G.P. Review Article

ORAL SULPHONYLUREAS IN THE MANAGEMENT OF DIABETES*

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Today many thousands, even millions, of diabetics are grateful for the existence of oral hypoglycaemic agents, even when they merely obviate the need for injections for a longer or shorter period. But they do more than this. By avoiding injections the patient may also avoid insulin allergy, bumps, fat atrophy and infection at the injection site. More important is the greater (though not complete) freedom from hypoglycaemic attacks, which may be particularly hazardous to patients with coronary, cerebral or peripheral artery disease. In unintelligent patients and those with poor vision, with parkinsonism, arthritis, hemiplegia, or other conditions that render injection difficult or dangerous, the oral agents may be a real boon. Psychologically they are also useful.

It is possible that both the sulphonylureas and the diguanides have a minor rejuvenating effect on the beta-cells of the pancreas when used, for example, in young or mild diabetics, or prediabetics. Fajans and Conn[1] have presented fairly convincing evidence that tolbutamide can induce improvement in glucose tolerance in some juvenile diabetics in their early, non-insulin-requiring phase. Occasionally a sulphonylurea has been reported as effective in treating insulin-resistance, but this is uncommon in cases where insulin requirement exceeds 200 units a day.

Finally, and not uncommonly, an oral drug or combination may produce far better and smoother control of the diabetes than has been attained with insulin, even when the dose of the latter has been quite high. In the past some people were afraid to use oral drugs on the grounds that they might 'exhaust' the pancreatic beta-cells—this does not happen.†

WHAT ARE SULPHONYLUREAS AND WHAT DO THEY DO?

The early sulphonamides were observed to have hypoglycaemic properties and the modern sulphonylureas have been developed from them. They are no longer true sulphonamides nor do they exhibit antibacterial properties, though occasionally a patient may be allergic to both groups of drug (cross-sensitivity).

Their main and only important action is to stimulate the beta-cells of the pancreas to release insulin into the blood stream. Plainly they can have this effect only in a patient whose pancreas is still capable of producing insulin. Hence they are ineffective in established, juvenile-type, ketosis-prone diabetes at any age. Individual sulphonylureas differ in chemical side-chains, duration of action, elimination and detoxication, in some side-effects and in potency, but their basic mode of action is identical. The other oral hypoglycaemic drugs, the diguanides, have quite a different mode of action.[2]

Who May Benefit?

Large numbers of maturity-onset diabetics have responded to sulphonylureas by improved control of their blood sugar levels; many have become totally aglycosuric for long periods. Most authorities agree that some 60-70% of adult-onset diabetics benefit from the sulphonylurea drugs. Nevertheless, apart from juvenile diabetics, there remains a substantial proportion of apparently highly suitable middle-aged non-ketotic diabetics who simply do not respond to sulphonylureas. There is no simple way of picking out these non-responders. You cannot be sure until you try.

Absolute contraindications are:

1. The presence of or liability to ketoacidosis (a single episode of ketosis or even coma in the past is not necessarily a contraindication).
2. Uncontrolled diabetes in emergencies.
3. Obesity for which diet alone has not been given a fair chance.

Minor degrees of ketonuria do not necessarily preclude a drug trial.

Although less likely to be effective in subjects under 40 years, sulphonylureas can be useful in two circumstances in young people: (*a*) in children after an acute onset of diabetes the need for insulin may remain temporarily in abeyance, and oral drugs suffice *for a time only;* and (*b*) children and young adults occasionally manifest symptom-free or mild diabetes. Fajans and Conn[1] found several such patients while testing relatives of known diabetics and have produced evidence of the value of tolbutamide in some of them. In this country young, mild, sulphonylurea-sensitive diabetics are particularly common in the non-White races.

Old people may be especially sensitive to the hypoglycaemic effect of sulphonylureas, so that caution in initiating and in maintaining therapy must be used.

The longer the duration of known diabetes the less the likelihood of adequate response to oral therapy. Nevertheless I have seen satisfactory control achieved in diabetics of over 20 years standing.

Previous Insulin Therapy

There is no dose relation between insulin and sulphonylurea. Certainly the likelihood of good response diminishes with increasing prior insulin requirements,[3] so that subjects taking more than 60 units a day are unlikely to respond, but occasionally very large doses may be replaced satisfactorily by a sulphonylurea. This good result is more frequent when a combination of oral drugs is used.[2]

Other Considerations

The higher the previous blood sugar levels the less likely are we to obtain a good response to sulphonylureas. Usually the fasting level is not reduced by more than 150 mg/100 ml, so that patients with fasting levels over 250 mg may be expected not to respond satisfactorily.[4] Again this is not an invariable rule.

Sex, race and family history are unimportant in assess-

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†For further consideration of all aspects of oral drugs for diabetes see Campbell, G. D., ed. (1969): *Oral Hypoglycaemic Drugs.* London: Academic Press.

ing probable response. Concomitant disorders, even acute emergencies, do not contraindicate sulphonylureas provided control is maintained. The long-acting sulphonylureas (e.g. chlorpropamide) should not be given in the presence of hepatic or renal failure. Even the short-acting drugs must be used warily in these situations.

Obesity, Body-weight, and the Importance of Diet

The blood sugar level of overweight diabetics usually falls rapidly when sulphonylureas are administered but this is not the way to deal with the basic disorder. An obese diabetic is a problem of obesity, not of diabetes. Workers in different countries have emphasized the importance of dieting and weight loss in obese patients as the first line of treatment rather than running immediately to the much simpler oral therapy.

Nevertheless we must all admit that the results of dietary therapy in obese diabetics are appallingly poor, with at most a 5 - 10% satisfactory response. One may therefore feel reluctantly compelled to use oral therapy (or insulin) in subjects who are still overweight after months of unsuccessful cajolement, especially if they still have symptoms or if they develop vascular disease. A good argument can be made out for using a diguanide rather than a sulphonylurea as the initial oral drug, since the diguanides tend to cause loss of weight rather than gain.[5]

Even the diabetic who is within ±5% of his ideal weight should first of all be allowed a trial of dietary therapy alone unless he suffers moderately severe symptoms. It is remarkable how frequently the symptoms do improve and the blood sugar returns to normal or near-normal with a simple rearrangement of dietary regimen without change in total calorie intake and without loss of weight. Underweight adult-onset subjects tend to respond less well to sulphonylureas, but nevertheless often deserve a trial.

On the whole a gain in weight tends to occur during successful treatment with sulphonylureas even in subjects believed to have maintained their correct diet. The reason for this phenomenon is uncertain.

Continuing and Discontinuing

The 'excellent responder' is easy. The 'partial responder' is a problem. In some cases we must settle for partial success as being better than we could otherwise have achieved; in others we must not be deterred from seeking a further improvement. We must always be willing to try a change of sulphonylurea or to combine it with a diguanide or if necessary to revert to insulin. We must not be satisfied with initial control by urine sugar testing only, because of the possibility of a raised renal threshold. Nor should fasting blood sugar readings alone satisfy us completely, since these may be normal despite gross hyperglycaemia after meals.

Patients should feel well on their sulphonylureas. Frequently they do in fact appear to do so despite poor control having been achieved.

Subjects who fail to respond to sulphonylureas and to a combination with diguanide should be given insulin, and insulin must be substituted for tablets if the patient continues to have symptoms, or remains or becomes poorly controlled. We often find, after the initial antipathy to injections, a real pleasure in the physical improvement derived from insulin in previously incompletely controlled subjects.

Patients may respond initially to sulphonylureas and later become uncontrolled. Whether the drug failure is primary or secondary, it is bad practice to continue the drug—it is expensive, unfair and even dangerous to the patient. Periodic checks are therefore mandatory.

Not infrequently the opposite occurs. A patient who really needed oral therapy for control is found later to maintain normal blood sugar levels without the drug. Consequently periodic attempts to reduce or stop oral therapy should be made in well-controlled patients.

SOME GENERAL EFFECTS OF THE SULPHONYLUREAS

Effects on Glucose Tolerance and Glycosuria

It is usually stated that sulphonylureas do not alter the tolerance for glucose.[6,7] When effective in therapy, they reduce the fasting blood sugar level and bring down the whole tolerance curve in a more or less proportional manner. Thus a normal fasting level may be obtained but the one-hour and later levels may remain abnormally high and postprandial glycosuria is frequent. Clear early morning urine tests or normal fasting blood sugar levels are therefore not enough to establish that excellent control has been achieved.

Sulphonylureas have no effect on the renal handling of glucose and will not cause any change in renal threshold.

Relation to Vascular Disease

The effect of the sulphonylureas on vascular disease of diabetics has been a subject for speculation and difference of opinion. It would seem most probable that they have no specific effects on the development of ischaemic heart disease, peripheral vascular disease, retinopathy, neuropathy or nephropathy, apart from anything that might be achieved by improving the control of the diabetes. Their effect on plasma lipids has also been controversial, but is probably unimportant.

A recent report that patients on tolbutamide may be more liable to die from ischaemic heart disease has not been generally accepted, and should not deter one from using such drugs.[8]

Effect on Endocrine Glands

Long-term effects on the pancreatic islets appear to be beneficial rather than the reverse, and regeneration of beta-cells has occasionally been reported.

The sulphonylureas have been shown to be goitrogenic in animals and there have been reports suggesting an increase in the amount of hypothyroidism in treated patients,[9] but further confirmation is required—our impression is that this is not an important feature in our own clinics.

Toxicity

Mild side-effects. These include gastro-intestinal upsets. Most published series have contained up to 5% of symptoms including nausea, vomiting, diarrhoea, abdominal pain, weakness, anorexia, and general malaise. The frequency of such symptoms with moderate doses of sulphonylureas differs little from that in placebo-treated groups and can usually be overcome by perseverance, antacids and taking the tablets on a full stomach. Similar reactions are more frequent with the diguanides.

Skin allergy also occurs in some 1 - 5% in reported series and takes various forms, e.g. urticarial, maculopapular and morbilliform rashes. These usually respond readily to antihistaminics and do not necessarily require withdrawal of the drug. Tolbutamide causes fewer cutaneous reactions (0·4 - 0·8%) than other commonly used sulphonylureas.

On account of these various minor effects about 1 - 2% of patients demand discontinuation of the drug in most series.

More severe reactions. Photosensitivity, with a dermatitis of the exposed areas, can be induced by all sulphonylureas. The mucocutaneous syndrome (Stevens-Johnson) and exfoliative dermatitis can be produced (rarely with tolbutamide). These particular skin lesions may be the forerunners of jaundice or agranulocytosis and are an indication for stopping the drug. Acute attacks of porphyria are not induced.

Bone-marrow depression occurred with the early drug, carbutamide, but is rare or coincidental only with the more recent sulphonylureas. Mild, transient and unimportant thrombocytopenia, however, may be found after the inception of oral treatment.

Jaundice of cholestatic type with occasionally severe liver-cell damage, frequently preceded by a cutaneous hypersensitivity rash, can be produced by chlorpropamide,[10] but probably not by tolbutamide.

Patients taking chlorpropamide may become sensitive to alcohol and develop flushing, headache, nausea and vomiting and thoracic discomfort similar to that following disulphuram (Antabuse) within 5 - 10 minutes of drinking small quantities. As many as one-third of the patients may be affected to some extent.[11] Similar symptoms have been encountered by patients taking carbutamide and acetohexamide, and comparatively mild flushing with tolbutamide. Glibenclamide may be free from this side-effect. Patients taking sulphonylureas may also be more sensitive to the cerebral depressant effect of barbiturates and other sedatives.

Hypoglycaemia

Hypoglycaemia merits special consideration as a side-effect of the sulphonylureas; strictly speaking it is not so much a 'toxic' effect as an excessive amount of the therapeutic effect that we are aiming to obtain.

Bauer[12] observed several cases of 'severe hypoglycaemic shock' (including one with acetohexamide) particularly characterized by cerebral manifestations in older people. Such a patient might appear to have had a stroke. Bauer wondered whether permanent cerebral lesions may not be produced in such individuals without recognized hypoglycaemic episodes. It certainly behoves the physician to look out for minor attacks as well as major ones in his patients.

As might be expected, hypoglycaemia is a more serious hazard with the long-acting drugs that are cumulative, such as carbutamide and chlorpropamide. The drug has usually been in use for several weeks, allowing a build-up in the blood to occur before hypoglycaemia appears. Severe hypoglycaemia seems most likely to occur in old people, especially when the diabetes is very mild.

Certainly the larger the dose the greater the hazard, but even moderate doses can be dangerous. Because of the long-lasting effect of chlorpropamide, the hypoglycaemia that it causes may continue for 2 or 3 days even if the tablets are stopped. The doctor must therefore be prepared to give repeated doses of glucose as necessary.

Mild hypoglycaemic reactions are more frequent than generally realized. There is a particular risk of hypoglycaemia during the night, leading to early morning headaches. With long-acting sulphonylureas between-meal snacks may be necessary (as with insulin), and especially a 'buffer meal' before retiring to bed at night. Such snacks must, of course, not be allowed to add to the daily intake of calories, but adjustment is made by reducing the food taken at standard mealtimes.

Even the short-acting sulphonylureas are not entirely free from danger. Occasional mild reactions occur, often in the middle of the morning. One or two fatalities have been reported in old people, apparently from hypoglycaemia. Despite the short half-life of tolbutamide and other short-acting drugs, occasional cases of severe, protracted hypoglycaemia have occurred, even with ordinary doses, especially in non-diabetics and elderly people. Other factors that may potentiate the hypoglycaemic effect of sulphonylureas are hepatic and renal disease, malnutrition and certain drugs including the sulphonamides, monoamine-oxidase inhibitors, phenylbutazone, probenecid, the salicylates and propranolol.

THE SULPHONYLUREAS AVAILABLE IN SOUTH AFRICA

The sulphonylureas available in South Africa are set out in Table I.

TABLE I. SULPHONYLUREAS AVAILABLE IN SOUTH AFRICA

Approved names	*Trade names*	*Tablet sizes*
Tolbutamide	Rastinon (Hoechst) Artosin (Boehringer Mannheim)	500 mg
Chlorpropamide	Diabinese (Pfizer)	250 mg
Acetohexamide	Dimelor (Lilly)	500 mg
Tolazamide	Tolinase (Upjohn)	100 mg 250 mg
Glymidine (Glycodiazine)	Gondafon (Schering) Lycanol (Bayer)	500 mg
Glibenclamide	Daonil (Hoechst) Euglucon (Boehringer)	5 mg

Tolbutamide

Tolbutamide has become an enormously successful drug, not only as a safe oral agent for diabetes but for various clinical tests, in laboratory experimentation and even for use in non-diabetic disorders. Though it is somewhat less potent than carbutamide, chlorpropamide or tolazamide, it carries a very small risk of toxicity—it is a safer drug than aspirin.

Because of its short half-life, low fasting blood levels of tolbutamide are found during long-term therapy. Hence it was considered that 2 or 3 doses throughout the day should produce better control than a single large dose; this was believed confirmed by clinical investigation, and consequently a split-dose regimen was recommended. However, it has recently been shown that single daily doses usually, but not always, produce as good or better control than divided doses.[13] In any event there is seldom need for more than 2 g (4 tablets) daily; 3 g should be the absolute maximum.

Chlorpropamide

Chlorpropamide contains a chlorine atom attached to its benzene ring in place of the methyl group of tolbutamide. It is long-acting, cumulative and rather more powerful than tolbutamide in that some tolbutamide-failed patients can be controlled with chlorpropamide.

Secondary drug failure is probably less frequent with chlorpropamide than tolbutamide, while some patients with secondary tolbutamide failure can be well controlled by chlorpropamide.[14]

Minimum and maximum effective doses are 100 and 500 mg respectively. Higher doses than this are dangerous because of the cumulative effect. In fact the lower the dose the safer the drug, so that a start with 250 mg or less is recommended. The danger of severe hypoglycaemia from higher doses is greatest in elderly, mild diabetics. The full daily amount required should be taken in one dose.

Acetohexamide

Acetohexamide is another non-cumulative drug with very infrequent side-effects that has proved acceptable to diabetic patients. It is probably a little more potent than tolbutamide, but because it does not show any clear-cut advantage over the earlier drugs it has not achieved such popularity. In fact this statement applies to most of the sulphonylureas that have come onto the market after chlorpropamide.

The maximum maintenance dose is 1·5 g (3 tablets) a day; usually less is needed, and a single daily dose is usually satisfactory.

Tolazamide

This drug has been said to be as potent as chlorpropamide,[15] and to be without serious toxic consequences. However, the manufacturers admit that a fair number of patients complain of dizziness, weakness, nervousness and lethargy. The effective dose range appears to vary from 100 to 1 000 mg per day.

Glibenclamide

This is the most recent of the sulphonylureas and by far the most powerful, weight for weight, being some 200 times as potent as tolbutamide as a hypoglycaemic agent in man.[16-19] It is remarkably non-toxic in animal tests and probably its only side-effect in therapeutic use is an occasional mild allergic rash. The peak concentration in the blood after a single oral administration is reached in about 4 hours and its effect usually lasts up to 24 hours.

It is possible that its action is slightly different from some of the other sulphonylureas in that it produces a longer-lasting stimulation of insulin release from beta-cells, and this may partly account for reports of frequent hypoglycaemic episodes in its clinical use. Anyway, on account of its potency, it must be used cautiously, especially in mild and elderly diabetics, and with due attention to food coverage, as mentioned above.

Each tablet contains 5 mg of glibenclamide and the effective dose range is between 2·5 and 20 mg daily. In therapeutic effectiveness (as opposed to weight-for-weight potency) it seems to be roughly on a par with chlorpropamide.

Glymidine

This substance is a sulphapyrimidine and not a true sulphonylurea, although closely related. It has no antibacterial activity. Its mode of action is apparently the same as that of the sulphonylureas. It is well tolerated by patients and side-effects appear to be trivial. One gram (2 tablets) daily is generally a sufficient dose, and 2 g is the absolute maximum.

Occasionally a better response can be obtained with glymidine than with the sulphonylureas.[20]

General Note Regarding Sulphonylurea Therapy

Loading doses are *not* recommended at the commencement of therapy. The total required daily amount can always be given in a single dose in the case of chlorpropamide and usually with the other drugs.

Sulphonylureas should not be used in combination with each other, or with insulin except in very special circumstances under hospital supervision. The great value of the combination of sulhonylureas with diguanides (Insoral and Glucophage) has already been considered in this series of articles.[2]

RECOMMENDATIONS FOR USE OF SULPHONYLUREAS (RESUMÉ)

In the 'New' Patient

The newly diagnosed maturity-onset diabetic should normally be tried on diet alone at first, even if not overweight. After diet fails, the choice of which oral drug to use first is a personal matter. It should be remembered that the long-acting sulphonylureas such as chlorpropamide must be prescribed warily in an elderly, mild diabetic, who may readily become hypoglycaemic. Further, one might logically prefer a diguanide to a sulphonylurea for initial trial in an overweight subject.

The Patient on Insulin

Many maturity-onset diabetics who take insulin can be better controlled by sulphonylureas, but generally I would recommend that the change-over be made under hospital supervision. I believe the best method to be adopted in general practice involves the gradual reduction of insulin dosage until none is being given or until symptoms occur. A sulphonylurea can then be started if it is required, but insulin must always be recommenced if ketosis intervenes. Testing for ketonuria when heavy glycosuria is present is an important safeguard in the attempted change-over.

Importance of Diet

The successful reduction of the blood sugar by tablets does not permit laxity with the diet—rather should more stringency be striven for. Many patients who appear to fail to respond adequately to sulphonylureas, either initially or later, do so because of indiscretions in diet.

Primary Failure

Subjects who do not respond satisfactorily to the drug within a reasonable time—usually 2 weeks—constitute 'primary failures'. On no account should the drug be continued indefinitely in such instances; this elementary behest is remarkably frequently ignored, usually because trouble is not taken to check the effect of the therapy.

Remission

If oral therapy appears highly successful for several months, with virtually normal blood sugar levels and no glucosuria, it is possible that the drug is no longer needed and it should be stopped periodically for this to be checked. Bloom[21] in particular noted remission in 68% of 75 maturity-onset patients after 6 weeks of tolbutamide therapy. To continue a drug when no longer required is unfair to the patient with regard to expense, to inconvenience and even to the danger of toxic effects. Similarly, attempts should be made to reduce the dose periodically even if complete discontinuation is not possible. Conversely, better results may often be obtained by increasing the dose where control is less than maximal.

Late Failure

Patients who respond well initially to an oral drug but later become uncontrolled constitute 'secondary failures'. This may happen with an oral drug or a combination and illustrates the necessity for good follow-up for all patients. Thirst and polyuria during the night are frequently the first symptoms of deteriorating control.

Dealing with Drug Failures

First the diet should be checked and corrected if necessary. The dose of the drug used can be increased to the maximum recommended. If this fails, a switch can be made to a different sulphonylurea. As a final trial of oral therapy the combination of a sulphonylurea with a diguanide may be used. Insulin should be started if this fails, and at any stage if severe diabetic symptoms, significant ketosis or physical deterioration develops.

SULPHONYLUREAS IN SPECIAL CIRCUMSTANCES

Sulphonylureas during pregnancy do not appear to be harmful provided that control is maintained and that maximum doses of the more powerful drugs (e.g. chlorpropamide) are not used.

In acute emergencies, such as relate to infections, operations, trauma, etc., the only contraindications to sulphonylureas are inability to swallow and lack of control of the diabetes; and certainly the appearance of ketoacidosis. Temporary hyperglycaemia is without danger, and much safer than the risk of hypoglycaemia from insulin in a patient of unknown sensitivity undergoing anaesthesia. Even if insulin becomes necessary during an infection or other intercurrent 'stress', the sulphonylurea will almost always become as satisfactory after the complicating disorder is cured as it was before. Frequently the oral drug remains effective throughout and the management of the patient is much simpler than with insulin.

In patients with cerebral or peripheral arteriosclerosis the short-acting sulphonylureas are preferable to insulin because of the lesser likelihood of hypoglycaemic reactions.

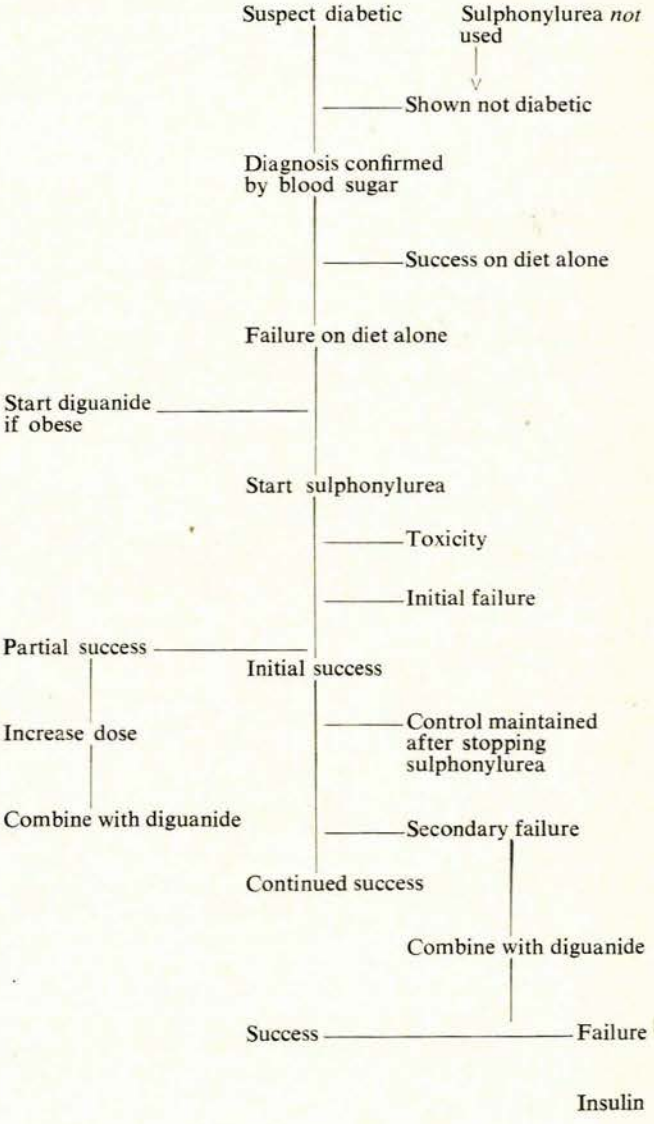
Secondary diabetes associated with acromegaly, Cushing's syndrome, corticosteroid therapy, thyrotoxicosis and certain drugs (e.g. INH, chlorothiazide and other diuretics, and oral contraceptives) can often be controlled by sulphonylureas—at least these can be tried.

Subclinical diabetes, with only an abnormal glucose-tolerance test, and suspected prediabetes constitute an unsolved problem. Small daily doses of a sulphonylurea (e.g. 500 mg of tolbutamide or 100 - 125 mg of chlorpropamide) are unlikely to be harmful, but whether they will protect against the development of clinical diabetes later is uncertain.[1,22]

CONCLUSION

The sulphonylureas are being used successfully in the management of enormous numbers of middle-aged and elderly diabetics, to whom they are an inestimable boon. In these people they have taken the place of insulin, but they are no substitute for insulin in the younger or ketosis-prone diabetics. Initial doubts that they might eventually exhaust or otherwise further damage the pancreatic islets have proved unfounded, although their effectiveness frequently diminishes with time ('secondary failure'). Even the safest among them is not entirely free from danger and the doctor who prescribes them must be aware of their limitations and of their toxic effects. No patient should be allowed automatic and indefinite repeats of his

APPENDIX. FLOW SHEET FOR USE OF SULPHONYLUREA



prescription without careful supervision, nor should his dietary regimen be allowed to slacken.

The value of the sulphonylureas has been further extended by combination with the diguanides where indicated, but most authorities find no value in their combination with insulin. They have not been found to prevent, delay or benefit vascular disease, so that they are no panacea for the whole diabetic abnormality, any more than is insulin. In view of their relatively physiological mode of action in stimulating the patient's pancreas to discharge its own insulin it is just conceivable that they may have a place in the prevention of diabetes, but this is quite unproven.

An abridged version of much of the contents of this article is contained in the 'flow sheet' in the appendix.

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