A PRIMER ON ORAL THERAPY IN DIABETES TODAY

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In view of the extensive use and rapidly increasing experience of oral antidiabetic agents a few practical notes may not be out of place at this time. The suggestions that follow are designed for practice outside large hospitals. In the large hospitals it may well be justifiable to try such drugs in rather different or special circumstances.

A. PATIENTS UNSUITABLE FOR TRIAL OF ORAL THERAPY

1. Patients who are in diabetic ketosis or who have ever been in ketosis, unless this was precipitated by severe infection or other severe 'stress'.
2. Anyone under 30 years of age (except as under section B 3, below).
3. Anyone with severe symptoms (e.g. rapid weight loss, gross polyuria, weakness, etc.).
4. Patients more than 15% over their ideal weight. These patients should be treated by dietary measures first and oral therapy only later, if necessary, after they have lost weight, or as a last resort after their doctor has given up trying to make them reduce!
5. Patients with 'secondary diabetes', e.g. 'steroid diabetes', and chronic pancreatitis.
6. Usually, patients taking insulin (see under section B 2, below).
7. Patients with diabetes of over 15 years' duration may be less likely to respond to oral drugs, but this factor alone does *not* preclude a trial.

B. PATIENTS SUITABLE FOR ORAL THERAPY

1. Those over 30 years of age, without severe symptoms, who are not prone to ketosis and not using insulin, provided that dietary measures have failed to produce proper reduction of blood sugar and urine sugar. Even in people of correct weight a rearrangement of diet may often be sufficient to control both symptoms and sugar within 2 or 3 weeks. Another proviso is that patients who are to be started on oral therapy should be accessible to proper supervision and follow-up (see section E).
2. Patients taking not more than 40 units of insulin, who would otherwise qualify for a trial, provided that they are of reasonable intelligence and can be seen frequently during the period of change-over (see under section D 2, below). Patients taking higher doses of insulin may be suitable for trial of oral drugs, if admitted to hospital.
3. Younger subjects are occasionally found to have asymptomatic diabetes, discovered either accidentally, or, with increasing frequency nowadays, from routine testing because of diabetes in a close relative. In such people it is reasonable to try oral drugs initially, and sometimes these will correct the hyperglycaemia for months or even years. Such patients should be closely watched, and insulin should be initiated when control deteriorates.

C. ORAL DRUGS AVAILABLE, THEIR ADVANTAGES AND DISADVANTAGES

1. Sulphonylureas

These drugs act by releasing endogenous insulin from the beta cells of the pancreas. It follows therefore that they can act only when the pancreas is not severely damaged. Hence they are without effect in severe ketosis-prone diabetics.

Any good effect from sulphonylureas usually shows itself within 4 days, but it is reasonable to continue a trial for a fortnight unless the patient has severe symptoms, or is deteriorating, or if the time cannot be spared.

(*a*) *Tolbutamide ('rastinon', 'artosin').* This drug can be considered completely safe. Its only toxic effect seems to be the occasional production of mild erythematous rashes. Other apparent side-effects are probably no more than would occur from a placebo. Severe hypoglycaemia is not a danger and even mild symptoms are rare. Each tablet contains 500 mg. of tolbutamide, and the dose ranges from 1 to 4 tablets divided throughout the day. The very mild diabetic with normal or near-normal fasting blood-sugar levels may need only one tablet each morning. I do not believe there is any value in taking more than 4 tablets daily.

(*b*) *Chlorpropamide ('diabinese').* This drug is distinctly more powerful than tolbutamide, but it does have occasional important toxic effects. In sensitive patients a severe dermatitis may be produced within a few weeks of the start of treatment and also an intrahepatic obstructive jaundice with liver-cell damage. Further, because this drug is not detoxicated in the body and is more slowly excreted, the occasional patient may develop a profound hypoglycaemia quite unexpectedly after some days or weeks of treatment. Uncommon though this is, our awareness of its possibility reduces its danger. The tablets in use at

present contain 250 mg. of chlorpropamide, but 100 mg. tablets should be available soon. The dosage should *never* exceed 500 mg. daily and should be reduced to 375 or 250 mg. whenever possible. There is no need for doses to be divided throughout the day.

2. Diguanides (= Biguanides)

These substances, in some incompletely understood manner, render the peripheral action of circulating insulin more efficient and also to some extent may act independently of insulin. Thus they may have some effect in the juvenile type of insulin-requiring diabetic as well as in the maturity-onset group.

The diguanides in tablet form very frequently produce severe gastro-intestinal side-effects, with anorexia, nausea, vomiting, diarrhoea and general malaise and dizziness. For this reason they should be started in small doses (preferably a single tablet daily) and taken with or directly after meals. Aluminium hydroxide or magnesium trisilicate taken at the same time may alleviate symptoms until the patient develops tolerance to these side-effects.

There appears to be little danger in using the diguanides, except that a thin patient or one whose carbohydrate intake is grossly restricted may develop ketosis with relatively low blood sugar. This complication is not likely to occur in the maturity-onset diabetic.

(*a*) *Metformin (glucophage).* This substance produces less side-effects than phenformin, but is distinctly weaker, and it is doubtful whether it will survive in diabetic therapy in view of the newer developments. Tablets contain 500 mg. of metformin and the maximum dose worth taking is probably 2 tablets t.d.s.

(*b*) *Phenformin (insoral, DBI).* At present available in this country are tablets containing 25 mg. of phenformin. In some cases this drug may produce better control of diabetes than the sulphonylureas, but its unpleasant side-effects will surely make it unpopular when used alone. Its main use at present seems to be in combination with a sulphonylurea (see below, D 1 *c*), or in combination with insulin in special cases under hospital supervision.

The 'timed-disintegration' (T.D.) capsules, containing 50 mg. of phenformin in varying granule sizes, seem to allow a considerable increase in therapeutic usefulness of the drug. These capsules, not yet generally released in this country, cause fewer side-effects and also produce a smoother hypoglycaemic action throughout the whole 24 hours. The maximum dose worth using is probably 2 capsules daily, which can be taken at breakfast, or separately with different meals if the two together cause any nausea.

D. PLAN OF ACTION IN PATIENTS FOR TRIAL OF ORAL THERAPY

1. Patients not under Previous Treatment for Diabetes

(*a*) Diet. If a patient is distinctly overweight, a reducing diabetic-type of diet is first ordered. An 800-calorie diet should include in the daily ration $\frac{1}{4}$ - $\frac{1}{2}$ pint of skimmed milk, one article of fruit, at least one helping of lean meat, poultry, fish or skimmed-milk cheese, 2 slices of whole-wheat bread, unlimited green vegetables, and salads. Additional vitamins or minerals are not required. A conscientiously followed dietary regimen will usually alleviate the whole diabetic state. An appetite-suppressing drug (such as 'tenuate-dospan') can be used to help the patient who admits to having appetite difficulties.

Even if the patient is *not* overweight, a reconstruction of his dietary habits, with avoidance of between-meal nibbling, of readily soluble carbohydrates, of stodgy puddings, of irregular meal hours and of banquets, will frequently suffice to reduce hyperglycaemia and even alleviate minor symptoms.

(*b*) *Sulphonylureas.* When dietary measures fail, or in a not-overweight subject with moderately severe symptoms (always excluding ketosis, of course), a sulphonylurea may be started. It is a matter of choice whether one starts with tolbutamide, 1 tablet t.d.s., or with the rather more powerful chlorpropamide, 2 tablets daily. In either case the patient should be seen at weekly intervals until stabilization is satisfactory. Response to the drug should be judged by control of symptoms, maintenance of weight, absence or near-absence of glycosuria, and reduction in fasting blood-sugar level. It is reasonable to allow the trial to continue for at least 2 weeks before it is considered a failure; longer continuation of the drug if the diabetes is not reasonably controlled is a waste of money and highly unfair to the patient. If, however, tolbutamide fails, chlorpropamide may be tried.

Fasting blood-sugar levels that can be considered satisfactory depend to some extent on the individual patient. Initially we must try to reduce these to within the normal range, if necessary resorting to a combination of drugs (see below, D 1 *c*). It must be remembered that, even if the fasting blood-sugar level becomes normal on therapy, the post-prandial level may be up at 250 mg. per 100 ml. For this reason it is advisable to have knowledge of mid-evening or mid-afternoon levels also. In the very mild case, with normal fasting levels, 'control' will be judged entirely on post-prandial levels.

Having controlled the patient satisfactorily, one should gradually reduce the dose of sulphonylurea until the minimum requirement is found. Some patients do well on only one tablet of tolbutamide or one half tablet of chlorpropamide daily.

(*c*) *Combination of sulphonylurea and diguanide.* If incomplete control is obtained after a 2 - 3 week trial of chlorpropamide, our present procedure is to continue this with the addition of a diguanide, starting with half a tablet of the latter once or twice daily. The dose may be increased as necessary every 4 days until satisfactory control is reached or failure is evident. If control is satisfactory, the dose of chlorpropamide should be reduced, and in some instances it will be found that it can be completely omitted. In others it will be necessary to continue with 250 - 500 mg. of chlorpropamide daily plus 1 tablet of phenformin t.d.s.

Tolbutamide can be used in the combination in place of chlorpropamide if preferred.

When T.D. capsules of phenformin become generally available they will probably replace other forms of diguanide, either in combination or used alone.

2. Patients Already Taking Insulin

If the patient is content and well-controlled on insulin, a change is not recommended. Some maturity-onset subjects, however, are poorly controlled or may beg for a respite from injections.

(*a*) *Replacement with an oral drug.* Provided one maintains good contact with the patient, it is safe to halve the insulin dosage and add a sulphonylurea at the above-mentioned dose (section D 1 *b*). (A rare danger is that of hypoglycaemia from the insulin plus chlorpropamide.) If control becomes satisfactory, the insulin is then completely omitted, next the sulphonylurea is reduced, and finally it may be possible to omit this also. Diguanides can be tried in the same way.

(*b*) *Combination of insulin with oral drug.* I believe there is no place whatever for the combination of insulin with a sulphonylurea, except solely during the brief replacement trial period as described above.

Diguanides given with insulin can certainly reduce the requirement of insulin in some instances, but this would appear to be no advantage in the type of diabetic which we are discussing. (It may rarely be of advantage in the brittle, young, ketosis-prone case, but this is something for hospital practice only, and even here it has proved disappointing in our hands.)

Combinations with insulin, therefore, are not recommended.

(*c*) *Insulin-taking patients in hospital.* A safe and rapid method of trial of an oral drug is as follows: The patient is placed on soluble insulin 3 times daily before the main meals, the dosage being given according to the preprandial Benedict urine test, none being given if no sugar is present. A suitable dosage schedule might be: 30 units if urine gives an orange or brick reaction, 20 for yellow, 10 for green-with-deposit, and nil for blue or clear green; but the dose-range will vary according to the total daily dose of insulin which the patient took previously. An oral drug is added to this regimen and it is plain that if this is effective the amount of insulin given automatically drops to nil, and its prescription can be discontinued.

E. FOLLOW-UP

By careful observation initially it may be discovered that a patient needs no treatment other than diet. Similar careful observation during the use of oral therapy may reveal either that the patient no longer needs it, or is no longer properly controlled by it. Whatever the cause of so-called 'secondary failure' it is certainly not infrequent, and must be borne in mind constantly. After months or years of satisfactory control by a sulphonylurea, glycosuria returns and the blood-sugar level rises. When this occurs a change must be made. The dose may need to be raised, or, if this is already at the maximum level, a change made to a different drug or combination of drugs, or insulin may have become necessary. *It is a waste of money and a grave disservice to the patient to continue an oral drug when it is no longer acting satisfactorily.*

On the other hand, if control remains completely satisfactory on oral therapy, after several months it is again worth trying to reduce the dose and possibly stop the drug completely. In some cases by this time dietary measures alone will have become sufficient, even though they were unsatisfactory in the beginning.

F. EMERGENCIES IN PATIENTS ON ORAL THERAPY

Generally speaking there is no necessity to change from oral therapy as long as the blood sugar remains reasonably controlled.

1. *Anaesthetics and operations.* There is no need to resort to insulin if the diabetic subject is reasonably controlled before the operation. Brief hyperglycaemia and heavy glycosuria during the operative and immediate postoperative period are of no importance — they can even be considered a safeguard against hypoglycaemia, provided that no significant degree of ketosis develops. If the 'Acetest' becomes positive, or nitroprusside *and* ferric chloride tests are both positive, then soluble insulin is indicated. Certainly, after the immediate postanaesthetic period and during convalescence and wound healing, good control of the diabetic state should be obtained.

2. *Infection, gangrene, etc.* The healing process in a diabetic is certainly facilitated by good metabolic control. Consequently, if the control is upset by an infection, insulin should be given, though it may well be needed only temporarily.

3. *Pregnancy.* At present there appears to be no evidence against the use of tolbutamide during pregnancy, though chlorpropamide may be best avoided. (We have reason to believe that this substance may contribute to perinatal death of the foetus.) We do not know enough about diguanides during pregnancy to comment on these.

Observation of the patient must be particularly careful during pregnancy, owing to the frequent worsening of the metabolic state. On the other hand, continued glycosuria is not in itself an indication for change of therapy unless symptoms occur or the blood sugar is found to be elevated.

4. *Toxic reactions.* These have been commented upon above. In general, gastro-intestinal side-effects may be counteracted by spacing the drug or giving non-absorbable alkalis. A skin rash developing in a patient on chlorpropamide, however, is a danger signal, and the drug must be stopped at once.

The occasional severe hypoglycaemic reaction caused by chlorpropamide may need repeated injections of glucose to produce and maintain euglycaemia.

G. SUMMARY OF COMMON ERRORS

1. *Starting wrong patient on oral therapy* (see under section A above). This may be dangerous in a young, or ketosis-prone patient, or wasteful in a mild, obese diabetic. In the latter it may be the 'easy way out', since glycosuria may be reduced without weight loss, but this is bad medicine, and unfair to the patient. The obese subject needs weight reduction rather than pills.

2. *Starting oral drugs too soon.* We sometimes see patients taking oral drugs who are not even diabetic! The diagnosis must, of course, be confirmed first. Furthermore, diet must be tried before pills, wherever possible, even when the patient is not overweight.

3. *Continuing oral therapy when not effective.* Tablets should not be continued longer than 2 - 3 weeks if they do not bring about control. Further, they may become ineffective later and should then be stopped or changed.

4. *Continuing oral therapy when not necessary.* Periodic attempts to stop oral therapy in well-controlled diabetics should be made.

5. *Using doses which are too high* (see section C above). This is not only expensive but may also be dangerous. The converse error, that of too low a dosage, seems to be rare.

6. *Using unsatisfactory mixtures.* Diguanides with insulin may occasionally bring doubtful benefit (probably best avoided in general practice), but sulphonylureas with insulin, never. Likewise, 2 sulphonylureas or 2 diguanides together simply indicate lack of understanding on the part of the doctor.

7. *Improper follow-up.* We sometimes see patients who have been started on tablets and left for months or years unsupervised, getting 'repeats' from pharmacists. This obviously may produce errors 2, 3 and 4.

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The views expressed in this paper do not necessarily represent those held by other members of the Diabetes Clinic.