



# Insulin Dependent Diabetes Trust

## THE 'DEAD IN BED' SYNDROME

### **A review of the "Dead-in-Bed" Syndrome comparing "human" (synthetic) insulin with natural (animal) insulin**

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The "Dead-in-Bed" syndrome is disturbing for all of us, and while it seems to have been confined to history, it should not, and cannot be forgotten. Not only because lessons can be learned but above all, there are some families for whom this is not just history. They will never forget and can never forget because their son, their daughter, their husband or their wife, previously healthy, died unexpectedly in bed at night.

Understandably, those of us living with diabetes prefer not to think about this, but the families of those who died never received an explanation for the death of their loved one, making a very sad and difficult situation even more difficult.

It is for these families that we are publishing a Review of the "Dead-in-Bed" Syndrome by Professor Arthur Teuscher. Professor Teuscher has worked tirelessly for many years to seek recognition of the adverse effects that some people experience with synthetic human insulin and to help to maintain supplies of animal insulin for people who need it and to maintain a choice of treatment.

It is with the support of Professor Matthias Egger and Professor Phil Corfman, that IDDT is publishing this review.

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# A review of the 'Dead-in-Bed' Syndrome comparing 'human' (synthetic) insulin with natural (animal) insulin

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## **Introduction**

The "dead-in-bed" syndrome occurs almost exclusively in type 1 diabetics under the age of 40. They go to bed in apparently good health and are found the following morning dead either in or near their bed. The direct cause of death has been attributed to dysrhythmia, a variation of the normal regular heartbeat, but it also may be due to unperceived nocturnal hypoglycemia<sup>1</sup> caused by insulin.

As described below, there appears to have been an increase in the dead-in-bed syndrome since so-called "human" insulin came into wide use. The first case, that of "J.B.", who was my patient, prompted my strong interest in this issue.

## **A Case of the "Dead-in-Bed" Syndrome: J.B. a student**

In the words of his parents: "From October 1990 on, our 24 year old son, J.B., lived alone as a student. His type 1 diabetes was diagnosed in 1975 and he was treated with 'human' insulin starting in 1982. From November 1987 to his death in 1994 he had about 20 severe hypoglycemic events, sometimes with convulsions and loss of consciousness, usually at night between 2 and 3:30 a.m. We or the emergency doctor often had to inject him with glucagon. He was hospitalized several times".

In 1994, he did not wake up from one of these hypoglycemic attacks. His parents tried to call him several times and finally called the police. The officers found him in a sleeping position with no signs of a break-in or suicide, so there was no post-mortem. After his death, J.B.'s parents allowed his electronic diabetes diary to be analyzed. The insulin doses as well as the blood sugar levels had been normal the day of his death.

Two years later, the couple was alerted to the existence of other cases of the dead-in-bed syndrome in Switzerland in an article published in Subkutan, a magazine published by the German Diabetic Federation.<sup>2</sup> They saw parallels between the case of their son and other cases described in the article and they wanted the doctors who had treated him to make it clear if "human" insulin could possibly be the cause of his sudden death.

In 1994 the family doctor's questions were answered by Novo Nordisk by referring to the thesis of Horst-Lorenz Fehm, a neurologist at the University of Lübeck, which

postulated that although pork and 'human' insulin have a different ability to pass the blood-brain barrier, there is no indication at present that the cognitive functions of the brain during low blood sugar differ according to the use of various insulin species".

I take a statement such as this as evidence that industry resists considering that "human" insulin might at times be dangerous for some diabetics, even though the "Dead-in-Bed Syndrome" had been reported in as early as 1989, as noted below.

## **Reports of the "Dead-in-Bed" Syndrome**

Dr. Patrick Toseland, a physician and pathologist at Guy's Hospital in London, was also a coroner for Greater London and Southern United Kingdom. In 1989, he reported that from 1985 to 1989, there was a rise in unexpected deaths among younger type 1 diabetics (as displayed in table 1)

**Table 1. Sudden or unexplained death in younger type 1 diabetics** [Toseland, pers. commun., September 17, 1989]

Year	Total deaths investigated by coroner	Sudden or unexplained deaths of type 1 diabetics
1985	856	2
1986	762	4
1987	803	3
1988	774	9
1989	612 <sup>1</sup>	22 <sup>1</sup>

<sup>1</sup> 10 months only

Out of 22 cases in 1989, 9 were under 35 years old and 14 definitely had used "human" insulin. Three had used "human" and pork insulin, and it could not be determined which type of insulin they had used before their deaths. In 5 cases, the type of insulin was unknown. In all cases other causes of death (including insulin overdoses) were ruled out. The patients had simply been found dead in bed. In two cases, when blood sugar could be measured within the critical time of half-an-hour after death, a hypoglycemic value was found. Later in the year The Economist argued that, even though the reasons for the sudden increase in the number of hypoglycemic deaths were not known, "a case can be made for withdrawing the drug ["human" insulin] from the mass market where alternatives are available.

**Table 2: List of patients from Dr. Patrick Toseland, physician and forensic pathologist. Guy's Hospital London (Legacy 1989)**

The patients all died between February 1988 and August 1989

Age at the moment of death	Insulin	Circumstances of the death	Profession
17	Actrapid Monotard HM	Found dead in bed at 9 p.m. The evening before he had a normal behaviour	pupil
22	Neusulin and Neuphane	Not reported	Graduated mathematician
27	Monotard, HM	Not reported	Not reported
11	Initard HM, (Mixed insulin) Nordisk	Found unconscious at 7 a.m.	pupil
27	Not reported	Found dead in bed in his apartment. Time of death: probably 2 days previously	unemployed
53	Switched three months earlier to Humulin	Died in his hotel room. Showed normal behaviour the evening before	Professor for African Epidemiology
27	Initard HM, (Mixed insulin) Nordisk	Found dead at home by her husband at 8 p.m. Was pregnant (12th week). Showed normal behaviour 10 hours previously	Housewife
50	Lente Insulatard HM	Wife out of town. Was preparing dinner. Sat on an armchair with a glass of gin. Found two days later	Gynaecologist
41	Not reported	Found dead in bed. No noises during the night. Dead in "status epilepticus"	Tire inspector
18	Switched from beef insulin to Novopen, HM and Ultratard HM.	Not reported	Not reported
20	Not reported	Found dead at 12.30 a.m. in the bathroom. Two hours previously had shown normal behaviour but was pale	Not reported
30	Novopen HM, Insulatard, HM	Found dead in bed. Bed undisturbed	Assistant physician
18	Actrapid, HM Insulatard, HM	Found dead in bed at 1 a.m. Bed undisturbed. Showed normal behaviour the evening before.	Pupil
56	Not reported	Found dead in bed at 10 p.m. Was seen to be normal 30 hours before	Teacher
29	Actrapid, HM Ultratard, HM	Found dead on the floor. Had used insulin inhalator. A half-full bottle of Whisky was at the floor, no signs of suicide	Geologist
35	Mixtard, HM	On Friday she was fine. Husband left her Saturday morning at 6 a.m. and returned at 7.30 p.m. He found her dead in bed. The bedside table was overturned, but everything else was in order	Directress

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Age at the moment of death	Insulin	Circumstances of the death	Profession
26	Mixtard 30, HM	Found dead in bed with a head wound apparently caused by the bedside table. The room was a mess. Dextrazol pills scattered all over on the floor; one was in her hand	Public Relations Specialist, Radio
38	Mixtard, HM	Found dead at home. An insulin syringe was near the body. Drug screening was negative	Unemployed
39	Not reported	Found dead in bed at 8 a.m. His parents saw him the evening before when he showed normal behaviour	Electronics technician
27	Actrapid, HM and Monotard, HM	Found dead at 8 a.m., had showed normal behaviour the evening before	Bank Employee
25	Novopen, HM and Ultratard, HM	Found dead on an armchair in the apartment	Manager of Market Stands
25	Just switched to Humulin	Found dead in his house	Not reported
30	Velosulin, HM and Insulatard, HM	Found dead in bed; had showed normal behaviour the evening before	Medical secretary
22	Novopen, HM and Ultratard, HM	Found dead in bed on Easter Sunday. The evening before he acted normally. Undisturbed bed. He bit his lips. His face was down on the bed	Student at the Glasgow University
32	Not reported	Found dead in bed at 8 a.m. His fiancée who slept in the same bed, didn't detect anything abnormal during the night.	Unemployed
29	Switched to 'human' insulin six months before she died	Found dead in bed. Hadn't been seen for two days. Undisturbed bed. Had foam around her mouth	Clerk in Church
26	Actrapid, HM and Insulatard, HM	Left girlfriend at 5.30 p.m when he appeared to be normal. Found by his mother in a weird condition – he "acted like as a zombie". Died 2 days later in a mental hospital	
43	Actraphane, HM since 1985	Not reported	Not reported
36	Humulin( since 1986	Collapsed and was found unconscious at home	Not reported
25	Mixtard, HM	Found dead face down on his bed	Not reported

**Table 3: Further investigations of the “Dead-in-Bed” Syndrome**

Year	Countries	Authors	Possible cause of “Dead-in-Bed” Syndrome
1987	USA	DCCT	The study showed an increase in severe hypoglycaemia episodes that was three times higher in the intense medicated group than in the traditional medicated group.
1991	CH	Egger et al. <sup>4</sup>	The authors demonstrated that during the enforced change from animal insulin to “human” insulin the <b>hypoglycemia</b> episodes were three times higher with “human” insulin.
1991	GB	Tattersall et al. <sup>5</sup>	In 22 death cases the diabetics had gone to bed in good health, in none were anatomical lesions found, and their diabetes had been uncomplicated and well-controlled in most cases. <b>Treatment with “human” insulin</b> was common to all.
1992	S	Nyström et al. <sup>6</sup>	Between 1983 and 1987 they found 18 fatalities that could be related to diabetes. Among the 10 fatalities with type 1 diabetes, only in one case hypoglycemia could be confirmed. In six other cases <b>hypoglycemia</b> could not be excluded as a cause of the death.
1993	DK	Borch Johnson (Novo Nordisk) and Helweg-Larsen <sup>7</sup>	The authors identified 226 cases of younger insulin-treated diabetics under age 50 who died between 1982 and 1988, a period during which the <b>market share of “human” insulin increased from 0.2 to 70%</b> . The authors concluded that there was <b>no connection between the introduction of “human” insulin and increasing mortality in younger insulin-dependent diabetics</b> . The Danish study suffers from an obvious conflict of interest because one of the diabetologists involved was so closely associated with Novo Nordisk.
1994	USA	DCCT	Here is an extract from the DCCT Follow-up of the American Diabetes Association, Boston, Massachusetts which reproduces the options of the Insulin-Management as follows: Diabetologist: <i>“With Ultralente “human” insulin the blood sugar values vary more often during the night. What do you recommend?”</i> Dr. D.M. Nathan, Chairman of the DCCT Research Group: <i>“I prescribe the animal insulin NPH.”</i> Several Diabetologists: <i>“We absolutely have to maintain animal insulin.”</i> <b>Dr. Nathan: “I would be very disappointed, if animal insulin would disappear from the market. I prefer animal insulin (Porcine or Bovine) during the night, because it allows a better control and less hypoglycemia episodes.”</b>
1995	N	Søvik and Thordarson <sup>8</sup>	They observed four cases of unexpected deaths in young type 1 diabetic patients. All patients were found dead in an undisturbed bed, after having been in apparently good health the evening before and had been on “human” insulin. This prompted the investigators to perform an observational study on “human” insulin hypoglycemia deaths during the period of enforced transfer from highly purified animal to ‘human’ insulin. They studied 240 death cases in the period from 1981 to 1990. Sixteen of these cases fulfilled the criteria of the dead-in-bed syndrome. Twelve of the patients were reported as having had frequent episodes of hypoglycemia, with nocturnal episodes in 10 cases.
1999	N	Søvik and Thordarson <sup>9</sup>	The conclusion by Søvik and Thordarson 4 years later, 1999, was that: <b>“The causes are by definition unknown, but a plausible theory is a death in hypoglycemia, since a history of nocturnal hypoglycemia is noted in most cases”</b> .

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Year	Countries	Authors	Possible cause of "Dead-in-Bed" Syndrome
1999	GB	Heller <sup>10</sup>	He established that many patients could no longer recognise the warning symptoms and only with many daily and nightly measurements, the hypoglycemia episodes could be prevented. <b>The dead-in-bed syndrome can be a consequence of nocturnal hypoglycemia.</b>
1999	GB	Weston et al. <sup>11</sup>	The assumption of the authors: That premature neuropathy leads to an over activity of the sympathetic system which during a nocturnal hypoglycemia may be associated with an increase of the electrocardiograph Q-T interval, and Q-T dispersion.
2002	GB	Heller <sup>12</sup>	The author found among children a significant change in QTc during their nocturnal hypoglycemia he found the same among adults. He showed that a pre-treatment with beta-blocking agents prevents abnormal cardiac repolarisation during experimental hypoglycemia.
2004	N	Ramsli et al. <sup>13</sup>	117 cases of death could not be properly identified. Four patients died of the dead-in-bed syndrome. They were between 21 and 36 years old. Three of these patients previously suffered from heavy hypoglycemia. A relation with nocturnal hypoglycemia remains hypothetical.
2005	S	Dalquist et al. <sup>14</sup>	They investigated all sudden death cases at bedtime to next morning from 1977 to 2000 and found that at least 17 patients with type 1 diabetes died of the dead-in-bed syndrome, but they didn't identify the cause of the syndrome.
2008	CDN	Koltin <sup>15</sup>	He stated that the dead-in-bed syndrome accounts for 5-6% of mortality cases in patients with type 1 diabetes. The causes for the dead-in-bed syndrome must be found in the hypoglycemia or in cardiac autonomic dysfunction.
2008	F	Rothenbuhler et al. <sup>16</sup>	The authors studied the QT-Intervals in relation with hypoglycemia among adolescents. They found out that the QTc was very high among all adolescents during a hypoglycemia episode.
2008	AUS	Tu et al. <sup>17</sup>	The reasons for the dead cases among young type 1 diabetic patients were attributed to acute complications, unnatural causes and sudden death. Among the sudden death cases, ten patients have been found dead in their bed (dead-in-bed syndrome).
2009	GB	Gill et al. <sup>18</sup>	During the nocturnal hypoglycemia the authors established that the QT-Intervals were longer and that in eight episodes cardiac rate and rhythm disturbances were identified. The dead-in-bed syndrome could therefore have, according to the authors, an arrhythmic background.
2009	GB	Woodward et al. <sup>19</sup>	The authors assumed that nocturnal hypoglycemia is a risk factor for dead-in-bed syndrome. In conclusion the authors note that the blood sugar value before going to bed is a significant factor for nocturnal hypoglycemia.
2009	USA	Tannenberg et al. <sup>20</sup>	For the authors the dead-in-bed syndrome accounts for approximately 6% of the mortality in patients with type 1 diabetes under age of forty. The authors analyzed the data of an insulin pump and the continuous glucose monitoring system (CGMS) in a 23 year old man with type 1 diabetes who was found dead the next morning in his bed. The data showed a blood sugar value of 1.6 mmol/l around the time of death. According to the authors, this value is definitely evidence that the cause of the dead-in-bed syndrome is nocturnal hypoglycemia.
2010	AUS	Tu et al. <sup>21</sup>	The authors assumed that the reason for the dead-in-bed syndrome was what they termed to be "terminal malignant arrhythmia". This disorder may be caused by hypoglycemia, by a prehistory of cardiac illness or by genetic influence.

Year	Countries	Authors	Possible cause of "Dead-in-Bed" Syndrome
2010	AUS	Tu et al. <sup>22</sup>	Autopsy reports from dead-in-bed syndrome cases between 1994 and 2006 have been investigated to find changes in the myocardial tissues. Genetic analysis also has been made. 22 dead-in-bed syndrome cases were identified but there were no differences between them and the control group. Although their results were not conclusive, the authors are hoping that as soon as the cause and the trigger of the dead-in-bed syndrome are determined, therapeutic measures can be used to protect type 1 diabetic patients with a higher risk.
2010	USA	JDRFCGMSG <sup>23</sup>	The authors concluded that among type 1 diabetic patients nocturnal hypoglycemia occur very often. Low HbA1c-values in the evening facilitate a higher the risk of a nocturnal hypoglycemia.
2010	USA	Buckingham et al. <sup>24</sup>	The aim to prevent hypoglycemia worked as follows: if the glucose value went below a certain parameter value the insulin pump suspension was deactivated. With three algorithms the hypoglycemia could be prevented in 6 of 10 nights. With two algorithms the hypoglycemia could be prevented in 12 of 16 nights.

JDRFCGMSG = Juvenile Diabetes Research Foundation Continuous Glucose Monitoring Study Group

### ***Comments and Recommendations***

As the dead-in-bed syndrome is a result of night-time hypoglycemia, patients who live and sleep alone should be brought into a social network. Furthermore, in my experience previous episodes of "human" insulin hypoglycemia unawareness are likely to predict the occurrence of this life-threatening syndrome. I believe that the life of many young diabetics using "human" insulin could have been saved if the problems had been recognized earlier. Among diabetics who do not recognize hypoglycemia when they are affected by it, I strongly recommend that animal insulin be tried. In many cases the classic warning symptoms such as sweating, tremor and hunger will return if animal insulin is used. I strongly believe that it is the responsibility of physicians and diabetic organizations to inform patients and thereby enable them to make informed choices about which insulin to use.

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DCCT = Diabetes Control and Complications Trial Study

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