citizens paid attention to the mechanism that would fund this piece of benevolent legislation.

Shell shocked congressmen

During the spring and summer, however, they did. They noticed that the dollars would be coming not out of general revenues but out of their own pockets. And they revolted. They wrote to their congressmen in such profusion that the latter were shell shocked. They marched on Washington. They banged on their representatives' cars. The chairman of the ways and means committee was chased down the street in Chicago by irate elderly citizens. So congress took fright, its members being up for re-election every two years, and voted in October to repeal the whole bill. At first the senate demurred. It tried to work out a compromise to preserve at least some of the benefits. The administration might have saved the bill but sat on the sidelines. The health secretary made some feeble gestures of support but was silenced by the budget office. The issue came to the reconciliation committee, where the congressmen would not budge. In November the entire law was dumped into oblivion.

Among the immediate consequences is some confusion about what taxes need to be paid this year and how the tax forms are to be filled in. Some of the collected money was to be used to help the complicated process of balancing next year's federal budget. Some Medicare beneficiaries, having come to rely on the new law, may find themselves without cover or subject to bills for being too long in hospital. Supplementary "Medigap" health policies may rise from \$50 to \$60-80 a month. The states will need to pay more for the health care of the uninsured elderly and for certain federally mandated benefits. And observers commented that this repeal was the first retreat in a long sequence of

expensive entitlement programmes, predicting that congress may think twice before trying again.

Indeed some people thought that more congressmen should study the bills they are voting for, this being what they are paid for, especially as many of them admitted that they never quite understood what the benefits were and who would pay for them. Congress, and even society at large, may have to face up to the reality that somebody has to pay for new programmes and that somehow somebody has to find the money. One approach, a selective tax on a restricted group, is clearly not the way, as shown by the angry protests of the bruised Medicare recipients.

But others spoke about justice between generations, painting an unflattering picture of the wealthy elderly not willing to pay for their less fortunate fellows and leaving the burden to the working young. They suggested that the image of the poor widow living on cat food may rapidly give way to that of selfish retired folk feasting on crab food and playing volley ball in Florida. They also predicted that young workers currently paying taxes and having large social security contributions taken out of their pay cheques will, on account of inflation, by no means enjoy the same affluence when the enormous baby boom generation in its turn reaches retirement age in the next century.

There also remains the issue of how to provide medical care for the 37 million Americans without health insurance, including the 30% elderly people who are too poor to afford private insurance. Many hope that this will be achieved through a pluralistic system, provided largely at local level. But a strong contingent still favours a universal health system. Unfazed by the failures of centralised planning in eastern Europe, they dream of past and future glorious revolutions and look to a monolithic system run by the bureaucrats in Washington.

New Drugs

Insulin

J Niall MacPherson, John Feely

Since insulins were reviewed in *Today's Drugs* in 1983, human insulins have become the most commonly prescribed preparations. Their advent has stimulated further assessment of insulin pharmacokinetics and of insulin regimens for achieving good control of diabetes. Intense controversy has been occasioned recently by the suggestion that the counterregulatory hormone response to hypoglycaemia may be less in patients taking human insulin.

Research is being directed to the feasibility of using alterations in the structure of the insulin molecule to produce preparations with therapeutic advantages over existing insulins. Disposable plastic syringes and needles and blood glucose concentration testing strips have become prescribable by general practitioners in the United Kingdom, and pen devices are being used more for subcutaneous insulin administration. The remaining uncertainties about whether near normoglycaemia can prevent complications in type I diabetes have stimulated the long term study phase of the diabetes control and complications trial. The use of insulin for non-insulin dependent diabetics has attracted increased interest, and the United Kingdom prospective diabetes study will include an assessment of the effect of this treatment on outcome. The importance of educating diabetic patients about their

self care and the complexities of this education process have also been increasingly recognised.

Insulin preparations

FORMULATIONS

The table summarises currently available insulin preparations. Soluble insulins consist of insulin in simple solution and are therefore absorbed rapidly when injected subcutaneously. They are the only insulins available for intravenous administration. The insulin zinc suspensions use the relative insolubility of insulin combined with zinc in acetate buffer to retard absorption from the injection site. As amorphous suspensions (semilente insulins) have small particles they are absorbed rapidly and have a duration of action somewhat longer than that of soluble insulin, whereas crystalline suspensions (ultralente insulins) have larger particles, are more slowly absorbed, and have a duration of action of more than 24 hours. Lente insulins comprise a 30% amorphous 70% crystalline mixture. Isophane (NPH) and protamine zinc (PZI) insulins use the relative insolubility of a combination of protamine zinc and insulin to retard insulin absorption.

Soluble and isophane insulins may be mixed in the syringe without the quick action being lost, whereas

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Type and species	Proprietary name	Peak activity (hours)	Duration (hours)
Short acting neutral soluble insulins			
Human	Actrapid (pyr)	2-5	5-8
	Human Velosulin (emp)		
	Humulin S (prb)		
Porcine	Velosulin		
Bovine	Hypurin Neutral		
Intermediating acting			
Isophane (NPH) insulins:			
Human	Human Insulatard (emp)	4-12	12-24
	Protaphane (pyr)		
	Humulin I (prb)		
Porcine	Insulatard		
Bovine	Hypurin Isophane		
Biphasic insulins:			
Human	Humulins M1, M2, M3, and M4 (10% soluble 90% NPH to 40% soluble 60% NPH) (prb)	3-8	12-24
	Penmix 30/70 (pyr)		
	Actraphane (pyr)		
	Human Mixtard (emp)		
	Human Initard (emp)		
	(50% soluble 50% NPH)		
Porcine	Mixtard		
	Initard		
Mixed species	Rapitard MC (25% porcine soluble 75% bovine IZS)		
Insulin zinc suspensions (IZS):			
Porcine	Semitard MC	5-10	12-16
amorphous			
Human lente			
(30% amorphous 70% crystalline)	Monotard (pyr)	6-14	16-22
	Humulin Lente (prb)		
Long acting			
Insulin zinc suspensions (IZS):			
Mixed species	Lentard MC (porcine amorphous, lente bovine crystalline)	6-14	18-30
Bovine lente	Hypurin Lente		
Human		8-24	24-28
ultralente (IZS crystalline)			
	Human Ultratard (pyr)		
	Humulin ZN (prb)		
Bovine	Hypurin Protamine Zinc	10-20	20-36
protamine zinc insulin (PZI)			

emp=enzymatic modification of porcine insulin.
prb=proinsulin recombinant bacteriol.
pyr=precursor yeast recombinant.

mixing soluble insulin with insulin zinc suspensions leads to some loss of quick action, probably by soluble insulin interacting with excess zinc. Mixing soluble with protamine zinc insulin also gives rise to loss of some quick action. Biphasic insulins are marketed as mixtures of soluble and isophane (Mixtard, Actraphane Initard, Penmix 30/70, and Humulins M1-M4) or a mixture of 25% porcine soluble with 75% bovine ultralente (Rapitard MC). All insulins are marketed in U100 strength (100 units/ml). Bovine insulins remain available as the Hypurin series of neutral, soluble, isophane, lente, and protamine zinc insulins.

DURATION OF ACTION

For clinical use insulins have been classified traditionally into short, intermediate, and long acting. The rate of absorption of the same insulin, however, shows considerable variation and decreases with the size of the dose. Thus large doses of "intermediate" acting insulins can have a long duration of action. Insulin absorption tends to be fastest from the abdomen and slowest from the resting thigh. Antibodies to insulin can also affect absorption. The classification in the table should therefore be interpreted in this light.

Administration of insulin

INSULIN SYRINGES

Most diabetic patients use disposable plastic insulin syringes available in 0.5 ml (up to 50 units) and 1 ml (up to 100 units) sizes for subcutaneous injection. Since September 1987 combinations of syringe and

needles for this purpose have been prescribable. Separate disposable needles are to become prescribable shortly. Instructions from the DHSS and National Pharmaceutical Association have been that needle and syringe should be used once only. Extensive studies have shown, however, that the reuse of disposable insulin syringes and needles by the same person is safe. The British Diabetic Association has advised that plastic syringes may be reused up to five times, although if patients wish to use their syringes only once they are free to do so.¹ A needle clipping device to remove needles from their hubs is prescribable, which ensures their safe disposal.

PEN DEVICES

Increasing numbers of patients are using pen devices in place of insulin syringes for injection. The NovoPen I is a robust device like a fountain pen and uses cartridges of insulin, Human Actrapid Penfills, that can deliver measured doses of insulin in two unit increments. Studies have shown a high level of patient acceptance of the device, which is particularly suitable for facilitating regimens incorporating Actrapid injections before each of the three main meals. The cartridge insulin, but not the pen or its special needles, is available on prescription. Other currently available pen devices are Penject, which incorporates a disposable insulin syringe, and Autopen and Accupen. Further pen devices becoming available are the Insuject pen (for Human Velosulin) and the Insuject X pen (for Human Insulatard, Mixtard, and Initard formulations, all provided in cartridges). NovoPen II now provides a device for injecting Protaphane and Penmix 30/70 formulations.

JET INJECTION

Jet injectors are high pressure devices that eject insulin through a fine nozzle.² The high velocity thus generated permits insulin to penetrate the skin without a needle being used. Jet injectors appear to be able to deliver accurate and reliable amounts of insulin to subcutaneous tissue. The greater dispersion obtained gives more rapid absorption of short and intermediate acting insulins and consequently reduces the total duration of action. Although the initial pain of injection may be reduced, delayed pain and bleeding may be greater. Denaturation of some insulin by the jet, and consequently increased immunogenicity, is a theoretical possibility. Despite having been available for some years jet injectors have not yet achieved wide usage.

Insulin species

As recombinant DNA technology has become the usual mode of insulin manufacture most diabetics in the UK are now treated with human insulins.^{3,4} Human insulin differs from bovine in that the alanine of A8 and valine of A10 of the bovine A chain are threonine and isoleucine respectively in the human A chain, and the C terminal (B30) amino acid of the B chain (which is alanine in the cow) is threonine in the human molecule. Human and porcine insulins differ only in that the B30 amino acid is alanine in the pig.

To date, human insulin has been produced on an industrial scale by four different processes. The Novo/Nordisk company has previously produced human insulin by enzymatic modification of porcine insulin (emp) but the Novo division now uses recombinant DNA technology in yeasts to produce human insulin (pyr) derived from proinsulin. Lilly originally made insulin from the combination of separate A and B chains produced by recombinant DNA technology using fermentation in *Escherichia coli* with subsequent chemical combination of the chains (crb). This process

has now been supplanted by production from pro-insulin in *E coli* (prb).

Human insulin is slightly more soluble than porcine and bovine insulins, and a more rapid subcutaneous absorption, particularly of long acting formulations, might therefore be predicted. Pharmacokinetic studies of human ultralente insulin confirm that it is more rapidly absorbed than the bovine formulation, has earlier and more definite peak insulin levels, but has a sufficiently long duration of action to make human ultralente a suitable preparation to provide basal insulin requirements by injection once a day.⁵ Most studies of intermediate acting isophane and lente human insulin formulations and of human soluble insulins show that they have a slightly shorter action than porcine preparations when subcutaneously injected.

The controversy about human insulin and hypoglycaemia

From 1985 to 1989 the proportion of British diabetic patients treated with human insulin increased from around 6% to more than 75%.⁴ As with previous changes in the 1970s to highly purified (mono-component) insulins and in the early 1980s to U100 insulin, some patients reported changes in their warning symptoms of hypoglycaemia on transfer to human insulin.⁶ The possibility that human and animal insulins might cause different counterregulatory hormone responses to hypoglycaemia, however, and media coverage of the further suggestion that change to human insulin had been associated with an increase in sudden unexplained deaths, led to the current intense interest in possible relations between human insulin and hypoglycaemic unawareness.^{4,7}

Several cases of altered experience of hypoglycaemia after transfer to human insulin can be explained fairly readily. Bovine insulin is more immunogenic than human or porcine insulin, and a lower antibody titre on transfer to human insulin may alter dose requirements and duration of action. The change to human insulin may be made when the regimen is altered to improve control. Such improvement in glycaemic control has been associated with a lowered glucose threshold for the release of counterregulatory hormones,⁸ with a consequent delay in experiencing adrenergic symptoms. The more rapid absorption of human insulin may also on occasion give rise to quicker changes in blood glucose concentrations, thus altering symptoms of hypoglycaemia.

These factors operating when there has been change from bovine insulin or an alteration in insulin regimen may account for much of the altered symptoms of hypoglycaemia on transfer to human insulin. More difficult to explain are suggestions of altered hypoglycaemic awareness after transfer from highly purified porcine insulins to the same regimens of human insulin, when the altered pharmacokinetics might be expected to cause only minor differences. Several crossover trials have not shown any difference in hypoglycaemic experiences between human and porcine insulin,⁹ but other studies suggest a high incidence of hypoglycaemic unawareness on transfer to human insulin.^{10,11} These, however, have been criticised for inappropriate questionnaire design and implausibly high rates of severe hypoglycaemia.⁷ Surveys of experience of hypoglycaemia after change to human insulin are similarly conflicting. A British Diabetic Association questionnaire showed that 24 out of 158 patients changing to human insulin experienced less hypoglycaemic warning,¹² whereas in The Netherlands Heine and van de Veen recorded a steady reduction in the number of patients with severe hypoglycaemia admitted to hospitals during 1983-8, when the use of

human insulin was increasing.¹³ About a third of diabetic patients usually lose adrenergic symptoms of hypoglycaemia during the first 20 years. Gale has pointed out how this could lead to attribution bias,⁷ so 1500 of 100 000 patients a year can be expected to report altered symptoms even if treatment is not changed.

Studies of the counterregulatory hormone response to experimental hypoglycaemia in normal subjects are similarly conflicting: some show no difference between insulins⁹ and others show reduced responses of noradrenaline or altered symptoms when human insulin is taken.¹⁴ Although the trigger to counterregulatory hormone response is hypoglycaemia, insulin affects the release of noradrenaline independently of its effects on blood glucose concentrations. This leads to suggestions that porcine insulin (which is slightly more lipophilic than human insulin) could have a quicker action because it penetrates the blood-brain barrier more quickly. The relevance of these mechanisms to the hypoglycaemia experienced by diabetic patients is not known.

While controversy over human insulin and hypoglycaemia continues, certain policies seem to be appropriate. Newly diagnosed patients should be given human insulin, and those who have been taking human insulin since their diagnosis are very unlikely to gain benefit from a transfer to animal insulin. Tight control of diabetes is associated with increased hypoglycaemia and reduction in warning symptoms whatever insulin is used, so treatment objectives should not be unrealistically high. During the past six years many patients have been successfully transferred from bovine to human insulins, so those in the United Kingdom still taking bovine insulins are increasingly likely to be a small group of patients with long standing diabetes, the course of which has been particularly favourable. The only indications for transfer from bovine insulins—lipoatrophy or allergy to insulin—are unlikely to apply to these patients, and as long as suitable bovine preparations remain available doctors may deem it wise to avoid unnecessary change. When change is required an initial dose reduction of 10% has been suggested for patients taking less than 0.9 units/kg and a 25% reduction for those taking higher doses. Return to original animal insulins should be considered for patients who have experienced problems on transfer from animal to human insulin that cannot be explained by changes in regimen or control and for patients who have lost confidence in human insulin.

Indications for and objectives of treatment with insulin

By definition, insulin is indicated for type I (insulin dependent) diabetes. Regimens sufficient to avoid primary diabetic manifestations of thirst, polyuria, weight loss, and ketosis are easily achieved. The aim for most patients, however, is to normalise their metabolism sufficiently to prevent the long term complications of diabetes developing. A wealth of data and results of recent trials to maintain near normoglycaemia for relatively short periods provide encouragement that this may prove possible. Current evidence is not conclusive, however, which justifies the investment in the currently running diabetes control and complications trial of intensified versus conventional glycaemic control.^{15,16} This follows up a primary prevention group as well as patients with early retinopathy and assigns adolescents as well as adults for randomisation. The numbers enrolled give hope for clear conclusions. Meanwhile, for young type I patients it is reasonable to aim for the best glycaemic control possible within the following constraints.

Sudden near normoglycaemia after mediocre control of diabetes can cause acute deterioration in retinopathy, so monitoring optic fundi is particularly important during acute improvement in control. Near normoglycaemia is associated with a significant incidence of hypoglycaemic episodes,¹⁶ and for most patients can only be achieved at the expense of considerable time and effort. Near normal glycated haemoglobin values achieved in clinical trials are not representative of the general diabetic population, in whom values several standard deviations above normal are the norm. For many patients, achievements in diabetic control are perhaps most realistically measured against improvement over this norm rather than an unrealistic goal of normality.

Insulin has a place in the management of some type II (non-insulin dependent) diabetic patients. The dominance of hyperglycaemia as the major risk factor determining outcome is perhaps more controversial for type II than type I diabetes. In populations with early onset of type II diabetes (such as Pima Indians and Asians in Britain) the natural history and the role of hyperglycaemia in determining outcome may be similar to that in type I patients. In European populations presenting with type II diabetes in middle or later life, however, the outcome is heavily influenced by an excess of cardiovascular disease, which may as plausibly be related to the interaction of hyperglycaemia with hypertension, hyperlipidaemia, hyperinsulinaemia, and a postulated genetic association between type II diabetes and cardiovascular disease as to hyperglycaemia alone. The only major prospective trial of insulin treatment in type II diabetes, the university group diabetes programme showed no better outcome with insulin than with diet alone, despite better glycaemic control with insulin.¹⁷ The United Kingdom prospective diabetes study has enrolled a substantial cohort of type II subjects treated with insulin¹⁸ but has not as yet produced any reports on outcome. Pending these results it is reasonable to aim for as good glycaemic control as possible in type II diabetic patients who are not old and whose life expectancy is not limited by other medical conditions. Most type II patients are overweight, and strenuous efforts should be made to achieve good control through dietary measures before considering the use of insulin. Underweight or normal weight patients receiving maximum oral treatment but who have poor glycaemic control are severely insulin deficient and should be treated with insulin.

For insulin dependent and non-insulin dependent diabetic patients the control of hypertension, smoking, and hyperlipidaemia are increasingly recognised as being important to prevent macrovascular disease. Control of hypertension also substantially slows the rate of progression of diabetic nephropathy.

Insulin regimens

In normal subjects insulin is secreted at two rates: a basal rate during fasting to exert an inhibitory control on the catabolic processes of glycogenolysis, gluconeogenesis, lipolysis, and the breakdown of proteins, and a rapid rate in response to meals to promote the storage of absorbed fuels. Insulin regimens should mimic this pattern to achieve good control.

INTENSIFIED CONTROL REGIMENS

In continuous subcutaneous insulin infusion a battery powered pump infuses soluble insulin through a subcutaneous cannula to provide the basal rate and boluses are given before meals through the pump. In one form of intensified conventional treatment soluble insulin is given three times a day before meals, often using a pen device for convenience of injection; the

basal insulin concentration is provided by an injection of ultralente insulin, usually given at night before bed, as this preparation's prolonged absorption time provides fairly consistent background insulin concentrations once a steady state has been reached. Alternatively, an intermediate acting insulin given at bedtime can be used to provide overnight basal insulin concentrations. If patients are carefully selected, motivation is maintained, and intense supervision is applied then both these techniques can produce near normal glucose and glycated haemoglobin concentrations, though continuous subcutaneous insulin infusion tends to give slightly better results.^{19,20} It is equally clear, however, that if these conditions do not apply continuous subcutaneous insulin infusion or frequent injections do not give better results than less intense regimens. Patients most suitable for these approaches to self management are likely to be those who have already shown high motivation and the ability to obtain good glycaemic control with conventional regimens. Patients with brittle diabetes or who on psychological testing perceive the pump or pen technology as externalising the responsibility for their diabetes are unlikely to do well. Continuous subcutaneous insulin infusion carries the possible disadvantage that if the pump fails the onset of ketoacidosis may be more rapid and more likely to be associated with dangerous hyperkalaemia because there is no continuing depot of subcutaneous insulin. For these reasons continuous subcutaneous insulin infusion has not achieved widespread use in the United Kingdom. By contrast, the use of frequent injection regimens using pen devices is increasing as, even when good diabetic control is not achieved, they may help patients achieve flexibility of mealtimes and activities and the psychological benefit of the feeling that they have more control over their diabetes.

TWICE DAILY INSULIN REGIMENS

The insulin regimen used by most type I diabetic patients remains the combination of short and intermediate acting insulin injected twice daily, before breakfast and before the evening meal. The morning short acting insulin is intended to produce a rise in insulin concentration after breakfast, and the intermediate acting insulin injected in the morning reaches its peak action in the afternoon. Insulin action after the evening meal and during the night is similarly provided by the evening injection of short and intermediate acting insulins respectively. Soluble and isophane or lente formulations are used. A common difficulty with these regimens is morning fasting hyperglycaemia because the duration of action of the evening intermediate acting insulin is insufficient.²¹ Increasing the dose of evening intermediate acting insulin tends to produce hypoglycaemia (often asymptomatic) around 3 am. Delaying the intermediate insulin injection to before bedtime may help. Substituting ultralente formulations for the intermediate acting insulin can also be tried, but may produce more hypoglycaemia in the hours before waking.

In the adjustment of twice daily regimens patients have been asked traditionally to adjust the dose of medium acting insulin given before breakfast according to the blood glucose concentration before the evening meal and the evening dose according to the blood glucose concentration before breakfast. The variability of absorption of medium acting insulins is such, however, that these adjustments can only logically be made on the basis of a trend in blood glucose concentrations for several days.²² The lack of need for fine adjustment of dose in these regimens justifies the use of premixed biphasic soluble isophane combinations and adjusting the mix and dose to long term trends in blood glucose concentrations. The

pharmacokinetics of subcutaneous soluble insulin injections are more favourable for rapid adjustments in dose and provide further justification for the use of soluble insulin three times a day and intermediate acting insulin at bedtime by patients seeking flexibility and good glycaemic control.

INSULIN REGIMENS FOR NON-INSULIN DEPENDENT DIABETICS

When insulin is used to treat non-insulin dependent diabetic patients²³ regimens for patients with dominant insulin deficiency need not differ from those used for type I subjects, and twice daily biphasic insulins are a reasonable choice. Insulin requirements will be increased, often substantially, in obese patients. In subjects with less pronounced insulin deficiency the relief of fasting hyperglycaemia caused by overnight insulin deficiency will probably improve endogenous insulin response to meals, thereby also reducing postprandial glycaemic excursions. Regimens using a single daily injection of bedtime ultralente or isophane insulins at a dose adjusted to the fasting morning blood glucose concentration have therefore been proposed for those with moderate insulin deficiency.

Using the insulins

Unlike most other drug treatments, achieving good metabolic control of diabetes is not simply a matter of adjusting insulin dose to response. This is because of the very imprecise relation between effect and the dose of subcutaneous insulin and because many variables other than insulin affect the control of diabetes. In normal physiology insulin is secreted in a pulsatile manner into the portal circulation, and its secretion is finely regulated from minute to minute by stimulation by gut derived factors and the prevailing blood glucose concentration, which is in turn influenced by the processes of feeding, fasting, exercise, prevailing level of insulin sensitivity, and counterregulatory hormone levels.

Current replacement treatment is an attempt to imitate this physiological activity with subcutaneous injections of insulin that have coefficients of variation for half time of absorption of about 25% in individual patients. Insulin is then absorbed into the systemic, as opposed to portal, circulation to act on tissues with a sensitivity to insulin that varies considerably from day to day. The whole system is administered by the patient, for whom treating and monitoring diabetes is only one of life's many daily tasks. This dominance of variability in determining the effect of subcutaneous insulin injections implies that insulins cannot be used as "precision tools," that attention to factors other than insulin is important in determining diabetic control, and that any regimen producing near normoglycaemia must carry a certain incidence of hypoglycaemia.

Newly diagnosed insulin dependent diabetic patients presenting with hyperglycaemia but not ketosis may be introduced to insulin treatment as outpatients provided that regular adequate contact with a diabetic specialist nurse is available. Urgent restoration of normoglycaemia is not required for such patients and the initial insulin requirement may be found empirically over a period of days. Those seeking a guide to determining initial insulin requirements may find the tables published by Holman and Turner helpful.²⁴ All patients who are capable of benefiting should be instructed in monitoring blood sugar concentrations at home.

For patients already taking insulin who encounter problems with poor or unstable diabetic control, the basic practicalities of diabetic self care should be assessed before considering complexities in the insulin regimen. Some recently diagnosed patients may inter-

mittently stop taking insulin either because in their remission phase they believe they no longer have diabetes, or as a form of denial of the condition, or simply because they forget an injection, particularly those using multiple injection regimens. Problems of this type will be detected only if a suitably relaxed listening environment, in which the patients' views and feelings may be expressed, is provided. Lipohypertrophy caused by repeated injection into the same site may cause pronounced variability in insulin absorption and must be looked for. Chaotic life styles of teenagers, particularly regarding the times of sleeping, waking, and eating, may severely disrupt control. Conversely, obsessional patients may generate diabetic instability by the overfrequent and excessive adjustment of insulin dose in response to home monitoring of blood sugar concentrations.

Even when adherence to treatment is good, fasting hyperglycaemia is a common problem.²¹ Three conceptually separate but interacting phenomena probably contribute to this.²⁵ The waning of free insulin concentrations in the early hours of the morning after taking intermediate acting insulins in the evening has already been referred to. The dawn phenomenon is an increase in insulin requirement in the few hours before waking, which may be caused by a rise in growth hormone concentration among other factors. In theory continuous subcutaneous insulin infusion regimens that increase the basal rate at about 4 am to 8 am might overcome this problem. When a decrease in sensitivity to insulin is caused by the counterregulatory hormone response to preceding hypoglycaemia the resultant hyperglycaemia is commonly referred to as the Somogyi phenomenon. Hypoglycaemia at about 3 am is common with twice daily insulin regimens and can give rise to fasting hyperglycaemia through the Somogyi effect. This phenomenon and other effects of excess insulin may possibly operate at other times of the day. When insulin requirements exceed one unit/kg/day the possibility that the insulin dose is too high should be considered if recognised causes of high insulin requirement (such as adolescence, obesity, or pregnancy) are absent. An increase in the insulin requirement of a previously well controlled patient may be caused by the onset of hyperthyroidism, which occurs more often in type I diabetics. Decreased requirements may also be caused by hypothyroidism, Addison's disease, or, advancing diabetic nephropathy. Concurrent illness of any type may increase the insulin requirement.

The need to educate insulin dependent patients about their self care has long been recognised. The limitations of simply imparting information, however, have increasingly been apparent,²⁶ and attention is being directed to ways of changing the attitudes to diabetes that impede self care. Such techniques start with patients' existing concepts of their diabetes and encourage their exploration of these concepts. Although opinions about educational methods may vary, patients should reasonably expect to attend a centre where an active interest in education is maintained.

Future developments

The advent of recombinant DNA technology in the manufacture of human insulin has resulted in the availability of effective insulins of lower immunogenicity but with relatively few obvious therapeutic advantages over the highly purified porcine insulins that they replace. The technology created has, however, permitted the creation of new amino acid substitutions that favourably alter the pharmacokinetics or pharmacodynamics of the molecules of what have been called "designer insulins."²⁷

Commercially available soluble insulin preparations

exist in the form of hexamers, and the delay in absorption from subcutaneous tissue is contributed to by the time required for dissociation into dimeric or monomeric forms. Substituting aspartate for the B9 and glutamate for the B27 threonine residues of human insulin alters the interaction between insulin monomers and results in monomeric insulins with normal receptor binding. Recent studies show quicker subcutaneous absorption of this insulin analogue and more rapid hypoglycaemic effect, which promises better matching between rises in glycaemia after meals and insulin concentrations.²⁸

The insulin molecule has also been modified to change the isoelectric point towards neutral values while preserving stability, thus producing insulin that, when injected as a slightly acid solution, crystallises at neutral pH in the tissues and delays absorption. Such insulins may be able to combine less variable absorption than current suspensions with long absorption times.²⁹

The possibility of insulins with greater activity on hepatic glucose output than on peripheral glucose disposal has also been raised. Proinsulin was at one time a candidate for such a substance but has now been withdrawn from clinical trials.

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ANY QUESTIONS

Is there any basis for the belief that stout enhances the quality of breast milk?

A prevalent belief is that beer drinking increases production of breast milk. Most drugs that increase milk production—for example, dopamine blocking agents like sulpiride and metoclopramide—do so by increasing the plasma prolactin concentration. Yet the effects of alcohol on prolactin release are arguable.¹ De Rosa and coworkers, however, studied young, non-lactating women to distinguish between the effects of beer from those of alcohol on plasma prolactin concentration.² In the fasting state one litre of beer resulted in a more than twofold increase in the plasma concentration of prolactin within 30 minutes. In contrast, neither a litre of sparkling water nor a litre of a mixture of alcohol and sparkling water (with the same alcohol content and effervescence as the beer) had any effect on plasma prolactin concentration. Apparently, beer specifically affected prolactin release, perhaps independently of its alcohol content.

Whether beer should be unreservedly recommended for lactating mothers is another matter. A recent American study of 400 mother and

infant pairs suggested that regular alcohol consumption by breast feeding mothers (one standard drink or more a day over three months) was associated with a significant fall in the infant's psychomotor development scores at 1 year.³ The authors speculatively attributed this to alcohol induced neuroanatomical damage at a vulnerable period of brain development. It would seem prudent for doctors to advise caution over the regular use of alcohol during breast feeding. Nevertheless, if beer does stimulate the production of prolactin, which is independent of alcohol intake, then it might be worth while exploring whether alcohol free beer was effective. — A LUCAS, *head of infant and child nutrition, MRC Dunn Nutrition Unit, Cambridge*

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