Review

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Murder by insulin: suspected, purported and proven – a review

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Murder by insulin – whether attempted, suspected or proven – is rare. Only 66 cases worldwide could be found for this review. A conviction was secured in 31 cases and additional weapon was employed in 11. Differentiation of attempted homicide from Munchausen syndrome by proxy in the young and from 'mercy killing' in the elderly was not attempted. Most perpetrators were close relatives and most victims were alive when discovered and responded to treatment. Hypoglycaemia is the first clue to homicidal insulin use in living subjects and requires the demonstration of a plasma insulin concentration of generally more than 1000 pmol/L and undetectable plasma C-peptide concentration to establish the diagnosis. Serum glucose measurements are valueless in victims found dead. The presence near the body of insulin vials, syringes or needles, loose talk by the suspected perpetrator or their ready access to insulin may be the only clue. The demonstration of insulin in tissue around an injection site by immunohistopathology or by measuring it in an extract clinches the diagnosis. Immunoassays suitable for clinical use to detect and measure insulin and C-peptide are subject to random errors and cannot be relied upon unless special precautions including separation by gel filtration or HPLC are undertaken prior to analysis. They do not detect or measure accurately a new generation of synthetic insulin analogues. Mass spectrometry will be required to do this and to validate clinical immunoassays, upon which convictions have always had to rely in the past.

Keywords: insulin; murder; homicide; C-peptide; immunoassay

Introduction

Insulin is a rare cause of death, which it brings about by producing hypoglycaemia. Hypoglycaemia when sufficiently severe (blood glucose concentration below about 1.5 mmol/L) and not corrected by restoring the blood glucose concentration to 'normal' (in the range 3.5–10 mmol/L) within a few hours can lead to permanent brain damage and occasionally death. It is also suspected, though unproven, that hypoglycaemia can also cause rapid death in people with a pre-existing heart disorder by stimulating the release of adrenaline, which is an early physiological response to hypoglycaemia.[1] Insulin has, since within a few years of its introduction for the treatment of diabetes in 1921, enjoyed an unwarranted reputation as an efficient and undetectable method of killing people. This is however the reverse of the truth, as this review illustrates. It is an inefficient and ineffective weapon, largely because of the length of time it takes to cause death and the ease with which it can be diagnosed and treated.

Definitions

Murder is a legal concept, as is attempted murder. It defines a type of unlawful killing or attempted unlawful killing. In this review I have made no distinction between varieties of unlawful killing or attempted unlawful killing and have included cases described as Munchausen by proxy in the latter category. This term was originally applied to the perpetrator of offences against children but has also, by common usage, become applied to the victim. This is almost always an infant or small child assaulted on one or more occasions by a parent. Differentiating the different types of unlawful killing, including murder and manslaughter, and defining attempted murder is a matter for the courts. I have also included cases in which serious allegations of malicious use of insulin have been levelled at innocent people but which have led to police enquiries regardless of whether they came to trial or not.

Material and Methods

Case histories of 66 people alleged or proven (Table 1) to have been poisoned by insulin were analysed. They were obtained from the biomedical literature by scanning PubMed and Embase for publications containing the terms murder/manslaughter/homicide/Munchausen-by-proxy and insulin and/or hypoglycaemia/hypoglycemia. The Web of Science was scanned for papers citing earlier publications describing homicidal insulin use. The Internet has been scanned for the past ten years using Google, Ask and other search engines for the same combination of key words and finally I have drawn on my own experience of cases about which I have been consulted or asked for help by undertaking and interpreting peptide hormone assays for the investigation of hypoglycaemia. In many cases, especially those reported in the biomedical literature, the legal outcome was unreported.

Results

Sixty-six cases of suspected or proven cases of murder/manslaughter/attempted murder/Munchausen-by-proxy, using insulin as a weapon, were available for review. They came from ten countries (Table 2).

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Table 1. Brief details and references to cases of murder, attempted murder, suspected murder reviewed

Case Number/ Reference	Sex/age	Relation of alleged perpetrator to victim	Glucose: mmol/L	Insulin: pmol/L	C-peptide: pmol/L	Died/survived in hospital	Comment
1–3[43]	F76	nurse	2.0			died in hospital	All three cases originally described as suffering from a 'new' syndrome of 'post-operative' hypoglycaemia after relatively trivial surgery. Intravenous glucose up to 1000 g per day needed to maintain normoglycaemia. Cases 1 and 2 explored for insulinoma but died. Reported 14 years later by Holland (1960) as due to insulin injection by psychotic nurse. **No one charged.**
	M27		2.2			died in hospital	
	M55		2.4			survived	
4[44]	F30	husband: (a nurse)	found dead				Suspicion aroused by posture in bath; cause of death drowning whilst hypoglycaemic. Insulin at injection sites detected by bio-assay. **Barlow* – husband convicted of murder**.
5[45]	F32	husband	found dead			died	Insulin found by bio-assay in tissue removed post-mortem from injection site. **Breslau* – husband – convicted of murder.**
6–10[46]	F	4th wife	not done			died in coma	First victim found in coma having allegedly been injected, along with perpetrator, in the buttocks by intruders. Insulin suspected but not proved. Other victims, over a 20-year period, related in some way to killer. Last crime investigated by same officer as first. Insulin said to have been demonstrated in preserved brain tissue of third victim by crude immunoassay but unlikely to have been present several days after administration. **Archerd* – perpetrator – Convicted of murder**.
	F	5th wife	found dead				
	M	former husband of 6th wife	found dead				
	M	nephew	found dead				
	F	7th wife	found dead				
11[47]	M2	mother	0.5	1332		survived	Child admitted to hospital twice with insulin-induced hypoglycaemia: immediate recovery with glucose. Finally admitted with scalds, chemical burns to mouth. Mother accused babysitter of abuse. Mother became psychotic. **Outcome unknown.**
12[48]	M4	mother (a nurse)	1.1	19 000		survived	Hypoglycaemic attacks in hospital: but only when mother visited. Mother abused insulin herself. **Outcome unknown.**
13[49]	Ten 'old' people	Unknown 'carers'	dead/exhumed			died	Police suspected that elderly victims in home had been murdered with insulin. Ten bodies were exhumed 4–60 months after burial. Tissue taken from 'usual sites of IM injection', extracted and subjected to RIA. Insulin 'found' in tissues of only one subject said to have died within 10 minutes of an injection!. **No-one charged.**
14[50]	F 'old'	Unknown 'carer' in hospital	0.1	246 000	<600: below limit of detection	died	Patient had 'metastatic renal cancer' and was awaiting discharge from hospital: became comatose from hypoglycaemia. No malignancy at PM. **No-one charged.**
15[51]	M 13/12	Mother (uncle IDDM)	1.3	6000	<45	survived	Lethargic for several days. On admission Blood glucose 1.3 mmol/L. Recovered with glucose but relapsed two days later while in hospital. Insulin: seven hours after admission: 6000 pmol/L. Fell to 600 pmol/L by nine hours. Perpetrator's brother was diabetic: bovine insulin found in victim's blood. **Outcome unknown.**

Table 1. (*Continued*)

Case Number/ Reference	Sex/age	Relation of alleged perpetrator to victim	Glucose: mmol/L	Insulin: pmol/L	C-peptide: pmol/L	Died/survived in hospital	Comment
16[51]	F 18/12	Mother	<2.2	18 800	<45	survived	Suffered several hypoglycaemic episodes from 7 months of age. PI: 15 000 pmol/L, C-Peptide <75. Treated with diazoxide. Complete remission but recurred at 18 months. Plasma contained bovine insulin 390 pmol/L. Source of insulin unknown. **Outcome unknown.**
17[52]	M2	Mother (boyfriend IDDM)	1.1	234	<198*	survived	Case referred to authorities. **Outcome unknown.**
18[53]	M6	Mother (IDDM)				survived	Brought to hospital by father having been given insulin by psychotic mother after argument with husband. **Outcome unknown.**
19[54]	F12	Parents (?) Sister IDDM	1.6	15 500	<75	survived	Admitted four times in hypoglycaemic coma. Findings during last episode indicated use of sister's pork insulin. Not determined whether hypoglycaemia due to self administration or child-abuse. **Outcome unknown.**
20[55]	M59	Wife (a nurse)	1.6	294	<397: below limit of detection	died	Patient was suffering from an inoperable glioma. He was given insulin in an IV drip by syringe. He died shortly afterwards. Insulin and C-peptide data held to be inadmissible on grounds of 'hearsay' since analyst not called to give evidence and insecure chain of custody of samples! **Miller* – wife – convicted of capital murder** on basis of her confession.
21[56]	F5/12	Mother (baby's uncle had IDDM)	found dead	10 045			Infant found dead when police arrive to enforce a committal order on mother after suicide attempt. Insulin present in blood and demonstrated immunohistochemically around needle tracts in baby's thigh. **Outcome unknown.**
22[57]	M2.5	Mother (a nurse)	N/A	2160	<75	survived brain damaged	Brought to A&E with seizures due to hypoglycaemia. Recovered with severe brain damage but discharged into care of parents. Readmitted in hypoglycaemia. Treated but placed in residential home. Later evidence established endocrine cause for hypoglycaemia. Died age around 20 years. An older child was said to have died from caffeine poisoning but subsequently shown not to have been. **Mother convicted** – almost certainly incorrectly – released after intense campaign.
23[58]	M49	Lover and her daughter (a nurse)	1.6	2400	231	survived	Victim separated from wife: lived with lover – beneficiary of large life insurance policy. Admitted to hospital for investigation of intractable nausea and malaise. Developed insulin-induced hypoglycaemia soon after admission whilst on IV drip and several times thereafter whilst an inpatient. Shown to be suffering from arsenic poisoning. Hostile to suggestion that he was being poisoned. Left hospital. **No one charged with criminal activity.**
24[59]	13/12	Mother (nurse auxiliary)	1.6	63 448	<10	survived	Child had 11 episodes of hypoglycaemia during 2 months in hospital. On all but one occasion insulin was very high: C-peptide low. Child also suffered from methyl-glutaconic aciduria. Mother managed grandfather's diabetes with insulin but denied all knowledge of hypoglycaemia in the child. Case was referred to authorities. **Outcome unknown.**

Table 1. (*Continued*)

Case Number/ Reference	Sex/age	Relation of alleged perpetrator to victim	Glucose: mmol/L	Insulin: pmol/L	C-peptide: pmol/L	Died/survived in hospital	Comment
25[60]	F 'old'	Nurse [in hospital]	Found dead				**Convicted of murder** of this victim and of causing grievous bodily harm to three others by injection of insulin. No blood glucose measurements made but injection site identified, excised and assayed for insulin. High biological activity found. No immunoassay. Jury returned verdict of guilty: **overturned** on appeal on procedural grounds.
26[61]	M88	Unknown carer	Found dead			died	Ten days after patient's death an anonymous phone call suggested unnatural death. Two injection sites identified in exhumed body but no insulin was found in surrounding tissue by immunohistochemistry. **Nurse confessed: found incompetent to stand trial.**
27[62]	M 18/12	Mother: IDDM	Low	1500	<170	survived	Admitted with tentative diagnosis of insulinoma. Several hypoglycaemic episodes in hospital. Impossible to distinguish from history from Munchausen syndrome by proxy. **Outcome unknown.**
28[63]	F39	Husband (a physician)				survived	Accused of attempting to kill his wife by injecting her with insulin whilst she was in hospital. Recovered consciousness after two days. **Husband found guilty of attempted murder at a retrial; sentenced to not less than eight years and four months and not more than 25 years!**
29[64]	M71	Nurse [in hospital]				survived	Two of 41 patients subjected to homicidal or attempted homicidal attacks by nurses in a Viennese hospital. Given 400–800 units soluble insulin iv. **Two nurses sentenced to life imprisonment**: two more to long jail sentences.
30[64]	M80	Nurse [in hospital]				survived	Two of 41 patients subjected to homicidal or attempted homicidal attacks by nurses in a Viennese hospital. Given 400–800 units regular insulin intravenously. **Two nurses sentenced to life imprisonment: two more to long jail sentences.**
31[65]	3/12	Mother (IDDM)	Low	High		survived	Mother (a diabetic) injected baby with insulin and fed it paracetamol while she was in hospital suffering from depression. Baby had a fit giving first clue to cause of illness. **Guilty of 'inflicting grievous bodily harm'; sentenced to probation.**
32[4]	F48	Husband	1.6	unreliable	350	survived brain damaged	Two attacks of hypoglycaemia 1 year apart. Failed to recover consciousness after second. Husband accused of attempted murder. **Von Bulow* – husband – convicted of attempted murder but reversed at retrial** when evidence brought forward to establish hypoglycaemia as due to natural causes: toxic shock on first occasion: alcohol induced hypoglycaemia on second.
33[4]	F 2/12	Nurse (godmother)	Found dead	72 440	<75		Died at home 10 hours after discharge from hospital and immediately (30–60 minutes) after being given feed made up by killer. Original thought to be SIDS plasma specimens taken immediately after death for virus testing subsequently found in freezer and analyzed. Plasma potassium 18.8 mmol/L **Allitt* – a nurse – convicted and sentenced to life imprisonment.**
34[4]	M 5/12	Nurse (same as above)	1.7	323 600		survived	In hospital for minor illness. Had three severe hypoglycaemic comas, the last one requiring four days' continuous intravenous glucose infusion. **Allitt – a nurse – convicted of this attempted murder** and four others.

Table 1. (*Continued*)

Case Number/ Reference	Sex/age	Relation of alleged perpetrator to victim	Glucose: mmol/L	Insulin: pmol/L	C-peptide: pmol/L	Died/survived in hospital	Comment
35[66]	M 20/12	Mother (IDDM)	2.6	20 800	<75	survived	Mother suffered from IDDM. Baby admitted in hypoglycaemic coma. **Nothing known about outcome.**
36[41]	F43	Work colleague (physician)	Found dead				Nurse: found dead with colleague – a physician dead from intravenous insulin. Injection sites both upper arms and gluteal regions. **Murder or assisted suicide (?).**
37[67]	F33	Boyfriend (IDDM)	Found dead	720	<60		Attempted suicide previously. On this occasion also took 48 paracetamols before giving herself (being given) insulin. Boyfriend taught her how to inject and was said by a witness to have given it to her. Body found 12 hours after last being seen alive. Tissues around injection site contained excess insulin. **Boyfriend charged with culpable homicide but dropped** because suicide could not be ruled out.
38[68]	M51	Wife (a nurse)		High		died in hospital 11 days later	Found in coma: at home by wife. Diagnosed as hypoglycaemia but died 11 days later. Insulin high '16 times normal'. Reliability of sample on which insulin assay performed queried from start. Original verdict of **guilty overturned** by appeal court and by second trial.
39[69]	F57	Husband (IDDM)	Found dead				Found dead with husband in their house. Farewell letter and 2 empty insulin vials found next to bodies. Insulin found by immuno-histochemistry in both corpses in tissue removed from injection sites. **Mutual or assisted suicide**.
40[70]	M5	Mother (a nurse)	Found dead				Mother schizophrenic nurse: injected this child and his sister with insulin before injecting herself. All three found dead with suicide note. **No action**.
41[71]	M48	Wife (a nurse)	0.3	525 rising to 1680 over next few hours	<100 pmol	died after 2 months in hospital	Patient admitted in coma said by wife to be due to decompression sickness. Routine blood glucose was 0.3 mmol/L. Insulin but not C-peptide assays were performed and led to suspicion of insulinoma but subsequent tests ruled out. Plasma taken at time of admission and held in fridge for one month was then analysed and showed low C-peptide. Victim survived two months Forensic investigation revealed monetary motive and forged suicide note. **Wife convicted of murder.**
42[66]	M13/12	Father (claimed to be a nurse)	1.4	1300	<130	survived	Admitted in evening having had convulsion. Not in coma: no symptoms of hypoglycaemia but BG 1.4 mmol/L. Collapsed seven hours later. BG: 0.4 mmol/L Glucose given with full recovery. Father had passed himself off as a nurse for many years. Admitted giving child insulin. **Father convicted of assault**.
43[66]	M10	Mother (a nurse)	1.3	23 000	<50	survived	Epileptic boy admitted in coma with history of drowsiness for several weeks. BG: 1.1 mmol/L; plasma insulin: high, C-peptide low: IV glucose infusion set tested at three days contained insulin. Mother detained by police whilst visiting patient. She had insulin and syringes in her handbag. Charged with attempted murder: pleaded **guilty to assault**.
44[66]	F8	Mother (IDDM)	1.2	17 300	<75	survived	Neighbours suspicious because children had not gone to school on time, unable to get response, called grandfather who was unable to get in. Police broke in and found her, her brother (case 45) and mother in coma. Taken to hospital and all three recovered. **Mother pleaded guilty to attempted manslaughter.**
45[66]	M 3.5	Mother: same as above	low BM (BM is a point of care device for measuring blood glucose	22 668	<75	survived	Neighbours suspicious because children had not gone to school on time, unable to get response, called grandfather who was unable to get in. Police broke in and found him and his sister (case 44) and mother in coma. Taken to hospital and all three recovered. Mother **pleaded guilty to attempted manslaughter.**

Table 1. (*Continued*)

Case Number/ Reference	Sex/age	Relation of alleged perpetrator to victim	Glucose: mmol/L	Insulin: pmol/L	C-peptide: pmol/L	Died/survived in hospital	Comment
46[66]	F83	Unknown 'carer'	0.1	83 360	175	died within a year	Frail woman who became hypoglycaemic in nursing home: Biochemical evidence of kidney failure. Never regained mental faculties: Died 11 months later. Coroner's jury's verdict: **unlawful killing by persons unknown**.
47[66]	M69	Neighbour sometime lover	Found dead	11 500	<75		Neighbour – also named as 'next of kin' argued with victim during previous evening and accused him – an insulin using NIDDM – of molesting her daughter. At trial – **Shickle*** – accused her son of giving victim insulin. **Found guilty of murder.**
48[46]	F34	Landlord (wife IDDM)	Found dead	125 115	<75		**Wagstaffe***, a healthy non-diabetic woman found dead in bed. No suicide note, insulin or syringes found near body but insulin vials in fridge (landlord's wife IDDM). Victim (Wagstaff) said to have been pursued by landlord but resisted advances, Evidence of recent sexual intercourse at PM. Landlord admitted SI but denied murder. Injection sites found and insulin identified but suicide not excluded. **Coroner returned open verdict**.
49[46]	M60	Lover (a nurse)	Found dead	Unreliable: grossly hemolysed	Unreliable: grossly hemolysed		**Whiston*** lived as wife of victim who was a hypertensive but otherwise fit man. He had 'proven' episodes of factitious insulin induced hypoglycaemia three years before death (glucose 1.3 mmol/L: insulin 1576 pmol/L: C-peptide <75 pmol/L) but which he vehemently denied. No one including him had injecting insulin. Apart from coronary narrowing autopsy revealed no cause for death. Small amounts of various drugs in blood, urine and vomit. Blood deemed unsuitable for hormone assay. PM urine was analysed: insulin 200 pmol/L: C-Peptide 500 pmol/L. Circumstantial evidence of financial benefit to Whiston – a nurse – by victim's death. No injection sites were found **– found guilty of murder**.
50[72]	F79	Carer	2.2			survived	Purported victim developed insulin-dependent diabetes in her 70s. Befriended by neighbour who took on responsibility for giving insulin after community nurses declined to do so. Frequent hypoglycaemic episodes thereafter led to carer being charged with 'attempting to administer noxious substances'. **Charged with offence but case abandoned for lack of evidence.**
51[46]	M35	Wife (a nurse)	0.7	887	<75	died	Obese paraplegic confined to wheelchair. Taken to hospital in coma. No suicide note was found but suicide could not be excluded. No motive. Urine collected by catheter: insulin 800 pmol/L: C-Peptide 7500 pmol/L. **Winzar*** – the wife – was accused of murder despite excellent alibi. The only evidence of insulin misuse were plasma insulin and C-peptide levels for which alternative explanations were offered. **Found guilty of murder sentenced to life imprisonment. Currently under appeal.**
52[46]	F43	Friend (a junkie)	0.2	346	Below limit of detection.	died just before ambulance arrived	Elaine Robinson, the victim, was grossly underweight. She voluntarily accepted unknown dose of intramuscular insulin from her friend **Andrews*** – in order to get a 'buzz'. She had been drinking alcohol and her post-mortem alcohol was 45 mg/100 ml. Two other normal weight 'victims' who received the same treatment survived. **Pleaded guilty to manslaughter and received two-year jail sentence.**

Table 1. (*Continued*)

Case Number/ Reference	Sex/age	Relation of alleged perpetrator to victim	Glucose: mmol/L	Insulin: pmol/L	C-peptide: pmol/L	Died/survived in hospital	Comment
53[73]	F2	Parents	0.8	520	<70	survived	Brought to A&E by mother; hypotonia only feature. Blood glucose 0.8 mmol/L & K^+ = 2.5 mmol/L. Given glucose in huge doses. Insulin was undetectable using Elecsys but using IRMA insulin was 520 pmol/L on admission – falling to 420 four hours later C-peptide was undetectable but rose normally once blood sugar was restored to normal. Munchausen by proxy. Child removed from parents. **No criminal charges.**
54#	M70	Carers	1.7	7092	Below limit of detection	survived	Patient in an old peoples home having had stroke seven years earlier. Needed comparatively small amounts of glucose (less than 30 g) to make him grossly hyperglycaemic. Inquest verdict: not proven due to insulin. After recovery oral GTT perfectly normal with normal insulin and C-peptide responses He survived in good health for six years. Care-home owners, husband and wife, were accused of attempting to kill him. **Case dismissed – insufficient evidence**.
55[74]	F25	Random victim of fraud	Very low	High	low	survived	Victim escaped after being hit over the head several times. Reached a shop and called police, Collapsed. Found to have hypoglycaemia; told how she had been injected with insulin in murder attempt. **Convicted attempted murder; 20 years.**
56[46]	F25	First wife rival (a nurse)	Found dead			dead	Husband told police that Jensen, the perpetrator, had threatened his first wife death by injecting her with insulin. Accomplices told of injecting victim with insulin and amphetamine to make it look like drug death. **Sentenced to life imprisonment.**
57[75]	M8	Neighbour – 'playmate'	Found dead	Autopsy specimen '15 times normal'		dead	Perpetrator – a 16-year-old boy - was irritated by 8-year-old victim. Took him to a field nearby- tied him up and injected him with insulin. Insulin bottle, needle and syringes found near body. Perpetrator also beat and cut victim. Probably died from choking. Trial two years later. **Tried two years later as an adult and found guilty. Sentenced to life imprisonment.**
58[76]	M71	Wife (a nurse)	Found dead	–	–	found dead	Wife – a nurse – doped her husband's tea with sedatives and injected him with insulin stolen from diabetic daughter. Next morning he was dead. Concealed the body with aid of her daughter. Wife had stolen money from joint account and husband threatened to leave her. Confessed in court. **Found guilty; sentenced to life imprisonment**. Appeal confirmed sentence.
59[77]	M	Lover and diabetic friend.	Found dead				Lover admitted injecting five times the 'legal' dose of insulin obtained from friend an insulin using diabetic. **Both women sentenced to life imprisonment.**

Table 1. (*Continued*)

Case Number/ Reference	Sex/age	Relation of alleged perpetrator to victim	Glucose: mmol/L	Insulin: pmol/L	C-peptide: pmol/L	Died/survived in hospital	Comment
60[78]	M55	Wife				survived	Wife attempted to kill her husband by Injecting him with 300 units of insulin. Motive money. He survived. Wife **sentenced to 15 years**
61#	F83	Unknown 'carer'	0.1	83 360	175	died within a year	Frail woman who became hypoglycaemic in nursing home. Biochemical evidence of kidney failure. Never regained mental faculties. Died 11 months later. Coroner's jury's verdict: **unlawful killing by persons unknown**.
62[79]	M25	Lover (a nurse)	Found dead	388	166		After having given victim (Kato) triazolimat home to make him drowsy his lover injected 1200 units long acting insulin iv. This did not kill him quickly enough so she injected 100 cc air through the iv drip she had set up. This killed him one hour after the intravenous insulin injection, **Lover found guilty of murder**.
63[66]	F84	Unknown carer in hospital	0.6	14 576 one hour after 25 g glucose iv.	Below limit of detection	survived	Admitted to hospital for investigation of dementia. Unexpectedly found hypo in ward – nothing untoward previously except dementia. Described as physically fit. Low plasma potassium concentration (3.0 mmol) during hypo. Responded to glucose but relapsed. IV glucose needed for 24 hours. **A nurse with 'Munchausen syndrome' was suspected but never came to trial.**
64#	F4/12	Nurse (friend of mother)	0.7	6517	<75	survived	Victim collapsed in swimming pool. Found to be hypoglycaemic – given large doses of glucose but kept becoming hypoglycaemic. Plasma insulin rose to 7850 pmol/L over 24 hours. After child had recovered, insulin and C-peptide were both normal. Offender given three years **suspended sentence** because judge said she was grossly bereaved
65[72]	F90	Nurse	low	12 000	<75	died	Norris, a male nurse forecast when victim would die. **Convicted on the evidence of this case of three other deaths deemed to be similar** but for which no analytical data were available.
66[46]	F47	Husband (a physician)	Found dead				**Bouwer*** the victim's husband poisoned victim with sulphonylureas obtained over a period of a month on false prescriptions. Victim investigated for insulinoma in hospital. Sulphonylureas were tested for but with an insensitive method and were missed. She was discharged from hospital after partial pancreatectomy Died a week later: many drugs, including sulphonylureas were found in her body but she probably died from an injection of insulin, which had been obtained on forged prescription the morning of the day of her death. No insulin assay done on corpse. Motive financial gain. **Found guilty and sentenced to life imprisonment**.

More details of cases marked with * are available in reference 46.
- previously unreported.

Table 2. Countries of origin of reports

County of origin	Number of reports
USA	26 (2 multiple)
UK	25 (3 multiple)
Germany	3
Belgium	2
Austria	1 (multiple)
Finland	1
Japan	1
France	1
South Africa	1
New Zealand	1

Forty-nine were recorded in the biomedical literature, some of them on two or more occasions, 12 were in newspapers accessed through the Internet and five have not previously been reported. I have not differentiated between cases of Munchausen by proxy and murder or attempted murder in children nor between murder and so called mercy-killing in the elderly. The disproportional number of cases from the UK probably reflects my interest in the subject but also suggests underreporting or under diagnosing from the rest of the world.

Fifteen of the purported victims (henceforth referred to simply as victims unless specifically excluded) were aged between 0–3 years; seven were aged 4–9 years, 30 were aged 10–60 years and 15 were aged over 60. Thirty-one victims were female, 33 were male and in two cases the sex was unknown. Thirty-one purported perpetrators (henceforth described as perpetrators or alleged perpetrators), including four multiple killers, were convicted; 18 for capital offences that were overturned at retrial or appeal in three (cases 25, 32, 38) and are suspect, on the evidence (cases 22, 51), in a further two. In over half the total number of cases no further action was taken or the outcome is unknown.

In 15 cases the authorities took no further action either because no individual emerged as a likely suspect or because the evidence against them was insufficiently strong to make the chance of a successful prosecution likely. In four cases the alleged perpetrator was judged to be too mentally unstable to stand trial and 3 of the perpetrators were partners to a suicide pact or killed themselves as well as their victims. In six cases there is no information about the fate of the alleged perpetrator. A proposed classification of murder or attempted murder by insulin is shown in Table 3.

Twenty-three of the victims were already dead when their bodies were discovered and 43 were alive when taken to hospital where ten of them died within ten days despite attempts at resuscitation. Thirty-five regained consciousnesses and all but three, who were left permanently brain damaged, made a complete recovery although their subsequent mental state was rarely mentioned. One victim (case 55) was able to identify her assailant, who had forcibly injected her with insulin.

Table 3. Classification of malicious or purported malicious insulin use

Description	Number of victims
Mass murder of elderly inmates in nursing homes and infants in hospital	9
Capricious murder of	
Helpless people	5
Infants	18
Murder of sentient adults and children	
Motivated by financial gain or jealousy	16
No recognisable motive	18

Glucose was measured using a variety of techniques in the blood of all victims who were found alive. It was less than 2.6 mmol/L or 'low' in all of them. Glucose was also measured in several corpses but provided no useful information and in one it was initially misleading

Three of the perpetrators were physicians (cases 28, 36, 66) and 22 were or had been nurses. Eight were carers of one sort or another. Thirty-six of the alleged perpetrators, 14 of whom were or had been nurses, were close relatives of the victim and 14 were insulin-using diabetic patients with insulin-dependent diabetes mellitus (IDDM) or had a close relative who was. The mother was the likely perpetrator in 14 of the cases and the father, who falsely claimed to be a nurse, in one. The alleged perpetrator was the husband or lover in nine cases and the wife or mistress in another 11. In only four of the cases not involving a nurse or carer was there no close personal relationship between the alleged perpetrator and victim. In only a small proportion of the cases (14/66) was a motive alleged or discernible.

Plasma (serum) insulin concentrations were measured in 41 cases. In three the results were was so unreliable as to be useless as evidence. In one of these (cases 32) it was, however, relied upon to secure a conviction that was dismissed at retrial after the result was challenged (case 32). Values ranged from 234–323,600 pmol/L (Figure 1) and in 3 others it was described merely as high. Plasma insulin concentrations bore no relationship to whether the victim was alive or dead when found or whether they lived or died after attempted resuscitation. An injection site was identified in nine cases, excised and subjected to analysis for insulin, which was confirmed in every case but one (case 26). In most cases an injection site was either not actively sought or not found. Urine insulin was measured and relied upon as evidence of exogenous insulin administration in one case (case 49). Plasma or serum C-peptide was measured in 33 subjects but considered unreliable in two. In all but three cases (23, 32, 46) the plasma C-peptide concentration was less than the detection limit of the assay. Of the three cases in which C-peptide was detected at measurable levels one was a false accusation (case 32), another had renal failure (case 46) and the third (case 23) refused, possibly correctly, to undergo further investigation for

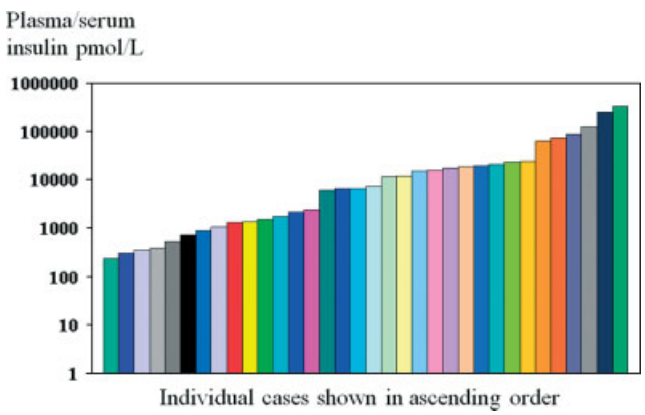

Figure 1. Plasma/serum insulin levels in victims of malicious insulin use.

the cause of his hypoglycaemia or to accept that he had been poisoned.

Clues to malicious insulin use

Insulin in overdose causes death through prolonged hypoglycaemia. This provides the first clue to insulin abuse in victims found alive but no such unifying clue occurs in victims who are found dead. In them the overt or covert presence of insulin vials, syringes or needles at the scene may provided a clue but in others it comes from anonymous phone calls, remarks made by the perpetrator and recalled by someone who overheard them, confessions, or an unexpectedly large number of deaths in a single institution within a short timeframe. Insulin is not picked up during a 'drug screen' for cause of death where this is unknown.

Glucose

It is impossible to prove that a person died from hypoglycaemia once he or she is dead[2] except by inference. Measurements of glucose in blood or other fluids are unreliable and potentially misleading. Glucose disappears from blood in peripheral blood vessels at a rate of 1–2 mmol/L per hour and, paradoxically can make an even more rapid appearance in blood collected from central blood vessels – especially the right side of the heart, the site favoured by most forensic pathologists for collecting blood sample at autopsy. It is caused by enzymatic breakdown of glycogen in the liver after death and consequently occurs only in previously well fed individuals.[3,4]

Glucose can be measure in the vitreous humour of the eye, from which it disappears slightly more slowly than from peripheral blood. It can be used to confirm a diagnosis of death in diabetic coma or to exclude a diagnosis of hypoglycaemia but never to confirm it. The molar concentrations of glucose and lactate, its breakdown product, when summed, have been used to support a post-mortem diagnosis of hypoglycaemia in a suicide victim[5] but it is too unreliable to use as evidence in cases of suspected murder, although it may provide a clue to further investigation.

The measurement of blood glucose was comparatively tedious, time consuming and expensive before about 1950 and was never conducted at the bedside. It was used mainly to establish a diagnosis of diabetes and not performed routinely on unconscious patients as it is today. This may explain why more than 35 years elapsed between the time that insulin was first used for the treatment of diabetes and its use as a murder weapon was established (Table 4). The simplification and application of point-of-care testing for glucose as a routine on unconscious patients may account for the apparent increase in cases of murder with insulin during the second half of the twentieth century.

Table 4. Decade in which cases were reported

	Number of reports
1920–1949	(not recognised until 1960)
1950–1959	1
1960–1969	2
1970–1979	2
1980–1989	11
1990–1999	34
2000–2009	13

Proof of the use of insulin for malicious purposes had to await the ability to measure it at the very low concentrations at which it occurs in the body after administration.[6] The inability to do so prior to about 1960 led to the popularity of insulin as a murder weapon with fiction writers and its absence from the biomedical and legal literature.

Insulin, C-peptide and proinsulin

These three peptides have a close relationship with one another and are measured by similar methodologies. Insulin and, to a much lesser extent, proinsulin lower blood glucose levels and can produce hypoglycaemia; C-peptide does not and its physiological function is still largely unknown.[7]

Proinsulin is, with exceedingly rare exceptions,[8] produced exclusively in the pancreas on the endoplasmic reticulum of the B-cells of the islets of Langerhans. It is transported within the B-cell to tiny organelles, called beta granules, where it is cleaved by two specific enzymes into equi-molar amounts of insulin – a peptide made up of 51 amino acids (molar mass 5808) – and a smaller C-peptide (molar mass 3020). The two peptides remain together until both are released in equimolar amounts in response to stimulation of the B-cells by a rising blood-glucose concentration. A trickle of insulin and C-peptide enters the circulation even in the complete absence of stimulation (so called constitutive secretion)[9] but it remains under homeostatic control. Constitutive secretion prevents the breakdown in carbohydrate, fat and protein metabolism that is seen in untreated patients with type-1 diabetes caused by destruction of the B-cells and characterised by unbridled release of fatty acids from adipose tissue, the inability to extract glucose from the circulation by the tissues or to store glucose as glycogen in the liver, and exaggerated protein breakdown.

Proinsulin is not ordinarily released into the circulation except in miniscule amounts, cannot be split into insulin and C-peptide in the circulation and has no physiological function apart from being a precursor of insulin and C-peptide. It is ordinarily measured in blood only for research purposes and the differential diagnosis of spontaneous hypoglycaemia.[10] C-peptide has no universally recognised physiological function and consequently is rarely measured in blood except for research and clinically for the differential diagnosis of spontaneous hypoglycaemia.[11] It is sometimes measured in urine as an indication of the ability of the B-cells to respond to stimulation in patients with diabetes and the reason that commercial kits for its measurement in urine are readily available.

The accurate identification and measurement of both insulin and C-peptide and, to a lesser extent, proinsulin in blood plasma or serum – but never on whole blood – plays a key role in establishing guilt or innocence in many cases of suspected murder by insulin. On occasions the methodology used though adequate as a guide to the management of patients in a clinical setting where progress could be monitored has fallen short of the standard required for forensic purposes.

The measurement of insulin, C-peptide and proinsulin

The first cases of homicidal insulin misuse were mistakenly reported as postoperative hypoglycaemia; a hitherto unrecognised – and now known to be unreal – cause of spontaneous hypoglycaemia (cases 1–3). Only many years later were they revealed to have been caused by a nurse using insulin to harm her patients. Many similar cases of carers harming their patients for no apparent reason have been reported since that time.[12]

In what is usually regarded as the first case of insulin murder to have been properly documented, an industrial bio-assay used to standardise and quality control pharmaceutical insulin preparations was applied to tissue removed from around injection sites identified on the corpse suspected, on other evidence, of having been poisoned with insulin. In all subsequent cases in which an attempt was made to measure insulin in a living victim or corpse some form of immunoassay of blood plasma or serum, or immunohistological examination of excised tissue for insulin, was used, although it was not invariably successful.

Although problems with the reliability and specificity of immunoassays in a forensic context were recognised from quite early on they have only rarely led to sufficient confusion to prejudice the court proceedings. This will be addressed in greater detail below.

In contrast to most other causes of poisoning analysis of urine for insulin obtained either during life or post mortem cannot be relied upon. Insulin is ordinarily filtered at the glomerulus of the kidney but is almost completely reabsorbed by the kidney tubules so that, in healthy subjects, only a tiny and highly variable fraction of the insulin in the blood enters the urine. Even very slight kidney tubular malfunction impairs reabsorption with the result that much larger amounts of insulin enter the urine than in normal healthy subjects and can be misinterpreted as poisoning with insulin. Currently, urinary insulin measurements have no place in the investigation of suspected insulin misuse but the situation may change with the greater availability of synthetic insulin analogues and the ability, using mass spectrometry,[13] to identify them and their metabolic breakdown products in people in whom they should not be present.

Plasma C-peptide levels in blood fall to low or undetectable levels during insulin-induced hypoglycaemia and that arising from other causes of spontaneous hypoglycaemia apart from those caused by pathological B-cell activity, as occurs with insulin secreting tumours of the pancreas, or poisoning with insulin stimulatory drugs such as member of the sulphonylurea class of compounds.[14] They therefore provide, in all but a few exceptional circumstances, a simple and rapid means of distinguishing hypoglycaemia associated with hyperinsulinaemia of exogenous origin from that of endogenous – but not necessarily innocent – origin.[15] In hypoglycaemia due to endogenous secretion, insulin and C-peptide enter the circulation in equimolar amounts and the plasma C-peptide: insulin ratio remains in the region of 3 : 1 or more just as in people with normal blood glucose levels.[16] In hypoglycaemia due to exogenous insulin C-peptide secretion is suppressed and the plasma C-peptide to insulin molar ratio falls below to below 1. Though useful as a means of differentiating between exogenous and endogenous insulin induced hypoglycaemia the plasma C-peptide : insulin ratio can only be interpreted effectively when taken in conjunction with the blood glucose concentration and the absolute concentrations of the two peptides in the blood sample being analysed.[17]

Co-measurement of C-peptide with insulin is now standard practice in the investigation of cases of hypoglycaemia by specialist laboratories but not necessarily in those investigate only a few cases of spontaneous hypoglycaemia each year. When this practice was introduced into my own laboratory it soon became apparent that self-generated, insulin-induced factitious hypoglycaemia – having previously been considered very rare – is comparatively common and not confined to patients with diabetes.[18] Felonious use of insulin on the other hand – at least that which leads to conviction – remains a rarity.

The concentration of insulin and C-peptide in blood plasma or serum insulin

Insulin was not amenable to accurate measurement in biological fluids prior to the invention of immunoassay in 1960.[19] Bio-assays that could distinguish the presence from the absence of insulin in biological fluids with a fair degree of reliability were available but the results expressed in molar units bore little resemblance to those actually prevailing in living subjects.[6] Plasma and serum are treated in the literature and in practice as though they are interchangeable. This may not be true in so far as the measurement of insulin by immunoassay is concerned[20] but any differences are likely to be too small to have any significant effect in a case of suspected insulin murder.

Immunoassays, all of which use at least one antibody directed at some part of the target molecule, have the requisite sensitivity and specificity to make them an invaluable tool in metabolic research and clinical medicine. They can be automated and used for screening for endocrine diseases, foetal abnormalities and drug misuse but lack the diagnostic specificity and reliability[21] required for modern forensic work.

All three hormones circulate free and unbound to larger proteins in the blood at picomolar concentrations. Occasionally, under pathological conditions, spontaneously generated antibodies directed at insulin appear in the blood making it inaccessible to its receptors. As a result blood glucose continues to rise after a meal, as does insulin secretion, until its concentration in the blood reaches pathologically high concentration as in its bound form it is removed from the circulation very slowly. C-peptide on the other hand is either bound very much less avidly by such antibodies, or not at all, and is consequently removed normally. This leads to distortion of the relationship that normally exists between in the blood between C-peptide and insulin and is a rare but potential cause of error in interpretation of analytical results. In this condition the insulin that is measured is real and must be distinguished from a measurement that is false due to interference in the assay procedure.[22]

Attempts to improve the specificity of immunoassays by using two antibodies directed at different sites or epitopes on the molecule – in a so-called sandwich format – rather than just one as in the original methods have been partially successful but whilst improving the specificity of assays in one respect they have introduced potential sources of error from others. These potential sources of analytical error assume great importance when the results of an immunoassay are the sole piece of evidence upon which a conviction for murder rests. Duplication of analytical results in a second laboratory using reagents made by another manufacturer is no guarantee of the accuracy of either.[21]

The specificity of immunoassays can be improved by combining them with a pre-analytical fractionation step. This combination has been used in the past to establish whether the insulin in the circulation was of animal rather than of human origin (for example, cases 4, 16) and its use would probably have exonerated the purported perpetrator in case 22. It became impossible to distinguish endogenous from exogenous insulin in this way when biosynthetic human insulin was largely substituted for porcine or bovine insulin in therapeutics. Consequently fractionation prior to immunoassay for insulin went out of fashion and is no longer used either in clinical or forensic investigation except for research.

The past decade has seen the introduction of a number of synthetic insulin analogues, loosely referred to as 'insulins', that have similar biological but different physico-chemical properties to human insulin. Chief amongst these differences, from a forensic

point of view, are their variable reaction in immunoassays[23] designed to measure human insulin and the fact that, if present in body fluids of victims who have not been prescribed them, is strong evidence of their misuse. Because of their variable reaction with immunoassays designed to measure human insulin they may go completely undetected (for example, case 52) or react only partially giving an inaccurate and falsely low result. Hypoglycaemia produced by them may therefore be dismissed as being due to one of the many rare causes of spontaneous hypoglycaemia produced by mechanisms that do not involve insulin and in which plasma C-peptide and insulin are both low.

A method for measuring insulin in blood using mass-spectrometry was first described in 1997. It used insulin labelled with N^{15} as an internal standard but probably because of its complexity found little clinical or forensic application.[24] Other mass-spectrometry methods have been published,[25] although none has yet been employed in forensic cases involving murder or suspected murder even when, because of the possibility of analytical error, their use was indicated.

Suspicion of insulin misuse is ordinarily only aroused in the live victim when the results of clinical assays for insulin and C-peptide used to elucidate the cause of hypoglycaemia arrive from the laboratory. By then it may be too late to do anything about it unless a sufficiently large amount of blood was collected, separated and stored properly, before treatment with glucose or glucagon began, to enable further analyses to be done. This is partly because malicious insulin administration does not, due to its rarity, figure high in the list of possible causes of hypoglycaemia when a victim is first seen in the accident-and-emergency department of a hospital. Consequently appropriate precautions to collect, preserve and establish a chain of custody of essential blood plasma samples adequate to convince a jury may not be taken sufficiently early in the proceedings to be useful.

In victims found alive samples of blood collected at regular intervals to ascertain whether the plasma insulin concentration is rising or falling and the rate at which they do so[26] may help in establishing the time when the lethal injection was given and which may be important in establishing an alibi. But this is questionable.

In a victim found alive other causes of hypoglycaemia must be excluded especially those that may produce, or are known to produce, erroneous plasma insulin measurements. It is essential to exclude interference in the assay by substances that are uniquely present in the victim's blood but not in the quality controls. Ideally, identification and quantification of insulin should be by mass-spectrometry or failing that by immunoassay after preliminary separation by gel filtration or HPLC.[27]

Proinsulin secretion, like that of endogenous insulin and C-peptide, is suppressed by hypoglycaemia. It is absent from pharmaceutical insulin preparations so that its presence in the plasma of a hypoglycaemic subject is strong evidence that any insulin present is also of endogenous origin or that there is an analytical error. Proinsulin measurements may, therefore, help resolve questions that arise with regard to the origin and nature of a patient's hypoglycaemia.

Interpretation of Laboratory Data

The lowest concentrations of C-peptide and insulin ordinarily occur in blood during fasting and are detectable and measurable with all modern clinical immunoassays. C-peptide has a half life in the circulation of about 30 minutes[28] whereas that of insulin is only 3–5 minutes.[29] Consequently they reach their maximum concentrations at different times after a meal depending on its size and composition. In the steady physiological state associated with fasting the molar plasma C-peptide : insulin ratio ranges from about 6 : 1 to 10 : 1 and is a measure of their respective pool sizes. With stimulation of B-cell function in response to the rise in blood glucose created by a meal equal amounts of insulin and C-peptide are added to the circulation so that within half-an hour of so of eating a meal the molar plasma C-peptide to insulin ratio falls to 3 : 1 or even lower. It rises rapidly thereafter to re-attain a value greater than that of the steady (fasting) status.

Insulin and C-peptide secretion drops to little more than constitutive secretion levels as the blood glucose concentration[30] falls to about 4.5 mmol/L and virtually ceases altogether when it falls below 3 mmol/L. A plasma C-peptide below 75 pmol/L (or the sensitivity level of the assay which ever is the larger) and a plasma insulin concentration above 100 pmol/L in a sample of blood with a glucose concentration below about 3mmol/L is therefore a powerful clue to exogenous insulin administration – although it is not diagnostic.

Insulin, C-peptide and proinsulin are ordinarily stable at $-20\,^{\circ}C$ in plasma or serum for many months but unstable in blood at room temperature. The rate at which they disappear from blood once it has been removed from the body has not been studied in detail and is not the same for all three peptides. Factors that influence the rate of disappearance include how rapidly the plasma was separated from the cellular elements, the temperature at which the plasma was stored and what enzymes capable of destroying each of the peptides are or are not present as a result of disease. This is important because whereas unrecognised loss of insulin from the post-collection plasma sample may lead to a case of malicious insulin administration being overlooked, unrecognised loss of C-peptide may lead to a false murder charge. This can happen especially if insufficient attention is paid to the absolute molar concentration of each hormone rather than their relationship to one another.

Plasma insulin levels below 1000 pmol/L were found in only six of the 37 cases in which it was measured in the present series of cases. Evidence of insulin administration with murderous intent was present in two – both of whom were given it intravenously (cases 20, 62). In a third who also received intravenous insulin it was taken voluntarily (case 37) and a further two were cases of Munchausen by proxy (17, 53). In the one case of a sentient adult who was found alive with a plasma insulin concentration of less than 1000 pmol/L the accuracy of the insulin assay result was called into doubt by several experts but accepted by the jury as evidence of malicious insulin administration (case 51).

No systematic studies have been undertaken on interference with immunoassays for insulin by substances present in the blood plasma of some but not most individuals. There is ample evidence from other studies of polypeptide hormones using essentially identical procedures to those used to measure insulin to suggest that such interference can occur and lead to erroneously high (or occasionally low) results. Misdiagnosis from this cause is unfortunately common and has led to enormous monetary awards for damages. Of particular interest in the context of murder by insulin is evidence that sepsis can temporarily produce falsely high results in immunoassays for choriogonadotropin and presumably that of other immunoassays.[31] Sepsis and severe infection are themselves important causes of spontaneous hypoglycaemia and death, especially in the elderly. They do so through mechanisms that do not ordinarily involve insulin. Consequently both plasma

insulin and C-peptide concentrations might be expected to be low - as they have been in the very few cases in which they have been measured. If, however the plasma insulin concentration measured by an immunoassay happens to be falsely elevated in a patient with sepsis-induced hypoglycaemia it could easily lead to a serious miscarriage of justice as I believe happened in case 51.

Sulphonylureas

Sulphonylurea drugs stimulate endogenous insulin production and can, in overdose, produce severe and even fatal hypoglycaemia. Though sometimes used to commit suicide they have only very rarely been used to commit homicide[32] and, when they are, may lead to a mistaken diagnosis of endogenous hypoglycaemia due to an insulinoma (case 66). When given together with insulin they produce hypoglycaemia in which not only plasma insulin but also plasma C-peptide levels are inappropriately high and the vital clue to insulin poisoning provided by an absence of C-peptide from the blood is lacking. It is essential, therefore, to search, with a sensitive method,[33] for sulphonylureas in the blood of any suspected victim of insulin poisoning in whom C-peptide is detected. The sulphonylurea used should be confirmed by mass spectrometry.[34]

Post-Mortem Serum Assays

Thus far I have dealt largely with victims of malicious insulin poisoning who are found alive and in whom plasma samples can be collected under good or ideal conditions for subsequent analysis. This is not true for C-peptide and insulin assays carried out on serum samples recovered from a corpse at post mortem. They often suffer from the disadvantage that haemolysis has occurred and so the results may be invalid because they fail to detect insulin that was present during life but destroyed in the body after death. This is, however, more of a theoretical than practical problem providing the autopsy is done within a month or so of the victim's death and the serum used for analysis is not collected from the inferior vena cava or right side of the heart where it may have become contaminated by insulin and C-peptide leaching out of the pancreas,[4] just as it can be by glucose leaching out of the liver.

Quantities and Doses

The formulation and quantities of insulin used maliciously cannot be determined in the laboratory. Clues to the amount of insulin needed to achieve a fatal outcome come largely from confessions by perpetrators and by inference from information available from cases in which insulin was used to commit suicide. These suggest that in an otherwise healthy subject something in the region of 300–500 units of regular insulin are required to produce a fatal outcome (for example, case 60) and even then it is rarely achieved if insulin is used alone in an otherwise healthy adult. An additional weapon, such as drowning or hitting with an instrument, was required to achieve the murderer's intention in many of the cases reviewed here (for example, cases 4, 5, 55, 56, 57).

Smaller doses of insulin are probably required to produce a fatal outcome in children, the elderly and sick but there is no evidence on this issue. The duration of supportive therapy with intravenous glucose in victims who arrive in hospital provides, at best, a rough guide to the amount of insulin injected and says nothing about its type or formulation. Identification of insulin analogues in blood, urine or tissues from victims of insulin murder is likely to improve with the greater availability of mass-spectroscopy in the future.

Sources of Insulin

There is often, but far from invariably, an obvious source of insulin available to the perpetrator either because they are a professional, for example a nurse or doctor, have diabetes and used insulin themselves legitimately or have a close relative or friend with insulin dependent diabetes. Indeed this often provides the first clue to the cause of a victim's death in cases that are found dead. In many communities insulin is still available over the counter as it was in the United Kingdom until it was made a 'prescription only drug' in 1997.

Morbid Anatomy

Post-mortem examination of a victim found dead solely from insulin induced hypoglycaemia generally reveals nothing of diagnostic importance. An injection site may be identifiable and if found can be excised and analysed by immunohistochemistry or by analysis of a tissue extract.[35] The growing availability of synthetic insulins makes it less likely that this will be effective[36] unless mass spectrometry rather than immunoassay is used for detection.

The brain of a victim found dead from insulin poisoning has probably had insufficient time to develop the characteristic abnormalities produced by hypoglycaemia.[37] In victims found alive who survive several days or longer after their blood glucose has been restored to normal, the brain should be preserved intact until examined by a skilled neuropathologist. The absence of characteristic changes produced in the brain by hypoglycaemia should raise suspicion that the hypoglycaemia observed was not the cause of the victim's death but an epiphenomenon of an underlying illness.

Hypoglycaemic coma takes at least 20 minutes to develop after an insulin injection into tissues and only slightly less time after intravenous injection. It is not known how long victims of insulin poisoning can suffer from hypoglycaemic coma before they develop irreversible brain damage but it is rarely less than 3 hours and generally 6 hours or more.

Concluding Comments

Murder by poisoning is a popular subject in books – both fiction and non-fiction – plays, films and magazines but has not been systematically reviewed. According to Glaister,[38]

> *Poisoning, of course, differs considerably from many other crimes, frequently committed in uncontrolled passion and in the heat of the moment. The innate character of the crime of homicidal poisoning demands subterfuge, cunning, and, what is equally important, usually a period of careful planning, and also not infrequently the repetition of the act of administering poison. . . Its characteristic being one of premeditation, it is a method of murder, which, therefore, cannot be the subject of extenuation as some other forms of killing can. . .*

It may also masquerade as natural illness. Nowhere is this truer than in cases of murder by insulin, which, though possible, is rare, unpredictable and often unsuccessful as this review demonstrates. Most of the reported cases have involved infants or the elderly and infirm and were perpetrated by people with a professional or personal knowledge of the effects of insulin on the body.

Acute poisoning due to accidental or deliberate ingestion, injection or inhalation of drugs or other chemicals is a common medical emergency in the developed and, more especially, developing world but is seldom due to homicide.[39] Statistics on the incidence of homicidal poisoning are rare. An exception is the report by Westveer and coworkers of the 186 971 murders committed in the USA during 1990-1999 of which 346 (0.185%) were due to poisoning.[40] The nature of the poisons used was neither recorded nor reported but to put things into perspective just five of the 66 cases described in this review (cases 25, 32, 22, 26 and 28) occurred or were tried in the USA during this period. Only two (cases 26 and 22) would have been included in Westveer's review as cases of homicide and one of them (case 22) is probably a wrongful conviction. Two of the cases were accusations that did not lead to conviction and the fifth case (case 28) was convicted of attempted rather than of successful homicide. Of the seven cases of homicide by injection reported by Peschel and coworkers[41] only one used insulin as the weapon and that case was one of mutual suicide. Insulin was used as the murder weapon by six of the 77 healthcare professionals charged with or found guilty of serial murder reviewed by Yorker and her coworkers.[12] Expressed differently insulin accounted for 13% of cases killed by injection compared with 17% killed by potassium chloride and 23% by opiates and opioids. These were the drugs mainly used by Dr Harold Shipman, probably the most prolific mass poisoner of modern times, who was found guilty of killing 15 patients but probably killed as many as 200 over a murderous career extending over several decades. He did not, as far as is known, ever use insulin probably because it would take too long to achieve its objective. The enquiry set up to investigate him in 1999 was wrongly informed by a consultant pathologist who gave evidence that it 'would probably not be detected. . .'[42]

The small increase in number of cases of murder, attempted or purported murder with insulin reported in the 30 years since, compared with before, 1980 probably reflects the introduction of routine testing of blood glucose in all comatose patients, greater availability of methods capable of detecting insulin in a corpse as well as better investigation of hypoglycaemia made possible by immunoassay. Undoubtedly some cases still go undetected and others are not reported; nevertheless, the number of proven cases of homicidal insulin misuse remains small and is likely to do so as its ineffectiveness as a murder weapon becomes more widely appreciated.

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