likely. Nevertheless, many patients believe that they are more susceptible to urinary tract infections in cold weather, so that we must ask whether there is any scientific justification for this belief.

Stansfeld¹ found that urinary tract infection occurred more commonly in children in the winter months, an observation recently confirmed by Elo *et al.*² They showed a definite seasonal incidence in 992 verified episodes of urinary tract infection in boys and girls aged 2-15, with the overall incidence being highest in November and lowest in the summer months. Summer episodes, however, tended to be more severe. Seasonal variations were less definite in girls than boys, except in the teenage girls, in whom peak incidences occurred in March and September; in the boys a single peak incidence was recorded in July. The incidence of episodes of infection was related to the prevailing meteorological conditions: the lower the temperature and the higher the humidity, the greater their frequency. When weather conditions deviated from those expected for the time of year the monthly number of episodes of urinary tract infection increased appreciably.

Several explanations have been offered for this climatic variation. Upper respiratory tract infections may precede urinary tract infections³⁻⁵ and since coughs and colds are more common in the winter months the same would apply to urinary

infections. Stansfeld,¹ however, could not confirm any such association between infections of the respiratory and urinary tracts. The observation that unexpected weather conditions favour urinary tract infections may suggest that dressing in a fashion inappropriate for the weather conditions could be a key factor—some years ago there was a clinical impression that the introduction of the miniskirt had created a wave of urinary tract infections.

Even so, while the explanation for seasonal trends in urinary tract infection may be in doubt, the observations of Elo *et al.*² are relevant to prophylaxis. The simple message is dress for the weather and not for the season and be prepared. Or, as Angela Kilmartin⁶ put it, "If you decide to go to Greenland take some woollen combinations."

¹ Stansfeld JM. Clinical observations relating to incidence and aetiology of urinary-tract infections in children. *Br Med J* 1966;ii:631-5.

² Elo J, Sarna S, Tallgren LG. Seasonal variations in the occurrence of urinary tract infections among children in an urban area in Finland. *Ann Clin Res* 1979;11:101-6.

³ Woodruff JD, Everett HS. Prognosis in childhood urinary tract infections in girls. *Am J Obstet Gynecol* 1954;68:798-809.

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Regular Review

Insulin infusion systems, diabetic control, and microvascular complications

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The introduction of insulin in 1922 had dramatic effects: many lives were saved, and the quality of others was transformed. Since the development of long-term microvascular complications seems likely to be due to poor diabetic control, we must now attempt to improve it by finding new methods of treatment. Measurement of 24-hour blood-glucose profiles has shown considerable diurnal fluctuations of blood glucose concentrations—even with the best twice-daily regimens—and oscillations from severe hyperglycaemia to disabling hypoglycaemia present a daily hazard to diabetics treated with insulin. Recent years have therefore seen an intensive search for more physiological methods of delivering insulin.

Blood glucose control and microvascular complications—How good is the evidence that better control of the blood glucose would reduce the severity of microvascular complications? One recent comprehensive review¹ concluded that tight diabetic control is indeed worthwhile, but only the previous year Ingelfinger² had argued that the case was still highly contentious. Setting up appropriately designed studies is forbiddingly difficult, not least because of the diverse nature of tissues affected and the facts that (except for nephropathy) they may be affected singly or in combination and that base-

ment membrane thickening is neither specific nor universal in diabetics—and even its exact relation to the microvascular complications is uncertain.

While neither complications nor basement membrane thickening are present in young diabetics at the onset of the disease,³ their prevalence increases with its duration; but a few patients (perhaps as many as one-fifth) are spared altogether.⁴ There is a genetic influence on the development of diabetic complications: thus diabetics who do not require insulin and also react positively to the chlorpropamide-alcohol-flush test seem to be protected from retinopathy when compared with those who do not flush.⁵ Retinopathy (or its absence) is remarkably similar in pairs of identical twins concordant for diabetes.⁶ Sex and racial differences have also been described in the prevalence of microvascular complications.⁷ No totally convincing answer seems likely to be found to the problem, not least because any study would need to last a minimum of 10 years and because of the difficulties of assessing "control" over such a long period.

Nevertheless, many observations suggest that persistent hyperglycaemia is harmful. The effects of poor control are most obvious in pregnancy. Fetal mortality is higher in badly

controlled diabetics, the rate of congenital malformation may be greater with poor control in the first trimester,^{8,9} and skinfold thickness is greater at birth if control is poor in the last trimester.¹⁰ Diabetic retinopathy increases in parallel with hyperglycaemia and the decline of glucose tolerance,¹¹ and the rate of appearance of microaneurysms is higher in diabetics taking only one injection of insulin daily than in those taking two or three.¹² A Japanese study with serial renal biopsies suggested that glomerulosclerosis progresses more rapidly in patients with poorer control,¹³ and proteinuria may increase most in those with the worst control.¹⁴ Pirart's very large personal study¹⁵ showed that all complications occurred most frequently in those with the poorest long-term control. Studies on animals have reached similar conclusions: retinopathy develops most rapidly in poorly controlled diabetic dogs,¹⁶ and basement membrane thickening is greatest in the most hyperglycaemic rats.¹⁷ In diabetic rats treated by islet transplantation renal histological changes have actually regressed¹⁸ and urinary albumin excretion has decreased.¹⁹ The picture is not, however, as clear as this summary might suggest: many of the observations are not wholly convincing, and several older studies have failed to show a relation between control and complications.

Even so, close control of blood glucose concentrations improves several functional alterations which occur even early in diabetes. Among these reversible abnormalities Tchobroutsky¹ listed glycosylated haemoglobin, blood viscosity, and red cell deformability. The renal structural hypertrophy and raised glomerular filtration rate which have been described as early features of diabetes may also be reduced by strict reduction of blood glucose, while abnormal loss of albumin from peripheral capillaries or in the urine may also be decreased. As yet, however, no relation has been shown between these abnormalities and the long-term complications of diabetes.

Insulin infusion systems—How, then, can we improve control? Continuous infusion of insulin with adjustments at mealtimes mimics the physiological state much more closely than does intermittent parenteral injection. If either were practicable intraperitoneal²⁰ or intraportal²¹ insulin infusion might be even more physiological, since insulin is normally delivered directly to the liver by the portal vein. In practice, insulin infusions are given either intravenously or subcutaneously. Insulin may be given intravenously either by the "artificial pancreas"—also known as the artificial beta cell, closed loop system, or glucose-controlled insulin infusion system—or by a simple intravenous infusion pump with preprogrammed or manual control of the infusion rate. The same sort of pump may be used for subcutaneous infusions. The development of portable pumps has meant that such insulin infusions can now be maintained for several months.

The artificial pancreas controls the blood glucose concentrations by a servo-regulated intravenous infusion of insulin or glucose responding to a blood-glucose sensor mechanism. With this system a normal glucose tolerance may be achieved in insulin-dependent diabetics,²² the blood glucose profiles may become normal after meals²³ and during exercise,²² and almost normal metabolic profiles are possible.²⁴ The device has been used successfully to treat ketoacidosis²⁵ and to control blood glucose through surgery²⁶ and labour.²⁷ If it is used early after the onset of acute diabetes, remission of the diabetes may possibly be prolonged.²⁸ The artificial pancreas is, however, complex and expensive: it can be used at most for only a few days in individual patients and there are many technical problems to master. For the present it remains an elaborate research tool.

Delivery of insulin by intravenous infusion without servo control has, however, become established as a very simple and effective technique for short-term use in treating ketoacidosis,^{29,30} and for controlling the blood glucose during labour and major surgery.^{31,34} The infusion may easily be continued for several days³⁵ if required. Insulin dosage is relatively constant from one patient to another regardless of the usual subcutaneous dose or the presence of insulin antibodies.³⁶ Indeed, low-dose intravenous insulin infusion may even be effective in patients severely resistant to subcutaneous insulin.³⁷ Improved regulation of the blood glucose concentration in ambulant but unstable diabetics has been described with controlled infusions lasting a few days,^{38,39} and recently longer-term intravenous infusions have been used,⁴⁰ based on an infusion system preprogrammed after studies with an artificial pancreas system. The blood glucose profiles obtained with the simple infusion technique, which were very similar to those using the more elaborate equipment, were at times almost physiological and were continued up to 117 days. There were many technical problems, and whether this approach can ever become established for routine treatment of diabetics over many years is difficult to predict.

The description from Guy's Hospital of a method for the long-term subcutaneous infusion of insulin has aroused considerable interest, and there are now several reports on this technique.^{41-45,49} A basal insulin infusion is boosted before meals by fixed or variable preprogrammed amounts. Both mean blood glucose concentrations and severe excursions of the blood glucose are reduced, although the fluctuations are not always reduced as much as might have been expected and a "brittle" diabetic may remain unstable.⁴⁶ The insulin requirement is similar to that with conventional subcutaneous regimens (though some patients require more, others less). Exercise appears to have a negligible effect on blood glucose controlled by infusion of insulin. Even more important is the freedom from hypoglycaemia despite blood glucose concentrations which are lower overall. This might result from the absence of a depot of insulin⁴³ or alternatively changes in glucose production might be responsible.⁴⁷ Certainly patients can be maintained by subcutaneous infusions for several months with relatively few hazards, though there is always the danger of the rapid onset of ketoacidosis with a technical failure. The technique might be of value for short-term management of difficult diabetics where control is of importance, such as during pregnancy, though one recent study showed no significant benefit in these circumstances. For the moment, however, as with intravenous techniques, the place of any long-term application remains speculative.

In the clinical terms hyperglycaemia is the most important biochemical abnormality of diabetes, but many others may themselves have long-term effects. Insulin infusion techniques have been shown to correct some of the metabolic abnormalities which persist during conventional insulin treatment. Almost normal diurnal profiles of ketone bodies, lactate, and alanine may be obtained both by use of the artificial pancreas²⁴ and after long-term subcutaneous insulin infusion.⁴² More physiological concentrations of branched-chain amino acids⁴⁴ and an impressive return towards normal of growth hormone and catecholamine responses to exercise after 14 days' treatment in this way have both been recorded.⁴⁵ Improvements have been described in lipid fractions, free fatty acids, cholesterol, and triglyceride, though no controls were reported for this particular experiment.⁴⁴ Excessive microalbuminuria has been reduced to normal after subcutaneous insulin infusion for as little as one to three days.⁴⁸ The long-

term consequences of these observations remain unknown, but they represent impressive improvements of a wide range of abnormalities present in diabetics having conventional insulin treatment. Confirmation of many of these findings is, however, still needed, and it is still possible that multiple insulin injections might have the same effect.

Conclusion—Our conviction that diabetic control influences microangiopathy is now sufficient to justify attempts to improve it by new methods of treatment. Techniques such as the self-measurement of blood glucose will help patients to improve their control, and measurement of glycosylated haemoglobin concentration may help doctors in its long-term

assessment. By their very nature the traditional methods of insulin delivery result in abnormal oscillations of the blood glucose concentration, and if tight control is attempted the dangers of hypoglycaemia become very real. The new techniques of control by insulin infusion have proved successful in the short term and seem to avoid serious hypoglycaemia. Their development during the next few years will show whether or not they prove as successful for long-term use.

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