stimulation by glucose, but there is also evidence that sulphonylureas have an effect on peripheral insulin resistance. The numbers of insulin receptors in peripheral tissues are increased by treatment with the sulphonylureas thus enhancing the action of insulin.⁹⁻¹⁰ Yet this appears to be only part of the story since the action of insulin after binding has been shown to be improved.¹¹⁻¹²

Of more practical importance than How? is Which? The sulphonylureas seem to share a common mechanism of action, the second generation ones being distinguished from the first generation by a simple increase in potency. Claims for a third generation of sulphonylureas, with effects on abnormalities in other systems, should be treated with scepticism, since many haematological abnormalities are corrected by control of hyperglycaemia.¹³ Others of the more recent sulphonylureas are marketed on the basis of their safety in liver disease (the drug is metabolised in the kidney) or in renal disease (it is metabolised in the liver). Safety is equated with less hypoglycaemia—which remains the only side effect of real importance. Such claims are difficult to assess—in that context the safest drug would be one with little or no hypoglycaemic effect.

There is no "best buy" in sulphonylureas. Efficacy, potency, convenience of dose, incidence of side effects, and cost will be weighed differently by physicians. Though the division into first and second generation drugs may be of little value, the distinction between short acting and long acting is useful. Manufacturers have clouded this issue by quoting half life figures for the drug; this bears little relation to the half life of the hypoglycaemic effect. For convenience of dosage a long acting sulphonylurea should be used in patients under the age of 65 with normal renal function. In those with declining renal function and those who may be forgetful about food or who depend on external sources for their meals a short acting drug is safer. Clearly, then, as patients grow older they may need to be switched from a long to a short acting sulphonylurea, and general practitioners interested in looking after this particular group of patients should recognise this need. Common sense decrees that experience is best gained with one drug from each category. In our clinic tolbutamide and glibenclamide are dominant (despite brief flirtations with other drugs) and we believe that any new sulphonylurea will need to have proved advantages over the current tried and tested choices.

Two further practical points deserve mention. The first is the relation between the minimum and maximum doses. Treatment should be started with the minimum dose—which often produces a reassuring fall in the blood glucose concentration and an alleviation of symptoms. When control deteriorates again is it worth working up to a maximum dose? Dose response relations suggest that it is not (I Peacock, MD thesis, University of Cambridge, 1985). Doubts on this score, suggestions that only a short time is bought by an increase in dose, and the observation that the technique of insulin treatment is best learnt by the patients while they retain their manual dexterity have tended to lead towards earlier treatment with insulin. Recognising when treatment with sulphonylureas has failed is an important part of the management of non-insulin-dependent patients.

Secondly, though drug interactions are of less clinical concern than the textbook lists may imply, a lack of awareness of these possibilities is inexcusable.¹⁴ Alcohol is a major concern—not through its interaction with chlorpropamide to cause embarrassing flushing but because the consumption of alcohol by a patient with alcoholic liver

disease who is taking a sulphonylurea provides other mechanisms for hypoglycaemia.

While sulphonylureas dominate the oral hypoglycaemic market, metformin remains appropriate for overweight patients with poor dietary compliance. It has a less potent hypoglycaemic effect than the sulphonylureas,¹⁵ there is a small risk of lactic acidosis, and its ability to cause diarrhoea is the cause of many unnecessary large bowel investigations. Yet in hyperglycaemic overweight patients sulphonylureas or insulin may cause further undesirable weight gain, and metformin has a better record.¹⁶

The combination of metformin with a sulphonylurea is of more dubious value. Often this regimen has been used to avoid insulin treatment at all costs but in practice, though insulin may not improve control, it may be preferred by the consumer.¹⁷

Oral hypoglycaemic agents will, then, correct symptoms and provide adequate control of hyperglycaemia for many patients but the physician's approach should be flexible. He or she should recognise that patients often benefit from a change in sulphonylurea with advancing years and control of the blood glucose may best be achieved not by increasing doses or by combinations of sulphonylureas and metformin but by a readiness to institute and subsequently reconsider insulin treatment.

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Akathisia—or not sitting

The term akathisia (not to sit) was coined by Haškovec at the beginning of this century to describe a psychological condition characterised by the patient's inability to sit still. Though Haškovec related akathisia to hysteria, later

was seen to occur in patients with both idiopathic and postencephalitic parkinsonism.² Nowadays, however, the most important presentation of akathisia is in patients taking neuroleptic drugs.³

Akathisia has two components: subjective (psychological) and objective (motor). The subjective symptoms include a feeling of tension, an inability to tolerate being still, and an urge to move; the motor component (which is believed to be secondary to the psychological symptoms) consists of restlessness and hyperactivity—shuffling and tapping of feet, rocking of the body, or, in more severe forms, inability to remain seated, standing, or lying (impatience musculaire); and continuous changing of the position of the body, pacing, or even running (tasikinesia).⁴⁻⁷ The psychological symptoms and motor signs usually coexist, but in the mildest form of akathisia only the psychological component may be present.⁷ The term pseudoakathisia has been used to describe a syndrome of motor restlessness without the psychological symptoms of true akathisia.^{8,9}

Akathisia induced by neuroleptics may be due to reserpine, phenothiazines, thioxanthenes, and butyrophenones; more potent neuroleptics such as trifluoperazine and haloperidol are more likely to cause the syndrome than less potent ones such as chlorpromazine or thioridazine.¹⁰ Other neuroleptic-like drugs which block central dopamine receptors such as metoclopramide¹¹ and amoxapine¹² may produce the syndrome. Akathisia is the most common motor side effect of treatment with neuroleptics; the overall incidence has been reported to be around 20%.^{7,10} The neuronal basis of akathisia is not clear: possibly it may reflect the blockade of dopamine receptors in the frontal cortex innervated by the mesocortical dopamine pathway.^{13,14}

Although akathisia may occur in isolation it is often combined with other extrapyramidal syndromes induced by neuroleptics, such as parkinsonism⁷ or dyskinesia.^{9,15} Akathisia may appear early or late in the course of treatment with neuroleptics. Acute akathisia usually develops within a few days of the start of treatment, is dose dependent, and disappears if the dose is reduced or the drug is stopped. It often responds to anticholinergic drugs, and if treatment is continued it commonly subsides after two to three months.^{9,10} Tardive akathisia, by contrast, like tardive dyskinesia, appears after several months of continuous treatment, is not dose dependent, does not respond to anticholinergic drugs, and is made worse by stopping treatment.^{8,15} Tardive akathisia is often of the "pseudoakathisia" type.^{8,9} Another clinical variant is prolonged or persistent akathisia.^{9,15} This is the continuation of the acute akathisia syndrome over several months; this syndrome usually merges with tardive dyskinesia.⁹

The differential diagnosis includes conditions simulating either the psychological or the motor components of the syndrome. The tension and inner restlessness of akathisia may be mistaken for the agitation of some psychotic and depressive states, leading the clinician to increase the dosage of the neuroleptic.^{5,9} The motor restlessness may be confused with dyskinesia^{5,8} and some neurological disorders affecting the legs, such as restless leg syndrome and meralgia paresthetica.⁵

The most effective treatment of acute akathisia is reduction of dosage or withdrawal of the offending drug, or substitution of a less potent neuroleptic. Anticholinergics,^{7,15} benzodiazepines,¹⁶ β adrenoceptor antagonists,¹⁷ clonidine,¹⁸ and amantadine¹⁹ have been reported to alleviate akathisia induced by neuroleptics.

The early recognition of akathisia induced by neuroleptics is of considerable clinical importance: a subjectively distressing condition,^{6,20} it may lead to acts of violence,²¹ suicide,²² and to discontinuation of neuroleptic treatment by the patient.²³

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Subcortical dementia

A characteristic slowness of response and mental processing has been recognised for many years in patients suffering from disease of cerebral subcortical structures. The response to a proposition is considerably delayed, but ultimately the response is accurate and appropriate—a simple slowing down of the thought process. Some of these patients may be found to have frontal gliomas, and their slow responses are accompanied by specific neurological signs produced by the presence of the tumour. In 1974 Albert and his colleagues used the term subcortical dementia to describe the intellectual deterioration seen in progressive supranuclear palsy,¹ and in 1975 McHugh and Folstein described a similar pattern of deterioration in patients suffering from Huntington's chorea.² These workers suggested that the forgetfulness and slowness of thought processes, the altered personality with specific apathy and depression, and the impaired ability to manipulate acquired knowledge constituted a specific syndrome; and they contrasted it with the dementia of Alzheimer's disease.

Further study of the subcortical dementias might possibly lead towards treatment and they give neurologists an opportunity to study the progressive memory loss associated with