

ideas well, those who waffle, those who are obstructive, and those who always try to help. There are some who are always listened to with respect and those who lose the audience straightaway.

Committee work is now a vital part of the work of a doctor who is concerned with getting the best he can for the National Health Service and those it serves and those in its service. Those who recognise its importance are valuable members of the medical community, serving it and its patients. Such doctors have understood something of their relations with their fellows and with society as a whole and how it works in a democracy. They must learn to live with the opprobrium of being called medical politicians and bureaucrats by more ignorant colleagues.

### Bureaucracy

Just as there is irritation about administrators so there is about bureaucrats. This is amusing since doctors are all bureaucrats. The characteristics of a bureaucracy are (i) division of labour, (ii) authority structure, (iii) the position and role of the individual member of the bureaucracy, and (iv) the rules regulating relations between members. It is all based on specialisation. Authority in a bureaucracy is based on the office held and is not personal to the holder. Selection for office is based on the possession of a diploma showing formal quali-

fications and not on social connections. The rules are intended to design and regulate the whole organisation on the basis of technical knowledge and with the aim of achieving maximum efficiency. It will be seen that clinical medicine and its staffing fits exactly into the definition of bureaucracy.

What is really criticised is not bureaucracy itself but its stupidities and red tape. This is reasonable, provided that it is realised that all human organisations display these undesirable characteristics. Do not contribute to them. Remember too "Why beholdest thou the mote that is in thy brother's eye, but considerest not the beam that is in thine own eye?" Do not add unnecessarily to other people's problems. The final piece of advice therefore is to recognise the non-problem, on which much energy and emotion is spent. Too many people see problems that are simply not there. They are figments based on inadequate facts and irrational thought. All of us are prone to this, but try to keep it to an irreducible minimum in yourself, and be patient of others who may seem to be wasting your time. They do not think that they are. Another quotation from the Bible might suitably be "A soft answer turneth away wrath." Tolerance might be the paramount virtue in administration as well as in much else. It is not a weakness but a strength and is a virtue practised every day by doctors in dealing with the frailties of their patients.

In the next article I shall discuss how postgraduate education is organised.

## New Drugs

### Oral hypoglycaemic agents

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Patients with non-insulin dependent diabetes mellitus, usually type II diabetes of maturity onset, have a comparatively mild metabolic disorder compared with insulin dependent patients. Nevertheless, they suffer considerable morbidity and mortality, and up to 20% of such patients have diabetic complications at the time of presentation. They comprise a heterogeneous group, the common feature being the ability to produce enough insulin to avoid ketosis. While some patients have insulin deficiency of varying degree many are hyperinsulinaemic (particularly the obese) and show resistance to the peripheral action of insulin by virtue of receptor or postreceptor defects.

Recently, the approach to these patients has changed in several ways, and there have been major alterations in emphasis where diet is concerned. In addition, our understanding of the mode of action of oral hypoglycaemic agents has increased, and many new sulphonylurea drugs have become available. While goals in treating patients with non-insulin

dependent diabetes must be realistic, particularly in the elderly, the ideal aim should be to control symptoms, achieve ideal body weight, normalise glycaemia, and treat (or better prevent) complications while avoiding iatrogenic disease. Monitoring control in non-insulin dependent diabetes has traditionally consisted of urine analysis, with a negative urine test after the main meal representing satisfactory control (provided the patient has a normal renal threshold for glucose), and occasional blood tests performed at outpatient visits as an additional index of control. In general, blood glucose estimations two hours after meals correlate reasonably well with fasting blood glucose and with glycosylated haemoglobin (reflecting control over the previous weeks). A fasting blood glucose concentration of less than 6.5 mmol/l (117 mg/100 ml) and a postprandial concentration of less than 8 mmol/l (144 mg/100 ml) (10 mmol/l (180 mg/100 ml) in elderly patients) represent good control.

### Diet

Irrespective of whether oral hypoglycaemic agents are used diet is the mainstay of management. For obese patients this means restriction of total energy and carbohydrate intake with a view to weight reduction, and this appears to restore insulin sensitivity. Recent work suggests that an increase in the amount of various forms of dietary fibre improves carbohydrate tolerance

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in non-insulin dependent diabetes. The mechanisms of this effect include slowing of gastric emptying, changes in the release of gut hormones, and alterations in the rate of absorption from the small bowel. Several studies have shown that Guar gum will improve diabetic control and this substance has also been used in association with Acarbose, an alpha glucoside hydrolase inhibitor, to reduce postprandial glycaemia. Unfortunately, diets high in fibre and with such additives are unpalatable (and sometimes socially unacceptable), but, none the less, the fibre content of the diet of many patients could be increased, particularly with vegetables.

For the patient who is near to his ideal weight the traditional diet restricted total, and in particular concentrated or refined, carbohydrate. It seems, however, that isocaloric diets with an increase in carbohydrate content, especially using complex high fibre carbohydrates, up to 55-60% (from the more usual 40%), accompanied by a reduction in the total fat (to 25-30%) and particularly the saturated fat content, are associated with improved diabetic control and enhanced insulin sensitivity with increased binding of insulin to its receptors.

Compliance with dietary advice is, however, generally poor. The success rate of dietary management in non-insulin dependent diabetes depends largely on the enthusiasm with which the diabetic team pursues the dietary objective, and the importance of adopting a simple dietary approach in the context of the patient's normal diet and environment has been emphasised. While also being beneficial, exercise should be introduced in a graded and regular fashion in view of the prevalence of coronary heart disease in this group of patients.

Despite these measures an appreciable proportion of patients with non-insulin dependent diabetes will fail to achieve satisfactory diabetic control and it is for such patients that oral hypoglycaemic agents are prescribed.

### Sulphonylureas

Sulphonylureas are most clearly indicated for the patient who is near the ideal weight and in whom diet fails to control symptoms and hyperglycaemia. Since these drugs tend to encourage some weight gain there is some reluctance to give them to obese patients. None the less, sulphonylureas may be useful in obese patients particularly when symptoms and hyperglycaemia persist despite adherence to diet. An appreciable proportion of patients will fail to achieve satisfactory control with these drugs (primary failures), the proportion varying from 10% to 30%. Likewise a few patients—about 5% a year—although initially achieving satisfactory control will become secondary failures. There is no convincing evidence that any one sulphonylurea has greater efficacy than the others (potency on a weight for weight basis should not be equated with efficacy), but undoubtedly some patients who are not controlled with one drug may be controlled with another. Sulphonylureas should not be prescribed to pregnant women.

### MODE OF ACTION

Sulphonylureas depend on the presence of functioning pancreatic beta cells for their effect and stimulate the release of insulin particularly in response to a glucose load. While acute studies show that improvement in carbohydrate tolerance is associated with an increase in insulin secretion this may not be the case during chronic treatment, which suggests that treatment with sulphonylureas may have pronounced effects outside the pancreas; these include potentiation of the effects of insulin on the liver, inhibition of hepatic gluconeogenesis in response to glucagon, stimulation of glucose uptake by muscle, and perhaps an effect on insulin disposal. More recently the mechanisms of these effects have become clearer with the finding that treatment with sulphonylureas increases the number of insulin receptors on various peripheral tissues in vivo.

Whether this is a direct effect of the drug on target tissues, as has been suggested from in vitro studies, or a secondary phenomenon resulting from the overall improvement in metabolic control remains unclear. Whatever the mechanism of action the net result is an improvement in glucose tolerance with a deterioration in most patients when the drug is withdrawn. Abnormalities of various intermediary metabolites are also reversed.

Haemostasis in diabetic patients has recently received attention since these patients may have a thrombogenic tendency that could be implicated in the development of several long term complications. Although some sulphonylureas—and gliclazide in particular—may have various effects on platelet aggregation, clotting factors, and fibrinolysis both in vitro and in vivo, it has also been shown that controlling diabetes by dietary means in non-insulin dependent diabetes tends to normalise haemostatic variables in parallel with the reduction in blood glucose concentrations.

First generation oral hypoglycaemic agents, particularly chlorpropamide, continue to be widely used. Sulphonylureas are in general well absorbed from the intestine and are highly protein bound in the blood, which makes them subject to drug binding interactions. The binding sites on albumin for glibenclamide and glipizide are different from those for first generation agents, and hence displacement interactions with drugs such as phenylbutazone, salicylates, and warfarin—which increase the hypoglycaemic response to tolbutamide and chlorpropamide—may perhaps be less likely with these newer agents. Oral hypoglycaemics that are extensively metabolised are susceptible to hepatic enzyme induction (phenytoin, rifampicin) or inhibition (cimetidine), with the risk of hypoglycaemia in the latter case. The second generation drugs are in the main extensively metabolised in the liver, and some of the older drugs—aceto-hexamide (Dimelor) in particular—have active metabolites that are further excreted unchanged in the urine and may be responsible for much of the hypoglycaemic activity of the parent compound. The differing pharmacokinetic properties of these drugs give the clinician a group of agents with a wide range of elimination half life and duration of hypoglycaemic effect from which to choose (table).

Comparison of established and newer sulphonylurea hypoglycaemic agents

Drug	Elimination and approximate half life (h)	Duration of action (h)	Daily dose range (mg/day)
<i>First generation</i>			
Tolbutamide (Pramidex, Rastinon)	Hepatic (4-8)	6-12	500-2000 (divided doses)
Chlorpropamide (Diabinese, Glymese, Melitase)	Hepatic/renal (36)	24-72	100-500 (once daily)
<i>Second generation</i>			
Glibenclamide (Daonil, Euglucon)	Hepatic (6-12)	12-16	2.5-15 (once or twice daily)
Glibornuride (Glutril)	Hepatic (6-10)	8-16	12.5-75 (once or twice daily)
Gliclazide (Diamicron)	Hepatic (12)	12-18	40-320 (once daily)
Glipizide (Glibenese, Minodiab)	Hepatic (3-5)	6-10	2.5-30 (above 10 mg twice daily)
Gliquidone (Glurenorm)	Hepatic (1-2)	2-4	45-180 (divided doses)

There is considerable interindividual variation (up to 20-fold) in the steady state concentrations of sulphonylureas in patients during chronic treatment. Some of this is undoubtedly due to poor drug compliance, although for tolbutamide genetic factors may control the rate of drug metabolism. In general there is no simple relation between drug and blood glucose concentrations. Care must be exercised when these drugs are given to patients with chronic liver disease. Not only may drug metabolism be affected and the amount of carrier protein reduced but such patients are particularly likely to develop hypoglycaemia.

Renal insufficiency may also have profound effects on the excretion of acetohexamide and of unchanged chlorpropamide. Recent evidence suggests that in addition to renal excretion of unchanged drug chlorpropamide is also extensively metabolised in the liver. Because of its very long elimination half life the drug accumulates over seven to 10 days so that the dosage should not be adjusted more often than every fortnight and the drug not given more than once daily. Its use should be avoided in elderly patients. Chlorpropamide alcohol flushing, which may be a dominantly inherited condition, is not a problem with the second generation sulphonylureas. Acute ingestion of alcohol may, however, potentiate the action of sulphonylureas.

#### SECOND GENERATION SULPHONYLUREAS (TABLE)

*Glibenclamide* was the first of the second generation high potency drugs to become available. Some accumulation of glibenclamide occurs during chronic dosing and the duration of action extends over 12 hours. If blood sugar concentrations are not controlled then the drug should be given twice daily in larger doses. Hypoglycaemia may be a problem particularly after meals as glibenclamide produces prolonged glucose stimulated insulin release.

*Glipizide* is totally absorbed with peak serum concentrations occurring two hours after a dose. While slowing of absorption may occur if a dose is taken with food—because of delayed gastric emptying—the hypoglycaemic effect is, however, enhanced by administration before meals. It has a shorter duration of hypoglycaemic effect than glibenclamide. When the daily dosage exceeds 10 mg, to avoid hypoglycaemia, it is best given in divided doses about 30 minutes before the morning and evening meals. This also provides better glycaemic control in the evening than does a once daily dose.

*Gliquidone* is the most extensively metabolised of the sulphonylureas, the metabolites being inactive. It has a short duration of hypoglycaemic action and is, therefore, given twice or three times daily before meals. There is no evidence of accumulation of gliquidone in patients with renal failure. It may prove useful in subjects with impaired renal function and may be an alternative to tolbutamide in the management of elderly patients. It is, however, relatively expensive.

*Gliclazide*—Some data from animal studies and observations in patients with diabetic retinopathy suggest that the effects of this drug on platelet aggregation and haemostasis may be beneficial. Unlike other sulphonylureas gliclazide does not seem to cause weight gain. Further evidence is, however, required to establish the clinical benefits of these effects in the long term. It has a long duration of hypoglycaemic effect and should therefore be given once daily.

*Glibornuride* is a drug of moderate potency with a duration of effect in terms of insulin release and reduction in blood sugar concentrations similar to that of tolbutamide and much shorter than that of glibenclamide. Glibornuride should be given in divided doses at higher dosages.

#### UNWANTED EFFECTS

Before a sulphonylurea is prescribed the possibility of provoking hypoglycaemia must be considered. In a recent large study of drug induced hypoglycaemic coma most patients had been taking a sulphonylurea, usually chlorpropamide. There was considerable mortality (11%) and morbidity (3% were left with serious neurological sequelae). Hypoglycaemia occurs most commonly in patients over 60 years, particularly in those with renal impairment. The second generation sulphonylureas may also cause hypoglycaemia, but with the exception of glibenclamide this is usually short lived compared with chlorpropamide. Tolbutamide, glibornuride, and gliquidone are more appropriate choices for elderly patients at risk of developing hypoglycaemia. Drug interactions with sulphonylureas are also

an important cause of hypoglycaemia. While the conclusions of the University Group Diabetes Program in the USA, reporting an excess of cardiac mortality among patients being treated with tolbutamide, are not widely accepted in the United Kingdom they have, nevertheless, been responsible for a reappraisal of the place of drugs and diet in non-insulin dependent diabetes.

Overall, side effects occur in 5-10% of patients given sulphonylureas, but they are rarely responsible for drug withdrawal. Gastrointestinal disturbances are among the more common adverse effects with all these drugs, and allergic conditions—particularly a variety of skin reactions—may also occur. Patients allergic to sulphonylureas tend not to have cross sensitivity to the sulphapyrimidine drug glymidine (Gondafon, a first generation agent which is otherwise rarely used). Transient abnormalities of liver function may occur, and dose related cholestatic jaundice has been reported with chlorpropamide. Water intoxication simulating an inappropriate antidiuretic hormone secretion syndrome occasionally occurs with chlorpropamide—and to a lesser extent with tolbutamide—but not with the newer agents, which may possibly be weakly diuretic.

#### Biguanides

There has been a notable decline in the use of phenformin (Dibotin) since the recognition of an association (about one case in 1000 users a year) with the development of lactic acidosis, which carried a 25% mortality. Although biguanides require the presence of insulin for their hypoglycaemic action, they do not stimulate insulin release and hence do not cause hypoglycaemia when given alone. The precise mode of action of biguanides in reducing blood glucose concentrations remains unclear but may include a degree of intestinal malabsorption, reduction in hepatic glucose production, and particularly an increase in peripheral glucose uptake by making more receptors available to insulin. Metformin (Glucophage) is as effective as chlorpropamide in reducing blood sugar concentrations in both obese and non-obese patients, and treatment with metformin is associated with a notable reduction in weight. The cause of this weight loss may partly relate to an anorectic effect, malabsorption, and also perhaps a reduction in hyperinsulinaemia. Metformin is used in obese patients who fail to achieve satisfactory diabetic control with diet alone and as additional treatment for patients who are failing with sulphonylureas.

Metformin is not appreciably metabolised in man and is rapidly eliminated by the kidneys by both glomerular filtration and active secretion, having a plasma half life of about two to four hours. Absorption is, however, slow and variable. Twice or three times daily dosage (to a maximum of 2 g) is necessary. Excretion is less rapid in patients with impaired renal function resulting in accumulation. Metformin should not be used in patients with renal failure and in those who are predisposed to develop lactic acidosis because of coexistent cardiovascular or hepatic disease. The most important untoward effect of metformin is gastrointestinal disturbance and this may be reduced if patients take the tablets after meals and if the dose is built up slowly.

#### Oral hypoglycaemic failure

Although patients with deteriorating glycaemic control, despite maximal dosage of sulphonylureas, and severe symptoms require insulin, there is also a grey area of symptomless hyperglycaemia. The addition of metformin improves glycaemic control a little, but such patients often have increased concentrations of lactate and other gluconeogenic precursors. The appropriateness of insulin treatment in this situation remains controversial. Nevertheless, there has been a trend to accepting insulin treatment at an earlier stage in these patients, even in the older age groups.



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- A conventional and simply explained diabetic diet appropriate to the socioeconomic circumstances of the patient can be very successful when patients and relatives are intensively followed up by dietitian, health visitor, and doctor.

**MATERIA NON MEDICA****Mutton bird island**

One of the highlights of a recent tour of Victoria was an hour spent in the twilight on a little island just off the shore at Port Fairy, a small farming centre and holiday resort along the southern coast of that state. The island is one of many in that part of Australia which are riddled with the nesting burrows of the short-tailed shearwater (*Puffinus tenuirostris*). This is probably the most abundant Australian bird but nevertheless it is not often seen by most Australians, who know of it only as the "mutton bird," which supports a small seasonal industry on some of the islands of Bass Strait, between the mainland and the island state of Tasmania, where some young birds are "harvested" for their meat, feathers, and oil in the autumn. Fortunately, many of the nesting islands are fairly inaccessible, but the one at Port Fairy can be reached by a short causeway. It is a sanctuary to which the local authorities have encouraged interested observers to come by constructing a small observation bay in an unobtrusive spot, and it appears that visitors do respect this privilege.

During the day these very oceanic birds form vast black rafts out at sea where they feed on krill, little surface fish, and small cephalopods or sleep; but at sundown they return in a bewildering flock, to mill around over one's head, like a swarm of giant black moths, until one by one they flop to the ground, near their respective burrows. They then scramble to their homes and send up veritable fountains of sand as the burrows are fussily cleaned out to their satisfaction. As darkness falls the birds become more vocal, and you also become more aware of a distinctly "guano-ish" aroma which you hadn't noticed before in the fascination of being in the midst of such accident-free aerobatics.

Mating takes place in the burrow. In November one egg is laid; it hatches in about 53 days, and at the end of April or the beginning of May the fledgling is ready for an incredible journey. By then the birds are the same size as their parents, about 16 inches long and with a wingspan of about three feet, and they immediately set off to make the most of the northern hemisphere summer, which they spend in the Northern Pacific and Arctic Oceans. The journey of approximately 10 000 miles can be accomplished in about six weeks. However, happily they do not forget the land of their birth, and so they return to us across the Pacific on a huge figure-of-eight flight path, in September, apparently to their old burrows on many of the islands off the south-eastern Australian coast. Needless to say, much tidying up of the old home is then necessary, breeding pairs are re-established, and the whole mysterious business starts all over again. It is all rather baffling—but as an entertainment on a shining night it is unsurpassed, in the season of the year.—ERIC SIMS, paediatrician, Adelaide.

**130 000 cases of good behaviour**

Nineteen eighty-two, as the sporting world knows, was the year that the Open Championship came to Troon. For almost 12 months dismantled stands lay in heaps about the course. The ground staff, aided and abetted by the agronomists—I think that is the term—from the Royal and Ancient Golf Club of St Andrews, had been at work with slit-tine and sub-air vibratory plough. Our weekly fourball

was in despair. The course would be forever unplayable. Never fear, the R and A know a thing or two and all comes beautifully right for the appointed week.

In the club house a new notice board appears and members are invited to volunteer for duty. The long-handicap doctor scans the list for "assistant medical officer" or "first aid"—in vain. The R and A know a thing or two about this also, and though Royal Troon Golf Club could staff a district general hospital they bring their own experienced medical team. "We'll find the right job for you," said the secretary as he hurried past. I prayed it would be something well out of the limelight for my golf is cheerfully undistinguished.

It is half-past seven on a wet and windy morning when I take up my position. An hour later the clouds are gone, the wind drops, and the next four days are ones of unbroken sunshine. The names of the great are on everyone's lips. Every stroke is watched, analysed, and discussed ad infinitum. From my privileged vantage point I can observe much of the action and drama. How well everyone behaved! Four long days, vast crowds, the excitements, triumphs, and disappointments of a great tournament and everywhere there was good manners, good sportsmanship, and good humour.

Much of the credit must go to the contestants themselves. Their professionalism and discipline do not permit angry exchanges with umpires or exaggerated gestures towards the galleries—not in the noble game of golf. A delicate bond, a true empathy links watcher and player. A hush falls and the crowd is still. The shot is played and distant clapping signifies that it is good, or a sigh which one senses rather than hears tells that it has not quite come off. At most the player can permit himself a tightly controlled smile or the briefest of gestures. The next shot is to come and it must be good. The winner was Mr Tom Watson of the United States, who held the trophy aloft, spoke modestly, and sent us a letter beginning "Dear Fellow-golfers."

And what was the job the secretary found which suited my particular talents and gave a close-up view? He put me in charge of a squad of bunker-rakers!—ROBERT BAIN, general practitioner, Ayr.

*How can an obese patient lose weight if a reducing diet of 500 calories (2.1 kJ) fails?*

Such patients are not adhering to the advised diet for even if taking no exercise a person would be bound to lose weight on an intake of only 500 calories a day. Indeed, 500 calories a day is too low for an ambulant outpatient to keep to. The problem is excellently discussed in the recent report on obesity by the Royal College of Physicians,<sup>1</sup> but it is best first to ensure regular supervision by a dietitian. If this fails it may help to try the "milk diet."<sup>2</sup> Three pints of milk gives 1170 calories (4.9 kJ), and any cheating is overt; vitamin and iron supplements are required. If all else fails the patient may be admitted for dieting under inpatient supervision.—J BENNETT, consultant physician, Kingston upon Hull.

<sup>1</sup> Royal College of Physicians. Obesity. *J R Coll Physicians* 1983;17:5-65.  
<sup>2</sup> Garrow JS. *Treat obesity seriously*. London: Churchill Livingstone, 1981.