Today's Treatment

Modern approach to diabetes mellitus—I

J M STOWERS

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Diabetes may be functionally defined as a relative or absolute deficiency of insulin which may or may not be associated with symptoms. There are several different reasons for insulin insufficiency but the net result is the syndrome of diabetes. It is important to recognise the many years that usually elapse between the appearance of the first stigmata or chemical abnormality of diabetes and the presentation of the patient because of the primary symptoms, for the chronic mild hyperglycaemia and hyperlipidaemia are significantly correlated with ischaemic heart disease, atheroma more generally, and with retinopathy and precocious development of cataracts. About 20% of new diabetics presenting to clinics already have recognisable diabetic complications. If diabetes is diagnosed early, perhaps as a result of investigating symptomless glycosuria or because of recognising a characteristic known to correlate with diabetes it is certain that simple treatment can delay the onset of such degenerative complications, which are likely to disable a patient far more than the mere presence of mild diabetes itself. Diabetes is the commonest endocrine disease in Britain, affecting overtly at least 2% of the population, and thus the epidemiological approach assumes major importance, since it should facilitate early recognition, explanation to the patient, and his co-operation in effective treatment.

The general practitioner is best placed to find the people at risk and arrange for them to be screened for diabetes. The criteria for screening are: strong family history of diabetes in first-degree relatives; symptomless glycosuria; chronic obesity; precocious onset of occlusive arterial disease, especially in women before the menopause. The obstetric data are: multiparity (more than four pregnancies lasting for at least 28 weeks); heavy-for-dates baby, remembering maternal height and gestational age, for example over 4.5 kg for a woman of average height after 40 weeks gestation; glycosuria to Clinistix in a second fasting urine specimen; one or more stillbirths or neonatal deaths; islet hyperplasia in pancreas of stillborn baby in absence of Rh isoimmunisation; congenital anomaly in baby; hydramnios; and history of two or more abortions.

If chemical diabetes—that is, abnormal glucose tolerance but a normal fasting blood sugar level—is confirmed by oral or intravenous glucose tolerance tests, dietary treatment is usually sufficient to restore glucose tolerance to normal. Such treatment includes reduction of excess weight in the obese and restriction of refined carbohydrate in those of normal weight. If these measures prove inadequate small doses of sulphonylureas can apparently often reverse chemical diabetes in patients aged 35 or under. By the time overt diabetes has developed in a patient with a normal weight and without intercurrent illness the possibility of reversing diabetes is extremely remote.

Overt diabetes

Patients with mild overt diabetes with fasting capillary blood sugar levels from 6.7 mmol/l (120 mg/100 ml) to 11.1 mmol/l (200 mg/100 ml) may usually be treated by diet alone if there is associated obesity, but not so predictably if the patient is of normal weight or thin. While the energy content of the diet has to be tailored to the degree the patient is overweight, other features are more consistent. Thus refined carbohydrate, which would call forth a greater insulin response than the patient can achieve, must be avoided and food taken in several smallish meals. In this way hyperglycaemic peaks may be avoided, for the blood sugar level is still the best measure of the degree of control. Generally this means taking food in as natural a state as possible—that is, when it is more bulky to satisfy the appetite of the naturally hungry yet only slowly converted into its constituent sugars, amino-acids, and fatty acids.

Other qualitative aspects of food selection are more controversial, but as, for ethical reasons, hard biological facts are difficult to obtain in man, it seems rational to rely on more definite animal studies and on the weight of circumstantial human evidence. Thus epidemiologists have shown clearly a close association between a plasma cholesterol level above about 5.2 mmol/l (210 mg/100 ml) plasma and a rise in the mortality from ischaemic heart disease. Diabetes is associated with a tendency to hypercholesterolaemia because of relative insufficiency of insulin and to some extent because of the relatively high proportion of fat to carbohydrate in most diabetic diets not designed for weight reduction. About two-thirds of the body cholesterol pool is synthesised and the remaining one-third is derived from saturated animal fat in the diet, largely egg yolk and dairy products. Unsaturated fats, mainly vegetable fats, can actually lower the plasma cholesterol level more than a fat-free diet. These considerations suggest that replacing as much saturated fat by unsaturated fat as possible by suitable selection of commonly available foods would tend to reduce atherosclerosis in diabetics in parallel with the long-term fall in the serum cholesterol level. This is not a fact but circumstantial evidence makes it highly probable, and where the stakes are high such leads are worth following.

Tablets

The advent of treating diabetics with tablets on a large scale opened a new era, the full implications of which are now becoming apparent. The sulphonylureas enabled many patients with maturity onset diabetes without ketonuria to control their blood sugar when diet alone was insufficient and when insulin was the only alternative. The bright prospects of tablet treatment have recently been marred by reports of increased cardiovascular mortality in patients taking the sulphonylurea, tolbutamide, to be followed a little later by even worse results with the biguanide, phenformin, compared with patients treated by diet alone or diet and insulin.

Evidence is by no means one-sided but there seems to be little doubt that sulphonylurea drugs are associated with an

Aberdeen Royal Infirmary, Aberdeen AB9 1GS

J M STOWERS, MD, FRCP, consultant physician

increased mortality rate after myocardial infarction. Such considerations must temper our approach to the treatment of long-term diabetes and more and better trials are needed to compare the cardiovascular risks of treatment with insulin and with sulphonylureas.

SULPHONYLUREAS

The number of commercially available sulphonylureas continues to proliferate, more for commercial than medical reasons for there is little to choose between the properties of the last three additions to the list—glibenclamide, glipizide, and glibornuride. They are suitable when diet alone has proved inadequate and in diabetics without ketonuria, but they are not the best treatment for the maturity onset diabetic who is still notably obese. Nevertheless, sulphonylureas may sometimes usefully supplement the hypoglycaemic action of biguanides which have been used initially in treating obese maturity-onset diabetics.

All the sulphonylureas may produce rashes in about 3% of patients and there is some cross-reactivity between the different drugs. When this occurs it is worth trying glymidine (Gondafon) as it is chemically most distinct being actually a sulphapyrimidine, rather than a sulphonylurea. Flushing after alcohol occurs with several of these drugs but most consistently with chlorpropamide, which also has a definite but rare association with cholestatic jaundice. Dyspeptic side effects, however, are more likely to occur with the shorter acting compounds which are usually given more than once a day before meals.

Hypoglycaemia is an overdose effect rather than a side effect but has been troublesome, mainly when there has been a failure to recognise the great potency of small doses of compounds such as glibenclamide or glipizide: as little as 2.5 mg may cause hypoglycaemic coma. It is important to remember the long biological half life (about 40 hours) of chlorpropamide, for in the presence of renal failure even a small daily dose may lead to an excess accumulating in the plasma, so that long-lasting hypoglycaemia may occur, particularly in elderly diabetics living alone. This type of hypoglycaemia is harder to treat than the more transient type due to insulin overdose, not only because of the long persistence of the chlorpropamide in the blood but because it inhibits the glucose-6-phosphatase in the liver required

for the release of glucose from glycogen. Injected glucagon may then prove effective and glucose needs to be given by continuous infusion over many hours and not just as a single intravenous dose as is the case after an overdose of short-acting insulins. Table I gives comparative features of the sulphonylurea drugs now available in Britain.

BIGUANIDES

The biguanides have done much to improve the oral treatment of diabetic patients who have the dual problem of continuing obesity and hyperglycaemia without ketonuria, for in carefully adjusted doses they may favour loss of weight without risk of hypoglycaemia. Patients may continue to have high blood sugar levels in spite of calorie restriction or may simply have failed to restrict their diet properly after adequate instruction. Left with the choice of letting them suffer the inevitable consequences of precocious cataract, neuropathy, and atheroma that follow chronic hyperglycaemia it is rational to build up the dose of the biguanide slowly to a point where the appetite and the weight begin to fall. Metabolic studies have shown that the weight so lost is due not only to eating less but also to actual malabsorption, which may occur for essential elements such as folic acid and vitamin B₁₂ as well as for the diet more generally. Patients on more than about 2 g metformin a day should be screened about once a year for low levels of plasma folate and B₁₂. These will rise on withdrawing Metformin or alternatively folic acid and B₁₂ may be used as supplements to the diet.

Phenformin in large doses has purposely been left out from this account, for there is a definite if small risk of lactic acidosis developing in a few diabetics taking over about 100 mg/day—even if they have no evidence of renal or hepatic failure or known ischaemic disease, which are positive contraindications to its use. The fact that, unlike metformin, phenformin is concentrated in the liver may help to explain its greater association with clinical lactic acidosis, for the liver is normally a main site of lactate uptake. The biguanides are often used to control the blood sugar level after a secondary failure of a sulphonylurea, the two types of drug having quite different mechanisms. The biguanides increase the permeability of cells in general to glucose but do not increase endogenous insulin production

TABLE I—Sulphonylureas—comparative features

Official name	Proprietary name	Tablet Size (mg)	Range of dose (mg)	Potency	Approximate Biological half life (h)	Particular aspects
Acetohexamide	Dimelor	500	500-1500	Medium	5	Flushing after alcohol, occasional cholestatic jaundice
Chlorpropamide	Diabinese	100	100-500	Strong	40	
	Melitase	250				
Glibenclamide	Daonil	5	2.5-25	Strong and quick	12	
Glibornuride	Euglucon	25	12.5-75	Strong	8	
Glipizide	Glutril	5	2.5-30	Strong	3.5	
Glymidine	Glibenese					A sulphapyrimidine with virtually no cross-reaction with sulphonylureas in regard to skin rashes
	Minidiab					
	Gondafon	500	500-2000	Medium	4	
Tolazamide	Tolanase	100	100-750	Strong	7	Metabolite gives flakey precipitate with sulphosalicylic acid or picric acid (Esbach's reagent) or when acidified and boiled; hence false positive tests for proteinuria (not with Albustix)
		250				
Tolbutamide	Promidex	500	500-3000	Relatively weak	4	
	Rastinon					

TABLE II—Biguanides—comparative features

Official name	Proprietary name	Tablet size (mg)	Range of dose (mg)	Particular aspects
Metformin	Glucophage	500, 850	500-3000	Occasional severe lactic acidosis, especially with renal or hepatic failure, ischaemia, or after alcohol
	Metiguanide			
Phenformin	Dibotin	25	25-300	
	Dibotin SA	50		
	Dipar SR	50		
	Meltrol SR	50		

Occasionally it is worth introducing a biguanide in modest doses to insulin-dependent diabetics to reduce their tendency to unpredictable hypoglycaemic attacks. The biguanide may partly replace insulin by a drug which in itself causes no risk of hypoglycaemia. This is seldom necessary if insulin is used intelligently by the patient and his adviser.

The therapeutic dose of biguanides is often near to the dose which will start to produce side effects, which occur in the following order: anorexia, nausea, and then vomiting or diarrhoea, or both, with associated malaise. Susceptibility to such side effects varies greatly between individuals and they occur more often if the dosage of the drug is increased too quickly. With-

drawal of the biguanide produces an improvement within eight hours. Rashes are less often associated with the biguanides than with the sulphonylureas.

The biguanides are no better than sulphonylureas in relation to long-term vascular effects. In the University Group Diabetes Programme study, in which phenformin was used in a dose of 100 mg/day, the cardiovascular mortality was over two and a half times that in the diet-treated group, despite the fact that phenformin's potential to lower cholesterol and triglyceride levels in the plasma and produce fibrinolysis might have been expected to exert a favourable effect. The comparative features of the two biguanides are given in table II.

Hospital Topics

Pseudomonas aeruginosa in hospital pharmacies

ROSAMUND M BAIRD, W R L BROWN, R A SHOOTER

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Summary

The environments of hospital pharmacies and the preparations made in these pharmacies were examined for *Pseudomonas aeruginosa*. This organism was widely distributed in the pharmacies and was isolated from 9% of preparations. In 11 instances strains of *Ps aeruginosa* from the preparations bore a close resemblance to strains previously found in the pharmacy environments.

Reports of the microbial contamination of pharmaceutical products date from the beginning of the century. A wide range of products may be contaminated, including intravenous fluids, injections, vaccines, antibiotics, creams, hand creams, powders, tablets, mixtures, ophthalmic preparations, and disinfectants. In 1971 the Public Health Laboratory Service reported on the examination of 1220 samples of hospital medicaments intended for oral or topical application.¹ Of these 32% were contaminated and 2.7% contained *Pseudomonas aeruginosa*. We present the results of a search for *Ps aeruginosa* in eight hospital pharmacies and in the preparations made in five of these hospitals.

Examinations

The investigation was carried out in this hospital and seven others (pharmacies A-G), four of which were teaching hospitals.

The environment in the pharmacies was examined using moistened serum-coated swabs. These were incubated overnight at 37° in nutrient broth and then subcultured on to 0.03% cetrimide agar.

Departments of Medical Microbiology and Pharmacy, St Bartholomew's Hospital, London EC1A 7BE

ROSAMUND M BAIRD, PHD, principal pharmacist
W R L BROWN, PHD, pharmacist; present address: G Horton Ltd
R A SHOOTER, FRCP, FRCPATH, professor of medical microbiology

Liquids and non-oily medicaments were examined by adding 1 ml or 1 g to 20 ml of nutrient broth. We added 1 g or 1 ml of oily medicaments to 20 ml of 4% Lubrol W in nutrient broth and this was homogenised in a Stomacher 80 blender (Seward). All broths were incubated overnight and subcultured on to cetrimide agar. Antibacterial agents were neutralised as follows: phenols and alcohols by dilution (1 g or 1 ml in 100 ml of nutrient broth); hexachlorophane or quaternary ammonium compounds by 3% Tween 80 in nutrient broth; formaldehyde and other aldehydes by 2% sodium sulphite broth; halogen compounds by 1% sodium thiosulphate broth.

Gram-negative oxidase-positive bacilli were identified as *Ps aeruginosa* by pyocyanin production or methods previously described.² Typing of strains of *Ps aeruginosa* was by both serological and phage typing methods. *Pseudomonas* spp were identified as Gram-negative oxidase-positive bacilli which grew on 0.03% cetrimide agar and gave an oxidative reaction in Hugh and Leifson's medium.

Results

The pharmacy in this hospital and that of hospital D were examined at intervals over two and a half years (November 1971 to May 1974). Pharmacies in the other hospitals were examined once only. Table I shows the isolation of *Ps aeruginosa* from these departments. The distribution of the organism appeared fairly predictable, as, in addition to being present in moist sites such as sinks, drains, draining boards and taps, it was invariably isolated from cleaning equipment which had been stored wet. It was rarely found where attention was paid to the correct storage and use of the equipment.

TABLE I—Isolation of *Ps aeruginosa* and *Pseudomonas* spp from all hospital pharmacies (1971-4)

Hospital	No of sites examined	No with <i>Pseudomonas</i> spp	No (%) with <i>Ps aeruginosa</i>	No of different types <i>Ps aeruginosa</i> *
Barts	332	84	60 (18)	10
A	61	7	11 (18)	5
B	50	8	21 (42)	7
C	77	18	16 (21)	5
D	249	64	52 (21)	5
E	46	2	3 (6)	NT
F	49	12	8 (16)	NT
G	39	2	1 (3)	NT

*Excluding non-typable strains.
NT = Not typed.