

30 YEARS OF SYNTHETIC INSULIN, ARE PEOPLE WITH DIABETES GETTING THE BEST DEAL?

A report of patients' concerns



The Insulin Dependent Diabetes Trust



The Insulin Dependent Diabetes Trust [IDDT] is a registered charity founded in 1994 to promote informed choice of insulin treatment and specifically to represent the estimated 30,000 people who need to use natural animal insulins because they experience serious adverse effects when using synthetic human and/or analogue insulins. This work continues as increasing numbers of people contact the Trust.

The Trust offers information and support to people with diabetes and their families through a Helpline, free information leaflets and a regular Newsletter.

The Trust is funded entirely by voluntary donations with a policy not to accept funding from the pharmaceutical industry.

IMPORTANT INFORMATION

Following Novo Nordisk's announcement of the discontinuation of their pork insulins, many people have been misinformed about the continued availability of pork insulin.

Pork and beef insulins continue to be manufactured in both vials and cartridges by the manufacturer [Wockhardt UK] and in the UK are available with an NHS prescription. [www.wockhardt.co.uk]

People in other countries who are denied access to the animal insulin they need, can import it from the UK for personal use.

FOREWORD

Genetically engineered so-called 'human' insulin was introduced in 1982.¹ Following persistent and aggressive marketing by the pharmaceutical industry, plus their unsubstantiated claims of superiority of 'human' insulin, by the mid to late 1980s 84% of people with insulin requiring diabetes in the UK had been transferred from natural pork or beef insulin to 'human' insulin. The vast majority of these patients were not given any choice and many were not even informed that their insulin was being changed. There were immediate reports of adverse reactions to the new insulin with the most common being hypoglycaemia without warning symptoms, a dangerous and frightening condition. Other serious adverse reactions were also reported by both people with diabetes and their families.

With a change of treatment in such a vast number of people, there could be no other group better able to judge the differences between the animal insulin they had been using and the new synthetic 'human' insulin. However, their reports were largely ignored by everyone, including the regulatory authorities, insulin manufacturers and diabetes associations across the world.

It was left to patients, their families and a small number of physicians to raise awareness of the serious adverse effects that 'human' insulin was having on some people and above all, they lobbied to try to ensure that natural animal insulins remained available as a treatment option, especially for those people unable to tolerate synthetic 'human' insulin.

By the end of 2007, the three major multi-national insulin manufacturers will have discontinued the supply of all their pork and beef insulins and they have even started to discontinue some of the original 'human' insulins, which are no longer in patent.

People with diabetes now face a different situation, the next generation of synthetic insulins - insulin analogues. These are not proven to be superior to 'human' or to animal insulins in terms of metabolic control, nor has their long-term safety been established, but more importantly, they have the potential for carcinogenic effects.

The Insulin Dependent Diabetes Trust was formed in direct response to the needs of people who experienced adverse reactions to 'human' insulin and now over 10 years later, it is witnessing history repeating itself with the marketing of insulin analogues.

This Report brings all the issues together in one concise and explicit document in order to draw the attention of everyone with an interest in the welfare of people with diabetes. The aim is not to recount history but look forward to developing ways of protecting the best interests of people with diabetes who need and deserve treatment that is based on evidence of benefit while at the same time, being cost effective.

Philip Corfman, former Director, Center for Population Research, National Institutes of Health, and Reviewing Medical Officer, Food and Drug Administration, USA

1: Use of terminology when referring to insulins

Genetically engineered, genetically modified and GM are used interchangeably throughout this document. The same applies to the names of insulin and their brand names.

30 YEARS OF SYNTHETIC INSULIN, BUT NOT A CELEBRATION

It is 30 years since the first clinical trial of synthetic insulin.

In this trial of six patients [ref 1] it was noted that 2 patients experienced more sudden hypoglycaemic events than with animal insulin, a finding that was later supported by the experience of many patients when ‘human’ insulin came to the market. Three decades on, we are witnessing the pharmaceutical industry globally discontinuing the supply of animal insulins and beginning to discontinue a number of ‘human’ insulins in favour of the latest generation of synthetic insulins – insulin analogues. This has led to a subsequent reduction in patient and physician choice and an increased cost of insulin treatment for what we now know to be no proven benefits.

Significant numbers of people with diabetes experienced adverse effects after the introduction of so-called ‘human’ insulin, the first genetically engineered drug to reach the market. In the trials patients withdrew because of these adverse effects [ref 2], however, the adverse experiences were largely ignored by doctors, by regulatory authorities, and by national and international diabetes associations who were apparently set up to protect the best interests of people with diabetes.

In reality the only interests that were being served were those of the pharmaceutical industry – synthetic ‘human’ insulin was significantly cheaper to produce but far more profitable for the pharmaceutical companies than pork and beef insulins.

The British National Formulary states: “If a patient believes that human insulin is responsible for loss of warning [of hypoglycaemia] it is reasonable to revert to animal insulin.”

In a recent paper, Professor Edwin Gale states [ref 3]: “No sensible and human physician or manufacturer would, however, attempt to deny the validity of patient experience”.

So is this 30 year anniversary one to celebrate for people with diabetes?

We think not. Health providers are faced with the increased costs of providing insulin treatment to the growing numbers of people with diabetes and we are receiving more and more calls to our helpline from worried patients and their carers who are all describing the same side effects – which surely cannot be a coincidence?

IDDT believes that it is time to question the power and influence of the pharmaceutical industry who have very successfully marketed synthetic insulins despite a lack of proven benefit and significantly increased costs.

From an industry perspective, the marketing of ‘human’ insulin was highly successful - the choice of the name ‘human’ insulin was possibly the best marketing strategy in history. It implies that in some way this genetically modified protein is derived from real human beings, not manufactured in a laboratory from yeast or e-coli. However, from a patient perspective, the marketing was misleading and devious, suggesting that animal insulins were being removed from the market and raising fears of shortages of animal pancreases. But above all the marketing made claims of superiority that have never been substantiated.

As the patent ran out on ‘human’ insulin, the pharmaceutical companies introduced new, in-patent insulin analogues at an even higher price. From the outset, their similarity to insulin-like growth factor [IGF-1] and their

carcinogenic potential were known and the evidence of benefit sparse, but despite this, they were successfully marketed and are now taking over as first line treatment.

We are now witnessing marketing techniques similar to those used for 'human' insulin. Insulin manufacturers are using the terms 'modern insulins' and 'designer insulins' which imply superiority - however, there is no evidence to suggest that they are superior nor does this description have any useful meaning. They are also being marketed as "convenient" because they can be given immediately before food, when in reality many people have done this with their predecessors: and they have marketed them as lowering after-meal blood glucose levels despite a lack of evidence from research that this improves overall blood glucose control.

Yes - the marketing of insulin analogues is 'history repeating itself' but there are several differences:

- The quality of research has improved.
- There are high quality reviews that provide evidence to inform treatment choices.
- There is greater awareness of the influence of the pharmaceutical industry.
- Patients are much less trusting and more aware of the need to be fully informed from *independent* research when making treatment decisions.

Nevertheless, the marketing of insulin analogues has resulted in people with diabetes and health professionals believing that the new insulins are superior. But this has not been proven to be the case and they do have risks. Their potential for carcinogenic effects and the growing evidence that concerns about these risks are justified should be investigated. Whatever the magnitude of these risks, people with diabetes should be made aware of them as they may wish to choose a safer insulin and so that can make a truly informed choice.

BACKGROUND

Insulin was discovered in 1921 and was extracted from beef pancreases. The first insulin was beef insulin but it was impure and caused injection site reactions. Highly purified pork insulin became available in the 1970s after which beef insulin also became highly purified.

In 1982, genetically engineered insulin, misleadingly named 'human' insulin, was the first genetically engineered drug to be marketed. Regulatory authority approval was given with indecent haste, only 5 months, with an apparent failure to recognise that drugs produced by biotechnology could have different patterns of toxicity. 'Human' insulin was given marketing authorisation:

- Without consideration of the method of manufacture and possible unexpected adverse reactions.
- With little attention paid to the quality of the post-marketing studies.
- Without any large, long-term studies to compare complication and mortality rates or long-term safety.

The assumptions

'Human' insulin was widely prescribed but only on *assumptions* of its superiority over animal insulins and not on *evidence* of its superiority. The assumptions were:

- [i] the insulin would be more effective
- [ii] no antibodies would be produced.

Research carried out subsequently showed that these assumptions were untrue.

The promise

The promise was that 'human' insulin would be cheaper and would result in accessible and affordable sources of insulin so that people in developing countries would no longer die for lack of affordable insulin. Again this turned

out to be a false claim as the cost of synthetic insulins has increased with each new development making it unaffordable for many people in developing countries and increasing the cost of diabetes treatment to individuals and health providers throughout the world.

The lack of informed choice

People with diabetes were not made aware of the above facts or their rights to a choice of insulin treatment. They were informed that ‘human’ insulin was better because it is identical to the insulin the body produces naturally but only the insulin molecule itself is identical. The reality proved to be different, even for people who did not have adverse reactions to it. ‘Human’ insulin proved to be more aggressive in its actions and had different duration times from animal insulins, hence the British National Formulary warns: *“Great care should be taken to specify whether a human or an analogue preparation is required.”*

The adverse reactions

During the 1980s in the UK over 80% of people with insulin-requiring diabetes were changed to ‘human’ insulin. For the majority of people the change was not made for clinical reasons or on evidence of benefit, but on *assumptions* of its superiority as a result of the marketing by industry.

In the late 1980s, Diabetes UK [formerly the British Diabetic Association] received almost 3,000 reports of adverse effects to human insulin. This matter was raised with the then Medicines Control Agency. Diabetes UK commissioned a report into these effects with the intention of publication in the British Medical Journal. The report was never made public. This was because the charity considered the report to be *“too alarmist”* but the author, Dr Natasha Posner, commented in 1999: *“Many correspondents reported that a diabetic condition which had been stable and well-controlled for many years and allowed a full and active life, suddenly changed and became problematic and life disrupting. . . . the letters examined constitute a source of data which amount to much more than anecdotes.”*

Initially the reported problems were loss of warning symptoms of hypoglycaemia resulting in sudden coma but also personality changes. In some cases these adverse reactions did not occur for several years after the initial use of ‘human’ insulin and a survey carried out by IDDT showed the following adverse reactions were common to many people:

- extreme lethargy
- mental confusion
- memory loss
- joint and muscle pains
- depression
- general feeling of being unwell.

The reports from patients and their family carers have largely been dismissed and people have not been believed by their doctors and health professionals despite a change to animal insulin resulting in the adverse reactions largely regressing. Many people have been refused their right to try animal insulin for the first time or to return to the animal insulin that had previously suited them. With little or no evidence of benefit of synthetic insulins but a long history of safety of animal insulins, people with diabetes find it difficult to understand why many doctors took, and still take, this stance.

As a result, it is not surprising that for many patients and their family carers, this resulted in a lack of trust in health professionals and there have been cases of a complete breakdown in the doctor/patient relationship.

Patient: *I found that GM insulin caused me to have hypoglycaemia and to feel very unwell most of the time. I did research into animal insulin and decided it must be worth trying but I met a lot of resistance from diabetic nurses and consultants. I insisted and they finally allowed it. After only a short time I felt better and haven't had a serious hypo since and that was over a year ago. I feel that there are many diabetics who may be suffering as I did because animal insulin is never offered and many are frightened to go against the system for fear of being seen as difficult by nurses and doctors. B.T. 2006*

Family carer: *My husband's health was deteriorating so we asked our GP if he could change from analogue insulins to pork insulin but he refused. When we asked the reason for the refusal, he became angry and said that we were doubting his judgement. Following an exchange of letters, we were removed from his practice. Another doctor changed him to pork insulin and there is little doubt that he is making progress, he has lost the swelling in his ankles and the pain has gone from his joints. He is certainly less tired and no longer feels weak and wobbly and although he still experiences some difficulty walking he is able to do it free of pain. T.P. 2007*

The introduction of insulin analogues

In 1996 the first rapid-acting insulin analogue, Humalog [lispro], was introduced. Insulin analogues are made by a further genetic modification of 'human' insulin so that it is in fact, no longer identical to the human insulin molecule produced by the body – one of the main selling points of the original 'human' insulin.

Although insulin analogues are still under intensive surveillance by the regulatory authority [MHRA] and amidst warnings of a cautious approach to their use due to their unknown long-term safety and carcinogenic potential, many patients have been transferred to them and they have become first line treatment for newly diagnosed patients.

Restricting the choice of insulins

By the end of 2007, the three multinational manufacturers will have discontinued all animal insulins and they have already started to discontinue some of the 'human' insulins. Novo Nordisk, the largest supplier of insulin, has already stated their intention to discontinue all 'human' insulins, now patent expired, to have an in patent insulin analogue-only portfolio. This will further deny patients and clinicians a range of insulin types to suit the varying needs of people with diabetes. Already large numbers of people are being 'forced' to change to insulin analogues for commercial, rather than clinical need.

Cost effectiveness

Insulin analogues are significantly more expensive for the NHS to purchase than either 'human' or animal insulins and the evidence of benefit for the majority of people is negligible.

In 2002, The National Institute of Health and Clinical Excellence (NICE) estimated that switching all potentially eligible people from 'human' insulin to the long-acting insulin analogue, Lantus, would cost an extra £16million per year and if a similar number of patients are also switched to rapid-acting insulin analogues, the estimated cost could be doubled to £32 million. These figures do not take into account the widespread transfer of people to insulin analogues simply because their older insulins have been discontinued or their clinicians have changed their insulin in the mistaken belief that insulin analogues are superior.

Standards of care

Targets for standards of care and treatment are not being met in many areas of the country [Healthcare Commission, 2007]. For instance:

- Everyone with diabetes must be screened for retinopathy by the end of 2007 – this will not be met.
- The care of children with diabetes is suboptimal.
- Education standards are not being met.
- People are being denied the numbers of glucose test strips they need.

The failure to meet these targets is because Primary Care Trusts [PCTs] do not have the resources. Yet these same PCTs are not considering the additional costs of analogue insulins and the savings that could be made to direct resources towards essential diabetes services.

Note: recently Professor Edwin Gale has questioned whether people with diabetes are getting the best deal when the choice is between treating 150-200 patients with long-acting analogues instead of 'human' insulin or employing a full time specialist nurse educator at the same cost. [ref 3]

CHOICE IS IMPORTANT TO PEOPLE WITH DIABETES

As a largely self-managed condition, being involved in treatment decisions is extremely important for people with diabetes. They are making constant daily decisions about diet, lifestyle, exercise and their insulin regime in relation to self-monitored blood glucose levels. Different insulins have different speeds and durations of action and it is important that each patient has the choice of insulin which is the one most suitable for their lifestyle whilst also providing the best possible control of blood glucose levels.

For people with diabetes, this choice is not based solely on blood glucose control but can be influenced by many factors, especially quality of life. For example, someone who drives for a living may choose an insulin and regime that reduce the risk of hypoglycaemia. An elderly person may prefer to use insulin that requires a simple regime of twice daily injections rather than be confused by 2 different insulins and 4 or more injections a day and for very different reasons, parents may prefer their young children to use a similar regime so that they do not have to inject and test at school.

***Patient's son:** My very elderly father's usual twice daily human insulin has been changed so that he now has two types of insulin and four injections a day. This is causing him great distress because he is confused by the two types of insulins and afraid that he may give the wrong dose at the wrong time. Does he have to be on this regime at his age? D.M 2006*

Choice becomes of vital importance for people who have adverse reactions to synthetic 'human' and analogue insulins. Without choice, this significant minority of people suffer adverse reactions which can affect their health, their lives and the lives of their families.

In July 2005, the Minister of Health, the RT Hon Jane Kennedy MP recognised the importance of the choice of animal insulin and said: *"The Department of Health fully accepts that some people are better suited to animal insulin and it should remain available."*

The importance of choice was later recognised by the Health Minister, Andy Burnham MP, and in answer to a Parliamentary Question [May 3rd 2006] he replied: “The NICE guidance on patient education has required all primary care trusts to implement NICE guidance on patient education by providing all people with diabetes with high quality, structured education which should include information on insulin use.”

If healthcare professionals are to implement this guidance and if patients are to be able to take an active and informed role in decision-making about management of their diabetes, then comprehensive and easily accessible NICE guidance on the clinical effectiveness of all insulins is essential.

AVAILABLE GUIDANCE ON THE USE OF ALL INSULINS

It could be expected that patients in the UK would look to NICE for guidance to help to inform their choices. However, at the time of this report, NICE guidelines offer little help and patients largely have to rely on the information provided by their doctors. Sadly, people with diabetes are realising that they are rarely offered a truly informed choice of insulins including their risks and benefits and in the absence of choice, newly diagnosed people often wrongly assume that there is no choice.

Worthy of note:

Recommendations of the Health Select Committee Report, April 5th 2005 “The Influence of the Pharmaceutical Industry”

- People are being prescribed too many drugs, before the full consequences of adverse side effects are known.
- Tighter controls on the promotion of new drugs should be introduced until more is known about their potential side effects.
- Post-marketing surveillance in the UK is inadequate. This has several causes: lack of investigation of a drug’s benefits and risks in real life situations and institutional indifference to the experience and reports of medicine users.

NICE Guidelines for Type 1 diabetes state that the type of insulin prescribed is that which, “*will allow people optimum well-being.*” However, this provides no guidance on the safety and efficacy of the various insulin species or their clinical and cost effectiveness.

NICE Guidelines for Type 2 diabetes state that, “*your doctor will talk to you about the different types of insulin that are available and when they should be taken so that you can agree on the one that will suit you best.*” Again this offers no guidance on the safety and efficacy of the various insulins or their clinical and cost effectiveness.

NICE Guidelines on the use of long-acting analogue insulin, Lantus [glargine] advise that it can be used as an option for people with Type 1 diabetes but not for those with Type 2 diabetes, except under special circumstances. This guidance was issued before the introduction of Levemir [determir] and therefore there is no guidance for the use of Levemir in either Type 1 or Type 2 patients.

Although classed as a long-acting insulin analogue, Levemir has a shorter duration of action than Lantus and the manufacturers class it as a once or twice daily insulin so it cannot be assumed that the recommendations for its use are the same as Lantus, a once daily insulin. Consequently it remains unclear whether Levemir is not recommended for patients with Type 2 diabetes as is the case with Lantus. This Guidance has not been updated despite the initial Guidance stating that:

[i] it will be updated in November 2005 which was confirmed by the Minister of Health [Hansard 24.11.2005]

[ii] further research is necessary and

[iii] Levemir has not been included.

NICE has not issued guidance on the use of rapid-acting insulin analogues.

THE EVIDENCE FOR CONCERN

The key points from the available evidence

Human insulins:

- Are not superior to animal insulin - Cochrane Review, 2002

Rapid-acting insulin analogues

- Have only minor benefits for the majority of patients - Cochrane Review, 2004.
- They are not superior to human insulin for the treatment of Type 2 - [IQWiG], July 2006.
- They are not superior to human insulin for the treatment of adults with Type 1 diabetes and the benefits for children and adolescents are unclear. IQWiG, June 2007.

Long-acting insulin analogues

- Can be used as an option for people with Type 1 diabetes but not for those with Type 2 diabetes - NICE guidance, 2002.
- They are not superior to NPH human insulin for Type 1 and Type 2 diabetes - Canadian Expert Drug Advisory Committee, June and Sept 2005.
- They have only minor benefit, if at all, for the treatment of Type 2 diabetes - Cochrane Review, April 2007.

Safety and efficacy

- Animal insulins have a long history of safety and efficacy supported by epidemiological evidence. Large-scale, long-term trials to compare 'human' and animal insulins have never been carried out. A Cochrane Review, 2002 [ref 4] concluded that although no differences could be found between 'human' and animal insulins, the research was 'methodologically poor' and there is no research comparing mortality and complication rates or quality of life.
- A Cochrane Review, 2004 [ref 5] of short-acting insulin analogues again concluded that the research was largely 'methodologically poor' and that short-acting insulin analogues have only minor benefit for the majority of patients.
- The Drugs and Therapeutics Bulletin [2004] reported on the use of insulin analogues as first line treatment: *"This approach is not justified given what still needs to be established about the analogues, long-term benefits*

and safety. Also there is no convincing evidence to justify switching patients from existing conventional therapy to analogues if they have appropriate glycaemic control without troublesome hypoglycaemia.”

- The International Diabetes Federation Position Statement, 2005 [Ref 6] states: *‘Newer insulins (analogues) 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.’*
- The Canadian Expert Drug Advisory Committee [CEDAC] [ref 7] has recommended that Lantus is not to be listed for patients with Type 1 or Type 2 diabetes because studies did not find statistically or clinically significant differences between Lantus and NPH in serious morbidity, glycaemic control and the incidence of severe hypoglycaemia.
- The German Institute for Quality and Cost Effectiveness in the Health Care Sector [IQWiG] review on the use of short-acting analogues in Type 2 diabetes concluded that with certain exceptions, the treatment of patients with Type 2 diabetes is equally effective with ‘human’ insulin as with a short-acting insulin analogue [ref 8]. In July 2006, the German Joint Government Committee, the G-BA, took the decision that the cost of short-acting insulin analogues for Type 2 diabetes would no longer be borne by the compulsory health insurance (GKV), unless they were no more expensive than human insulin. The manufacturers have subsequently reduced the cost of insulin analogues.
- A large observational study [ref 9] of 7,266 children with Type 1 diabetes for the years 2000-2005 investigated the use of insulin in three age groups of children. The results showed that when taking into account confounding factors such as duration of diabetes, the likelihood of elevated overall blood glucose levels [HbA1cs higher than 7.5%] was greater in children using long-acting analogues and the likelihood of severe hypoglycaemic episodes was significantly higher. No differences were found with the use of short-acting analogues.
- A Cochrane Review [April 2007] [ref 10] comparing long-acting insulin analogues and NPH [‘human’ isophane insulin] for Type 2 diabetes concluded that “if at all” there was only a minor benefit of treatment with long-acting insulin analogues for patients with Type 2 and there should be a cautious approach to their use until long-term safety and efficacy information is available. There was no difference in metabolic control, hypoglycaemic events and adverse events and no conclusive information exists on late complications, on possible differences in the number of fatalities or on quality of life.
- In June 2007 IQWiG published a review comparing rapid-acting insulin analogues with short-acting ‘human’ insulin for the treatment of Type 1 diabetes [ref 11]. It concluded that there is no evidence that rapid-acting insulin analogues are superior to ‘human’ insulin in the treatment of adults with Type 1 diabetes. Their benefit in children and adolescents and in insulin pump therapy is unclear due to lack of data as no long-term studies have been carried out. Claims of an improved quality of life and greater patient satisfaction could not be evaluated as evidence of an additional benefit because the comparisons were not based on a fair comparison.

THE CARCINOGENIC POTENTIAL OF INSULIN ANALOGUES

Insulin analogues are the most recent biotechnology products used in the treatment of diabetes and are designed to have absorption profiles that more nearly mimic the action of normal insulin production by the body than synthetic 'human' insulin. However, analogues differ in their biological effects with unknown consequences, such as their effects on:

- Mitogenicity [promotion of division and proliferation of any cell, including tumour cells]
- Apoptosis [see glossary].
- Glucose and lipid metabolism.
- Thrombocyte function.
- Protein degradation.

As already shown, extensive investigations of the therapeutic effects of insulin analogues have shown them to have negligible clinical benefit for patients but the biological effects have not been systematically studied. It is of special concern that their carcinogenic potential remains to be determined on human carcinoma tissue as recommended by the European Agency for the Evaluation of Medical Products [EMA] in their document, Points to consider CPMP/SWP/372/01.

Trials with Novo Nordisk's first insulin analogue were halted in 1992 due to the development of breast cancer in rats - so the carcinogenic potential of insulin analogues has been known throughout their development. In 1998 Professor Stephanie Amiel advised caution [ref 12]: *"there remains a risk of unexpected problems with any new agent and we should remember that the structure of the new insulin is a little closer to IGF than the old insulin"*.

Lantus was found to be highly mitogenic on in-vitro testing with human osteosarcoma cells before the European Medicines Evaluation Agency [EMA] had been asked for approval of the compound [ref 13]. On February 17, 2000 this unpublished information was reported to the EMA in an oral explanation by Aventis. The EMA accepted the company's claim that the finding was irrelevant, and subsequently approved the drug. A paper in June 2000 [ref 14] publicly disclosed the mitogenicity of Lantus on osteosarcoma cells and in June 2001, Aventis publicly confirmed this information [ref 15].

The European Agency for the Evaluation of Medical Products Points to consider document, CPMP/SWP/372/01 issued in London, 15 November 2001, recommended investigations into the biological effects of insulin analogues and in particular their effects on neoplastic tissues. However, this research has not been carried out leaving an uncertainty that will remain until the carcinogenic potential of insulin analogues has been determined on human carcinoma tissue.

A Danish study [ref 16] involving patients with Type 1 diabetes acknowledges that diabetic patients are at higher risk of cancer than the non-diabetic population. It also states that it is still unknown whether lifelong treatment with the analogue, NovoRapid [aspart], will lead to an elevated IGF-1-like bioactivity and subsequent mitogenic potency, especially in a subgroup of patients who have high levels of insulin antibodies.

Recent research [ref 17] has shown that all insulin analogues tested were more mitogenic than insulin - they caused greater cell proliferation which can lead to benign or non-benign tumours. It also showed that this mitogenic effect was greater in cells from patients with a high IGF-1 receptor system expression putting such patients at greater risk than those with a low IGF-1 receptor system expression.

Supplementing this work, research at Tel Aviv University [ref 18] tested whether the two long-acting analogues, Lantus and Levemir, show IGF-1-like activities including enhanced mitogenic and antiapoptotic effects. Colon, prostate and breast cancer-derived cell lines were used in tests with IGF-1, regular insulin, Lantus and Levemir. Both Lantus and Levemir showed potent mitogenic and antiapoptotic activities which were significantly greater than those of 'human' insulin and seemed to resemble IGF-1 action.

The question of carcinogenicity of insulin and insulin derivatives is of growing relevance, because it is increasingly recognised that insulin is a growth promoting hormone, and is associated with colorectal cancer [ref 19]. Furthermore, it is becoming increasingly clear that there exists a genetic predisposition for carcinoma development, which is likely to be linked to the insulin/insulin-like growth factor system. People with such a genetic background may be particularly harmed by compounds like insulin analogues, the carcinogenic properties of which are undefined.

RECOMMENDATIONS OF THE REPORT

Protection of the present and future health and wellbeing of people with insulin-requiring diabetes is paramount and must be protected therefore:

- 1. People with diabetes must receive a fully informed choice of insulin treatment by their clinicians including risks and benefits of all insulins before deciding on their treatment.**
- 2. Greater transparency and identification of gaps in research is essential to ensure that insulin treatment is safe, effective and evidence based.**
- 3. Studies of 'human', analogue and animal insulins should be carried out to compare the outcomes that are important to patients, such as mortality rates, complication rates and quality of life.**
- 4. Insulin treatment must be based on clinical need and patient choice and not based on the commercial decisions of pharmaceutical companies.**
- 5. The long-term safety and efficacy of insulin analogues must be established because they have the potential for carcinogenic effects and certain categories of people may be more susceptible to these risks, therefore their biological effects must be systematically studied.**
- 6. There should be no further discontinuations of insulins unless or until such time that the safety of all synthetic insulins has been established for everyone requiring insulin treatment.**
- 7. As there are no comprehensive guidelines for insulin use in the UK and if patients' safety is to be protected, it is essential that a comprehensive assessment of all insulins is conducted and the National Institute for Health and Clinical Excellence [NICE] is best placed to carry this out.**
- 8. Insulin analogues are significantly more expensive than either 'human' or animal insulins for little or no proven benefits in the majority of people, therefore their cost effectiveness must be investigated to ensure that valuable NHS resources are not being wasted.**

REFERENCES

- Ref 1** The biological effect of purely synthetic human insulin in patients with diabetes mellitus. *Schweiz Med Wochenschr* 1979;109:743-747 Teuscher A
- Ref 2** Biosynthetic Human Insulin in the Treatment of Diabetes. A Double-blind crossover Trial in Established Diabetic Patients. *The Lancet* (1982) 8294:354-357. Clark AJL, Adeniyi-Jones RO, Knight G, et al.
- Ref 3** Nice insulins, pity about the evidence. *Diabetologia* (2007) 50:1783-1790. Holleman F, Gale EAM.
- Ref 4** 'Human' insulin versus animal insulin in people with diabetes mellitus. *Cochrane Database Syst Rev* 2002; 3: CD003816.
- Ref 5** Short acting insulin analogues versus regular human insulin in patients with diabetes mellitus. *Cochrane Database Syst Rev* 2004; 4: CD003287. Siebenhofer A, Plank J, Berghold A, et al.
- Ref 6** International Diabetes Association website: www.idf.org
- Ref 7** Common Drug Review, CEDAC Meeting - June and September 2005
- Ref 8** The G-BA website: <http://www.c-ba.de> The text of the recommendation will shortly be published on http://www.g-ba.de/cms/front_content.php?idcat=56.
- Ref 9** *Eur J Pediatr* April 2007, DOI 10.1007/s00431-007-446-7
- Ref 10** Long-acting insulin analogues versus NPH insulin (human isophane insulin) for type 2 diabetes mellitus. *Cochrane Database of Systematic Reviews* 2007 Issue 2.CD005613.pub3 K Horvath, K Jeitler, A Berghold, SH Ebrahim, TW Gratzler, J Plank, T Kaiser, TR Pieber, A Siebenhofer.
- Ref 11** Review of rapid-acting insulin analogues versus human insulin in type 1 diabetes. The Institute for Quality and Cost Effectiveness in the Health Care Sector [IQWiG], June 2007
- Ref 12** Learning to Use New Drug - the Fast-acting Insulin Analogues. *Diabetic Medicine*, 1998;15:537-538. S Amiel
- Ref 13** EMEA. Scientific Discussion Lantus 2000. CPMP/615/00.
- Ref 14** Correlations of Receptor Binding and Metabolic and Mitogenic Potencies of Insulin Analogs Designed for Clinical Use. *Diabetes* 2000;49:999-1005. P Kurtzhals, L Schäffer, A Sorensen, C Kristensen, I Jonassen, C Schmid, T Trüb.
- Ref 15** In Vitro Pharmacology Studies with Insulin Glargine and Human Insulin: IGF-1 Receptor Binding and Thymidine Incorporation. Abstract. *Diabetes* 2001;50/Suppl.1: A 429, J Sandow, G Seipke.
- Ref 16** Impact of insulin antibodies on insulin aspart pharmacokinetics and pharmacodynamics after 12-week treatment with multi daily injections of biphasic insulin aspart 30 in patients with type 1 diabetes. *European Journal of Endocrinology* [2005]; 153: 907-913. J W Chen, J Frystyk, J Lauritzen, J S Christiansen.
- Ref 17** Enhanced Mitogenic Potency of Insulin Analogs in Human Fibroblasts and Smooth Muscle Cells is mediated by IGF-I Receptor Signaling *Diabetes, ADA Diabetes Care*, June 2006 Vol 55 Suppl 1 463-P
K Eckardt, C May, M Koenen, J Eckel
- Ref 18** Long-acting insulin analogues have mitogenic and antiapoptotic activities. US Endocrine Society Meeting, Toronto, June 2007. D Weinstein, Z Laron, H Werner.
- Ref 19** Insulin therapy and colorectal cancer risk among type 2 diabetes mellitus patients. *Gastroenterology* 2004;127:1044-1050. Y X Yang, S Hennessy, J D Lewis.

GLOSSARY OF TERMS

Apoptosis - normal self-induced termination of a cell's life, to become replaced by a new one.

Carcinogenic - a substance that has cancer forming properties.

Carcinoma - a type of cancer.

IGF-1 or insulin-like growth factor - a hormone which has a broad range of effects including promotion of cell survival, proliferation of cells, inhibition of apoptosis, stimulation of metabolism.

In-vitro testing - literally means 'in glass' and is a research term for observations made outside the body e.g. the action of drugs on bacteria, in-vitro fertilisation means the fertilisation of the egg outside the body.

In-vivo testing - studying something in living creatures [human beings and animals].

Mitogenicity - promotion of the division and proliferation of any cell, including malignant and non-malignant tumour cells.

Neoplasm – new cells involved in the formation of benign or non-benign tumours.

NPH - Neutral Protamine Hagedorn insulin also referred to as isophane insulin and is the most commonly used long-acting insulin in the UK.

Subcutaneous injection - injection into the tissue beneath the skin.

Thrombocytes - blood platelets involved in coagulation to stop bleeding.

Toxicity - the poisonous effects of a substance.

RECOMMENDATIONS OF THE REPORT

Protection of the present and future health and wellbeing of people with insulin-requiring diabetes is paramount and must be protected therefore:

1. People with diabetes must receive a fully informed choice of insulin treatment by their clinicians including risks and benefits of all insulins before deciding on their treatment.
2. Greater transparency and identification of gaps in research is essential to ensure that insulin treatment is safe, effective and evidence based.
3. Studies of 'human', analogue and animal insulins should be carried out to compare the outcomes that are important to patients, such as mortality rates, complication rates and quality of life.
4. Insulin treatment must be based on clinical need and patient choice and not based on the commercial decisions of pharmaceutical companies.
5. The long-term safety and efficacy of insulin analogues must be established because they have the potential for carcinogenic effects and certain categories of people may be more susceptible to these risks, therefore their biological effects must be systematically studied.
6. There should be no further discontinuations of insulins unless or until such time that the safety of *all* synthetic insulins has been established for everyone requiring insulin treatment.
7. As there are no comprehensive guidelines for insulin use in the UK and if patients' safety is to be protected, it is essential that a comprehensive assessment of *all* insulins is conducted and the National Institute for Health and Clinical Excellence [NICE] is best placed to carry this out.
8. Insulin analogues are significantly more expensive than either 'human' or animal insulins for little or no proven benefits in the majority of people, therefore their cost effectiveness must be investigated to ensure that valuable NHS resources are not being wasted.



Insulin Dependent Diabetes Trust

PO Box 294, Northampton NN1 4XS

Telephone: 01604 622837 Email: enquiries@iddtinternational.org

Website: www.iddtinternational.org

Registered Charity No: 1058284
Company Registration No: 3148360