Reviews in Medicine

Diabetes mellitus

Andrew B. Johnson and Roy Taylor

Human Metabolism Research Group, Department of Medicine, Floor 4, William Leech Building, The Medical School, University of Newcastle upon Tyne, Framlington Place, Newcastle upon Tyne NE2 4HH, UK

Introduction

This review aims to summarize the major advances of the preceding year and to put them into the context of current opinion on diabetes mellitus. Coverage of subjects is uneven and reflects the areas of most intensive research activity. Classification of the major two syndromes of diabetes remains problematical, but the terminology of non-insulin dependent diabetes (NIDDM) and insulin dependent diabetes (IDDM) will be used throughout.

What causes NIDDM?

Although consideration of both genetic and environmental influences in the aetiology of NIDDM remains appropriate, the importance of the former has been underlined by study of family pedigrees and identical twin pairs. Search for environmental factors continues, although the commonly assumed factors of diet, obesity and lack of physical exercise probably only modulate the speed of progression to symptomatic disease. Epidemiological studies have highlighted the variation in prevalence of NIDDM in different racial groups. In a population based study of Coventry, UK, the overall prevalence of diabetes was four times higher in Asian than Caucasian men. The prevalence of diabetes was twice as high in Asian women than in Caucasian women.¹ These findings are all the more striking when it is considered that the prevalence in Caucasian subjects (2.8% and 4.3% for men and women respectively), was higher than expected. New information continues to flow from the study of Pima Indians, and this has been recently reviewed.² In this population the prevalence of NIDDM is over 50% above the age of 55, and peaks at almost 70% around the age of 60 years. Amongst those who develop NIDDM before the age of 25 years

the pattern of transmission from patients to offspring is consistent with an autosomal dominant mode of inheritance. Individuals with one Pima and one non-Pima parent have a risk of developing NIDDM midway between that of the two parent populations. In the Pima Indians, abnormally low tissue sensitivity to insulin precedes the development of hyperglycaemia, and hence possible causes of this have been hotly pursued. However, the insulin receptor gene from a young NIDDM Pima Indian, both of whose parents were diabetic, has been shown to be normal.³ Further work is required to exclude any possible abnormal post-translational modification of the insulin receptor.

Eriksson *et al.* divided the first degree relatives of NIDDM patients into those with normal glucose tolerance and those with impaired glucose tolerance according to a standard oral glucose tolerance test.⁴ Insulin-stimulated glucose metabolism was assessed using the euglycaemic clamp technique and a comparable defect in glucose uptake was observed in both groups compared to healthy controls with no family history of NIDDM. However, the first phase insulin response was normal in subjects with normal glucose tolerance, whilst subjects with impaired glucose tolerance had a decreased first phase response. No difference in blood glucose or insulin response was observed during an oral glucose tolerance test when obese, sedentary subjects with a first degree relative with NIDDM were compared to controls with no family history of diabetes.⁵ The ability of insulin to stimulate glucose disposal was, however, markedly decreased in those subjects with a positive family history. Interestingly, both basal hepatic glucose production and fasting blood glucose have been shown to be higher in non-diabetic, first degree relatives of patients with NIDDM than controls.⁶ Together, these studies suggest that both insulin resistance and impaired insulin secretion are necessary for the development of impaired glucose tolerance.

The offspring of parents who both have NIDDM have a high prevalence of diabetes and impaired glucose tolerance. Ramachandran *et al.* studied such a

Correspondence: R. Taylor, M.D., F.R.C.P., Visiting Professor, Division of Endocrinology, Department of Internal Medicine, Yale Medical School, Fitkin, I PO Box 3333, Connecticut, USA

group of lean offspring with normal glucose tolerance.⁷ Although plasma glucose responses during a glucose tolerance test were similar to those of control subjects, the corresponding insulin responses were higher. Furthermore, insulin sensitivity was lower in the lean offspring of two NIDDM parents than the non-diabetic controls. This suggests that these subjects have decreased insulin sensitivity and that the increased insulin response may be compensatory.

The debate about the relationship of hyperinsulinaemia to the development of NIDDM shifted ground considerably with the demonstration that conventional radioimmunoassays for insulin cross-reacted with both pro-insulin and split pro-insulins.⁸ Different radioimmunoassays are likely to over-report plasma insulin concentrations by differing degrees. However, fasting C-peptide concentrations are not low in NIDDM, and many individuals secrete apparently adequate amounts of insulin in the fasting state. A clear distinction must be made between the marked inability to secrete insulin in response to an elevation in blood glucose concentration, which is characteristic of NIDDM, and a normal, or moderately elevated, basal insulin secretion in the face of hyperglycaemia.

The nature of the pancreatic abnormality has moved to centre-stage with the recognition of the importance of amyloid deposition in proximity to the beta-cell membrane. The islet amyloid is distinct from that found in systemic amyloidoses in that it contains a novel 37 aminoacid peptide (amylin) which is secreted by the beta-cell.⁹ This polypeptide appears to be secreted by both normal and non-diabetic subjects.¹⁰ Amylin deposition is also found to a lesser extent in the islets of non-diabetic individuals, especially in elderly subjects.¹¹ It may be hypothesized that propensity to deposit amylin in the pancreatic islet at a greater rate than normal explains the development of the insulin secretory defect in NIDDM.

Observations that amylin, infused in pharmacological dosage, may bring about a decrease in insulin sensitivity has led to the concept that amylin could underlie both the insulin insensitivity and insulin secretory defect of NIDDM.¹² The presently available experimental evidence is of interest, but *in vivo* relevance is uncertain.

What causes insulin dependent diabetes?

The incidence of insulin dependent diabetes has been reported to be increasing over the last 3 decades.¹³ As this time scale is too short for any appreciable change in the gene pool, such an increased incidence, if genuine, would argue for the operation of some environmental influence. However, there are major problems in comparing incidence data over such periods of time. As most studies have concentrated on

IDDM in young individuals, it is possible that the susceptible individuals are developing the disease at an earlier age rather than the disease becoming more common overall. Viruses of various types remain the most frequently cited environmental trigger for IDDM, although confirmatory evidence is lacking.

Ninety five percent of Caucasians developing IDDM express either or both HLA DR3 or DR4 histocompatibility antigens, compared with approximately 40% of the non-diabetic population. It is now clear that the DQ locus also affects susceptibility to IDDM, and recent studies have demonstrated that susceptibility is most likely to require specific products of both the DR and DQ loci.¹⁴ Specifically, two alleles of the DR4 locus (Dw4 and Dw10) and the DQw3.2 allele of the DQ locus appear to be highly diabetogenic in combination. It is now well established that a single aminoacid substitution at position 57 of the DQ beta-chain (replacement of aspartic acid by alanine, valine or serine) increases the susceptibility to type I diabetes markedly, at least in Caucasians. It is clear that this single amino acid substitution does not act equally in all races, and in Japanese IDDM subjects, there is a high frequency of aspartic acid at the critical site.¹⁵

The cellular mechanism of beta cell destruction continues to pose puzzles. In several animal models of autoimmune diabetes, macrophages precede lymphocytes in infiltrating the islets.¹⁶ Not surprisingly, cellular cooperation is required for complete expression of β -cell killing, and this involves activated T-cells and natural killer cells. In view of the obvious difficulty in assessing the pancreatic infiltrate in human disease, peripheral blood, T-cell subsets have been studied. Both a decreased and an increased percentage of suppressor T-cells have been reported.^{17,18} Before the onset of insulin dependent diabetes, a persistent reduction of the ratio of helper to suppressor T-cells has been reported.¹⁹

The detection of antibodies directed against a cytoplasmic component of the islet cell is likely to vary depending on the assay used. Provided a high cut off point is used (more than 40 Juvenile Diabetes Foundation units), the antibody test does indeed identify high risk individuals.²⁰ A small group of such islet cell antibody (ICA) positive, first degree relatives of insulin dependent diabetic subjects were studied before the onset of overt diabetes. Fasting blood glucose was stable for up to 2.5 years, after which there was a steady rise over a further 1.5 years before overt diabetes. Both the tendency for a rise in fasting blood glucose and a fall in acute insulin response were predictive for the development of diabetes in this group.

In the greater Seattle area, screening of first degree relatives of IDDM patients between 1983 and 1988 revealed that 21 out of 724 (2.9%) individuals were ICA⁺.²¹ β -cell responses to intravenous glucose and arginine were assessed in 9 of

the ICA⁺ relatives and also in 11 ICA⁻ relatives and evaluated prospectively. Subclinical β -cell dysfunction was demonstrated in 18 of these relatives. After a median follow-up period of 42 months, 10 of the ICA⁻ relatives remained ICA⁻ and none had evidence of deteriorating β -cell dysfunction or had developed diabetes. Five ICA⁺ relatives remained persistently immunologically positive and 2 of these developed IDDM. The β -cell function of the other 3, however, remained stable. The subjects who demonstrated fluctuating ICA status had stable β -cell function and had not developed IDDM at the time of the report. Bruining *et al.* followed up 4,806 schoolchildren aged 5–19 years from a town in Holland for at least 10 years after screening them for islet cell antibodies to determine if subclinical autoimmunity precedes the onset of non-familial IDDM.²² In that period 4 of the 8 ICA⁺ subjects became insulin dependent, whereas those who were ICA⁻ had a 99.9% probability of being free from IDDM. Thus these two studies suggest that a positive ICA test on a single occasion and the persistence of ICA positivity is sometimes but not always associated with deteriorating β -cell function.

Several studies have demonstrated that the immunological damage to the pancreas may be modified in the short term by treatment with cyclosporin A. This observation is not of direct clinical applicability as the potential side effects of treatment are considerable in relation to the temporary advantage. However, identification of a marker for a subgroup of individuals most likely to demonstrate a major response to immunotherapy would indeed be of value. Unfortunately, a large randomized study of cyclosporin therapy has demonstrated a lack of relationship of response to either islet cell antibody titre or HLA DR phenotype.²³ Cyclosporin selectively inhibits T-lymphocyte immunity, whereas azathioprine inhibits both T- and B-cell function. In a double-blind controlled trial of azathioprine therapy in children with newly diagnosed IDDM, insulin secretion was better preserved in the active treatment group up to 6 months, but there was no difference between the two groups at 12 months.²⁴ Although immunotherapy appears attractive for secondary prevention, the appropriate magic bullet is not yet in our hands.

Interesting reports have followed the use of immunosuppressive agents such as cyclosporin and azathioprine, but their side effects place limitations on their use. Studies are therefore being undertaken in IDDM with agents that are less toxic. In 1989 the use of one such agent, nicotinamide, an inhibitor of poly (ADP-Ribose) synthetase, has been reported. Animal experiments have demonstrated that nicotinamide prevents the induction of diabetes by streptozotocin, promotes regeneration of β -cells

following partial pancreatectomy and slows diabetes induced by immune processes. This prompted its use in human studies. In newly diagnosed IDDM treatment for 45 days with either nicotinamide, 1 g daily, or placebo, the C-peptide response to intravenous glucagon was greater in those receiving nicotinamide than those on placebo. This effect, however, was transient and β -cell function deteriorated once the drug was discontinued.²⁵ In an open, controlled trial lasting 1 year, Pozzilli *et al.* demonstrated a significant improvement in C-peptide secretion at 6 months and 1 year in patients with recent onset IDDM who were treated with 250 g nicotinamide daily.²⁶ It should, however, be pointed out that basal and stimulated C-peptide secretion was not significantly different from the control group of IDDM patients although the C-peptide response (stimulated minus basal) was greater at 1 year in the nicotinamide treated patients. In a double-blind study (placebo or nicotinamide, 3 g daily for 9 months) performed on patients with established IDDM (1 to 5 years' duration) but residual insulin secretion both basal and post-glucagon C-peptide levels decreased in the control group, whereas the nicotinamide treated patients showed no such deterioration. Furthermore, fasting and stimulated C-peptide levels were higher in the treated than the non-treated group.²⁷ Together these studies suggest that nicotinamide treatment may improve residual β -cell function, but further studies are required to assess the clinical implications of such therapy.

Using insulin therapy alone, Shah and colleagues examined whether a period of early, intensive insulin treatment improved β -cell function in IDDM.²⁸ Fourteen newly diagnosed IDDM were randomized to receive conventional insulin treatment, whilst 12 patients were treated for 2 weeks in hospital with an external artificial pancreas (Biostator) and blood glucose levels maintained between 3.3 and 4.4 mmol/l. This group was subsequently managed on the same regimen as the controls. At 1 year the stimulated C-peptide levels were significantly higher in the Biostator group and the glycosylated haemoglobin levels were lower. Metabolic control, however, was poor at 1 year in the patients who received conventional therapy alone making it difficult to distinguish between cause and effect.

Pathophysiology of NIDDM

(a) Impaired insulin secretion

It is well established that the first phase insulin response following an intravenous bolus of glucose is absent in NIDDM, and furthermore, during the transition from normal glucose tolerance to

glucose intolerance reduction or complete loss of first phase secretion is a characteristic finding. The precise relevance of this secretory defect to subsequent glucose metabolism is, however, uncertain. In normal volunteers Luzi *et al.* demonstrated that the loss of the first phase response results in a marked delay and incomplete suppression of hepatic gluconeogenesis. Peripheral glucose disposal, however, was not impaired.²⁹ When the initial prandial insulin response was corrected by the delivery of exogenous insulin a 33% reduction in the subsequent glycaemic response to a mixed meal ensued in NIDDM patients.³⁰ The early delivery of insulin also resulted in a faster rate of fall in free-fatty acid levels and attenuated the initial rise in blood glucagon levels. Thus the loss of first phase insulin secretion may contribute to prandial hyperglycaemia glucose intolerance via a delay in inhibition of hepatic gluconeogenesis and the abnormal glucagon and fatty acid responses.

(b) Insulin action

The initial step in insulin action on target cells is the binding of the hormone to a specific receptor situated on the cell membrane. In NIDDM, the main site of resistance in peripheral tissues to the effects of insulin action is thought to occur after this step. The mechanism by which the insulin signal is transmitted across the cell membrane, resulting in the activation/inactivation of target enzymes, remains unclear. Discussion of this rapidly moving field³¹ is beyond the scope of this article and consequently only the clinical aspects of insulin action will be focused upon.

Once insulin has bound to its receptor, the insulin receptor complex is internalized and processed by the target cell. Processing involves the recycling and degradation of both insulin and its receptor or their translocation to other intracellular organelles.³² Previous studies have suggested that internalization and processing of the insulin-receptor complex may be important to the action of the hormone and it therefore follows that defects in these events may be related to insulin resistance in NIDDM. Recently Trischitta *et al.* have demonstrated that insulin receptor internalization in monocytes from obese NIDDM was lower than that observed in matched controls.³³ Abnormalities of both receptor and insulin processing were also demonstrated. Four weeks treatment with metformin (850 mg twice daily) significantly improved blood glucose control in obese NIDDM.³⁴ Insulin internalization and degradation also increased in this group but not in obese, non-diabetic control subjects who were treated in the same way with metformin. The relationship of studies on monocytes to pathophysiology of major metabolic tissues must, however, be viewed with caution.

Insulin receptor binding leads to activation of a tyrosine kinase intrinsic to the insulin receptor β -subunit, resulting in autophosphorylation of the insulin receptor. Once this has occurred, the β -subunit is capable of phosphorylating substrates within the cell. It has been suggested that human adipocytes contain two distinct receptor populations, both of which bind insulin, but only one of which is capable of insulin stimulated tyrosine autophosphorylation. The proportion of receptors that bind insulin but are incapable of insulin-stimulated tyrosine kinase autophosphorylation has been reported to be increased in NIDDM.³⁵ In NIDDM, Thies and colleagues observed decreased insulin receptor autophosphorylation, but the coupling between receptor autophosphorylation and phosphorylation of a possible endogenous substrate of the insulin receptor kinase, pp 185, was normal.³⁶ This implies that the decreased β -subunit autophosphorylation results in decreased phosphorylation of the pp 185 substrate. Treatment with gliclazide is known to improve peripheral tissue insulin action in NIDDM subjects, but it does so without altering skeletal muscle insulin receptor kinase activity.³⁷

Point mutations of the tyrosine kinase domain of the β -subunit bring about impaired tyrosine kinase activity. These mutations have been reported to be associated with diabetes in isolated cases.^{38,39} A number of cases of NIDDM associated with other mutations of the insulin receptor gene have been reported,⁴⁰ but it is unlikely that these abnormalities will explain more than a minority of cases of impaired insulin action.³

Recent progress has also been made in understanding the mechanisms by which insulin alters the activity of its target enzymes. As glycogen synthase is rate limiting for insulin stimulated glucose storage and is thus important in regulating glucose tolerance⁴¹ the present discussion will be limited to this enzyme. Using ¹³C nuclear magnetic resonance spectroscopy, Shulman and colleagues have demonstrated that skeletal muscle glycogen synthesis is decreased in NIDDM compared to non-diabetic control subjects.⁴² Extrapolation of this data to the whole body confirms that glycogen synthesis is the main route of glucose disposal and thus that defective glycogen synthesis plays a central role in the insulin resistance observed in NIDDM. Decreased insulin stimulated glucose disposal as a consequence of the failure of insulin to activate glycogen synthase has been demonstrated in newly presenting untreated NIDDM subjects, complementing the findings of the previous papers.⁴³ However, despite both improved blood glucose control and glucose disposal following intensive diet, no improvement of glycogen synthase activation was observed in these patients. Following treatment with the sulphonylurea glicla-

zide, insulin action on skeletal muscle glycogen synthase was potentiated without any change in insulin receptor kinase activity,³⁷ suggesting that sulphonylureas may enhance insulin action distal to the insulin receptor kinase. In IDDM patients physical training has a restorative effect, normalizing the maximal glycogen synthase activity in skeletal muscle.⁴⁴ Conversion of glycogen synthase from an inactive phosphorylated form to an active dephosphorylated form is brought about by glycogen synthase phosphatase. Fasting skeletal muscle glycogen synthase phosphatase activity in American Indians with varying degrees of glucose tolerance and intolerance was found to correlate with whole body glucose disposal, glucose storage and insulin stimulated glycogen synthase activity. This implies that decreased glycogen synthase activation might be secondary to a low fasting glycogen synthase phosphatase activity.⁴¹

There has been an explosion of research into glucose transport, as this step appears to be rate limiting for the entry of glucose into muscle and adipose tissue cells under physiological conditions of insulin stimulation. Glucose transport is mediated by a family of glucose carriers which are facilitated diffusion channels.⁴⁵ To date the cDNA clones encoding 5 different functional glucose transporters have been isolated and characterized.⁴⁶ These transporters have a distinct tissue distribution and biochemical properties.⁴⁷ In skeletal muscle and adipose tissue, a specific insulin regulatable transporter exists.⁴⁸ In adipose tissue and skeletal muscle, insulin recruits these transporters from an intracellular site to the plasma membrane and thus by increasing their numbers at this location stimulates glucose uptake. The insulin-regulatable glucose transporter is being intensively studied at present as a possible contributor to insulin resistance in NIDDM. Decreased insulin stimulated glucose transport has been demonstrated in adipocytes from NIDDM patients and this has been shown to be partly due to both reduced numbers and impaired functional activity of the insulin-regulatable glucose transporter.⁴⁹ However, most recently Pedersen *et al.* have demonstrated no significant alteration in either the amount of insulin-regulatable transporter protein or messenger RNA in skeletal muscle from NIDDM patients when compared to non-diabetic controls.⁵⁰ Thus despite the initial optimism there is contradictory, but no compelling evidence to suggest that a molecular defect at the level of the insulin-regulatable glucose transporter will relate to the aetiology of NIDDM.

NIDDM is also characterized by abnormalities of both carbohydrate and lipid metabolism. Several recent studies have shown that suppression of free fatty acid (FFA) levels are impaired in non-obese and obese NIDDM^{51,52} resulting in

increased plasma FFA levels. As skeletal muscle can metabolize both glucose and FFA, these substrates might compete with each other for metabolism and possibly enhanced oxidation of FFA may be partially responsible for the decreased insulin sensitivity observed in NIDDM. A number of investigators have attempted to demonstrate that the elevated FFA levels observed in NIDDM can contribute to peripheral insulin resistance. When plasma FFA levels have been elevated in non-diabetic subjects by the administration of heparin and intralipid, decreased insulin stimulated whole body glucose uptake⁵³ and, most recently, decreased glucose uptake by the forearm muscle have been demonstrated.⁵⁴ The competition between FFA and glucose metabolism is time dependent, and high plasma FFA levels have no effect on insulin mediated glucose disposal once this has been stimulated.⁵⁵ When FFA levels and lipid oxidation rates were maintained at fasting levels during clamp studies in NIDDM patients a further decrease in insulin stimulated glucose uptake occurred.⁵⁶ Despite this supportive evidence, increased FFA levels and lipid oxidation are unlikely to contribute more than 30% of the observed decrement in peripheral insulin sensitivity in NIDDM.

What is new in treatment?

(a) Diet

The last decade has seen marked changes in the dietary advice handed out to patients with diabetes. The long established low-carbohydrate (and therefore high-fat) regimes have been swept away in favour of higher complex carbohydrate and low fat diets. The glut of studies reporting short term metabolic benefit of antisocially high-fibre diets has receded. At least in some quarters, the realization is dawning that patients do not eat diets; they actually eat food. Eating behaviour is strongly determined by habits, peer pressure, and beliefs, and it is appropriate that more attention is now being paid to these factors. An analysis of the patterns of behaviour which led to sustained weight loss over a one year period was able to identify a small number of strategies which appeared to be successful in the group of over a hundred NIDDM patients studied.⁵⁷ Doubtless specific strategies successful for some individuals may not suit others, but it is of clinical utility to note that advice (a) to record all foods eaten and (b) to refuse food offered by others, could be employed fairly simply.

Blood glucose control is often strikingly poor in adolescent females and in the same group obesity is a common problem. In a group of IDDM women aged between 18 and 30 years, 58% reported that

they went on eating binges and over 10% met the accepted criteria for bulimia nervosa.⁵⁸ Over one third of the group admitted to intentionally decreasing the dosage of insulin to lose weight. More widespread recognition of the problems common in this group of individuals should at least allow more sympathetic handling in the routine diabetic clinic with appropriate referral in severe cases. It has been suggested that the human race should be divided into nibblers, gorgers, snackers and grazers.⁵⁹

The discussion rumbles on about whether to advise diabetic patients to include sucrose in their diet. Short term studies, especially in IDDM, suggest that inclusion of sucrose-containing snacks up to 7% of total daily calories does not affect blood glucose control.⁶⁰ Such studies tend to ignore the practical realities of managing people who have diabetes, largely because of the ease of taking large quantities of calories as sucrose in an effortless fashion. This is a problem for all overweight people, whether diabetic or not. A further concern is that consumption of moderate amounts of sucrose may result in hypertriglyceridaemia.⁶¹

(b) Sulphonylureas

Since the acceptance that the major difference between the various sulphonylurea agents was the duration of action, little new has emerged. Search for a significant extra pancreatic action continues, but is as yet inconclusive.⁶² Of considerable importance is the report by Jennings *et al.* on the prevalence of hypoglycaemic symptoms during treatment with sulphonylurea agents. Symptoms were experienced in over 20% of patients during the previous 6 month period and a subgroup experienced symptoms at least once per month. There was a marked difference in rate of hypoglycaemia with those individuals who had been taking sulphonylureas for less than 4 years being at greater risk than those who had been taking the agents for longer.⁶³

The possible utility of combining insulin with sulphonylurea therapy continues to attract attention.⁶⁴ Many such studies show a modest improvement in glycaemic control when both agents are used together. In view of the confusion inherent in using 2 therapeutic agents where one (usually insulin) would suffice, the cost of combination therapy would appear to weigh heavily against any potential therapeutic benefit.

(c) Metformin

The mechanism of action of this agent remains an enigma. A review of putative action upon intestine liver and muscle concluded that evidence was strongest for a stimulatory effect of metformin

upon muscle tissue.⁶⁵ Nonetheless, in a study of 12 NIDDM patients satisfactory decrease in diurnal blood glucose control was achieved without change in insulin stimulated glucose uptake as measured by the hyperinsulinaemic clamp method.⁶⁶ In the latter study, beneficial effects of treatment with metformin upon lipoprotein metabolism were demonstrated, with decreases in plasma triglyceride concentration and increases in plasma HDL-cholesterol concentration.

(d) Insulin therapy

The key to successful insulin therapy lies in achieving appropriate rates of absorption from the site of injection. In thin patients intramuscular injection of insulin is likely to occur from time to time. It has been known for some time that soluble insulin is absorbed from intramuscular injection sites more rapidly than from subcutaneous injection sites, and recently this has been shown to be the case also for isophane insulin.⁶⁷ Their observation that the within patient coefficient of variation was almost 30% for intramuscularly injected insulin emphasizes this possible pitfall as a potent cause of unstable diabetic control. Of equal interest was their observation that the between patient coefficient of variation for absorption of a correctly placed subcutaneous insulin injection was 50%. This underscores the clinical impression that different individuals absorb their insulin with differing characteristics.

Patients are frequently changed from isophane to lente based insulin regimens in the belief that lente insulin, when injected in combination with soluble insulin, gives rise to a longer duration of insulin action. In a double-blind cross-over trial of isophane and lente based insulin regimens, no evidence to support this concept was found, and diurnal blood glucose profiles were identical on each treatment.⁶⁸ This study involving 82 patients was sufficiently large to avoid a type II statistical error, but it must be considered that any one individual could conceivably respond differently to each type of insulin preparation. The persistent problem of fasting hyperglycaemia on twice daily soluble, plus intermediate acting insulins, was approached by comparing a Monotard based regimen with a human ultra-lente based regimen, both being given as twice daily injections combined with soluble insulin.⁶⁹ Over the 6 month double-blind cross-over study period it was demonstrated that use of human ultra-lente insulin in this manner did indeed produce significantly lower fasting blood glucose levels, but only at the expense of more serious hypoglycaemic events (0.38 versus 0.09 events/patient month). The authors conclude that ultra-lente insulin offers no clinical advantage over lente insulin in a twice daily insulin injection

regimen, and this conclusion reflects the day to day variability in insulin absorption which becomes more marked with the longer acting insulins.

This problem of unsatisfactory absorption characteristics of the intermediate and longer acting insulins has led to a search for an insulin analogue which is long acting, but more reliably absorbed. Substitution of 2 amino acids in the insulin molecule gives rise to a soluble but long acting insulin analogue, and the pharmacokinetics of this appear favourable.⁷⁰ The within patient coefficient of variation was markedly less with the analogue compared to human Ultratard insulin (18% versus 45%). This may well be the first step in the production of an insulin which can provide stable reproducible 24 h insulin concentrations after subcutaneous injection.

Three studies have looked at insulin regimens for NIDDM. In a group of poorly controlled non-obese NIDDM subjects, fasting blood glucose was equally controlled by use of either once daily lente insulin, or continuous subcutaneous insulin infusion.⁷¹ Not surprisingly, lower postprandial blood glucose levels were noted when three meal doses of short acting insulin were given, but this regime did not bring about such a marked fall in fasting blood glucose. Detailed studies of splanchnic and peripheral uptake of glucose demonstrated that basal insulin supplementation alone improved postprandial glucose metabolism, although this was made even more similar to normal subjects by addition of a pre-meal bolus of insulin.⁷² In a prospective cross-over study involving 8 month study periods, Blackshear and colleagues observed much lower rates of hypoglycaemia when insulin was administered as a constant basal rate intravenous infusion compared with single daily injections of either lente or ultra-lente insulins.⁷³ The findings of the latter study emphasize the problems of expecting once daily injections of intermediate or long-acting insulins to behave in a reliable manner.

(f) Pancreas transplantation

Even in the best of centres, segmental pancreatic transplantation achieves graft survival rates of between 56% for non-uraemic subjects and 77% for simultaneous pancreas-kidney transplants.⁷⁴ It is doubtful whether segmental pancreatic transplantation will ever achieve the status of a routine therapeutic modality.⁷⁵ Nonetheless, the technique has allowed further insight into the impact of near-normal blood glucose control upon glomerular structure in renal allografts of IDDM patients.⁷⁶ Transplantation of islets or insulin producing cells is far more attractive. This has proved difficult using human islets, but this year has seen the first report of successful islet transplantation

into an IDDM subject.⁷⁷ This subject received approximately 800,000 islets (from 1.6 human pancreas) into the portal vein. Twenty two days after transplantation mean fasting blood glucose was 6.4 mmol/l with a 2-hour post-prandial blood glucose of 7.8 mmol/l. It may well be a long time before transplantation of islet or at least insulin producing cells can be regarded as an established treatment for IDDM, but observations on the quality of life achieved after successful segmental pancreatic transplantation suggests that further work in this direction is well justified.^{78,79}

(g) Monitoring diabetic control

Information continues to accrue demonstrating the relationship between poor blood glucose control and microvascular complications. In a study of young IDDM subjects after only 5 years of disease mean HbA_{1c} was higher in those who had developed retinal micro-aneurysms.⁸⁰ Rather more surprisingly, some girls already exhibited an elevated albumin excretion rate, and they had a higher 5 year mean HbA_{1c}.

Assessment of blood glucose in hospitals by routine capillary blood glucose monitoring has deservedly attracted critical evaluation. Using a meter with built-in memory, marked variation between different wards in one hospital has been demonstrated.⁸¹ Even though all nurses had been informed of the study, numerous discrepancies were found in both the accuracy and existence of data. A second study, performed by 4 nurses and one scientist, found that 19% of all readings deviated from simultaneous laboratory results by more than 20%.⁸² Nurses in the one hospital which required certification before blood glucose monitoring was undertaken, had significantly more accurate results than nurses in the other 3 hospitals studied. Clearly, careful quality control schemes are required, together with adequate training for all staff who may carry out capillary blood glucose monitoring.

In the drive to decrease costs of laboratory investigations, fructosamine has been advocated as an alternative to HbA_{1c} in the assessment of overall blood glucose control. In a comparative study the coefficient of analytical variation for fructosamine (7.6%) was very much worse than that for HbA_{1c} (3.0%).⁸³ The authors point out the severe analytical deficiencies of fructosamine assays associated with the reflection (albeit inaccurate) of blood glucose control over too short a time interval to be of practical utility.

Evaluation of the quality of diabetes care achieved in general practice miniclinics is very topical at the present time, and the results of a 3 year prospective valuation bear close examination.⁸⁴ After 3 years, foot examination had been

carried out within the previous 12 months in only 67% of patients, and fundoscopy in 72%. These figures were approximately double those of a group of control practices without miniclinics. Hence even in the keen and interested practices, clinical management fell short of the ideal, although no comparable data for performance of a hospital clinic was included in the study. The logistics of providing care for the approximate 1 million diabetic people in the UK remain problematical.

Long term complications of diabetes

(a) Retinopathy

The importance of long term glycaemic control in determining the risk of diabetic retinopathy was clearly shown in a well designed study from Belfast.⁸⁵ Although maintaining a HbA1 level of below 10% is by no means an absolute insurance against developing retinopathy, it is obviously very worthwhile in the longterm preservation of vision. Clearly other factors are involved in the development of microvascular complications, and this raises the possibility of successful prevention by pharmacological means. In a 3 year double-blind randomized controlled trial of aspirin, aspirin plus dipyridamole, and placebo, the mean yearly increase in microaneurysms detected on fluorescein angiography was significantly less during either aspirin or aspirin/dipyridamole therapy. The change in number of microaneurysms correlated with other ophthalmoscopic features of diabetic retinopathy.⁸⁶ In this study, which was designed in the mid 1970s, the total daily dose of aspirin was 1 g daily, and 14% of patients (compared with 6% on placebo) discontinued therapy because of side effects. Further studies of low dose aspirin are warranted in view of the interesting findings in this study.

In NIDDM, maculopathy is the commonest cause of blindness, and this tends to distract attention from the occurrence of proliferative retinopathy in this group of patients. A long-term study of Pima Indians has found a cumulative incidence of proliferative retinopathy of 14% after 20 years of NIDDM. The presence of background retinopathy was the most important predictor of the risk of proliferative retinopathy, this occurring in all cases before proliferative change.⁸⁷ A systolic blood pressure of > 140 or a diastolic > 90 mmHg was associated with a two-fold increased risk of proliferative change. The practical clinical message from this study is clear: perform fundoscopy at least annually in all subjects, but more often in those with hypertension and background retinopathy.

The problem of screening for diabetic

retinopathy continues to attract attention, and use of the non-mydriatic retinal camera, to take polaroid photographs of each eye has been examined as a screening service for general practitioners.⁸⁸ Clear photographs were obtained in 158 out of 168 eyes photographed. In 18 out of the 84 patients photographed action was recommended as a result of photography. In this study the polaroid photographs were read in batches by a hospital physician, and it remains to be determined whether other results would be obtained by general practitioners reading the photographs.

Photocoagulation therapy for proliferative retinopathy is strikingly successful, with good results on 10 year follow-up. However, photocoagulation therapy for diabetic macular oedema, for exudative maculopathy has been introduced more recently.⁸⁹ A 10 year follow-up study from the Hammersmith Hospital reports preservation of vision of better than 6/60 in 76% of a group with exudative change and 65% in a group with oedematous or ischaemic change.⁹⁰ It is, however, chilling to note that the mortality in this group of patients was 45% over 10 years.

(b) Neuropathy

The major focus of work in this area remains that of investigating the potential benefit of aldose reductase inhibitors. These agents prevent excessive accumulation of sorbitol within nerve fibres, and are strikingly successful in reversing neuropathic change in experimental animals. Results of clinical studies have recently been reviewed, and are far less encouraging in general.⁹¹ It is possible that aldose reductase inhibitors would be successful in preventing development of neuropathy if given before capillary closure had caused irreversible ischaemic nerve damage. In view of the interest in a possible common metabolic basis for the development of microvascular complications, it is of interest to note that two years of aldose reductase inhibition demonstrated apparent prevention of rise in albumin excretion rate.⁹²

There is a major difficulty in assessing beneficial therapeutic effects on diabetic polyneuropathy in that neurophysiological tests do not necessarily agree, and certainly may not agree with change in neuropathic symptoms. Clinical efficacy is vitally related to change in symptoms, but they are notoriously difficult to assess, and hence objective measures have an attraction. In an attempt to establish acceptable criteria for change in neuropathy such as exist in retinopathy and nephropathy, Dyck and O'Brien have derived, from cross-sectional epidemiological data, the suggestion that a change in motor nerve conduction velocity of 2.9 metres per second should be regarded as meaningful.⁹³

It is now well established that tests of peripheral autonomic function, such as lack of sweating over the foot do not correlate with tests of central autonomic function. The R-R variation during deep breathing was found to be the most frequently abnormal vascular autonomic function.⁹⁴ However, in 12 out of 34 patients with any autonomic abnormality on testing, R-R variation during deep breathing was normal, and hence would have underestimated the prevalence of autonomic neuropathy. It is clear that multiple tests are required for an overall assessment of autonomic function, but rather more intriguing is the question of why neuropathy of any kind should be so patchy, in view of its likely metabolic basis.

(c) Nephropathy

Abnormal albumin excretion is now widely accepted as an early indicator of diabetic nephropathy. Contrary to popular belief, abnormal albumin excretion has been shown to be approximately twice as common in NIDDM compared with IDDM subjects.⁹⁵ The microalbuminuria of NIDDM may be present at any stage of the disease, doubtless reflecting uncertainty of true duration, whereas in IDDM it does not usually occur until after 5 years of disease. It is frequently necessary to consider whether proteinuria in any one individual is a reflection of diabetic nephropathy, or whether it could represent another primary renal disease. In a series of diabetic patients referred for renal biopsy because of proteinuria (and therefore necessarily biased towards problematical cases) primary renal pathology coexistent with some diabetic change was found in 28% of individuals.⁹⁶ Retinopathy, not surprisingly, was a useful indication of the likelihood of the presence of significant diabetic nephropathy.

The observation that only approximately 40% of all diabetic subjects will go on to develop diabetic retinopathy, even if they live long enough to have more than 40 years of diabetes, continues to be thought provoking. In a study of renal allografts residing for between 6 and 14 years in IDDM subjects there was a significant relationship between the degree of mesangial expansion and glycaemic control. However, there was evidence that factors relating to the individual kidney itself influenced the subsequent development of diabetic changes.⁹⁷ Such endogenous factors may be magnified by comparison between races. A study of Mexican Americans compared with non-Hispanic whites showed a 2.6-fold excess of clinical proteinuria after controlling for possible confounding variables. However, in the normotensive groups, the prevalence of proteinuria was similar between races, whereas in the hypertensive individuals there was a 3–4 fold excess of clinical proteinuria in the

Mexican Americans. These findings underscore the current belief that genetic susceptibility factors interact with degree of metabolic control in determining the rate of development of complications.⁹⁸

A survey carried out in the United Kingdom in 1985 identified 181 diabetic patients with advanced renal impairment. At follow-up analysis in 1989, two thirds of patients had received renal support (an increase on previous years), but one third of patients died without having received renal support treatment. This was partly accounted for by acute myocardial infarction, but half the untreated group died from renal failure. In view of the relatively rapid changes in views on contraindications to renal support treatment, the authors recommend that diabetic patients with nephropathy should be attended jointly by renal and diabetes physicians working together.⁹⁹

Hopefully, with better management, the problem of diabetic nephropathy should become less common. Parving and Hommel report that the cumulative death rate from diabetic nephropathy has fallen dramatically between 1971 and the present day.¹⁰⁰ Over this period of time much greater attention has been paid to control of blood pressure. Even though this study relied upon historical controls, the data are striking. Antihypertensive therapy involved use of various agents in the former study, and controversy continues as to whether angiotensin converting enzyme inhibitors have any specific effect in protecting renal function in view of their ability to diminish glomerular capillary pressure. In an attempt to dissect apart the effects of captopril upon systemic blood pressure and those upon intraglomerular pressure, this agent was used in a group of normotensive IDDM with nephropathy. Fractional albumin clearance fell by 17% in the captopril treated group, but increased by 66% in the controls. It is tempting to interpret this finding as indicating a specific effect of angiotensin converting enzyme inhibition, but significant difference in mean arterial pressure also developed between the control and treatment groups.¹⁰¹ At the present time, decrease in blood pressure must be regarded as the most important therapeutic goal in diabetic patients with or without microalbuminuria. Choice of agent should be guided by likelihood of symptomatic and metabolic side effects.

(d) Hypertension

The observation that essential hypertension is characterized by the relative insensitivity to insulin has been confirmed, with demonstration that this phenomena is independent of obesity.¹⁰² A study of 2,480 Californians has confirmed the relationship between glucose tolerance and hypertension.¹⁰³ In this series of subjects not taking antihypertensive

medication, the age adjusted systolic blood pressure ranged from 134 in metabolically normal men, 139 in those with impaired glucose tolerance, 144 in newly diagnosed NIDDM and 142 mmHg in those with previously diagnosed NIDDM. In women, the same relationship held, but those with known NIDDM had an even higher age adjusted systolic blood pressure (145 mmHg). The mechanism of this effect has received much attention. In hyperinsulinaemic NIDDM subjects, proximal tubule sodium absorption is increased.¹⁰⁴ In IDDM subjects similar findings were observed.¹⁰⁵ In the latter study, the hyperinsulinaemia appeared to inhibit an adequate atrial natriuretic peptide response to infusion of saline, and in these subjects, the exchangeable sodium pool was 10–12% greater than in control subjects regardless of the presence of hypertension.

With increasing interest in antihypertensive agents which have no adverse metabolic side effects, including angiotensin converting enzyme inhibitors, calcium channel blockers and prazosin,¹⁰⁶ quantification of the adverse metabolic effects of the more established agents has progressed. Insulin sensitivity to glucose disposal decreased significantly during therapy with both metoprolol and atenolol.¹⁰⁷ During treatment with metoprolol, highly significant changes were observed in VLDL cholesterol (+ 0.2 mmol/l), HDL cholesterol (– 0.06 mmol/l) and serum triglycerides (+ 0.59 mmol/l), with similar changes being noted during atenolol therapy. In a randomized double-blind study of diltiazem and atenolol, insulin sensitivity decreased during atenolol treatment, but not during diltiazem treatment. Atenolol, but not diltiazem, had adverse effects upon the lipid profile.¹⁰⁸ In a comparative study with captopril, hydrochlorthiazide was shown to decrease insulin sensitivity and disturb lipoprotein metabolism.¹⁰⁹ Clearly, agents which have potentially adverse metabolic side effects should be used in diabetes only with very careful monitoring, and only then when more satisfactory alternatives are contraindicated.

(e) Macrovascular disease

Mortality in diabetes after acute myocardial infarction has been known for some time to be greater than in non-diabetic subjects. In a group of 228 non-insulin dependent diabetic subjects mortality at 30 days was greater in the diabetic group (27 vs 17%).¹¹⁰ As expected, women made up almost half of the diabetic cohort in contrast to less than one third of the non-diabetic cohort. The relative risk of dying in the NIDDM group was greatest amongst patients with the lowest number of evident risk factors prior to myocardial infarction, this being 7-fold higher within 30 days. Transmural myocar-

dial infarction in NIDDM was particularly lethal in this study.

The impact of diabetes on intermittent claudication and coronary heart disease was examined in the 34 year follow-up data from the Framingham study. Diabetes was associated with a 2–3-fold increased risk of developing intermittent claudication, and the risk was greater in those subjects who required anything other than diet therapy. In the presence of intermittent claudication and diabetes, the risk of coronary heart disease was increased 3–4 times in women and 3 times in men.¹¹¹ Whilst these conclusions are not surprising, they serve to emphasize the personal and economic cost associated with diabetes. As a further illustration of this, the age adjusted rate of lower leg amputation in the diabetic population of the United States is approximately 15 times that of the non-diabetic population.¹¹² In an assessment of the risk factors, being male, black, and having had previous amputation or foot lesion, was associated with considerably greater risk of amputation. Surprisingly the authors did not evaluate the risk associated with living alone.

(f) The diabetic foot

Use of plaster casts to relieve focal pressure, particularly in the presence of plantar foot ulceration of neuropathic type has been accepted for some time, but it has never received appropriate attention and is probably underused. In a study of use of plaster casts compared with traditional dressing treatment, 19 of 21 ulcers healed in a mean of 42 days after plaster cast treatment, whereas only 6 out of 19 ulcers healed in a mean of 65 days with conventional treatment.¹¹³ In a further prospective study, which included both ischaemic and neuropathic ulcers, 100% of those patients with plantar ulcers healed.¹¹⁴ Although care is required with application of plaster casts, together with adequate regular supervision, the overwhelming advantages of out-patient treatment should see a steady increase in usage of this form of therapy.

Arguably the most significant advance in the care of the diabetic foot comes in the form of socks.¹¹⁵ Specially designed shoes tend to be unpopular with patients, and Vevs and colleagues point out the advantages of using padded socks. This follows from the increasing interest in the use of special socks to protect the feet of sportsmen. Using a dynamic optical paedobarograph, a decrease of peak forefoot pressure of 26% was observed with the padded socks, and this reduced the highest peak pressure observed in the diabetic group to the upper limit of the non-diabetic range. Perhaps people with diabetes should be encouraged to bound around in frequently-changed sports socks and training shoes (of adequate size).

Pregnancy in diabetes

There is a current tendency to regard the problems of managing pregnancy in IDDM as being simple: one must merely achieve very good blood glucose control from before conception to after delivery. However, a false sense of security has sprung up because of the use of the traditional index of perinatal mortality, which has fallen from 32% to 4% over the last 50 years.¹¹⁶ This statistic does not include late neonatal deaths (i.e. after one week in the intensive care unit), still births before 28 weeks' gestation and missed abortions (which are commoner in IDDM). Major congenital malformations have become very much less common following the widespread realization of the need for excellent glycaemic control periconception and during the first few weeks of pregnancy, but the problem has certainly not gone away. Revision of the indices used to audit the outcome of pregnancy to include the concept of 'total fetal loss' would introduce a suitable degree of realism.

Although many women achieve good control at least after the pregnancy is confirmed; there remain some individuals whose control is persistently poor. A detailed study of 48 IDDM pregnancies was unable to detect any predictive factors between the group who achieved all weekly mean blood glucose values below 6.0 mmol/l and those who had values greater than 6 mmol/l on more than 6 of the weeks monitored.¹¹⁷ Compliance itself would appear to be the most important predictive factor, but the tools to manipulate this are as yet imperfect.

Gestational diabetes, as variously defined, continues to attract attention. Although it would be difficult not to advise conventional treatment (dietary, with insulin added if aims of treatment are not met), the debate continues on whether treatment of gestational diabetes affects the perinatal outcome.¹¹⁸⁻¹²⁰ Surprisingly, unrealistically energy-restricted diets continue to be investigated.¹²¹ All such studies observe a marked increase in fasting ketones achieved together with a very modest effect on plasma glucose profiles.

References

What causes NIDDM?

1. Simmons, S., Williams, D.R.R. & Powell, M.J. Prevalence of diabetes in a predominantly Asian community: preliminary findings of the Coventry diabetes study. *Br Med J* 298: 18-20.
2. Knowler, W.C., Pettitt, D.J., Saad, M.F. & Bennett, P.H. Diabetes mellitus in the Pima Indians: incidence, risk factors and pathogenesis. *Diabetes Metab Rev* 1990, 6: 1-28.
3. Cama, A., Patterson, A.P., Kadowaki, T. *et al.* The amino acid sequence of the insulin receptor is normal in an insulin-resistant Pima Indian. *J Clin Endocrinol Metab* 1990, 70: 1155-1161.

Driving and diabetes

IDDM subjects are occasionally refused employment which involves driving. These decisions are often backed by doctors who have no special experience in managing diabetes. Although individual factors always have to be taken into account, there is now substantial data upon the risk of road traffic accidents amongst IDDM drivers. In a study of 302 drivers in Belfast, accident rates over the previous 5 years were found to be similar in IDDM (23%) and non-diabetic drivers (25%).¹²² The authors point out that 107 of the 302 drivers had been required to pay an increased premium because of their diabetes. In an 8-year follow-up study, the overall accident rates were not different to the accident rate of a non-diabetic driving population of similar age.¹²³ Less information is available from USA, but a recent conference recommended that commercial drivers with IDDM should be considered eligible for consideration of licensing.¹²⁴ An accompanying editorial recommended that IDDM drivers should be regarded as innocent until proved guilty.¹²⁵ Obviously care is required in the assessment of every individual patient, but it is clear there are no grounds for the operation of discriminatory policies by employers.

Conclusion

Significant advances have occurred in all aspects of diabetes over the past 12 months. The most dramatic have involved concepts relating to aetiology of NIDDM and IDDM and pathogenesis of NIDDM. Both forms of diabetes remain amongst the most misunderstood and mismanaged of conditions, and it is to be hoped that current discussion about who should manage these conditions will focus attention on desirable standards of care.

4. Eriksson, J., Franssila-Kallunki, A., Ekstrand, A. *et al.* Early metabolic defects in persons at increased risk for non-insulin-dependent diabetes mellitus. *N Engl J Med* 1989, 321: 337-343.
5. Laws, A., Stefanick, M.L. & Reaven, G.M. Insulin resistance and hypertriglyceridaemia in non-diabetic relatives of patients with noninsulin-dependent diabetes mellitus. *J Clin Endocrinol Metab* 1989, 69: 343-347.
6. Osei, K. Increased basal glucose production and utilization in nondiabetic first-degree relatives of patients with NIDDM. *Diabetes* 1990, 39: 597-601.

7. Ramachandran, A., Snehalatha, C., Mohan, V., Bhat-tacharya, P.K. & Viswanathan, M. Decreased insulin sensitivity in offspring whose parents both have Type 2 diabetes. *Diabetic Med* 1990, **7**: 331–334.
 8. Temple, R.C., Carrington, C.A., Luzzo, S.D. *et al.* Insulin deficiency in non-insulin-dependent diabetes. *Lancet* 1989, **i**: 293–294.
 9. Mitsuoka, T., Takemura, J., Asai, J. *et al.* Islet amyloid polypeptide response to glucose, insulin and somatostatin analogue administration. *Diabetes* 1990, **39**: 639–642.
 10. Butler, P.C., Chou, J., Carter, W.B. *et al.* Effects of meal ingestion on plasma amylin concentration in NIDDM and non-diabetic humans. *Diabetes* 1990, **39**: 752–756.
 11. Clark, A. Islet amyloid and Type 2 diabetes. *Diabetic Med* 1989, **6**: 561–567.
 12. Molina, J.M., Cooper, G.J.S., Leighton, B. & Olefsky, J.M. Induction of insulin resistance *in vivo* by amylin and calcitonin gene-related peptide. *Diabetes* 1990, **39**: 260–265.
- What causes IDD?**
13. Bingley, P.J. & Gale, E.A.M. Rising incidence of IDDM in Europe. *Diabetes Care* 1989, **12**: 289–295.
 14. Sheehy, M.J., Scharf, S.J., Rowe, J.R. *et al.* A diabetes-susceptible HLA haplo-type is best defined by a combination of HLA-DR and -DQ alleles. *J Clin Invest* 1989, **83**: 830–835.
 15. Awata, T., Kuzuya, T., Matsuda, A. *et al.* High frequency of aspartic acid at position 57 of HLA-DQ β -chain in Japanese IDDM patients and non-diabetic subjects. *Diabetes* 1990, **39**: 266–270.
 16. Hanenber, H., Kolb-Bachofen, V., Kantwerk-Funke, G. & Kolb, H. Macrophage infiltration precedes and is a prerequisite for lymphocytic insulitis in pancreatic islets of pre-diabetic BB rats. *Diabetologia* 1989, **32**: 126.
 17. Johnston, C., Alviggi, L., Millward, B.A. *et al.* Alterations in T-lymphocyte subpopulations in Type 1 diabetes. Exploration of genetic influence in identical twins. *Diabetes* 1988, **37**: 1484–1488.
 18. Faustman, D., Eisenbarth, G.S., Breitmeyer, J. & Schlossman, S. Analysis of T lymphocyte subsets in all stages of diabetes. *J Autoimmun* 1989, in press.
 19. Al-Sakkaf, L., Pozzilli, P., Tarn, A.C., Schwarz, G., Gale, E.A.M. & Bottazzo, G.F. Persistent reduction of CD4/CD8 lymphocyte ratio and cell activation before the onset of Type 1 (insulin-dependent) diabetes. *Diabetologia* 1989, **32**: 322–325.
 20. Bleich, D., Jackson, R.A., Soeldner, J.S. & Eisenbarth, G.S. Analysis of metabolic progression to Type 1 diabetes in ICA⁺ relatives of patients with Type 1 diabetes. *Diabetes Care* 1990, **13**: 111–118.
 21. McCulloch, D.K., Klaff, L.J., Kahn, S.E. *et al.* Nonprogression of subclinical B-cell dysfunction among first-degree relatives of IDDM patients. *Diabetes* 1990, **39**: 549–556.
 22. Bruining, G.J., Molenaar, J.L., Grobbee, D.E. *et al.* Ten-year follow-up study of islet-cell antibodies and childhood diabetes mellitus. *Lancet* 1989, **i**: 1100–1102.
 23. Mandrup-Poulsen, T., Molvig, J., Andersen, H.U., Helqvist, S., Spinas, G.A., Munck, M. and the Canadian-European randomised control trial group. Lack of predictive value of islet cell antibodies, insulin antibodies, and HLA-DR phenotype for remission in cyclosporin-treated IDDM patients. *Diabetes* 1990, **39**: 204–210.
 24. Cook, J.J., Hudson, I., Harrison, L.C. *et al.* Double-blind controlled trial of azathioprine in children with newly diagnosed type 1 diabetes. *Diabetes* 1989, **38**: 779–783.
 25. Mendola, G., Casamitjana, R. & Gomis, R. Effect of nicotinamide therapy upon B-cell function in newly diagnosed Type 1 (insulin-dependent) diabetic patients. *Diabetologia* 1989, **32**: 160–162.
 26. Pozzilli, P., Visalli, N., Ghirlanda, G., Manna, R. & Andreani, D. Nicotinamide increases C-peptide secretion in patients with recent onset Type 1 diabetes. *Diabetic Med* 1989, **6**: 568–572.
 27. Vague, P., Picq, R., Bernal, M., Lassmann-Vague, V. & Viallettes, B. Effect of nicotinamide treatment on the residual insulin secretion in Type 1 (insulin-dependent) diabetic patients. *Diabetologia* 1989, **32**: 316–321.
 28. Shah, S.C., Malone, J.L. & Simpson, N.E. A randomized trial of intensive insulin therapy in newly diagnosed insulin-dependent diabetes mellitus. *N Engl J Med* 1989, **320**: 550–554.
- Pathophysiology of NIDDM**
29. Luzi, L. & DeFronzo, R.A. Effect of loss of first-phase insulin secretion on hepatic glucose production and tissue glucose disposal in humans. *Am J Physiol* 1989, **257**: E241–E246.
 30. Bruce, D.G., Chisholm, D.J., Storlien, L.H. & Kraegen, E.W. Physiological importance of deficiency in early prandial insulin secretion in non-insulin-dependent diabetes. *Diabetes* 1988, **37**: 736–744.
 31. Taylor, R. Insulin Action 1990. *Clin Endocrin* in press.
 32. Carpentier, J.-L. The cell biology of the insulin receptor. *Diabetologia* 1989, **32**: 627–635.
 33. Trischitta, V., Brunetti, A., Chiavetta, A., Benzi, L., Papa, V. & Vigneri, R. Defects in insulin-receptor internalization and processing in monocytes of obese subjects and obese NIDDM patients. *Diabetes* 1989, **38**: 1579–1584.
 34. Benzi, L., Trischitta, V., Ciccarone, A. *et al.* Improvement with metformin in insulin internalization and processing in monocytes from NIDDM patients. *Diabetes* 1990, **39**: 844–849.
 35. Brillion, D.J., Freidenberg, G.R., Henry, R.R. & Olefsky, J.M. Mechanism of defective insulin-receptor kinase activity in NIDDM. *Diabetes* 1989, **38**: 397–403.
 36. Thies, R.S., Molina, J.M., Ciaraldi, T.P., Freidenberg, G.R. & Olefsky, J.M. Insulin-receptor autophosphorylation and endogenous substrate phosphorylation in human adipocytes from control, obese, and NIDDM subjects. *Diabetes* 1990, **39**: 250–259.
 37. Bak, J.F., Schmitz, O., Sorensen, N.S. & Pedersen, O. Post-receptor effects of sulphonylurea on skeletal muscle glycogen synthase activity in Type 2 diabetes. *Diabetes* 1989, **38**: 1343–1350.
 38. Odawara, M., Kadowaki, T., Yamamoto, R. *et al.* Human diabetes associated with a mutation in the tyrosine kinase domain of the insulin receptor. *Science* 1989, **245**: 66–68.
 39. Taira, M., Taira, M., Hashimoto, N. *et al.* Human diabetes associated with a deletion of the tyrosine kinase domain of the insulin receptor. *Science* 1989, **245**: 63–66.
 40. Taylor, S.I., Kadowaki, T., Kadowaki, H., Accili, D., Cama, A. & McKeon, C. Mutations in insulin-receptor gene in insulin-resistant patients. *Diabetes Care* 1990, **13**: 257–279.
 41. Freymond, D., Bogardus, C., Okubo, M., Stone, K., Mott, D. Impaired insulin-stimulated muscle glycogen synthase activation *in vivo* in man is related to low fasting glycogen synthase phosphatase activity. *J Clin Invest* 1988, **82**: 1503–1509.
 42. Shulman, G.I., Rothman, D.L., Jue, T., Stein, P., DeFronzo, R.A. & Shulman, R.G. Quantitation of muscle glycogen synthesis in normal subjects and subjects with non-insulin-dependent diabetes by ¹³C nuclear magnetic resonance spectroscopy. *N Engl J Med* 1990, **322**: 223–228.
 43. Johnson, A.B., Argyraki, M., Thow, J.C., Broughton, D., Jones, I.R. & Taylor, R. Effects of intensive dietary treatment on insulin-stimulated skeletal muscle glycogen synthase activation and insulin secretion in newly presenting Type 2 diabetic patients. *Diabetic Med* 1990, **7**: 420–428.
 44. Bak, J.F., Jacobsen, U.K., Jorgensen, F.S. & Pedersen, O. Insulin receptor function and glycogen synthase activity in skeletal muscle biopsies from patients with insulin-dependent diabetes mellitus: effects of physical training. *J Clin Endocrinol Metab* 1989, **69**: 158–164.

45. Kasanicki, M.A. & Pilch, P.F. Regulation of glucose-transporter function. *Diabetes Care* 1990, **13**: 219–227.
 46. Bell, G.I., Kayano, T., Buse, J.B. *et al.* Molecular biology of mammalian glucose transporters. *Diabetes Care* 1990, **13**: 198–208.
 47. Thorens, B., Charron, M.J. & Lodish, H.F. Molecular physiology of glucose transporters. *Diabetes Care* 1990, **13**: 209–218.
 48. James, D.E., Strube, M. & Mueckler, M. Molecular cloning and characterization of an insulin-regulatable glucose transporter. *Nature* 1989, **338**: 83–87.
 49. Garvey, W.T., Huecksteadt, T.P., Matthaei, S. & Olefsky, J.M. Role of glucose transporters in the cellular insulin resistance of Type 2 non-insulin-dependent diabetes mellitus. *J Clin Invest* 1988, **81**: 1528–1536.
 50. Pedersen, O., Bak, J.F., Andersen, P.H., Lund, S., Moller, D.E., Flier, J.S. & Kahn, B.B. Evidence against altered expression of GLUT1 or GLUT4 in skeletal muscle of patients with obesity or NIDDM. *Diabetes* 1990, **39**: 865–870.
 51. Groop, L.C., Bonadonna, R.C., DelPrato, S. *et al.* Glucose and free fatty acid metabolism in non-insulin-dependent diabetes mellitus. *J Clin Invest* 1989, **84**: 205–213.
 52. Zancanaro, C., Cigolini, M., Bonora, E., Moghetti, P., Querena, M. & Muggeo, M. Glucose and insulin suppression of plasma free fatty acids in obese subjects with normal glucose tolerance or mild, newly diagnosed Type 2 (non-insulin-dependent) diabetes. *J Endocrinol Invest* 1990, **13**: 55–59.
 53. Felley, C.P., Felley, E.M., van Melle, G.D., Frascarolo, P., Jequier, E. & Felber, J.-P. Impairment of glucose disposal by infusion of triglycerides in humans: role of glycaemia. *Am J Physiol* 1989, **256**: E747–E752.
 54. Walker, M., Fulcher, G.R., Catalano, C., Petranyi, G., Orskov, H. & Alberti, K.G.M.M. Physiological levels of plasma non-esterified fatty acids impair forearm glucose uptake in normal man. *Clin Sci* 1990, **79**: 167–174.
 55. Bonadonna, R.C., Zych, K., Boni, C., Ferrannini, E. & DeFronzo, R.A. Time dependence of the interaction between lipid and glucose in humans. *Am J Physiol* 1989, **257**: E49–E56.
 56. Bevilacqua, S., Buzzigoli, G., Bonadonna, R. *et al.* Operation of Randle's cycle in patients with NIDDM. *Diabetes* 1990, **39**: 383–389.
- New treatment**
57. Guare, J.C., Wing, R.R., Marcus, M.D., Epstein, L.H., Burton, L.R. & Gooding, W.E. Analysis of changes in eating behaviour and weight loss in Type 2 diabetic patients: which behaviours to change? *Diabetes Care* 1989, **12**: 500–503.
 58. Stancin, T., Link, D.L. & Reuter, J.M. Binge eating and purging in young women with IDDM. *Diabetes Care* 1989, **12**: 601–603.
 59. Southgate, D.A.T. Nibblers, gorgers, snackers and grazers. *Br Med J* 1990, **300**: 136–137.
 60. Wise, J.E., Keim, K.S., Huisinga, J.L. & Willmann, P.A. Effect of sucrose-containing snacks on blood glucose control. *Diabetes Care* 1989, **12**: 423–426.
 61. Hollenbeck, C., Coulston, A.M. & Reaven, G.M. Effects of sucrose on carbohydrate and lipid metabolism in NIDDM patients. *Diabetes Care* 1989, **12**: 62–66.
 62. Gerich, J.E. Drug therapy – oral hypoglycaemic agents. *N Engl J Med* 1989, **321**: 1231–1245.
 63. Jennings, A.M., Wilson, R.M. & Ward, J.D. Symptomatic hypoglycaemia in NIDDM patients treated with oral hypoglycaemic agents. *Diabetes Care* 1989, **12**: 203–208.
 64. Simpson, H.C.R., Sturley, R., Stirling, C.A. & Reckless, J.P.D. Combination of insulin with glipizide increases peripheral glucose disposal in secondary failure Type 2 diabetic patients. *Diabetic Med* 1990, **7**: 143–147.
 65. Klip, A. & Leiter, L.A. Cellular mechanism of action of metformin. *Diabetes Care* 1990, **13**: 696.
 66. Wu, M.-S., Johnston, P., Sheu, W.H.-H. *et al.* Effect of metformin on carbohydrate and lipoprotein metabolism in NIDDM patients. *Diabetes Care* 1990, **13**: 1–8.
 67. Vaag, A., Handberg, A., Lauritzen, M., Henriksen, J.E., Pedersen, K.D. & Beck-Nielsen, H. Variation in absorption of NPH insulin due to intramuscular injection. *Diabetes Care* 1990, **13**: 74–76.
 68. Tunbridge, F.K.E., Newens, A., Home, P.D. *et al.* Double-blind crossover trial of isophane (NPH) and lente-based insulin regimens. *Diabetes Care* 1989, **12**: 115–119.
 69. Tunbridge, F.K.E., Newens, A., Home, P.D. *et al.* A comparison of human ultralente- and lente-based twice-daily injection regimens. *Diabetic Med* 1989, **6**: 496–501.
 70. Jorgensen, S., Vaag, A., Langkjaer, L. *et al.* Novosol basal: pharmacokinetics of a novel soluble long acting insulin analogue. *Br Med J* 1989, **299**: 415–418.
 71. Kawamori, R., Bando, K., Yamasaki, Y. *et al.* Fasting plus prandial insulin supplements improve insulin secretory ability in NIDDM subjects. *Diabetes Care* 1989, **12**: 680–685.
 72. McMahon, M., Marsh, H.M. & Rizza, R.A. Effects of basal insulin supplementation on disposition of mixed meal in obese patients with NIDDM. *Diabetes* 1989, **38**: 291–303.
 73. Blackshear, P.J., Roussel, A.M., Cohen, A.M. & Nathan, D.M. Basal-rate intravenous insulin infusion compared to conventional insulin treatment in patients with Type 2 diabetes: a prospective crossover trial. *Diabetes Care* 1989, **12**: 455–463.
- Pancreas transplantation**
74. Sutherland, D.E.R., Moudry, K.C., Dunn, D.L., Goetz, F.C. & Najarian, J.S. Pancreas-transplant outcome in relation to presence or absence of end-stage renal disease, timing of transplant, surgical technique and donor source. *Diabetes* 1989, **38**: 10–12.
 75. Tattersall, R. Is pancreas transplantation for insulin-dependent diabetics worthwhile? *N Engl J Med* 1989, **320**: 112–114.
 76. Bilous, R.W., Mauer, S.M., Sutherland, D.E.R. *et al.* The effects of pancreas transplantation on the glomerular structure of renal allografts in patients with insulin-dependent diabetes. *N Engl J Med* 1989, **321**: 80–84.
 77. Scharp, D.W., Lacy, P.E., Santiago, J.V. *et al.* Insulin independence after islet transplantation into type 1 diabetic patient. *Diabetes* 1990, **39**: 515–518.
 78. Brons, I.G.M., Calne, R.Y., Jamieson, N.V., Rolles, K., Williams, P.F. & Evans, D.B. Results with combined kidney and paratopic segmental-pancreas transplantation. *Diabetes* 1989, **38**: 18–20.
 79. Nakache, R., Tyden, G. & Groth, C.G. Quality of life in diabetic patients after combined pancreas-kidney or kidney transplantation. *Diabetes* 1989, **38**: 40–42.
- Monitoring diabetic control**
80. D'Antonio, J.A., Ellis, D., Doft, B.H. *et al.* Diabetes complications and glycaemic control: The Pittsburgh Prospective Insulin-dependent Diabetes Cohort Study Status Report after 5 yr of IDDM. *Diabetes Care* 1989, **12**: 694–700.
 81. Phillipou, G., Farrant, R.K. & Phillips, P.J. Computer based quality assessment of hospital capillary blood glucose monitoring. *Diabetic Med* 1990, **7**: 234–237.
 82. Lawrence, P.A., Dowe, M.C., Perry, E.K., Strong, S. & Samsa, G.P. Accuracy of nurses in performing capillary blood glucose monitoring. *Diabetes Care* 1989, **12**: 298–301.
 83. Howey, J.E.A., Bennet, W.M., Browning, M.C.K., Jung, R.T. & Fraser, C.G. Clinical utility of assays of glycosylated haemoglobin and serum fructosamine compared: use of data on biological variation. *Diabetic Med* 1989, **6**: 793–796.

84. Williams, D.R.R., Munroe, C., Hospedales, C.J. & Greenwood, R.H. A three-year evaluation of the quality of diabetes care in the Norwich Community Care Scheme. *Diabetic Med* 1990, 7: 74–79.

Long term complications

85. McCance, D.R., Hadden, D.R., Atkinson, A.B. *et al.* Long-term glycaemic control and diabetic retinopathy. *Lancet* 1989, ii: 824–827.
86. The Damad Study Group. Effect of aspirin alone and aspirin plus dipyridamole in early diabetic retinopathy; a multicentre randomized controlled clinical trial. *Diabetes* 1989, 38: 491–498.
87. Nelson, R.G., Wolfe, J.A., Horton, M.B., Pettitt, D.J., Bennett, P.H. & Knowler, W.C. Proliferative retinopathy in NIDDM: incidence and risk factors in Pima Indians. *Diabetes* 1989, 38: 435–440.
88. Rogers, D., Bitner-Glindzic, M., Harris, C. & Yudkin, J.S. Non-mydiatic retinal photography as a screening service for general practitioners. *Diabetic Med* 1990, 7: 165–167.
89. Ferris, F.L., Podger, M.J. & Davis, M.D. Vascular oedema in diabetic retinopathy study patients. *Diabetic Retinopathy Study Report Number 12. Ophthalmology* 1987, 94: 754–760.
90. Kohner, E.M. & Porta, M. Diabetic retinopathy. In: Alberti, K.G.M.M. & Krall, L.P. (eds) *Diabetes Annual 5*. Elsevier, 1990.
91. Ward, J.D. Diabetic neuropathy. In: Alberti, K.G.M.M. & Krall, L.P. (eds) *Diabetes Annual 5*. Elsevier, 1990.
92. Jennings, P.E., Nightingale, S., Le Guen, C. *et al.* Prolonged aldose reductase inhibition in chronic peripheral diabetic neuropathy: effects on microangiopathy. *Diabetic Med* 1990, 7: 63–68.
93. Dyck, P.J. & O'Brien, P.C. Meaningful degrees of prevention or improvement of nerve conduction in controlled clinical trials of diabetic neuropathy. *Diabetes Care* 1989, 12: 649–652.
94. Fisher, B.M. & Frier, B.M. Usefulness of cardiovascular tests of autonomic function in asymptomatic diabetic patients. *Diabetes Res Clin Pract* 1989, 6: 157–160.
95. Marshall, S.M.M. & Alberti, K.G.M.M. Comparison of the prevalence and associated features of abnormal albumin excretion in insulin dependent and non-insulin dependent diabetes. *Q J Med* 1989, 70: 61–72.
96. Taft, J.L., Billson, V.R., Nankervis, A., Kincaid-Smith, P. & Martin, F.I.R. A clinical-histological study of individuals with diabetes mellitus and proteinuria. *Diabetic Med* 1990, 7: 215–221.
97. Mauer, S.M., Goetz, F.C., McHugh, L.E. *et al.* Long-term study of normal kidneys transplanted into patients with type 1 diabetes. *Diabetes* 1989, 38: 516–523.
98. Haffner, S.M., Mitchell, B.D., Pugh, J.A. *et al.* Proteinuria in Mexican Americans and non-Hispanic whites with NIDDM. *Diabetes Care* 1989, 12: 530–536.
99. Treatment of and mortality from diabetic renal failure in patients identified in the 1985 United Kingdom survey. *Br Med J* 1989, 299: 1135.
100. Parving, H.H. & Hommel, E. Prognosis in diabetic nephropathy. *Br Med J* 1989, 299: 230–232.
101. Parving, H.-H., Hommel, E., Nielsen, M.D. *et al.* Effect of captopril on blood pressure and kidney function in normotensive insulin dependent diabetics with nephropathy. *Br Med J* 1989, 299: 533–536.
102. Pollare, T., Lithell, H. & Berne, C. Insulin resistance is a characteristic feature of primary hypertension independent of obesity. *Metabolism* 1990, 39: 167–174.
103. Reaven, P.D., Barrett-Connor, E.L. & Browner, D.K. Abnormal glucose tolerance and hypertension. *Diabetes Care* 1990, 13: 119–125.

104. Mbanya, J.-C., Thomas, T.H., Taylor, R., Alberti, K.G.M.M. & Wilkinson, R. Increased proximal tubular sodium reabsorption in hypertensive patients with Type 2 diabetes. *Diabetic Med* 1989, 6: 614–620.
105. Trevisan, R., Fioretto, P., Semplicini, A. *et al.* Role of insulin and atrial natriuretic peptide in sodium retention in insulin-treated IDDM patients during isotonic volume expansion. *Diabetes* 1990, 39: 289–298.
106. Levy, P. Effects of prazosin on blood pressure and diabetic control in patients with Type 2 diabetes mellitus and mild essential hypertension. *Am J Med* 1989, 86: 59–62.
107. Pollare, T., Lithell, H., Selinus, I. & Berne, C. Sensitivity to insulin during treatment with atenolol and metoprolol: a randomised, double blind study of effects on carbohydrate and lipoprotein metabolism in hypertensive patients. *Br Med J* 1989, 298: 1152–1157.
108. Pollare, T., Lithell, H., Morlin, C., Prantare, H., Hvarfner, A. & Ljunghall, S. Metabolic effects of diltiazem and atenolol: results form a randomized, double-blind study with parallel groups. *J Hypertens* 1989, 7: 551–559.
109. Pollare, T., Lithell, H. & Berne, C. A comparison of the effects of hydrochlorothiazide and captopril on glucose and lipid metabolism in patients with hypertension. *N Engl J Med* 1989, 321: 868–873.
110. Singer, D.E., Moulton, A.W. & Nathan, D.M. Diabetic myocardial infarction: interaction of diabetes with other preinfarction risk factors. *Diabetes* 1989, 38: 350–357.
111. Brand, F.N., Abbott, R.D. & Kannel, W.B. Diabetes, intermittent claudication, and risk of cardiovascular events: the Framingham study. *Diabetes* 1989, 38: 504–509.
112. Bild, D., Selby, J., Sincock, P., Browner, W., Braveman, P. & Showstack, J. Lower-extremity amputation in people with diabetes: epidemiology and prevention. *Diabetes Care* 1989, 12: 24–31.
113. Mueller, M.J., Diamond, J.E., Sinacore, D.R. *et al.* Total contact casting in treatment of diabetic plantar ulcers: controlled clinical trial. *Diabetes Care* 1989, 12: 384–388.
114. Borsen, B. & Lithner, F. Plaster casts in the management of advanced ischaemic and neuropathic diabetic foot lesions. *Diabetic Med* 1989, 6: 720–723.
115. Veves, A., Masson, E.A., Fernando, D.J.S. & Boulton, A.J.M. Use of experimental padded hosiery to reduce abnormal foot pressures in diabetic neuropathy. *Diabetes Care* 1989, 12: 653–654.

Pregnancy in diabetes

116. Hadden, D.R. Pregnancy problems in diabetics. In: Lawson, D.H. (ed.) *Current Medicine*, vol. 2. Churchill Livingstone, Edinburgh.
117. McCance, D.R., Hadden, D.R., Traub, A.I. & Harley, J.M.G. Self-monitoring of capillary blood glucose in diabetic pregnancy. *Practical Diabetes* 1989, 6: 81–86.
118. Langer, O., Anyaebunam, A., Brustman, L. *et al.* Management of women with one abnormal oral glucose tolerance test value reduces adverse outcome in pregnancy. *Am J Obstet Gynecol* 1989, 161: 593–599.
119. Langer, O., Levy, J., Brustman, L. *et al.* Glycaemic control in gestational diabetes mellitus – how tight is tight enough – small for gestational age versus large for gestational age? *Am J Obstet Gynecol* 1989, 161: 646–653.
120. Jacobson, J.D. & Cousins, L. A population-based study of maternal and perinatal outcome in patients with gestational diabetes. *Am J Obstet Gynecol* 1989, 161: 981–986.
121. Magee, M.S., Knopp, R.H. & Benedetti, T.J. Metabolic effects of 1200 kcal diet in obese pregnant women with gestational diabetes. *Diabetes* 1990, 39: 234–240.

Driving and diabetes

122. Stevens, A.B., Roberts, M., McKane, R. *et al.* Motor vehicle driving among diabetics taking insulin and non-diabetics. *Br Med J* 1989, **299**: 591–594.
123. Eadington, D.W. & Frier, B.M. Type 1 diabetes and driving experience: an eight-year cohort study. *Diabetic Med* 1989, **6**: 137–141.
124. Ratner, R.E. & Whitehouse, F.W. Motor vehicles, hypoglycaemia and diabetic drivers. *Diabetes Care* 1989, **12**: 217–222.
125. Songer, T.J. Drivers with diabetes: innocent until proven guilty. *Diabetes Care* 1989, **12**: 233–234.