Handbook of Life Stress, Cognition and Health
Edited by S. Fisher and J. Reason

21

Stress and Diabetes

CLARE BRADLEY
University of Sheffield, England

INTRODUCTION

In the 1980s, there has been a surge of interest in stress and diabetes. It is commonly believed that stress can both precipitate diabetes onset and disrupt diabetes control. Growing evidence suggesting a causal association between chronic hyperglycaemia and subsequent complications of diabetes has motivated research into stress and other factors believed to affect diabetes control.

Stress research in general, and particularly life events research, has been accused of mindless empiricism in failing to consider mechanisms linking life events and illness outcome (Waterhouse, 1984). In diabetes-related stress research, models and mechanisms have been described (e.g. Tarnow and Silverman, 1981–2; Evans, 1985), though the models are unable to accommodate many of the data being produced. A second form of mindlessness noted by Waterhouse (1984) and common in diabetes research is the failure to appreciate and allow for individual variability in the appraisal of stress and failure to consider individual differences in responses to stress. Individual differences all too often ignored also include basic parameters concerning the nature of the subjects' diabetes and their treatment regimens. Some researchers in this field are, however, now recognizing the importance of differences between diabetic individuals responding to apparently similar stressors (Carter *et al.*, 1985; Stabler *et al.*, 1986) or exposed to the same stress management programme (Bradley, 1985), and there is greater recognition of differences between individuals in response to the diabetes itself (e.g. Johnson, 1980; Kosub and Cerreto, 1981).

THE PATHOPHYSIOLOGY OF DIABETES MELLITUS

It is now becoming clear that diabetes mellitus is not a single disorder but is a collection of several disorders with different underlying causes and with multiple

Preparation of this chapter was supported by NIH grant number AM28196 to the author.

hormonal abnormalities. All forms of diabetes mellitus are characterized by disordered carbohydrate metabolism with hyperglycaemia. Diabetes results from a deficiency of insulin function; either the beta cells of the pancreas produce insufficient insulin or the insulin produced may not be used effectively. Relative insufficiency of insulin may be due to hypersecretion or hyperactivity of insulin antagonists such as glucagon from the alpha cells of the pancreas, pituitary, adrenomedullary, or thyroid hormones.

The World Health Organization (1985) estimated that 2%–5% of the UK population and 5%–10% in the USA have some form of diabetes. Estimated prevalence rates elsewhere in the world vary from zero in the highland population of Papua New Guinea to 25% among the Pima Indians and Nauruans.

Insulin from beta cells of the pancreas promotes the uptake of glucose from the blood by the body cells. Without insulin, glucose metabolism and storage are inadequate and glucose accumulates in the blood. When the glucose reaches a sufficiently high level (approximately 10 mmol/l) it spills over into the urine and the volume of urine may increase considerably, causing dehydration. Thus thirst is a common symptom of untreated diabetes. Fat may be used as a metabolic substrate but complete metabolism of fat requires the presence of substances produced during the combustion of glucose. Thus, in the absence of glucose metabolism, fat combustion is incomplete, toxic intermediate metabolites (ketone bodies) are produced which accumulate in the blood. If ketone bodies collect in sufficient amounts, they cause acidosis and eventually coma, which may be fatal. This form of coma associated with untreated diabetes is the high blood glucose, or hyperglycaemic, coma. With insulin-treated diabetes, hypoglycaemic coma is more of a risk. Hypoglycaemia may occur if insulin is not balanced with sufficient carbohydrate intake or if unusual amounts of exercise are not compensated for by increased carbohydrate allowance or reduced insulin dosage. Recovery is rapid if glucose is given orally or intravenously or when the hormone, glucagon, is injected intramuscularly.

Some 85% of people with diabetes do not require insulin to manage their disorder. They have some effective endogenous insulin and some homeostatic control of their blood glucose. There is only a small risk of ketoacidosis and hyperglycaemic coma in people with this form of non-insulin-dependent diabetes (NIDD). In overweight people with NIDD, it is often possible to reduce carbohydrate intake to within a range in which endogenous insulin can cope. In such cases the diabetes can be managed by diet alone. In cases of people with NIDD who are not overweight, there is likely to be insufficient utilization of carbohydrates. Sulphonylureas (hypoglycaemic agents in tablet form) may be used to stimulate insulin secretion or to increase insulin effectiveness (see Lebovitz (1985) for review).

THE CLASSIFICATION OF DIABETES

There is currently active debate over how best to categorize the various types of diabetes which can be identified. The terms used are important for stress researchers to understand as stress responses would be expected to differ between subjects with different kinds of diabetes.

At one time diabetes was classified according to age at the time of diagnosis into 'juvenile-onset' or 'maturity-onset' diabetes. However, although all juvenile-onset patients would be dependent on insulin, the maturity-onset patients form a heterogeneous group including patients treated by diet alone, diet and tablets, and diet and insulin. In the interests of greater precision, diabetes was often described in terms of treatment prescribed. By the beginning of the 1980s a new terminology was being recommended which was intended to reflect different pathogenic mechanisms underlying the diabetes. A distinction between 'type I' and 'type II' diabetes was made on the basis of certain immunological phenomena and genetic markers. However, the methods for measuring these immunological and genetic characteristics are not commonly available. In practice the terms type I and type II have tended to be used synonymously with the labels insulin-dependent diabetes (IDD) and NIDD which refer to clinically descriptive sub-classes where the distinction is based on the patients' dependence for survival on exogenous insulin. Some patients are not easily classified as having IDD or NIDD. The term IDD is sometimes used to refer to anyone who uses insulin in treating their diabetes. A proportion of such patients, however, will have substantial amounts of effective endogenous insulin but have found it impossible to achieve good glycaemic control using other forms of therapy alone. Thus 'insulin treated' is not the same as 'insulin dependent' and this distinction is of particular importance to stress researchers investigating the effects of stress on diabetes control. Only truly IDD patients can be expected to have a complete absence of endogenous insulin and hence to have a lack of homeostatic control over any stress-related changes in blood glucose. Unless precise terminology is used in research reports, the reader may be misled about insulin availability in the subjects studied. C-peptide measures of endogenous insulin availability or details of clinical criteria which may be used in the absence of C-peptide measures (Welborn *et al.*, 1983) are needed to establish the nature of the subject samples studied in psychophysiological research on stress and diabetes control.

COMPLICATIONS OF DIABETES

Both IDD and NIDD are associated with a widespread pattern of tissue damage. Complications may precede diagnosis in older people with NID diabetes and the complications increase with duration of both ID and NID diabetes. It is unusual for people to be complication free after 20 years of diabetes.

Hypertension and hyperlipidaemia are more common among diabetic than among non-diabetic individuals and may contribute to the increased risk of coronary heart disease, cerebral vascular accidents and peripheral vascular disease in the diabetic population. The specific microvascular complications of diabetes include retinopathy, nephropathy and some aspects of neuropathy. There is now substantial evidence (Pirart, 1978; Tchobroutsky, 1978) to suggest that chronic hyperglycaemia associated with poor control of diabetes is one of the major factors responsible for the microvascular (though not the macrovascular) complications of diabetes. Attempts to avoid the microvascular complications are directed mainly at improving blood glucose control.

VARIABILITY OF GLYCAEMIC CONTROL

Variability of glycaemic control would be expected to be greatest for ID patients who have little if any endogenous insulin and least for people with obesity-related NIDD who have normal insulin production and homeostatic control of blood glucose. In IDD, any change in insulin requirements due to unexpected exercise, intercurrent illness, or other factors not anticipated by a well-judged adjustment to insulin dose, will be reflected in deviations of blood glucose levels.

A small proportion of individuals with IDD experience extreme swings of glycaemic control, occasionally with recurrent hypoglycaemic coma, but more often with frequent episodes of ketoacidosis and hyperglycaemic coma. This kind of extreme lability is often called 'brittle diabetes' (Tattersall, 1977) and accounts for a high proportion of emergency admissions in a small number of patients. The cause of brittle diabetes is the subject of much debate (e.g. Pickup *et al.*, 1983; Gill *et al.*, 1985). It is possible that, in some individuals, brittle diabetes is caused by overreactivity to stress. However, most of the studies of stress and diabetes control have ignored individual differences in response to stress, though the little evidence available suggests that such differences are considerable. Before considering these studies, however, the role of stress in the onset of diabetes will be considered and, first, attention will be given to the notion of diabetes as a stressor.

DIABETES AS A STRESSOR

Undoubtedly the onset of diabetes is a stressful experience for many individuals. Although much of the stress and coping literature may be of relevance to helping people with newly diagnosed diabetes, there is little evidence that research on the impact of diabetes has been influenced by this literature. Bradley and Marteau (1986) reviewed recent studies investigating the impact of diabetes on families and found little of direct relevance to health professionals attempting to help patients to cope with diabetes onset. A problem with much of this research has been that the meaning of the diabetes to the individual families has not been considered when investigating families' response to diabetes.

The dangers of assuming that diabetes has uniform implications for all those who have the disorder can be well illustrated with reference to a study by Felton *et al.* (1984). Felton and colleagues chose to study people with one of a number of chronic diseases selected to represent a dimension of controllability. Diabetes was viewed, by the authors, as offering intermediate control between certain forms of cancer and rheumatoid arthritis at the uncontrollable extreme and hypertension at the other extreme. There was no recognition that the degree of actual control possible will vary within diagnostic categories. Certainly, within the category of diabetes, controllability of the disorder would vary widely with the type of diabetes and the treatment regimen followed. It is apparent from research using a recently developed diabetes-specific measure of perceived control that individuals also differ considerably in their perceptions of control of diabetes (Bradley *et al.*, 1984). Furthermore, this measure has proved useful in predicting both choice and efficacy of different forms of treatment (Bradley *et al.*, 1987) and the

occurrence of diabetic ketoacidosis (Bradley *et al.*, 1986). It would not be surprising if this measure was also a useful predictor of coping strategies adopted in managing diabetes, but such relationships have yet to be investigated.

Many of the problems in Felton *et al.*'s study could be overcome by studying diagnostic groups separately. If the sample were limited to those with a particular kind of diabetes, differences in diabetes-specific perceived control could be measured and the relationships between perceived control and coping strategies, psychological and physiological adjustment could be investigated. Measures of adjustment could be selected that were known to be appropriate for people with diabetes (but might not have been appropriate for other subject groups), and the coping strategies considered could include those specific to diabetes.

By sharpening up the measurement instruments used, future studies could more precisely test hypotheses derived from the literature on stress and coping. Furthermore, cognitions and coping strategies predictive of positive physiological and psychological adjustment might be identified which would be useful in educating and counselling people with diabetes.

STRESS AND DIABETES ONSET

It is generally accepted that a wide range of environmental factors together with some degree of genetic predisposition are the cause of most forms of diabetes mellitus (Lebovitz, 1984). NIDD appears to have a strong genetic factor, with a 95% to 100% concordance rate in identical twins. However, the nature of the genetic abnormalities associated with insulin resistance and alterations in beta cell function of NIDD are unknown (Lebovitz, 1984).

There is evidence to suggest that IDD (but not NIDD) is an autoimmune disease which arises in susceptible individuals exposed to environmentally triggering events. The genetic contribution of IDD is no more than 50% since this is the maximum estimate of concordance in identical twins with IDD (Bottazzo *et al.*, 1985). The environmental contributions to the aetiology of IDD remain to be identified. Hypothesized events leading up to the clinical manifestation of IDD have been described by Lebovitz (1984). The first postulated step involves some toxic or infectious insult to the beta cells of a genetically susceptible individual. This insult leads to an immunological process that results in circulating antibodies to various components of islet cells. Chronic destruction of beta cells may be caused by one or more of these antibodies. When sufficient beta cells are destroyed, insulin secretion will be reduced to a point where hyperglycaemia and eventually ketoacidosis follow.

The literature on psychoimmunology (reviewed by Solomon *et al.*, 1985) suggests various ways in which psychological stress may be implicated in the initial stage of development of IDD hypothesized above. Stress-related changes in immune function may increase the likelihood of viral or bacterial disease, which may provide the initial insult to the beta cells. The Barts Windsor prospective family study showed that islet cell antibodies preceded the development of overt diabetes by at least 3 years (Gorsuch *et al.*, 1981). Thus any effects of stress on immunocompetence leading to damage to pancreatic

beta cells may have occurred long before onset of symptomatic diabetes.

A second mechanism whereby stress may be implicated in diabetes onset may operate around the time when diabetes becomes symptomatic. Stress-related counterregulatory hormone activity may aggravate the metabolic disturbance that has already developed. Indeed, if the already elevated blood glucose levels increase to beyond the renal threshold, dehydration associated with glycosuria may then produce the first symptoms of overt diabetes. The many anecdotal accounts and descriptive reports of life stresses contiguous with symptomatic IDD onset probably reflect this second mechanism.

Some retrospective studies of life events and diabetes onset have used designs prone to recall bias (e.g. Kisch, 1985), such that patterns of life events reported may reflect attempts to find an explanation for diabetes onset rather than a difference in events actually encountered. Other studies have avoided any problem of recall bias. Clayer and colleagues (1985) followed up 1526 victims who survived the 1983 bushfires in South Australia. The prevalence of a number of disorders, including diabetes, was significantly increased 12 months after the bushfires. Another study (Robinson and Fuller, 1985) made efforts to reduce recall bias and to estimate the influence of stressful life events on diabetes onset independently of any influence of individual differences in response to such events by employing Brown and Harris' Life Events and Difficulties Schedule. This study investigated thirteen ID diabetic/sibling pairs and neighbourhood controls involved in the Barts Windsor prospective family study. While the parent study was prospective, the offspring was retrospective in design: 77% of the diabetic subjects reported one or more severe life events in the 3 years prior to diagnosis, compared with 39% of siblings and 15% of age- and sex-matched neighbourhood controls. The authors concluded that stressful life events may be triggering factors involved in the aetiology of ID diabetes. This particular study restricted the period over which life events were recalled to 3 years. All diabetic subjects in the study would, therefore, have been expected to have had islet cell antibodies during this entire period. Thus the stresses identified in this study, and in the studies by Clayer *et al.* and Kisch described above, were probably not causally implicated in beta cell damage but more likely simply speeded up the manifestation of diabetes which would have become apparent eventually even in the absence of stress.

Early work which documented retrospectively an increased incidence of stressful experiences among an ID diabetic sample compared with non-diabetic comparison samples (e.g. Stein and Charles, 1975) have been viewed doubtfully by several reviewers (e.g. Fisher *et al.*, 1982; and Johnson, 1980) on account of the length of the period considered prior to symptomatology. Some of the stressful events in Stein and Charles' study were reported to have occurred as much as 10 years before onset of symptomatic diabetes. However, the recent evidence, reviewed above, suggests that many years may elapse between the actions of possibly stress-related causal agents initiating cell damage and the appearance of symptomatic diabetes. It would seem that, after all, it is not unreasonable to consider life events experienced over longer time periods when exploring the role of stress in the aetiology of ID diabetes.

THE EFFECTS OF STRESS ON DIABETES CONTROL

Life Events Research

Studies of life events and diabetes control have produced reasonably consistent results suggesting increased life events are associated with higher levels of blood glucose. Prior to the 1980s, studies were hampered by the lack of convenient measures of glycaemic control. Nevertheless, two studies (Grant *et al.*, 1974; Bradley, 1979) suggested that Holmes and Rahe-type life event measures were associated with disturbances of diabetes measured by a variety of indices.

A number of recent studies followed the development of long-term measures of glycaemic control. Glycosylated haemoglobin (GHb) and the related measures of haemoglobin A1 (HbA1) and haemoglobin AIC (HbAIC) reflect average blood glucose levels over the previous 6 to 8 weeks. These measures are far from perfect, and it is important that their limitations be recognized. In particular, they do not reflect blood glucose variation, only mean blood glucose. Nevertheless, GHb and related measures appeared to offer convenient alternatives to the single blood glucose and urine glucose measures which until recently were the only measures of glycaemic control readily available.

Recent studies have investigated relationships between HbA1 or HbA1C measures of glycaemic control and measures of perceived stress or impact of life events (Linn *et al.*, 1983; Jacobson *et al.*, 1985). One study by Cox *et al.* (1984) related HbA1 to the number of reported 'Hassles and Uplifts' elicited by Kanner *et al.*'s (1981) instrument to measure day-to-day stressful events. These studies indicated that life stress, measured in various ways, was associated with increased HbA1 levels. It has usually been presumed that life stress causes increased HbA1 in the simple manner shown in Figure 21.1.

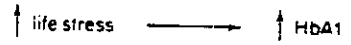

FIG. 21.1. A unidirectional causal model of the relationship between life stress and diabetes control.

Where studies of life events and diabetes control have compared subgroups of patients, subgroups with stronger associations between life events and HbA1 also reported more life events. Linn *et al.* (1983) compared Type I and Type II men and found that Type I men reported more life events as well as demonstrating a stronger association between perceived stress associated with life events and HbA1. Comparable findings were reported by Bradley (1979). Jacobson *et al.* (1985) found that a subgroup of patients with recent onset proliferative retinopathy reported more life events and a stronger life events/HbA1C association than subgroups of patients with long-standing retinopathy or no retinopathy of this kind. The greater number of life events in those who had stronger associations between life events and HbA1 could be explained in a number of ways. A perceptual bias may lead people who experience greater disturbance in association with life events to be more likely to note the occurrence of life events. Thus it

could be that the subgroups did not differ in the number of life events actually encountered, only in their perceptions of this number. However, if we assume that differences in the number of life events reported do reflect differences in the number encountered, and if we also assume that the association between life events and glycaemic control is a causal one, then the data may be economically encompassed by the model described in Figure 21.2, where the causal link works both ways: life events disrupt glycaemic control which in turn leads to more life events.

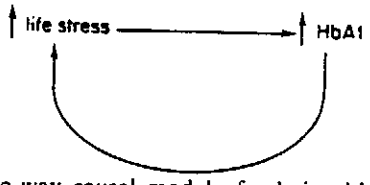

FIG. 21.2. A simple two-way causal model of relationships between life stress and diabetes control.

There are two kinds of mechanism which may account for life events causing raised blood glucose levels. The mechanisms by which counterregulatory hormones (CRHs) may mediate stress-related increases in blood glucose levels are well understood (Tarnow and Silverman, 1981–2; Evans, 1985). However, behavioural mediation of stress-related glycaemic fluctuations is also probable (e.g. Barglow *et al.*, 1984; Cox *et al.*, 1986).

Two of the above studies (Linn *et al.*, 1983; Cox *et al.*, 1984) concluded that the most obvious kind of behavioural influence, compliance with treatment recommendations, did not mediate the relationship between glycaemic control and life stress. However, the measures of compliance used were self-reports of the level of compliance over each study period as a whole. These ratings would not reflect any variability in compliance. Even a conscientious follower of their treatment regimen may well cut corners or temporarily abandon their diet during periods of stress. Such temporary aberrations might not be reflected in the patients' general ratings of compliance, but it is this kind of fluctuation which is interesting in the context of delineating the mechanism whereby stress is associated with poorer glycaemic control. The possibility of behavioural mediation of the relationship between life stress and glycaemic control cannot be excluded on the basis of studies conducted to date.

There are various possible mechanisms whereby poor glycaemic control may cause life events to occur or increase the impact of life events in ID patients. There is growing evidence that cognitive functioning may be impaired with hyperglycaemia (Holmes *et al.*, 1983; Holmes, 1987). Subjective symptoms, both physical symptoms (Cox *et al.*, 1983) and mood symptoms (Moses and Bradley, 1985), have been shown to vary with blood glucose levels. The experience of the hyperglycaemic state by some individuals as arousing, stressful or fatiguing may prime those individuals to note more life events or, indeed, to create more life events. Extremes of hypoglycaemia have also been shown to cause impaired cognitive function (Holmes *et al.*, 1983; Holmes, 1987) and aversive physical

symptoms and moods (Gonder-Frederick et al., 1986). Hypoglycaemic episodes can directly cause falls and accidents. Recurrent hypoglycaemic episodes may cause life events by undermining the confidence of the individual and the confidence of employers and others in the individual's reliability. Whatever the psychological impact of hypoglycaemic episodes, the metabolic impact on HbA1 levels will be trivial. In research relating life events to levels of HbA1, only relationships between long-lasting hyperglycaemia and life events will be apparent. Given the transitory nature of hypoglycaemic episodes and the limitations of HbA1 and similar measures of long-term glycaemic control, any associations between life stress and low blood glucose levels will go unnoticed in such research.

Few studies have provided data on individual differences rather than subgroup differences. However, available data point to considerable interindividual variation in the associations between metabolic control and life events experienced (Grant *et al.*, 1974). Cox and colleagues (1984) asked 35 ID patients who had monitored their blood glucose levels for 12 months about their perceptions of how various stress-related states affected their blood glucose levels. Although for most of the negative affects described, the majority of patients reported that their blood glucose levels would be raised, some reported lowered blood glucose, and a substantial number of patients reported no change in their blood glucose. If such differences were reflected in variable responses to life events, then the moderate overall relationship between life events and metabolic control observed masks far more dramatic glycaemic fluctuations among a more reactive subgroup which would include individuals with brittle diabetes.

Figure 21.3 offers a model which acknowledges the possibilities of individual differences in glycaemic response to life events and takes account of the data which suggest that subgroups of individuals not only demonstrate stronger associations between life events and glycaemic control but also report more life

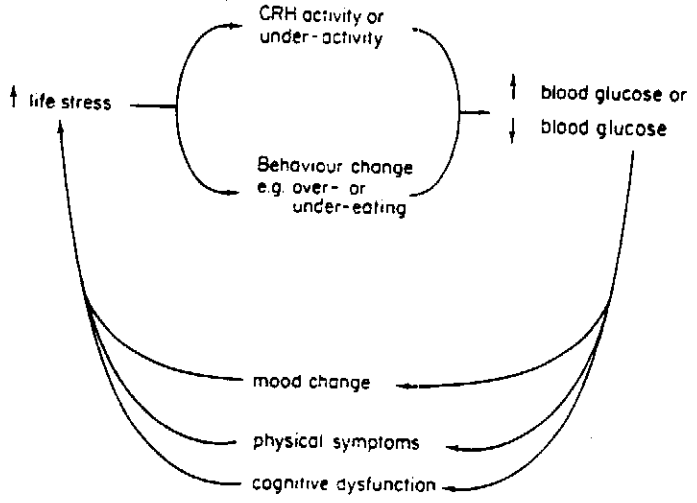

FIG. 21.3. An elaborated two-way causal model of relationships between life stress and diabetes control.

events. Since CRH activity would be likely to be more disruptive in people who have no endogenous insulin secretion, the model has no difficulty in accounting for differences between subgroups of patients likely to reflect the degree of homeostatic control.

In summary, therefore, life events research using HbA1, or similar measures of long-term glycaemic control, is likely to give a very oversimplified view of the relationship between stress and diabetes control. Mechanisms have been identified which may combine to cause life events to disrupt glycaemic control (CRH activity or inappropriate deviation from usual treatment regimen at times of stress) or to cause poor glycaemic control to increase the frequency or impact of life events (impairments to cognitive function, altered mood states). What few data there are on individual differences suggest that life stress is not infrequently associated with decreased blood glucose levels, though any such associations are obscured by the use of HbA1 measures of long-term glycaemic control.

Studies of the effects of acute stress on diabetes control have produced inconsistent and apparently contradictory findings both between the studies themselves and in comparison with life events research. The use of blood glucose as the measure of glycaemic control in studies of acute stress allows for hypoglycaemic effects of stress to be observed in a way that HbA1 measures used in life events research do not. Thus the range of measurable responses increases. In the section below it is argued that there is a need for greater attention to individual differences in response to acute stress.

Acute Stress and Diabetes Control

Reviews of the early literature (Watts, 1980; Fisher *et al.*, 1982; Bradley, 1982; Barglow *et al.*, 1984) concluded that the stressors used in the early studies had destabilizing effects on diabetes control but that the direction of blood glucose change was not consistent. The studies considered by these reviewers have been criticized by them and others (notably Lustman *et al.*, 1981) on a variety of methodological and conceptual grounds. The variability of findings concerning the direction and extent of blood glucose change associated with various forms of psychological stress have stimulated doubts about the potency of stressors used, the heterogeneity of subjects (both in terms of type of diabetes and degree of glycaemic control), and the adequacy of experimental design and statistical analyses. While such criticisms have been appropriate, the possibility that some of the variability in the findings may be due to individual differences in response to stress has been overlooked. A few more recent studies, while dealing with many of the criticisms of the earlier studies, have looked only for group differences, ignoring individual variability (Edwards and Yates, 1985; Naliboff *et al.*, 1985; Kemmer *et al.*, 1986). Naliboff and colleagues studied subjects with NID diabetes. The other two studies were of ID subjects (though 3 of the 10 diabetic subjects in Edwards and Yates' study had detectable C-peptide levels). Kemmer *et al.*'s study included a group of ID subjects made hyperglycaemic by omission of insulin injections. Stressors included a digit-symbol substitution task, mental arithmetic and public speaking. In none of the three studies did any of the

stressors used affect blood glucose levels in any of the groups. Two of the studies showed that self-reports of stress experienced increased significantly with the experimental tasks (Edwards and Yates, 1985; Kemmer *et al.*, 1986). Despite this and despite the evidence for increases in physiological and catecholamine measures of stress in two of the studies (Naliboff *et al.*, 1985; Kemmer *et al.*, 1986) and cortisol increases with one form of stress in one study (Kemmer *et al.*, 1986), no effects of stress on blood glucose levels were observed. Kemmer *et al.* cited Berk *et al.* (1985) in suggesting that plasma adrenaline must rise by at least 150–200 pg/ml to cause a clinically relevant increase in hepatic glucose production, and pointed out that the mean increase in their own study barely reached these levels in any of the groups. Mean increases in Naliboff *et al.*'s groups were even less. No data were provided on individual differences and there is a real possibility that the mean levels reported are misleading. Naliboff and colleagues noted large variability in the levels of catecholamines in their NID subjects, but this was only mentioned in explanation of the lack of significance for the apparently different catecholamine levels in diabetic and non-diabetic comparison groups.

Naliboff and colleagues went on to look for evidence of diabetic autonomic neuropathy which might cause decreased responsiveness in terms of both physiological and metabolic measures. Unfortunately, only group data were presented. The subjects as a group were said to have 'mild autonomic neuropathy' but it is unlikely that the label applied equally to the various members of the group. It would have been more informative to have related the degree of autonomic neuropathy present in an individual subject to that subject's responses to the stressful tasks. This was not done.

It seems that in their very thorough efforts to meet the criticisms levelled at earlier studies, these later studies have overlooked the possibility that individual differences in response to stress might be real and interesting and not a reflection of methodological inadequacies. None of the three studies has addressed the individual differences in their data.

There is some evidence from recent work of individual differences in responses to stress of the kind observed in the early, classic work of Hinkle and Wolf (e.g. Hinkle and Wolf, 1952). Carter and colleagues reported some preliminary data (Carter *et al.*, 1985) indicating that blood glucose change in response to the stress of mental arithmetic was idiosyncratic across subjects but significantly reliable across a 12-week period. Furthermore, the extent of the absolute change in blood glucose was significantly related to the pre-stress level of blood glucose. Further investigations are required to identify the characteristics of stress-responsive individuals and those of individuals with different kinds of blood glucose response.

One obvious candidate for a measure which may differentiate stress-responsive diabetic subjects from those whose blood glucose levels remain stable is a measure of Type A behaviour indicative of competitive drive for achievement, impatience and aggression. There is some evidence from a study by Stabler *et al.* (1986) that young IDD subjects classified as Type A in behaviour pattern differed from those classified as Type B in their blood glucose responses to 10 minutes of a challenging video game. All but one of the 6 Type A subjects showed increased blood glucose

in response to the stress, whereas all but one of the Type B subjects showed a decrease. Stabler and colleagues' study thus lends support to the findings of Carter *et al.* suggesting that individuals with IDD differ in their glycaemic responses to stress. Furthermore, Stabler *et al.* showed that the direction of blood glucose change was related to ratings of Type A behaviour.

The evidence for individual variability in glycaemic response to stress supports the view that a simple model of life stress leading to increased blood glucose levels is inadequate. It is likely that individual differences in the nature and extent of glycaemic response to life stress, comparable to the differences observed in patients under acute laboratory stress, would be observed if the methodology used allowed such differences to be detected.

The simple model of life stress causing raised blood glucose levels inspired much of the use of stress management training as an aid to diabetes control. The results of studies, reviewed below, evaluating the effects of stress management techniques on diabetes control, lend further evidence for the idiosyncratic nature of glycaemic responses to stress in diabetic subjects.

STRESS MANAGEMENT AND DIABETES CONTROL

There is growing evidence to suggest that stress management techniques may be valuable aids to diabetes management for some individuals, while being unhelpful or even damaging to diabetes control for others. Two of the earliest case reports illustrated these two extremes in ID individuals. Fowler *et al.* (1976) and Seeburg and DeBoer (1980) reported that insulin requirements were reduced by relaxation training with electromyographic (EMG) biofeedback. In Seeburg and DeBoer's study, training was terminated when the diabetes became unstable and hypoglycaemic symptoms were troublesome. Unlike the subject of the previous case report by Fowler *et al.*, this subject's diabetes was previously well controlled and no stress-related metabolic disturbances were experienced. It was not clear why relaxation training was thought to be appropriate in such a case.

Surwit and Feinglos (1983) investigated the effects of progressive relaxation training on 12 patients with type II diabetes who were selected because they reported experiencing stress-related fluctuations in diabetes control. Three-hour glucose tolerance tests and intravenous insulin tolerance tests were carried out before and after 5 days hospitalization during which six subjects received relaxation training. The glucose tolerance of the relaxation group was significantly improved and there was no associated change in insulin sensitivity or glucose-stimulated insulin secretory activity; findings which led the authors to suggest that the increases in glucose tolerance were mediated by hepatic mechanisms. In a subsequent letter, Surwit and Feinglos (1984) reported that improvements in glucose tolerance in the relaxation group were associated with decreases in plasma cortisol levels. Plasma levels of catecholamines were reported to have been within normal limits in all subjects and did not change with relaxation. Individual data presented in the original report (Surwit and Feinglos, 1983) suggested that individual differences in response to relaxation in this carefully controlled study of selected patients with NIDD were minimal.

The same authors conducted a comparable study of patients with poorly controlled type I diabetes who reported stress-induced hyperglycaemia (Feinglos *et al.*, 1987) and found no significant differences between relaxation and control groups in glucose tolerance, GHb levels or insulin requirements after 6 weeks practising relaxation at home. The groups did not differ in changes in plasma catecholamines or cortisol levels during the study period. The authors considered various possible explanations for the lack of effect of relaxation on this group of type I patients when significant positive effects had previously been noted for type II patients. They suggested that stress might play a greater role in disturbing control of type II diabetes since endogenous insulin secretion (which will not occur in type I diabetes) is likely to be inhibited by stress in type II individuals, which may add to any problem of raised blood glucose levels due to catecholamine and cortisol effects which would be expected to occur in both type I and type II patients. Secondly, the authors suggested that the patient population with type I diabetes may be heterogeneous in terms of glucose response to stress. They also pointed out that type I subjects tend to show more baseline variability in glycaemic control, which may influence stress response. Unfortunately the authors did not provide any information about the variability of the individual type I subjects. They suggested that future investigations of various means of stress reduction with type I patients should study subjects who have demonstrated hyperglycaemic responses to stress, and that attempts should be made to stabilize the baseline blood glucose of subjects beforehand for better evaluation of stress-related fluctuations and the effects of stress management.

One study in which blood glucose control was stabilized prior to relaxation training was reported by Landis and colleagues (1985). From the HbA1 levels, it appeared that there was little room for further improvement in glycaemic control with relaxation training. Indeed, given that such tight control was possible without relaxation training, it could be argued that stress could not be having much of a disruptive influence on the diabetes control of these individuals. Though it is possible that relaxation training might enable subjects to achieve the same degree of diabetes control more easily, with less juggling of insulin dose, carbohydrate intake and other variables, the data provided indicated that insulin dose, HbA1 levels and average blood glucose levels decreased for some patients and increased for others. However, variability of blood glucose (as indicated by daily range of blood glucose) decreased for four of the five patients studied and remained constant for the fifth patient.

Other recent reports of the use of relaxation in the management of ID diabetes include detailed case reports (Rosenbaum, 1983) and a small-scale study of four subjects by Lammers *et al.* (1984). Considerable variation in response to relaxation treatment was apparent both within and between studies. What little information is available on individual differences suggests that relaxation training was least useful for those subjects whose glycaemic control was good to start with (Landis *et al.*, 1985; Lammers *et al.*, 1984) and was most useful when used by subjects who not only had poor control of diabetes but also felt that stress was a factor in disrupting their control (Lammers *et al.*, 1984).

An extensive study of relaxation techniques to improve control of

insulin-requiring diabetes has recently been completed in Sheffield (Bradley *et al.*, 1985). Attempts were made to recruit patients in poor glycaemic control who felt that stress was a factor which affected their blood glucose levels. Thirty-two patients were studied in a baseline, treatment, follow-up design. Treatment involved one of two forms of relaxation training for two of three groups, the third group acting as controls. Measures of glycaemic control improved significantly from baseline to follow-up in all three groups. Differences between the groups did not reach significance. However, within-group differences were considerable: of 22 subjects who received relaxation training, 11 showed clinically significant improvements in glycaemic control. Preliminary analyses suggest that the 11 subjects who benefited from relaxation, differed from the 11 who did not on a number of variables. Those who benefited had poorer glycaemic control at baseline, and higher ratings of stress experienced on an English translation of Kanner *et al.*'s (1981) Hassles and Uplifts scale. These findings suggest that the patients who benefited from relaxation in terms of their glycaemic control were those the recruitment procedure attempted to select. Measures of health beliefs and perceptions of control of diabetes (Bradley *et al.*, 1984) were also obtained and their value in predicting treatment efficacy will be examined. It is plausible that relaxation training, in offering a means of control over psychophysiological reactions which might otherwise disrupt glycaemic control, will be of most use to those people who initially feel least personal control over their diabetes.

There is enormous scope for systematic investigation of the mediating role of cognitive factors in evaluations of stress management techniques as aids to diabetes management. Indeed, cognitive factors have been given scant consideration in research throughout the whole area of stress and diabetes, even though cognitions and beliefs about diabetes are generally considered to be factors important in determining the quality of diabetes care. Recent developments of reliable, diabetes-specific measures of health beliefs (Given *et al.*, 1983; Bradley *et al.*, 1984) and perceived control (Bradley *et al.*, 1984) may encourage wider consideration of individual differences in beliefs and cognitions in the context of research into diabetes and stress.

Mechanisms Whereby Stress Management may Affect Diabetes Control

It has usually been assumed that stress-related sympathetic nervous system activity disrupts diabetes control via mobilization of counterregulatory hormones and that stress management interventions serve to promote parasympathetic nervous system activity thereby counteracting the effects of stress. The evidence presented above suggests that individuals differ in the extent to which stress management techniques are beneficial. Adverse consequences of relaxation training experienced by a minority of individuals (e.g. Seeburg and DeBoer, 1980) may be due to inappropriate promotion of parasympathetic nervous system activity in circumstances where there is no stress-induced sympathetic nervous system activity to counteract. However, positive benefits of relaxation are seen more often than negative, even among IDD subjects with good glycaemic control prior to relaxation training (Landis *et al.*, 1985). One mechanism by which

relaxation techniques may be beneficial to glycaemic control is by reducing mood swings which in turn may reduce variability in skin blood flow and hence decrease variability in the absorption rates of subcutaneously injected insulin. There has been considerable interest in the role of skin blood flow and insulin absorption in accounting for within-subject variation in glycaemic control, but the effects of stress and stress management on these parameters have yet to be investigated. A further mechanism by which stress management techniques may improve glycaemic control is via behavioural mediation, perhaps by minimizing disruptive behaviour change associated with periods of life stress. Stress management interventions may break the vicious circle described in Figures 21.2 and 21.3 at the point where life events cause blood glucose change either by moderating CRH activity or by minimizing behavioural reactions to life events. The vicious circle may also be broken at the point where glycaemic disturbance increases the number of life events if the individual uses relaxation to cope with dysphoric moods associated with elevated blood glucose levels.

Thus a number of possible mechanisms can be identified by which stress management may influence diabetes control. Most of the mechanisms postulated would act to improve glycaemic control, though there is a risk of hypoglycaemia due to inappropriate suppression of CRH action or perhaps due to relaxation-induced increase in skin blood flow causing more rapid insulin absorption. Given the present state of knowledge, caution is needed when stress management techniques are used by diabetic individuals; relaxation practice should be avoided when blood glucose is in the low normal range (4 mmol/l or below), and treatment for hypoglycaemia should be readily available.

SUMMARY AND CONCLUSIONS

Few researchers have viewed diabetes as a stressor and approached the study of diabetes from the perspectives offered by the stress and coping literature. Where such a perspective has stimulated research, the unrealistic view of diabetes as a single disease entity with universal demands and consequences has undermined the work. Understanding of the nature of diabetes and its treatment is necessary for understanding the implications of existing research and provides a sound basis for future research.

It seems clear that stress can trigger onset of diabetic symptoms. There is a theoretical possibility that stress may also play a causal role in the initial damage to pancreatic islet cells, though evidence for such a role is thin.

It is becoming clear that individuals with diabetes differ in their response to stress and stress management. Researchers are beginning to appreciate the need to evaluate the effects of stress and the efficacy of therapeutic interventions on individuals rather than heterogeneous groups. It is argued that the apparent consistency of findings from life events studies indicating that HbA1 levels increase with life stress may be due, in part, to measurement artifacts, and that the lack of significant effects of laboratory stress on groups of diabetic subjects masks considerable individual variation in response to stress. By focusing attention on individual differences and working within a more complex model of relationships

[illegible] and diabetes control, we can begin to identify individuals for whom stress management is indicated as a useful addition to their diabetes treatment regimen.

REFERENCES

Berger, P., Hatcher, R., Edidin, D.V., & Sloan-Rossiter, D. (1984). Stress and metabolic control in diabetes: psychosomatic evidence and evaluation of methods. *Psychosomatic Medicine, 46,* 127–144.

Boyle, M.A., Clutter, W.E., Skor, D. *et al.* (1985). Enhanced glycaemic responsiveness to epinephrine in insulin-dependent diabetes mellitus is a result of the inability to secrete augmented insulin secretion normally limits the glycaemic but not the lipolytic or ketogenic response to epinephrine in humans. *Journal of Clinical Investigation, 75,* [illegible].

Bottazzo, G.F., Rujol-Borrell, R., & Gale, E. (1985). Etiology of diabetes: the role of autoimmune mechanisms. In K.G.M.M. Alberti & L.P. Krall (eds), *The diabetes annual vol. 1* (pp. 16–52). Amsterdam: Elsevier Science.

Bradley, C. (1979). Life events and the control of diabetes mellitus. *Journal of Psychosomatic Research, 23,* 159–162.

Bradley, C. (1982). Psychophysiological aspects of the management of diabetes mellitus. *International Journal of Mental Health, 11,* 117–132.

Bradley, C. (1985). Psychological aspects of diabetes. In K.G.M.M. Alberti & L.P. Krall (eds), *The diabetes annual.* vol. 1 (pp. 374–387). Amsterdam: Elsevier Science.

Bradley, C. & Marteau, T.M. (1986). Towards an integration of psychological and medical perspectives of diabetes management. In K.G.M.M. Alberti and L.P. Krall (eds), *The diabetes annual* vol. 2 (pp. 374–387). Amsterdam: Elsevier Science.

Bradley, C., Brewin, C.R., Gamsu, D.S., & Moses, J.L. (1984). Development of scales to measure perceived control of diabetes mellitus and diabetes related health beliefs. *Diabetic Medicine, 1,* 213–218.

Bradley, C., Moses, J.L. Gamsu, D.S., Knight, G., & Ward, J.D. (1985). The effects of relaxation on metabolic control of Type I diabetes: a matched controlled study. *Diabetes, 34,* 17A.

Bradley, C., Gamsu, D.S., Knight, G., Boulton, A.J.M., & Ward, J.D. (1986). Predicting risk of diabetic ketoacidosis in patients using continuous subcutaneous insulin infusion. *British Medical Journal, 293,* 242–243.

Bradley, C., Gamsu, D.S., Moses, J.L., Knight, G., Boulton, A.J.M., Drury, J., & Ward, J.D. (1987). The use of diabetes-specific perceived control and health belief measures to predict treatment choice and efficacy in a feasibility study of continuous subcutaneous insulin infusion pumps. *Psychology and Health, 1,* 123–132.

Carter, W.R., Gonder-Frederick, L.A., Cox, D.J., Clark, W.L. & Scott, D. (1985). Effect of stress on blood glucose in IDDM. *Diabetes Care, 8,* 411–412.

Clayer, J.P., Bookless-Pratz, C., & Harris, R.L. (1985). Some health consequences of a natural disaster. *The Medical Journal of Australia, 143,* 182–184.

Cox, D.J., Gonder-Frederick, L.A., Pohl, S., & Pennebaker, J.W. (1983). Reliability of symptom blood glucose relationships among insulin dependent adult diabetics. *Psychosomatic Medicine, 45,* 357–360.

Cox, D.J., Taylor, A.G., Nowacek, G., Holley-Wilcox, P., Pohl, S.L., & Guthrow, E. (1984). The relationship between psychological stress and insulin-dependent diabetic blood glucose control: preliminary investigations. *Health Psychology, 3,* 63–75.

Cox, D.J., Gonder-Frederick, L., Pohl, S. & Pennebaker, J.W. (1986). Diabetes. In K.A. Holroyd & T.L. Creer (eds), *Self-management of chronic disease,* pp. 305–346. New York: Academic Press.

Edwards, C., & Yates, A.J. (1985). The effects of cognitive task demand on subjective stress and blood glucose levels in diabetics and non-diabetics. *Journal of Psychosomatic Research, 29,* 59–69.

Evans, M.B. (1985). Emotional stress and diabetic control: a postulated model for the effect of emotional distress upon intermediary metabolism in the diabetic. *Biofeedback and Self-Regulation, 10,* 241–254.

Feinglos, M.N., Hastedt, P., & Surwit, R.S. (1987). Effects of relaxation therapy on patients with Type I diabetes mellitus. *Diabetes Care, 10,* 72–75.

Felton, B.J., Revenson, T.A., & Hinrichsen, G.A. (1984). Stress and coping in the explanation of psychological adjustment among chronically ill adults. *Social Science and Medicine, 18,* 889–898.

Fisher, E.B. Jr., Delamater, A.M., Bertelson, A.D., & Kirkley, B.G. (1982). Psychological factors in diabetes and its treatment. *Journal of Consulting and Clinical Psychology, 50,* 993–1003.

Fowler, J.E., Budzynski, T.H., & VandenBergh, R.L. (1976). Effects of an EMG biofeedback relaxation program on the control of diabetes: a case study. *Biofeedback and Self-Regulation, 1,* 105–112.

Gill, G.V., Walford, S. & Alberti, K.G.M.M. (1985). Brittle diabetes—present concepts. *Diabetologia, 28,* 579–589.

Given, C.W., Given, B.A., Gallin, R.S. & Condon, J.W. (1983). Development of scales to measure beliefs of diabetic patients. *Research in Nursing and Health, 6,* 127–141.

Gonder-Frederick, L.A., Cox, D.J., Bobbitt, S.A., & Pennebaker, J.W. (1986). Blood glucose symptom beliefs of diabetic patients: accuracy and implications. *Health Psychology, 5,* 327–341.

Gorsuch, A.N., Spencer, K.M., Lister, J., McNally, J.M., Dean, B.M., Bottazzo, G.F., Cudworth, A.G. (1981). The natural history of Type 1 (insulin dependent) diabetes mellitus: evidence for a long pre-diabetic period. *Lancet ii,* 1363–1365.

Grant, I., Kyle, G.C., Teichman, A., & Mendels, J. (1974). Recent life events and diabetes in adults. *Psychosomatic Medicine, 36,* 121–128.

Hinkle, L.E. & Wolf, S. (1952). Importance of life stress in the course and management of diabetes mellitus. *Journal of the American Medical Association, 148,* 513–520.

Holmes, C.S. (1987). Cognitive functioning and diabetes: broadening the paradigm for behavioural and health psychology? *Diabetes Care, 10,* 135–136.

Holmes, T.H. & Rahe, R.H. (1967). The social readjustment rating scale. *Journal of Psychosomatic Research, 11,* 213–218.

Holmes, C.S., Hayford, J.T., Gonzalez, J.L., & Weydert, J.A. (1983). A survey of cognitive functioning at different glucose levels in diabetic persons. *Diabetes Care, 6,* 180–185.

Jacobson, A.M., Rand, L.I., & Hauser, S.T. (1985). Psychologic stress and glycaemic control: a comparison of patients with and without proliferative retinopathy. *Psychosomatic Medicine, 47,* 372–381.

Johnson, S.B. (1980). Psychosocial factors in juvenile diabetes: a review. *Journal of Behavioral Medicine, 3,* 95–116.

Kanner, A.D., Coyne, J.C., Schaefer, C., & Lazarus, R.S. (1981). Comparison of two modes of stress measurement: daily hassles and uplifts versus major life events. *Journal of Behavioural Medicine, 4,* 1–39.

Kemmer, F.W., Bisping, R., Steingruber, H.J., Baar, H., Hardtmann, F., Schlaghhecke, R., & Berger, M. (1986). Psychological stress and metabolic control in patients with type I diabetes mellitus. *New England Journal of Medicine, 314,* 1078–1084.

Kisch, E.S. (1985). Stressful life events and the onset of diabetes mellitus. *Israel Journal of Medical Sciences, 21,* 356–358.

Kosub, S.M., & Cerreto, M.C. (1981). Juvenile diabetes: current trends in psychosocial research. *Social Work in Health Care, 6,* 91–101.

Lammers, C.A., Naliboff, B.D., & Straatmeyer, A.J. (1984). The effects of progressive relaxation on stress and diabetic control. *Behavior Research and Therapy, 22,* 641–650.

Landis, B., Jovanovic, L., Landis, E., Peterson, C.M., Groshen, S., Johnson, K., & Miller, N.E. (1985). Effects of stress reduction on daily glucose range in previously stabilised insulin-dependent diabetic patients. *Diabetes Care, 8,* 624–626.

Lebovitz, H.E. (1984). Etiology and pathogenesis of diabetes mellitus. *Pediatric Clinics of North America, 31,* 521–530.
Lebovitz, H.E. (1985) Oral hypoglycaemic agents. In K.G.M.M. Alberti & L.P. Krall (Eds), *The diabetes annual,* vol. 1 (pp. 93–110). Amsterdam: Elsevier Science.
Linn, M.W., Linn, B.S., Skyler, J.S., & Jensen, J. (1983). Stress and immune function in diabetes mellitus. *Clinical Immunology and Immunopathology, 27,* 223–233.
Lustman, P., Carney, R., & Amado, H. (1981). Acute stress and metabolism in diabetes. *Diabetes Care, 4,* 658–659.
Moses, J.L., & Bradley, C. (1985). Accuracy of subjective blood glucose estimation by patients with insulin-dependent diabetes. *Biofeedback and Self-Regulation, 10,* 301–314.
Naliboff, B.D., Cohen, M.J., & Sowers, J.D. (1985). Physiological and metabolic responses to brief stress in non-insulin dependent diabetic and control subjects. *Journal of Psychosomatic Research, 29,* 367–374.
Pickup, J., Williams, G., Johns, P., & Keen, H. (1983). Clinical features of brittle diabetic patients unresponsive to optimized subcutaneous insulin therapy (continuous subcutaneous insulin infusion). *Diabetes Care, 6,* 279–284.
Pirart, J. (1978). Diabetes mellitus and its degenerative complications: a prospective study of 4,400 patients observed between 1947 and 1973. *Diabetes Care, 1,* 168–188.
Robinson, N., & Fuller, J.H. (1985). Role of life events and difficulties in the onset of diabetes mellitus. *Journal of Psychosomatic Research, 29,* 583–591.
Rosenbaum, L. (1983). Biofeedback-assisted stress management for insulin-treated diabetes mellitus. *Biofeedback and Self-Regulation, 8,* 519–532.
Seeburg, K.N. & DeBoer, K.F. (1980). Effects of EMG biofeedback on diabetes. *Biofeedback and Self-Regulation, 5,* 289–293.
Solomon, G.F., Amkraut, A.A., & Rubin, R.T. (1985). Stress, hormones, neuroregulation and immunity. In S.R. Burchfield (ed.), *Stress: Psychological and Physiological interactions* (pp. 207–221). Washington: Hemisphere.
Stabler, B., Morris, M.A., Litton, J., Feinglos, M.N., & Surwit, R.S. (1986). Differential glycemic response to stress in Type A and Type B individuals with IDDM. *Diabetes Care, 9,* 550–551.
Stein, S.P., & Charles, E.S. (1975). Emotional factors in juvenile diabetes mellitus: a study of early life experience of 8 diabetic children. *Psychosomatic Medicine, 37,* 237–244.
Surwit, R.S., & Feinglos, M.N. (1983). The effects of relaxation on glucose tolerance in non-insulin-dependent diabetes. *Diabetes Care, 6,* 176–179.
Surwit, R.S., & Feinglos, M.N. (1984). Relaxation-induced improvement in glucose tolerance is associated with decreased plasma cortisol. *Diabetes Care, 7,* 203–204.
Tarnow, J.D., & Silverman, S.W. (1981–2). The psychophysiologic aspects of stress in juvenile diabetes mellitus. *International Journal of Psychiatry in Medicine, 11,* 25–44.
Tattersall, R. (1977). Brittle diabetes. *Clinical Endocrinology and Metabolism, 6,* 403–419.
Tchobroutsky, G. (1978). Relation of diabetic control to development of microvascular complications. *Diabetologia, 15,* 143–152.
Waterhouse, I.K. (1984). Presidential address: perspectives on stress, coping and vulnerability. *Australian Psychologist, 19*(2), 115–133.
Watts, F.N. (1980). Behavioural aspects of the management of diabetes mellitus: education, self-care and metabolic control. *Behaviour Research and Therapy, 18,* 171–180.
Welborn, T.A., Garcia-Webb, P., Bonser, A., McCann, V., & Constable, I. (1983). Clinical criteria that reflect C-peptide status in idiopathic diabetes. *Diabetes Care, 6,* 315–316.
World Health Organisation Study Group (1985). *Diabetes mellitus.* Technical Report Series, No. 727. Geneva: World Health Organisation.

KEY WORDS

Diabetes mellitus, stress, stress management, relaxation training, psychological, life events, brittle diabetes, aetiology, psychoimmunology, locus of control, perceived control, health beliefs, type A behaviour, individual differences, counterregulatory hormones, autonomic neuropathy, glycaemic control, blood glucose levels, glycosylated haemoglobin.