A PRACTICAL GUIDE TO DIABETES CARE

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INTRODUCTION

This book was originally written in June 1990 to provide a guide to the management of diabetic patients in the community, especially those with type 2 diabetes, who comprise the majority of patients. Since then it has been updated on three occasions, in close collaboration with many friends and colleagues from Ealing Hospital and elsewhere, to form a practical guide to diabetes care for colleagues working in West London.

These are exciting times in diabetes care ! Remarkable advances have taken place since the last edition in 1999, necessitating extensive revision of this book. There are several new hypoglycaemic treatments - both tablets and insulin - providing new choices in treatment, although we have little comparative data to support the different options, so our guidelines need to be flexible and not too dogmatic. There are some new drugs for lowering lipids and blood pressure, and crucial new landmark studies defining their central role in treatment. Cardiovascular disease is by far the most important threat to our patients, and we now know that we can reduce this by up to 50% with intensive reduction of blood pressure and lipids. We can thus prolong the lives of thousands of local patients living locally by simple tablet treatments. This is both exciting and daunting – we have a huge potential to benefit patients, but there is a mountain of work out there, not least in persuading our patients to take their tablets !

The single most important factor in diabetes care is enthusiasm. A good diabetes service will soon produce its own momentum, and be immensely rewarding to everyone concerned - both patients and staff. However, it needs an abundance of energy, commitment, and a genuine concern for the welfare of people with diabetes.

There are many other published guides to diabetes care, but they differ on various important aspects of management. This is because there is often no hard scientific information on which to base treatment - diabetes care remains as much an art as a science ! We have therefore produced this revised document to reflect our current local policies. It is intended to be a wholly practical guide, and we hope that it will provide answers to most problems which arise in diabetes care within the community - and within hospital clinics as well. Please ensure that it is readily available for reference. We hope that you find it useful and informative.

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DIABETES POLITICS

Diabetes care has been heavily 'politicized' in recent years, by 3 important initiatives, each designed to improve standards of care.

Firstly, **the National Service Framework (NSF)** has given a whole new impetus, encouraging us to review all aspects of our work and to establish local networks to improve standards. It is an important and welcome initiative, although it comes with little extra funding. The most specific targets relate to the construction of practice registers by *** and the introduction of digital retinal screening by ****.

Secondly, **the National Institute for Clinical Excellence (NICE)** has produced detailed guidelines on diabetes care, recommending many treatment targets. Unfortunately, they are rather idiosyncratic. In the case of glycaemic control, they are over-optimistic and unrealistic, and in the case of lipids and blood pressure they seem insufficiently rigorous. Most diabetologists regard them with scepticism despite their 'official' status, but they are useful guidelines to therapy rather than rigid rules.

Thirdly, **the new GMS contract** will provide a real incentive to primary care colleagues to improve control and reduce cardiovascular risk, although the effort in collecting all the necessary data will be considerable. Extra payments will be made for achieving clinical quality indicators, and of the total of 550 points, 99 (18%) are for diabetes, with payments of about £2500 per GP in 2004/5 and £4000 in 2005/6. The top indicators are concerned with control of glycaemic, blood pressure and lipids, and are as follows.

55% of diabetic patients - last BP ≤ 145/85	17 points
50% - last HbA1c ≤7.4%	16 points
85% - last HbA1c≤10.0%	11 points
60% - last total cholesterol ≤5.0 mmol/l	6 points
90% - smokers offered advice or referral	5 points
90% - retinal screening in last 15 months	5 points

etc. etc.

Thus the total points are awarded for control of glucose, BP and cholesterol are 27,17 and 6 respectively! Points will still be awarded if GPs achieve a lower percentage cover, subject to a minimum of 25% cover. Three points each are awarded for several other targets, including achieving 90% targets in the recording of BMI, smoking status (in smokers), HbA1c, peripheral pulses, neuropathy testing, serum creatinine recorded, blood pressure, total cholesterol – all within the last 15 months.

The disproportionate attention to glucose control, with 2 threshold levels at 7.4 and 10.0 %, and the large number of points they attract, may have considerable practical consequences. The lower threshold can be achieved by more vigorous early treatment of type 2 diabetes with combination

therapy, and by screening more assiduously to detect 'milder' cases and thus boost the numbers of patients with lower HbA1c values – the best argument for screening advanced so far ! Patients above the higher threshold certainly justify a trial of insulin, although this may not improve their control. The target for total cholesterol conflicts with the NICE guidelines, which state that the decision re primary treatment should depend on overall cardiovascular risk rather than on the cholesterol value alone – the GMS target will undoubtedly encourage more liberal prescription of statins.

PHILOSOPHY AND AIMS OF CARE IN TYPE 2 DIABETES

The main threat to patients with type 2 diabetes is from macro-vascular disease. The prevalence of ischaemic heart disease is an alarming 2-3 times higher than in non-diabetic subjects, and peripheral vascular disease and strokes are also increased. Up to 80% of patients will die from circulatory diseases. This is by far the most important consequence of type 2 diabetes. Patients are also susceptible to micro-vascular complications, namely retinopathy, nephropathy and neuropathy, but perhaps to a lesser extent than in type 1 diabetes. The Diabetes Control and Complications Trial (DCCT) and the United Kingdom Prospective Diabetes Study (UKPDS) have shown that tight glycaemic control decreases micro-vascular complications in both types of diabetes. However, there is still no rock-solid evidence that improving glucose control will decrease either mortality or morbidity from ischaemic heart disease. By contrast, the benefits of treating hypertension, hyperlipidaemia and other risk factors are truly amazing, with studies showing a reduction of 40-50% in cardiovascular events. Thus diabetes care is not synonymous with glucose control - it requires a much broader approach, especially in type 2 patients - with special emphasis on reducing cardiovascular risk above all else.

The aims of care of type 2 diabetes can be summarised as follows:

1. To control blood glucose levels as tightly as possible, so that the patient has no symptoms due to hyperglycaemia or hypoglycaemia, and the risk of microvascular complications is reduced.

2. To screen for, and treat when necessary, diabetic complications, and risk factors for vascular disease, with special emphasis on treating hypertension, giving aspirin and/or lipid-lowering therapy, stopping patients smoking, and screening for retinopathy, early foot problems and nephropathy.

3. To educate patients to cope practically and psychologically with the diabetic life - we aim to produce happy and informed patients !

ASSESSMENT OF CONTROL

Whenever a patient is seen, we have to decide whether glycaemic control is satisfactory. It is useful to consider how these decisions are made. Five factors are usually taken into account - 1) the HbA1c concentration, if a recent value is available, 2) home blood or urine test results, 3) the presence or absence of symptoms, 4) the clinic blood and urine glucose, and 5) serial weights.

1. HbA1c estimations

These give an indication of average blood glucose concentrations prevailing about 4-6 weeks before the test is performed. They are currently the 'gold standard' of glycaemic control, although they reflect baseline glucose values more than post-prandial rises. They help to identify patients who starve themselves to obtain a good glucose result in the clinic, but whose control is otherwise less than ideal. Instant HbA1c readings are not yet available in most clinics, but patients are usually encouraged to attend for a blood test a week before the clinic, to provide a current reading. By NICE guidelines, HbA1C readings should be obtained twice yearly, even in stable well-controlled patients. *** Hb A1c readings can be misleading in patients with haemoglobinopathies, as occurs in 10% of Afro-Caribbeans, and occasionally it can be useful to measure fructosamine, which is an alternative measure of medium-term glucose control, although in practice the test is now rarely performed.***

2. Home blood glucose or urine test results

Always look through the patient's test results, and discuss them with the patient, to give appropriate feedback. Patients using home blood glucose monitoring should aim to keep their 2 hour postprandial results below 10 mmol/l, but should avoid readings below 5 mmol/l, especially if taking sulphonylureas, because of the important risk of dangerous hypoglycaemia. In practice these targets are difficult to achieve in many patients. Patients performing urine tests should aim for negative results, because then they will avoid all symptoms of hyperglycaemia (nocturia, polyuria, thirst and weight loss). These generally occur only when urine tests are persistently 2% - patients with tests of up to 1% are usually symptom-free. Many poorly controlled older patients with high blood levels have no symptoms because they have a high renal threshold and thus have little or no glycosuria.

3. Presence of hyperglycaemic or hypoglycaemic symptoms.

The most useful indicator of poor control is nocturia. If patients have nocturia, ask them to test their urine when they get up in the night, and also see whether they have glycosuria in the clinic. If this is 2%, their nocturia probably relates to poor control. However, if nocturnal tests are negative, it implies that diabetes is not responsible for the nocturia, and it is more likely to be due to other causes, notably prostatism, renal impairment or diuretic therapy. Other symptoms of poor control are thirst, undue tiredness or lethargy.

It is important to enquire for symptoms of hypoglycaemia in patients on sulphonylureas or insulin. Ask whether they feel unduly hungry, shaky or 'sweaty', particularly before lunch or the evening

meal. Another important symptom is morning headache, which often follows nocturnal hypoglycaemia, and is a useful clinical indicator of over-control. Patients on insulin who drive need to be asked very carefully about their hypos - whether they have warning symptoms, whether their hypos have ever been disabling and whether they check their blood glucose before driving. Fortunately, severe hypos are relatively uncommon in type 2 patients on insulin, presumably because of their insulin resistance.

4. Clinic blood and urine glucose concentrations.

The fasting blood glucose (FBG) is a reasonably good guide to control in patients who are not receiving insulin, because it is fairly constant from day to day. It is of much less value in insulin treated patients. Thus clinics are ideally held in the morning, and patients not on insulin should be asked to come fasting and to omit their morning dose of hypoglycaemic drugs – although they must continue to take their other tablets, particularly their anti-hypertensive medication. Random (post-prandial) glucose values are less useful, although by asking the time of the last meal and assessing whether this was a light snack or a heavy meal, one can hazard a rough guess at the fasting value. Fasting samples are less essential if a current HbA1C reading is available. The presence or absence of glycosuria is useful in interpreting the significance of any polyuria or nocturia.

5. Weight

Serial weight readings are very helpful in assessing control, and adjusting therapy. They usually remain remarkably constant, from year to year, even when diabetic control is only moderate. A sudden marked change in weight always requires an adequate explanation.

A decrease in weight usually indicates successful dieting. It might suggest poor control, but this is unlikely unless blood glucose and HbA1c values are very high and the patient is markedly symptomatic. If weight suddenly falls, for no obvious reason, this may suggest an unrelated cause, particularly malignant disease or thyrotoxicosis, and needs investigation.

An increase in weight may indicate that patients are not adhering to their diet. It may also show that they are being overtreated with sulphonylureas or insulin, especially if their blood glucose and HbA1c values are normal or only slightly elevated, and if they have hypoglycaemic symptoms. Another common cause is congestive cardiac failure or nephrotic syndrome- look for ankle oedema !

THE TREATMENT OF TYPE 2 DIABETES

PRELIMINARY OBSERVATIONS

Evidence from outcome studies – which is the best treatment ?

The only good evidence comes from the UKPDS, using the older treatments, and this showed firstly that insulin and sulphonylureas produced similar effects on both control and complications (ie insulin didn't do any better than sulphonylureas) and secondly that metformin monotherapy showed significant cardiovascular benefit in obese patients, although this was counter-balanced by an unexpected adverse impact when added to sulphonylureas in poorly controlled patients. Nevertheless, metformin is now the initial drug of choice for most patients, and has overtaken sulphonylureas in this respect. Our choice of drugs has recently been expanded by the introduction of the thiazoledinediones (rosiglitazone, pioglitazone) and the prandial glucose regulators (repaglinide and nateglinide). They have promising theoretical advantages over older treatments, but there are no long-term outcome studies, so we don't yet know whether they are better or not. There are several large studies using the newer drugs in progress, and they may alter our management when the results are available. Meanwhile, we have to adopt a flexible 'best guess' approach. We simply don't know which treatment is best !

Targets for glycaemic control

We aim to improve glucose levels as much as possible, both to abolish symptoms and to decrease susceptibility to complications. But what is an acceptable degree of control ? We need to be realistic ! The NICE guidelines specify a target HbA1C of 6.5-7.5%, but this is simply unachievable in many patients, particularly in those who are overweight and have been diabetic for many years. Our current treatments simply aren't good enough ! The GMS contract provides incentives to optimise control, with liberal quality payments depending on the proportions of patients at or below thresholds of either 7.4% or 10.0%. Yet the UKPDS showed that control deteriorates inexorably with time, regardless of type of treatment – and insulin treatment doesn't prevent this deterioration. It is an inherent feature of type 2 diabetes – and not necessarily due to poor concordance or inadequate treatment. The average HbA1c in virtually all hospital clinics is around 8.5%. So it is important not to become over-awed by published 'targets' for glucose control. Its importance may be overemphasised, since the link with macrovascular complications is still unproven, and even the reduction in microvascular endpoints in the UKPDS with tighter control was small and unimpressive.

More aggressive early treatment

There is a new vogue to treat patients more aggressively in the early stages of diabetes, in the hope of preventing the deterioration in control found in UKPDS. Thus, some colleagues recommend giving patients 2 drugs, or switching them to insulin, soon after diagnosis. This fits in well with the targets set down by NICE and the GMS contract, and seems a sensible option, at least as far as increasing the dose of tablets, and progressing from one type of oral therapy to two. The difficulty comes in deciding when a trial of insulin is indicated in individual patients.

Tighter control versus increasing body weight

The influence of treatment on body weight is an important practical consideration, since most patients are overweight. All treatments (even Metformin) tend to increase weight, because of the reduction in glycosuria associated with improved control. This is especially so with insulin, but also occurs with sulphonylureas and TZDs (to an equivalent degree), and (less so) with metformin or acarbose. No-one knows how to treat the typical patient with a HbA1C of 9% and a BMI of 35 on maximum doses of metformin and a sulphonylurea ! Treatment with insulin will lead to an increase in weight, may not improve control, may worsen cardiovascular risk factors, and there is little evidence that it will extend the duration or quality of life. Often a compromise has to be struck, between improving glycaemic control (usually with insulin), and a further increase in weight, and a worsening of other adverse cardiovascular risk factors. The individual patient needs to be involved in these difficult treatment decisions.

OVERVIEW OF TREATMENT – A STEP-WISE APPROACH…

The traditional treatment of type 2 diabetes is along a step-wise approach, and can be summarized in note form as follows:

1. Diet alone – provided the patient is not too symptomatic – fasting blood glucose below 16 mmol/l – and scope from dietary history for improvement. Duration debatable – 3 months traditionally, in practice 1 month probably sufficient.

2. Tablet monotherapy – if HbA1C > 7.0% - required for most patients. Metformin now the drug of choice for both overweight and normal weight patients, although a sulphonylurea or prandial glucose regulator might be used in the latter. Avoid in renal impairment or severe gastroenterological problems. Initial dose 500 mg bd with food – increase gradually to 1 gram bd.

3. Two types of tablets - if HbA1C still above 7.5% despite maximum doses of single drug, add a second drug – either a sulphonylurea (gliclazide 40 mg mane) (if on metformin) or metformin (if on a sulphonylurea). A TZD (rosiglitazone 4 mg or pioglitazone) might be used instead of either - theoretical advantages but more expensive, not supported by NICE and contraindicated in heart failure. Build up the dose of second drug to maximum.

4. Next step – the big problem ! If HbA1C still 'unacceptable' (difficult to define – currently HbA1C >8*%) consider trial of insulin – depending on presence of symptoms, degree of obesity, age, ability to cope and willingness to start insulin etc. Bedtime long-acting insulin usually added to tablet regime.

However if patient unwilling, or unable, or unlikely to benefit (eg BMI >35) consider alternatives – triple therapy – metformin & sulphonylurea & TZD , or addition of acarbose, or trial of orlistat, or accept current control & concentrate on cardiovascular risk profile !

DIET

The diet required for type 2 patients is simply the same 'prudent' or healthy diet that we should all be eating, whether diabetic or not ! The main aims are to reduce fat and sugar consumption, to increase the intake of unrefined carbohydrate (wholemeal bread and cereals, rice, pasta, potatoes) and high-fibre foods (fruits and vegetables such as beans and lentils). Total calorie intake should be reduced if the patient is overweight. The most important single measure is the reduction in total and saturated fat intake, because this may help to prevent coronary artery disease, in addition to its effect on calorie intake. These principles can and must be taught by all of us, whether doctors, nurses or dietitians, and require constant reinforcement at each clinic visit. Most type 2 patients are overweight, and it is important to stress that even a modest reduction in weight may produce a marked beneficial effect on glucose control. All dietary advice must be practical, and should discuss specific foods rather than nutrients - e.g. potatoes not carbohydrate.

It is worth quoting the basic advice given in one of our introductory leaflets for type 2 patients:

"Diet is the most important part of your treatment. Being on a diet does NOT mean starving yourself ! It just means choosing healthy food, which we should all eat, whether diabetic or not. Follow these simple rules - they are very important :
1. Eat less fat - this is the single most important rule - to control weight and reduce heart disease. Do not fry food - grill or boil instead. Use a low fat spread instead of margarine or butter. Use skimmed or semi-skimmed milk, not full fat. Use leaner meats, and check food labels for large amounts of hidden fat.

2. Eat some starchy food with each meal – pasta, rice, bread, chapattis, potatoes or cereals.

3. Reduce sugar and sugar-containing foods, eg cakes, biscuits, sugary drinks. Use sweeteners, such as Canderal or Sweetex instead of sugar.

4. Eat more fruit and vegetables. Aim for at least 5 portions a day !

5. Reduce the amount of salt in your cooking, and don't add salt at the table– this may raise blood pressure.

6. Avoid diabetic foods - these are fattening and expensive - but sugar-free or low-cal drinks are useful.

7. Drink alcohol in moderation. Never drink on an empty stomach. Have at least 2 alcohol-free days/week

If you are overweight, losing weight - by reducing your fat, sugar and alcohol intake and taking regular exercise - will help your diabetes control, and make you feel much better. Even a little weight loss will make a big difference ! Buy some bathroom scales, weigh yourself regularly and record the results.

It is important to be realistic about the limitations of dietary treatment. The problems of achieving long-term concordance are obvious, and relatively few type 2 patients remain controlled on diet alone. Most of us are all too aware, from personal experience, of the problems in adhering to any diet for any length of time ! Treatment of obese patients is especially difficult, and needs time and sympathy. Setting achievable goals is extremely important. Encourage patients to set their own targets, and record these for reference at their next visit. Some manage to lose weight initially, but the long term results are usually disappointing. If patients cannot lose weight, it is cruel to bully them incessantly ! Encourage them to ensure that their weight does not increase still further. Ask them to buy some bathroom scales, and to weigh themselves twice weekly. Patients with particular difficulties can be referred to the hospital clinic, or directly to the hospital or community dietitians.

METFORMIN

Metformin is now the drug of choice for most patients who are inadequately controlled on diet alone, particularly those who are obese, since it may help weight reduction, or at least avoid any further weight increase. Its popularity is increasing because it is cheap, effective, safer than the sulphonylureas and may confer extra cardiovascular benefit. Curiously, it never causes hypoglycaemia - although it is a hypoglycaemic agent! It is absolutely contra-indicated in patients with severe renal impairment (plasma creatinine >140 µmol/l) because of the risk of lactic acidosis. Its use in the many patients with intermediate plasma creatinine values - between 120-140 µmol/l - is controversial, but the risks of lactic acidosis have been overemphasized, and most colleagues are now less concerned now about its use in this situation. It should also be avoided in patients with severe cardiac failure and hepatic failure, but it is probably safe in patients with less serious cardiac and liver problems – again the risks have been exaggerated. It is contraindicated in patients with significant colonic problems, such as inflammatory bowel disease, because of its well-known propensity to cause diarrhoea.

Metformin (Glucophage) is available in tablets of 500 or 850 mg. The latter tablets are quite large – veritable 'gob-stoppers' - and may cause swallowing problems in elderly patients. Hence, most clinicians use 500mg tablets. The cost of 500 mg bd is £21/year. The important practical points are to start on a low dose (500 mg bd), to take the tablets with or after meals, and to build up the dose gradually, to a maximum of 1 gm bd. This will reduce the incidence of gastrointestinal side effects – mainly diarrhoea but sometimes dyspepsia as well - which otherwise affect about 25% of patients. If they occur, try a reduction in dosage, rather than stopping the drug altogether. With these precautions, most patients tolerate the drug well. Further increases in total daily dosage beyond 2 grams per day have no additional benefit. Its effect on glycaemic control is roughly

equivalent to that of sulphonylureas, usually reducing HbA1C levels by 1-2% in type 2 patients. The full impact is delayed for a week or more, so if a very rapid effect is needed, as in some symptomatic patients, sulphonylureas are a more suitable choice. Metformin should be omitted for 2 days after X-ray procedures using intravenous contrast media because of the remote risk of renal failure and lactic acidosis.

SULPHONYLUREAS

These drugs are still a reasonable choice as first-line treatments for patients who are not overweight, if diet alone fails to achieve adequate control. They are very effective in rapidly relieving symptoms due to hyperglycaemia (with a quicker treatment response than metformin), and any previous doubts about their long-term safety have been dispelled by the results of the UKPDS, which showed that they are as beneficial to control and complications as insulin treatment. However they generally lead to weight gain (less so than insulin, but equivalent to TZDs) so obesity is a relative contraindication.

Always start with small doses (gliclazide 40 mg, glimepride 1 mg, or glipizide 2.5 mg). Some patients are very sensitive to these doses. Patients can be advised to increase the dose if home glucose readings remain higher than the target range or urine tests remain persistently positive after a week. Their dose-response curves are remarkably flat, compared with metformin which is more linear. Thus doubling the dose of a sulphonylurea (say from gliclazide 80 bd to 160 bd) may have little or no additional effect, whereas doubling the dose of metformin will have more obvious impact. Hypoglycaemia is the main side-effect, and can be severe or even fatal. Minor degrees of hypoglycaemia are very common, and severe episodes not uncommon. Always enquire for hypoglycaemic symptoms, especially feeling very hungry and slightly shaky and 'sweaty' before lunch. If symptoms are present, especially if the weight is increasing and if blood glucose and Hb A1c values are relatively low, the dose of sulphonylurea must be reduced. Many patients are overtreated. It is unfair to ask obese patients to lose weight, and give tablets which make them hungry ! They can be dangerous especially when patients become ill, and stop eating but continue to take their drugs. Elderly patients with renal impairment are most at risk, and deaths still occur every year - please take care. If patients become severely hypoglycaemic, they must be admitted to hospital - not sent home from Accident and Emergency department - and given an IV glucose infusion for at least 24 hours, because the tendency for the hypoglycaemia to recur extends over many hours.

Gliclazide is a reasonable first choice sulphonylurea.. It is safe and effective, and is especially useful in the elderly, and in those with renal impairment because it is safer in these circumstances than glibenclamide, and less likely to cause hypoglycaemia. The initial dose is 40 mg mane (1/2 tablet), and this can be increased to 80 mg, then to 80mg bd, and then increased to a maximum of 160 mg twice daily. However, as stated above, the dose response curve is very flat, and the benefit from increasing the dose from 80 mg bd to 160 mg bd is negligible in practice. Check cost of generic gliclazide*** It can also be given in a once daily form as modified release (Diamicron MR), and this

may be a useful aid to improving concordance. Diamicron MR 30 mg mane is equivalent to gliclazide 40mg bd, and costs £52/year. The dose can be increased to a maximum of 120mg mane (4 tablets mane – equivalent to gliclazide 160 mg bd, and costing £208/year.

Glimepride also has the advantage of once-daily dosage. Its starting dose is 1 mg mane, and the maximum dose is 6 mg. Glimepride (Amaryl) 1mg costs £57/year. Tablets of 1mg, 2mg, 3mg and 4mg are available.

Glibenclamide is possibly the most potent agent, but is also the most dangerous and often causes mild hypoglycaemia before lunch, because of its shorter effective half-life. It is generally less preferable than the other sulphonylureas. Patients already on the drug can usually continue on the drug, but elderly patients (aged over 70 years), or those with any renal impairment (creatinine >120 µmol/l) should be changed to a safer agent, such as gliclazide.

THIAZOLIDENEDIONES

The thiazolidenediones (TZDs) (rosiglitazone and pioglitazone) reduce insulin resistance, acting particularly on muscle and fat, and lower HbA1C in type 2 patients by about 1%, similar to (or slightly less than) sulphonylureas and metformin. They also improve other cardiovascular risk factors, with a small but useful BP lowering and a decrease in microalbuminuria. Thus it is hoped that they will decrease cardiovascular risk, in addition to improving glycaemic control. There are good theoretical reasons for this, but we await the outcome studies currently in progress to see whether this happens in practice. Their full effect takes six weeks - and thus the benefit on HbA1C (reflecting control about 6 weeks previously) is not seen for about three months. It is important to emphasize this delayed onset of action, otherwise patients may assume that the drugs are useless and stop them after a week or so!

The main side effect of TZDs is fluid retention, and they are contraindicated in patients with overt or incipient heart failure. Body weight increases, partly due to fluid retention and partly due to fat deposition, to a similar degree to that seen with sulphonylureas, so marked obesity is also a relative contra-indication. They are safe in renal impairment unless end-stage (plasma creatinine > ****µmol/l. Our worries about hepatotoxicity, following the withdrawal of triglitazone, have proved unfounded, and although the guidelines state that liver function tests should be checked regularly, this may be unnecessary.

TZDs are indicated firstly in patients on maximum doses of a sulphonylurea who need a further oral agent, but cannot tolerate metformin, either because gut side-effects or renal impairment. Secondly, they can be added to maximum doses of metformin, instead of adding a sulphonylurea, in patients who require a second drug. Many colleagues prefer this approach on theoretical grounds, although it is against the NICE guidelines and is more expensive. Thirdly, they are licensed for use as mono therapy in patients who cannot tolerate metformin because of renal impairment or gut side

effect. This usage is not supported by NICE, but many colleagues feel that this is the most logical use of TZDs. They are not generally used in combination with insulin because of concerns of precipitating heart failure. There is no point trying to improve control in patients on metformin and a sulphonylurea by stopping either metformin or a sulphonylurea and replacing it with a TZD, because the latter is no more powerful and takes six weeks to have its impact.

The two available TZDs are rosiglitazone (Avandia) and Pioglitazone (Actos), and their profiles are very similar. There are some minor benefits in the impact on lipids with pioglitazone but these are probably of little clinical significance. The once daily dosage is an important aid to concordance. Rosiglitazone is given as 4mg mane (cost £312/year) and can be increased to 8mg (£650/year) but there is relatively little extra effect with the higher *(and very expensive)** dose. Pioglitazone is given as 15mg mane (£312/year) and can be increased to 45mg (£444/year). A combination of metformin and rosiglitazone – Avandamet – has recently been introduced, as an aid to patient concordance. This comes in 2 strengths – 500 mg metformin combined with either 1mg or 2 mg rosiglitazone, and the starting dose is 1 tablet of the weaker strength twice daily (£358/year).

ACARBOSE

This drug works by reducing the breakdown of complex carbohydrates in the gut, and has a useful effect in reducing post-prandial rises in blood glucose. It is safe and does not induce any weight gain, but the effect on glycaemic control is relatively slight effect (usually lowering HbA1c by about 0.5%) and its gastro-intestinal side-effects are often severe. The latter can be reduced by starting with a small single daily dose (25mg or half a tablet), taken with the first mouthful of a meal, increasing to 50 mg daily and then gradually (by 50 mg per week) to 50 mg t.d.s. Acarbose has become less popular in recent years, but it may still have a role in poorly controlled patients who are unwilling to start insulin therapy. If used with sulphonylureas, it can cause hypoglycaemia, and in this situation treatment with glucose rather than sucrose (sugar) is needed because Acarbose inhibits the breakdown of sugar to glucose in the gut. Acarbose (50mg tds) costs about £116/year.

PRANDIAL GLUCOSE REGULATORS

These drugs comprise repaglinide (Novonorm) and nateglinide (Starlix), and act like quick-acting sulphonylureas, causing a brisk release of insulin. They are taken with each meal, and their rapid action means that the post meal glucose "spikes" are well controlled and the short duration renders them less likely to cause hypoglycaemia or weight gain than sulphonylureas. However, the HbA1C concentration (which generally reflects base line rather than postprandial glucose levels) is no better. Theoretically, control of glucose spikes might prevent long term complications but this remains unproven, in the absence of outcome studies.

Repaglinide may be useful as monotherapy in T2D patients who are recently diagnosed and have an erratic meal pattern, perhaps with normal fasting blood glucose but elevated postprandial levels. Both drugs may be added to metformin to improve control. Their use requires a motivated patient to ensure that the drug is taken with each meal – most patients have concordance problems with

once-daily drugs, let alone thrice daily ! They should not be used with a sulphonylurea since they act on the same receptor on the beta cells, and will have no extra effect. Repaglinide (Novonorm) 1mg before each meal costs £149/year, and nateglinide ('Starlix') 120 mg before each meal costs £293/year. Nateglinide is not licensed for use as monotherapy. The prandial glucose regulators occupy only a small niche in treatment currently, although this might alter if studies confirm the importance of control of glucose spikes in preventing complications.

INDICATIONS FOR INSULIN TREATMENT

This a notoriously difficult 'grey area'. As stated earlier, no-one really knows how to treat poorly controlled type 2 patients, and there is no really solid evidence to suggest that insulin therapy will extend either the life-span or quality of life of asymptomatic type 2 patients. Many patients fare little better when switched to insulin, and simply put on more weight. Yet some colleagues are switching many more type 2 patients to insulin earlier in the natural history of the disease, perhaps reinforced by NICE and GMS targets. It is difficult to give precise criteria for a trial of insulin, but currently we rarely switch type 2 patients to insulin unless the HbA1C level is over 8.0%. Above this level, the decision is influenced by several factors. These include:

(1) the presence of symptoms particularly nocturia, especially if associated with prostatic problems, polyuria and polydypsia. However, many poorly controlled patients have few or no hyperglycaemic symptoms.

(2) the patient's weight markedly influences the decision. The case for insulin is much stronger in patients who are not overweight, especially if actually losing weight, because they will be less resistant to insulin, and more likely to benefit from therapy. However, if a patient is very obese, insulin therapy may not help. Control may not be improved, and weight will almost certainly increase further.

(3) the ability to cope with insulin injections, which is influenced by age, family back-up, language ability and other factors, is vitally important.

(4) the presence of complications such as neuropathy or retinopathy, which reinforce the need for tighter control.

(5) the height of the HbA1c concentration. Patients over 10% justify a trial of insulin. Those with HbA1C levels between 8 and 10% will require consideration of all the above factors in order to make a decision.

In many instances, we offer patients insulin for a trial period of 1-3 months, and then leave the choice of treatment largely to them. Some patients feel much improved on insulin, and continue indefinitely, whereas others beg to restart tablets!

INSULIN AND TABLET COMBINATIONS

Until recently, patients were treated with either tablets or insulin (plus diet) – rarely both together. Now, combinations of insulin and tablets are increasingly used, particularly with use of bedtime intermediate or long-acting insulin in combination with day-time tablets, for poorly-controlled type 2 patients. A dose of 10-20 units of isophane, lente insulin or insulin glargine at bedtime controls glucose levels overnight, and the tablets maintain control during the day. The advantages of this regime, compared with switching to insulin entirely, are that smaller and fewer doses of insulin are needed, less weight gain occurs and the risk of nocturnal hypoglycaemia is slight. The once-daily injection also seems more acceptable to patients who may be reluctant to switch to twice-daily insulin. The dose of bedtime insulin can be adjusted depending on the fasting blood glucose on the following morning, and often needs to be increased. This regime is sometimes called 'BIDS' - Bed-time Insulin Daytime Sulphonylurea, although a combination of insulin with metformin may be preferable, especially in obese patients. It is probably unnecessary to continue both sulphonylureas and metformin in this situation. TZDs should not be used with insulin.

ALTERNATIVES TO INSULIN IN POORLY CONTROLLED PATIENTS

'Triple therapy'

An increasingly popular but 'unofficial' role is as 'triple therapy', added to the regimen of patients who are poorly controlled on both metformin and a sulphonylurea but who adamantly refuse insulin therapy, because of fear or lack of motivation. Although this is against both the drug's license and NICE, there are no good reasons why it should not be used in this way, and the prescription of 'triple therapy' is now widespread.

Some patients are terrified of insulin treatment, and refuse point blank to commence injections, even with supportive counselling. In this situation it seems perverse and unjustified to 'twist arms' of patients, especially since the evidence base for insulin treatment may be rather flimsy. Now of course there is an alternative, in the use of 'triple therapy' – the addition of a TZD to both sulphonylurea and metformin. This is strictly 'off license' and against NICE guidelines, but it is a logical drug combination, carries no known safety risks, and avoids the psychological trauma of insulin injections. This treatment strategy is now commonly used by most diabetologists, although long term efficacy remains to be established. At least it provides another therapeutic option, in a difficult clinical situation.

Anti-obesity drugs

Another option is to try **Orlistat (Xenical).** This is a lipase inhibitor which interferes with fat absorption producing malabsorption with liquid oily stools, which can lead to urgency and faecal incontinence, particularly after a fatty meal. They induce weight loss primarily by acting as a 'behaviour therapy' to persuade patients not to eat sinful fatty meals! It is a safe therapy and is licensed for diabetic patients whose BMI is >28. However, according to the NICE guidelines, patients must lose 2.5 kg with diet and exercise in the month prior to starting orlistat, to show that they really can adhere to a low fat diet. After starting the drug, they should lose 5% of their weight in the first 12 weeks (when most weight loss takes place) and 10% in the first six months. If these targets are not met, the drug should be withdrawn. Patients on orlistat needs supervision and dietary support and this is usually provided in primary care.

Its place in long term diabetes treatment is unclear. It is currently only licensed for two years use, and is usually not given for more than a year, but most patients regain their former weight when the drug is stopped. It can certainly improve glycaemic control, reducing HbA1C by about 0.5% in T2D, but whether a short course of orlistat will reduce vascular risk accruing over several decades is unclear, and there are no outcome studies in diabetes. Nevertheless, treatment of grossly obese T2D patients is notoriously difficult, and orlistat at least provides an alternative, safe treatment. Perhaps we don't use it sufficiently and colleagues in primary care might be encouraged to use it more often.

Sibutramine is the other anti-obesity drug treatment. It is centrally acting, avoids the gastro-intestinal side effects of Orlistat, and seems equally good in achieving weight bss and improving control. Unfortunately, may can elevate blood pressure, and is contra indicated in ischaemic heart disease and uncontrolled hypertension. This is a severe limitation, and probably prohibits its use in diabetes, until more evidence is available.

CONCORDANCE IN TYPE 2 DIABETES

This is the most underrated problem in diabetes care. Many patients are currently receiving 6-10 different drugs – perhaps 2 for diabetes, 2-4 for hypertension, a statin and aspirin, possibly with other tablets for heart failure, obstructive airways disease or hypothyroidism. We all know how difficult it is to complete even short courses of antibiotics ourselves ! It requires exceptional motivation to take several tablets per day for years on end, for prognostic rather than symptomatic benefit. The DARTS study, from Dundee, showed that only one third of patients bothered to collect their diabetic tablets from pharmacies, and the proportion was even less among patients taking twice daily therapy, or on multiple drugs. We have turned a blind eye to this issue for years !

There is no single solution to concordance problems, but several measures might help. Firstly, once daily drugs should be used whenever possible. Thus the use of once daily sulphonylureas (either gliclazide MR or glimepride) may improve concordance, and a once daily metformin preparation (available in the USA) is sorely needed in Europe as well. Secondly, the use of drug combinations should be encouraged, and our purist objections to these should be set aside. Thirdly, and most importantly, we must educate our patients about the importance of their tablets in

preventing unpleasant and life-threatening complications, to ensure their involvement and concordance. We need to reinforce these messages at every visit. Otherwise, our treatment regimes may perhaps be little more than expensive charades !

TREATMENT OF CARDIOVASCULAR RISK FACTORS

HYPERTENSION

Measurement – some practical points

Measurement of blood pressure is as important as that of blood glucose, and should be performed with similar care. Important practical points are firstly to the record the BP to within 2 mm Hg (not to the nearest 10 mm Hg!), and secondly to use an appropriate size of cuff - if the arm circumference exceeds 30 cm, in obese patients, a large cuff must be used. The sphygmomanometer pressure must fall slowly, not rapidly. High readings should be confirmed after resting for 5-10 minutes, and treatment should only be instituted after hypertension has been demonstrated on at least 2, and preferably 3, separate occasions, at intervals of 1-2 weeks. Standards of BP measurement are generally unsatisfactory - please take care and time, because important treatment decisions are based on their results. In elderly patients, particularly those on several drugs, it is necessary to test for postural hypotension by measuring the lying and standing BP, waiting a full minute ***before taking the latter. 24 hour ambulatory BP monitoring may be useful in patients with suspected 'white coat hypertension'.

Target Blood pressure

The importance of BP control in diabetes care is absolutely crucial – certainly as important, if not more important, than glucose control ! Hypertension needs to be treated more vigorously in diabetes, because patients are more susceptible to target organ damage at any given BP level. Several studies have shown dramatic benefit from modest reductions in BP. Lowering BP from about 155/90 to 145/85 produces a 30% - 40% reduction in cardiovascular risk, regardless of the drug used. The target BP in diabetic people should be 140/80. Paradoxically, the NICE guidelines don't recommend drug therapy unless the BP is 160/100 or higher, when overall cardiovascular risk is <15%, but most colleagues would aim for 140/80 in everyone. The GMS contract awards points for ensuring that 55% of diabetic patients have a BP ≤145/85, as a compromise value. Even more aggressive lowering, down to 135/75, is recommended in patients with MA or proteinuria. The target levels may be difficult to achieve in practice, and 3-4 or more drugs may be necessary. We used to be less aggressive in treating hypertension in the elderly, but studies have shown impressive benefits at virtually any age. However, control is difficult in elderly patients with systolic hypertension - it may be impossible to lower systolic BP to 140 mm Hg without reducing diastolic BP below 60mm Hg and this should be avoided – the coronary arteries fill in diastole !

General Measures and hypertension

Some non-pharmacological measures can help treatment. A reduction in salt intake, by avoiding it either in cooking or on the table, produces a modest but useful decrease of about 5 mm Hg

(systolic) and 3 mm Hg (diastolic). Excess alcohol raises blood pressure and reduction of heavy alcohol intake is important, as is weight loss in obese patients. These simple measures are useful and important, and don't receive the attention they deserve.

Which drug?

It probably does not matter unduly, because all main classes seem equally effective in reducing both BP and (more importantly) cardiovascular risk. ACE inhibitors or A2 blockers are the drugs of choice in patients with microalbuminuria or overt proteinuria, because of their additional renoprotection benefit. However, the massive ALLHAT study showed that the benefits from chlorthalidone (a thiazide diuretic), lisinopril and amlodipine were virtually identical – in fact chlorthalidone was marginally superior to lisinopril. In practice, many patients require 2 or more drugs, so our basic strategy is to use small doses of several drugs, in an attempt to increase effectiveness and reduce side effects. Patients below 55 tend to have 'high renin' hypertension and may respond better to ACE inhibitors or beta blockers, whereas older patients tend to have more volume dependent, low renin hypertension and respond better to calcium channel blockers or diuretics. This gives rise to the ABCD rule, which states that A(ce inhibitors) or B(eta blockers) work better with either C(alcium channel blockers) or D(iuretics), than with another similar drug. It is necessary to wait about 2-4 weeks to see the full effect of a drug, before giving additional treatment – treatment shouldn't be stepped up too quickly.

Thiazides are definitely drugs of choice in diabetes, following ALLHAT and other studies. No more than 2.5mg bendrofluazide should be given – this gives maximum effect on BP and minimizes effects on glucose and lipids – and on the drug budget, costing £* /year ! A small proportion may develop erectile dysfunction and will need other therapy. Thiazides are contra-indicated in gout, and should not usually be given to patients already on loop diuretics, such as frusemide, because of the synergistic diuretic effect. They are relatively ineffective in renal impairment, when hypertension is more volume dependent and frusemide is a better choice.

ACE inhibitors are drugs of choice in patients with proteinuria or MA, and in those who have heart failure or a history of myocardial infarction. They are relatively ineffective when used alone in Afro-Caribbeans, although they still work in these patients in combination with other drugs. They are markedly harmful to the foetus, and thus are contra-indicated in premenopausal women unless they have reliable contraception. There is a slight but important risk of severe renal impairment in patients with renovascular problems. Thus urea and electrolytes must be checked after 7-10 days therapy. A modest rise in plasma creatinine is commonly observed, but an elevation of 30% or more requires the drug to be stopped. About 15% of patients develop a troublesome cough with ACE inhibitors, and can be switched to an A2 blocker. All the once-daily preparations - lisinopril, ramipril, perindopril etc - are probably equally suitable. Lisinopril ('Zestril') 5mg costs £102/year, ramipril ('Tritace') 2.5mg costs £107/year, perindopril ('Coversyl') 2mg £139/year.

The angiotensin II antagonists – or 'A2 blockers', such as irbesartan, losartan and valsartan are gaining popularity because of their freedom from the 'ACE' cough, and because of their renoprotective effect in type 2 patients with MA and proteinuria, although the evidence for benefit in

patients with CCF or IHD is not as strong as with ACE inhibitors. They may also cause renal impairment in the presence of reno-vascular insufficiency, and thus urea and electrolytes need to be checked a week after commencing therapy. They can usefully be combined with ACE inhibitors, to produce extra BP lowering and reduction of MA. Irbesartan ('Aprovel') 150mg costs £214/year, losartan 50mg costs £224/year and valsartan ('Diovan') 80mg costs £205/year,

Beta-blockers (given as atenolol) achieved similarly impressive results to ACE inhibitors in the UKPDS, and are also drugs of choice. They must be avoided in patients with asthma or obstructive airways disease, but concerns about the risk of hypoglycaemia are rarely a problem in practice. They are especially important in the secondary prevention of myocardial infarction. They can cause slight lethargy, cold extremities or erectile dysfunction, and thus may be less preferable as monotherapy to the newer agents. Atenolol (Tenormin) 50 mg costs £74/year.

Calcium antagonists (or calcium channel blockers) are effective anti-hypertensive agents, and the ALLHAT study showed that amlodipine produced equivalent benefit on vascular events to lisinopril and chlorthalidone. Short acting dihydropyridine drugs such as nifedipine should no longer be used. The predisposition to ankle oedema is often a limiting factor in the use of these drugs, but their safety in asthma and heart failure may be valuable. Diltiazem and verapamil are less suitable than the dihydopyridine drugs (amlodipine, felodipine etc) because of their tendency to cause heart failure and bradycardia, and lack of evidence of long-term benefit. Amlodipine ('Istin') 5mg (cost £170/year) or felodipine (('Plendil') 5mg (cost £116/year) are suitable drugs.

Doxasozin has fallen from favour because it was withdrawn from the ALLHAT study because of a slight predisposition to heart failure. However, the significance of this result is controversial, and most colleagues continue to use it, although incipient or overt heart failure are contraindications. It is effective, relatively free of side-effects, and useful when other drugs are contraindicated, such as in peripheral vascular disease. It is also useful in patients with prostatic outflow obstruction, since it benefits this as well. It can cause ankle oedema, in common with most vasodilator drugs. The initial dose is 1 mg daily, increasing after 1-2 weeks to 2 mg daily. The dose needs to be titrated carefully upwards, over the first few weeks, to a maximum of 8 mg daily. The cost of 1 mg ('Cardura') is £138/year, and a useful long-acting form (Cardura XL) is available at 4mg (cost £183/year).

Concordance with BP therapy

Concordance is a huge problem, but can be improved by patient empowerment. Patients should know their BP reading, their target BP, and should be taught to take responsibility for their BP control. Never tell a patient that their BP is 'not too bad' or 'only up a bit' – give them the figures! Emphasise to all patients the need for life-long therapy, and the importance of BP control in avoiding heart-attacks and strokes. Encourage patients to buy their own BP meter, preferably one which measures at the elbow rather than the wrist. Home readings are usually lower than those at clinics by about 12 mm Hg systolic / 7 mm diastolic, and this difference needs to be taken into

account when assessing the significance of home readings. All the key studies on BP lowering have used clinic readings so these should still form the basis of our targets and treatment.

HYPERLIPIDAEMIA

Statins

The introduction of statins to diabetes care is perhaps the most important advance since the discovery of insulin, and their impact may be as large as that of antibiotics in the 1940's. They reduce cardiovascular disease – the main killer - by 30-40%, and this benefit is over and above that achieved by other treatments, notably BP lowering and aspirin. Furthermore, they have a remarkably good safety record. The only limitation to their use in virtually all middle-aged and elderly diabetic people is their high cost. However, the patent for simvastatin has now expired and that of pravastatin will expire in August 2004, so the cost of the older statins should fall rapidly in the near future.

So who should receive statins for primary prevention?

This is currently very confusing ! The landmark Heart Protection Study concluded that effectively all groups of diabetic patients between 40 and 80 with a total cholesterol >3.5 mmol/l would benefit from statin therapy (simvastatin 40 mg in the study), and the EHHHA expert lipid group supported this policy. If statins were as cheap as aspirin, there is little doubt that all diabetic patients over 40 (except those with liver disease) would receive them. However, they are currently very expensive and NICE have recommend statins only if the total cholesterol is ≥5.0 mmol/l or more (or triglyceride is ≥2.3 mmol/l) and the patient's combined cardiovascular risk score over 10 years is 15% or more. This policy is flawed because the scores are derived from the Framingham study, which had relatively few diabetes people, and which did not allow for the effects of microalbuminuria, family history and ethnicity. Being Asian, for example, probably justifies a 50% increase in risk score. In addition, it is illogical to define a cut-off point in total cholesterol – one component of cardiovascular risk - rather than considering overall combined risk. By contrast, the GMS contract awards points for ensuring that 60% of all patients have a total cholesterol ≤5.0 mmol/l – regardless of their cardiovascular risk scores.

Nevertheless, we are obliged to adhere in principle to these NICE guidelines. This may deny statins to two at-risk groups. These are, firstly, patients whose total cholesterol is <5 mmol/l, but whose cardiovascular risk is 15% or more – some colleagues would give statins regardless. The second group comprise patients whose cholesterol is ≥5.0 mmol/l, but whose risk score is under 15% - here the case for statins is less robust here, but it might be reasonable to take a lower threshold of 10% in Asians patients because of their increased risk, especially since the GMS contract wishes us

to do so ! The use of older, potentially cheaper statins might perhaps compensate for a more liberal prescription policy. There is little evidence to support the use of statins in primary prevention in patients aged over 80, although the absolute risk (and thus the potential benefit from therapy) may be higher, and many colleagues prescribe them regardless.

Which Statin?

The benefits from statins are probably class effects, common to all, although this is not strictly proven. The key studies have used simvastatin and pravastatin, and these drugs have the best evidence of both efficacy and safety. Furthermore they may become cheaper with the expiry of their patents. Atorvastatin is slightly more powerful than simvastatin but the evidence of outcome benefit is currently less good (although more studies are imminent) and its patent will not expire until 2009, so ultimately it may prove more expensive. Another statin, cerivastatin, was withdrawn because of an unexpectedly high incidence of rhabdomyolysis, so the safety profile of newer statins cannot be taken for granted. The newly introduced rosuvastatin is the most powerful of all and may be valuable in patients with resistant hyperlipidaemia but as yet there are no long term outcome studies and less safety data. Pravastatin is preferable if there is a risk of drug interactions (particularly in renal transplant patients) and may be less likely to cause myopathy, particularly in combination with fibrates. Thus a reasonable plan might be to use either simvastatin or pravastatin as a first line drug and switch to atorvastatin, and then finally to rosuvastatin if the lipid lowering effect is insufficient. Another option is to add in ezetimibe (see below).

***** put in data from Stellar*****

Which dose of statin?

The dose response curve to statin therapy is relatively flat, with little further lipid lowering from increasing doses. Colleagues with a 'purist' streak would advocate the doses used in the landmark studies, so 40mg of simvastatin, as used in the Heart Protection Study, is a popular choice, because of its know efficacy and safety. Although a fixed dose was used, in this study, with no 'fine tuning' to achieve a target level, most colleagues continue to adjust the dosage, starting with simvastatin 10 mg nocte and increasing as necessary. Further studies are in progress to see whether extra benefit can be obtained by more aggressive lipid lowering. Most types of statins need to be taken at night, since this is the time of maximum cholesterol synthesis but this may lead to problems with concordance. The need for night-time dosage may be less important with atorvastatin and rosuvastatin.

The current costs of statins are uncannily similar, with 10mg of proprietary simvastatin, atorvastatin and rosuvastatin all costing an identical £235/year. The cost of simvastatin 20mg, 40mg or 80 mg daily is identical to that of rosuvastatin 20mg and 40mg or atorvastatin 20, 40 and 80 mg – all the different statins and dosages retail at about £387/year. This bizarre pricing structure at least allows us to use higher doses without worrying about its effect on our drug budgets !

Problems with liver function tests and CPK levels

Many diabetic patients have minor elevations of liver enzymes, usually due to fatty infiltration. Although statins are stated to be hepatotoxic, severe hepatic necrosis is excessively rare, and this risk is usually far outweighed by the potential benefit in reducing vascular disease. Thus, we have a liberal approach to giving statins even when hepatocellular enzymes are elevated, although it is difficult to give precise figures. Nevertheless, statins are best avoided in patients with overt liver disease, such as alcoholic cirrhosis. Serial LFTs may not be routinely necessary. Myalgia was reported by over 30% of patients in the Heart Protection Study, but the prevalence was similar in both placebo and statin groups, so patients complaining of this symptom may be reading the package insert too assiduously. Severe rhabdomyolysis is very rare and usually occurs either in renal failure or in combination therapy with fibrates, It is worth checking the creatine phosphokinase (CPK) level if patients complain of myalgia, and statins should be stopped if there is more than a 5-fold rise. It is worth remembering that Afro Caribbeans have a markedly raised normal range for CPK.

***check when need to stop statins temporarily when on cipro etc ***

Ezetimibe

This new drug inhibits cholesterol absorption from the gut, and acts as a useful adjunct to statins if these drugs don't lower lipid levels sufficiently. It might also be used as monotherapy in patients who can't tolerate statins. It is contraindicated in established liver disease, but otherwise seems safe and useful, although as yet there is little evidence of long-term efficacy in reducing vascular disease. Ezetimibe ('Ezetrol') is given in a dose of 10 mg daily, cost £343/year.

Fibrates

Fibrates are well suited for use in diabetes, because they tackle the classic lipid abnormalities of elevated triglycerides and lowered HDL. However, trial data so far is limited, and confined largely to secondary rather than primary prevention, compared with the huge body of evidence on the benefits of statins. The significance of mildly raised triglyceride levels, and the benefits of lowering them, are still unclear. The data suggest that fibrates are indeed beneficial, but unless patients have a grossly raised triglyceride (say over 5 mmol/l) and relatively normal cholesterol, statins remain the drugs of choice, especially since they also lower triglyceride levels. An obvious option is to add fibrates to statins, but there are concerns re the risk of rhabdomyolysis, following the fatalities from combined use of cerevastatin and gemfibrozil. These dangers may be less with fenofibrate and with pravastatin but there are residual concerns amongst many clinicians, and there is no good evidence of extra prognostic benefit from the use of both agents. Nevertheless, combination therapy might be tried in high risk patients, for example in secondary prevention if triglycerides are still elevated on statins. Fibrates should be avoided in patients with renal impairment or a history of gallstones. Bezafibrate (Bezalip Mono) 400mg daily (cost £113/year) is a suitable drug for initial therapy, as is fenofibrate (Lipantil) 200mg daily (cost £234/year), which may be more potent. Omega fatty acids (Maxepa 5 capsules daily (£250/year)(** check – 5 caps daily or 10 caps daily!*) or Omacor (£362/year) might also might also have a role in patients with grossly elevated triglycerides – say over 10 mmol/l.

ASPIRIN

The case for aspirin therapy in diabetic patients with ischaemic heart disease is overwhelming, and must be given to all such patients unless there is a clear contra-indication such as a peptic ulcer or allergy to the drug. The case for aspirin in primary prevention is less robust, but it seems prudent to give it to all diabetic patients who are middle-aged and have any other evidence of complications or risk factors, such as proteinuria, retinopathy or hyperlipidaemia. South Asians diabetic patients in middle-age should probably receive aspirin therapy even in the absence of other risk factors, in view of their increased vascular risk. Since over 70% of type 2 patients have vascular deaths, and since aspirin has such a beneficial effect on myocardial infarction and acute coronary syndromes, this is a vitally important part of diabetes care. The debate on dosage - 75, 150 or 300 mg - is unresolved, but there is now a move towards lower doses, such as 75mg, as advocated in the NICE guidelines. If patients are "allergic to aspirin" or cannot tolerate its gastric side effects, clopidogrel might be given instead although this is much more expensive. There is circumstantial evidence that the effects of aspirin are nullified by concurrent ibuprofen therapy so this should be avoided if at all possible. Aspirin should be avoided if patients have systolic hypertension – say systolic BP>150 – because of the increased risk of cerebral haemorrhage may outweigh the reduction in ischaemic heart disease.

SMOKING

The importance of stopping smoking can hardly be exaggerated. Diabetic subjects have such an alarming increase in ischaemic heart disease that it is sheer madness to superimpose another major risk factor voluntarily. Tell patients that we prefer them to stop smoking, even if it means putting on weight and poorer diabetic control ! Use any tactics you like - there are no holds barred ! This is the most important part of the management of any type 2 patient who smokes. With suitable threats and coercion, it is possible to persuade some patients to stop, although many still persist despite our best endeavours. Nicotine 'patches' or gum may have a limited role, but depend above all on adequate patient motivation, and their involvement in support groups. They are now available on prescription, but are contra-indicated in patients with established ischaemic heart disease ******Felicity / Ann Hamerton to check !!! Bupylpropion* ('Zyban') is now less popular after being incriminated in fatal epileptic seizures. There are local stop-smoking clinics in Ealing – phone 020 8321 2321 and an NHS smoking helpline – 0800 169 0169. Quality payments are earned, in the GMS contract, by offering advice to all smokers every 15 months.

DIABETIC COMPLICATIONS

NEPHROPATHY

Microalbuminuria

The term microalbuminuria (MA) refers to minor degrees of proteinuria which are elevated above the normal (very low) levels, but cannot be detected by routine urinalysis. It is a good early marker for nephropathy in type 1, and is also a surprisingly good marker for vascular disease in type 2 – ie 'leaky kidneys' are associated with a 'leaky endothelium', leading to atheroma. MA can be measured with a stick test, or by laboratory analysis of a urine sample for albumin and creatinine, preferably on an early morning sample. If the albumin/creatinine ratio (ACR) is elevated (strictly, on 2 out of 3 occasions), this constitutes MA, provided that a urinary tract infection has been excluded by the absence of leucocytes and nitrates on urinalysis. The upper limit of normal for ACR is 2.5 for men and 3.5 for women. By NICE guidelines, all type 2 patients should be tested for microalbuminuria every year.

The detection of MA is important because it indicates the need for treatment with either ACE inhibitors (in type 1 or type 2 patients) or A2 blockers (in type 2 patients) – even in patients who are normotensive. Several studies have shown that this preserves renal function, delaying the progression to renal failure, in addition to the effect on blood pressure. The best evidence in type 2 patients is with irbesartan (300 mg) or losartan (50mg), where their use prevents 2-4 deaths, or patients developing renal failure, in every 100 patients treated. ACE inhibitors (rather than A2 blockers) are the first-line treatment in type 1 patients with MA. The combined use of ACE inhibitors and A2 blockers together gives extra benefit both in renal protection and blood pressure lowering. However, care is needed with these drugs in premenopausal women to ensure that there is no risk of pregnancy, because they are significantly teratogenic. As renovascular disease may co-exist with the nephropathy, especially in patients with peripheral vascular disease, it is essential to check urea and electrolytes within a week of commencing ACE inhibitors or A2 blockers (and strictly within a week of changes in drug dosage as well). Some rise in plasma creatinine is commonly observed but provided this under 30% no further action is needed. If it rises more than this, the drug should be stopped. Fortunately, this only happens rarely, but it is nevertheless vital to monitor renal function carefully.

Overt proteinuria

If overt proteinuria is detected on routine urinalysis, check for leucocytes and nitrates or send off an MSU to exclude infection. If the MSU shows sterile pyuria, send off EMUs, to exclude renal TB, especially in Asian patients, although, in practice, this is very rare. If proteinuria persists, and is not due to infection, this strongly suggests early nephropathy, and indicates that the patient has an increased risk of vascular disease. This requires aggressive management, with vigorous treatment of any associated hypertension or lipid abnormalities. The target blood pressure in patients with either MA or proteinuria is 135/75. Tight glycaemic control will also help to preserve renal function. Nephropathy usually develops concurrently with retinopathy, and so if the fundi are normal it is much

less likely that the patient has significant diabetic nephropathy, although they may have other serious renal disease. Asian patients are more prone to nephropathy than are Europeans.

Patients with raised plasma creatinine

Please refer any patient with plasma creatinine > 130 µmol/l to the hospital for assessment. It is important to obtain a renal ultrasound examination if the creatinine value is over 150 mmol/l, particularly in men to exclude obstructive uropathy from prostatic enlargement. Often such patients have other medical problems, particularly CCF treated with powerful diuretic therapy and ACE inhibitors. If the proteinuria is heavy (+++ on urinalysis), obtain a 24 hour urine collection to quantify it, and check the plasma albumin. A full-blown nephrotic syndrome is relatively uncommon. The risk of end-stage renal failure due to nephropathy is relatively small compared with the risk of serious vascular disease, and will hopefully be further reduced by strict control of hypertension.

Patients approaching end-stage renal failure (with a creatinine >150 µmol/l, according to NICE guidelines) should be managed jointly with a nephrologist, although many clinics have raised this threshold to 200 because of the logistic pressures. Poor glycaemic control at this later stage has little influence on the rate of decline in residual renal function. Insulin requirements often fall quite markedly because insulin is partly metabolised by the kidney, and some patients may even be able to stop their insulin or glicazide. Decreased insulin requirements are often an indicator of declining renal function. Metformin and glibenclamide must never be used when the creatinine rises above 150 µmol/l, because of the real risk of lactic acidosis or profound hypoglycaemia. The preferred oral treatment is gliclazide, but rosiglitazone or pioglitazone can also be used unless the patient is in end-stage renal failure, with a * .

RETINOPATHY

Screening for retinopathy is crucially important, and it is everyone's responsibility to ensure that it happens! All patients attending hospital clinics can reasonably be assumed to receive eye screening there. Arrangements for patients managed entirely within the community will vary depending local circumstances. Some have set up schemes with trained optometrists, others use local ophthalmology services, and yet others use a mobile camera unit. The main priority is to ensure that some system is in place to cover all patients ! A system of district-wide digital retinal screening will be set up in **** to comply with the NSF *** details….

The benefits of early detection and treatment with laser are so impressive that blindness due to retinopathy is now largely preventable. Approximately 25% of all diabetic patients have retinopathy of some degree, and in about 10% this is severe enough to require laser therapy. Approximately 15% of type 2 patients may have retinopathy at diagnosis. Many retinopathy patients have already been diagnosed, are attending an eye unit and obviously do not require screening. The purpose of screening is to identify the small but vitally important proportion of patients - say 10% - who have undiagnosed retinopathy. Thus most fundi you examine will be entirely normal.

Examination of fundi is remarkably easy under the right conditions. Many doctors are deterred from this when doing housejobs, looking at undilated eyes in bright wards, with poor ophthalmoscopes ! The important practical points are:

1) to dilate up the eyes with 1% Tropicamide drops.
2) to examine eyes in a darkened room,
3) to ensure that there are new or recharged batteries in the ophthalmoscope.

Use 1% Tropicamide drops - not 0.5%. These may take 10 minutes to have their full effect, especially with dark irises. The risk of inducing acute glaucoma is negligible, but the drops should not be given to patients with known glaucoma, who will be attending an eye clinic in any case. All patients with type 1 diabetes must have their fundi viewed every year. By NICE guidelines, all type 2 patients also need yearly retinal screening, although although those with no retinopathy only need screening every 2 years. Some patients may object to the drops if they have to drive home. The drops do not affect distant vision, but lead to increased 'glare', which may make driving difficult. They wear off after 1-2 hours or more.

When looking at fundi, you only need to decide whether they seem entirely normal or not. The main abnormalities are, of course, haemorrhages and exudates, which means any red or yellow/white lesions. Proliferative retinopathy ('new vessel formation') is uncommon in type 2, and is usually superimposed on obvious haemorrhages and exudates. So you should search carefully for any red or white/yellow blobs on the retina! The earliest changes are microaneurysms, which are tiny red spots, and small whitish exudates. Look particularly around the disc, and towards the macula, which is on the temporal (lateral) side. This is the commonest position for sight-threatening retinopathy. If you have any doubts whatsoever about whether the fundus is normal, please refer the patient to the hospital diabetic clinic.

There are some normal, or at least non-diabetic, appearances which can cause confusion. Degenerative changes in the elderly often produce yellow lesions which look rather like hard exudates, but are not as clearly defined, and are not associated with haemorrhages. Many patients referred to hospital may not have retinopathy, but it is better to have a low threshold for referral. You don't need to be able to distinguish the different sorts of diabetic retinopathy - either the eye is totally normal, or it is possibly abnormal, in which case the patient needs referral to a hospital clinic. Those who have definite retinopathy will be referred on to a specialist eye unit.

Some patients may develop macular oedema, with marked loss of vision and relatively little - or even no - evidence of retinopathy seen on fundoscopy. This is a potential diagnostic trap, and is suggested by an unexplained decrease in visual acuity which cannot be corrected by use of a pinhole. Thus it is essential to measure visual acuity in all patients before instilling eye drops. If this is impaired to 6/9 or less, the patient should be re-tested, using glasses or a pinhole, which will correct for refractive problems. If visual acuity remains impaired, and cannot be readily explained, for example by lens opacities, urgent referral to an ophthalmologist is necessary to exclude macular oedema.

Some patients who are markedly hyperglycaemic have temporary blurring of vision, especially when newly diagnosed, due to changes in the lens shape produced by large blood glucose fluctuations. This is temporary, and is unrelated either to lens opacities or retinopathy. Nevertheless it can cause patients much anxiety, and it is important to explain to them that it has no long-term significance, and to advise them not to go to the optician for new glasses until their treatment is stabilised.

CATARACTS

Cataracts (or lens opacities) are a major cause of poor vision in elderly diabetic patients. The best guide to their severity is the visual acuity (VA) - the correlation between the appearances on ophthalmoscopy and their impact on vision is remarkably poor. Until recently, ophthalmologists were unwilling to remove cataracts unless the VA in the better eye was reduced to 6/l8 or less. Now, with increasing skill in lens implantation, patients with less severe cataracts are being offered surgery.

Unfortunately, cataract operations are generally less successful in diabetic patients, particularly if there is also significant retinopathy. It is important to establish how much inconvenience is caused by the lens opacities. Some elderly patients may not be unduly troubled by poor vision, and may wish to avoid the trauma of an operation. Conversely, younger patients may be severely distressed by a visual acuity of say 6/12. If in doubt, the patient should be referred for an eye opinion. Lens opacities often make fundi difficult to visualize, even when they don't need surgery. If this is a problem please refer the patient to the hospital clinic for an eye assessment.

NEUROPATHY

Patients with neuropathy usually complain of paraesthesia - 'burning feet' - and numbness particularly in the lower limbs. Sometimes patients have symptoms despite preserved reflexes, although usually they are absent. Neurofilaments are a useful aid in assessing the severity of peripheral neuropathy, and identifying feet which are at risk of neuropathic ulceration, and are generally more useful than eliciting ankle reflexes. The 10 mg neurofilaments should be placed on the plantar surface of ** toes ***

The treatment of severe neuropathic symptoms is unsatisfactory. They can sometimes be controlled with paracetamol and the importance of taking this drug regularly should be emphasised. If it is insufficient, try imipramine or amitriptyline, starting at low doses, such as 10 mg nocte (when symptoms are usually most troublesome) and increasing as necessary. These are sometimes effective, and their beneficial effect on neuropathic symptoms does not relate simply to its anti-depressant action. However, their use is often limited by daytime somnolence, and they are relatively contra-indicated in the presence of heart disease. Unfortunately, there is little evidence for similar benefit from SSRIs. If symptoms persist, the next drug to be tried is gabapentin, but at that stage they should be referred to a neurologist for assessment. Gabapentin has been proven to benefit neuropathy, and is relatively free of side-effects, but its dosage schedule is rather unusual –

the dose needs to be increased rapidly over ** daysto 900mg and then *** Capsaicin cream (0.075%) applied to the affected areas is beneficial in some cases, and patients often find the cream more acceptable than additional tablets. Capsaicin is derived from peppers, and the cream initially causes warmth and burning, but with additional use it desensitises the skin, producing useful symptomatic benefit. Fortunately, painful neuropathy of this severity is relatively uncommon, and it tends to improve gradually. There is evidence that strict glycaemic control may help some patients with severe neuropathy particularly when it presents with weakness.

Patients sometimes have a superimposed alcoholic neuropathy, and it is important to enquire for a high alcohol intake, which may exacerbate the neuropathy. If this seems a possibility, the patient should be given B vitamins, such as Thiamine compound forte tabs 1 t.d.s. which contain extra thiamine. The usual vitamin B preparations such as Multivite have too little thiamine. B vitamins are of no value in diabetic neuropathy.

FOOT PROBLEMS

The treatment of early foot problems, and their prevention by education, are crucially important aspects of care. All patients should be taught to look after their feet. They should be advised to wash their feet daily, on how to cut their nails, to wear appropriate shoes and socks, and to avoid 'corn plasters'. Educational leaflets on foot care must be given to patients with potential foot problems. Many foot ulcers and amputations could be avoided by good patient education. Elderly patients need to be told to avoid self-chiropody, and instead should regularly see a State Registered Podiatrist. They are entitled to free priority treatment at Health Centres. Examination of feet in the clinic is important to document whether pulses and/or reflexes are absent, indicating that the feet are at risk. The importance of not walking 'barefoot' and of having correctly fitting shoes must be emphasised.

If a patient develops an infected foot lesion, particularly if the skin is 'broken', early vigorous treatment with antibiotics is mandatory. Such patients should be referred urgently to the hospital clinic, for podiatry and careful follow-up. Please do not hesitate to refer any patient with these early but potentially serious foot problems.

PERIPHERAL VASCULAR DISEASE

Patients with intermittent claudication should be strongly advised to stop smoking if they do so! Beta-blockers are contra-indicated in claudication, and ACE inhibitors should be used with caution because of the risk of concurrent renovascular disease. Alpha-blockers such as doxazosin are useful as anti-hypertensive agents in this situation. If the patient’s claudication distance is several hundred yards nothing more need be done. No drugs are beneficial, and symptoms often improve spontaneously. Low-dose aspirin should be given. If symptoms become severe, they need referral to a vascular surgical unit for Doppler studies initially, often leading to angiography. Surgical

intervention is often unsuccessful in diabetic patients because their vascular disease tends to be more peripheral, but some patients may benefit from angioplasty or surgical revascularisation procedure, such as a femoro-popliteal bypass.

ERECTILE DYSFUNCTION

It is important to enquire for this common problem. The cause is usually multifactorial, and is often compounded by psychogenic factors, especially when morning erections are preserved, or when it is intermittent. If peripheral reflexes are well preserved it is unlikely that the patient has autonomic neuropathy. Try to stop diuretics and betablockers, and advise the patient to reduce excessive alcohol intake. Endocrine causes are rare (<5%), and usually produce loss of libido rather than erectile dysfunction, but it is still worth estimating serum testosterone and prolactin.

As everyone knows, the treatment has been transformed by sildenafil ('Viagra') which is taken about 1 hour before intercourse, and produces an erection in about 50% of diabetic patients in response to sexual stimulation, with little effect on the vasculature elsewhere, although some patients develop headache or dyspepsia, and rarely experience disturbances of colour vision. Patients with cardiac problems usually tolerate the treatment very well, but nitrate therapy is an absolute contraindication – this is extremely important ! The usual dose is 50mg, but this can be increased to 100 mg if necessary, and the cost is about £5 per tablet. They are allowed on prescription for diabetic patients at a rate of one per week. Newer related drugs – all PDE5 inhibitors - have now appeared, namely vardenafil (Levitra) which may work slightly faster and be marginally more effective, and tadalafil (Cialis) which lasts for 12-36 hours – perhaps more suitable for a romantic weekend ! All are strictly contraindicated in patients on nitrates.

Patients who don't respond to sildenafil or related drugs should be referred to an erectile dysfunction clinic. There are a range of more invasive and less aesthetic treatment options. The transurethral 'MUSE' (medicated urethral system for erection), in which alprostadil is administered directly into the urethra by a plastic cannula, works surprisingly well, with virtually no systemic side-effects and much better acceptability than some previous treatments, although about 10% experience local trauma from the urethral cannula. Another option is injection therapy. Many patients find this to be satisfactory, although it may have side-effects, particularly priapism and local pain, and surprisingly few patients persist with its use in the long-term. Various vacuum devices are now available. These have no side-effects, but patients have to buy them at a cost of about £300. The choice of therapy lies with patients and their partners. Patients who have an obvious psychogenic component may also benefit from referral to a Clinical Psychologist or a Psycho-sexual clinic.

EDUCATION AND LIFESTYLE

EDUCATION

Patient education is one of the most important aspects of diabetic care. It should be a continuing process, and involve all the medical, nursing, dietetic and chiropody staff. It is obviously important that everyone delivers the same basic messages. There are many booklets which provide detailed information for interested patients. Build up stocks of those which you find useful. Keep all your educational sheets and leaflets together in your clinic. Give them out personally, and ask your patients to read them carefully - this 'personal touch' lessens the chances of the leaflets ending prematurely in the waste-paper basket!

There are good opportunities for group education sessions in mini-clinics. These approaches have potential, although in practice they are quite difficult to initiate and sustain. Try to form an educational group, with a few patients 'facilitated' by the diabetes or practice nurse.

EXERCISE

Exercise has many potential benefits for type 2 patients. It may improve diabetic control, help weight reduction and decrease ischaemic heart disease. A reasonable target would be three sessions of a suitable exercise for 15-30 minutes per week. The aim is to have a pulse rate of 110/min at the end of the exercise. This should be modified in patients with known ischaemic heart disease.

ALCOHOL

Alcohol abuse is a major health problem, especially in some sub-groups of Asian patients, and it is illogical to concentrate on prevention of long-term diabetic problems, whilst ignoring an obvious alcohol problem. Reducing alcohol consumption will improve diabetic control by decreasing calorie consumption. Pils lager is no more suitable for type 2 patients than ordinary beer, because it has just as many calories. Patients with severe alcohol problems are more prone to develop hypoglycaemia, and recovery is impaired, so tight control may be dangerous in this situation. However, a moderate alcohol intake is associated with reduced cardiovascular risk, at least in non-diabetic subjects.

DRIVING

Type 2 patients who are taking oral hypoglycaemic drugs must inform the DVLA (Swansea) and their insurance company that they have diabetes.

INSULIN-TREATED PATIENTS - PRACTICAL POINTS

Most patients on insulin attend a hospital clinic, and most of their practical problems will be sorted out there. The following notes cover some common and important topics which may arise when

they attend a community clinic. Many patients will need to obtain supplies of a wide and bewildering range of items connected with their insulin treatment - syringes, pens, needles, lancets, needle clippers, strips etc. These are also summarised in the next few paragraphs.

TYPES OF INSULIN

Insulin regimes overview

The range of different insulin regimes follow a few basic patterns, detailed below.

1. Twice daily insulin mixtures (Mixtard, Novomix 30 or Humalog Mix 25 insulin). This is the basic pattern used for the majority of type I and some type II patients. They receive a fixed mixture of both quick and intermediate-acting insulin, usually in a ratio of 30:70, and usually take two thirds of the daily dose in the morning and a third in the evening. This works reasonably well but there is no extra insulin to cover the post-lunch rise in blood glucose, and the evening intermediate insulin may not last throughout the night.

2. **Basal bolus regimes**, with 4 injections a day, in which a long-acting insulin (ultratard or glargine insulin) (usually injected at bedtime) provides a baseline of insulin, and short-acting insulin injections are taken to cover each meal. This provides more flexibility and is the treatment of choice for motivated type 1 patients and some type 2 patients, although glucose control in practice may be no better than those on twice daily injections, and the regime requires 4 rather than 2 injections daily. We previously used ultratard as the long acting insulin and actrapid insulin with each meal, but now our standard regime is glargine insulin at bedtime, and Novorapid insulin with each meal.

3. **Addition of bedtime insulin to tablets,** for type 2 patients. This is a safe treatment for patients who are poorly controlled despite full doses of tablets. Approximately 10 units of intermediate or long acting insulin (Isophane, Ultratard insulin or glargine) are given at night, to reduce nocturia and to lower early morning blood glucose. This regime serves as an introduction to insulin treatment, with little risk of hypos and better acceptability than with two injections per day. The evening insulin dose can be gradually increased, depending on the fasting blood glucose on the following morning. Metformin is usually continued with bed time insulin, but sulphonylureas may be stopped.

4. **Once daily insulin (without tablets)** may rarely be given to elderly or infirm type 2 patients in whom tight control may not be so crucial, and the main priority is the avoidance of hypoglycaemia. Once daily monotard, mixtard or glargine insulin might be used for this.

New Insulin analogues

1. Rapidly acting insulin analogues - insulin aspart (Novorapid) and insulin lispro (Humalog) - act extremely rapidly and can be taken before, during or even after a meal. Their peak of action is 5-50*** minutes compared to 30-60 minutes of Actrapid insulin. This produces better cover of the postprandial rise in glucose, and fewer hypos, especially at night. However, it produces little or no

improvement in the observed Hb A1C level, although this generally reflects basal rather than post prandial blood glucose levels. Nevertheless, patients prefer these newer insulins, partly because it is more convenient to take insulin immediately before a meal, or even after a meal, rather than half and hour beforehand, and partly because they are delivered in better pen devices!

The rapid insulins are also used in Novomix 30 (Novorapid with Insulatard insulin), which is similar to Mixtard insulin but which can be taken immediately before breakfast and supper, rather than 30 minutes beforehand. Humalog Mix 25 is the analagous produce from Lilley.

2. Insulin glargine (Lantus insulin) is a long acting insulin analogue which has a smoother profile than other long acting insulins such as Ultratard. Thus, when given at bedtime it is less liable to cause nocturnal hypos and it also produces less weight gain. Nevertheless, the absolute reduction in hypos is relatively slight, and the insulin is expensive. Thus there is no need to switch all patients requiring long acting insulin to this new agent. By NICE guidelines they are not recommended in type 2 patients unless the patient needs a carer, has recurrent symptomatic hypos or would otherwise require two injections of a basal insulin per day. This last exception covers most type 2 patients in practice !

Problems with glucose control

It is worth mentioning the inherent limitations to all insulin regimes. Whereas endogenous insulin is secreted by the pancreas into the portal vein to act directly on the liver, exogenous insulin is injected into subcutaneous tissues of diabetic patients as an unphysiological bolus, and leaches out into the systemic (rather than the portal) circulation in a variable manner. Not surprisingly, this is an imprecise art and blood glucose values often fluctuate widely in type 1 patients, in ways which cannot easily be explained by food, exercise and insulin patterns. Many patients have unrealistic expectations of achieving tight control. Insulin treatment is a crude art and not for the obsessional! All patients should adjust their insulin dosage and base these changes on trends in glucose values, rather than on individual values.

Human insulin versus animal insulins

The 'scare' that human insulin may cause hypos without any warning symptoms (and even unexplained deaths), has now largely subsided. A few patients had problems, and have remained on pork insulin again, but it has largely been a false alarm. Nevertheless, patients wishing to switch back to pork (or beef) insulins should be permitted to do so. There are a range of pork and beef insulins available.

INSULIN PENS AND SYRINGES

Insulin pens – disposable (prefilled) or cartridge

Insulin pens are an important practical advance, because they are more convenient to use, and to carry around, than syringes and insulin bottles, and virtually all patients now use a pen, although patients should still be taught how to use conventional syringes and bottles in an emergency. There are two types of pen - the disposable (or pre-filled) pens, which are discarded after all the insulin in the pen is used, and cartridge pens, which take replacement insulin cartridges and are thus re-usable. Disposable pens are slightly easier to teach to patients and more convenient, but are slightly more expensive (see below). The major insulin manufacturers produce a range of both disposable and cartridge pens, to take their respective insulins. As a rough guide, the annual cost of insulin cartridges for a patient using 30 units of Mixtard 30 insulin daily is about £163, whereas the annual cost of this insulin in disposable pens is £193. The equivalent costs for Novo Mix 30 are £196 (cartridges) or £216 (disposable pens). Insulin glargine is currently the most expensive insulin, costing £287/year for 30 units per day, but in this case the cost of cartridges (for the OptiPen Pro 1) and prefilled pens (Optiset pens) are identical.

Disposable (prefilled) pens

The new insulin analogues have been marketed in slightly better disposable pens, which are easier to use and to teach to patients. The disposable pen for the Novo Nordisk insulin analogues (eg Novo rapid, Novo Mix 30 etc) is the 'Flexpen', that of the Lilley analogues (eg Humalog, Humalog Mix 25) is simply called the 'Humalog pen' and that of insulin glargine, made by Aventis, is the 'Optiset' pen. The older Novo Nordisk insulins, such as Mixtard insulin, are contained in Novolet disposable pens, and the Lilley range in the Humaject pen. Novo Nordisk also manufacture an unusual disposable pen termed the 'Innolet' which looks more like an egg-timer than a pen, and is useful both for older or arthritic patients, and for anxious patients.

Cartridge pens

The cartridge pen for older Novo Nordisk insulin, such as Mixtard insulin, is the Novopen 3, and this takes Mixtard 30 penfills (or Actrapid or Insulatard penfills). The equivalent Lilley pen, for Humulin M3, S or I insulins, is the Humapen Ergo. The cartridge pens now all take 3 ml (300 units) insulin cartridges – the smaller 1.5ml cartridges are now obsolete.

Needles

Needles are required for both cartridge and disposable pens – they are prescribed separately, and are not an integral part of the syringe. They are available in different needle lengths, and most patients use 8mm lengths. Markedly obese patients may use 12mm needles, and children or very thin adults may use 6 mm length. They are available on prescription. The cost to the NHS is £8/100 needles or about £30/year for once daily injections etc. They are interchangeable and can be used with all pens (disposable or cartridge pens) except for the Optipen Pro 1 pen, a cartridge pen from Aventis, which specifically require Penfine needles, produced by Disetronic. Safe disposal of used needles is obviously important. They should be placed in a safe container, such as

an old plastic bleach bottle. *** used syringes should first be clipped to remove the needle, using a B D Safe-clip sharps disposal device (which is available on prescription)

Problems with injection technique

Patients who complain of painful injections are usually inserting the needle at too shallow an angle, and thus in effect giving the insulin intradermally. It should be inserted virtually at right-angles, with a fold of skin pinched up. Patients should avoid using the same small area of skin repeatedly, since otherwise fatty lumps appear, which are unsightly and interfere with insulin absorption. The needle should not be withdrawn too rapidly after the insulin has been injected – patients are advised to count to 10, with the plunger depressed, to reduce leakage of insulin after removal of the needle. There is no need to swab skin prior to injection.

Storage of insulin

There is no need to store insulin (either the current pen or insulin bottle) in a refrigerator - it is stable at room temperature for up to a month in non-tropical climates, and injections are more painful with cold insulin. However, prefilled pens, cartridges or bottles which are not currently in use should be kept in a 'fridge'. When patients travel to warm countries they should take a thermos flask to keep the insulin from becoming excessively hot. 'Frio' insulin cooling wallets are also available for use when travelling. They may also need a letter informing customs officials that they are bona fide diabetic patients, rather than IV drug abusers !

Insulin syringes and bottles

As stated above, patients should still be taught how to use conventional syringes and bottles in an emergency, and carers usually give insulin to their patients use syringes and bottles rather than insulin pens to reduce the risk of needle-stick injuries. There are 3 standard sizes of syringe, namely 0.3ml, 0.5ml or 1ml, giving maximum injection doses of 30, 50 or 100 units. Most patients use 0.5 ml syringes, unless they take over 50 units in a single injection. The smaller syringes (up to 50 units) are graduated in steps of 1 unit, whereas the 1.0 ml syringe is marked in 2 unit amounts - thus patients on over 50 units of insulin should be prescribed doses in even numbers - 64 or 66 units, not 65 units ! There is no need to inject air into an insulin bottle before withdrawing the insulin. Disposable syringes cost about 11 p each.

Prescribing for patients on insulin

Insulin-treated patients need a bewildering array of different items relating to their insulin therapy and blood-glucose monitoring. Insulin syringes and disposable pens, needles for insulin pens, all blood and urine glucose strips and sticks, lancets to fit finger-pricking devices, and the B-D Safe-clip needle clipper are all available on prescription. The only standard items which are not available on prescription are glucose meters and finger pricking devices, and these must be bought. Cartridge pens are also not available on prescription, but are provided free by the insulin manufacturers and

are available from diabetes specialist nurses. Thus a type 1 patient on twice daily treatment might typically need:
1) Insulin either as
Disposable (preloaded) pens (e.g. NovoMix 30 insulin in a Flexpen, or a Humalog Mix 25 pen)
or:
Cartridges for the cartridge pen (e.g. Mixtard 30 penfills for Novopen 3) (or Humulin M3 cartridges for Humapen Ergo)

2) Needles for insulin pens – usually 8 mm length
3) Meter strips
4) Lancets for finger pricker
5) B-D Safe-Clip Needle Clipper for sharps disposal **?

and will have to buy a blood glucose meter and a finger pricker.

HYPOGLYCAEMIC ATTACKS

Hypos are the main source of anxiety for insulin-treated patients. They usually occur before meals, particularly before lunch, and in the early hours of the morning. They are caused either by too little food (a missed or delayed meal or snack), undue exercise (such as gardening) or too much insulin. They can be avoided 1) by spreading out food intake to include snacks, particularly at mid morning, mid afternoon and bedtime, 2) by taking extra food before undue exertion, and 3) by reducing insulin if they occur repeatedly.

Patients should always carry glucose tablets with them. Hypoglycaemic attacks are extremely dangerous when driving or swimming alone. In most other situations, patients are unlikely to come to serious harm. If patients lapse into a hypoglycaemic coma, there is virtually no risk of death or long-term cerebral damage. Even if left unaided, they almost always recover spontaneously. It is very important to reassure all patients accordingly. Patients should always carry a card giving information about hypoglycaemic attacks and their treatment. A glucagon injection kit can be given to partners or parents if severe hypoglycaemia occurs commonly. This is totally safe, but it is important to show them how to use it in an emergency. Novo Nordisk produce a 'GlucaGen' kit which has a prefilled syringe with water for the injection. 'Hypostop' is a sugar gel which can be rubbed on a patient's gums during a hypo, and may be useful to parents in aborting severe hypos in diabetic children. Hypos are relatively uncommon in type 2 patients treated with insulin because of their insulin resistance - nearly all problems with hypos occur in type 1 patients.

SICKNESS

It is vital that no patient stops insulin because he/she is vomiting, because this can rapidly produce fatal ketoacidosis. Deaths occur every year from this catastrophic mistake! Vomiting and abdominal pain may be caused by ketoacidosis itself, and such patients need more insulin - not less! Everyone taking insulin - particularly type 1 patients - must understand this. If patients are vomiting and cannot take solid food, they should perform HBGM tests regularly. If readings are not elevated, they should take a sweet drink instead of their meal, say half a glass of Lucozade (which contains about 20 grams carbohydrate), with their insulin. Ketostix are useful in this situation, and should be supplied to younger patients, especially if their control is erratic. If vomiting occurs, especially when associated with heavy ketonuria, the patient must be assessed urgently in hospital, and will probably require admission.

DRIVING

All patients on insulin must inform the DVLA (Swansea) and their insurance company. Studies have shown that they are no more prone to accidents than the general public, and their premium should be no higher. The BDA can recommend insurance agents who cater specifically for diabetic subjects. Patients with HGV or PSV licences will almost certainly lose them, but those with ordinary licences rarely do so. The new legislation also precludes insulin-treated patients from driving vehicles over 3.5 tonnes, such as a minibus or large van. All patients on insulin should be strongly encouraged to check their blood glucose level before driving, and to consume some carbohydrate at least every 2 hours during a long drive. It is vital to carry glucose tablets, and patients should be especially aware of the danger of hypos before lunch, especially if this is delayed. If patients become hypoglycaemic when driving, they must get out of the car and switch off the ignition. In practice, accidents due to hypoglycaemia are rare, but the consequences may be so disastrous that extreme care is needed.

PATIENT MONITORING

HOME BLOOD GLUCOSE MONITORING

Blood glucose meters

There are at least 10 different blood glucose meters currently in common use, all of which are satisfactory, and choice depends on personal preference. They include the Medisense Optium meter, the Lifescan One-touch Ultra meter, the Meanarini Glucomen meter, the Roch Accu-Check meter, and the Bayer Ascensia meter. New models continually emerge, and each uses its own strips exclusively, so there is a baffling array of testing strips, all of which are available on prescription. Although the meters are not available on prescription, the manufacturers sell them cheaply - typically £10-20 – as a 'loss-leader' to encourage the sale of their strips ! Designs have improved markedly in recent years, and modern meters require only tiny amounts of blood and their results are more reliable. There are differences in the time required for the test and in the calibration

procedures. Most are presented as a starter kit, also including a finger pricker, test strips and lancets. All need careful calibration when a new pack of strips is used. It is important for patients to register with the manufacturers so that they can obtain customer support if necessary, rather than phone the Diabetes Specialist Nurses! All the different testing strips cost around £15 for 50 strips, or 30p per test. Thus 4 tests a day cost £440 per year !
*****
There are also several different designs of finger-pricking devices. Currently the 'Soft-touch', made by Roche is popular and costs about £8- 15. The lancets of gauges above 26 should enable the user to get sufficient blood with maximum comfort.
OR

There are several different designs of finger-pricking devices. Currently the 'Soft-touch', made by Boehringer is popular and costs about £8. The B-D Lancer device costs about £5. The lancets are of standard size, are available on prescription, and will fit either device.
! ** WHICH IS RIGHT ?? – ask DSNs….please check this bit ***

Use of home blood glucose monitoring

Home blood glucose monitoring (HBGM) is used by most type 2 patients to monitor their control nowadays. It provides information not available from urine testing, and helps patients understand their diabetes better, and is especially useful in patients with a high renal threshold due to renal impairment, and in detecting any tendency to over-treatment. However (and rather surprisingly) several studies have consistently shown that it leads to no better glycaemic control than with urine testing.

Patients should test their blood on rising in the morning and at bedtime (i.e. fasting and 2 hour post-prandial values), initially every day, reducing to 1-2 days per week when their treatment is stabilised. Some patients become rather obsessed with their results, and perform far too many ! The expenditure on strips has grown enormously, and this is difficult to justify in the absence of proven benefit on control, particularly in patients not receiving insulin, in whom fluctuations of glucose levels, and risks of hypos, are less. A maximum of 4 tests per week might be sufficient for stable patients not on insulin, as detailed above.

It is vital to teach patients the significance of their HBGM results – the tests have little value without this education. They need to learn how to use the results to adjust their treatment, to record their results and to bring their records with them to their clinic appointments.

Urine testing

Urine testing remains a useful method for many type 2 patients, especially if they are unwilling or unable to perform home blood glucose monitoring, since as stated above it is equally effective in improving control. Negative urine tests imply control of hyperglycaemic symptoms, regardless of blood levels, because polyuria, thirst and weight loss are largely caused by the osmotic diuretic

effect of glycosuria. Glycosuria usually indicates that the blood glucose level is above 10 mmol/l, in patients with preserved renal function. In elderly patients and in those with declining renal function, the renal threshold rises and urine tests may be less valuable.

Patients should test their urine on rising in the morning and at bedtime (i.e. fasting and 2 hour post-prandial values), initially every day, reducing to 1-2 days per week when their treatment is stabilised.

They should record the results either on the sheet provided with the sticks, or in a urine testing booklet, and should always bring them to the clinic. They can use the results to adjust their dose of tablets, especially when newly diagnosed.

NOTES ON COMMUNITY CLINICS

Shared Care philosophy

The Ealing health economy has unique problems in providing adequate diabetes services for all its citizens, because of our unique ethnic mix, and because diabetes is 4 to 5-times more common within the Asian community. The number of diagnosed patients is rising sharply, and all our services, whether in the primary or secondary sector, are 'bulging at the seams'. About 2500 patients attend the Ealing Hospital clinic, and there are perhaps another 7000 patients within the community. The care of many hospital patients might be transferred back to primary care, where most aspects of diabetes care could be provided, perhaps including starting insulin treatment. However, general practitioners are hopelessly overworked and most community diabetes care is undertaken by practice nurses. There is a widespread fallacy that care of type 2 patients is both easy and boring, whereas that of type 1 patients is difficult and interesting. In fact it is probably the other way round!

Type 1 diabetes is often straight forward but type 2 patients often require up to 10 drugs and their management is complex and requires skill. Our basic plan is currently for patients either to be treated entirely in the community or to be treated by 'shared care' with the hospital overseeing the overall treatment plan (the strategy), particularly the choice of drugs, every 12-24 months, and delegating the fining tuning (the tactics) of glucose, blood pressure and lipid control to colleagues working in primary care. We are also investigating the establishment of intermediate care clinics, liaising with both primary and secondary care. Our two over-riding philosophies, across primary and secondary care, are to reduce cardiovascular risk, particularly by lowering lipids and blood pressure, and to improve concordance with therapy.

Logistics of community clinics

1-2 % of the population have known diabetes, and about one third are on insulin therapy. Thus, a practice with about 5000 patients may have about 70 diabetic patients, of whom 20 will be receiving insulin and 50 will be on tablets or diet alone. However, because diabetes is so much more common with the Asian community, practices in Southall may have 300-500 or more diabetic patients. Diabetes is also more common within African Caribbean people. Community clinics will cater primarily for type 2 patients treated by tablets or diet alone. The optimum frequency of clinic attendance for stable type 2 patients is debatable, but most patients prefer to attend every 3 months.

Patients with no problems could be seen less often - say every 6 months. Virtually all insulin-treated patients attend hospital every year or 18 months. They often become very experienced in coping with any problems, and may be reluctant to attend GP miniclinics. Nevertheless, they should be informed of the miniclinics, and given the option of attending. The clinics require input from the GP, and should not be delegated solely to practice nurses working alone, unless they have had considerable experience and training in diabetes care. Diabetes nurses may also be involved, to provide educational input - for both patients and staff!

CLINIC PROCEDURE

Clinics should preferably be held in the morning, when patients can come fasting, and fasting blood glucose values obtained. However, many practices choose to hold afternoon clinics, and to rely on HbA1 values, random blood glucose values and the patients' own home monitoring. Patients should be sent a letter informing them about the clinic, with an appointment, and instructions to 1) bring a urine sample, 2) to come fasting (if a morning clinic and not on insulin) and 3) to bring testing records. An appointments and call/recall system is obviously necessary.

The following list of procedures includes all those required to obtain maximum clinical indicator points by the new GMS contract :

l. Weight recorded (and height on the first visit), and BMI recorded in notes
2. Urinalysis for glucose, ketones, protein, leucocytes and nitrates. Urine sample saved and tested for microalbuminuria - annually
3. Blood pressure estimation.
4. Capillary blood glucose, using a meter.
5. Consultation with the GP / practice nurse – discussion re glycaemic control / concordance
6. Enquiry re smoking, and offer of practical help if still smoking (every year)
7. Foot inspection – pulses & microfilament test - annually.
8. Enquiry re retinal screening arrangements – annually
9. Enquiry re influenza immunisation in previous 1st Sept to 31st March
10. Education - and provision of educational material
11. Venepuncture for HbA1c, urea and electrolytes, and lipids, every 6 months.

WHICH PATIENTS SHOULD BE REFERRED TO HOSPITAL ?

The following patients should be referred urgently :

1. **Newly diagnosed young patients** especially with ketonuria. These should be referred immediately - by phone or fax - to initiate insulin therapy before ketoacidosis supervenes.
2. Patients with **foot problems** so that they can be seen jointly with a hospital chiropodist, and given intensive management.
3. Patients with **other complications** (retinopathy, nephropathy, and severe neuropathy or hypertension).
4. **Pregnant patients**, and all women planning a pregnancy.

Other patients who should attend the hospital clinic include
5. Any patient who is on insulin therapy.

In addition, please refer up:
6. Any patient who you do not feel confident dealing with.
7. Any patient who insists on hospital attendance !

PRACTICAL NOTES FOR COMMUNITY CLINICS

1. Urine tests.

Urine tests for glucose, ketones and protein are needed at every visit. Patients should be encouraged to bring a fresh urine sample with them. On leaving the clinic, please give them a Universal Container ('MSU pot'), which they can use for their next visit. Otherwise they may bring jam-jars, which can be rather unwholesome !

The test for ketones is rather sensitive, and a 'small' amount is often found and has little importance. However, the finding of 'moderate' or 'heavy' ketones in patients not on insulin, especially when newly diagnosed, indicates that they may need insulin therapy, and should be referred urgently. If found in patients already on insulin, it usually indicates that they need more insulin. If associated with vomiting, it may herald diabetic ketoacidosis, and urgent hospital referral is necessary.

Testing for proteinuria is essential at every visit. If more than a trace of proteinuria is found, the urine should be tested for leucocytes and nitrites to see whether it is due to a urinary tract infection. The need to obtain an MSU in patients with leucocytes and nitrites on urinalysis has been questioned in recent years. Similarly, the need to treat asymptomatic urinary tract infections is also disputed, since there is no evidence that this improves or protects renal function, except in children and in pregnant women, although it may affect glycaemic control.

3. Weight and height

These should be measured without shoes. The Body Mass Index, or BMI, is weight(kg) /height(m)2 and can either be read off a chart, or calculated if records are computerised. The desirable range is 20-25. Below 20 is underweight, 25-30 is overweight, and >30 is obese. This is a useful figure to obtain, although many patients prefer to have an actual target weight to aim for.

4. Visual acuity (VA)

This is measured in each eye using the Snellen chart, read at six metres. The Snellen chart should be in a well-lit part of the room. If VA is impaired to 6/9 or less, the patient should try again, using glasses (if worn) or a pinhole. This will correct for any refractive problems. If it produces an improvement, the patient needs to see an Optometrist for new glasses. It is often difficult to measure VA in Asian patients who cannot read English. Sometimes the use of a Snellen chart with numbers can help.

5. Diabetes notes

These need to be structured, and kept on customised sheets. Various companies have produced 'Co-operation cards' which are designed to be kept by the patient, and taken to either hospital or community clinics, as with Ante-Natal care. Some patients may forget or lose their cards, and some practices prefer to keep them together in a box at the surgery. Although this means that no information will be available if they also attend the hospital, it ensures that their records are kept securely, and the box can serve as a register, and as an aid to reports and to call/recall procedures. Other practices give the cards to the patients to bring to the hospital.

THE NEW DIAGNOSTIC CRITERIA FOR DIABETES

In practice the diagnosis of diabetes is not usually a problem, because most patients present with symptoms, glycosuria and a elevated blood glucose (over 11 mmol/l). There is rarely a need for a glucose tolerance test. It is worth emphasising that patients with 'moderate' or 'heavy' ketones in the urine at diagnosis, particularly if young and losing weight, must be referred immediately to the hospital for urgent insulin treatment.

Problems arise with the classification of asymptomatic patients with more borderline abnormalities. Values for capillary blood glucose (as read in a meter) are slightly lower than those for venous (laboratory) samples, because laboratories usually measure plasma rather than whole blood glucose, and this is about 1 mmol/l higher. The exact diagnostic criteria are muddling, but have recently been revised and simplified, with more emphasis on fasting values rather than those obtained during a glucose tolerance test, and a lower cut-off level of fasting glucose (7.0 mmol/l v 7.8 mmol/l) needed for the diagnosis of diabetes. This has resulted in more patients being labelled as having diabetes.

As a simple guide, if a patient has a raised random glucose (over 8 mmol/l), obtain a fasting laboratory sample. If this is $\geq$7 mmol/l on two occasions, this signifies diabetes. If it is below 6 mmol/l it is normal. Classification problems arise with the many patients whose fasting plasma values are between 6 and 7 mmol/l. Previously a glucose tolerance test was required to distinguish impaired glucose tolerance (IGT) from normal. In the new criteria, a fasting plasma value between 6.1 and 6.9 mmol/l will be termed ‘impaired fasting glucose’ (IFG), which is broadly analogous to the previous IGT. This is an intermediate category, in which subjects are at increased risk of developing diabetes in the future, but do not develop retinopathy and other microvascular complications. However, they have an increased risk of ischaemic heart disease. In practice, the

management of IGT - or IFG - and uncomplicated type 2 diabetes is broadly similar - adapting diet, treating hypertension, stopping smoking etc, to minimise cardiovascular risk, although patients with diabetes will also need eye screening. Glucose tolerance tests are hardly ever indicated nowadays, in routine practice, except in pregnancy, and possibly for insurance purposes.

**check all this!!

Details needing tidying up **********

NSF dates for registers & digital screening

- Details of HBA1c errors / ethnics etc / fructosamine…
- Diet - ? stuff on Atkins diet etc ? – ask Majda
- Cost of generic glicazide
- Use of rosi in end-stage renal failure – cutoff of creat ?
- How long to wait to assess postural hypotension – see BMJ ABC
- Cost of generic bendrofluazide (& statins)
- Data from stella on relative strengths of statins
- Stopping statins temporarily when on cipro etc ??
- Check dose / cost of Maxepa
- Smoking – safety of patches / Zyban etc…
- Details of digital screening programme
- Neuropathy – dosage build-up of gabapentin, and sites to test microfils
- Used syringes / needles – sharps boxes ? clippers ?
- Finger prickers and lancets – check which version OK – check details
- Check stuff re IFG/IGT etc