CHAPTER I

INTRODUCTION

In pregnancy, the changes which occur in the uterus during pregnancy are truly remarkable. In addition to alterations in size, consistency, position and contractility which are largely related to the changing character of its content, there are also growth changes in its mucosa, in its myometrium and in its vascular structure (Taylor, M.D., 1976). The major properties of uterine muscle are the same as those possessed, by smooth muscle in general: contraction, relaxation, co-ordination and changes in length without changes in tension (Danforth, D.N. and Hendricks, C.H., 1977). The intermitten contractions of pregnancy differ from the true labour contractions in that they are painless and recur at irregular intervals. Also, unlike the contractions of labour, they are not accompanied by retraction of the muscle and do not dilate the cervix. The contractions aid in maintaining the circulation of maternal blood through the placental lake (Taylor, M.D., 1976).

As the time of labour approaches the intermittent contractions become gradually more regular in frequency, duration and intensity; and they are propagated for increasing distances over the myometrium. In labour, the most beautiful co-ordination is achieved, such that the contractions are precisely regular in strength, duration and

frequency; and each contraction spreads uniformly to involve the entire myometrium (Danforth, D.N. and Hendricks, C.H., 1977).

Labour or parturition is the process by which the mature products of conception are expelled from the uterus (Hellman and Pritchard, 1971; Taylor, M.D., 1976). Labour is conveniently divided into three distinct stages :-

:- the first stage of labour, or the stage of cervical dilation, begins with the first true labour pain and ends with the complete dilation of the cervix.

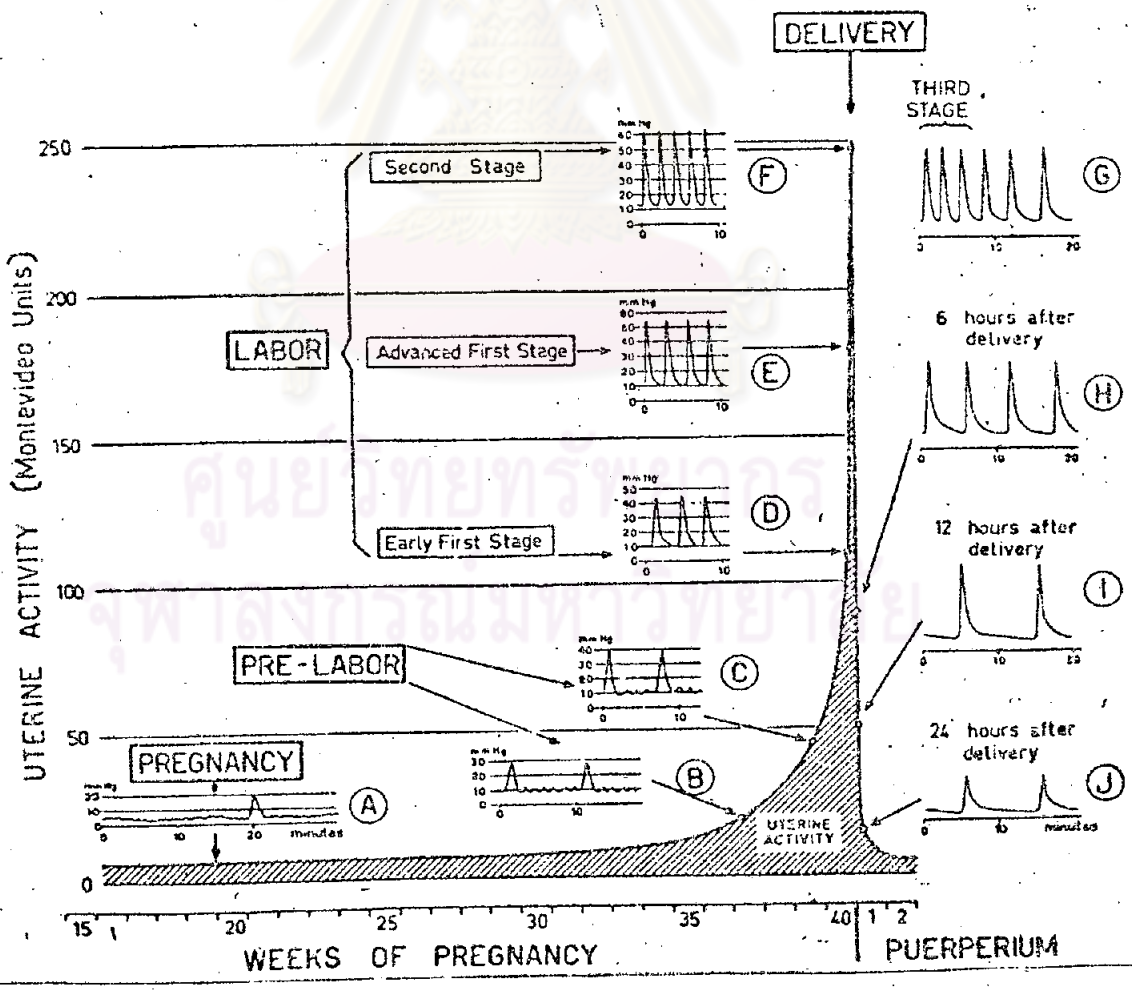
:- the second stage of labour, or the stage of expulsion, begins with the complete dilation of the cervix and ends with the birth of the baby.

:- the third stage of labour, or the placental stage, begins with the delivery of the baby and ends with the delivery of the placenta.

Figure 1 summerized the frequency and intensity of uterine contractions of normal labour and also partways uterine tonus (Taylor, M.D., 1976).

The uterine contractions are involuntary and are independent of the central nervous system (Taylor, M.D., 1976). When labour is fully established, the process is inexorable; it does not stop and it cannot be permanently stopped until the uterus is empty (Danforth, D.N. and Hendricks, C.H., 1977). The contraction wave of uterus

Figure 1. Uterine contractions during normal pregnancy, labour, and the early puerperium. A, small uterine contractions of early pregnancy. B and C, minimal basic activity of the uterus. D and E, graphs of first stage of labour uterine action. F, representation of second stage of labour uterine contraction. G, third stage of labour. H, I, and J, tracing taken during the puerperium. (Taylor, M.D., 1976, p. 197).



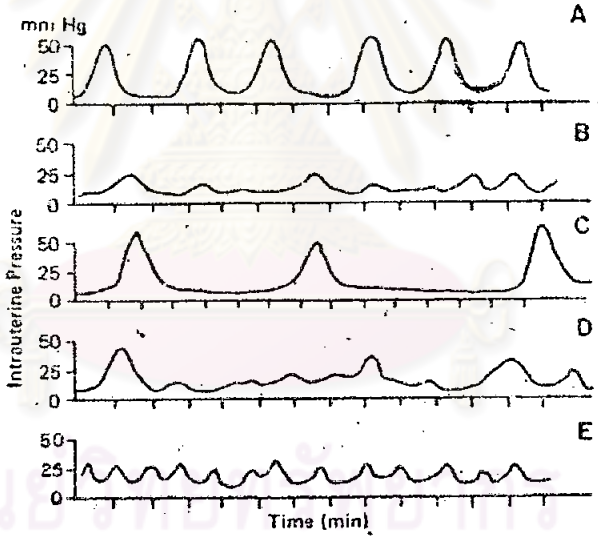
depend on many factors including estrogen, progesterone and prostaglandin (PG.) influence; electrochemical phenomena at the cell surfaces; actinomycin (AM.) and adenosine triphosphate (ATP.) concentration; electrolyte environment; stretch and apparently the density of the post ganglionic nerve axons which varies according to the physiologic state of the uterus (Danforth, D.N. and Hendricks, C.H., 1977).

At term progesterone dominance gives way to increasing estrogen influence with all its attendent stimuli. Among these are an increase in the working capacity of the uterus, an increasing in myometrial synthesis, contraction and release of PG_s, and changes in ionic environment and membrane potential that permit a contraction to be propagated from one cell to the next. PG_s and possibly also endogenous oxytocin, cause the release of calcium from the storage sites in the sarcoplasmic reticulum. The released calcium activates ATPase, with consequent splitting of ATP and activation of AM, the contractile protein. The most pressing problem in obstetrics is the absolute control of uterine action:- the ability to start co-ordinated contraction at will or to stop them at will (Danforth, D.N. and Hendricks, C.H., 1977).

The development of dysfunctional labour is usually accompanied by one or more of the following:-

1. contractions that seem less intense to the obstetrician and often are less painfull to the patient (figure 2-B)

Figure 2. Uterine contractility patterns in labour. A, typical normal labour. B, subnormal intensity, with frequency greater than needed for optimal performance. C, normal contractions, but too infrequent for efficient labour. D, incoordinate activity. E, hypercontractility. (Danforth and Hendricks, 1977).



2. contractions coming at less frequent intervals (figure 2-C) and
3. contractions with a poorly co-ordinated pattern (figure 2-D) (Danforth, D.N. and Hendricks, C.H.,1977).

There are many drugs posses oxytocic activity namely, the ability to stimulate the smooth muscle of the uterus. However, only a few have uterine effects sufficiently selective and predictable to justify their use as oxytocic agents in obstetrical practice. There are oxytocin, certain of the prostaglandins and the ergot alkaloids ergonovine and methylergonovine. Each, in appropriate doses during pregnancy, is capable of eliciting graded increase in uterine motility from a moderate increase in the rate and force of spontaneous motor activity to sustained "tetanic" contraction, while causing minimal side effects in healthy subject (Goodman and Gilman, 1975). There are many indications for the clinical use of the oxytocic agents. In brief, the clearest indications are :-

1. to induce labour at term.
2. to control post-partum hemorrhage.
3. to correct post-partum uterine atony.
4. to cause uterine contraction after caesarean section or during other uterine surgery.
5. to induce therapeutic abortion after the first trimester.

6. to overcome stubborn and prolonged uterine inertia.

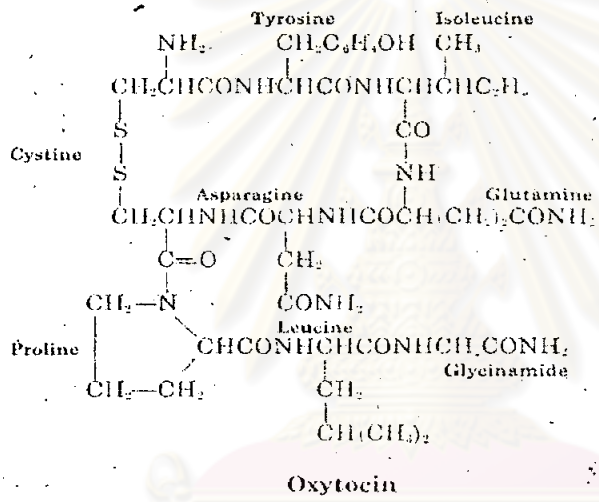
In general, oxytocic agents are contraindicated during the first and second stages of labour (Goodman and Gilman, 1975). Oxytocin is the drug par excellence for stimulation of the uterus and for testing uterine's reactivity (Danforth and Hendricks, 1977).

The name "Oxytocin" refers to a specific octapeptide, which has been isolated from the posterior pituitary gland. The uterotonic activity of a posterior pituitary factor was used for the induction of labour by Watson (1913). The structure (figure 3) of the active principle oxytocin, was determined by Du Vigneaud and his collabolators in 1954-1955. A significant clinical advance was realized in 1948, when Theobald (1968) reported on the administration of dilute oxytocin solution by intravenous drip. Now the use of oxytocin in clinical obstetrics is ever increasing (Pauerstein, C.S., 1973; Tepperman, H.M., et al., 1977).

Oxytocin is bound to plasma protein in the human, but this binding is relatively weak and rapidly reversible. Administered oxytocin disappears rapidly from the circulation, a half-life of 1-6 minutes being reported in different studies. Only small amounts of oxytocin are excreted unchanged in the urine, most of it being inactivated, principally by the kidney and the liver (Tepperman, H.M., et al., 1977).

The mechanism of action of oxytocin which increase the intensity and frequency of uterine contractions when infused into

Figure 3. Structure of oxytocin. (Remington's Pharmaceutical Sciences, 15th edition. 1975).



pregnant women; however, is poorly understood (Soloff, M.S., et al., 1974; Tepperman, H.M., et al., 1977). In early pregnancy, the uterus is exceptionally refractory to oxytocin, large doses being required to produce contractions even vaquely resembling those seen in early labour (see fig. 4). Doses of oxytocin that in early pregnancy have little effect can; at term, produce the most violent and sustained tetany (Danforth, D.N. and Hendricks, C.H., 1977). In the final weeks of pregnancy the uterus becomes increasingly response to oxytocin, and by the time labour begins it exquisitely sensitive. It is possible that the increased sensitivity of the uterus of oxytocin, occurring as pregnancy progresses, results from an increased affinity and/or capacity of uterine receptors for oxytocin (Soloff, M.S., et al., 1974; Pauerstein, C.S., 1973). Carsten (1974) found that oxytocin inhibited ATP-dependent calcium binding which caused calcium released from intracellular storage sites or that it increases the entry of calcium into the cell, these results are consistent with the uterine contractile action of oxytocin. Oxytocin in physiologic dose may be effective in stopping the hyper-contractility and in bringing about a uterine activity pattern indistinguishable from normal spontaneous labour (figure 5) (Danforth, D.N. and Hendricks, C.H., 1977).

The use of oxytocin is now widespread in obstetrics, and it is particularly useful for induction of labour and shortening the induction-delivery interval (Bradford and Gordon, 1968; Turnbull and Anderson, 1968; Liston, W.A., et al., 1974). Oxytocin is a potent and useful drug of enormous benefit to women in labour (Liston, W.A., et al., 1974).

Figure 4. Response to increasing doses of oxytocin administration, by constant pump infusion at 20, 30 and 40 weeks gestation. Contraction pattern inheavy squares is within range usually observed in normal labour that begins spontaneously. Hyper-contractility and increased tonus result from administration at excess rate; this abnormally high activity may interfere with fetal oxygen supply and occasionally may even cause repture of uterus (Danforth and Hendricks, 1977).

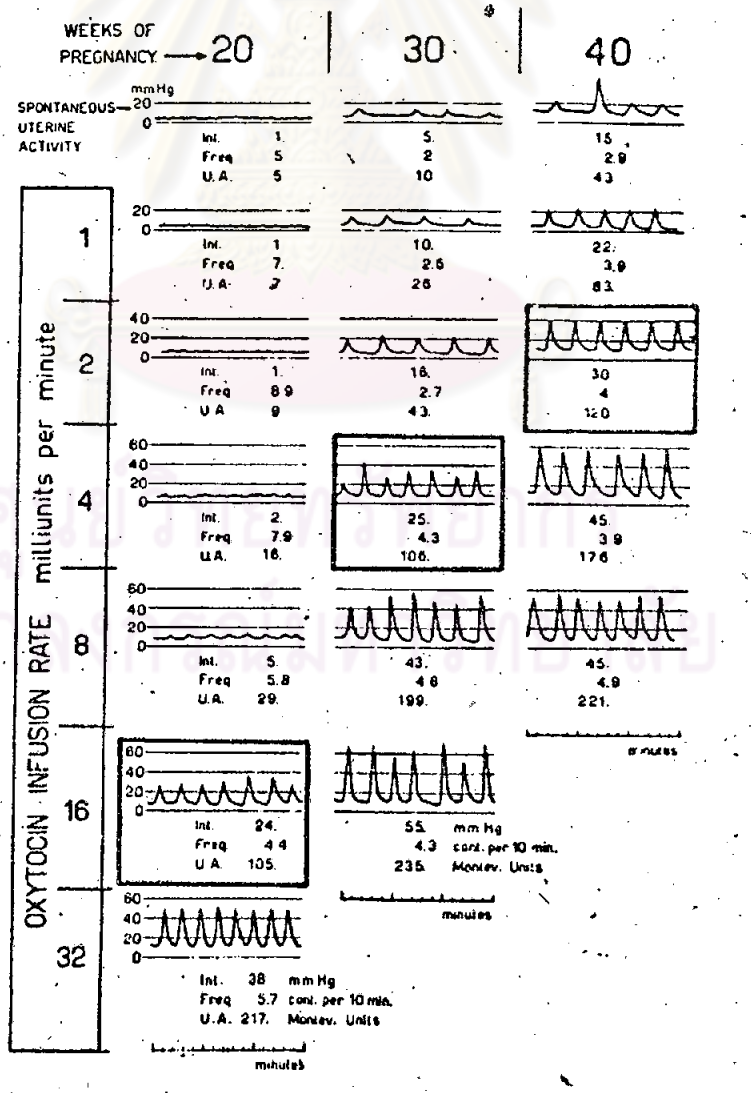
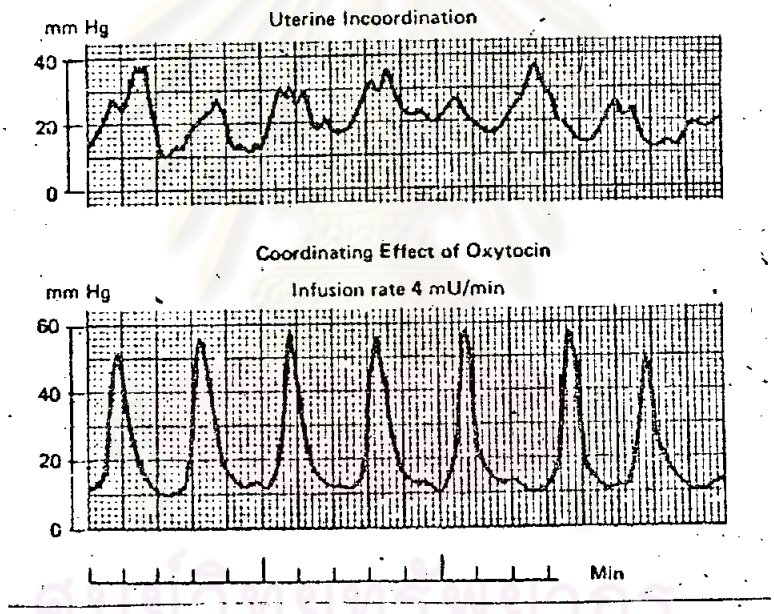


Figure 5. Effect of oxytocin in correcting uterine incoordination. Grossly incoordinated activity characterized by excessive frequency causing hypertonus (top), was converted to normal labour (bottom) by infusion of oxytocin, 4 mU/min. (Danforth and Hendricks, 1977).



If given orally, oxytocin is inactivated by trypsin. However, it is effective after administration by any parenteral route (Goodman and Gilman, 1975). Intravenous infusion of oxytocin is widely accepted as an effective and safe method for induction of labour. It has been shown that oxytocin given intramuscularly and the excessively large doses employed caused many serious obstetric accidents. Oxytocin given buccally does not ripen the cervix (Pauerstein, C.S., 1973 ; Ulmsten, U., et al., 1979). The regimen used was a modification of that described by Turnbull and Anderson in 1968, control of the rate of flow of an intravenous oxytocin infusion is required for safe induction of labour (Anderson, C.A., 1973). The infusion started with 2 nU./min. and was subsequently increased by 2 mU. every half hour up to 24 mU./min. (Ulmsten, U., et al., 1979). Steer, P.J. (1975) and Wolfson, J. (1976) had demonstrated that there is a stable phase in induced labour in which increased in oxytocin dosage do not produced any further increase in uterine activity. This enables the physicians to select the lowest dose of oxytocin which will produce the optimal uterine activity in each patient (Wolfson, J., et al., 1976).

The increased use of oxytocin for induction and stimulation of dangerous complications. Oxytocin should be administered to patient of high parity of advanced obstetric age (35 years old) with great caution. The dose should probably not exceed 8 mU./min. Oxytocin should be considered a potentially dangerous drug to be administered only when indicated, and under close supervision (Pauerstein, C.S., 1973). The side effect of oxytocin of clinical significance include :-

In Maternal

Uterine :- Excessive uterine contractility is almost always the result of excessive dose (Danforth, D.N. and Hendricks, C.H., 1977). Hypersensitivity of the uterus to oxytocin could trigger uterine hyperactivity, tumultius labour or uterine contracture that may lead to uterine rupture, cervical and vaginal lacerations, postpartum hemorrhage and fetal hypoxia, hypercarbia or death. The infusion should be immediately discontinued and appropriate measures taken as soon as any evidence of uterine hyperactivity or fetal distress occurs (Tepperman, H.M., et al., 1977).

Cardiovascular :- Intravenous administration of a bolus of 0.5-10 iu. oxytocin is associated with a transient fall (up to 30%) of blood pressure within 20-30 seconds followed by approximately at 30% increase in heart rate. (Tepperman, H.M., et al., 1977; Pauerstein, C.S., 1973). A healthy pregnant women can successfully cope with those side effect (Tepperman, H.M., et al., 1977). In 1913, Watson had noted that intravenous administration of this agent could cause pollar, cyanosis, tachycardia and sweating. After a dose of about 500 mU. the cardiac output rises the heart rate initially increases and then may fall during a period of secondary hypertension. The increase in heart rate is significant, varying from 10-34 beats/min. This immediate hypertension was followed by recovery within 3 minute and then return to base line within 10 minute (Pauerstein, C.S., 1973).

Renal :- Water intoxication is an uncommon complication of the infusion of oxytocin. It occurs when large dosages of oxytocin are administered with large volumes of electrolyte-free fluid over a prolonged period, so that the patient becomes water logged. This happens because oxytocin administered infusion rates of around 15 mU./min. and in excess of 45-50 mU./min. may act as an antidiuretic or to an increase in the renal tubular reabsorption of sodium and water. Water intoxication characterized by confusion, nausea, convulsion, and coma; was described in 1962 in association with the use of high doses of synthetic oxytocin for the treatment of missed abortion (Pauerstein, C.S., 1973; Danforth, D.N. and Hendricks, C.H., 1977; Tepperman, H.M., et al., 1977).

In Fetal or Neonatal,

To our knowledges the only complication that might be due to direct action of oxytocin on the fetal is "neonatal hyperbilirubinemia". A relation between oxytocin administration in labour and the subsequent development of neonatal jaundice was first suggested by Mast, et al. in 1971 and later studies have tended to confirm. Buchan, (1979) suggested that the vasopressin-like action of oxytocin caused osmotic swelling of erythrocytes leading to destruction deformability and hence more rapid destruction with resultant hyperbilirubinemia in neonate. Davies, et al., (1973); Chalmer, et al., (1975) and D'Souza, et al., (1979) had found a highly significant increase in the incidence of hyperbilirubinemia in neonates of mothers whose labour were induced by oxytocin. They postulated that there is an association between

neonatal jaundice and oxytocin, it may be due to a toxic effect of synthetic oxytocin. Liston and Campbell's study (1974) did not really show these effects to be due to oxytocin. Beazley and Alderman (1975) demonstrated that the proportion of babies who developed hyperbilirubinemia was directly related to the "total" dose of oxytocin used with a sharp rise when 20 units or more were given. D'Souza, et al. (1979) showed that higher doses of oxytocin administered are reflected by higher level of plasma bilirubin. Ghosh and Hudson (1973) "virtually eliminated neonatal hyperbilirubinemia of unknown etiology" in their hospital by lowering the dose of oxytocin used for induction. Friedman and Sachtleben (1974); Chalmers, et al. (1975) and Sim & Neligan (1975), all supported the suggest that there is a dose relationship. Jeffares (1977) suggested that a dose of about 20 mU./min. is required before the effect is apparent. This results suggested that oxytocin in high doses should be used with caution.

Other authors have failed to substantial of neonatal jaundice. Gould, et al. (1974) and Boylan (1976) had demonstrated that the infusion of 10 units of oxytocin during labour has no significant effect on mean bilirubin level of neonate on the fourth day. The discrepancy may be in the fact that these investigators compared mean neonatal bilirubin levels rather than the incidence of hyperbilirubinemia. However, when babies who develop hyperbilirubinemia are studied separately, it is possible to demonstrate a clear association between the use of oxytocin to induce labour and subsequent neonatal hyperbilirubinemia (Tepperman, H.M., et al., 1977).

Jaundice is the visible facet of many abnormalities, both of ever production of bile pigment "Bilirubin" and of underexcretion (Bissell, D.M., 1975). Jaundice is a frequent and important sign in the neonatal period. The sign jaundice was known in antiquity, but only vague references can be found in medical writing prior to 1750. At the beginning of this century, several authors published clinical description of neonatal jaundice and remarked that the disease could progress in intensity, leading to the appearance of neurologic signs, and ending in death (Amanullah, A., M.B., 1976; Schmid, R., M.D., 1970; Catz, C., M.D., 1974 and Levine, R.L., 1979). In 1916, Holmes referred to icterus as an common phenomenon during the first few weeks of life, present in 30 to 80% of all newborn infants. In 1974, Catz had observed that in newborn nurseries, about 50% of the full-term and 80% of the premature infants appear jaundiced. This review will cover selected aspected of bilirubin metabolism, with a concluding section on hyperbilirubinemia. The sources sites and mechanisms of bilirubin production are understudy (Bissell, D.M., 1975).

Bilirubin is a waste product of heme catabolism and prior to excretion must undergo metabolic transformations and be transported in and out of cells. Source of bilirubin consists of two components, one is from the metabolism of non-hemoglobin heme in extraerythroid tissue, primarily in liver and the other is an erythropoietic component brought about by ineffective erythropoiesis in the bone marrow (Amnullah, M.B., 1976). Approximately 80-85% of formed bilirubin originated from the breakdown of old red blood cells, which liberate

hemoglobin (Gartner, L.M., 1969 and Catz, C., M.D., 1974); 20% originated from other non-hemoprotein, viz, cytochromes catalases and myoglobins and so forth by an enzymatic mechanism (Mukerjee, A.B., et al., 1970 and Schmid, R., 1972). Over 90% of total heme in the body exists in this form (Bissell, D.M., 1975). Nearly 300 mg. of bilirubin is formed daily in a normal person and is handled entirely by the liver to maintain a serum level of less than 1 mg.%. Conversion of hemoglobin to bilirubin was showed in figure 6. Table 1 showed metabolic pathway of bilirubin and factors that may elevate bilirubin levels in the serum. The metabolic pathway of bilirubin is complex. From figure 7, bilirubin is primarily formed in the reticuloendothelial system (step 1), the enzyme heme oxygenase converts heme to biliverdin. Biliverdin reductase rapidly reduced the biliverdin to bilirubin (Amanullah, M.B., 1976). It is then transferred into the blood (step 2) where it is almost completely bound to serum albumin (step 3) in a molecular ratio of 2:1 (Gartner, and Arias, 1969; Bissell, 1975 and Miller, et al., 1978) leaving only a minute fraction unbound (Schmid, R., M.D., 1972). Albumin bound bilirubin does not enter intracellular fluid compartments and is non-toxic to mitochondrial suspensions. Ths binding is influenced by many factors and competition of fatty acids, drugs and so forth, and has resulted in the displacement of bilirubin (Amanullah, M.B., 1976). When the bilirubin arrived at the sinusoidal surface of the liver cells, the free fraction is rapidly taken up into the cell (step 4) and converted primarily to bilirubin diglucuronide complex (step 5). This conjugated from (direct-bilirubin) is then excreted in the bile (step 6) and passage in the intestine where bacterial flora convert in majority

Figures 6. Conversion of hemoglobin to bilirubin (Miller, et al. 1978, Smith's Blood Disease of Infancy and Childhood, 4th ed. p. 252).

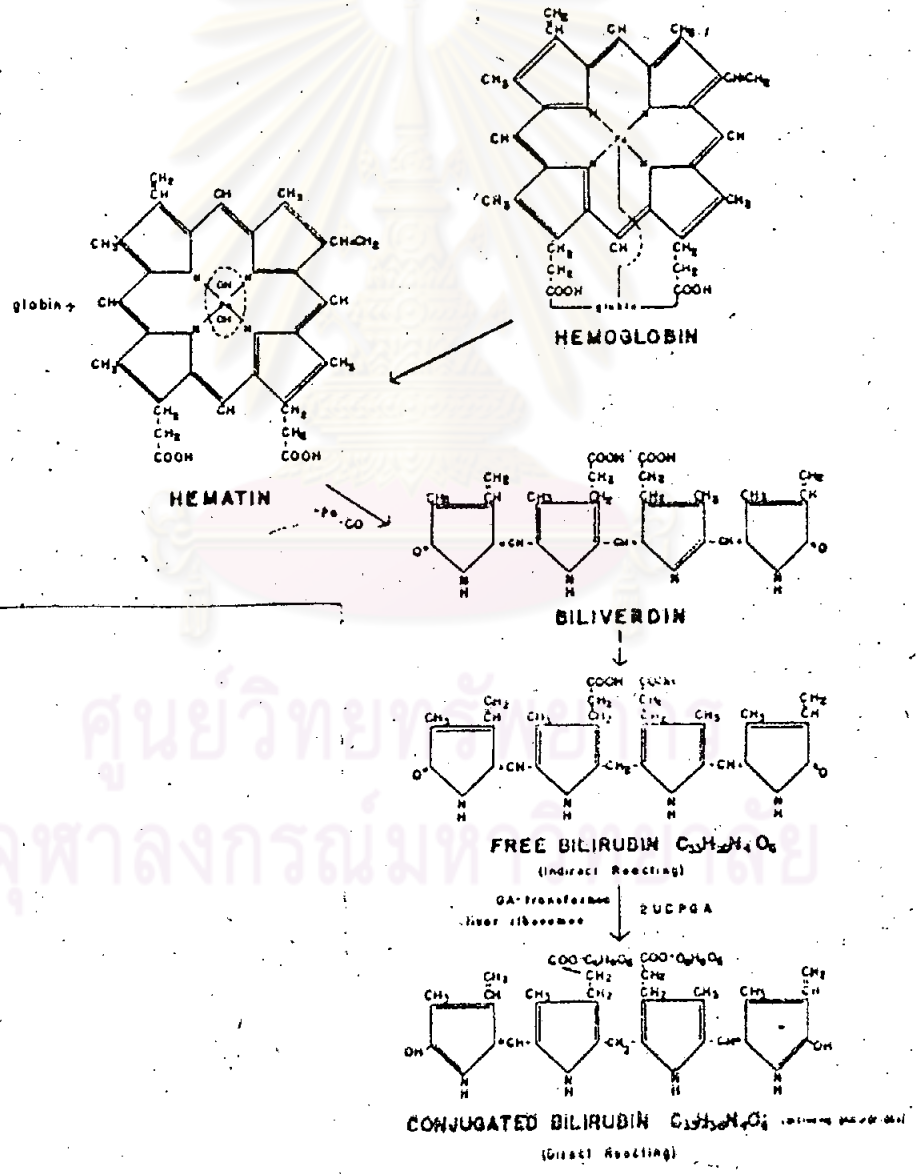
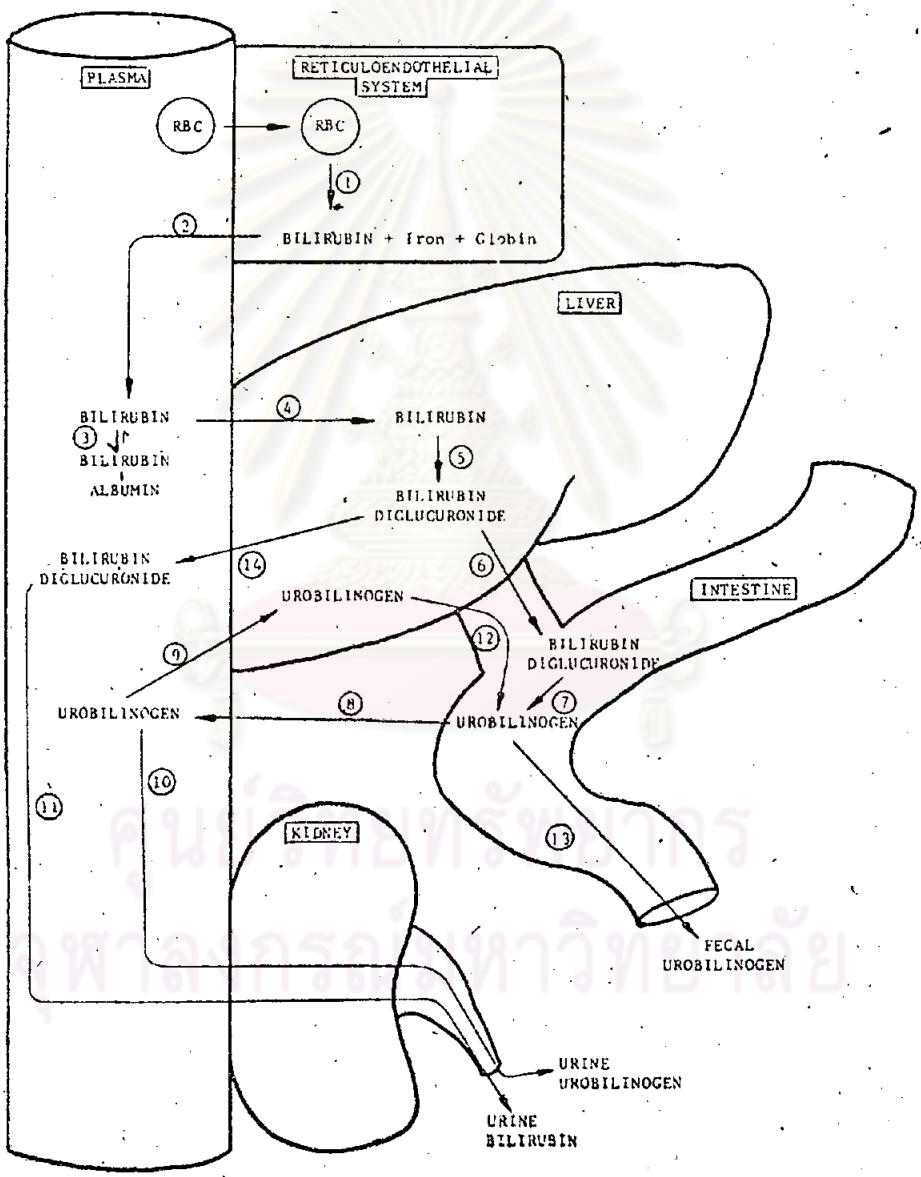


Table 1. Metabolic pathway of bilirubin and factors that may elevate bilirubin levels in the serum. (Sophie, H., et al., 1976, Medical Care of The Sick Newborn, 2d ed., p. 175).

Metabolic pathway of bilirubin	Factors that may elevate bilirubin level
Production RBC ⟶ Lysis ⟶ Unconjugated bilirubin (indirect acting)	Increased in hemolytic disease; sepsis (bacterial, viral, toxoplasmosis); hematomas, extensive ecchymoses, any enclosed hemorrhage; inherited red cell defect (G6PD, congenital spherocytosis)
Transport Plasma transport Bound to Albumin	Decreased serum albumin concentration; presence of substances competing for binding with albumin: sulfonamides, salicylates, heparin, caffeine, sodium benzoate, hematin, free fatty acids; acidosis impairs binding power of albumin
Conjugation and excretion Liver Intracellular binding to Y and Z proteins Glucuronyl transferase conjugation Bilirubin (direct type)	Immaturity of glucuronyl transferase system (preterm infants); defects in enzyme conjugating system (Crigler-Najjar); anoxia to liver cells—impaired function; pregnanediol (mother's milk) inhibition of glucuronyl transferase system
Excreted Bile, intestine	Blockage of bile canaliculi—biliary atresia, "inspissated bile syndrome"; increased absorption from intestine (enterohepatic circulation)
Enterohepatic circulation	

Figure 7. Metabolic pathway of bilirubin in man.
(Koda-Kimble, M.A., et al., 1978, Applied Therapeutics for Clinical Pharmacists, 2d ed., p.8).



of it to urobilinogen (step 7). Most of the urobilinogen is destroyed or excreted in the feces (step 13), very small amount is reabsorbed in the ileum into the circulation (step 8) and excreted through the urine (step 10). A portion of the small amount of urobilinogen in the blood is then reabsorbed into the liver (step 9) and sequently excreted in the bile (step 12). The mechanism by which conjugated bilirubin in liver cell is transferred to the blood (step 14) is not well understood. However, with many types of liver diseases, this conjugated form of bilirubin (direct-acting) is present in increased concentrations in the blood. When this concentration exceeds 0.2 to 0.4 mg.% bilirubin will begin appear in the urine (step 11). Unconjugated bilirubin (indirect-acting) is not water soluble and is highly bound to serum albumin. (Koda-Kimble, M.A., et al., 1975).

Clinically important jaundice undoubtedly is complex, involving more than one defect (Bissell, D.M., 1975). Jaundice in the neonatal period could be due to an accumulation of either unconjugated or conjugated bilirubin. The causes significance and treatment of these two types of neonatal jaundice are different (Amanullah, M.B., 1976). General mechanisms which increase the risk of jaundice and kernicterus can be divided into

a. increased bilirubin production,

b. decreased bilirubin excretion, due either to disturbance of liver function or to the presence of substances competing with bilirubin for conjugation by

the liver,

c. decreased albumin or substances competing with bilirubin for albumin-binding sites,

d. increased in unconjugated (indirect) bilirubin from the enterohepatic circulation, and

e. breakdown of the blood-brain-barrier to bilirubin (Gupta, J.H., 1977).

During pregnancy, the women should maintain her haemoglobin in excess of 11 grams per 100 ml. and their haematocrit over 33%. Childbearing represents a drain of approximately 725 mg. of iron from mother, and the maternal requirements for iron are 1 mg. per day in the first trimester, 4 mg. per day in second trimester and 12 to 15 mg. per day there after. Many authors had suggested routine oral iron therapy 10.6 to 1.8 gm. ferrous sulfate per day for all pregnant women. If pregnancy was healthy and the diet was normal, folic acid supplementation was not necessary. However, if the mothers had persistant vomiting or diarrhoea, supplemental folic acid should given. Megaloblastic anemia in pregnancy is almost always due to folic acid deficiency (Walters, W., W.A., and Humphrey, M.D., 1980).

Maternal diet and drugs during late pregnancy may have an influence on the subsequent bilirubin levels (Marx, G.F., 1961; Tan, K.L., 1977). Pregnant women suffered frequently from discomforts and disease such as headaches, anxiety, morning sickness, constipation, acid

ingestion and heart burn, urinary tract infection or pelvic pain etc.; and often needed some medication. Prescribed drugs given to a pregnant women may pass to the fetus (Marx, G.F., 1961) by the transplacental passage occurred as simple diffusion, active transport, pinocytosis, leakage and placental metabolism of drugs (Rennert, O.M., 1975). The pharmacokinetic considerations in maternal/fetal drug transfer were summerized in table 2 (Van Petten, G.R., 1975). Difference from adults in absorption, distribution, metabolism and excretion make neonates extremely sensitive to medication (Johnson, F.L., et al., 1977).
Some guidelines about drugs effects which regarded the prescription of drugs in the second half of pregnancy, can be drawn in three catagories:-

1. Drugs to be avoided totally because
    a. risks outweigh therapeutic benefit or
    b. safer alternatives are available.

        Barbiturates (in labour)

        Chloroquine (for rheumatoid arthritis)

        Chloramphenicol

        Iodides

        Live viral vaccines

        Methotrexate (for psoriasis)

        Tetracyclines

        Diethylstillbestrol (in early pregnancy)

2. Drugs in which safety not fully established

        Co-trimoxazole

        Diazoxide

Table 2. Pharmacokinetic factors in the fetal response to drugs administered during pregnancy. (Van Petten, G.R., 1975, British Medical Bulletin, 31:75-79).

Drug pathway	Factors determining fetal effect
Drug given to mother	Action of drug in mother: maternal absorption, distribution, metabolism and elimination.
↓	
Placental transfer	Bidirectional rate, matabolism and binding.
↓↑	
Fetal distribution	Unique aspects of fetal circulation, tissue and plasma protein binding.
↓	
Site of action in fetus	Fetal responsiveness.

Moduretic

Ethacrynic acid

3. Drugs used only with specialist supervision and with unequivocal indications.

Anticoagulants

Aminoglycoside antibiotics

Cytotoxic drugs

Hypotensive agents

Lithium carbonate

Oral Hypoglycemic agents

Systemic corticosteroids

Thiouracil (Stirrat, G.M., 1976).

Drugs which mothers had received in the third trimester of pregnancy and may have effects on bilirubin level in neonatal were shown in table 3 (Schenkel, B., et al., 1974). Durgs which displace bilirubin from binding sites on plasma albumin may also produce kernicterus in neonates, such drugs include sulphonamides, aspirin and other acidic anti-inflammatory drugs, and vitamin K analogues. These drugs can cross the placenta and should be avoided in pregnant women near term and used with caution in neonates (Bowman, W.C. and Rand, M.J., 1980). Drugs which displace bilirubin from binding sites on plasma albumin such drugs include :- Diuretic (Shankaran, S., et al., 1977; Wennberg, R.P., et al., 1977; Bowman, W.C., and Rand, M.J.,1980); Co-trimoxazole (Foar, B., et al., 1975); Antibiotic combination (Foar, B., et al., 1975; Loria, C.J., et al., 1976; Bowman, W.C. and Rand,

Table 3. Drugs reported to affect the fetus bilirubin level in the third trimester of pregnancy (Schenkel, B., et al., 1974).

Drugs	Effects
1. Anticoagulants of coumarin Type	Fetal hemorrhage and death
2. Long-acting sulphonamides:- Sulfadimethioxide Sulfamethoxypyridazine Sulfisoxazole	Hyperbilirubinemia and Kernicterus
3. Vitamin K (synthetic)	Hyperbilirubinemia and Kernicterus
4. Aspirin	Neonatal bleeding
5. Phenobarbital	Neonatal bleeding
6. Diphenylhydantoin	Hemorrhagic disease
7. Nitrofurantoin	Hemolysis
8. Antihistamine (phenothiazines)	Hyperbilirubinemia
9. Primidone	Fetal or neonatal hemorrhage
10. Thiazides	Fetal or neonatal jaundice.

M.J., 1980); Indomethacin (Rasmussen, L.F., et al., 1978); Diazepam (Drew and Kitchen, 1976); Vitamin K analogue (Bowman, W.C. and Rand, M.J., 1980); Sulfisoxazole and Sulfonamide (Yocabi, A., et al., 1977; Øie, S., et al., 1979); Salicylic acid (Yocabi, A., et al., 1977; Odell, G.B., 1959; Levy, G., 1975; Øie, S., et al., 1979); Sodium benzoate (Odell, G.B., 1959).

Other numerous factors which have been implicated as causes of neonatal hyperbilirubinemia and jaundice, they include :- gestational ages (Scheidt, P.C., et al., 1977); excessive hemolysis resulting from Rh factor and/or ABO blood group incompatibility (Sophie, H., et al., 1976, and Gupta, J.M., 1977); epidural anesthesia (Gould, S.R., et al., 1974); infection (Gupta, J.M., 1977; and Jeffares, M.J., 1977); glucose 6-phosphate dehydrogenase deficiency (Arias, I.M., et al., 1964; and Millbauer, B., et al., 1973; Panizon, F., 1960; Smith and Vella, 1960; O'Flynn, M., E.D., and Hsia, D.Y., 1963; and Eshaghpour, E., et al., 1967)' breast feeding and oral contraceptive (Newman and Gross, 1963; Lauritzen and Lehmann, 1967; Kovisto, et al., 1971: Wong and Wood, 1971; McConnell, et al., 1973; Gould, S.R., et al., 1974; Jeffares, M.J.,1977); sex (O'Flynn, M., E.D., and Hsia, D.Y., 1963; Fenwick, J.D., 1975; and Lathe, G.H., 1979); instrumental delivery (Champbell, et al., 1975); smoking (Bowman, W.C., and Rand, M.J., 1980); and low birthweight (Billing, B.H., et al., 1954; Fenwick, J.D., 1975; and Schedit, P.C., et al., 1977).