THE ORAL HYPOGLYCEMIC AND ANTIDIABETIC SULPHONAMIDES—A REVIEW.

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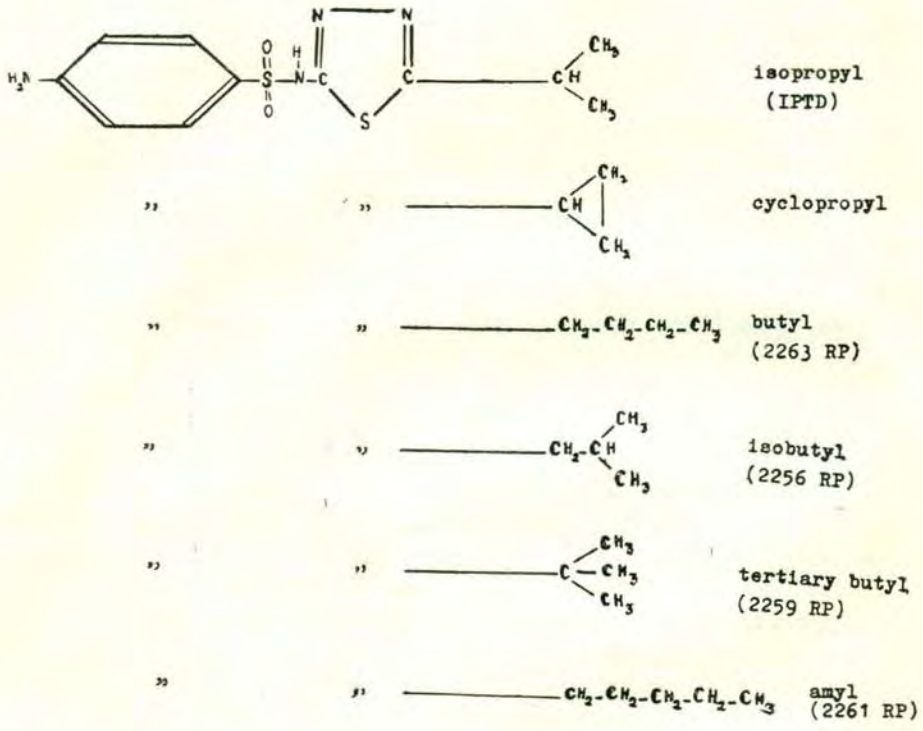
The discovery of insulin and its isolation, no doubt, were of immense value in the treatment of diabetes. But because of certain evident draw-backs of insulin therapy, the unpleasantness of frequent injections and the risk of serious hypoglycemia, searches were made in the past to discover antidiabetic agents which would be effective orally and which would maintain the blood sugar within normal levels. Although a variety of products, both natural and synthetic, were found to exert a beneficial effect, none of them proved adequate or harmless (Lewis, 1949). The current interest in the arylsulphonylureas, however, stems from an accidental observation by Janbon *et al*, (1942) while investigating the therapeutic effect of a new sulphonamide derivative in typhoid fever. These French physicians noticed that administration of *P*-aminobenzol-sulphonamidoisopropylthiodiazole (2254 RP; IPTD or PAIST) caused profound and even fatal hypoglycemia in some patients, especially in those who were in a poor nutritional state. The subsequent studies of Loubatieres (1944a, 1946a 1946b, 1946c) suggested that IPTD exerted its hypoglycemic action probably by stimulating the pancreatic beta-cells to discharge more insulin into the circulation. Chen, Anderson and Maze (1946) reached a similar conclusion from a study of the hypoglycemic effect of the cyclopropyl derivative of IPTD in intact and alloxanized animals.

The initial observation of Janbon *et al.* (1942, 1943) and the subsequent findings of Loubatieres (1944a, 1946a, 1946b, 1946c) remained largely unknown until interest in hypoglycemic sulphonamides was renewed by the observation of Holt and associates (Holt *et al*, 1954, 1955a ; Holt and Ferner 1955) that IPTD caused severe lesions of the alfa-cells in experimental animals, which suggested a mode of action different from that postulated by Loubatieres. Meanwhile several new sulphonamide derivatives were being evaluated for their chemotherapeutic action. One of these derivatives, N-sulphanilyl-N'-butylurea (BZ-55 or carbutamide) was found to initiate hypoglycemic reactions in the test animals used for assessing its antibacterial potency. The obvious therapeutic potentiality of the compound in the treatment of diabetes was immediately investigated and the initial results which were made known in 1955 seemed rather encouraging (Franke and Fuchs, 1955; Achelis and Hardebeck, 1955 ; Bertram *et al*, 1955). Shortly afterwards it was shown that the methylated analogue of carbutamide, N-(4-methyl-benzolsulphonyl)-N'-butylurea, which has no bacteriostatic effect (Ortel and Mohnike, 1956) was also equally effective in lowering the blood sugar of normal men, diabetic patients and experimental animals when administered orally (Bander *et al*, 1956 ; Miller[2] and Dulin, 1956 ; Mirsky *et al*, 1956a). Although these sulp-

honylurea compounds have been introduced only a short time ago it is evident from the numerous publications on them that they have evoked intense and widespread interest. BZ-55 is known by the trade names: Nadisan(R) (C.F. Boehringer, Mannheim, Germany); Invenol (R) (Ferbwerke Hoechst, Frankfurt/M, Germany); and Carbutamide (Eli Lilly and Co; Indianapolis, Indiana, U.S.A.). Similarly D-860 is known by the names : Rastinon (R) (Farbwerke Hoechst, Frankfurt/M, Germany); Artosin [R] (C. F. Boehringer, Mannheim, Germany); and Orinase (R) (Upjhon Co ; Kalamazoo, Michigan, U.S.A.).

CHEMISTRY AND METABOLISM

(1) THIODIAZOLE DERIVATIVES



(2) Urea derivatives

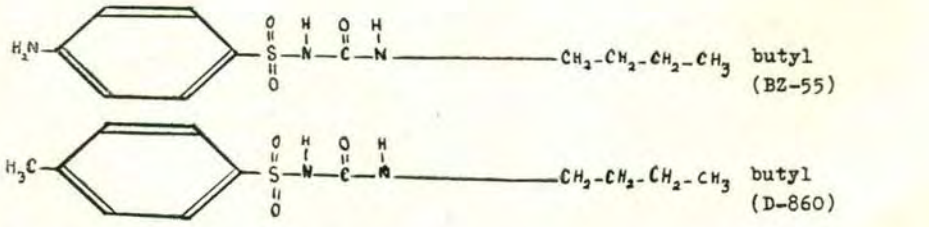


Fig. 1. HYPOGLYCEMIC SULPHONAMIDES.

It is apparent from the structural formulas of the three compounds which have been extensively studied, that they are closely related to each other. While IPTD and carbutamide are alike in having an aminogroup on the benzene ring in para position, tolbutamide has a methyl group instead. IPTD differs from the urea compounds in possessing an isopropyl side chain in place of their butyl radical and a thiodiazole nucleus corresponding to their carbamide portion.

Studies with IPTD and its congeners(Bovet and Dubost, 1944; Loubatieres, 1944b, 1946b) on chemical structure and hypoglycemic action revealed that the aliphatic side chain could be modified with butyl, isobutyl, amyl, isoamyl or propyl group without much diminishing the activity. However, substitution of a methyl or ethyl group was found to abolish the blood sugar lowering capacity of the compound. Although the *P*-amino group on the benzene ring was shown to be indispensable, it is obivous from the structure of tolbutamide that hypoglycemic action does not necessarily depend upon its presence.

The pure substances are practically insoluble in water, but they readily form soluble salts with alkalis. The sodium salts are usually used in experimental studies involving parenteral administration. When given by mouth these compounds are converted into the soluble salts within the intestine and absorbed as such. Absorption seems to be fairly rapid since detectable amounts of the sulphonylureas appear in the blood half an hour after oral administration. But 3 to 5 hours are required to obtain a peak concentration (Achelis and Hardebeck, 1955 ; Franke and Fuchs, 1955 ; Bander and Scholz, 1956 ; Miller[2] and Dulin, 1956 ; Miller[2] *et al*, 1957). They circulate mainly in the free form but bound to plasma albumin ; tolbutamide appears to be attached more firmly than carbutamide. There are indications to believe that tolbutamide remains merely in the extracellular spaces, whereas carbutamide enters the intracellular spaces to some extent (Bander and Scholz, 1956) Both compounds are excreted rather slowly, more than 24 hours being required to completely eliminate a test dose of either of the substances ; but tolbutamide is cleared relatively faster than carbutamide. Owing to the presence of the *P*-amino group carbutamide undergoes acetylation in the liver and kidneys and a major portion of carbutamide is excreted in the acetylated form (Achelis and Hardebeck, 1955 ; Franke and Fuchs, 1955). The main excretory product of tolbutamide in man is the corresponding carboxy acid, butyl *P*-carboxyphenylsulphonylurea, which has no hypoglycemic action (Wittenhagen and Mohnike, 1956 ; Dorfmuller, 1956 ; Louis *et al*, 1956). In rats tolbutamide is excreted as a conjugate the structure of which has not yet been identified (Miller[2] *et al*, 1957).

PHYSIOLOGICAL AND BIOCHEMICAL ASPECTS

Evidently, because of their hypoglycemic action, investigations on the effects of these sulphonamide derivatives in so far as they affect metabolic

processes have entirely centered on their influence on carbohydrate metabolism and the various endocrine organs which play important roles in this connection. The results obtained by various investigators are often contradictory, possibly because of differences in experimental conditions.

Effect on Blood Sugar

Minimal amounts of all the three compounds when administered orally or parenterally induce a fall in the fasting blood sugar of the common laboratory animals and of human beings. Huge doses are likely to produce hyperglycemia rather than hypoglycemia (Achelis and Hardebeck, 1955). The onset of hypoglycemia is fairly rapid and is a function of the concentration of the drug present in the blood stream (Janbon *et al*, 1943 ; Loubatieres, 1944a ; Achelis and Hardebeck, 1955 ; Franke and Fuchs, 1955 ; Miller[2] and Dulin 1956). The degree and duration of hypoglycemia vary with the dosage and with the species. In the rat tolbutamide given by mouth in a dose of 270 mg/kg produces within half an hour a rapid and substantial fall in the blood sugar level which is maintained for more than 6 hours. In the dog a dose of 25 mg/kg causes not only a more rapid action but keeps the blood sugar far below the fasting value for more than 24 hours. Increasing the dosage to 100 mg/kg induces a more intense and prolonged fall in the blood sugar level, but a dose of 600 mg/kg does not lead to further hypoglycemia. Relatively large doses are required to obtain appreciable hypoglycemic effect in the rabbit ; even then it is of transient duration (Miller[2] and Dulin, 1956). In man increase in oral dosage from 10 to 50 mg/kg causes a progressive increase in the intensity and persistence of hypoglycemia ; however, doses greater than 50 mg/kg do not increase the intensity of fall in the blood sugar level (Deingott and Mirsky, 1956). Intravenous administration of tolbutamide in normal subjects produces a prompt reduction in blood glucose within 10 minutes and a maximum depression at about 30 minutes after injection. As with oral administration the hypoglycemic response tends to vary directly with the dosage, 13 to 40 mg/kg (Frawely *et al*, 1957). Diabetic subjects respond to tolbutamide with a gradual fall in the blood sugar level rather than with the rapid decrease observed in healthy subjects, (Deingott and Mirsky, 1956).

Effect on Peripheral Tissues

Whether the sulphonamide compounds induce hypoglycemia by eliciting increased peripheral utilization of glucose has been studied in various ways. In the eviscerated animal (Fiitz *et al*, 1956 ; Wick *et al*, 1956 ; Dulin and Johnston, 1957) these compounds have no recognizable effect on the rate of glucose utilization. *In vitro* addition of these drugs does not enhance the uptake of glucose or deposition of glycogen by the rat diaphragm (Clarke *et al*, 1956 ; Cahill *et al*, 1957). The utilization of glucose by rat diaphragms isolated at varying intervals after intraperitoneal injection of tolbutamide is also not increased (Recant and Fischer, 1957). Loubatieres (1946b) noticed

that glucose loading after administration of IPTD raised the R. Q. of the normal dog, but not of the totally depancreatized animal. Similarly administration of glucose following that of tolbutamide elevated the R. Q. of normal human beings (Stotter *et al*, 1957), but the drug evoked no such effect in fasting normal subjects (Renold *et al*, 1957) or in diabetic patients (Goetz, 1957). Studies with labelled glucose (Miller[2] *et al*, 1957) reveal that tolbutamide accelerates the rate of glucose oxidation in normal rats but not in alloxan diabetic animals. However, several investigators (Beringer and Linder, 1956; Beringer and Keibel, 1956; Tyberghein *et al*, 1956; Miller[2] and Dulin, 1956; Dulin and Johnston, 1957), have demonstrated that the glycogen content of muscle in the intact organism remains unehanged after treatment with the sulphonylureas. The observation of Ashmore *et al*, (1957) that when a tracer dose of C^{14}—glucose (1 mg) is injected into normal fasted rats no significant increase occurs in specific activity of muscle glycogen and peripheral fatty acids also suggests the same conclusion. However, the studies of Miller[2] *et al*, (1957) indicate that when a larger dose (1 93 mg) of radio glucose is injected into fasted and not fed animals tolbutamide favours the formation of glycogen. Clarke (Wrenshall, 1957) has also reported a significant increase in the glycogen content of the diaphragms of rats injected with carbu tamide for several days.

That the fall in blood sugar produced by the sulphonylureas in normal and diabetic subjects is not accompanied by any significant increase in the arteriovenous blood sugar difference is evident from the results of several studies (Volk *et al*, 1956; Anderson[1] *et al*, 1956, 1957; Purnell *et al*, 1956; Hunt *et al*, 1956; Mckenzie *et al*, 1956; Recant and Fisher, 1957; Renold *et al*, 1957). However, Goetz *et al*, (1956) observed a definite increase in peripheral arteriovenous glucose difference following intravenous infusion of tolbutamide when capillary "arterial" instead of true arterial blood was used. While it has been observed by many investigators that the sulphonylureas do not affect the rise in blood sugar after meals (Chute and Bain, 1956; Duncan *et al*, 1956; Wolff *et al*; (1956) or the configuration of the glucose tolerance curve (Achelis and Hardebeck, 1955; Creutzfeldt and Finter, 1956; Renold *et al*, 1956: Purnell *et al*, 1956; Fajans *et al*, 1956; Mortimore *et al*, 1956; Moorhouse and Kark, 1956; Duncan *et al*, 1956; Frawley *et al*, 1957) there are reports indicating that after tolbutamide administration the blood sugar rises less and declines faster or the disappearance rate of injected glucose is enhanced (Frawley *et al*, 1957; Bander, 1957; Stotter *et al*, 1957). The effect of these drugs on blood inorganic phosphate and potassium is also conflicting; while some have observed a prompt fall in these constituents accompanying the sulphonamide hypoglycemia (Mohnike and Bibergeil, 1956; Goetz *et al*, 1956; Constam *et al*, 1956; Frawley *et al*, 1957), others have found no demonstrable effect (Renold *et al*, 1956; Purnell *et al*, 1956; De Venanzi, 1957, Elrick and Purnell, 1957).

Studies of the influence of tolbutamide on the blood levels of intermediary metabolites of glucose such as pyruvate and lactate also do not reveal uniform results. In normal subjects Steigerwald *et al*, (1956) found an increase in pyruvate and a decrease in lactate, while Hennes *et al*, (1957) and Recant and Fisher, (1957) observed an initial decrease in blood pyruvate after tolbutamide. The latter authors also observed diminished pyruvate production by diaphragms isolated from rats pre-treated with tolbutamide. Since no increase in pyruvate utilization occurred when such diaphragms were incubated with added pyruvate this would indicate an actual decrease in pyruvate formation in muscle of tolbutamide treated rats. However, Moorhouse and Kark (1956), Renold *et al*, (1956) and Miller[1] *et al*, (1957) could not detect any significant change in either the blood lactate or pyruvate levels in normal or in diabetic patients after tolbutamide.

Effect on Liver

In hepatectomized rats and dogs the sulphonylureas evoke hypoglycemia almost to the same degree as in intact animals (Cox *et al*, 1956b, Dulin and Johnston, 1957). The effect of these compounds on hepatic glycogen levels appears to vary with the dosage, the route of administration, the species, the nutritional state and the timing of the samples. Loubatieres (1944a, 1946b) found that in the dog administration of IPTD resulted in increased deposition of liver glycogen, while Creutzfeldt and Tecklenborg (1955a, 1955b) and Beringer and Keibel (1956) showed that in the rabbit hepatic glycogen remained either unaltered or elevated. However, Holt *et al* (1955b) observed a decrease in the liver glycogen contents of rats treated with IPTD. Administration of non-toxic doses of carbutamide causes less depletion of liver glycogen in the fasting rabbit (Creutzfeldt and Bottcher, 1956 ; Beringer and Keibel, 1956) but of large doses markedly decreases the hepatic glycogen in the dog (Root, 1957). Similarly small doses of tolbutamide favour retention of glycogen in the liver of normal rats and guinea pigs, whereas large doses either abolish this effect or cause slight depletion (Miller[2] and Dulin, 1956 ; Bander and Scholz, 1956; Creutzfeldt and Finter, 1956; Beringer and Keibel, 1956 ; Tyberghein *et al*, 1956 ; Lang and Sherry, 1956 ; Dulin and Johnston, 1957), Studies of the effect of tolbutamide on liver glycogen of rats given a tracer dose of isotopic glucose show conflicting results. Ashmore *et al*, (1957) could not detect any appreciable effect on deposition of liver glycogen by fasted rats one hour after an intravenous injection of tolbutamide (20 mg) while Miller[2] *et al*, (1957) found that tolbutamide (270 mg/kg) when fed to fasted and well-fed rats increased the liver glycogen content of the former but not of the latter, five hours after ingestion of tolbutamide.

That the sulphonylureas interfere with hepatic production of glucose is evidenced by the marked decrease in its output from this organ during treatment with these drugs (Purnell *et al*, 1956, Anderson[1] *et al*, 1956, 1957 ; Kibler and Gordon, 1956 ; Recant and Fisher, 1957 ; Ashmore *et al*, 1957) or during

insulin induced hypoglycemia in the presence of these compounds(Bastenie, 1956 ; Ashmore *et al*, 1957), Corroborative evidence for this comes from the observation that the elevation in blood glucose which usually occurs after infusion of fructose or galactose in diabetic patients is considerably diminished by the previous administration of carbutamide or tolbutamide (Renold *et al*, 1956 ; Moorhouse and Kark 1959 ; Miller[1] and Craig, 1956 ; Miller[1] *et al*, 1957). *In vitro* studies with liver slices obtained from rabbits (Tyberghein *et al*, 1956) and rats (Recant and Fisher, 1957) pretreated with tolbutamide also show a diminished production of glucose. Recant and Fisher (1957) also showed that the decrease in the release of glucose by such liver slices could be correlated with the fall in blood sugar of the intact animal. They also observed that in human beings as the hepatic glucose output decreased following tolbutamide administration, a concomitant rise occurred in the hepatic pyruvate level. This would suggest that the retention of glucose by liver is associated with an increase in its utilization, The increased rate of incorporation of C^{14}—glycine by liver slices removed from rats pretreated with tolbutamide also indicates that the drug increases the over-all metabolism of carbohydrate in the liver.

In vitro addition of the sulphonylureas to liver slices obtained from normal animals shows that at concentrations approximating therapeutic levels they have no significant effect on the release of glucose (Ashmore *et al*, 1956 ; Vaughan 1957) and that the concentrations required to cause appreciable inhibition of glucose production are considerably greater than those necessary for the *in vivo* effect (Mohnike and Kintsch, 1956 ; Berthet *et al*, 1956 ; Clarke *et al*, 1956).

Since glucose–6–phophatase is the immediate enzyme involved in the release of glucose from liver, the effect of the sulphonylureas on the activity of this enzyme has been investigated. Hawkins *et al*, (1956) observed that administration of carbutamide for 3 weeks to normal rats led to a reduction in the glucose–6–phosphatase activity of the liver. Cahill *et al*, (1957) noticed that while a single dose of either carbutamide or tolbutamide was ineffective, a marked decrease occurred in the activity of hepatic glucose–6–phosphatase when the drugs were given every 12 hours for 48 hours. Tyberghein *et al*, (1956) also found a definite decrease in the enzymatic activity in livers of rats given tolbutamide. Kuether *et al*, (1957) as well as Recant and Fisher (1957) could not detect any significant change in glucose–6–phosphatase activity in the liver of rats sacrificed at varying intervals after a test dose of carbutamide or tolbutamide. Incubation of liver homogenates of normal animals with carbutamide or tolbutamide does not decrease the glucose–6–phosphatase activity (Berthet *et al*, 1956 ; Kuether *et al*, 1956 ; Ashmore *et al*, 1956 ; Vaughan 1957) unless relatively high concentrations of the drugs are added. No reduction in the glucose–6–phosphatase activity could be demonstrated in the liver of alloxan diabetic rats treated with a single dose or several doses of these drugs (Kuether *et al*, 1957 ; Haist *et al*, 1957).

Several investigators (Fajans *et al*, 1956 ; Miller[1] and Craig 1956 ; Cox *et al*, 1956a ; Volk *et al*, 1956, 1957 ; Mortimore *et al*, 1956 ; Moorhouse and Kark, 1956 ; Heineman *et al*, 1956 ; Constam *et al*, 1956) have demonstrated that *in vivo* the sulphonylureas do not alter the glycogenolytic effect of either glucagon or epinephrine. However, there are reports indicating that they antagonize the hyperglycemic effect of glucagon in normal animals (Creutzfeldt and Finter, 1956) and in diabetic patients (Izzo and Roncone, 1957) or that they markedly increase the sensitivity to glucagon (Anderson[1] *et al*, 1957). Vaughan (1957) observed a definite inhibition of the glycogenolytic effects of both glucagon and epinephrine in liver slices treated with carbutamide or tolbutamide. However, similar studies by others (Tyberghein *et al*, 1956 ; Berthet *et al*, 1956 ; Clarke *et al*, 1956) have shown only normal responses or that relatively high concentrations are required to cause significant inhibition.

Clarke *et al*, (1956) observed that carbutamide when added to liver slices *in vitro* diminished the uptake of oxygen and the activity of cytochrome oxidase. However, Bander and Scholz (1956) noticed that while small concentrations of tolbutamide did not influence either the oxygen consumption or the succinic dehydrogenase activity of liver homogenates, relatively large concentrations caused inhibition of the aerobic phase of glycolysis.

Purnell *et al*, (1956) noted a decreased bromosulphalein clearance by the liver of normal dogs following intravenous tolbutamide, which would indicate that the drug caused an impairment of liver function. Later studies by Elrick and Purnell (1957) however, did not reveal such an impairment of liver function in normal subjects and diabetic or cirrhotic patients. Per Schambye (1957) as well as Sirek *et al*, (1957) have reported that in normal and pancreatectomized dogs chronic administration of large doses of carbutamide causes a fall in serum albumin concentration and a pronounced decrease in the prothrombin value of the blood and finally development of jaundice. Morphologically and histologically the liver tissue in such cases revealed fatty degeneration.

Effect on Pancreas

The intact pancreas or at least some functioning pancreatic beta-cells appear to be indispensable for the hypoglycemic effect of the sulphonamide compounds. In totally depancreatized human beings (Fajans *et al*, 1956 ; Miller[1] and Craig. 1956 ; Goetz *et al*, 1956 ; Ogryzlo and Harrison, 1956, Cox *et al*, 1956a) and animals (Loubatieres, 1944a ; Houssay and Penhos, 1956 ; Becker *et al*, 1956 ; Sirek and Sirek, 1956 ; Campbell, 1956 ; Gordon *et al*, 1957 ; Per Schambye, 1957 ; Houssay *et al*, 1957a) as well as in the completely alloxan diabetic organism (Chen *et al*, 1956 ; La Barre and Reuse, 1947 ; Loubatieres *et al*, 1956a ; Achelis and Hardebeck, 1955 ; Bander and Scholz 1957, Lang and Sherry, 1956 ; Beringer and Linder, 1956 ; Creutzfeldt and Bottcher, 1956 ; Mirsky *et al*, 1956b ; Dulin and Johnston, 1957) these com-

pounds are ineffective. But in the partially depancreatized man and animal (Loubatieres, 1944a ; Becker *et al*, 1956 ; Miller[2] and Craig, 1956) or in the mildly alloxanized animal (La Barre and Reuse. 1947 ; Achelis and Hardebeck, 1955 ; Loubatieres *et al*, 1956a ; Creutzfeldt and Bottcher, 1956) they readily supress hyperglycemia and glycosuria. Prolonged administration of relatively large doses of tolbutamide in moderately severe alloxan diabetic rabbits without ketosis induces even fatal hypoglycemic shock (Creutzfeldt and Bottcher, 1956).

The perfusion experiments of Loubatieres (1944a, 1946b) and of Colwell *et al*, (1956, 1957) demonstrate that small doses of these drugs which are ineffective systematically cause hypoglycemia when injected directly into the pancreatic artery. However, similar studies by Houssay *et al*, (1957b) using tolbutamide do not confirm this finding. Loubatieres (1946b) demonstrated that blood from the pancreatic but not mesenteric vein of a donor dog treated with IPTD induces a fall in the blood sugar of a recepient alloxan diabetic animal. Similar cross-circulation experiments by Pozza *et al*, (1956) show that carbutamide is also effective.

Although it has been observed by Holt *et al*, (1954 ; 1955a; 1955b) that prolonged treatment with IPTD causes alpha-cell destruction in the rabbit and the rat, Creutzfeldt and Tecklenborg (1955b) could not detect gross lesions of alpha-cells. Loubatieres *et al*, (1955a, 1955b, 1956a) also noticed that only large doses of IPTD caused degranulation of alpha-cells. Chronic, intensive therapy with carbutamide or tolbutamide does not seem to affect the alpha-cells in the rabbit and the rat (Creutzfeldt and Botcher, 1956 ; Creutzfeldt and Finter, 1956 ; Cox *et al*, 1956b ; Volk *et al*, 1956). Infusion of either of these compounds directly into the arterial supply of the pancreas also does not cause any damage to the alpha and beta-cells (Colwell *et al*, 1956). Histological examination of the pancreatic islets of diabetics treated with tolbutamide for more than 6 months also reveals no changes different from that found in the alpha and beta-cells of untreated cases (Creutzfeldt, 1956). Ashworth and Haist (1956) have observed an increase in the weight of the islet tsssue in the pancreas of animals fed carbutamide for several days. Others have reported that prolonged administration of high doses of carbutamide causes degranulation of the beta-cells (Creutzfeldt and Finter, 1956 ; Gepts *et al*, 1955, 1955 ; Holt *et al*, 1956 ; Volk *et al*, 1956, 1957 ; Anderson[2] *et al*, 1957 ; Bander, 1957) or a severe decrease in the amount of extractable insulin (Root 1957).

Effect on Thyroid

Although thyroidectomy does not prevent the hypoglycemic effect of the sulphonamides (Loubatieres *et al*, 1956b,c) there are several reports indicating that these compounds affected the function and histology of the thyroid in experimental animals and human beings. Carbutamide appears more toxic

than tolbutamide in this respect. Achelis and Hardebeck (1956) noticed that feeding of carbutamide induced hypertrophy of the thyroid in rabbits. A similar effect after large doses of tolbutamide was observed by Miller[2] and Dulin (1956) in rats. However, Anderson[2] *et al*, (1957) as well as Houssay *et al*, (1957a) could find hyperplasia of the thyroid only in animals treated with carbutamide but not with tolbutamide. The latter investigators also reported that the thyroids of pancreatectomized and of hypophysectomized-pancreatectomized dogs treated with IPTD for several days, weighed approximately two and a half times as much as those of controls of similar body weight. The studies of Logothetopoulos and Salter in rats as reported by Wrenshall (1957) show that while chronic administration of tolbutamide does not induce any change in the weight or histological picture of the thyroid or grossly affect the uptake of radioiodine, similar treatment with carbutamide seriously depresses the uptake of I^{131} and causes goiter, and that daily injections of thyroxine counteract the goiterogenic effect of carbutamide.

As measured by the uptake of I^{131}, carbutamide has been found to decrease temporarily thyroid function in human beings (Renold *et al*, 1956 ; Brown and Solomon, 1956 ; Fajans *et al*, 1956 : Duncan *et al*, 1956 ; McGavack *et al*, 1956, 1957a), Lowered levels of protein-bound iodine have also been occasionally observed (Brown and Soloman, 1956 ; McGavack *et al*, 1957a) after treatment with carbutamide. Although several investigators (Renold *et al*, 1956 ; Fajans *et al*, 1956 ; McGavack *et al*, 1956, 1957a, Stotter and Creutzfeldt, 1956) have reported no thyroid depressant effect by tolbutamide in dosages up to 2 gm. daily ; a slight lowering of thyroid function has been observed by some with larger doses (Brown and Solomon, 1956 ; Mortimore *et al*, 1956). A recent study (McGavack *et al*, 1957b) of the comparative effects of these two compounds in diabetic patients treated acutely and chronically shows that when a single dose (4 gm.) of carbutamide or tolbutamide is given, the former depresses the uptake of I^{131} strikingly whereas the latter exerts little or no influence. Administration of these drugs (1 or 2 gms) for several weeks causes no significant change either in basal metabolism or in serum protein-bound iodine. Further, while tolbutamide does not appreciably disturb the uptake of radioiodine, carbutamide interferes with this function of thyroid uptill the end of the 9th week, but after 19 to 22 weeks this disturbance subsides and radioiodine uptake and excretion return to normal. This would suggest that the impairment of thyroid function caused by carbutamide is of temporary nature and of no consequence. In hyperthyroidism tolbutamide causes hypoglycemia but does not alter the elevated uptake of I^{131} by thyroid (Bergenstal *et al*, 1957).

Effect on Pituitary and Adrenals

Functional disturbance or extirpation of the pituitary and adrenals does not prevent the hypoglycemic action of the sulphonamide derivatives. While in hypophysectomized animals these compounds induce a normal or slightly

marked hypoglycemic effect, in adrenalectomized animals they produce unusually severe and prolonged hypoglycemia (LaBarre and Reuse, 1947 ; Dulin and Johnston 1957 ; Bertram *et al*, 1955 ; Houssay and Penhos 1956 ; Goetz *et al*, 1956 ;Volk *et al*, 1956 ; Renold *et al*, 1956 ; Lang and Sherry, 1956 ; Gordon *et al*, 1957 ; Houssay *et al*, 1957a). Administration of corticoids or epinephrine and to a lesser extent of glucose exerts a protective action against the hypoglycemic and toxic effects of these compounds in adrenalectomized animals (Dulin and Johnston 1957 ; Houssay *et al*, 1956, 1957a), Hypophysectomized-depancreatized animals do not respond to these drugs (Gordon *et al*, 1957, Houssay *et al*,1957a); but when such animals are made to fast and injected with IPTD or its tertiary butyl derivative (2259RP) a fall in blood sugar occurs. Adrenalectomized-pancreatectomized dogs treated with carbutamide and the tertiary butyl derivative of IPTD (2259RP) exhibit a gradual decrease of blood sugar ; however, when such animals are treated with tolbutamide a progressive rise in blood sugar ensues (Houssay *et al*, 1957a).

In man neither the peripheral effects of adrenal corticoids nor the reduced glucose tolerance caused by cortisone nor the action of ACTH on adrenals is antagonized by these compounds. (Fajans *et al*, 1956 ; Miller[1] and Craig, 1956 ; Volk *et al*, 1956 ; Constam *et al*, 1956 ; Bergenstal *et al*, 1957). In normal men as well as in diabetic patients who respond to these drugs no significant changes occur in the excretion of 17-hydrocorticoids and in the renal clearance of electrolytes and nitrogen (Fajans *et al*, 1956 ; Renold *et al*, 1956 ; Mortimore *et al*, 1956 ; Izzo and Roncone 1957, Erlick and Purnell, 1957). Administration of tolbutamide to acromegalic patients with or without associated diabetes causes hypoglycemia and does not alter the glucose tolerance curve. In patients with coexisting diabetes although the hyperglycemia and glycosuria are controlled no significant changes occur in the urinary excretion of electrolytes and 17-corticosteroids or 17-ketosteroids. In patients with severe adrenal insufficiency tolbutamide produces a similar hypoglycemic effect whether they are maintained on cortisone or not. The response to tolbutamide of patients maintained with cortisone after adrenalectomy or hypophysectomy or hypophysectomy and adrenalectomy also indicates that decreased function of the pituitary-adrenal system does not affect its hypoglycemic effect. (Fajans *et al*, 1956 ; Bergenstal *et al*, 1957).

CLINICAL

Field of usefulness

Clinical trial of IPTD showed that in certain diabetics, the middle-aged obese patients, it exerts a beneficial effect on the hyperglycemia and glycosuria (Loubatieres, 1955), Studies on the comparative effects of the thiodiazole derivatives and the sulphonylureas in this connection show that while the isopropyl (IPTD) and the isobutyl (2256 RP) derivatives are less active than either carbutamide or tolbutamide, the tertiary butyl derivative (2259 RP) is as active and well tolerated as the sulphonylureas (Boulet *et al*, 1956 ; Louba-

tieres, 1957). The sulphonylureas have been tested on a large number of diabetic subjects of varying ages and etiologies. The results of these extensive studies (Franke and Fuchs, 1955 ; Bander *et al*, 1956 ; Mirsky *et al*, 1956a ; Kirtley *et al*, 1956 ; Cox *et al*, 1956a ; Volk *et al*, 1956; Duncan *et al*, 1956; Hunt *et al*, 1956 ; Mckenzie *et al*, 1956 ; Miller[1] and Craig, 1956 ; Beaser, 1956; Kinsell *et al*, 1956; Leibel, 1956; Bruce, 1956; Metzler. 1956; Chase, 1956; Hall *et al*, 1956; Spauldings 1956; Chute and Bain, 1956; Clarke, 1956; Wolff *et al*, 1956; Walker *et al*, 1956; Murray and Wang: 1956; Robbers and Speck, 1956; Kuhl, 1957; Wilderberg and Ricketts, 1957; Talpers *et al*, 1957; Feld and Federman, 1957; Camerini-Davlos *et al*, 1957; Bergenstal *et al*, 1957; Duncan *et al*, 1957; Marble and Camerini-Davlos, 1957; Sherry *et al*, 1957; Sugar, 1957; Beaser, 1957; Dolger, 1957; Stotter, *et al*, 1957;) reveal that after an initial priming dose of more than 2 gm, administration of 1 to 2 gm of the sulphonylureas daily for several days readily diminishes the hyperglycemia and glycosuria, though not always to normal, in approximately half to two thirds of the subjects treated. Carbutamide appears sightly more effective than tolbutamide when equal doses are employed. Continuous treatment for a prolonged period with restricted diet is required to control the disease adequately without supplementary insulin. Cessation of treatment results in the reappearance of diabetes except in exceptional cases. Generally best results are obtained in elderly obese patients with mild diabetes of short duration. Juvenile diabetics as well as those who require large doses of insulin and who readily relapse into ketosis on withdrawal of insulin, show little or no response at all. However, the effectiveness of these compounds seems to depend upon the presence of sufficient endogenous insulin, rather than upon the age of onset or the duration of the disease or the duration of insulin therapy. Single dose test of response, though not entirely reliable, is of value in predicting whether satisfactory control of hyperglycemia and glycosuria might be anticipated on maintenance therapy.

Toxicity

Unfavourable side reactions, largely of a minor nature, such as skin rashes, gastrointestinal disturbances, fever, agranulocytosis, leucopenia, and generallized allergy have been frequently noticed during treatment with the sulphonylureas (Volk *et al*, 1956 ; Beaser, 1956; Cox *et al*, 1956a; Duncan *et al*, 1956 ; Chute and Bain, 1956 ; Wolff *et al*, 1956 ; Walker *et al*, 1956 ; Robbers and Speck, 1956 ; Talpers *et al*, 1957 ; Camerini-Davlos *et al*, 1956 ; Duncan *et al*, 1957; Marble and Camerini-Davlos, 1957; Sherry *et al*, 1957; Sugar, 1957; Dolger;1957 ; Stotter *et al*, 1957). Apparently manifestations of these allergic sequelae do not seem to depend upon the blood level of the drugs as they develop independently of the intensity and duration of treatment, In one compilsation of data (Kirtley, 1957) consisting of about 7000 cases treated with carbutamide approximately 5% experienced such untoward effects. In another study (Marble and Camerini-Davlos, 1957) the incidence of side effects was 9% in

328 patients treated with carbutamide and 0.9% in 314 patients treated with tolbutamide. Liver function tests carried out in patients who had received carbutamide for a prolonged period indicate that though most of the conventional tests remain normal except the van den Bergh reaction in obvious cases of jaundice, the bromosulphalein and alkaline phosphatase tests show increasingly greater incidence of abnormal results. No evidence of impaired liver or renal function has been observed during treatment with tolbutamide. Thus the incidence of side reactions due to tolbutamide appears relatively low and less severe ; however, there is a prominent tendency to gain weight in those patients who respond favourably to tolbutamide. Serious hypoglycemic reactions have also been encountered in several patients treated with carbutamide or tolbutamide. So far 9 deaths have occured during carbutamide therapy which might be directly attributed to the drug (Kirtley, 1957 ; Marble and Camerini-Davlos, 1957).

MECHANISM OF ACTION

Considering their close structural resemblance and similar pharmacological effects the sulphonamide compounds have presumably a common mode of action. Since the level of blood sugar in the post-absorptive state is the resultant of the rate of its removal into the tissues and the rate of its release from the liver, apparently these drugs could lower the blood sugar by affecting either the one or the other or both of these processes. If they accelerate the entry of glucose into the peripheral tissues, they could accomplish this by simulating the action of insulin or by influencing the endocrine systems which have profound effects on carbohydrate metabolism. A direct influence on the pituitary-adrenal system seems unlikely since altered function or absence of the pituitary or adrenals does not prevent the activity of these compounds (La Barre & Reuse, 1947; Dulin & Johnston 1957; Bertram *et al*, 1955 Houssay & Penhos, 1956; Goetz *et al*, 1956; Volk *et al*, 1956; Renold *et al*, 1956; Lang and Sherry, 1956; Fajans *et al*, 1956; Mortimore *et al*, 1956; Miller[1] and Craig, 1956; Constam *et al*. 1956; Gordon *et al*, 1957; Izzo and Roncone, 1957; Houssay *et al*, 1957a; Bergenstal *et al*, 1957). Removal of the thyroid does not affect the activity of these compounds and the impaired thyroid function observed occasionally is also not sufficient by itself to account for their hypoglycemic effect (Achelis and Hardebeck, 1956; Miller[2] and Dulin 1956; Anderson[2] *et al*, 1957; Houssay *et al*, 1957a; Wrenshall; 1957; Renold *et al*, 1956: Brown and Solomon, 1956; Fajans *et al*, 1956; Duncan *et al*, 1956; McGavack *et al*, 1956 1957a,b; Mortimore *et al*, 1956; Stotter and Creutzfeldt, 1656; Bergenstal *et al*, 1957). It would appear, therefore, that the action of these compounds is mediated through the pancreas. If they act through the pancreas, they could exert their effect by activating the release and or production of insulin from the beta-cells or by diminishing the secretion of glucagon from the alpha-cells. It is also conceivable that they may potentiate the action of insulin peripherally by inhibiting its rate of destruction or by enhancing the rate of glucagon degradation. On the other hand, if these drugs decrease the output of glucose

by the liver,they could do so by inhibiting one or more enzymes of the glycogenolytic pathway or the glycogenolytic effects of glucagon.

Insulin like action

There is little evidence to suggest that the sulphonylureas mimic the action of insulin peripherally or lead to increased utilization of glucose in the peripheral tissues independently of insulin. In the eviscerated animal (Fritz *et al*, 1956; Wick *et al*, 1956; Dulin and Jhonston, 1957) they do not alter the rate of glucose utilization. Neither do they affect the volume of distribution of metabolically inert sugars which readily respond to insulin in such preparations (Fritz *et al*, 1956). They do not augment the uptake of glucose or deposition of glycogen by the isolated rat diaphragm. (Clarke *et al*, 1956; Cahii, *et al*, 1957). Evidently they have no "insulin like" effect and they are not substitutes for insulin.

Stimulation of insulin secretion

The concept that the sulphonamide compounds might stimulate the pancreatic betacells to release more insulin into the circulation was originally put forward by Loubatieres (Loubatieres 1944a; 1946a; 1946b, 1946c). The hypertrophy of the pancreatic islet system and the degranulation of beta-cells observed after the administration of these compounds seem to suggest that the pancreatic beta-cells are the preferential site of action of these compounds (Ashworth and Haist, 1956; Loubatieres, 1944a; 1946c; Gepts *et al*, 1955, 1956; Holt *et al*, 1956; Creutzfeldt and Finter, 1956; Volk *et al*, 1956, 1957; Ander son[2] *et al*, 1957, Bander, 1957). That the pancreas is essential for the activity of the sulphonylureas is also borne out by the facts that while they are effective in animals without a liver but with a functioning pancreas (Cox *etal*, 1956b; Dulin and Johnston, 1957), they are ineffective in animals in which both the liver and the pancreas are absent (Fritz *et al*, 1956; Wick *et al*, 1956). The inability of these compounds to depress blood sugar after complete destruction of beta-cells or removal of the pancreas (Chen *et al*, 1946; La Barre and Reuse, 1947; Loubatieres *et al*, 1956a; Achelis and Hardebeck, 1955; Bander and Scholz, 1956; Lang and Sherry, 1956; Beringer and Linder, 1956; Creutzfeldt and Bottcher, 1956; Mirsky *et al*, 1956b; Houssay and Penhos, 1956; Becker *et al*, 1956; Sirek and Sirek, 1956; Campbell, 1956; Gordon *et al*, 1957; Per Schambye, 1957; Houssay *et al*, 1957a; Fajans *et al*, 1956; Miller[1] and Craig 1956; Goetz *et al*, 1956; Ogryzlo and Harrison, 1956; Cox *et al*, 1956b) and their ability to do so when some functional beta-cells are present as after partial pancreatectomy (Loubatieres 1944a; Becker *et al*, 1956; Miller[1] and Craig, 1956) or after the administration of suboptimal amounts of alloxan (La Barre and Reuse, 1947; Achelis and Hardebeck, 1955; Loubatieres *et al*, 1956a; Creutzfeldt and Bottcher, 1956) tend to rule out a primary extra-pancreatic action. Further evidence for such a view comes from the abundant clinical experience indicating their effectiveness in instances where the pancreas is likely to contain some functioning beta-cells or an adequate amount of insulin.

This is substantiated by the autopsy findings of Wrenshall and Best (1956) and of Creutzfeldt (1956) that the pancreas of diabetics who responded to sulphonylureas usually contained amounts of insulin averaging 25% to 30% of the normal, while the pancreas of those who did not respond had practically no extractable insulin. The observation of Bierman *et al*, (1957) and of Renold *et al*, (1957) that administration of tolbutamide resulted in decreased levels of plasma unesterified fatty acids or blood ketones only in those patients who showed a blood glucose response also support the theory that the sulphonylureas stimulate insulin discharge. Such a view is strengthened by the fact that the initial fall in blood sugar elicited by tolbutamide in normal human beings closely resemble the hypoglycemia after intravenous insulin (Diengott and Mirsky, 1956; Hennes *et al*, 1957; Frawley, 1957). However, if the sulphonylureas act by inciting the beta-cells to discharge more insulin into the circulation, it is logical to expect effects similar to those observed after injection of insulin accomanying the administration of these compounds. Thus there should be a fall in blood inorganic phosphate, a rise in blood pyruvate, an increase in the arteriovenous blood sugar difference, improved glucose tolerance, increased deposition of muscle glycogen, increased breakdown of glucose etc. Attempts to demonstrate these effects have yielded conflicting results. The fact that hypophysectomized animals do not exhibit extreme hypoglycemia when treated with the sulphonylureas also seems to be incompatible with excitation of beta-cells. Besides, whereas an increase in plasma insulin activity (rat diaphragm method) is demonstrable after injection of insulin to normal subjects; no such increase is evident after administration of tolbutamide (Renold *et al*, 1957).

INHIBITION OF INSULINASE AND POTENTIATION OF INSULIN ACTION

There is some experimental evidence to suggest that the sulphonylureas might prolong the effect of circulating insulin or enhance the action of exogenous insulin. In healthy subjects administration of tolbutamide produces an almost identical response in the blood sugar as after intravenous injection of insulin (Diengott and Mirsky, 1956), Although in both instances the same degree of hypoglycemia is produced in the first half hour there is a significant delay in the return of blood glucose to control values after tolbutamide. Mirsky *et al*, (1956a,c) attributed this difference in the response to tolbutamide to a decreased rate of destruction of the insulin discharged into the circulation They, therefore, postulated that the sulphonylureas might be acting by inhibiting the liver enzyme, insulinase, which normally destroy insulin. In support of this hypothesis they (Mirsky *et al*, 1956b) demonstrated a marked reduction in the insulinase activity of the livers of rats one hour after treatment with tolbutamide. However, the contention of Mirsk y*et al*, (1956a,b,c) has not been borne out by experiments with labelled insulin. While Cox *et al*; (1956b), Berson *et al*, (1957) and Volk *et al*, (1957) have shown that the sulphonylureas in doses sufficient to induce significant hypoglycemia do not alter the rate of

metabolic degradation of insulin-I^{131} in the intact organism; Wick *et al*, (1957) have reported that tolbutamide does not influence the rate of insulin-I^{131} degradation in eviscerated preparations. It has also been demonstrated that at concentrations approximating to those causing marked hypoglycemia *in vivo*, they do not inhibit insulinase *in vitro* (Vaughan, 1957) and that the concentrations required to cause significant inhibition are of such a magnitude as to suggest that inhibition of insulinase is not the way they act, (Berson *et al.* 1957; Williams and Tucker, 1956), However, Young (1956) has advanced the hypothesis that the sulphonylureas might be acting by inhibiting certain bacterial flora which usually inhabit the liver of many species and which normally destroy insulin. This might no doubt explain the action of carbutamide or of the thiodiazole derivatives, but it would hardly account for that of tolbutamide which is devoid of bacteriostatic activity, unless its metabolic degradation produces a chemotherapeutically active derivative.

However, that the chronic administration of the sulphonylureas might enhance the action of insulin, whether through inhibition of insulinase or through other means, is evident from the lowering of blood and urine glucose observed in totally depancreatized dogs maintained on sub-optimal amounts of insulin (Sirek and Sirek, 1956; Campbell, 1956; Becker *et al*, 1956; Houssay *et al*, 1957b; Ricketts *et al*, 1957). The ability of these substances to supress hyperglycemia and glycosuria in partially depancreatized and mildly alloxan diabetic animals as well as in certain diabetic patients is also compatible with, though does not prove, a potentiation of the available insulin. Although Mirsky and Diengott (1957) have found a marked enhancement of injected insulin in diabetic patients who did not respond to the sulphonylureas alone, acute experiments on depancreatized human beings (Goetz *et al*, 1956; Ogryzlo ahd Harrison, 1956; Cox *et al.* 1956a; Craig and Miller, 1957) and animals (Fritz *et al*, 1956) and on severely alloxan diabetic animal (Dulin and Johnston, 1957) do not demonstrate any potentiation of injected insulin. The failure of these drugs to alter the insulin sensitivity curve (Fajans *et al*, 1956; Cox *et al*, 1956a,b; Bastenie, 1956; Constam *et al*, 1956; Smith and Kumar, 1956; Anderson[1] *et al*, 1957) or to augment the effect of added insulin on the uptake of glucose by isolated rat diaphragm (Wrenshall, 1957) also suggests a similar conclusion.

Alpha-cell depression

Holt and associates (Holt *et al*, 1954, 1955a; Holt and Ferner, 1955) on the basis of their observation that prolonged treatment with IPTD caused alpha-cell destruction postulated that the hypoglycemic effect of the compound might be due to a diminished release of glucagon and the consequent uncompensated action of insulin. Although the investigators (Franke and Fraches, 1955; Achelis and Hardebeck 1955; Bertram *et al*, 1955) who first studied the pharmacological effects and therapeutic usefulness of carbutamide discussed its mode of action from such a standpoint there is not enough

histological evidence to give such a functional interpretation (Creutzfeldt and Bottcher, 1956; Creutzfeldt and Finter, 1956; Cox *et al*, 1956b; Volk *et al*, 1956, 1957). *In vivo* and *in vitro* studies with labelled glucagon also indicate no significant alteration in the rate of its degradation in the presence of therapeutic levels of sulphonylureas (Berson *et al*, 1957; Volk *et al*, 1957). It is, therefore, unlikely that the action of these compounds is mediated through the alpha-cells or through stimulation of glucagonase activity.

Interference with hepatic glycogenolysis

Several investigators are of the view that the sulphonylureas induce hypoglycemia probably by affecting the release and uptake of glucose by the liver. support for such a view is adduced from the ineffectiveness of these compounds to influence peripheral utilization of glucose and from their capacity to diminish the hepatic output of glucose (Purnell *et al*, 1956; Anderson[1] *et al*, 1956, 1957; Kibler and Gordon, 1956, Recant and Fisher, 1957; Ashmore *et al*, 1957) especially that derived from fructose or galactose (Renold *et al*, 1956; Moorhouse and Kark, 1956; Miller[1] and Craig, 1956; Miller[1] *et al*, 1957). The findings that the liver glycogen of fasted animals treated with these drugs tends to increase or remains unaltered (Loubatieres, 1944a,1946b; Creutzfeldt and Tecklenborg, 1955: Beringer and Keibel, 1956; Miller[2] and Dulin, 1956. Bander and Scholz, 1956; Creutzfeldt and Finter, 1956; Tyberghein *et al*, 1956; Dulin and Jhonston, 1957) would suggest that while glycogenesis is not affected, glycogenolysis is diminished. In accord with this view is also the demonstration that liver slices obtained from animals pretreated with the sulphonylureas show a decreased production of glucose (Tyberghein *et al*, 1956; Recant and Fisher, 1957). However, a diminished production of glucose by liver slices could not be demonstrated *in vitro* when they were incubated with these drugs in concentrations approximating to those necessary for producing hypoglycemia in vivo (Mohnike and Kintsch, 1956; Berthet *et al*, 1956; Clarke *et al*, 1956).

Attempts to show that the site of action of the sulphonylureas in this regard is on the liver enzyme glucose-6-phosphatase, have not given convincing evidence. While it has been shown that chronic administration of these drugs causes a significant reduction in the activity of this enzyme, in no instance could the hypoglycemia produced after a single dose be correlated with a decrease in the activity of glucose-6-phosphatase (Cahill *et al*, 1956; Hawkins *et al*, 1956; Tyberghein *et al*, 1956; Kuether *et al*, 1957; Recant and Fisher, 1957). *In vitro* addition of these compounds to liver slices in concentrations approximating to those necessary for producing hypoglycemia *in vivo* also does not decrease the activity of glucose-6-phosphatase (Berthet *et al*, 1956; Kuether *et al*, 1956; Ashmore *et al*, 1956; Vaughan, 1957). Addition of relatively high concentrations of these compounds, no doubt, causes significant inhibition of glucose-6-phosphatase but this shows that the sulphonylureas in high concentrations might act as general enzymatic poisons, rather

than specifically inhibit a particular enzyme. The finding that repeated administration of these drugs diminishes the activity of liver glucose-6-phosphatase only in normal animals, but not in diabetic ones (Haist, *et al*, 1957) could be explained without invoking a direct effect on glucose-6-phosphatase. Since it has been observed that insulin reduces glucose-6-phosphatase activity, it is possible that the reduction of activity observed after prolonged treatment with the sulphonylureas might be due to the insulin released.

The observation that tolbutamide in low concentrations markedly inhibits the effects of epinephrine and glucagon on glucose release by liver slices would indicate that the hypoglycemia produced by the sulphonylureas *in vivo* might be due to an inhibition of the phosphokinase system which activates liver phosphorylase (Berthet *et al*, 1956; Vaughan, 1957). However, several studies on the glycogenolytic effects of glucagon and epinephrine with isolated liver tissue (Cox *et al*, 1956b; Clarke *et al*, 1956) and in the living organism do not warrant such a concept.

The fact that only hepatectomized animals that possess a functional pancreas respond to these drugs evidently indicates that liver is not essential for their activity (Fritz *et al*, 1956; Wick *et al*, 1956; Dulin and Jhonston, 1957). Finally, if the sulphonylureas lower blood sugar by primarily affecting some hepatic mechanism it is difficult is explain why they do not depress the blood sugar after complete removal or destruction of the pancreatic beta-cells or in the severely insulin deficient diabetic.

It is doubtful whether the discovery of the sulphonylureas has furnished us with the ideal oral antidiabetic agents for which searches were made during the past decades. Their only advantage over insulin is the convenience of oral administration. Their field of usefulness is limited, as they are ineffective in severely insulin deficient diabetics. Nevertheless, the initial hopes these compounds raised as potential anti-diabetic agents seem to be justified in a way, by their ability to diminish or abolish hyperglycemia and glycosuria in a great majority of diabetics. It is still uncertain whether they accomplish these by increased utilization of glucose and whether their continued administration is devoid of harmful effects. Already, the side reactions and toxic effects encountered with carbutamide have necessitated its withdrawal from therapeutic use. Although several suggestions have been put forward to account for the hypoglycemic and anti-diabetic effects of the sulphonylureas, the precise mode of action of these compounds is still unknown. Despite some controversial points, there is much evidence in favour of the original concept of Loubatieres that these compounds activate the release of insulin from the islets of Langerhans. There is also some evidence to believe that they inhibit the metabolic degradation of insulin or exert a synergistic or potentiating action. Apparently they influence the hepatic output and uptake of glucose, but it is yet to

be ascertained whether this is a direct or indirect effect. Whatever be the exact mechanism of action, the fact that insulin is essential for the activity of these drugs has intensified the enquiries into the formation and liberation of this hormone and its metabolic fate.

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