Brittle diabetes – present concepts

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"Brittle" diabetes is one of the most poorly defined terms of modern medicine: it is emotive, subjective and imprecise. None the less it is an attractively appropriate descriptive term *when clearly defined,* and could usefully replace the many synonyms, such as "superlabile", "oscillatory" and "unstable".

Woodyatt [1] was the first to describe patients with diabetes as "brittle". He defined such patients as "... insulin-dependent diabetics whose control is so fragile that they are subject to frequent and precipitous fluctuations between hyperglycaemia and insulin reactions and in whom causes of instability have been excluded." Used correctly this definition has proved useful although it has often been grossly abused. Rosenbloom [2], when discussing brittle diabetes in children, narrowed the definition to "those children whose sensitivity to insulin is such that a dosage change of 10% will result in either ketonaemia or reactions". Colwell [3] stated that "unstable diabetes is characterised by irregular, unpredictable behaviour of glycaemia and glycosuria with all insulins, especially the depot varieties, even though the food supply and amount of exercise are constant."

These definitions, although useful, are rather restrictive and exclude those patients with predominantly hyperglycaemic or hypoglycaemic instability, which often form two distinct clinical subgroupings. In addition, it is now possible to define the cause of instability in many "brittle" patients (even if treatment remains difficult), and this would take many cases outside Woodyatt's definition. For these reasons, a more useful definition is that proposed by Tattersall in 1977 [4] ... "insulin-dependent diabetics whose lives are constantly disrupted by episodes of hypo- or hyperglycaemia, whatever the cause". The concept of life disruption is an important one, which usefully separates problematic from non-problematic unstable diabetic patients.

Prevalence

No reliable estimates are available on the true prevalence of brittle diabetes amongst Type I (insulin-dependent) diabetic patients. One extreme is the suggestion

that almost 100% of children with diabetes are brittle [5]. Marble [6], referring to the Joslin Clinic, quotes a prevalence of 20%, whilst Rosenbloom [2] more realistically gives an estimate of "less than 3%". Plauchu et al. [7], in a classic study covering 18 years, reported that 12% of all diabetic patients referred to them were brittle, and when known causes were excluded this figure dropped to 2.3%. Similar figures were produced by Kissel et al. [8] and Chimenies and Laurent [9], of 2.8% and 1.3%, respectively. Based on our own experience, we would suggest that present-day figures are lower – perhaps between 1 and 5 per 1000, due no doubt to the improvements in therapy which have occurred in the last two decades. Modern brittle diabetic patients are generally well known and conspicuous, their diabetes disrupting not only their own lives, but also those of their families and hospital doctors. A few are more obscure, and vigilance is required to detect these patients who may uncomplainingly accept severe instability as a "normal" part of their diabetes.

Causes

The causes of brittle diabetes can be conveniently grouped as shown in Table 1, and these will be reviewed in turn.

Therapeutic error

It is difficult to define quantitatively the contribution made by therapeutic errors to the total problem. However, it is worth quoting Lufkin [10] who stated that "unstable diabetes is almost always caused by errors in treatment either on the part of the patient or professional personnel". In Plauchu's series of 222 patients, thera-

Table 1. Major underlying causes of brittle diabetes

Therapeutic error
Intercurrent illness
Psychological problems
Insulin resistance syndromes

Table 2. Therapeutic error as a cause of brittle diabetes

Inappropriate insulin regimes:
  General
  Overinsulinisation
Injection problems
Monitoring problems
Dietary errors
Obsessional attention

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peutic errors were felt to be a major part of the problem in 21% of referred patients [7]. In our own series of 33 brittle diabetic patients, referred from diabetic clinics throughout the UK, five (15%) were primarily unstable due to faults in treatment [11]. It must be emphasised that mistakes in treatment are made by doctors, nurses and patients; and that they are always potentially avoidable. The commoner faults are listed in Table 2.

Inappropriate insulin regimes

It is generally agreed that C-peptide negative patients with Type 1 diabetes require at least twice-daily insulin injections. Interestingly, in one study of brittle diabetes, 94% of patients were on once-daily injection regimes [12]. Another common problem is the use of intermediate insulins of too short a duration of action (e.g. semilente types), causing hyperglycaemia before the next injection (if the dose of intermediate insulin is then increased in response, hypoglycaemia may occur between injections). The most stable diabetic patient can thus be rendered "brittle" by inappropriate insulin therapy.

An extension of this concept concerns the "Somogyi" phenomenon. This is an intriguing, though ill-understood, form of iatrogenic instability characterised by asymptomatic nocturnal hypoglycaemia due to excessive evening insulin doses. Somogyi [13] reported a "glycosuric tide" following hypoglycaemia which was frequently asymptomatic and often occurred at night. Control was improved by reduction of insulin doses, and Somogyi proposed that "rebound hyperglycaemia" occurred due to counter-regulatory hormone secretion following hypoglycaemia. This interpretation remains controversial (see below), but there is no doubt that asymptomatic nocturnal hypoglycaemia exists. In an important study, Gale and Tattersall [14] studied overnight blood glucose control in 39 unstable Type 1 diabetic patients. In 22 (56%), blood glucose fell to < 2 mmol/l during the night, and in 17 (44%) it remained low for at least 3 h. Hypoglycaemic symptoms were rare, but many patients reported "hangover" effects in the morning (lethargy, depression and headaches).

Hormonal studies by Gale et al. [15] and ourselves [16] suggest that the secondary rise in blood glucose level is due to falling plasma free insulin levels, rather than counter-regulatory hormone excess (though catecholamines were not analysed in these studies), and the problem can be partially or entirely corrected by giving the intermediate insulin at bed-time [16]. The morning rise in blood glucose, or "dawn phenomenon" [17] is partly physiological, and is not necessarily preceded by nocturnal hypoglycaemia. In practice, however, in most insulin-treated patients it usually represents inadequate duration of the previous evening's insulin injection, and the majority of "Somogyi-type" problems occur when this dose is excessive. Nevertheless, "counter-regulatory swings" cannot be discounted, and some recent metabolic studies have provided some support for this concept [18].

Over-insulinisation

The Somogyi phenomenon can perhaps best be considered as part of a general syndrome of "over-insulinisation" [19], sometimes colloquially known as the "insulin sink" or the "insulin addiction syndrome". The features are: (1) high (over $1 \text{ U} \cdot \text{kg}$ body weight$^{-1} \cdot \text{day}^{-1}$) and often increasing insulin doses; (2) poor and often erratic control (though episodes of hypoglycaemia are by no means invariable); and (3) obesity or increasing body weight. Several factors may be involved in the genesis of this syndrome. In 1969 Bloom et al. noted marked posthypoglycaemic unresponsiveness to insulin [20], and this may be related to induced counter-regulatory hormone responses [18]. Excessive carbohydrate intake in response to hypoglycaemia may increase weight, lead to hyperglycaemia and increasing insulin doses. "Down regulation" of insulin receptors in response to chronic hyperinsulinaemia may also play a role. Treatment comprises reduction of insulin doses [20], which may have to be slow and gradual.

Case 1

An 18-year-old insulin-dependent diabetic patient had persisting high random blood glucose levels in clinic, as well as home "BM Glycaemie 20/800" readings, usually in excess of 20 mmol/l. Surprisingly, her glycosylated haemoglobin (HbA₁) was only 9.0%. Her weight was 86 kg and daily dose 150 U/day (as twice daily "Rapitard" injections). When admitted to hospital for control, her blood glucose was 2.0 mmol/l, and subsequent profiles showed her to have grossly fluctuating glycaemic control. Over the next week her doses were reduced to 70 U/day with consequent stabilistation and improvement in blood glucose levels.

Case 2

A 41-year-old female with "brittle" diabetes was on 60 U/day as twice daily short- and intermediate-acting insulins. Her weight was 55 kg and HbA₁ 13.9%. No cause could be found for her instability, and while in hospital her doses were gradually reduced over 2 weeks to a total of 30 U/day with no change in insulin types. Mean blood glucose fell from 13.5 mmol/l (on 60 U/day) to 7.2 mmol/l (on 30 U/day).

The message must be that escalation of insulin doses in response to poor control should be avoided, and that, when presented with a brittle diabetic in high doses of insulin, attempts at reduction should always be made.

Other therapeutic errors

Several other forms of therapeutic errors exist (Table 2). Injection problems (e.g. too deep, too shallow, into lipohypertrophic areas, etc.) and dietary excesses are usually obvious problems. Monitoring is often a source of instability - especially when urinary glucose tests are confounded by a low renal threshold. "Sliding scales" of insulin doses in response to arbitrary urine (or blood) test results may at best do no good, but at worst lead to considerable worsening of the situation. All brittle diabetic patients should monitor blood glucose at home with visually-read or meter-read reagent strips. Urine tests are quite inappropriate. Obsessional attention to monitoring and insulin treatment can in itself lead to instability if too frequent changes in insulin doses are made [12]. In these cases, home monitoring may have to be curtailed, and dosage changes restricted to every 48 h.

Therapeutic errors are often multiple, and a programme of total re-education may be necessary.

Intercurrent illness

As with inappropriate therapy, intercurrent illness should be an easily recognised and rectifiable cause of brittle diabetes. The major conditions, which are mainly infective and endocrine, are listed in Table 3. Overall, unrecognised intercurrent illness is a rare cause of long-standing brittle diabetes, and most cases are diagnosed reasonably early. Thus, in our own series [11] we identified no patients with brittle diabetes due to intercurrent illness.

Infections

Tuberculosis is the single commonest cause - 10% of Plauchu's series [7]. Like other infections, it induces hyperglycaemic instability, with or without ketoacidosis, rather than hypoglycaemia.

Case 3

A 26-year-old male diabetic patient attended a teaching hospital clinic. When initially referred he was receiving 148 U/day of monocomponent porcine insulin in a twice daily regime of short- and intermediate-acting insulins. Home blood glucose monitoring results were continuously between 13 and 22 mmol/l, and attempts to improve control or reduce insulin doses were unsuccessful. He had a strange personality and his compliance was thought doubtful. Nine months after referral, he was admitted because of cough and weight loss, and a chest X-ray showed bilateral cavitating apical tuberculosis. Soon after referral to the diabetic clinic he had had a chest X-ray, and the report (showing "faint bilateral apical shadowing - suggest repeat") had not been noticed.

Endocrine disease

Oversecretion of any counter-regulatory hormone may lead to unstable hyperglycaemia in patients with pre-existing diabetes. Such causes include thyrotoxicosis, ac-

Table 3. Intercurrent illness as a cause of brittle diabetes

Infections	Any, but especially - tuberculosis
	     - urinary infection
	     - abscesses

Hormonal	Menstruation Thyrotoxicosis Phaeochromocytoma Cushing's syndrome Hypoadrenalism Hypopituitarism Pancreatectomy
Others	Progressive renal failure Malabsorption Chronic pancreatitis

romegaly, phaeochromocytoma, glucagonoma or hypercortisolaemia. In practice, thyrotoxicosis is the only important one of these endocrinopathies causing brittle diabetes [21, 22]. The others will increase insulin requirements without necessarily increasing lability. Premenstrual insulin resistance is a well recognised and presumably hormonally-mediated phenomenon, though poorly documented. Continuous oral contraceptive or danazol therapy may be required.

Hypoglycaemic instability is well recognised with hypopituitarism, hypoadrenalism, and following pancreatectomy. The excessive insulin sensitivity following hypophysectomy was recognised by Luft et al. in 1955 [23]. Tattersall [4] recorded a case of a female with diabetes who suffered an antepartum pituitary infarction. Subsequently she became hypoglycaemic on 6 U insulin/day, and ketoacidosic on 4 U/day. The hypoglycaemic episodes following pancreatectomy are presumably related to glucagon deficiency.

Other illnesses

Progressive renal failure - usually due to diabetic nephropathy - may also induce recurrent hypoglycaemia, despite diminishing insulin requirements, secondary to a prolonged half-life of insulin [24]. Malabsorption may cause erratic control, with hypoglycaemia a particular problem. Important causes are coeliac disease, "blind-loop" syndromes, and impaired gut mobility due to autonomic neuropathy [22].

Chronic pancreatitis may cause diabetes due to islet destruction, and the disease may be "brittle" [22, 25]. Half of Linde et al.'s series [25] of 36 pancreatic diabetic patients were labile, with frequent periods of hyperglycaemia interspersed with severe hypoglycaemia (three of the 18 died in hypoglycaemia). Glucagon deficiency presumably plays a part in this instability.

Psychological problems

Although it is easy to label a patient, in whom a physical cause for brittle diabetes is not found, as having a psy-

Table 4. Psychological problems which may underly brittle diabetes

Anxiety
Personality disorders
Psychopathy
Adolescent crises
Family conflicts
Psychosexual problems
"Life failure"

Table 5. Possible mechanisms by which psychological disturbances may lead to glycaemic instability

Stress hormone release induced by anxiety
Impaired decision-making due to psychological stress or personality problems
Manipulation of therapy to induce poor diabetic control

chological or psychiatric problem, there is no doubt that psychological factors are important in the genesis of many cases of brittle diabetes [4, 19]. In our own series of 33 brittle diabetic patients [11], 11 (33%) had psychological factors as the major cause for their instability. In Pickup et al.'s group of 14 brittle diabetic patients [26], seven had major family and/or social problems. In Plauchu's series [7] 16% showed psycho-affective disorders, while Kissel et al. [8] found significantly more personality disorders in unstable than in stable diabetic patients.

The literature on the effects of psychological stress on metabolism is confusing and conflicting [27, 28]. There is some evidence that undesirable life events result in alteration in metabolic control [29], and overall the literature supports the view that "stress" destabilises diabetic control [27, 28, 30, 31].

The types of psychological problems which may disrupt diabetes are listed in Table 4. They are often difficult to uncover, and may require painstaking and prolonged interviews with the patients and their families.

Case 4

A 27-year-old female diabetic had been "brittle" for many years, with recurrent admissions in ketoacidosis. Her control was eventually improved by insulin delivery via an indwelling peritoneal catheter, but soon after she admitted that most of her admissions had been induced by stopping her insulin, to escape from a drunken father who frequently beat her.

Case 5

A 36-year-old male diabetic had a 7-year history of recurrent admissions due to both hypo- and hyperglycaemia. Extensive investigations were negative, but enquiries were pursued with the patient, his wife, his friends, the family doctor and an involved social worker. They revealed a story of an unhappy childhood, poor attainment at school, an unstable marriage, unemployment, total financial dependence on the state, and eventually legal actions because of debts. Although largely untreatable, the uncovering and discussion of this "total life failure" helped both the patient and his doctors to understand the problem better, and there followed a marked reduction in hospital admissions.

Though there is no doubt of the importance of psychological disorders in leading to diabetic instability, there is much less certainty as to the mechanisms by which they do so. Three major mechanisms are listed in Table 5, and are discussed below:

Counter-regulatory hormone secretion

Hypersecretion of catecholamines in response to emotional stress could disrupt diabetic control [32], but in general there is a surprising dearth of experimental data with which to evaluate the importance of the metabolic response to psychological problems. Hinkle and Wolf in 1952 were the first to show that stress increased blood glucose and ketone body levels [33], and Baker et al. suggested that the metabolic decompensation was a consequence of increased catecholamine secretion [32]. These latter workers reported dramatic benefit from β-blocker therapy [34], but this has not been since substantiated. It has also never been established that patients with brittle diabetes are more susceptible than others to the metabolic effects of emotional stress.

Impaired decision-making

It is thus likely that psychological stresses disrupt diabetic control by their effect on behaviour rather than by a direct influence on metabolic processes. The inter-relations between diabetes, behaviour and control are complex [35]; but an extremely important behavioural abnormality is subconscious impairment of normal decision-making processes, as the following case illustrates.

Case 6

A 29-year-old nurse had been diabetic for 8 years and had suffered recurrent ketoacidosis for 3 years. She had an excellent practical and theoretical knowledge of diabetes, yet she would repeatedly be admitted late at night having observed her blood glucose levels rising all day (or for several days) and done nothing about it. When questioned about her lack of intervention she could offer no explanation. Enquiries revealed considerable tension at home with her mother, and admission often coincided with particularly bad arguments. To date this patient's decision-making problems, and diabetic stability, remain problematic.

Manipulative behaviour

In this context, "manipulative behaviour" signified deliberate interference with prescribed therapy to induce glycaemic instability. Such therapeutic "cheating" is usually conscious and deliberate, but it may become repetitive, stereotyped and virtually subconscious when the pattern of behaviour is well-established and persistently undetected.

Manipulative interference with diabetic treatment has long been known. Thus, where the psychological background of patients with recurrent ketoacidosis has been carefully explored, patients have freely admitted

to preferring hospital to home [36], usually provoking admission by manipulation of diet or insulin [37] because of emotional conflict within the family from which the need to escape by any means was overwhelming [4]. It is interesting to consider why this apparently destructive use of diabetes is more prevalent in females than males [11, 26, 38] – an enigma for which there is as yet no obvious explanation.

Examples of the methods of therapeutic manipulation used by some brittle diabetic patients we have been involved with are listed in Table 6. It can be seen that over 40% were inducing instability. The patients included in this sub-group were only those in whom manipulation was proven or admitted to. Similar problems were suspected in other patients, and we believe that treatment-interference probably operates in over half of all severely brittle diabetics. The lengths to which some patients went to was astounding, as the following case shows.

Case 7

A 19-year-old female diabetic had been hospitalised for 3½ out of the previous 4 years – in two general and two teaching hospitals. In one hospital she developed septicaemias with unusual organisms, and dilution of her intravenous insulin infusion fluid with tap water was suspected, but could not be proved. Over a year later, in another hospital, poor control (again on intravenous insulin) led to suspicion of similar tampering. The sodium (Na) concentration of the fluid in the syringe was found to be 98 mmol/l (the insulin was made up in "physiological" saline and had an Na level of 148–150 mmol/l immediately after preparation). She admitted to diluting the infusion fluid with tap water whilst in the ward toilet, and the confrontation was followed by a period of improved control of her diabetes. However, recurrent hyperglycaemia returned some months later, this time whilst being treated with a continuous intraperitoneal insulin infusion. On this occasion, however, infusion fluid Na levels were consistently 148–150 mmol/l. A locker search revealed a large cache of secreted drugs, insulins, syringes, and several ampoules of "physiological" saline. After further confrontation, she admitted that she was now diluting her pump fluids with saline to induce hyperglycaemia, but avoid biochemical detection!

An interesting point is that not all such manipulators have obvious psychological reasons. Thus, in the 14 patients referred to in Table 6, only seven had identifiable socio-psychological problems, such as those in Table 4.

Insulin resistance syndromes

Insulin resistance is an arbitrary term, originally reserved for patients receiving over 200 units insulin/day [39], though nowadays doses in excess of 100 U/day or $1.5 \, \text{U} \cdot \text{kg}^{-1} \cdot \text{day}^{-1}$ are often considered in the "resistant" range. Intercurrent illnesses (infections and endocrine hypersecretion syndromes), obesity, and over-insulinisation are the commonest causes of insulin resistance – as discussed previously. However, a number of less common conditions associated with high insulin requirements exist (Table 7), and they are outlined below. It should be noted that insulin resistance and "brittle-

Table 6. Methods of therapeutic interference used in 14 brittle diabetic patients

	Number of patients
Stopping insulin therapy	6
Massive over-eating	5
Damage to infusion catheters and equipment	5
Dilution of infusion fluids	2
Factitious hypoglycaemia	2

Of the 14 patients, 12 were female. Patients often used more than one method of therapeutic manipulation. The patients came from a group of 33 brittle diabetic patients referred from various UK diabetic clinics to Newcastle-upon-Tyne in the last 5 years, thus comprising 42% of the total

Table 7. Insulin resistance syndromes as possible causes of brittle diabetes

Insulin receptor antibodies (e.g. acanthosis nigricans associated)

Other receptor abnormalities (e.g. lipoatrophic diabetes, ataxia telangiectasia, leprechaunism)

Insulin antibodies

Subcutaneous insulin resistance

Overinsulinisation syndrome

Obesity[a]

Type 2 (non-insulin-dependent) diabetes[a]

[a] Although apparently obvious, Type 2 diabetic patients – both obese and non-obese – may be put onto insulin and become insulin resistant and/or unstable. The situation is resolved when insulin is stopped and an appropriate diet, with or without oral hypoglycaemic drugs, is substituted

ness" are not synonomous, and many patients with the conditions described below do not have frequent hospitalisation or disruption of their lives, though they may remain chronically hyperglycaemic on large amounts of insulin.

Insulin receptor abnormalities

Flier et al. [40] described three female patients with insulin receptor autoantibodies, extreme insulin resistance, acanthosis nigricans, and often other evidence of autoimmunity. Since then, further cases have been reported, and these are sometimes known as "Type B extreme insulin resistance"; in contrast to "Type A" patients who are usually younger women with signs of virilisation, and in whom the reduction in receptor numbers is probably genetic [41]. Both these syndromes are exceedingly rare, as are other conditions where insulin receptor abnormalities are thought to be the cause of insulin resistance, e.g. lipoatrophic diabetes, leprechaunism and the ataxia telangiectasia syndrome. In many of these conditions of receptor dysfunction, there is argument as to the relative roles of altered receptor number or affinity, or even a post-receptor defect [42].

Insulin antibodies

Antibodies to insulin are almost universally present in established insulin-dependent patients, but when levels are very high, they may be associated with insulin resistance. Such patients may respond dramatically to a change in insulin species [43], or to steroid therapy [44, 45].

Subcutaneous insulin resistance

It has been previously noted that some patients on very large subcutaneous insulin doses can be controlled on moderate intravenous doses. Thus, in 1978 Dandona et al. [46] described six patients on daily subcutaneous doses of 120-3000 U/day, but who required only 50-63 U/day intravenously to achieve good glycaemic control. There has been considerable recent interest in this "subcutaneous insulin resistance", which is thought to be due either to poor and erratic insulin absorption [47], or to increased enzymatic degradation of insulin in the subcutaneous tissues [48, 49]. Most patients with this problem are young females who are frequently overweight and are chronically or repeatedly hospitalised with recurrent ketoacidosis [11, 26, 38, 50]. This is a very rare sub-group of brittle diabetes – only about 20-30 have been identified in Britain. A problem with this syndrome of "subcutaneous insulin resistance" is that many such patients – about 50% in our own group of 19 patients [11, 38] – have been found subsequently to have seriously manipulated their therapy; and indeed the very existence of the syndrome has been challenged [51]. However, there is no doubt that true episodes of insulin resistance have occurred in at least some of these patients, and this has led us to propose a possible aetiological chain of events in which initial therapeutic manipulation leads to hyperglycaemic instability, escalating insulin doses, increasing body weight, overinsulinisation, insulin resistance and established chronic instability [38].

Clinical and metabolic features

The diverse aetiologies described above preclude any convenient single description – either clinical or metabolic – of the brittle syndrome. Nevertheless, several sub-groupings have been attempted, and some patterns have emerged.

All patients reported to date who have fitted reasonable criteria of brittle behaviour have been C-peptide-negative [50, 52, 53]. Presumably endogenous insulin secretion protects the patient against many of the physician's and patient's therapeutic mistakes. No characteristic pattern has emerged with regard to insulin antibodies. Though it has been suggested that lack of anti-

bodies may be a cause of "labile" diabetes [54], this has not been substantiated by others [12].

One particular subgroup mentioned above are young females [11, 26, 38, 50], mildly overweight, on high insulin doses, with putative subcutaneous insulin resistance, and with proven manipulative behaviour in a high proportion. A second group comprises lean young males who are insulin sensitive, but have no common aetiological factor [22]. Plauchu's series was also predominantly male, and again aetiologies were obscure or diverse [7]. The marked female predominance in two recent UK series of severely brittle diabetic patients [11, 26] has led to speculation that female sex hormones may be involved in promoting the brittle state. This hypothesis is given added support by the reported relationship of the onset of "brittleness" to the age of menarche [26], together with the established effects of menstruation on diabetic control. Disappointingly, little proof has emerged, and interference with the menstrual cycle by sex hormone therapy has been of little benefit.

Endocrine abnormalities have been sought avidly over the years, but no pathognomonic changes have been found. Catecholamine hypersecretion has been suggested [32], but consistent abnormalities have not been found [55]. "Metabolic hypersensitivity" to catecholamines has also been suggested [32], but the failure of adrenergic blockade to modify the brittle state argues strongly against this hypothesis. Cortisol levels have not proved abnormal [55, 56, 57, 58], and growth hormone levels have been reported as high [55, 59], low [56], and unhelpful [57, 58]. Low plasma glucagon levels were reported in one study [60] and may be important in some patients, but have not proved unusual in our own experience [58].

Metabolic changes in brittle diabetes have also been looked for. It has been suggested that ketoacidosis develops more rapidly in brittle diabetic patients than in stable patients, using insulin deprivation testing [50]. We have also noted persistent hyperlactataemia [50, 58] in many of our patients, though the cause and significance of this finding has eluded solution. These and other metabolic and hormonal abnormalities in brittle diabetic patients have been recently reviewed [61].

Insulin receptor studies on brittle patients suggest decreased affinity of adipose tissue insulin receptors and diminished responsiveness to insulin, consistent with insulin resistance [62]. Surprisingly insulin receptor numbers were normal. In one patient, these abnormalities returned to normal when relative normoglycaemia was attained for a period with intraperitioneal insulin infusion therapy, suggesting perhaps that the abnormalities were related to poor control and/or overinsulinisation.

The syndrome of brittle diabetes is thus a heterogeneous entity, and not surprisingly there appears to be no characteristic metabolic or endocrine abnormality which could lead to a logical therapeutic approach.

Approach to the brittle diabetic patient

General principles (Table 8)

It is important to take a fresh approach with such patients, if possible by admission to a specialised unit. Re-education must be intensive, and a diabetes nurse specialist is invaluable. All decisions regarding management, however, must be taken by one specialist doctor of senior status. The seeds of brittle diabetes are frequently germinated by inexperienced medical management.

Search for intercurrent illness

Many patients will not have an organic disorder underlying their glycaemic instability, and the search for intercurrent illness must therefore be carried out quickly and logically, in the first few days of the admission. These tests are vital, and must not be omitted, but their very performance suggests to patient and ward staff alike that there is a treatable non-diabetic illness at the root of the trouble, and this is generally unlikely.

Our protocol of investigation is shown in Table 9. The "group 1" tests are applied to all patients. Note, however, that recent ketoacidosis or hypoglycaemia may transiently elevate catecholamine and cortisol levels. Moderately raised erythrocyte sedimentation rate (ESR) values may also be occasionally seen in brittle diabetes [11]. The "group 2" investigations are generally only performed if clinically indicated, and are designed to exclude hypoadrenalism, hypopituitarism, malabsorption and occult infections (with the exception of the latter, these are all usually associated with hypoglycaemia and insulin sensitivity).

Exclusion of therapeutic error

This is helped by a well taken history, though over-insulinisation syndromes and asymptomatic hypoglycaemia may need more active searches. The patient's daily insulin dose should be calculated in terms of units/kg, and if above 1.0 units/kg, a programme of dose reduction should be attempted. Nocturnal hypoglycaemia requires overnight blood glucose profiles for detection. Indeed, for the first 24–48 h of admission, we recommend 2 hourly blood glucose estimations (by ward reflectance meter).

History-taking in the brittle diabetic

In general, 60–70% of diagnostic information will be revealed by the history, 20% by the examination, and only 5–10% by the investigations [63]. In brittle diabetes, a new and complete history is all-important, and an hour or two should be set aside for this task, which should not be entrusted to inexperienced junior staff. It should include a detailed review of the history of the illness

Table 8. General principles in the initial management of brittle diabetes

Recognise the problem
"Start again" policy (usually admit to hospital)
Intensive re-education
"One person" medical care
Meticulous and rapid programmed search for organic causes

Table 9. Investigations to exclude intercurrent illness as a cause of brittle diabetes

Group 1 tests	Group 2 tests
24-h urinary hydroxy-methoxy-mandelic acid	Synacthen test
24-h urinary free coritsol	Pituitary function tests
Serum creatinine	Autonomic function tests
Serum thyroxine, triidiothyronine, and free thyroxine index	Intestinal absorption tests
	Search for obscure infections
Chest X-ray	
Plain X-ray of abdomen (for pancreatic calcification)	
Tuberculin test	
Mid-stream urine cultures, and early-morning urine examination for tuberculosis	
Erythrocyte sedimentation rate	

from diagnosis, and it must include a careful appraisal of the patient's own practical skills, compliance, motivation, attitudes and aspirations. Social and psychiatric factors must also be explored at this stage. It is surprising how much information comes to light when an interested person spends this amount of time talking, in a structured way, to a chronically unstable diabetic. In particular, factors under the "therapeutic error" and "psychological problems" headings frequently come to light. When psychological problems seem likely, these preliminary discussion also pave the way for further investigative and psychotherapeutic sessions.

"Imprisonment tactics"

Well-established brittle diabetic patients have had various treatments tried, almost invariably with no useful result. The question of "manipulation" or "cheating" has frequently been raised. To identify clearly the causes of ineffective therapy, a carefully controlled system of patient isolation may be used with considerable benefit. On admission, the patient is helped to unpack by an experienced nurse, providing the means for an informal search. The patient is then confined to a cubicle under close observation for at least 48 h, and all blood testing and insulin injections are performed by skilled and experienced staff. All food entering and leaving the room is also noted, and visitors are not allowed (except, perhaps, parents). If, in this environment, diabetic control is easily achieved, then patient manipulation is

highly likely. Even if control remains difficult, the possibility of cheating may still need to be considered, as the cunning with which deception can be accomplished may defeat even the most experienced (case 7). The "imprisonment technique" needs clinical courage, and patient objections need to be dealt with tactfully. The results, however, may be remarkable. Schade et al. [64, 65], and ourselves, have used the technique to confirm therapeutic manipulation. In addition, Schade's group advocates a subcutaneous insulin absorption test, performed under rigorously controlled conditions, to exclude "subcutaneous insulin resistance" [64].

Follow-up techniques

Regardless of the underlying causes, patients with brittle diabetes need careful and meticulous out-patient care. The "one-doctor" technique is appropriate, though it must be remembered that no single doctor can provide continuous coverage, and others will have to be involved. Some form of telephone contact is needed, as is regular home blood glucose monitoring. The aim of management is, at least initially, to avoid hospitalisation or other "life-disruption" rather than to achieve good glycaemic control.

Occasionally, technical apparatus, such as subcutaneous infusion pumps or blood glucose meters, give useful status and confidence to brittle patients, and may help in their rehabilitation. Follow-up visits may need to be "on the ward" or "in the office", usually at weekly or 2-weekly intervals, as the routine diabetic clinic is often a bad place to give the time, education, listening and counselling which is often necessary for the brittle diabetic.

Managing the brittle diabetic patients

It is most important that reasonable objectives be defined when treating brittle diabetic patients, and these should be made clear to the patient and other members of the diabetes team. Management objectives in terms of glycaemic control are often unrealistic, and the primary task should be to relieve the "disruptive" element that the patient's diabetes has on his or her life-style. In practice, this usually means aiming at avoidance of hospitalisation. Thus, in some of our brittle patients we have defined "successful" therapy as "that which results in freedom from hospitalisation (due to diabetes) for a period of 6 months or more, regardless of glycaemic control" [11]. By whatever means this is achieved, such freedom from hospital admissions can be remarkably therapeutic. Demoralisation and frustration are relieved, and confidence restored; often breaking what had become a vicious circle of therapeutic inadequacy and unattained glycaemic goals.

Therapeutic error

Therapeutic error is of course treated on an individual basis, and may involve extensive re-education. Nocturnal hypoglycaemia is usually easy to treat – initially a reduction of evening intermediate-acting insulins should be tried. Sometimes, fasting hyperglycaemia (with or without nocturnal hypoglycaemia) is a particular problem, and here it is often useful to divide the evening insulin so that the short-acting component is given before the evening meal, and the intermediate-acting component before bed [16]. Persistent nocturnal control problems can sometimes be helped by continuous subcutaneous insulin infusion, though it should be emphasised that in general this form of therapy is rarely of use in brittle diabetes [11].

Intercurrent illness

Intercurrent illness is treated appropriately when it is recognised, and will not be discussed further here.

Psychological problems

If therapeutic error and intercurrent illness can be confidently excluded, then a psychological cause is most likely. This principle is not widely appreciated, and functional instability is often rejected by doctors involved with brittle diabetic patients at an early stage, with no proper exploration of the possibility. This allows continued and unresolved psychological conflict to be expressed as diabetic instability, which becomes protracted and entangled in a web of confusion and expensive failure. This in itself leads to further anxiety, and strains of the doctor-patient relationship. Therapeutically, the most important contribution the diabetologist can make is to "uncover" the psychosomatic milieu which is responsible for the diabetic difficulties. Simple demonstration of this to the patient and the diabetic care team goes a long way towards resolving the problems. Most of the underlying psychological factors (Table 4) are not formal psychiatric diagnoses, and we have found that psychiatric and/or psychological referral is usually of little use [38]. Frank discussions of the problem and its implications between the patient and diabetologist must be held, and close and careful follow-up should be undertaken as described in the last section. Our long-term experiences are similar to those of Tattersall [4] in that the majority of brittle diabetics (and especially the younger ones) "settle down" as the years pass, either returning to normal diabetic behaviour, or achieving a more acceptable level of poor control.

Serious compliance problems, and overt manipulation of therapy, need to be at least considered in most cases, and when strongly suspected, "detective work" (such as described in Case 7) may be indicated. Care is needed, as such patients will sense a breakdown of trust

in their relationship with the doctor. Usually, suspicions of manipulation need to be discussed with the patient, and if proof is found, it should not be produced triumphantly and used punitively. It generally indicates severe psychological and social maladjustment rather than cynical disrespect for the efforts of doctor and nurses. When therapeutic cheating is seriously self-destructive, psychiatric help may be necessary, preferably from someone experienced in, or with access to, intensive family and psychotherapy.

Insulin resistance syndromes

Insulin receptor abnormalities, receptor antibodies and insulin antibodies are extremely rare as causes of brittle diabetes, and their management will not be discussed further. Overinsulinisation syndromes have been dealt with previously.

Subcutaneous insulin resistance, however, presents serious management problems. The possibility that such resistance is due to increased enzyme-mediated degradation of insulin in the subcutaneous tissues, has lead to the use of the proteinase inhibitor aprotin (Trasylol, Bayer, Newbury, England), usually mixed with subcutaneously injected or infused insulin [48]. However, early successes with this treatment have not been maintained [66]; in our experience with subcutaneously-resistant patients, aprotinin has been of no use. The alternative theory to explain this syndrome is that insulin absorption from subcutaneously injected sites is poor and erratic because of variably impaired blood flow [47] – indeed it has been suggested that aprotinin itself may improve insulin absorption by inducing local hyperaemia [67]. Anecdotally, both local and systemic vasodilator therapy has not proved useful [68]; but recently, addition of prostaglandins to the injected insulin has been shown to improve absorption [69], though it is uncertain whether this effect will be therapeutically useful.

Although studies of blood glucose [70] and plasma free insulin [71] profiles strongly support the concept of subcutaneous "malabsorption" of insulin, many of the patients studied in these reports have subsequently proved to be psychologically disturbed patients who often interferred with their treatment [38]. Using "imprisonment techniques" and subcutaneous insulin absorption tests, Schade et al. [51, 64, 65] were unable to confirm abnormal insulin absorption in any patients referred to them with possible "subcutaneous resistance". The exact nature of this syndrome thus remains uncertain, but in our view both psychological problems and insulin resistance may co-exist and interplay as described earlier in this article.

Whatever the aetiology, many of these patients present serious management problems. Avoidance of further ketoacidosis is important, as their venous access is always poor – often centrally as well as peripherally

[11]. Even when definite psychological conflicts are found, and documented therapeutic cheating is demonstrated, control may remain problematic unless and until the underlying problems can be resolved. Initially, we have found intramuscular insulin (usually as intermittent injections) useful in this situation, although control may remain poor and doses sometimes escalate [11]. Continuous intraperitoneal insulin infusion may then be necessary, either with a temporary line, or a permanently implanted catheter [11, 72, 73]. This technique is much safer than the alternative of continuous intravenous insulin infusion which, although on occasions successful, is fraught with mechanical, thrombotic and infective complications [11, 74, 75]. On occasions, continuous intraperitoneal insulin infusion can be spectacularly successful – one of our former patients has been managed in this way for over 3 years by a district general hospital. She has been well, free of hospitalisations, and has even recently had a successful pregnancy with continuous intraperitoneal insulin infusion in situ (E. Barnes – personal communication).

Finally, there is now growing interest in totally implantable pumps, e.g. the "Infusaid" system (Infusaid Corporation Norwood, USA) for treating very severe "end stage" brittle diabetes [68]. These pumps infuse at a constant rate by the intravenous or intraperitoneal route, and to date six brittle diabetic patients in the UK have had such pumps implanted. Short-term follow-up has shown a remarkable reduction in hospitalisation, usually with considerably improved diabetic control.

Management conclusions

Finally, we restate the importance of the continuing quest for an explanation or diagnosis in all cases of difficult diabetes. We would also emphasise psychodynamic aspects of the problem because we believe that there is a tendency for these areas to be neglected in the face of a preoccupation with trying to control the blood glucose concentration. Whilst this remains a difficult and time-consuming part of management, underlying psychological problems must be explored and discussed with the patient and his or her family. It is more often a change in psychosocial circumstances rather than any particular form of insulin therapy which has led to a successful outcome in the majority of patients whom we have managed. Frequent changes in treatment, sophisticated insulin delivery systems, and protracted admissions simply to improve glycaemic control are in themselves not rewarding either to the physician or the patient, who may become even more distanced from a normal pattern of behaviour and development.

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