CURRENT SURVEYS

The uses of biguanides in diabetes mellitus

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IN 1918, Watanabe first demonstrated the hypoglycaemic properties of guanidine. After nearly 40 years of sporadic investigation of its derivatives, including the misadventures with synthalin (Frank, Nothmann & Wagner, 1926), this observation bore clinical fruit in the first of the biguanides, phenylethylbiguanide (phenformin) see Fig. 1). Other biguanides have since appeared including dimethylbiguanide (metformin, 'Glucophage') and butylbiguanide. In the 10 years since their introduction into therapeutics the precise mode of action of these compounds has not been elucidated nor is there complete agreement on the indications for their use. Research and clinical experience have, however, provided both

theoretical and practical bases for their use in treatment.

Mode of action

The anti-diabetic effect of the biguanides appears to be distinct from their hypoglycaemic effect. In non-diabetic animals, the blood-sugar lowering dose of the biguanides is close to the lethal dose (Sterne, 1964); at clinically appropriate dose levels in man, blood sugar lowering is seen only in diabetic subjects. The anti-diabetic effect is unlikely to be due to increased insulin secretion for in obese and diabetic subjects, the administration of phenformin *reduced* the circulating insulin response to a glucose load (Grodsky *et al.*, 1963; Abramson & Arky, 1967). Furthermore, in human diabetics and in experimental animals, the administration of a biguanide reduces the quantity of insulin required to control hyperglycaemia (Sterne, 1964). In some way, therefore, the biguanides appear to augment the hypoglycaemic effectiveness of circulating insulin, possibly by enhancing its stimulation of glucose utilization in muscle (Butterfield & Whichelow, 1962). While this effect is most clearly apparent when the glucose/insulin interrelation is disturbed as in diabetes, it may, under special conditions, also be demonstrated in normals (Pereira, Wajchenberg & Schnaider, 1967).

In adult diabetics, the biguanides may also effect a reduction in body weight, in serum triglycerides and in serum cholesterol (Schwartz, Mirsky & Schaefer, 1966). Phenformin may owe these effects partly to its anorexigenic properties (Patel & Stowers, 1964) and partly to reduced circulating insulin in response to the lowered blood sugar, thus diminishing lipogenic and antilipolytic activity. Metformin has also been shown to have an antidiuretic effect in idiopathic diabetes insipidus (Katsuki & Ito, 1966).

FIG. 1. Structure of guanidine derivatives.

Side-effects

The commonest side-effects of the biguanides are upon the gastro-intestinal tract, causing a metallic taste in the mouth, loss of appetite, nausea, diarrhoea and abdominal cramps. By starting with small doses and increasing the dose level slowly, the incidence of these side effects can be reduced (Pomeranze *et al.*, 1959); in obese patients, particularly, a degree of anorexia may be a useful side-effect. Phenformin is available in timed-disintegration capsules, with which the incidence of gastro-intestinal side effects is said to be lower (Breidahl, 1961) or which permit higher doses before side-effects occur (Jakobson, Kahampaa & Berglund, 1965).

There is controversy about the possible metabolic side-effects of the biguanides. Earlier reports that phenformin therapy was associated with dangerous episodes of lactic acidosis (see Davidson *et al.*, 1966 for references) cannot be accepted unreservedly, for in the majority of cases hypoxaemia or circulatory collapse, both potent causes of lactic acidosis, were also present. Nevertheless, a recent case report (Proctor & Stowers, 1967) suggests that, in rare cases, lactic acidosis may be provoked by phenformin. Suspicion is based largely on *in vitro* tissue experiments where high concentrations of phenformin stimulate anaerobic glycolysis and hence increased lactate production (Sterne, 1964). Güttler, Petersen & Kjeldsen (1963) found in man that therapeutic doses of phenformin only infrequently lead to small rises in circulating levels of lactic acid. According to Sterne (1964), metformin does not inhibit tissue respiration *in vitro* and he quotes Debry to support the view that the blood lactic acid is not raised in diabetics receiving metformin therapy. It was concluded by an expert committee (*Special Communication*, 1963) that biguanides alone probably do not cause lactic acidosis.

Therapeutic indications

The prime aim of treatment in the diabetic is to normalize the blood sugar; to effect this, several oral hypoglycaemic preparations are now available. They include the sulphonylureas, the sulphapyrimidines and the biguanides. The indications for their use are generally similar and lie mainly in the management of the diabetic who is not insulin dependent, not prone to ketosis and who is inadequately controlled by dietary carbohydrate restriction. The initial use of oral preparations or their combinations is largely a matter of personal preference, though currently most clinicians would opt first for the sulphonylureas, using the biguanides alone or in

combination if the blood sugar response is inadequate or if an initial response is lost.

An additional claim for the biguanides is their usefulness as an adjunct to insulin in diabetics (sometimes called 'brittle') who show violent swings in blood sugar level. Pomeranze *et al.* (1959) claimed that there was improvement in overall control and a reduction in the frequency of hypoglycaemic attacks when phenformin was added to the regime. However, this improvement is usually attended by a reduction in the total insulin dosage which is itself likely to iron out the major swings from hypoglycaemia to reactionary hyperglycaemia and ketonaemia (Somogyi, 1959). Indeed, later reports are more critical of the value of phenformin in these difficult patients (Jakobson *et al.*, 1965; Pedersen, 1964), but there remains a strong clinical feeling among some physicians that on a few occasions, when alteration of insulin dosage, correction of diet, control of exercise or stabilization of emotional lability have failed to restore euglycaemia, the addition of biguanides may succeed.

The aim of normalizing the blood sugar in the diabetic has the long-term purpose of postponing or preventing the so-called complications of the disease. There is no evidence that the biguanides are better or worse than the other oral agents in their effects upon retinopathy, nephropathy and neuropathy; there is, however, some cause to suppose that the course of the accelerated atherosclerosis of the diabetic might be favourably influenced. In a series of studies over the past 5 years Fearnley, Chakrabarti and their colleagues have shown that phenformin increases fibrinolytic activity, decreases platelet adhesiveness and lowers the blood cholesterol (Fearnley & Chakrabarti, 1964; Fearnley *et al.*, 1967; Chakrabarti, Fearnley & Evans, 1967; Fearnley, 1968). Serum triglycerides and the pattern of circulating lipoproteins are also restored towards the normal by the biguanides (Schwartz, *et al.*, 1966). All of this lends weight to the view that the biguanides *might* confer some protection upon the vulnerable major arteries of the diabetic; there is as yet, however, no sound evidence that these desirable ends are actually attained.

Finally, Wilansky & Hahn (1967) have published the provocative results of a study of the effect of a 6 weeks' course of phenformin upon the subsequent development of diabetes in a group of relatives of diabetics who had abnormal cortisone-glucose tolerance curves. In a 3-year follow-up, they fared significantly better than a control group treated with placebo. If this observation is confirmed, phenformin might well have an important prophylactic role.

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Phenformin as a fibrinolytic drug

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DURING the past 20 years fibrinolysis, once an apparently rare and pathological phenomenon, has begun to emerge as the physiological antithesis of coagulation, a system whose function seems to be the removal of fibrin. Basically the system consists of plasminogen, an inactive enzyme precursor present in blood and other body fluids which can be converted to plasmin, an active proteolytic enzyme, by activators present in the blood, body fluids and the tissues. Anti-

plasmin is present in blood and neutralizes any plasmin liberated, so that in normal circumstance free plasmin is absent from circulating blood and the fibrinolytic system is in effect inert.

Since plasmin digests fibrinogen as well as fibrin, antiplasmin is a necessary safeguard against destruction of fibrinogen in fluid blood; but when fibrin is formed activator is adsorbed to it and converts the plasminogen incorporated with it to plasmin which in turn is adsorbed to fibrin