REVIEW OF LITERATURE
Since single drug prescriptions have become rare in current medical practice, the chances of drug-drug interactions at present have increased considerably. That many of these drug combinations have the potential to interact adversely (Hamsten, 1979). Gravity of adverse effects due to drug interaction is not fully known because of limited work done to explore interacting possibilities. Most of the work done to know the drug-drug interactions is limited to easily measurable parameters. Mechanism of many already reported drug-drug interactions are not well understood. However, changes in metabolism of interacting drugs may tell something about the mechanisms of interactions.

Fortunately the subject of drug interactions has developed a new field of interest in pharmacological research. Knowledge of drug interactions enables a physician to minimize or prevent drug toxicity by adjustment of dosage or schedule of drug administration or by choice of an alternative agent.

Drug interactions may occur by multiple mechanisms. Though every mechanism is of its own kind, even then, leaving a few exceptions they can be classified
as follows according to Cohen and Armstrong (1974).

(1) Interactions dependent on gastro-intestinal absorption.

(2) Interaction between drugs at their plasma protein binding sites.

(3) Interaction due to altered drug metabolism which may be
    (a) increased
    or
    (b) decreased

(4) Interaction resulting from altered renal excretion of a drug or its metabolites.
    (a) Increased Excretion
    (b) Decreased Excretion

(5) Interaction at drug receptor site.

(6) Direct physical or chemical interaction between concurrently administered drugs.

(7) Undefined mechanisms.

Pharmaceutical interference may occur between drugs that are included in the same intravenous (I.V.) solution. Such interference is strongly dependent upon drug concentration and on the ionic properties and/or pH of the IV solution and is often influenced by “fillers” or stabilizing substances that may be added to pharmaceutical preparations.
ABSORPTION INTERACTIONS

The rate of absorption of orally administered drugs is largely determined by the rate of gastric emptying (Prescott, 1974), the nature of gastric contents (volume, composition and pH), pathological states and physical-chemical properties of drugs. Likewise different mechanisms have been suggested to explain the drug interaction at the level of absorption which can be summarised as follows:

1. Effect of pH of gastrointestinal fluid on drug dissolution rate and/or solubility.
2. Pharmacological interference by drugs with active transport mechanisms involved in the absorption of other drugs.
3. Formation of drug-drug complex or ion-drug complexes which may either enhance or retard drug absorption.
4. Interference with gastrointestinal enzymes involved in drug absorption.
5. Effects of certain drugs on gastric emptying rate and/or gastrointestinal motility.
6. Direct toxic effects of drugs on gastrointestinal flora.

IN SUMMARY

In order to be absorbed, drugs must pass
through the lipoprotein membrane of cells that line the gastrointestinal lumen. The rate of diffusion across the membrane is affected by the state of ionization of the drug. Nonionized drugs are usually more lipid soluble and thus diffuse across the cell membranes more readily. At the normal acid pH of the stomach, basic drugs such as amphetamine, quinidine, chloroquine are highly ionized and thus are poorly absorbed. Drugs that are weak acids, such as aspirin, phenylbutazone and phenobarbital are less highly ionized at the pH of normal gastric fluid and are, therefore, more lipid soluble. Antacids by raising the intraluminal pH of the stomach, increase the ionization of acidic drugs. Conversely by raising the intraluminal pH of stomach, antacids decrease ionization of basic drugs and thereby increase their absorption (Cohen and Armstrong, 1974).

Elevation of stomach pH by antacids has also been shown to delay gastric emptying of food and drugs, and thus may either increase or decrease absorption—depending upon the site of absorption of the drug primarily from the stomach or from the intestine. In addition, the pH of the stomach and other organs of the gastrointestinal tract can affect absorption of
drugs by altering the solubility or stability of the drug. For example, oral penicillin G is degraded rapidly at the normally acid pH of the stomach, but degradation is decreased and absorption is consequently increased when an antacid is administered concurrently (Cohen and Armstrong, 1974).

The rate of absorption of salicylates, indomethacin, naproxen, pseudoephedrine, sulphadiazine and enteric-coated phenylbutazone or aspirin is increased at elevated pH. The absorption of dicumarol but not of warfarin, is also facilitated by the formation of a rapidly absorbable complex. Aluminium hydroxide accelerates the absorption and increases the bioavailability of dicumarol by an unknown mechanism (Gilja et al., 1980).

Other factors influencing drug absorption

Since most drugs are absorbed more slowly from the stomach than from the small intestine, the rate of gastric emptying can be an important factor in influencing drug absorption. Cathartics may reduce uptake of poorly absorbed medications from the small intestine as a consequence of their effects on gastrointestinal motility. Surface acting agents such as charcoal can bind various drugs in the gastrointestinal tract and decrease their absorption. Agents which reduce lipid absorption
(e.g., cholestyramine) may also interfere with the absorption of lipid soluble drugs. The absorption of certain pharmacologically active agents (e.g., folic acid) is accomplished by enzyme-dependent transport mechanisms operating in the gastrointestinal mucosa and these mechanisms can be affected by concurrent administration of various drugs (Cohen and Armstrong, 1974).

Drugs which alter the intestinal flora may necessitate change in dose and dose intervals of certain drugs. e.g., that after sterilization of gut following neomycin, oral anticoagulants have exaggerated effect and methotrexate produces toxicity (Hershko et al., 1969).

Salts of aluminium, calcium, magnesium and iron all chelate with tetracyclines and impair their absorption (Kouyama et al., 1961; Kunitz and Finland, 1970). These interactions, however, occur only if the interacting agents are administered simultaneously or within 30 to 60 minutes of each other.

Bioavailability of a number of drugs is decreased because of their capacity to form complexes with various antacids. Magnesium trisilicate and silicic acid forms these from strongly bind and interfere
with bioavailability of iron, digoxin, certain benzodiazepines and phenothiazine. Aluminium hydroxide decreases the bioavailability of propranolol, antimuscarinic drugs, digoxin, chlorpromazine and sulphadiazine (Gilman et al., 1980)

**DRUG DISPLACEMENT FROM PLASMA PROTEIN BINDING SITES:**

A fair number of drugs, especially those that are acidic, are reversibly bound to plasma or tissue proteins and the extent of competition between drugs for such binding sites depends on the affinity of each for the site and its concentration. These drug binding proteins function as storage sites for the drug; the pharmaceutically active unbound fraction of the drug is in equilibrium with the bound fraction which is pharmaceutically inert. It is the unbound fraction that has access to the cellular receptor sites where the drug exerts its pharmacological effects. In addition, the unbound fraction is subject to clearance from the body by metabolism and/or excretion.

In instances where drugs are very highly bound to plasma protein (e.g. 90 to 95 % bound), only a small fraction of the total circulating drug (i.e. the 2-10 % of the drug that remains unbound) is responsible for
pharmacological activity. In such a case, even a small decrease in plasma protein binding can lead to a doubling or tripling of the unbound fraction of the drug. The resulting increase in pharmacological activity is usually temporary, as rapid clearance from the circulation takes place and a new equilibrium is formed. Nevertheless even a temporary elevation of levels of pharmacologically active drugs may sometimes lead to demonstrable clinical consequences.

**ALTERATION IN DRUG METABOLISM FROM ADMINISTRATION OF OTHER DRUGS:**

**Increased Metabolism**

Most of the drugs are metabolized in hepatic microsomes with the help of different enzymes. It is now well recognized that various chemicals can increase (induce) the synthesis of microsomal drug metabolizing enzyme in various animal species. In many instances an increased rate of drug metabolism leads to decreased pharmacologic action, however, in some instances where the metabolite of a drug is more active than the parent compound, enzyme induction can lead to an increase in pharmacologic activity of the drug (Cohen and Armstrong, 1970).
Chlordiazepoxide, chlorpromazine, hemobarbital, mebrodinate, phenobarbital, phencyclidine, probenecid, and talbutamide are some examples of drugs which enhance their own metabolism (Melkon and Macrilli, 1975).

And there are some agents which enhance metabolism of other substances (Table - 1) by inducing hepatic microsomal enzymes.

Table No. - 1 : Drugs that enhance the metabolism of other drugs or substances.

<table>
<thead>
<tr>
<th>Inducing agent</th>
<th>Drugs or substances affected</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phenobarbital</td>
<td>Barbiturates</td>
</tr>
<tr>
<td></td>
<td>Phencyclidine</td>
</tr>
<tr>
<td></td>
<td>Warfarin</td>
</tr>
<tr>
<td></td>
<td>3-Meofenaline</td>
</tr>
<tr>
<td>Diphenylhydantoin</td>
<td>Corticosteroids and Steroid hormones</td>
</tr>
<tr>
<td>Chlorcyclazine</td>
<td>Corticosteroids and sex hormones</td>
</tr>
<tr>
<td>Norchlorcyclazine</td>
<td>Corticosteroids and sex hormones</td>
</tr>
<tr>
<td>Ephedrine</td>
<td>Corticosteroids and sex hormones</td>
</tr>
<tr>
<td>Phencyclidine</td>
<td>Corticosteroids and sex hormones</td>
</tr>
<tr>
<td>Amobarbital</td>
<td>Warfarin</td>
</tr>
<tr>
<td>Alcohol</td>
<td>Talbutamide</td>
</tr>
</tbody>
</table>

Certain drugs inhibit the activity of...
enzymes responsible for the metabolism of other drugs. Such inhibition may result from competition between the pharmacologic agents able to act as substrates for the same drug metabolizing enzyme, or from direct interference with the enzyme itself.

Table No. - 2: Following are the drugs which are thought to interact apparently by inhibiting other drug metabolism (Melmon and Norrelli, 1972; Birdwood, 1976).

<table>
<thead>
<tr>
<th>Drugs metabolised slowly</th>
<th>Drugs inhibiting metabolism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bishydroxyesc论证</td>
<td>Chloramphenicol, oxymetazoline and phenytoin.</td>
</tr>
<tr>
<td>Diphospholhydantoin</td>
<td>Alcohol, p-aminosalicylic acid, bishydroxyesc论证, chloramphenicol, cycloserine, diazepam, IM, PAS, phenytoin, phenobarbitone, phenytoin, propanolol, sulphonamides and salicylates.</td>
</tr>
<tr>
<td>Tobutamide</td>
<td>Alcohol, chloramphenicol, diazepam, IM, IM-inhibitors, phenytoin, phenobarbitone, phenytoin, propanolol, salicylates and sulphonamides.</td>
</tr>
<tr>
<td>Mirtgiptyline</td>
<td>Hydrocortisone, parphenes.</td>
</tr>
</tbody>
</table>

**INTERACTION AT LEVEL OF EXCRETION**

Drugs which have the ability to increase or decrease glomerular filtration by altering renal blood
flow may alter the rate of excretion of other drugs or metabolites theoretically. However, there is little clinical evidence of interaction by this mechanism.

Sulfinpyrazone in sufficient dosage is a potent inhibitor of the renal tubular reabsorption of uric acid. As with other uricosuric agents, small doses may reduce the excretion of uric acid, like probenecid, sulfinpyrazone reduces the renal tubular secretion of many other organic ions. The drug may induce hypoglycaemia by decreasing the excretion of the sulphonylureas (Hughes, 1969). The uricosuric action of sulfinpyrazone is additive to that of probenecid and phenylbutazone but is mutually antagonistic to that of the salicylates (Yli et al., 1963).

Table No. 3: Important interactions at the level of excretion are given as follows (Birdwood, 1976).

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Delay(s) excretion of</th>
</tr>
</thead>
<tbody>
<tr>
<td>Probenecid</td>
<td>Dapsone, Indomethacin, PAH, Sulphinpyrazone, penicillins, Schlethina, Schalezina</td>
</tr>
<tr>
<td>Diclofenac, phenylbutazone</td>
<td>Chlorpropamide</td>
</tr>
<tr>
<td>Salicylates, sulphonamides</td>
<td>Methotrexate</td>
</tr>
</tbody>
</table>

**INTERACTION AT DNA ENZYME SITE**

This mechanism of drug interaction involves competition for receptors at the cellular site where the
drugs ultimately exert their pharmacologic effects. Unlike plasma protein binding sites cellular receptor sites for drugs are usually highly specific. Competition may result from the blocking of a receptor site by another drug. In addition, competition for specific uptake mechanisms may also occur. A well studied example of this involves blockade of the noradrenergic pump by tricyclic antidepressants. Since uptake of guanethidine by the NE pump at the adrenergic nerve ending is required in order to exert its antihypertensive effect, competition for the uptake mechanism by tricyclic antidepressants renders guanethidine ineffective as an antihypertensive agent (Sachen and Armstrong, 1974).

Other interactions of an apparent pharmacodynamic nature are poorly understood. Halogenated hydrocarbons, including many general anesthetics, sensitize the myocardium to the arrhythmogenic actions of catecholamines. This effect presumably results from some action on the pathway leading from receptor to effector, but details are not clear. Many signs and symptoms of hypoglycemia are mediated through the adrenergic nervous system and are masked by beta-adrenergic blocking agents. Patients taking propranolol may thus fail to note reactions to insulin or oral hypoglycemic agents in time to prevent
dangerous consequences and further more, compensatory mechanisms, such as glycogenalysis, may be blocked by the beta-adrenergic antagonists (Kulman and Gillman, 1980).

**ORAL ANTIDIABETIC AGENTS**

The search for natural remedies for diabetes has been persistent as in most chronic ailments. Between 1912 and 1930 many compounds were tested as oral anti-diabetics e.g. gurumide (Nathan, 1912), synthaline A and synthaline B (Frank et al., 1928) but failed to survive as therapeutic agents due to their high toxicity.

Jansen and coworkers (1940) in the course of clinical studies on the treatment of typhoid fever, discovered that a sulphonamide (p-aminobenzenesulfonamide - sulfaphenamide - isopropylthiazonamide) induced hypoglycemia. Leblanciers (1947) then made a fundamental discovery that the compound exerted no hypoglycemic effects and suggested that the action was the result of stimulation of pancreas to secrete insulin. Franks and Pasha (1950) reported the use of tolbutamide (1955), a sulphonilurea compound and found that it could be successfully substituted for insulin in a number of middle aged elderly diabetics. Soon thereafter, the compound tolbutamide was introduced. The tolbutamide proved to be less toxic than carbamazepine
and soon became popular for the management of certain diabetic patients.

Another group of compounds, the biguanides, was developed independently of sulphonylurea. Historically, the development began with the discovery in 1926 by Watanabe that guanidine causes hypoglycaemia in rats. Subsequently the compound phenformin was introduced into clinical therapy and was used for several years. Now it has been replaced by better drugs.

**ORAL HYPOGLYCAEMIC AGENTS IN CURRENT USE**

Sulphonylureas and biguanides are the two classes of drugs used as oral hypoglycaemic agents. Mechanism of action of biguanides is entirely different from those of sulphonylureas. A large number of sulphonylurea derivatives have been studied. All are synthetic and have the same basic mechanism of action. They differ in metabolic fate, potency and toxicity. The most important difference among the sulphonylureas for clinical purpose, is in their duration of action. In increasing order they are tolbutamide, troglitazone, glibenclamide, acetohexamide and chlorpropamide (Mayers et al., 1976).

**PHARMACOLOGY OF TOLBUTAMIDE**

**Tolbutamide**

All sulphonylurea drugs are arylsulphonylureas with substitutions on the benzene and the urea groups.
Fig. 1: Shows chemical structure of tolbutamide, N-(P-tolyl sulphonyl) - N-butyl carbamide; and carbutamide, N-Sulphanilyl-N-butylcarbamide.
In the case of tolbutamide (Fig. 1) anhyd group is xytyl and the ame substitution is butyl. Tolbutamide differs from antibacterial compound carbenamide in having methyl instead of amino on the benzene ring. This substitution accounts for the loss of antibacterial properties and for the reduction of toxicity (Lerner, 1960).

**Physical Properties**

It is a white odorless powder with acid pH, soluble in alcohol and insoluble in water. It is soluble in alkaline intestinal contents of human beings and carnivorous animals (Shaw and Bassar, 1971). Tolbutamide is readily soluble in amyleacetate which is used for estimation of tolbutamide in biological fluids (Spingler, 1967).

**MECHANISM OF ACTION:**

Tolbutamide stimulates the islet tissue to secrete insulin like other sulphonylureas. Administration of sulphonylureas increases the concentration of insulin in the pancreatic vein in acute circulation experiments (Lerner, 1960). The stimulating effect of tolbutamide on insulin release can be demonstrated in vitro and in vivo experiments in normal animals and human beings. This is demonstrated biologically by peripheral migration and
discharge of beta-granules (Williamson et al., 1961). Furthermore, this stimulating effect is dependent on the functional state of beta-cell reserve (Pfeiffer, 1967). The action of the drug requires a minimum amount (at least 20% of normal) of functioning beta-cell tissue. This effect does not occur in pancreatectomised individuals or patients with an absolute deficiency of insulin like juvenile diabetes (Sher and Bassar, 1971). Hallman and associates (1971) concluded that labeled tolbutamide is restricted in its action to the extracellular space and does not need to enter the beta cells. The induced release of insulin is immediate and is intimately related to the action of glucose. The drug may sensitize the cell to the normal secretagogue.

In experimental animals and in diabetic patients conflicting results have been obtained on the effects of tolbutamide on the plasma concentration of glucagon. Amole and Harrison (1972) have suggested that tolbutamide can enhance glucagon secretion from the alpha-cells, although this may be masked by the effect of sulphonylureas to stimulate the secretion of insulin. Local actions of insulin within islet may cause a reduction in the secretion of glucagon; the net effect may be either stimulation or suppression of glucagon secretion.
During chronic administration, a significant portion of hypoglycemic action of the sulphonylureas may be due to extrapancreatic actions. Insulin biosynthesis may be actually decreased and peripheral tissues become more sensitive to a fixed dose of administered hormone due possibly to an increase in the number of insulin receptors (Lebovitz and Fainglos, 1978). Tolbutamide enhances the antilipolytic action of insulin in adipose tissue. This appears to be related to an altered effectiveness of cyclic AMP rather than to any change in metabolism of cyclic nucleotides (Brown et al., 1978; Fain et al., 1979) and an inhibitory effect of the drug on cyclic AMP-dependent protein kinase has been observed (Vrey and Harris, 1978). A reduction in the hepatic uptake of endogenous insulin has been described (Haskell et al., 1970) and a direct inhibitory effect of tolbutamide on hepatic glucose production may also be demonstrated in the presence of insulin (Hamby and Fawcett, 1968).

**PHARMACOKINETICS OF TOLBUTAMIDE**

**ABSORPTION**

When administered orally, tolbutamide is absorbed promptly from the small intestine (Kampfner, 1956) and appears in blood within 30 minutes. Its peak concentration is attained in 3 to 5 hours (Larsen, 1959).
The availability is 93% ± 10% when given orally (Nelson and O'Beilly, 1961).

**DISTRIBUTION**

Tolbutamide is distributed throughout the extracellular fluid compartment as the volume of distribution of tolbutamide is approximately equal to the extracellular fluid (Naha et al., 1963). Williams et al. (1977) calculated the volume of distribution of tolbutamide to be 0.15 ± 0.03 litres/kg. 93% ± 1% of tolbutamide is bound to plasma proteins which may decrease in acute viral hepatitis (Williams et al., 1977).

**Table 4**

Pharmacokinetic data of tolbutamide (Naha et al., 1963)

<table>
<thead>
<tr>
<th>Availability (oral) (%)</th>
<th>Urinary excretion (g)</th>
<th>Bound in plasma clearance (g al min kg⁻¹)</th>
</tr>
</thead>
<tbody>
<tr>
<td>95 ± 20</td>
<td>33 ± 1</td>
<td>0.30 ± 0.5</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Vol. Dist. (litres/kg)</th>
<th>Half-life (hours)</th>
<th>Effective concentration</th>
<th>Toxic concentration</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.15 ± 0.03</td>
<td>56 ± 26</td>
<td>80-200 mg/ml</td>
<td></td>
</tr>
</tbody>
</table>

No change in AEH decreased in AEH.<br>
No change in acute viral hepatitis.

**AEH = Acute Viral Hepatitis, Vol. Dist. = Volume of Distribution, DH = Drugs and Alcohol**
BIOTRANSFORMATION

Tolbutamide is oxidised in liver. It is first converted into hydroxytolbutamide which is partially excreted unchanged and the majority is further oxidized to carboxytolbutamide which is finally excreted. The oxidation of tolbutamide is the rate limiting step in the elimination of the drug and its metabolites. Subsequent oxidation steps are very rapid. Accordingly a short time after tolbutamide administration, the rate of excretion of the sum of the two metabolites equals the rate of tolbutamide oxidation and offers a very sensitive measure of changing tolbutamide oxidation (Brodland, 1974).

HALF-LIFE

The biological half-life of tolbutamide (defined as the time required for the blood level to decrease from the peak level by 50%) is 48 hours. The metabolic half-life (defined as half the interval of blood sugar lowering effect) is 4.7 hours (Shaw and Desser, 1971).

Williams et al. (1977) reported that half-life of tolbutamide in normal individuals is 6.9 ± 2.4 hours which was significantly decreased in acute viral hepatitis to 4.89 ± 0.5 hours.
TOXICITY OF TOLBUTAMIDE

The enormous use of sulphonylureas has confirmed their conspicuous freedom from serious side effects, Bloom (1969) has described tolbutamide to be the safest drug to be introduced after a long time.

Toxicity tests in animals have shown that in ordinary doses tolbutamide has no action on respiration, circulation or on the smooth muscles of the gut and does not affect the contraction of uterine produced by histamine and ergotamine(Oakley, 1965).

O’Donovan (1969) analysed the incidence of side effects of tolbutamide in 6233 cases. The total incidence of side effects was 3.8%; the drug had to be withdrawn in 1.6% of the patients. The reactions have been classified as haematological (0.36%), cutaneous (1.1%) and gastrointestinal (1.4%) of the 25 subjects exhibiting haematological abnormalities, 23 had transient leucopenia; in 9 instances, the leucocyte count returned to normal despite continuation of the drug.

HYPOLYCAEMIA

Hypoglycaemia, although relatively uncommon is still a significant complication. Severe fatal hypoglycaemic attack may occur which is refractory to treatment (Graham et al., 1963).
GASTROINTESTINAL DISTURBANCES

In susceptible individuals, symptoms consist of heartburn, upper abdominal discomfort, nausea, lower abdominal cramps and diarrhea. According to Malins (1968) gastrointestinal upset occurs in more than 6% cases treated with tolbutamide.

SKIN RASHES:

The rash has the usual feature of drug eruption and clears rapidly when sulphonylureas is withdrawn. Skin rashes may be seen in 3% cases taking tolbutamide (Malins, 1968).

LIVER FUNCTION

Rarely cholestatic jaundice may occur after the use of tolbutamide (Naired and Hall, 1963). On very rare occasions tolbutamide may aggravate hepatic porphyria (Schlesinger and Castel, 1961).

PANCYTOPENIA

Pancytopenia was reported following tolbutamide administration (Chapman and Cheung, 1963).

ALCOHOL INTOLERANCE

This consists of intense flushing of the face and neck immediately after taking even very small amounts.
of alcohol with sulphonylureas. The incidence of the reaction is less with tolbutamide than chlorpropamide (Malins, 1966).

**Antithyroid action**

Brown and Selman (1966) showed a fall in the $^{131}$ uptake and protein bound iodine levels in diabetics taking carbutamide and tolbutamide.

**Glucose Metabolism**

Final products of carbohydrate digestion in the alimentary tract are almost entirely glucose, fructose and galactose with glucose representing on the average about 80% of these monosaccharides. After absorption from the intestinal tract, most of the fructose and galactose are almost immediately converted into glucose. Therefore, very little fructose and galactose are present in the circulating blood. Glucose thus becomes the final common pathway for transport of almost all carbohydrates to the tissue cells. In liver cells, appropriate enzymes are available to promote interconversion among the monosaccharides before glucose can be used by the cells. Glucose is transported through the cell membrane by the mechanism of facilitated diffusion. The rate of glucose transport and also transport of some other monosaccharides is greatly increased by insulin with
the exception of the liver and the brain (Guyton, 1981). Immediately upon entry into the cells glucose combines with a phosphate radical to form glucose 6-phosphate. The phosphorylation promoted by glucokinase is almost completely irreversible except in the liver cells, the renal tubular epithelium and the intestinal epithelial cells in which glucose phosphatase is available for reversing the reaction. Therefore, in most tissues of the body phosphorylation serves to capture glucose in the cell.

**GLUCOSE-INDUCED INSULIN SECRETION**

Glucose stimulates insulin secretion in man, monkey (Kris et al., 1968), rabbit (Geese and Lampel, 1966) and rat (Orzisky et al., 1968). The rapidity of the insulin secretory response to glucose is best illustrated in vivo or in the perfused isolated pancreas (Guny et al., 1968; Orsisky et al., 1967; Kamens et al., 1969), but is also observed in a non-irrigated tissue. The secretory process undoubtedly consumes energy (Millaiz and et al., 1967; Bents, 1970).

**CAUTIOUS AND INSULIN SECRETION**

Renal or glucose induced insulin release is enhanced whenever sodium influx into the beta-cells is increased (Hales and Millen, 1968; Millaiz et al., 1972).
Milner and Hales, 1967), Dipyridyl hydantoin abolished glucose-induced secretion in vivo (Peters and Semann, 1969) or in vitro (Levin et al., 1970), apparently by inhibiting Na⁺ entry into the beta-cell (Milner and Dressler, 1969). Moreover glucose-induced secretion is inhibited by replacement of sodium ion by lithium ion (Milner and Hales, 1967) and stimulation of insulin secretion is accompanied by beta-cell depolarization (Dean and Nathan, 1968). These convergent observations support the concept that Na⁺ influx into the beta-cell is a significant event in the process of insulin release (Hales and Milner, 1968).

**Calcium requirements for insulin secretion**

The presence of extracellular Calcium is required for glucose or any other insulinotropic agents to stimulate insulin secretion (Curry et al., 1968; Gundersky and Bannet, 1968). Magnesium ion can be substituted for calcium ion (Malaissse et al., 1970; Milner and Hales, 1968). By contrast magnesium ion in high concentration inhibits glucose-induced insulin release (Bannet et al., 1969).

In view of the analogy between stimulus secretion coupling in the beta-cell and excitation-contraction coupling in the muscle, it is tempting to speculate that
Calcium ion induces insulin release by causing the contraction of the microtubular-microfilamentous system (Melaisce, 1972).

**THE ADRENERGIC MECHANISM:**

In 1964 Coore and Randle observed inhibition of glucose-induced insulin secretion by epinephrine in insulinized pieces of rabbit pancreas. Inhibitory effect of epinephrine on insulin secretion has also been confirmed in man (Karen et al., 1966) and rat (Melaisce et al., 1967).

The inhibitory effect of epinephrine is not restricted to the insulinstimulatory effect of glucose. Thus epinephrine also abolishes secretion in response to glucagon (Pinto et al., 1966), theophylline (Melaisce et al., 1970), tolbutamide (Melaisce, 1967; Pinto et al., 1966), anisomycin (Bertelhody et al., 1968).

Epinephrine is a more potent inhibitor of insulin secretion than norepinephrine (Melaisce et al., 1967; Pinto and Williams, 1966). Because epinephrine is also the most potent activator of alpha adrenergic receptors, these findings suggest that epinephrine-induced inhibition of insulin secretion results from the activation of alpha-adrenergic receptors. The hypothesis is substantiated by the fact that alpha-adrenergic blocking agents abolish the inhibitory effect of adrenaline, whereas, beta-adrenergic
Blocking agents fail to do so (Porte, 1967).

Porte (1967) first reported elevation in the level of circulating insulin during infusion of isoproterenol in human subjects. Oxprenolol has the same effect (Laudicina et al., 1966). In vitro, although beta-adrenergic blocking agents might also exert some inhibitory effect under appropriate experimental conditions (Malaissa et al., 1967), they do not suppress glucose-induced insulin secretion (Malaissa et al., 1967). Effects of different beta-blockers on glucose metabolism have been discussed subsequently.

CHOLINERGIC MECHANISMS

The direct stimulant effect of parasympathomimetic drugs on the beta-cell was confirmed in vivo in dog and man (Kajinuma et al., 1965; Kaneto et al., 1965). In these species the enhanced insulin output evoked by cholinergic agents could be antagonized by atropine (Frohman et al., 1967).

EFFECTS OF ANTILUMENATORY AGENTS ON GLUCOSE METABOLISM

Salicylates

The effects of salicylates on carbohydrate metabolism are complex. Multiple factors appear to be involved, some tending to lower and others to raise the
blood glucose concentration. In both animals and man, large doses of salicylates may cause hyperglycemia and glycosuria and deplete muscle and liver glycogen. These effects are partly explained by the release of epinephrine through activation of central sympathetic centers. In addition, such large doses might reduce aerobic metabolism of glucose, increase glucose-6-phosphatase activity and promote the secretion of glucocorticoids (Fleger et al., 1980; Pickering, 1963). Hypoglycemic action of salicylates may be seen in diabetic or nondiabetic patients having taken toxic doses of salicylates (Hansten, 1979).

PHENYL BUTAZONIDE

Phenylbutazone although does not produce any marked change in blood sugar independently (Shams et al., 1961) but potentiates hypoglycemic effect of insulin (Fleger et al., 1980).

INDOMETHACIN

Indomethacin in rare occasions produces hyperglycemia and glycosuria. However, in most studies indomethacin did not affect glucose tolerance (Rothmanick, 1989).

IBUHYDROL

It is a comparatively new anti-inflammatory agent. This drug has been seen to produce significant hypoglycemia
in rats and rabbits (Sharma et al., 1982). The mechanism by which it produces this effect has not been elucidated.

**Trombix**

This is latest drug in the series of anti-inflammatory agents. It is an anthranillic acid derivative claimed to be safer anti-inflammatory drug (Nathur et al., 1983; Sattar et al., 1980). Although, a large number of studies indicate that the drug has least toxic effects with high margin of safety, its biochemical effects are still not well studied.

**Ibuprofen**

Effects of ibuprofen on glucose metabolism are not well studied. In one study ibuprofen (10 mg/kg) produced hyperglycemia in rabbits (Sharma et al., 1981).

**MODE OF ACTION OF ANTI-INFLAMMATORY DRUG ON GLUCOSE METABOLISM**

The literature on this aspect does not depict a clear picture. Some of the anti-inflammatory agents (salicylates in toxic doses, indomethacin, ibuprofen) evoke a hyperglycemic response (Rothman, 1969; Flower et al., 1980; Sharma et al., 1981) whereas tolmetin and piroxicam induce hyperglycemia (Flower et al., 1980; Sharma et al., 1981). Anti-inflammatory agents are known potent potent prostaglandin synthesis inhibitors, thereby,
produce various pharmacological actions (Smith and Willis, 1971). PGs also have some insulin-like effects on carbohydrate metabolism (Nakano, 1973) and stimulate insulin release (Johnson et al., 1973). PGs, if really play such role, its inhibition is likely to be accompanied by hypoglycemic response. But this effect could be modified by centroganin involvements (Flower et al., 1980) leading to hypoglycemic or hyperglycemic effects.

Effects of Beta-Adrenergic Blockers on Glucose Metabolism

Propranolol acts synergistically with insulin in the rat to induce hypoglycemia much more severely (Ryan and Friedman, 1966). Cases have been reported where hypoglycemia has been associated with the use of nonselective beta-adrenergic antagonists (Propranolol) in insulin dependent diabetes (Ketler et al., 1966; Revans and Messerli, 1969) and evidence exists that there is a delayed recovery from insulin-induced hypoglycemia with propranolol (Bennet et al., 1977).

Further investigations suggest that the earlier selective agents atenolol (Bennet et al., 1977) and metoprolol (Hamm, 1980) have little or no effect on recovery from insulin-induced hypoglycemia. A recent study has shown that in insulin-dependent diabetic patients neither
metoprolol nor enproanol affected the recovery from hypoglycaemia (Keen et al., 1979).

The metabolic response to hypoglycaemia involves the mobilization of FFA (free fatty acids) and lactate, both of which are reduced by propranolol, so that a hypoglycaemic tendency is enhanced in the presence of propranolol (Fitzgerald, 1980). In contrast to previous study, Mower (1980) has reported that metoprolol may impair glucose tolerance in diabetic patients and perhaps in normal individuals. It seems clear that nonselective beta-blocking agents are more likely to affect glucose metabolism and induce hypoglycaemia. The newer cardioselective beta-blockers affect blood sugar level less adversely. However, in patients with hypertension and mild diabetes a change of therapy from nonselective beta-adrenoreceptor antagonists to metoprolol resulted in a significant improvement of glucose tolerance in 6 of 17 patients (Neil-Marling, 1976). The effect of acebutolol (a cardioselective beta-adrenoreceptor blocker) on plasma glucose level has also been studied in both normal volunteers and in diabetics. In general little action has been observed on the glucose level (Sibbons et al., 1977; Sibbons, 1977; Sibbons et al., 1977) or on insulin secretion (Sibbons et al., 1977), but Sibbons (1976) has noted a potentiation of the effects of insulin and a delay in recovery of the normal glucose level after administration of acebutolol.
INTERACTIONS OF ANTI-INFLAMMATORY AGENTS WITH TOLBUTAMIDE

Phenylbutazone

Phenylbutazone enhances the effect of sulphonylureas and the possible mechanism responsible for the effect is the combination of increased sulphonylurea - induced insulin release (Fleuret et al., 1980), inhibition of metabolism (Pourn et al., 1977; Christensen et al., 1962) of tolbutamides and inhibition of excretion of active metabolites (Field et al., 1967). Displacement of tolbutamide from plasma protein binding by phenylbutazone may also be involved in the enhanced hypoglycaemic effect of tolbutamide.

Saliplasate

Saliplasate may potentiate the sulphonylurea induced hypoglycaemia due to their intrinsic hypoglycaemic action (Fleuret et al., 1980). In vitro studies have shown sodium salicylate to displace tolbutamides and chlorpropamide from plasma protein binding thus increasing unbound (active) sulphonylureas. It has also been proposed that salicylates might interfere with the renal tubular secretion of chlorpropamide (Hannen, 1970).

Salvinam

It has been shown that salvinam potentiates glitazone-treated hypoglycaemia in rabbits (Sharma et al., 1983).
Ibuprofen

Ibuprofen antagonises glibenclamide-induced hypoglycaemia in rabbits (Shama et al., 1981).

INTERACTIONS OF BETA-ADRENERGIC BLOCKERS WITH TOLBUTAMIDE

It is shown that propranolol blunts the rebound of serum glucose following insulin-induced hypoglycaemia. The effect of propranolol/sulphonylurea-hypoglycaemia is less clear. In one study conducted on healthy subjects, propranolol impaired tolbutamide-induced hypoglycaemia response presumably due to inhibition of insulin secretion (Papitthitchon et al., 1968). Propranolol has also been reported to enhance hypoglycaemia from its ability to interfere with catecholamine-induced glycogenolysis (Hansten, 1975). However, in sulphonylurea treated patients who developed hypoglycaemia, propranolol also prevented the rebound of serum glucose (Hansten, 1975) as it does with insulin hypoglycaemia.