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PROGRESS IN THE UNDERSTANDING AND TREATMENT OF DIABETES MELLITUS*

BY

W. J. H. BUTTERFIELD, O.B.E., B.M., F.R.C.P.

Professor of Experimental Medicine, Guy's Hospital Medical School, London

The importance of therapy, day in and day out, for diabetes mellitus with its disabling complications is emphasized by the fact that the disease affects about 1% of the population—indeed, recent American studies aimed to detect the true incidence in the U.S.A. suggest that it may be 2–3%. The present paper is a rather parochial review, its purpose being to consider the therapy of diabetes in relation to current investigations in this field at Guy's Hospital, and the development of some new drugs. The discussion is largely confined to our ideas about the control of diabetes: our studies on complications (Fry, Trounce, and Cook, 1959; Thompson, Butterfield, and Fry, 1960) and our thoughts about treating them have been reported elsewhere (Butterfield, 1961).

Control of Diabetes: Physiological Considerations

Although not necessarily correct, it is customary and convenient to control diabetes by assessing the abnormalities of sugar metabolism rather than those of fat

By studying the forearm tissues in normal and diabetic subjects, we showed (Butterfield and Holling, 1959), contrary to expectations in some quarters—for example, Somogyi, (1949)—that negative arteriovenous glucose differences occur and that the peripheral tissues have a glucose threshold which must be exceeded by the blood-glucose level if glucose is to shift from the blood into the tissues, (see Fig. 1). In normal fasting subjects this threshold was 70–90 mg./100 ml. and the fasting blood sugar approximated very closely to it, so that, under those circumstances, the uptake of glucose by the tissues was negligible. (Mean of six subjects, 0.075 (S.D. $\pm$ 0.11) mg./100 ml. forearm tissue/min.) In fasting diabetic subjects the tissue glucose threshold was very much higher, and so was the systemic blood sugar. Again, in stable or severely diabetic subjects there was negligible or even negative glucose uptake in fasting conditions (-0.13 to $+0.04$ mg./100 ml. forearm tissue/min.). (Fig. 2 exemplifies results in elderly diabetics.) If the threshold in the peripheral tissues exceeded the renal

FIG. 1

FIG. 2

FIG. 3

FIG. 1.—Relationship between arterial glucose level and tissue glucose uptake in a normal subject, showing the tissue glucose threshold. FIG. 2.—Relationship between arterial glucose level and tissue glucose uptake in a normal subject (below) and in an elderly diabetic (above). Note the elevated tissue glucose threshold in the diabetic subject. FIG. 3.—Reduction of tissue glucose threshold in the elderly diabetic by a subcutaneous injection of insulin (30 units). (From Butterfield *et al.*, 1958.)

or protein metabolism. Recent investigations with colleagues have provided us with some new ideas about the mechanism of hyperglycaemia and glycosuria.

threshold (usually about 180 mg./100 ml.), glycosuria occurred. We have also observed that subcutaneous or intravenous insulin lowers the glucose threshold of the peripheral tissues (Butterfield, Fry, and Holling, 1958) in most subjects. Thus in the elderly diabetic (Fig. 2) the fasting threshold was 286 mg./100 ml. of blood, and

*Based on a communication to the Section of Medicine at the Annual Meeting of the British Medical Association, Torquay, 1960.

two hours after subcutaneous insulin the threshold had fallen to 110 mg./100 ml. (Fig. 3). Clearly insulin had reduced the tissue glucose threshold, with a consequent fall of the systemic blood level below the renal threshold and disappearance of glycosuria.

When we followed the local effect of small doses of intra-arterial insulin on the tissue glucose threshold of insulin-sensitive subjects we found that it exerted its action very quickly, measurable changes of uptake being detectable within five minutes (Hardwick, Butterfield, Fry, and Briggs, 1959), rising to peak values of over 1 mg./100 ml. forearm/min. by 15 minutes (Fig. 4). Insulin given intravenously to exert a systemic effect produces a fall in blood sugar of similar time response.

FIG. 4.—Effect of 0.1 units of insulin injected intra-arterially on the local tissue glucose uptake in an insulin-sensitive subject with normal carbohydrate metabolism. (From Hardwick *et al.*, 1959.)

All these findings suggest that the glucose threshold of the peripheral tissues is an important factor controlling the fasting blood sugar level.

Our studies have also shown that when glucose was taken by mouth it moved into the tissues. Thus, in lean normal subjects, of the 50 g. administered in the standard

FIG. 5.—Effect of 50 g. of glucose on the tissue glucose threshold in a normal subject (below) and in an insulin-dependent diabetic (above).

under these circumstances, but in all normal subjects studied it reverted to normal values within 1½ to 2½ hours, whereas in diabetic subjects the abnormally high

glucose - tolerance test, it may be calculated that 35 g. found its way into the cells of the peripheral tissues. By contrast, in elderly diabetics some 15 g., and in severe insulin - dependent cases only about 1 g., of the original dose enters the cells of the peripheral tissues (Butterfield and Whichelow, unpublished observations). The tissue glucose threshold rose

threshold of the fasting state rose to even higher values and stayed elevated, suggesting that there was insufficient insulin available for homeostasis (Fig. 5). From these findings, and from the overnight rise of tissue glucose threshold level observed in untreated diabetics, we can deduce that, as glucose finds its way into the tissues, the insulin effect is exhausted.

All the foregoing results are in harmony with the general hypothesis that insulin acts by increasing cell permeability to glucose, activating a transport system for glucose in the cell membrane. Furthermore, these studies in man, indicating tissue thresholds, suggest an amplification of this view: the effect of insulin on the systemic blood sugar may be due to an increase in the proportion of cells in the peripheral tissues acting as glucose acceptors. I stipulate proportion because effects have been observed under circumstances where the number of molecules of insulin fixed appears to be smaller than the number of cells in the forearm tissues under study. These findings have therefore brought us to regard the body's glucose metabolism in a much more anatomical way—we conceive that different tissues or organs may have different thresholds for glucose, the systemic blood sugar apparently following the peripheral tissue threshold very closely. When the peripheral glucose threshold in diabetes rises above the renal threshold, so that glucose is detectable in the urine, its value is roughly double that which obtains in normal fasting subjects. Thus when we control diabetics by urine-testing, their glucose metabolism may still be abnormal, even though the urine tests for sugar are all negative. The question at present under consideration is whether the brain has a glucose threshold, and, if so, whether it is affected by insulin and whether the symptoms of hypoglycaemia are due to the threshold of the peripheral tissues falling close to or even below the brain threshold.

Clinical Types of Diabetes

Young Diabetics

Elevated glucose thresholds of peripheral tissues may arise owing to inadequate production of insulin. It is generally believed that diabetes which starts during childhood and adolescence—growth-onset diabetes—is associated with an absolute deficiency of, and an inability to produce, insulin. In acromegaly associated with the overproduction of growth hormone in adult life we find that intra-arterial insulin is ineffective in lowering the glucose threshold of the peripheral tissues (Hardwick *et al.*, 1959) (Fig. 6). This seems to be due to failure of insulin to reach the tissues and exert its usual effect there (Briggs, Butterfield, Garratt, Pearson, and Whichelow, 1960). Could the growth hormone present during child-

FIG. 6.—Impaired response to intra-arterial insulin, 0.1 units, observed in acromegaly. (From Hardwick *et al.*, 1959.)

hood or adolescence act in a like manner, thereby taxing the β -cells and contributing to their eventual complete exhaustion, thus accounting for the absolute insulin deficiency observed in such cases both during life and in the pancreas at necropsy? Obviously this possibility deserves investigation, particularly in view of the recent evidence that in the early stages of their disease juvenile diabetics have large quantities of insulin in their blood (Steinke, Taylor, and Renold, 1961).

Meanwhile it is important to appreciate that such diabetics, whose disease began during growth, represent but a small fraction, perhaps a sixth, of the cases attending diabetic clinics. Their condition approximates to the concepts of diabetes based on laboratory studies of experimental diabetes produced in animals after pancreatectomy. More recently a new form of experimental diabetes has been produced by workers at Guy's Hospital. Stemming from his interest in insulin assay, recently reviewed (Vallance-Owen and Wright, 1960), my colleague Dr. P. H. Wright, of the department of chemical pathology, in collaboration with Dr. R. T. Grant and Mr. J. Armin (Armin, Grant, and Wright, 1960), has produced a diabetic state by the infusion of insulin antiserum, prepared by injecting bovine insulin into guinea-pigs, as described by Moloney and Coval (1955). The full potential of this new and specific method of blocking insulin action *in vivo* remains to be determined; its great advantage is that one knows the exact time of onset of insulin deficiency in the unanaesthetized, conscious animal.

Patients in whom the onset of diabetes occurred during growth invariably need insulin therapy, for in its absence the glucose threshold of the peripheral tissues rises higher and higher. So long as carbohydrate intake and gluconeogenesis in the liver can keep pace with this and glycosuria, the circulating glucose level will rise, and glucose will compete with other metabolic substances. But if the threshold rises so high that the cells are starved of glucose, the body must rely more and more upon fat mobilized from adipose tissue. This uncontrolled fat metabolism leads to acetonuria.

Older Diabetics

Diabetes is much more prevalent in elderly patients. They represent about 75% of those attending most diabetic clinics—and the proportion is increasing as more and more cases are detected by conscientious practitioners and at detection drives. They rarely have an acute onset of symptoms attributed to glycosuria—dehydration, loss of weight, or diabetic coma. The disease is insidious—indeed, the patient not infrequently presents with symptoms attributable to the complications of diabetes, or has asymptomatic glycosuria found at examination for an insurance policy. In these cases insulin can be found in the circulating blood, and at necropsy in the pancreas. Furthermore, these patients are not prone to develop acetonuria, and the disease can often be controlled simply by dietary restriction; presumably insulin production can keep pace with the slow utilization of insulin accompanying low glucose uptake by the tissues.

However, we are still grossly ignorant of the cause of such inadequate insulin secretion or defective action. Regarding inadequate secretion, one wonders if the β -cells, too, have a glucose threshold which must be exceeded before glucose enters them to act as a stimulus for insulin secretion. Elevation of the β -cell glucose threshold, as part of a generalized process independent

of insulin itself, would account for the elevation of blood sugar in these cases, by automatically gearing the release of insulin from the β -cells to a higher level of circulating blood sugar. In regard to defective action, the possibility exists that other cases may have impaired insulin fixation (Yalow and Berson, 1960).

Therapeutic Principles

Current trends of therapeutics for diabetes may be considered in relation to the foregoing information. Table I summarizes the clinical indications for selecting the therapeutic procedure available to-day that is likely to be best.

TABLE I.—*Selection of Therapy for Diabetes*

Presentation		
Diabetic coma or precoma	..	Insulin—urgent
Glycosuria and acetonuria	..	Insulin—at least at first—and diet
		Diet—especially if patient overweight
Glycosuria alone		or diet + oral antidiabetics
		or diet + insulin

Education of Patients.—Recent studies have indicated that the public is appallingly ignorant about diabetes (Reid, 1960). A prerequisite for proper and sustained control is an understanding of the disease by the patient and his family. This is especially true in severe cases. However, not many patients can grasp the intricacies of glucose assimilation by cells, insulin requirements, or how insulin deficiency causes hyperglycaemia and glycosuria which can be counteracted either by encouraging the β -cells to secrete insulin or by replacement injections. But most of them can grasp the idea that the blood sugar is like water in a wash-basin: add more, and it runs out of the overflow into the cells. Unfortunately the overflow silts up unless there is enough insulin. If it silts up, the level rises and the basin overflows. In the same way, glucose spills over into the urine, where it can be detected by testing. At Guy's Hospital we are looking into visual aids to engender this sort of understanding.

Urine-testing.—In the control of diabetes to-day glycosuria can be assessed without the paraphernalia of spirit-lamps and spurting test-tubes. Simpler methods have been developed involving the use of tablets which generate their own heat on dissolving. It is now reasonable to expect a conscientious patient to perform up to four urine tests for sugar each day, even at work, and record the results in a suitable book for inspection by the doctor at each visit. This has become a basis for assessing and controlling patients in most diabetic clinics.

Diet.—From the previous remarks it is clear that regular dietary control must be the central theme of therapy. In most elderly, obese cases it is the safest and best treatment, often the only treatment, required in the early stages of the disease. The insulin action, inadequate for high carbohydrate intakes, can cope with 80–100 g. a day, and keep the fasting blood sugar under control, to 120 mg./100 ml. of blood or less. Furthermore, glucose tolerance may be improved after effective dieting. It is the general experience that satisfactory gradual reduction of weight in such mild diabetics can be achieved by diets of 1,500–2,000 calories a day, with exercise. This quickly eradicates their glycosuria without resort to any other treatment: the problem in such cases is usually to maintain the initial good intentions of the patients about dieting. However, weight-reducing diets cannot be recommended for thin patients, growing children, or those of any age with severe insulin deficiencies manifest by persistent acetonuria in addition to glycosuria. In such cases it is important to ensure

that there is a suitable intake of carbohydrate for disposal into the tissues each day by insulin or oral antidiabetic drugs (see below.) Clearly, the patient receiving insulin injections risks hypoglycaemia if he eats too little, and hyperglycaemia if he overeats. Adult diabetics who require insulin are maintained on 150–200 calories of carbohydrate a day, with a total daily calorie intake of 1,500–2,500, or more, depending on weight and on physical activity. The latter demands more calories without a proportional increase of insulin dosage.

Insulin

Replacement therapy is imperative in those diabetics whose resources for insulin production are inadequate to maintain reasonable tissue glucose thresholds when they are dieting, or after an overnight fast. These circumstances apply continuously to almost all "growth-onset" cases, but may also arise intermittently in elderly diet-controlled patients in the course of intercurrent infections, illnesses, injuries, or operations. As explained earlier, insulin is indicated if the patient shows persistent acetonuria; its injection in the soluble form by the intravenous route is obviously urgent in the presence of impending diabetic acidosis or coma. Both of these metabolic disturbances, with their attendant clinical features of polyuria, polydipsia, dehydration, acetone-tainted breath, and clouded consciousness, must be regarded as dangerous enough to warrant early transference of the patient to a hospital where pathological laboratory services are available in order to ensure adequate replacement of the lost water and electrolytes as well as to control the blood glucose. The notion that diabetic acidosis could be adequately controlled by feeding fructose—a hexose which enters cells independently of insulin—has not been supported by the studies of Nabarro, Beck, and Stowers (1955).

Over the past 10 years various laboratories and pharmaceutical companies, especially in Denmark, have explored new possibilities for compounding insulin for routine use so that the rate of absorption from the injection site will permit adequate control of the blood sugar over the whole 24 hours. The main purpose has been to secure control overnight, with a view to suppressing diabetic complications. Insulin in the crystalline form is now available, and by grading the crystal size, and thus the surface available for absorption into the body fluids, the effect from a single injection can be extended to run through 24 hours. It has been our experience that larger dosages of these long-acting insulins are required than with two or three injections of soluble insulin, and this must be borne in mind when changing over to such preparations.

Although insulin therapy is universally accepted, we should not overlook the inadequacies of this form of treatment. Commercial insulins are prepared from beef pancreases, and the injections therefore contain a foreign protein-beef insulin, which differs slightly from human insulin, and traces of other animal proteins. A survey of Guy's Hospital patients by Robinson, Langman, and Banfield (1961) revealed antibodies to animal insulin in the blood of very few patients. Occasionally tissue allergies to the animal proteins are shown by local reactions at the site of injections.

Our ignorance about the rate of absorption of insulin injected into different sites is being dispelled. My colleague Dr. C. L. Joiner, using I-131-labelled (soluble) insulin, prepared as described by Pearson (1959), has shown that absorption from subcutaneous injections is

faster in the arms (half-period: females 55 minutes, males 67 minutes) than in the thighs (females 99 minutes, males 123 minutes) in normal subjects and somewhat longer in patients (Joiner, 1959). Although exercise had no effect on the absorption rates, more studies are projected to discover the effects of variations of lymph or subcutaneous circulation with alterations of skin and environmental temperatures.

It should also be noted that the endogenous insulin passes, possibly intermittently, into the portal circulation. There is recent evidence that intraportal infusions of small doses of insulin reduce hepatic glucose output in dogs with portocaval shunts but that larger doses do not (Madison, Combes, Adams, and Strickland, 1960). These results become intelligible if one assumes that the smaller doses have a predominant effect on the organ first perfused—the liver—whereas the larger doses also lower the threshold of the peripheral tissues, masking any liver action by reducing the systemic blood-sugar level and stimulating the release of adrenalin (Armin and Grant, 1959.) Such an interpretation may help resolve the confusion about the role of insulin in hepatic glucose metabolism existing between workers in different laboratories using various techniques and a variety of insulin doses and infusions. This is exemplified by the papers at a recent symposium in New York. Mahler, Shoemaker, and Ashmore (1959) found no insulin effect after a single injection of 0.2 unit/kg. intravenously in dogs; de Bodo and colleagues (1959), using intravenous infusions of 0.003–0.006 unit/kg./min., followed by C-14-glucose dilution, and deduced a "restraining" effect on glucose release from the liver, though Wrenshall and Hetenyi (1959) questioned the validity of this technique.

Again, at another meeting in London, de Duve (1960) reported hepatic action of insulin, based on rat-liver slices incubated with a medium containing 1 unit/ml., Tarding and Schambye (1960), using intravenous infusions of 0.02–0.12 unit/kg./hour in dogs, were doubtful if hepatic glucose output was altered; whereas Levine (1960), who has used up to 20 units/kg. in rats, was persuaded that insulin had no effect on the liver. Cori (1960) summarized with the words: "The amount of work on the action of insulin on the liver is large indeed, but it seems we need many more experiments before this problem is finally settled." In settling it, the effects of the insulin dosage, particularly through its route of administration and speed, upon the peripheral threshold must be borne in mind if any hepatic action is to be recognized (Madison, Unger, and Rencz, 1960). Meanwhile, so long as we remain uncertain of the action, in man, of insulin on hepatic metabolism or of the liver on insulin metabolism, we must consider the possibility that the non-physiological—that is, non-portal—route of absorption after insulin injections causes too much active insulin to be presented to the arteries. If arterial tissue has a glucose threshold the accumulation of deposits of fat in the arterial wall may be a reflection of periods when too much insulin was available in the circulating blood.

Oral Antidiabetic Compounds

Investigations in the field of oral diabetic compounds have brought important new developments in the treatment of diabetes. While many of the adult-onset non-ketotic diabetics, notably obese patients, can be controlled adequately by dieting alone, others require additional regulation, which for many years was achieved by insulin injections. It is for these latter that the quest for oral therapy seems to be successful.

The search is not new. Müller (1877) reported that large oral doses of salicylates reduced the blood sugar, and this was rediscovered by Reid, MacDougall, and Andrews (1957). During the first world war, Watanabe (1918) and others reported that biguanidines were effective hypoglycaemia agents and "synthalin" A and B were subsequently prepared and tested. Unfortunately they produced fatal hypoglycaemia and liver damage, and their use was soon set aside in favour of the newly discovered hormone insulin when it became available after 1921. During the second world war Loubatières (1944), working in Montpellier, investigated the hypoglycaemic effects of a sulphonamide, I.P.T.D. (2(*p*-aminobenzenesulphonamido) - 5 - isopropyl - thiadiazole) and concluded that its action must be directly on the β -cells, since it was ineffective both in pancreatectomized animals and in insulin-dependent, ketotic, growth-onset diabetics.

This discovery was taken up after the war, especially by the German laboratories, where over 300 compounds with hypoglycaemic properties were synthesized. Four of these have been subjected to clinical trial. The first was carbutamide (BZ 55) (*N*-sulphanilyl-*N*-butyl-carbamide). The next compound to be tried, tolbutamide ("rastinon"), enjoys a remarkable pharmaceutical record to date: it has been reported that over a million patients are taking it at present. Chlorpropamide ("diabinese"), a more potent compound with a longer action, has also been marketed: despite animal toxicity tests suggesting that high doses might be nephrotoxic, it seems safe. More recently metahexamide, another long-acting compound, was withdrawn owing to a 2% incidence of jaundice in extensive clinical trials. Other long-acting compounds are currently under study.

The success of these compounds reopened the possibility of oral therapy for diabetes, and it was not surprising that the guanidines were re-examined, since two, chlorhexidine ("hibitane"), used for its bactericidal action in the cleaning of wounds and burns, and an antimalarial drug, proguanil hydrochloride ("paludrine"), had been used extensively without toxic manifestations. At the moment two alternative hypoglycaemic guanidines are undergoing trial and are available—phenformin (D.B.I.; (phenethylbiguanide) and metformin hydrochloride ("glucophage"; methylbiguanidine). However, although these compounds are relatively free from serious side-effects, a proportion of the patients receiving them show loss of appetite, nausea, and vomiting, and may develop unexplained acetonuria, so that they are not recommended yet for general use.

The chemical interrelationships between the various oral antidiabetic compounds have recently been reviewed by Mahler (1960): the present status of the compounds in use and undergoing trial is set out in Table II.

Mechanism of Action of Oral Antidiabetic Compounds

Experience with the synthalins, suggesting that hypoglycaemia was due to some toxic action on the liver, dictated a cautious approach to oral preparations, and

some knowledge about the mechanism of action of the new oral antidiabetic compounds was demanded before the profession would use them. There was at first scepticism, which we shared, of Loubatières's views about stimulation of insulin release, despite the supporting evidence from animal experiments in which Creuzfeldt and Finter (1956) described degranulation of β -cells and from Pfeiffer and colleagues (1959), who reported elevation of plasma insulin levels in calves after sulphonylurea administration.

However, we have been much less concerned about using tolbutamide since we demonstrated in man (Butterfield *et al.*, 1958) that a few days' therapy reduces the glucose threshold of the peripheral tissues in a way which is indistinguishable from the action of insulin (see Fig. 7). We attribute this to stimulation of insulin

FIG. 7.—Tissue glucose threshold of an elderly diabetic before and after nine days' oral antidiabetic therapy. (From Butterfield *et al.*, 1958.)

secretion, as we have been unable to show any direct action of tolbutamide itself or other sulphonylureas on muscle glucose metabolism when given intra-arterially, either as a single dose or as a continuous infusion. Furthermore, Vallance-Owen, Joplin, and Fraser (1959) have since reported an increase of plasma-insulin-like activity hours after oral tolbutamide. There is therefore evidence in animals of β -cell stimulation, and in man of the appearance of insulin in the blood and of its action on the peripheral tissues, after tolbutamide.

Phenformin has a similar threshold-lowering effect, but is not hypoglycaemic in normal subjects and is stated to be hypoglycaemic in pancreatectomized animals maintained on insulin. Its action is therefore presumably different and independent of stimulation of insulin secretion. Our studies show that it does not increase muscle glucose uptake when injected intra-arterially in dose-ranges used clinically. We have recently accumulated evidence from several types of investigation that phenformin enhances the effect of circulating insulin (Butterfield, Fry, and Whichelow, 1961), which we could not demonstrate for sulphonylureas (Butterfield, Camp, Hardwick, and Holling, 1957).

Selection of Cases for Oral Antibiotics

The foregoing explanation about modes of action of oral antidiabetic compounds may now be dovetailed into our empirical clinical knowledge of the type of case that can be selected for their use.

TABLE II.—Oral Antidiabetic Compounds

	Found Unsatisfactory	In Use	On Trial
Salicylates (Müller, 1877)	Sodium salicylate, etc.	—	Orthocresotinate
Guanides (Watanabe, 1918)	Synthalin A and B	Phenformin	Metformin
Sulphonyl derivatives (Janbon <i>et al.</i> , 1942)	I.P.T.D. Carbutamide Metahexamide	Tolbutamide Chlorpropamide	Various analogues

Sulphonylureas

It has been pointed out by German investigators who pioneered the clinical trials of sulphonylureas that the prospects of successful therapy increased with the age of the patient—being very good over the age of 40—and that they were related to a less extent to the duration of the disease, being best if the diabetes was of less than five years' duration (Mohnike and Stötter, 1956). The idea behind the second principle was that after prolonged hyperglycaemia the islets became exhausted. In contrast, severely ketotic, intensely hyperglycaemic, or young diabetics are not amenable to control with the sulphonylureas. The two most widely used sulphonylureas are tolbutamide and chlorpropamide. Relevant information about both these drugs is presented in Table III.

Our general views about the steps to be taken when trying sulphonylurea therapy have been reported previously (Butterfield, Fry, Hardwick, and Holling, 1957). In those patients who are not on insulin—after suitable baseline observations of glycosuria (see above), including a check for renal glycosuria—the sulphonylureas—for example, tolbutamide—may be started 1 g. t.d.s. for one day, then 1 g. b.d., tapering off as and when the patient shows a response. As we pointed out, while this is usually effective after two to four days, it may take a week or even longer; we have also often noted a brief response at the second to fourth day in patients who have subsequently failed to maintain it.

If the patient is receiving less than 20 units of insulin a day it is possible to convert to tolbutamide without admission to hospital. We halve the insulin dosage during the first week as the oral compound begins to take over control.

If the patient requires over 20 units of insulin a day it is wise to try a conversion to tolbutamide in hospital: a successful conversion is very unusual in cases needing over 80 units of insulin a day. Therapy with a combination of tolbutamide and insulin has been tried but has little to recommend it.

Tolbutamide certainly seems to be the safest drug of this group, but needs frequent administration—up to three times a day. If control is tried with the other sulphonylureas, the possibility of the following side-effects must be borne in mind. With carbutamide, cases of agranulocytosis and liver damage have been reported. With chlorpropamide, also given once a day, the main difficulty is balancing between failure to maintain adequate control overnight and hypoglycaemia if effects accumulate. The main disadvantage of all sulphonylureas is that a proportion of cases fail to maintain their control (secondary failure). The cause of this loss of sensitivity is being investigated intensively in many centres.

Guanides

Although not yet in general use, a note may be added about the guanides. Phenformin is now available, and relevant information about it is given in Table III. Cases selected for trial embrace not only the type suitable for the sulphonylureas but also those whose control on insulin is adequate. In the latter cases it may be possible to "smooth" the effect of insulin and improve control. Guanides may therefore be suitable for younger patients and patients who show ketosis. Another difference compared with the sulphonylureas is that treatment is started at low doses and increased very slowly. With cases on diet alone this may be done on an out-patient basis, but for those on insulin admission to hospital is mandatory. The rate of response may be slower than that found with tolbutamide, but, in our experience, good results have been unusual in cases on high doses of insulin: our findings are comparable to those of Krall, White, and Badley (1958).

Although there seem to be few serious toxic effects with phenformin, there are unpleasant side-actions. About a third of all patients complain of nausea and vomiting, and we have some laboratory evidence that this is associated, sometimes at least, with non-absorption of glucose. Some patients have reported that their exercise tolerance is diminished by "fatigue," which may be due to accumulation of lactic acid (Walker, Linton, and Thomson, 1960). It is important to point out that acetonuria in the absence of hyperglycaemia may be observed in some patients on phenformin. Acetonuria is usually an indication for increasing the dose of antidiabetic drugs, such as insulin, but treating acetonuria in the absence of glycosuria may lead to serious complications with phenformin (Walker and Linton, 1959), and a closer analysis is required. Pomeranze (1960) has suggested that the acetonuria is due to non-absorption of food, like starvation ketosis. However, we have observed it in many patients who are gaining weight, and its true basis remains to be elucidated.

Perspective.—It may help to bring the various therapies into perspective by quoting current experience in diabetic clinics. All patients on dietary restriction are encouraged to check their urine for glycosuria and to record the results. About half the cases need insulin in addition to diet, and about a fifth use the sulphonylureas, while a much smaller fraction (1-2%) take guanides or mixed oral and insulin therapy.

Conclusions

Diabetes is a long-drawn-out disease, and it remains to be seen whether the oral antidiabetic drugs will maintain satisfactory control year after year. The secondary failures encountered after a few months may

TABLE III.—Comparison of Three Oral Antidiabetic Compounds Currently in Use

	Tolbutamide	Chlorpropamide	Phenformin
Formula
" Half-life "	4-8 hours	24-48 hours	6-8 hours
Dose rate	0.5-1.5 g./day	125-500 mg./day	50-200 mg./day
Cost (Guy's cases)	About 5d./day	About 5d./day	About 1s./day
Complications	Very rare	Rare	(Nausea)
Remarks	Probably the safest, but must be given several times/day	Probably the cheapest but not necessarily the safest	May have applications in some insulin-deficient cases

not so much be sporadic cases as those which show relatively early failure; a larger proportion may deteriorate later on. It has been suggested that the hyperglycaemia of secondary failure may be treated with salicylates or guanides, but the long-term success of these measures is unproved.

More important, though, is the question of diabetic complications, for we must appreciate that the real problem now hinges much more on the development of these than the question of controlling the blood-sugar level. We should be concerned with the prevention and amelioration of disability from vascular disease of the eye, lower limbs, and kidney, and the neuropathies of diabetes. In general practice much can be done to alleviate suffering by the early detection of diabetes by testing the urine with the sensitive glucose-specific tests available, thereby bringing therapy to the patient and getting the blood-sugar level under early control, which offers the best hopes of reducing the incidence and severity of complications. The ultimate value of any diabetic therapy, be it oral or by injection, must be judged by the progress of diabetic complications, and answers in these terms rather than glycosuria must now be sought.

The foregoing has focused attention on the hospital and laboratory view of diabetes, and it seems salutary to conclude by standing up from the bedside and workbench to take a broader look and to make some more general remarks about the team-work which is needed to deal with diabetes on a national scale. Diabetes offers an excellent example of the wider implications of chronic disease to-day, including the social, medical, public health, and occupational aspects, all of which must be considered. Furthermore, as the expectation of life is extended the proportion of diabetics in the elderly population will increase, so that the problems are likely to become more important in the future. This challenge demands the integration of many types of human activity, and in Table IV I have tried to summarize various responsibilities which must be met if the disease is to be mastered, and have attempted to set these against the groups who, it seems to me, must accept them.

If the medical profession is to play its proper part, it must take the overall responsibility for ensuring that all members of the team really appreciate their job and stick to it. Thus every doctor knows that, in the last analysis, the best dietetic advice is of no avail if the patient secretly consumes sweets—so the good doctor motivates his diabetics, emphasizing in their minds the importance of diet, and indicating that this is the patient's responsibility. Likewise, the relatives may need guidance before they will come forward for tests to detect any other members of the family who have diabetes. And, on general principles, the profession must encourage the pharmaceutical industry to produce the best possible insulin preparations and the safest oral antidiabetic drugs. Finally, we must always be prepared to help the lay organizations—diabetic associations—and

the public health authorities to provide group activities for diabetics and in tracing the other latent diabetics in the community. So long as this overall team-work is incomplete, diabetes will undermine the health of the community and produce disability.

Many of the studies referred to above were undertaken at Guy's Hospital. I am indebted to my colleagues for their co-operation and to my laboratory assistants. Some of the investigations were performed during an appointment with, and others aided by grants from, the Medical Research Council, to whom I am grateful for support. Figs. 4 and 6 are printed by courtesy of the Editors of the *Proceedings of the Royal Society of Medicine*, and Figs. 3 and 7 by kind permission of the Editors of *Diabetes*.

REFERENCES

- Armin, J., and Grant, R. T. (1959). *J. Physiol. (Lond.)*, **149**, 228.
 ——— and Wright, P. H. (1960). *Ibid.*, **153**, 146.
 de Bodo, R. C., Altszuler, N., Dunn, A., Steele, R., Armstrong, D. T., and Bishop, J. S. (1959). *Ann. N.Y. Acad. Sci.*, **82**, 431.
 Briggs, J. H., Butterfield, W. J. H., Garratt, C. J., Pearson, J. D., and Whiclow, M. J. (1960). In *Radioactive Isotope in Klinik und Forschung*, IV, edited by K. Fellinger and R. Höfer, p. 258. Sonderbände zu Strahlentherapie, vol. 45. Urban und Schwarzenberg, München.
 Butterfield, W. J. H. (1961). *Med. Press*, **245**, 5.
 ——— Camp, J. L., Hardwick, C., and Holling, H. E. (1957). *Lancet*, **1**, 753.
 ——— Fry, I. K., Hardwick, C., and Holling, H. E., (1957). *Brit. med. J.*, **2**, 325.
 ——— and Holling, H. E. (1958). *Diabetes*, **7**, 449.
 ——— and Whiclow, M. J. (1961). *Lancet*, In press.
 ——— and Holling, H. E. (1959). *Clin. Sci.*, **18**, 147.
 Cori, C. F. (1960). *The Mechanism of Action of Insulin*, edited by W. A. Broom and W. F. Wolff, Blackwell, Oxford.
 Creuzfeldt, W., and Finter, H. (1956). *Dtsch. med. Wschr.*, **81**, 892.
 de Duve, C. (1960). *The Mechanism of Action of Insulin*, edited by W. A. Broom and W. F. Wolff, p. 85. Blackwell, Oxford.
 Fry, I. K., Trounce, J. R., and Cook, C. A. G. (1959). *Diabetes*, **8**, 174.
 Hardwick, C., Butterfield, W. J. H., Fry, I. K., and Briggs, J. H. (1959). *Proc. roy. Soc. Med.*, **52**, 807.
 Joiner, C. L. (1959). *Lancet*, **1**, 964.
 Krall, L. P., White, P., and Bradley, R. F. (1958). *Diabetes*, **7**, 468.
 Levine, R. (1960). *The Mechanism of Action of Insulin*, edited by W. A. Broom and W. F. Wolff, p. 105. Blackwell, Oxford.
 Loubatières, A. (1944). *C.R. Soc. Biol. (Paris)*, **138**, 830.
 Madison, L. L., Combes, B., Adams, R., and Strickland, W. (1960). *J. clin. Invest.*, **39**, 507.
 ——— Unger, R. H., and Rencz, K. (1960). *Metabolism*, **9**, 97.
 Mahler, R. F. (1960). *Brit. med. Bull.*, **16**, 250.
 ——— Shoemaker, W. C., and Ashmore, J. (1959). *Ann. N.Y. Acad. Sci.*, **82**, 452.
 Moloney, P. J., and Coval, M. (1955). *Biochem. J.*, **59**, 179.
 Mohnike, G., and Stötter, G. (1956). *Dtsch. med. Wschr.*, **81**, 826.
 Müller, G. (1877). *Berl. klin. Wschr.*, **14**, 29.
 Nabarro, J. D. N., Beck, J. C., and Stowers, J. M. (1955). *Lancet*, **2**, 1271.
 Pearson, J. D. (1959). *Ibid.*, **1**, 967.
 Pfeiffer, E. F., Renold, A. E., Martin, D. B., Dagenais, Y., Meakin, J. W., Nelson, D. H., Shoemaker, G., and Thorn, G. W. (1959). *Diabetes Mellitus*, edited by K. Oberdisse and K. Jahnke, p. 298. Proceedings of the Third Congress of International Diabetes Federation, Düsseldorf, 1958. Thieme, Stuttgart.
 Pomeranze, J. (1960). *Brit. med. J.*, **1**, 425.
 Reid, J. J. A. (1960). *Med. Offr.*, **103**, 325.
 Reid, J. J., MacDougall, A. I., and Andrews, M. M. (1957). *Brit. med. J.*, **2**, 1071.
 Robinson, B. H. B., Langman, M. J., and Banfield, P. J. (1961). *Guy's Hosp. Rep.* In press.
 Somogyi, M. (1949). *J. biol. Chem.*, **179**, 217.
 Steinke, J., Taylor, K. W., and Renold, A. E. (1961). *Lancet*, **1**, 30.
 Tarding, F., and Schambye, (1960). *The Mechanism of Action of Insulin*, edited by W. A. Broom and W. F. Wolff, p. 93. Blackwell, Oxford.
 Thompson, R. H. S., Butterfield, W. J. H., and Fry, I. K. (1960). *Proc. roy. Soc. Med.*, **53**, 143.
 Vallance-Owen, J., Joplin, G. F., and Fraser, R. (1959). *Lancet*, **2**, 584.
 ——— and Wright, P. H. (1960). *Physiol. Rev.*, **40**, 219.
 Walker, R. S., and Linton, A. L. (1959). *Brit. med. J.*, **2**, 1005.
 ——— and Thomson, W. S. T. (1960). *Ibid.*, **2**, 1567.
 Watanabe, C. K. (1918). *J. biol. Chem.*, **33**, 253.
 Wrenshall, G. A., and Hetenyi, G., jun. (1959). *Metabolism*, **8**, 531.
 Yalow, R. S., and Berson, S. A. (1960). *Diabetes*, **9**, 254.

TABLE IV.—Responsibilities in Treatment of Diabetes on National Scale

The challenge of diabetes must be met by—	
1. The patient...	His diet
2. His family ..	Education about diabetes, urinalysis, personal hygiene, diabetic relatives
3. His doctors ..	Control therapy—insulin and oral anti-diabetic drugs
4. Research worker ..	Study of diabetes, especially complications
5. Pharmaceutical industry ..	Safe drugs
6. Lay organizations ..	Arousing public interest, raising funds, and helping patients
7. In collaboration with public health authorities	Detection of latent diabetics; prevention of disease