.org or website www.iddtinternational.org

People with diabetes are no exception to the principle that they should have an informed choice of treatment including risks and benefits but the majority are not aware of the carcinogenic potential of insulin analogues or that their long-term safety has yet to be established. Some patients may consider even a minimal carcinogenic risk with insulin analogues is unacceptable when there is little or no benefit in day to day blood glucose control.

THE INTERNATIONAL DIABETES FEDERATION

Position Statement 'Animal, human and analogue insulins'

The International Diabetes Federation [IDF] mission is to promote diabetes care, prevention and a cure worldwide and it has an umbrella organisation of 191 member associations in 151 countries. Many of the world's leading diabetologists are, or have been, involved with the IDF, so its statements are produced by the world's experts in diabetes.

In view of its mission, IDDT has approached the IDF several times for help in maintaining supplies of animal insulins, but we received no help and little sympathy. So it was a surprise and relief to find a Position Statement by the IDF on '*Animal, Human and Analogue Insulins*' which entirely supports patients' right to choice.

In order to not give a biased view of the Statement, here is the full version or it is available on the IDF website www.idf.org:

IDF - International Diabetes Federation, POSITION STATEMENT: Animal, Human and Analogue Insulins March 2005

Insulins are now available in different molecular forms, some because of species differences and some by design through molecular engineering. Modern highly purified animal insulins are safe, effective and reasonably reproducible in their actions. Human insulins, prepared usually by genetic engineering, are similar to highly purified pork insulins. Concerns that hypoglycaemia problems are greater with human insulins have not been substantiated by research. There is no overwhelming evidence to prefer one species of insulin over another and patients should not be changed from one species of insulin to another without reason. Genetically modified insulin analogues may provide advantages in patients with problematic hypoglycaemia but they are expensive and there are no long term safety data.

Early animal insulins were effective but had imperfect absorption profiles. There were also concerns about their ability to induce an immune response (immunogenicity), which increased the variability of their action profiles. The highly purified "mono-component" insulins reduced the immunogenicity, resulting in faster, shorter actions. Disappointingly, the immunogenicity of human insulin is similar to that of highly purified pork insulin, to which it is clinically equivalent.

Highly purified animal insulins are effective agents to treat diabetes. Human insulin is at least as good as highly purified pork insulin. In many parts of the world, beef insulin provides access to a low cost insulin. While their prices remain lower, highly purified pork and to a lesser extent beef insulins are entirely acceptable and there is no reason to convert. Human insulin has the theoretical advantage that it can be synthesized in limitless quantities at relatively low cost.

All insulins have slightly different properties and patients should not be changed from one to another insulin type unless there is a clear advantage. No insulin type will suit every patient and it is important that variety is maintained in order to find the insulin that suits each patient best.

More recently, genetically modified insulins are being introduced in which the human insulin gene is deliberately altered to confer some specific desirable properties, including a more reproducible action profile. Rapidly acting analogues give better post-prandial (after meal) glucose control and contribute less to nocturnal hypoglycaemia than earlier short acting insulins.

New "background or basal" insulins have flatter action profiles and are less prone to cause hypoglycaemia in the night. These insulins are more costly and it is important to recognize that they have not delivered overall improvements in glucose control in large studies. They may have different properties from human insulin and animal insulins and are likely to prove most beneficial in intensified therapy, when good control cannot be achieved without problematic hypoglycaemia.

All insulin therapy is associated with the risk of hypoglycaemia, sometimes severe. There is no evidence that this is worse with human rather than animal insulins. Concerns have been raised in some countries that human insulin use was associated with a different and higher risk of hypoglycaemia. The evidence for this has remained anecdotal, despite serious attempts to document it and find a mechanism. Patients with problematic hypoglycaemia need careful monitoring. Their insulin regimen should be prescribed with knowledge of the expected actions of the insulins involved. Insulin regimens should take into account risk factors such as exercise, alcohol ingestion and illness and these should be clear to the patient. Problematic hypoglycaemia can generally be treated effectively without changing insulin species although patient choices should be respected. Despite the lack of scientific evidence, some patients do better on specific insulin types and some older insulins may have individual benefits in some settings.

Conclusion

People with insulin deficient diabetes require adequate and secure supplies of safe and affordable insulins. Genetic engineering, currently used to make human insulin, should be able to deliver this, as its production capacity is theoretically limitless. Animal insulins remain a perfectly acceptable alternative and indeed some patients prefer them. Newer insulins offer potential advantages, but until these are proven to deliver real long-term benefits safely and affordably, it seems appropriate to use them in patients experiencing specific problems that a specific analogue might reasonably be expected to address. IDF believes that this ability to choose is important and should be supported.

WHAT DOES THE IDF STATEMENT MEAN FOR PATIENTS?

- There is now an authoritative document that provides patients, doctors and governments with the facts about all the insulins - not the sales jargon but facts so that the choice of insulin treatment is based in evidence and not influence.
- For people having difficulty persuading their doctors or healthcare professional that they wish to try animal insulin, this Position Statement provides valuable support and encouragement to be involved in making their own choice of insulin treatment.
- It offers people with diabetes and governments the truly informed choice for which they have been waiting and it supports them in making their choice of treatment.

ACTION AND DURATION TIMES OF ANIMAL AND GM HUMAN INSULINS ARE DIFFERENT

This chart shows the relative activity curves of synthetic 'human' and natural animal insulin. This is the information that the American Diabetes Association provide. It must be noted that these times of peak activity and duration are general, will vary in different people and beef insulin is longer acting with a smoother action than pork insulin.

Insulin type	Onset	Peak [hours]	Effective duration [hours]	Maximum duration [hours]
ANIMAL				
Regular [soluble]	0.5- 2 hours	3- 4	4- 6	6- 8
NPH [isophane]	4- 6 hours	8- 14	16- 20	20- 24
'HUMAN'				
Regular [soluble]	0.5- 1 hour	2- 3	3- 6	6- 10
NPH [Isophane]	2- 4 hours	4- 10	10- 16	14- 18

Since this chart was produced synthetic insulin analogues have been introduced and they have different actions.

Humalog and NovoRapid are short-acting analogues that are injected immediately before or straight after a meal and they are of short duration. They are designed to lower post-meal blood glucose levels but the manufacturers of Humalog still state that the significance of this is unknown.

Lantus [glargine] is a one injection a day, long-acting insulin analogue and manufacturers claim that it has no peak of action and provides basal cover with less night hypos than previous insulins, although they state that it may cause more early morning hypos. Reports to IDDT from people using Lantus show that while it suits some people, it still causes similar adverse effects to the other synthetic insulins in others.

Levemir is the newest longer-acting analogue and the manufacturers say that it is a once or twice daily insulin

Note: Multi-dose insulin regimes only appeared as a form of treatment after the introduction of GM (synthetic) insulin. Prior to this many people had controlled their diabetes well using twice daily mixtures of soluble and isophane animal insulin. The shorter duration of synthetic insulin does not give as good basal 24hour cover as animal insulin and therefore more doses of short-acting 'human' insulin are OFTEN necessary.

INSULIN SUPPLIES IN THE UK

GM 'human' and analogue insulins

Information about the availability of synthetic insulins from these companies is readily available from your GP or diabetes clinic.

By the end of 2005 Novo Nordisk will have discontinued some of their GM 'human' insulin insulins in cartridges and pre-filled pens. They recommend that people change to insulin analogues, despite the fact that the nearest equivalent insulins to those being discontinued are pork insulins, not analogues. By mid 2006 Eli Lilly also intends to discontinue some of their 'human' insulins.

Many people, especially parents of children with diabetes, are rightly concerned about changing to analogue insulins because of their unknown long-term safety and their potential for carcinogenic effects. The IDF Statement validates these concerns noting that no benefits from the use of analogues have been observed in large trials.

But there is a choice:

1. Use the same 'human' insulin in vials with a syringe.
2. Pork insulin is clinically equivalent to 'human' insulin and a nearer match than analogue insulin, so use pork insulins. They are available from Wockhardt UK in vials and cartridges for use with a pen.

Pork and beef insulins

Information about natural animal insulins is not so readily available and, all too frequently, patients are not informed of their availability. Many people do not realise that they are being prescribed a genetically modified drug and some believe that it is actually human insulin obtained from man. It is not - it is produced genetically from e-coli bacteria or yeast. Animal insulins are extracted from the pancreases of pigs and cattle. Even when suffering unaccountable symptoms and loss of warnings of hypoglycaemia, most people are not given the opportunity to try animal insulin. Animal insulins are supplied by two companies:

Novo Nordisk Pharmaceuticals Ltd supply only pork insulin. It is only available in vials and not in cartridges for pen injection devices. However, Novo Nordisk has announced that they intend to globally discontinue all animal insulins over the next few years, including the UK. The discontinuation has already taken place in most countries and they have informed the UK Dept of Health that a final decision will be made in 2006. They have given assurances that they will inform all 'relevant parties' at least 18 months in advance of the discontinuation and that they will issue information about availability of equivalent available pork insulins, including those made by other companies. But it is worth remembering that they did not abide by this promise with their discontinuations of the GM 'human' insulins in 2005.

Wockhardt UK supply pork and beef insulins as follows:

PORK

Hypurin Porcine Neutral	Short acting in 10ml vials and 3.0ml cartridges
Hypurin Porcine Isophane	Intermediate acting in 10ml vials and 3.0ml cartridges
Hypurin Porcine 30/70 mix	Mixture of 30% Neutral and 70% Isophane in 10ml vials and 3.0ml cartridges

BEEF

Hypurin Bovine Neutral	Short acting in 10ml vials and 3.0ml cartridges
Hypurin Bovine Isophane	Intermediate acting in 10ml vials and 3.0ml cartridges
Hypurin Bovine PZI	Long acting in 10ml vials
Hypurin Bovine Lente	Long acting in 10ml vials

Note: The packaging of Wockhardt insulins is in Braille to help blind and visually impaired people.

Future availability:

Wockhardt UK has confirmed that they have no plans to discontinue beef and pork insulins and in July 2005 the Dept of Health informed IDDT that Wockhardt is expanding their production facilities during the following year. Wockhardt also export animal insulins for personal use to people in countries where they are no longer available.

Choice will remain! - Department of Health recognise the need for animal insulin.

As a result of IDDT's lobbying campaign and the determined efforts of our members, in July 2005, the Minister of Health, the Rt Hon Jane Kennedy MP made a long-awaited statement of great reassurance to people who need animal insulins. She made the following points:

The Department of Health fully accepts that some people are better suited to animal insulin and that animal insulin should continue to be made available.

Wockhardt UK has no plans to discontinue supply of animal insulins. The company is increasing its sterile manufacturing facilities over the next 6 to 12 months and this will include animal insulins.

CHANGING YOUR INSULIN

In the UK insulin is a prescription only drug and therefore you will need to discuss your wishes to change your insulin type with your GP and/or clinic doctor.

The following guidelines are an extract from a talk given by Dr Laurence Gerlis, IDDT's Medical Adviser.

- Any change of insulin, type and brand, can alter your control in the first few days or weeks and so it is important to monitor your blood glucose levels more frequently.
- Dose changes should be made in only 1 or 2 units at a time.
- Dose changes should be kept to a minimum by altering the amount of exercise and the food at the next meal to cope with the odd high blood sugar.
- There is nothing wrong with what is called conventional therapy, twice daily doses of short and longer acting insulins, and it is quite possible to achieve 'good' control on this regime.
- Insulin is a delicate protein and small but subtle changes in the insulin molecule, such as the difference between the insulin molecule in pork and synthetic, can affect diabetic control in some patients.
- Both doctors and patients tend to raise the dose of insulin but rarely lower it. For example, if the morning blood sugars are high as a result of the body's reaction to a hypo in the night, then raising the insulin dose will only make this situation worse. This leads to a vicious circle of increasing insulin doses to cope with highs, leading to more hypos and so it goes on.

Note: If you are changing from either animal or GM human insulins to analogue insulins, it is important to remember that analogues work differently because they have different peaks of action and different durations of action. It is important to discuss this with your doctor or diabetes specialist nurse.

WHAT TO DO IF YOUR CONSULTANT REFUSES TO CHANGE YOU TO ANIMAL INSULIN.

Unfortunately IDDT still receives reports from people that their doctors and diabetes specialist nurses are refusing to change their insulin from synthetic GM insulin to animal and also reports from people that they are too nervous to ask their doctor to change them. There is nothing to be gained by this refusal for either the doctor or the patient and it merely serves to hinder the doctor/patient relationship because the patient feels not listened to, not understood, frustrated and angry.

IDDT's advice in this situation:

- Before your appointment with the doctor, make a list of your reasons for wanting to change so that you don't forget anything.
- Discuss your desire to change with your GP, he/she may well write to your consultant or just make the change for you.
- Take your spouse, partner or a friend with you to the clinic so that they can back you, especially if they recognise the changes in you or have to deal with your hypos.
- Discuss your concerns with your consultant in a non-aggressive way and ask to change to animal insulin.
- Be calm and forceful. Remember there was probably no good reason for prescribing synthetic insulin for you in the first place other than accepted policy and there is no research that shows it to be better than animal insulin. So if your doctor says 'there is no difference' take the opportunity and say 'Well then, I'll try animal insulin for 6 months, thank you.'
- If all else fails, use your rights as a patient. You, the patient, have the right to an informed choice of treatment and the right to be given a clear explanation of any proposed treatment, including risks and alternatives **BEFORE YOU** decide whether **YOU** will agree to the treatment. Your alternatives are synthetic GM insulin or natural animal insulin.

NB. Your doctor is in breach of his/her NHS contractual agreement if he/she failed to give you this choice and information. The Patients' Charter was abolished in January 2001 and rights have been replaced with 'expectations' but you still have the right to 'expect' an informed choice of treatment.

FREQUENTLY ASKED QUESTIONS:

'What is the difference between pork and beef insulin?'

Generally beef insulin is slower acting with a smoother peak of activity than pork insulin.

'What is the difference in the activity and duration of action between animal and GM (synthetic) insulins?'

Generally GM (synthetic) insulins are faster acting, have a more aggressive action and are of shorter duration than animal insulins.

'Is there any difference in the purity of animal and GM (synthetic) insulins?'

All insulins are highly purified and are equally pure.

'If GM (synthetic) insulin is the cause of my problems and I change to animal insulin, how quickly can I expect to feel better?'

This seems to vary from person to person. In some people some of the symptoms disappear in a matter of days with the other symptoms regressing over the following weeks or months. In other people the symptoms gradually disappear over weeks and months. Some people feel that changing to animal insulin simply stops the decline in their health. You should try the new insulin for at least 6 months.

'What will happen to my blood sugars during the changeover period?'

They may well be erratic for a few days but as with any change of insulin, you should always monitor your blood glucose levels closely. Some people find that their blood sugars are raised for the first few days, so if you increase your insulin to cope with this, be prepared for your blood sugar to drop and the risk of a hypo.

'I have heard that beef insulin can cause allergic skin reactions, is this true?'

This was a problem with the early beef insulin before it was highly purified. Now that all insulins are highly purified allergic skin reactions are far less common but any insulin species, including 'human' and analogues insulins, may cause skin reactions in some people. If this is the case, then a different insulin species should be tried.

'Is there any risk of BSE or nvCJD from using beef insulin?'

Since 1989 beef insulin has been extracted from the pancreases of US cattle and NOT cattle from the UK. Beef insulin is highly purified and the risk is extremely minimal but as there is no test available to prove that there are no prions present, it is impossible to prove that there is absolutely no risk. The UK Department of Health issued a statement to say that there was no reason to stop using beef medicinal products, including beef insulin. In Australia, where pork insulin is no longer available on the Pharmaceutical Benefits Scheme, the government confirmed this and stated that beef insulin is an essential medicine for people who cannot tolerate GM (synthetic) insulin [2003].

IDDT in AUSTRALIA

IDDT as an international body is represented in Australia.

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HYPOGYCAEMIA IS AN ADVERSE EFFECT OF INSULIN TREATMENT

Hypoglycaemia itself, or the avoidance of it, is an acute daily problem for people with diabetes but when accompanied by loss or partial loss of hypo warnings, it can have a dramatic effect on the lives of the person with diabetes and their families. There can be a marked reduction in the quality of life for all concerned.

A quote from an article in Practical Diabetes [Jan/Feb 2001, Vol 18, No1] says “**Severe hypoglycaemia with loss of consciousness and possible convulsion is a most distressing and life threatening condition**”.

IDDT is very aware that the vast majority of people appear to have no difficulties when using GM (synthetic) insulin. For the people who cannot tolerate it, the adverse reactions can have a serious effect on their day to day lives and those of their families, especially as hypoglycaemia and loss of warnings are the most frequently reported adverse reactions to synthetic human insulin. This is supported by information IDDT gathered in 1997 from people with diabetes and their carers who said that hypos and loss of warnings may result in the following:

- A feeling of insecurity and loss of independence.
- Embarrassment.
- Being a danger to oneself and others.
- Aggressive or violent behaviour.
- Family conflict, breakdown of relationships.
- Loss of driving licence – it is illegal to drive with loss of warnings.
- Loss of job
- A deliberate raising of blood glucose levels to avoid such situations.

There are also other areas of concern as a result of hypos and loss of warnings:
Hypoglycaemia automatism - when in a hypo the person is unaware of their actions, often described as ‘functioning on auto-pilot’.

Hypoglycaemia and crime – research has shown that hypoglycaemia has resulted in various crimes from disorderly conduct to murder, shop lifting to embezzlement and exhibitionism to sadism. [David Kerr and Joan Everett, Journal of Nursing Vol 1: NO 4 1997]

Repeated hypoglycaemia in children - has been shown to cause a slight reduction in their IQ and cognitive functioning and so avoidance of hypos and loss of warnings is very important in children.

‘**Dead in bed syndrome**’ a condition in which people have gone to bed perfectly healthy and been found dead in an undisturbed bed the next day. It is believed that hypoglycaemia is a contributory factor and these deaths have been mainly associated with GM (synthetic) insulin.

It is for these reasons, and many more, that IDDT believes that every possible option should be tried to reduce the risk of hypos and loss of warnings. Therefore if a person/child has unaccountable hypos, reduced or loss of warnings of hypoglycaemia, they should be offered a change to natural animal insulin for a trial period of at least 6 months.

PATIENTS CAN NOW REPORT ADVERSE DRUG REACTIONS

In the UK the cornerstones of monitoring the safety of drugs is a system for reporting suspected adverse drug reactions [ADRs] called the Yellow Card Scheme. Until 2005 only doctors and certain healthcare professionals were allowed to report ADRs and there has been a gross under-reporting, estimated to be a 90% under-reporting. From January 2005, patients now have the right to report any *suspected* adverse reactions they experience. Assuming that the correct monitoring is in place and the necessary action is taken by the Dept of Health, increased reporting is almost bound to increase the safety of drugs. So if you experience any *suspected* adverse reactions to the insulin, or any other drugs you are taking, do use this right. You only have to *suspect*, not prove, that adverse effects are caused by a drug. Adverse drug reactions can occur immediately or days, weeks or even years after taking a medication.

Here's how to report any adverse reactions:

- **If you have access to the internet:**

Go to www.yellowcard.gov.uk and CLICK on submit a Yellow Card report. On this site you can also check the adverse reactions reports already made.

- **If you prefer to use a paper Yellow Card reporting form:**

telephone the MHRA on 0207 084 2000 or e-mail patientreporting@mhra.gsi.gov.uk and ask for a form to be sent through the post.

IDDT believes that a more effective system for monitoring suspected adverse drug will result in greater safety for patients.

AUSTRALIA

In Australia, patients should report any adverse reactions to medications at the following Therapeutic Goods Administration (TGA) web page: <http://www.tga.gov.au/problem/>

IDDT PUBLICATIONS available free of charge from IDDT

- **Introducing IDDT** about IDDT and some facts about GM (synthetic) insulins
- **Quarterly Newsletter** up to date information, news and views. Also available on tape and in a format suitable for magnifying readers for people who are blind or visually impaired.
- **Information leaflets** - on diabetic complications and aspects of living with the condition.
- **Looking after your Insulin** do you discard your 'in use' insulin after 28 days? Read this leaflet to ensure that your insulin is in good condition.
- **Parents' Supplement** - Diagnosis in your child or teenager, growing up and letting go with a special feature by Dr Clare Williams entitled "Teenagers Living with Diabetes".
- **Information Pack for Parents** and an **Information Pack for Teachers**, to help teachers have a better understanding of children with diabetes.
- **Stickers for your hospital and GP notes saying:**
"This patient does **NOT** give consent for 'human' insulin to be administered"
The above are available FREE of charge - just contact IDDT or become a member of IDDT. Membership is free, although we do welcome donations to help us to help you.

THE TRUSTEES OF IDDT

Co Chairman	Jenny Hirst and Dr Matthew Kiln
Treasurer	Sue Morris
Medical Adviser	Dr Laurence Gerlis
Trustees	Veronica Readman Carol Baker (Canada) Larrane Ingram (Australia)

Membership of IDDT is free, although we do welcome donations to help us to help you.

For more information, FREE leaflets or to join IDDT contact:

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Visit our web site: www.iddtinternational.org

Your news, views, concerns and questions are always welcome.

There are IDDT Groups in other countries. Details can be obtained from IDDT in the UK or by visiting our website www.iddtinternational.org

Patients have a right to an informed choice of treatment. A survey by the Healthcare Commission in 2005 revealed that 41% of people in the UK felt they were not involved as much as they wanted to be in deciding the best medicine for them. There is a choice of insulin treatment – Natural (animal) & Synthetic (human or analogue) insulins. IDDT recommends that you discuss with your doctor the choice of insulins and their risks and benefits.

"The Department of Health fully accepts that some people are better suited to animal insulin, and that animal insulin should continue to be made available."

***The Rt Hon Jane Kennedy MP, Minister of State for Health
24th July 2005***

"There is no overwhelming evidence to prefer one species of insulin over another and patients should not be changed from one species to another without reason."

***"Animal, Human and Analogue Insulins"
Position Statement, International Diabetes Federation, March 2005***

"Genetically modified insulin analogues may provide advantages in patients with problematic hypoglycaemia but they are expensive and there are no long-term safety data."

***"Animal, Human and Analogue Insulins"
Position Statement, International Diabetes Federation, March 2005***
