INTRODUCTION PART - I
Diabetes Mellitus is a disease known since the time of Hippocrates. Of all the maladies that plague mankind few have a more ancient recorded lineage than diabetes mellitus. Four thousand years ago the Egyptians chronicled the symptoms of the disease. Two thousands years later physicians of the period of Christ described it in more detail, and by the time that Aretaeus the Coppadocian came along in the second century A.D. it had acquired at least part of the name by which it is known to day, for Aretaeus wrote that "Diabetes is a wonderful affection, being a melting down of the flesh and limbs into urine, the patients never stop making water but the flow is incessant, as if from the opening of aqueducts. The patient is short-lived, for the melting is rapid, the death speedy. Moreover life is disgusting and painful, thirst unquenchable, drinking excessive."

In naming the disease "diabetes" (meaning "to pass through") the Greeks gave recognition to one of its most conspicuous symptoms: the rapid passing of water through the body. Later the Romans noticed that the Urine of diabetics had a sweet taste and that bees swarmed around it, so that they elaborated
the name by adding "mellitus", the latin word for "Sweet as honey".

Diabetes Mellitus was known to the physicians in ancient India. Two books published over 2000 years ago (Charaka Samhita and Sushruta Ayurveda) give detailed descriptions and the aetiology, diagnosis and treatment. Diabetes or Madhumeh was one of the 20 varieties of urinary disorder resulting from provocation of the body humours. Four, including diabetes, were considered to be incurable, Glycosuria and diabetes were apparently distinguished, glycosuria was caused by "Kapha" and was curable, whereas diabetes was caused by vata and was incurable.

Glycosuria was described thus "That person who passes urine which is exceedingly sweet, cool, slightly viscid, turbid and resembling the juice of sugar cane, owing to the provocation of Kapha suffers from glycosuria", and diabetes "If vata by its dry quality changes the vital essence which is naturally of sweet taste into one of astringent taste and carries it to the urinary organs, then it causes the condition called madhumeh." The importance of heredity and obesity as predisposing factors in the development of diabetes were appreciated — "There are two types of urinary disorders — one natural due to genetic factors and the other due to indiscrete living or dietetic
indiscretions. The patient suffering from the former is thin, pale, eats less and drinks too much .... the patient with the later is usually obese, eats a lot, is stout and of sedentary habits and sleeps too much. Charaka noted that persons with congenital urinary disorders as those born of diabetic parents are incurable owing to germoplasmic morbidity. He also recorded that addictions to the pleasures of sitting, sleeping, the excessive use of curds (yogurt) meat-juice of domestic, aquatic and wet land animals, milk, freshcrop food grains and drinks and products of jaggery and all things that increase Kapha are the caustive factors of anomalies of urinary section.

The sings and symptoms were described by both authors. According to Sushruta, an important characteristic of diabetes was "If walking, he would like to stand if standing, he would like to sit, ; if sitting, he would like to lie down, and if lying down he would like to sleep."

Therapy of the disorder consisted of massage, emesis and purgation, after which cleansing of the system the regular treatment would commence. Diet was important. Barley and green gram (Phaseolus aureus, roxb) were emphasized by Charaka, while Sushruta described schedules for the rich man who did not co-operate, the indigent, the Brahmin and the lowly. He appreciated the importance of exercise and listed different sets
of exercises - from digging a well to following a cow in the jungle. Herbal and mineral remedies such as Shilajeet, an exudate from rocks in the Himalayas, were also used.

Similar reference to diabetes as a urinary disease occurred in a Singhalese writing, "Yoga Ratnakaraya", written in the fifteenth century.


A large number of plants have also been used in the folk medicine of other countries. The subject has been reviewed by

A short account of some plants reported to have antidiabetic properties is given below:

(1) *Scoparia Dulcis* Simn (Scrophulariaceae): A purified extract of this plant was prepared and tested by Nath (science and culture 1941–2, 7, 572) and found to give considerable relief from hyperglycemia, glycosuria, acidosis and acetonuria associated with diabetes mellitus (Ann. Biochem. Exper. Med. 1945, 5, 11) Winttaker (Brit. Med. J. 1948, 1, 546) could not substantiate these observations.

(2) *Gymnema sylvestre* (Asclepiadaceae): It contains gymnemic acid (C_{32}H_{55}O_{12}, quercital and hentriacontane (C_{31}H_{64}) Mhas Ran and Caius (Ind. Med. Res. Mem. 1930, No. 16, 1) and Guruswami, et al., (current Med. Prac. 1959, 2, 227) found that its leaves caused hypoglycemia in experimental animals. Recently Khastgir, et al., (Ind. Chem. Soc. 1958, 35, 650) have isolated an amorphous substance from this having antibiotic activity.

(3) *Coccinia Indica* (C. cardifolia) also shows antidiabetic activity (De and Mukherji, Ind. J. Med. Res. 1956, 44, 59a;
(4) Momordica charantia (Cucurbitaceae) also shows blood sugar lowering activity (Sharma, et al., Ind. J. Med. Res. 1960, 48, 471). Wood extract of ptero carpus Marsupium (Leguminoseae) was effective in lowering blood sugar in rabbits and in diabetic patients (Ojha, et al., Ind. J. Med. Pharmacy, 1949, 11, 188).

Rauwolfia Alkaloids (Apocynaeceae) - Reserpine shows hypoglycemic actions (J. Parmacol. Exp. therap., 1957, 142, 1886) while serpine shows hypoglycemic activity. (Chatterjee and co-workers, Bull. calcu. Sch. Trop. Med. 1957, 2, 172)


In interpreting the results obtained with these and similar preparations, it is necessary to keep in mind that a substance may be hypoglycemic without being able to correct the faculty metabolism of diabetes. It appears that certain oral preparations do have properties which alleviate some of the symptoms characteristic of diabetes mellitus. Extracts which contain tannins appear to decrease the distressing diabetic thirst, others which due to their nauseating or narcotic properties depress the
appetite, decrease blood and urine sugar levels and reduce acidoses, but this effect is produced by the reduced intake of food. In this respect, many of the successes attributed to alleged insulinoid preparation may be attributed not to the drug but to the strict diet imposed. It appears highly probable that in these cases, the diet alone would have an equally beneficial effect (Lewis, J. J. loc. cit.).

Some of the important hypoglycemic principles of known chemical structure which have been obtained from plants are mentioned below:

Galegin (isoamylencyl guanidine) from seeds of Galega officinalis (Tanret, Bull. Soc. Chim., 1924, 35, 404) has been found to be orally active but is toxic.

Hassal, et al., (Nature, 1954, 173, 356) isolated from the fruits of Blighia Sapida two substances hypoglycein A and hypoglycein B which are capable of lowering blood sugar but are toxic.

\[
\begin{align*}
\text{Hypoglycein A} & \quad \text{NH}_2 \quad \text{O} \\
& \quad \text{CH}_2 \quad \text{CH} \quad \text{CH}_2 \quad \text{CH} \quad \text{C} \quad \text{OH} \\
& \quad \text{CH}_2 \\
\end{align*}
\]

Hypoglycein B is a dipeptide glutamic acid oxide of hypoglycein A.
To the close of nineteenth century and the beginning of twentieth century, knowledge of the disease appears to have progressed but little. Physicians did learn, to be sure, that the illness might be controlled to some extent by extremely rigid diet, excluding many of the foods that the average craves. This method was a drastic one, however, for as one diabetic specialist has written since: "It was no fun to starve a child to let him live." Patients might continue to exist for five or six years under such a regimen, but only at the cost of a continual morbid preoccupation with the thought of food, an incessant hunger that was likely to make of life a savourless ordeal, with temptation to forbidden indulgence a constant threat.

And accompanying this near starvation there was always the likelihood of crippling or fatal complications. Some diabetic patients developed gangrene and had to have their feet amputated; others suffered agonies from neuritis and were free from pain except by addiction to morphine. Still others were victims of pneumonia, tuberculosis, or acidosis. Boils and carbuncles were frequent and often resulted in blood poisoning and death. A wound which in an ordinary person might have been trivial usually led to serious infections in a diabetic, while a surgical operation meant almost certain death.
What was the reason for this strange malady, with all its complications? For more than a quarter century before Banting undertook his experiments there had been general agreement that the immediate cause of diabetes was the failure of the pancreas to secrete enough of certain mysterious substance necessary for the proper utilization of carbohydrates as body fuel. As a result of this failure the unassimilated sugar was constantly passing out of the body into the urine, while the victim of the disease, failing to get any value from most of his food, was growing thinner and thinner and thirstier and thirstier, for he had to drink great quantities of water in order to dissolve the excess sugar for excretion. Intermediary products in the metabolism of fats and proteins, ketones or acetone bodies also appear in the blood and urine and their presence in large amounts is associated with diabetic coma and acidosis. Several subtypes of diabetes mellitus are recognised particularly the juvenile form, the senile form and the diabetes associated with obesity.

Besides the significant part of the failure of pancreatic secretion many factors are known to play a part. The most important are heredity, endocrine gland disturbances - chiefly involving the pituitary, the adrenal cortex and the thyroid,
obesity and, a variety of factors such as age, sex, race, infection etc.

Diabetes mellitus is on the increase all over the world. Recent organised study by the United States Public Health Service in Oxford, Mass., suggests that there are now in the United States over two million diabetics, and almost half of that number are unaware they have ailment. Approximately 4,750,000 other persons living today are potential diabetics, and about 65,000 persons become diabetic each year.

**Discovery of Insulin**:

Fred Banting (1891 - 1941) was instructor in physiology laboratory. He had to prepare assignments for students and give explanation and demonstration. In one of the assignment that he was preparing from a text book, it was mentioned that the removal of pancreas was followed by the development of diabetes. If some student asked, why the removal of pancreas leads to diabetes, Banting had no explanation. He searched in vain, through medical journals to find an explanation. Neither from the library nor from the dissecting room or microscope did he find just what he wanted to know. The only way to find out was to find out.

Sitting in his deserted office one evening he was reading the current number of "Surgery, Gynecology, and Obstetrics",
he came upon an article which noted an observation that glands of the pancreas secreting vital digestive ferments were likely to atrophy if gallstones obstructed the passage ways from the pancreas to the small intestines, that these glands would also shrivel when the pancreatic ducts were tied. The idea: "tying of the pancreatic ducts," excited Banting. It haunted him so much, that on that night he found sleeping impossible. At last he crawled out of bed in the dark, found the light, found his notebook, and scribbled "Ligate the pancreatic ducts of dogs. Wait six to eight weeks for degeneration. Remove the residue and extract." Treating the diabetic dog with the pancreatic extract was the logical step that he conceived.

On the 30th of July 1921 Banting and his collaborator, Best, took a diabetic dog which sank into coma, injected the newly made extract into its veins. Within a few hours they began to see signs of returning strength in the dog, which actually seemed to be coming out of its coma. This was something which no diabetic dog had ever done before. Quickly they made their test and found the urine free of sugar and blood sugar reduced to a normal level.

It was a solemn moment. They had found their "X" whose absence in pancreatic secretion developed diabetes and whose presence cured it. They named it "isletin" from the
name of islets of Langerhans which was later changed to Insulin.

The work of Sanger on insulin represents one of the greatest achievements in protein chemistry because it was the first to provide the complete amino acid sequence of a well-defined and most useful protein.

**Synthetic agents**

The fact that plant kingdom had not yielded any active antidiabetic principle, that the synthesis of insulin, or its oral use, was only a remote possibility and that every diabetic developed antibodies against insulin within 2-3 weeks revealing an inherent potential defect in this form of therapy (Forsham, Ann. N. Y. Acad. Sci., 1959, 82, 64D) had created a keen interest in finding a synthetic substitute of the hormone. Long acting insulins too could not abate this interest. The accidental discovery of the hypoglycemic action of carbutamide set off a world-wide research for insulin substitutes which could be effective when given orally. The more important groups of these synthetic hypoglycemic agents are discussed below.

The following types of compounds show hypoglycemic activity:
1. Salicylates
2. Guanidines
3. Sulfathiazoles
4. Sulfonylurethanes
5. Sulfonylurethane - Amine salts
6. Sulfonylthioureas
7. Sulfonyl ureas
8. Miscellaneous DERIVATIVES

1. Salicylate :

Salicylate and other benzoic acid derivatives have been used for several decades in rheumatism therapy. There are also numerous experimental and clinical publications on the blood sugar lowering properties of these drugs.

The hypoglycemic action of Salicylic acid (I) in diabetes mellitus has been known for a considerable time (Ebstein, Bert. Klin. Wschr., 1876, 13, 337-340; Bartels, Dtsch. Med. Wschr. 1878, 435-437; Nicolaier, Ther. Mh. 1893, 7, 102; Williamson, Brit Med. J., 1901, 1, 760-762). Sodium Salicylate (II), methyl salicylate (III) acetysalicylic acid (aspirin) (IV) and 2,3-dihydroxy sodium benzoate (3-hydroxy sodium salicylate) (V) were among the drugs which effectively reduced the total daily urinary glucose output in diabetic patients (Miller, Bert. Klin. Wschr. 1877, 14, 29 Smith, Ann. N.Y. Acad.
Aspirin was used in many clinics but was abandoned even before the advent of insulin, because of its unpleasant side effects particularly vomiting with worsening of ketosis (Gross and Greenberg, "The salicylate" p. 108, Hillhouse press, New Haven (1948). In 1957 clinical interest in aspirin as hypoglycemic agent was again aroused when Reid and coworkers reported an improvement in the state of some of their diabetic patients given fairly large doses of aspirin (Brit. Med. J. 1957, 2, 1071). Salicylates reduce the glycosuria and hyperglycemia in experimental diabetic animals like insulin, facilitate the entry of glucose into muscle. In diabetic patients the glycosuria may be abolished and the blood sugar lowered with subsequent clinical improvement. There is an insulin sparing effect and the action of synthetic diabetic drug may be enhanced (Smith, loc. cit.)

Hypoglycemic activity of the salicylates is in some way related to their ability to inhibit intracellular phosphorylation without interfering with the oxidative process in the cell (Brody. J. Pharmacol. 1956, 117 39).
2. GUANIDINES:

After the hypoglycemic activity of guanidine was published. Frank et al., (Klin wschr., 1926, 5, 2100) were the first to attempt a systematic variation of the guanidine molecule.

The active derivatives belonging to this group can be divided into three classes.

(i) Monoguanidines
(ii) Diguanidines
(iii) Biguanides

(i) **Monoguanidines**: Amongst the monoguanidines it was observed that the substituting group must have a free amino group for activity. Agmatine and guanyl piperidine belong to this category (Frank, et al., Klin wschr. 1926, 5, 2100; Bischoff, J. Biol. Chem., 1928, 81, 325).

\[
\begin{align*}
H_2N &- CH_2 - CH_2 - CH_2 NH - C &\xrightarrow{\text{Agmatine}} \\
&\phantom{-} NH_2 & \\
&\phantom{-} NH & \\
&\phantom{-} NH & \\
\end{align*}
\]

\[
\begin{align*}
\text{CH}_2 &- \text{CH}_2 &\xrightarrow{\text{Guanyl piperidine}} \\
\text{NH} &-\text{NH} & \\
\end{align*}
\]

Galegine found in the seeds of "goats clover" which is isoamylene guanidine has a significant blood sugar lowering activity (Muller, et al., Arch. Expt. Path. Pharmak; 1927, 125, 212). This indicates that an amino group in the lateral
chain is not always necessary.

\[
\begin{align*}
\text{CH}_3 & \quad \text{C} = \text{CH} - \text{CH}_2 - \text{NH} - \text{C} - \text{NH}_2 \\
\text{CH}_3 &
\end{align*}
\]

B-phenylethyl guanidine (Kroneberg, et al, Arznei mittel, Forsch., 1958, 8, 470) also possesses blood sugar lowering activity. However this activity is not very significant.

\[
\text{C}_6\text{H}_5-\text{CH}_2-\text{CH}_2-\text{NH}-\text{C} - \text{NH}_2
\]

(ii) **Diguanidines**: These have the general formula

\[
\begin{align*}
\text{NH}_2 & \quad \text{C} - \text{NH} - (\text{CH}_2)_n - \text{NH} - \text{C} - \text{NH}_2 \\
\text{HN} &
\end{align*}
\]

It was found that the blood sugar lowering effect of diguanidines increased proportionately with the lengthening of the aliphatic chain.

Thus pentamethylene diguanidine (\( n = 5 \)) is three times while decamethylene diguanidine (\( n = 10 \)) is as much as 150 times as active as guanidine. The later has been introduced in diabetes therapy as synthalin A.

Dodecamethylene diguanidine (\( n = 12 \)) synthalin B or synthalin neu is less active as compared to synthalin A.

(iii) **Biguanides**: These have the following general formula.
Studies by Slotta and Tsheshe (Ber. Dtsch. Chem. Gesell Sch. 1929, 62B, 1393) and Hesse and Taubmann (Naunyn Schmiedeberg's Arch. Exp. Path. Pharmak., 1929, 142, 290) indicated that mono substituted biguanidines are more active as compared to disubstituted derivatives.

Among the alkyl biguanidines

\[
\text{CH}_3(\text{CH}_2)_n - \text{NH} - \text{C} \equiv \text{C} - \text{NH}_2
\]

N, n-butyl, n-amyl and isoamyl derivatives show significant activity (Shapiro, loc.cit. Söling, et al., Internationales Biguanide - symposium stuttgart G. Thieme (1960), p. 17; Williams, Tenner and Odell, Diabetes 1958, 7, 87) n-butyl biguanide is introduced in therapy under the name-silubin (w 37) in Germany.

With the lengthening of the carbon-chain beyond 6 decreases the activity which disappears with a chain length of 10 carbon atoms.

Benzyl and B-phenethyl biguanides are also active blood sugar lowering agents (Shapiro, symposium, Barlov University...
The latter substance was introduced in therapy under the name DBI in U.S.A. (Ungar, Roc. Soc. Exp. Biol., 1957, 22, 190)

3. SULFATHIADIAZOLEs:

5-isopropyl-2-p-aminobenzenesulphanilamide-1:3:4-thiadiazole (I), first prepared by Rhone-poulence as Rp 2254 was originally tested against bacteria in 1941 (Von kennel, et al., Klin. Wschr., 1941, 20, 2) but in the following year was found by accident to have a strong hypoglycemic action in man (Janbon et al, Montpellier med., 1942, 21 - 22, 441)

\[
\begin{align*}
\text{isopropyl}- & -C_5^5
\end{align*}
\]

Bovet and Dubost (C.R. Soc.Biol., Paris, 1944, 138, 764) and Loubatieres (ibid, 1944, 138, 830) tested about 165-alkyl analogs of (I) and found that several produced hypoglycemia, the tert-butyl, iso-butyl, n-pentyl and n-butyl derivative being most active, in decreasing order. Kiyoshi Kawahara prepared thiadiazole derivatives of the type

\[
\begin{align*}
R & - C_5^5
\end{align*}
\]

(R and \( R' \) respectively are p. Me. ph, iso.Bu; p.Me\(^2\)Cph,iso-Bu, o-Me.ph, Fr; 2:4-Me\(^2\)ph, iso.Bu) and found them to be effective
in the treatment of Diabetes (Japan patent 12,580 ('60)
Sep. 2 - Chem. Abstracts 1961, 55, 571) 2-(2-chlorobenzene
sulfonamide-5-alkyl-1:3:4-thiadiazoles (alkyl groups are
Me, CH, sec. Bu, t-bu, hex) are reported to have hypoglycemic
action (British patent 824, 978 (1958) - Chem. Abstracts
1960, 54, 8853). Francis et al, has reported thiadiazole
derivatives of the type.

\[
\begin{align*}
\text{R} - \text{C}^5 & \quad \text{NH} - \text{SO}_2 - \text{R} \\
\text{S} & \\
\end{align*}
\]

\( \text{R} = \text{p-Me, p-MeO, p-\text{EtO, p-Cl, p-iso-Pr Bu, iso-Bu, sec-Bu, pentyl, iso-pentyl}} \) and found them
to be hypoglycemic (Can.J.Chem., 1959, 27, 1121-3)

4. SULFONYLURETHANES:

In a recent German patent (1,026,742 Mar. 27, 1958 -
Chem. Abstracts 1961, 55, 19664) Walter Aumuller has reported
some Benzenesulfonyl urethanes - 4-\text{CH}_3\cdot\text{C}_6\text{H}_4\cdot\text{SO}_2\text{NNa, CO}_2(\text{CH}_2)_2\text{ph},
4-\text{CH}_3\cdot\text{C}_6\text{H}_4\cdot\text{SO}_2\text{NNa, CO}_2(\text{CH}_2)_2\text{ph} \) and 3,4-(\text{ CH}_3\text{O})_2\text{C}_6\text{H}_2\cdot\text{SO}_2\text{NNa}
\text{CO}_2(\text{CH}_2)_2\text{ph}. The compounds are good oral antidiabetics without
undesirable side effects common to sulfonamides. The same
author has found a blood sugar diminishing effect in Bu,
N-(2-naphthylsulfonyl) urethane, Bu N-(5,6,7,8-tetrahydro-
2-naphthylsulfonyl) urethane (Bu=butyl) (German patent
and also in N-(p-tolylsulfonyl)-2-Methoxy-ethyl urethane, N-(p-chlorophenylsulfonyl)-2-Methoxyethyl urethane (German patent 1,075, 105 Feb. 11, 1960 Chem. Abstracts 1961, 55, 14380). Werner Loop et al, prepared the urethanes of the type \( \text{X.C}_6\text{H}_4\text{SO}_2\text{NH.CO}_2\text{R} \), where \( \text{R} = \text{Me or Et and X} = \text{halogen or alkoxy groups} \) and found them to be useful as oral antidiabetic compounds (German patent 1,028, Apr. 24, (1958) Chem. Abstracts 1960, 54, 14190. German patent 1029, 819 May 14, (1958) Chem. Abstracts 1960, 54, 13435) Et p-carbamido-benzenesulfonylcarbamate and Me p-(butylo carbamidobenzene- sulfonylcarbamate are also useful as oral antidiabetic compounds prepared by the same author (German patent 1,027, 196 Apr. 3, 1958 Chem. Abstracts 1960, 54, 10959). Alois Novacek et al, has reported antidiabetic activity in p-CH\(_3\) - C\(_6\)H\(_4\)SO\(_2\)NH.CO.OBu and in p-CH\(_3\).C\(_6\)H\(_4\).SO\(_2\).NH.CO.OEt (Czech. patent 96,582 Chem. Abstracts 1961, 55, 15420).

5. **SULFONYLURETHANE - AMINE SALTS**:

Urethane react with organic amines and form Amine salts. K.Lanyi et al, has described the preparation of \( \alpha\)-hexylamine allylamine, iso-butylamine, piperidine, iso-propylamine, n-amylamine, n-octylamine and n-laurylamine salt with p-x-C\(_6\)H\(_4\).SO\(_2\).NH.CO.OEt (X = H, Me, Eto, MeO, Cl, Ac.NH, 3:4-Cl\(_2\), 4:5-Ne(Ac.NH) urethanes and found them to be producing marked
Kalman et al. have also described aliphatic amines salts of the R - C₆H₄SO₂NH.CO₂Et (R = H, Me, Ac.NH, NH₂) urethane having significant hypoglycemic activity (Austrian patent 214, 936 May 10, 1961 - Chem. Abstract, 1961, 55, 17579).


6. SULFONYLTHIOUREAS:

Sulfonyl thioureas are also reported to have hypoglycemic action. p-toluenesulfonyl thiourea, p-CH₃C₆H₄SO₂NH.C.NH.Bu (butyl) and Bu.NH.C.NH.CH₂COOH have been reported by Budesinsky et al. to show hypoglycemic activity (Ceskoslov. Farm 8, 129-35 (1959) - Chem. Abstract 1960, 54, 3197).

Alkylsulfonyl ureas and thioureas of the type Bu.SO₂NH.C₅NH.R where R = ph, p-Cl-ph, p-tolyl, ph.C₂H₅, prepared by Polazzo et al. produce hypoglycemia in the rabbits after oral administration (Farmaco (pavia) Ed. Sci. 14, 358-62 (1959) Chem. Abstracts 1960, 54, 5532). Friedric prepared R.SO₂NH.C₅NH.C₄H₁₀.C₂H₄ sulfonylthioureas derivatives (R = Me, Bu, Ac.NH, C₆H₄). The compounds reduce glucose content of the blood and can be applied orally (German patent (east))
7. SULFONYL UREAS:

Carbutamide (p-NH$_2$C$_6$H$_4$.SO$_2$.NH$.CONH.(CH$_2$)$_3$.CH$_3$) was first tested as an antidiabetic in Germany and the results published in 1955 (Franke et al., Dtsch. med. wschr. 1955, 80, 1449; Archelis et al., ibid p.1452; Bertram et al., ibid p. 1455) following which it was studied extensively in Europe and America. By 1956 evidence of many undesirable and serious side-effects had accumulated (Duncan et al., Brit. med. J., 1956, ii, 454; (Leading article) ibid., 465; Peck, F. B. Diabetes, 1957, 6, 1) so it is now largely replaced by the less toxic, but equally effective tolbutamide (Mirsky, I.A. et al., science, 1956, 123, 583; Bander, A., et al., Dtsch. med. wschr., 1956, 81, 823, 887). CH$_2$.CO.SO$_2$.NHCONH.CH$_2$.C$_6$H$_5$ is 1/2 active as Tolbutamide (Marshall, et al., J. Med. Chem. 1963, 6, 60). Boehringer et al., described N-(mono or disubstituted (chloro / Me) benzene-sulfonyl)-N$^2$-(alkoxyalkyl)ureas as good oral antidiabetic compounds (British patent 819,447 Sep.2, 1959 - Chem. Abstracts 1960, 54, 10958). M.H$_2$.N.C$_6$H$_4$.SO$_2$.NH.CO.NHR (R = alkyl or cycloalkyl) are also orally effective antidiabetic compounds (British patent 835, 390 - Chem. Abstracts 1960, 54, 24550). Kiyoshi Kawahara reported to have a physiological action of lowering blood sugar in p-x-C$_6$H$_4$.SO$_2$.NH.CO.NHR, where X = iso-Pr, tert. bu, o.Me, and R = Et; Pr,
CHMe₂, Am. A patent by Chas pfizer & Co. Inc. (British patent 853,555 Nov. 9, 1960 - Chem. Abstracts 1961, 55 10390) has claimed p-Cl. C₆H₄.SO₂.NH.CO.NH.Pr to lower blood sugar level in humans at 5-600/ mg/day. 1-cyclohexyl-3-sulfanilyl urea is reported to be useful as a remedy for diabetes mellitus. Japan patent 9621 (60) July 21 - Chem. Abstracts 1961, 55, 8353). Bis(sulfonylureas) of the type (R₁SO₂.NH.CO.NH(CH₂)n.S)₂ where R = p-CH₂.C₆H₄, when given orally lower blood sugar level and had low toxicity (Swiss patent 340,819. Oct. 31, 1959 - Chem. Abstracts 1962, 56, 5888). Trifluoromethylated sulfonyl ureas prepared by Y.G.perron et al., show hypoglycemic activity (J. Med. Pharm. Chem. 4, 41-9 (1961) - Chem. Abstracts 1961, 55, 23410). Gerald et al., has reported significant hypoglycemic activity in a series of 1-aryl-3-arylsulfonyl ureas (J. Med. Pharm. Chem. 2, 99-110 (1961) - Chem. Abstracts 1961, 55, 12343). p.RO.C₆H₄.SO₂.NH.CO.NH.R (R = Me, et, Pr, Bu, iso-bu, and R' = phenyl) type of ureas by E. Delacoux et al., are hypoglycemics. A patent by Farbwerke Hoechst Akt.-Ges (British patent 815,885. July 1, (1959) - Chem. Abstracts 1961, 55, 7359) has prepared the sulfonylureas of the type R.SO₂.NH.CO.NHR where R = 3,4 - Me(MeO) C₆H₃; 3,4 - Me₂C₆H₃; 2-naphthyl, 4-iso-Pr C₆H₄; 4-MeC₆H₄; 3,4-ClMeC₆H₃; Et₂CH; 4-phoC₆H₄, and R' = ph.CH₂.CH₂; ph(CH₂)₂.CH₂; ph(CH₂)₃.CH₂. These compounds
were suitable for lowering the blood sugar level without the concomitant bacteriological activity associated with the 4-amino-sulfononimidase, they were also of unexpected low toxicity. 1-Arylsulfonyl-3-(cis-2-decahydronaphthyl) ureas (Aryl = ph, p-Meph, p-Cl-Ph) are useful as hypoglycemic agents (John Alfred et al, U.S. patent 2,974,166 Mar. 7, 1961 - Chem. Abstracts 1961 55, 18685).

8. Miscellaneous Derivatives:

There are a variety of compounds which have been described as possible hypoglycemic agents. Tiwari and Swaroop (Jour. Ind. Chem. Soc. 1962, 29, 195) have reported the following new substituted Benzimidazoles:

```
R1 = H Me Et, Pr
R2 = p-CH3.C6H4.SO2; α and β-C10H7SO2; p-CH3.CO.NH.
C6H4.SO2; Cl2.CH.CO
```

They evaluated the above compounds for their hypoglycemic activity. Dhar et al., also prepared a number of hydantoin and hydantoinic esters to evaluate as possible hypoglycemic agent (J. Sci. Industr. Res. 1961, vol. 20 c, No. 5, P. 145). Zubenko et al., synthesised antidiabetic derivatives of azolidine. Among them N-p-toluenesulfonyl-3-butyl-2-thiohydantoin showed the most antidiabetic properties.
CHEMICAL STRUCTURE AND HYPOGLYCEMIC ACTIVITY:

There is a large number of substances having a variety of structures which show hypolycemic activity. Two Structural features viz. Ureas and guanidines are more prominent in showing this activity.

**Sulphonyl ureas:**

\[ X-\text{SO}_2\text{NH CO NH-R} \]

1. Nuclear H may be substituted by halogen, alkyl, or trifluoromethyl groups with retention of activity. (Perron et al., *J. Medicinal pharmaceutical chem.*, 1961, 4, 41).

2. The position of the substituent is not very important.

3. The benzene ring can also be substituted by two radicals without loss of activity (Brit. pat. 819447, 1959).

4. The alkyl substituent at \( N_2 \) of the sulphonyl urea part which confers lipophilic properties to the molecule must be of a particular size to elicit an optimal response. Maximum activity is obtained with straight chain of 3 - 6 carbon atoms.

5. Replacement of alkyl by naphthyl group retains the activity (U.S. patent 2,974,166 (1961). Compounds having "S" in side chain are also active \( p-\text{CH}_3-\text{C}_6\text{H}_4-\text{SO}_2-\text{NH-CO-NH-} \).
-CH₂-S-C₂H₅ (Brit. patent 824218 (1959). The alkyl group on N₂ can be replaced by benzyl, phenethyl and acyl groups with retention of activity. Activity is retained in a compound in which alkyl group is replaced by pyrrole. Cycloheptyl tolbutamide and tolzamide are also active.

![Cycloheptyl tolbutamide](image)

Cycloheptyl tolbutamide

![Jolzamide](image)

Jolzamide

Azepinamide

![Azepinamide](image)

has a clinical potency of 6-8 times that of tolbutamide.

6. Aryl sulphonyl part has been replaced by naphthyl sulphonyl or hetero sulphonyl parts with retention of activity but the effect was not long lasting as in the case of chloropropamide.

7. Sulphenyl ureas also are shown to possess activity.

![Sulphenyl ureas](image)

With R = butyl, hypoglycemic activity, was better than tolbutamide (Yakugaku, Zasshi, 1962, 82, 191)
8. The following compound with a side chain at N is also found to be active.

\[
\text{CH}_3\text{-SO}_2\text{NHCON} \quad \text{CH}_3
\]

(Ger. 1075588. - Chem. Abstr. 1961, 55, 12359)

9. Holland et al (J. Medicin. Pharmaceutical Chem. 1961, 111, 99) have tried to correlate the physical properties like Pk values and the solubility with the hypoglycemic activity. They found that within a series, the most acidic compound was also the most active hypoglycemic agent. Compounds of the type were exceptions.

\[
\text{NH}_2\text{NH.CO.NH} \quad \text{CH}_3
\]

10. Most of the active compound have a solubility of more than 1 mg/ml at pH 7.4 and 25°C.

Guanidines

1. Here the optimum chain length was between 5 and 10 carbon atoms beyond which the activity decreased.

2. Normal chain was more effective than a branched chain.

3. Benzylic and β-phenylethyl chains can replace alkyl chains without loss of activity.
Mechanism of hypoglycemic action of sulphonamides:

The sulphonamides in general are enzyme inhibitors. Incorporation of sulphonamides in place of PABA on the surface of an enzyme system essential for the growth of bacteria leads to inhibition of growth of pathogens as the particular enzyme becomes inactivated. Sulphonamides show such enzyme inactivation in a more general way and some of them have an effect on insulin production by the Islets of Langerhans and on glucose metabolism of normal and diabetic animals. (Loubatieres, A. Compt. rend. soc. biol. 1955, 149, 1642; Presse med., 1955, 63, 1701)

Tolbutamide has been thought to inhibit insulinas and thus prevent destruction of endogenous insulin (Mirsky, et al., science, 1956, 123, 583) but it does not inhibit rat liver insulinase at suitable concentration in vitro (Vonkennel, et al., Med., 1940, 138, 695).

Although the emergence of chemicals like synthaline (Franke et al., Klin. Wochr. 1926, 2, 2100), phenylethylformamidinlyiminourea hydrochloride (Pomeranze et al., proc. soc. Exp. Biol. 1957, 95, 193), Carbutamide and tolbutamide (Franke and Fuchs Deutsh. med. woch., 1955, 80, 1449; Achelis and Hardebeck, ibid., 1955, 80, 1455),
and 5-propyl-2-p-aminobenzenesulfanilamide-1,3,4-thiadiazole (Janbon et al, Montpellier, 1942, 21-22, 489) undoubtedly points to the possibility of a positive chemotherapeutic approach to the problem of diabetes, a really potent antidiabetic agent remains yet to be discovered. Various theories put forward from time to time have so far not offered any definite clue as to the mode of action of hypoglycemic agents and in the present state of our knowledge it is difficult to pin-point an attack on this complex syndrome condition and to build effective antidiabetic compounds, on a specific rationale. It can be noted however, that most of the active antidiabetic compounds are built around a guanidine (e.g. Synthaline and phenylethylformidinyliminourea hydrochloride), a urea (e.g. Carbutamide, Tolbutamide and Chloropropamide) or a thiourea moiety (e.g. 5-propyl-2-p-aminobenzenesulphanilamide-1:3:4-thiadiazole (I; R=Pr') and 5-butyl-2-aminobenzenesulphanilamide-1:3:4-thiadiazole (I; R=Bu):

![Thiourea moiety shown under dotted lines]

(I) R = Pr'
In view of the above considerations, Arylsulfonyl thioureas and Arylsulfonyl ureas have been prepared and described in this part.

Arylsulfonyl thioureas were prepared by the action of Arylisothiocyanate on sulfonamide and by desulfurizing the resulting thiourea derivative by alkaline hydrogen peroxide solution, the required Arylsulfonyl urea derivatives were obtained.

\[ R \cdot \text{SO}_2 \cdot \text{NH}_2 \cdot + R' \cdot \text{NCS} \]
\[ \xrightarrow{\text{K}_2\text{CO}_3} \]
\[ R \cdot \text{SO}_2 \cdot \text{NH}_2 \cdot \text{C} \cdot \text{NH} \cdot R' \]
\[ \xrightarrow{\text{H}_2\text{O}_2(\text{alkali})} \]
\[ R \cdot \text{SO}_2 \cdot \text{NH} \cdot \text{C} \cdot \text{NH} \cdot \text{R} \]

R & R' are Aryl groups.