Ancient medicine took periodicities into account. Early western medicine inherited a residue from ancient moon cults, from fertility rituals calibrated to the phases of moon. Early Greek therapies involved cycles of treatment known as matasynchronasis.

The acceptance of circadian rhythmicity as a property of living organisms owes, much to the work of eighteenth and nineteenth century plant physiologist. According to Aschoff, the first doctoral thesis on biological clock was written by Julien - Joseph Virey in 1814. From qualified examples Virey concluded that any given drug (or food) is not indicated equally at all hours (within 24 hours scale) and that we need urgently to learn more about this problem. Credit must be given to Jores, Mollestrom & Menzel for their pioneer work in the foundation of today's chronopharmacologic investigations.

Richter (1952) was among the first to remark on the persistence of diel - rhythm of activity in mammals (The common rat housed in constant darkness). It was however, Jhonson's landmark study (1926) with wild caught peromyscus leucopus that anticipated further developments by about three decades and he concluded that the activity rhythm was not directly dependent on the daily fluctuation of environmental condition and was an internal physiological rhythm. Jhonson subsequently suggested that the animal has an exceptionally substantial and durable self winding and self regulating physiological clock.
Recurring phenomenon which take place at roughly 24 hours interval, such as the down chorus of the birds or the flights of bats, are well known. Most organisms living under natural conditions exhibit behavioural, physiological and biochemical rhythmic patterns. Rhythmicity is a fundamental property of all living organisms - from single cell to complex animals and plants.

The call for the "Working Out" of the clock mechanism remained unanswered from the 1920's until 1960's. Isolated investigations of diurnal rhythmicity subsequent to various natural interactions were reported in subsequent decades. Most prevalent view was expressed by Horker (1958) that there is a basic 24 hours rhythm present in the cells of all animals and that any cell or group of cells of all cells could constitute a circadian clock.

The term circadian was introduced by Halberg (1959) and has passed into general use owing to the ambiguity of the word diurnal which is better used in contrast to "nocturnal". Circadian is also useful to describe cycles whose length differs slightly from 24 hours, with "infradian" and "supradian" for those much shorter or longer. Cycle is likewise used for the smallest but of a rhythm that repeats itself irrespective of casual origin. The time occupied by a single cycle is called period. Other less common rhythms are circaceptan (weekly), circatrigintan (monthly) and circannual (annual). Circadian rhythms have major adoptive significance, because they help to synchronize the organism to periodic fluctuations in the external environment and also facilitates integration
of the individual's internal milieu. A phrase coined by Aschoff (1964) that Circadian rhythms establish a mirror of the changing external world in the internal milieu and thereby prepares organism for programmed or predictable environmental changes, clearly shows the importance of these rhythms in our day to day life.

Most men are subjected throughout their lives to an alternations of light and darkness, with an almost constant cycle length of 24 hours. This determines a pattern of behaviour with alternating periods of rest, activity, meal etc. extending throughout our social organization and thus potentially influencing in innumerable ways in persons without light and persons notably night and shift workers, whose habits depart from customary pattern. Aschoff (1955) refers to 40 known circadian variation in environment.

Each minute in the life of a human being, animal or plant is under the influence of a spectrum of biological rhythms oscillating at hourly, 24 hourly, monthly and some times seasonal intervals. These rhythms were given to man and animals by nature, they command his mood, determine his work efficiency, his inclinations and control his physiological functions (Halberg, 1969).

Biological rhythms are teleologically regulated (J.Blume, 1975) and are endogenous (Bunning, 1978). Human beings have a daily rhythm of sleep and wakefulness which inturn is correlated with the corresponding rhythmic activities of the respiration, cardiovascular, nervous, endocrine, digestive and excretory system (Sunder Raj, 1980). The characteristic
circadian rhythms of activity and sleep, of urine constituents, of temperature, and performance do not disappear, when man are removed from clocks and time cues of but have persisted in volunteers who lived for as long as 6 months in deep caves or in simulated space capsule. If a person were to see a calendar of his life he would be startled to see that many recurrences of his moods and his periods of illness or strength were predictable.

Today it is known that some rhythmicity of different physiological functions are inherited in every biological system, while other rhythms of the animal adopt themselves to the environment. As the adoptive value of living being and their system to the environmental rhythm was recognised the theme of chronobiology started.

Light is the principal entraining agent. In nature, the period of day-night cycle is constant at 24 hours (T is the period of entraining stimulus), although the duration of light phase and the intensity of the illumination are among the several parameters that vary on the daily and seasonal basis (B. Rusak, 1979). In tropics - the alternating phases of light and darkness are of similar length during the whole year but further from the tropical region they become unequal (Mills, 1966).

Circadian rhythm and their application in the diagnosis and treatment of some diseases:

Because the biological system is rhythmically changing, it follows that the organism is biochemically a different entity at different circadian phases. Therefore, it reacts differently to the same stimulus
at different times. This difference in response to identical stimulus at different phases of circadian system repeatedly has been documented for a variety of stimuli. These includes -

(1) Drugs.
(2) Poisons.
(3) Chemicals.
(4) Physical agents such as noise and X-Ray radiation and
(5) Biological agent such as endotoxins.

The study of biorhythms of the body is helpful not only in diagnosis but it also plays a very important role in optimizing the time of treatment, health monitoring and family planning to specified stages of circadian rhythmic variables, identified by chronotherapeutics or other marker rhythms (Halberg, 1977).

The applied importance of chronobiology is best demonstrated by citing some examples -

(1) How a single measurement of any variable may be misleading is exemplified by the blood levels of corticosteroids. In human each day, the concentration of adrenocorticosteroids in blood is transiently low enough to be consistent with the diagnosis of Addison's disease of adrenal insufficiency and about 12 hours later the concentration is likely to be compatible with Cushing syndrome of adrenal hyperfunction.

(2) Blood pressure of a person taken at one time may be normal while it may be more enough to level as hypertension at another time on the same day.
Alternations of normal circadian rhythms provide diagnostic cues to some illness as well. For example, many emotional illnesses are preceded by insomnia which can be described as a profound disruption and sleep-activity cycle. Patients with depression often complain of insomnia; many of them suffer from a broken sleep whose cycles are fragmented and shortened. Anti-depressant drugs that cause them to feel better also lengthen sleep cycle.

Dr. A. Reinberg has shown that dust sensitive housewives or hay fever victims will suffer their largest histamine reaction at night, just before their usual bed time. So at night antihistamine drugs may have their most palpable effect.

Immunity to infection is also rhythmic, for example mice have shown to be most vulnerable to pneumonia infection at the end of the activity period of darkness. Circadian rhythms in immunity or susceptibility could mean that the timing of vaccinations might enhance their effectiveness. Healthy volunteers, immunized against Venezuelan equine encephalomyelitis seemed better protected if they received their vaccine at 8:00 A.M. rather than 8:00 P.M. Since gamma globulin are different at one hour than another, immunization is likely to be altered by time.

Biological time is also important for accurate biopsy and laboratory tests, because protein binds differently according to the time the tissue and other biological samples taken from the body, even the histologist needs time of day information in making plates. Cell division reaches its peak in various tissues and organs at various times of the cycle. Thus in biopsy too, it is necessary to know the phase of the cycle from which the tissue was taken.
Dr. A. Reinberg and Jean Ghata have indicated that responses to penicillin, antihistamine and aspirin are biased by the time of day or night they are taken.

In Addison's disease, when patients are asked to choose a daily dosage schedule that minimized their fatigue and optimized a sense of well being they took two third of their dose upon rising in the morning, and a third later in the afternoon or evening.

Where it is known that death from a particular disease is more common in the small hours of morning, then obviously the appropriate emergency resuscitative services must be suitably altered at the appropriate hours.

Cyclophosphamide and cytosine arabinoside are far more toxic at one phase of the circadian system than at others (Chronobiologia, 1979).

Even susceptibility to drug and toxic agents varies with the body's circadian and circannual rhythm, e.g. a given dose of an E. coli endotoxin will be more lethal to mice when administered early in evening (95%) rather than when administered 8 hours later (17%).

**Development of Circadian rhythm in infancy:**

Any aspect of infant development can be considered as resulting from two distinct influences: a spontaneous maturation process and the accumulation of experience. Upon emerging from the uterus, the human infant is suddenly exposed to a great variety of new sensory
experience, and this sensory experience most notably follows a very pronounced nyctothemeral rhythm. The alteration of light and darkness is perhaps the most obvious of such external rhythm; but similar alterations of noise and silence, and perhaps of the attention which the infant receives from adults, may also be of importance.

Most workers agree that there is no rhythm of sleep and wakefulness during the first week of life, though in infants who are not fed during the night there may be a pronounced nyctothemeral rhythm of activity which simply represents a great increase in restlessness when the infant has been nearly 8 hours without meal (Hellbrugge, 1960).

In 1967, Franks reported that a change in plasma 17-hydroxy corticosteroids similar to the adult pattern did not emerge in infant before 3 years of age. However, it was later demonstrated that as early as 2.1 months of age, the morning plasma cortisol concentration was significantly higher than the afternoon concentration. The time of its emergence has great significance from the view points of developmental biology, especially developmental photobiology in phototherapy for neonatal hyperbilirubinaemia, chronopharmacology, chronotoxicology and others.

REVIEW OF CIRCADIAN PERIODICITY OF PLASMA CORTISOL:
Characterization & Physiological basis of the normal Circadian pattern of plasma corticosteroids and ACTH levels:

The existence of a circadian periodicity of plasma corticosteroid level has been well established in man (Migeon et al, 1956), numerous
mammals (Halberg, 1969; Singh et al, 1975) birds (Dussaeu and Meier, 1971) and teleosts (Singley and Chavin, 1971). A circadian rhythm of oxygen consumption has been described (Andrews & Folk, 1964) in cultured hamster adrenal glands which would imply some periodicity even at this level. In the adult human, the circadian pattern consists of corticosteroids level peaked in the morning hours with a smooth progressive decline over the ensuing 24 hours period (Perkoff et al, 1959). Reversal of the day-night schedule results in a phase reversal of the circadian pattern within a period of approximately 8 days (Perkoff et al, 1959). In nocturnal animals peaks corticosteroid levels are seen in the early evening hours (Guillemin et al, 1959).

The major early morning circadian rise of plasma corticosteroid and ACTH level reflects a circadian, neurally mediated release of corticotrophin-releasing factor and consequently of ACTH, during a delimited critical period in the 24 hours cycle with subsequent corticosteroid and ACTH levels reflecting a combination of metabolic disposition and the effects of environmental or other endogenous stimuli on CRH release (Krieger & Krieger, 1967; Ceresa et al, 1969).

A circadian periodicity of plasma ACTH levels has been reported in the human with Addison's disease (Graber et al, 1965; Besser et al, 1971) and in adrenalectomized rat (Cheifetz et al, 1968).

There is other evidence which support the concept of a central neural basis for the circadian periodicity of plasma ACTH and cortisol level, as the development of certain areas of the mammalian nervous
system continues postnatally and it is known that the development of many circadian processes (i.e. pulse, body temp.) is dependent upon a certain level of CNS maturity (Hellbruege, 1960).

Neurotransmitter regulation of basal and circadian aspects of ACTH secretion is generally accepted (Krieger, 1973) as a CNS regional circadian periodicity of acetylcholine (Hanin et al, 1970), nor-epinephrine (Reis et al, 1968) and serotonin (Reis et al, 1969).

It has been known for many years that the urinary excretion of 17-Ketosteroids varies throughout the day (Pincus & Hoagland, 1943). Similarly the plasma steroid level also varies, lowest values are found at night, around midnight and the highest value occurs around or before the time of awakening i.e. about 6.00 A.M. (Bayliss, 1955; Bartter et al, 1962). This variation persists whether the subject is up and about his daily work or whether he is confined to bed and receiving a constant amount of food, every two hours.

In Northern hemisphere the annual peak time in plasma cortisol and urinary 17-OHCS is located in cold months (Watanabe, 1964; Ahuja & Sharma, 1971; Weitzman et al, 1975 and Reinberg & Laboguey, 1978). A roughly similar pattern has been found for radio-immuno-assayable plasma ACTH (Copinischti et al, 1977).

Rhythm in plasma corticosteroids completely disappeared in a man who spent 3 moths alone underground, even though he followed a regular circadian cycle of activity, meals and sleep (Mills, 1964).
The rhythm is also absent in diseases associated with altered state or consciousness or an abnormal sleep pattern, delerium, semicoma or coma (Perkoff et al, 1959). It is also said that normal rhythm is lost only in C.N.S. diseases affecting temporal lobe or pretectal region (Krieger, 1961).

**Animal Studies in Plasma Cortisol Periodicity:**

(1) **Alteration of neurotransmitter levels**

Obliteration of the circadian variation of plasma corticosteroid level in the cat has been achieved by alteration of central neurotransmitter content or action like acetylcholine (Krieger et al, 1968) and serotonin (Krieger & Rizzo, 1969) as circadian periodicity in these neurotransmitter has been found as well.

(2) **Effect of CNS lesions**

In the rat, anterior hypothalamic lesion (Slusher, 1964), complete hypothalamic differentiation (Halasz et al, 1967; Palka et al, 1969 and Greer et al, 1972), anterior hypothalamic differentiation (Moore and Eichler, 1972), Fornix section (Moberg et al, 1971 and Lengvari & Halasz, 1973), suprachiasmatic lesions, (Moore & Eichler, 1972) and median, forebrain section (Moore & Qavi, 1971) have been reported to obliterate corticosteroid periodicity.

Section of the primary or accessory optic tracts in the rat does not affect corticosteroid periodicity.
(3) **Role of Light and Darkness:**

Light-dark transition and sleep-wake transition both have been implicated as phase regulators of corticosteroid periodicity. There is direct correlation between the amount of light entering the eye of young kittens and the number and histological appearance of cells in the lateral geniculate nucleus (Weisel & Hubel, 1963). The time of eye-lid opening in the newborn rat correlates closely with the time of appearance of neurosecretory material in the supra-optic and para-ventricular nuclei (Fiske & Leeman, 1964).

As regard to the effect on corticosteroid circadian periodicity, there is no critical period in development during which normal light-dark alteration has to be present for such corticosteroid periodicity to occur i.e. animals exposed to constant light or dark until adulthood (and manifesting abnormal periodicity at that time) can regain normal periodicity when exposed to normal light-dark condition. Conversely, animals reared in normal light dark until adulthood and then exposed to constant light or dark, lose their previously normal corticosteroid periodicity (Krieger, 1973). Animals sacrificed under constant light conditions had higher daily mean levels of plasma cortisol, while those reared in constant dark had lower levels. Enucleated animals also showed altered periodicity. Therefore, a non-visual, photically stimulated retinal mechanism is involved in such periodicity (O'steen & Anderson, 1971).

(4) **Relation to Feeding**

Restriction of the water intake of rats to a brief period within day time hours is associated with elevated morning corticosteroid
levels and perhaps an altered rhythmicity of these levels (Johnson & Levine, 1973). Thirst utilizes cholinergic mechanism, eating and adrenergic mechanisms (Grossman, 1962). The change in the levels of these neurotransmitter which is brought about by the thirst or hunger, is responsible for the change in corticosteroid periodicity.

(5) **Role of Neonatal Hormone Level:**

Cyclicity of plasma corticosteroid levels in the rat appears at 3-4 weeks of age (Krieger, 1972). It was found that the circadian periodicity of plasma corticosteroid levels of 30 days old animals was suppressed if corticosteroids were administered systematically between 2 to 4 day of neonatal life, but not if they were given between 12 to 14 day of neonatal life.

**Human Studies In Plasma Cortisol Periodicity:**

(1) **Characteristics of Normal Periodicity**

In order to assess the significance of any observed alterations in corticosteroid periodicity present in disease, or following pharmacological or environmental manipulations, criteria for normal periodicity must be well defined. To this end, data obtained from half hourly sampling studies (Krieger et al, 1971) were utilized to construct criteria for establishing the presence of normal periodicity under clinical conditions where less frequent sampling is feasible. Normal periodicity of plasma corticosteroid levels was defined as one in which all corticosteroid values after 0800 were less than 75% of the 0800 level excluding consideration of noon time.
level because of the great variability in the amount and height and of peak time at this time (12° levels 15% or more greater than 0800 level are considered abnormal). Age (between 15 and 95 years), sex, hospitalization, constant glucose infusion or half hourly feeding over a 2 day period had no effect on circadian patterns (Krieger et al, 1971). In a given subject corticosteroid levels and patterns were reproducible over 1 to 120 days interval. The circadian peak in steroid is suppressible.

(2) **Effect of Drugs** -

It has not been possible to block the circadian rise in plasma corticosteroid levels in man by the administration of either atropine (3-6 mg. s.c. administered between midnight and 02°) or sodium phenobarbital (400 mg. p.o. similarly administered). These drugs are effective in blocking such a rise in the experimental animals (Krieger et al, 1968).

Administration, in a therapeutic regimen, over a two week period of reserpine, chlorodiazepoxide, meprobamate or chlorpromazine or of diphenylhydantoin over a two or eight week period, was also ineffective in blocking the circadian rise (Krieger and Krieger, 1967). The last daily dose of any of these drugs was administered at 21°, perhaps a time too premature for the drug to be able to block subsequent naturally mediated CRF release during the critical period.

The degree of induced suppression of adrenocortical activity in health depends upon the dose and type of agent used, e.g. corticosteroids or others, the duration of treatment, the physiological time of agent administration (Induce et al, 1980). Dexamethasone 21-phosphate
was administered at different circadian stages in accordance with earlier work on the importance of timing in dealing with effects of corticoids and ACTH (Giusti et al, 1967 and Grant, 1965), and was found that in subjects resting from 22:00 - 06:30, administering dexamethasone at 16:00 can be viewed as treating 13:45 hours (Halberg et al, 1984). After midsleep, when cortisol seemed to be most suppressed. This is about the time when a single dose of methylprednisolone maximal imporves the mesor of peak expiratory flow in asthmatic children (Reindl et al, 1969).

(3) **Effect of non CNS diseases:**

Abolition of the circadian pattern of both plasma free and conjugated corticosteroids and urinary free and total corticosteroids has been reported in patients with liver disease (Tucci et al, 1966). This was assumed to be secondary to the decreased rate of cortisol removed from the plasma in such patients; the effect of possible alterations in proteins binding was not investigated. The reported absence of corticosteroid circadian periodicity in patients with chronic congestive failure (all of whom had right sided failure) may probably be ascribed to the hepatic involvement in such patients (Knapp et al, 1967). Patients with acute illness without mental confusion and chronically ill patients without liver or kidney disease exhibited normal circadian variation (Sholiton et al, 1961). These authors noted that alert, ambulatory lung cancer patient exhibited a slightly decreased circadian variation, whereas circadian variation was absent (there was no drop from normal peak levels) in patients with advanced bronchogenic carcinoma. It has been recently demonstrated (Gewirtz and Yalow, 1974) that after noon plasma
ACTH levels are elevated in 50% of patients with bronchogenic carcinoma without clinical Cushing's syndrome - the lack of clinical symptomatology being due to the fact that the ACTH measured was predominantly big ACTH which has decreased biological activity compared to normal, little ACTH (Gewirtz et al, 1974). Continued secretion of this less active form, especially should it be shown to have a larger half life than little ACTH, could explain the lack of circadian variation noted in the patients with bronchogenic carcinoma.

(4) Effect of Organic C.N.S. Diseases:

Patients demonstrating disturbances of consciousness with either acute systemic disease (Sholiton et al, 1961) or with chronic diffuse C.N.S. disease (Perkoff et al, 1959) have been reported to show absence or alteration of corticosteroid periodicity. In view of animal studies demonstrating the importance of hypothalamic-limbic system areas in the regulation of such periodicity, it was felt that abnormal periodicity might be encountered in conscious patients with disease delimited to these areas.

Krieger (1961 & 1973) and Krieger & Krieger (1966) have studied 43 conscious patients with radiographically and clinically localized hypothalamic or limbic system disease, of whom 53% had abnormal (phase reversal or peaking at normally quiescent times of day) corticosteroid patterns, as determined either by sampling at half hourly or 4 hourly intervals. In contrast, only one of 21 conscious patients had a normal pattern. Abnormal pattern were encountered in 31% of 27 patients with non-functioning pituitary tumours and in only 1 of 8 acromegalic subjects. Examination of human retardates and brain damaged patients for adrenocortical rhythm has been done. In Mangoloids, urinary 17-OHCS and 17-Ketosteroid were found to be lower than normal (Reis et al, 1965).
These studies would indicate that pathways involved in the regulation of circadian corticosteroid periodicity in the human occupy a delimited CNS area, roughly similar to that demonstrated in animal lesions.

(5) **Effect of Psychiatric Illness:**

Studies of circadian periodicity of corticosteroids in depressive states have yielded somewhat conflicting results. There appears to be general agreement that such periodicity is normal, though maintained at higher plasma cortisol levels in mental disorders (Bridges and Jones, 1966; Fullerton et al, 1968 and Carpenter et al, 1971). Carpenter and Bunney (1971) has investigated the aspects of central controls of cortical activity and peripheral metabolism. These results suggest that the central control mechanism function normally during depression but the peripheral measures of cortisol activity revealed interesting abnormalities. During depression both the production rate and the metabolic clearance rate were elevated, but a normal, 24 hours mean plasma cortisol concentration was maintained. On recovery of the production rate falls, while the metabolic clearance rate remained high, resulting in low plasma cortisol concentration. Sachar et al (1973) demonstrated an increase in the number, magnitude and duration of cortisol secretory episodes in such patients but the major rose still occurring in the early morning hours.

A study of manic patients also reports normal periodicity but there were only two sampling points over the 24 hour period (Carpenter & Bunney, 1971). Recently concluded studies with half hourly sampling over 48 hours, each during a manic and depressed stage in a patient with monthly depressive cycles, revealed normal periodicity during the depressed phase and an arrhythmic series of peak with no circadian rise during the manic
phase, A manic depressive with a short cycle is fortunate, for his swings will be detected and treated. Manic depressive with long swings are likely to go undetected and may do themselves harm in their manic phase by serious misjudgement and grandiose illusions whether the alteration during the manic stage is related to the lack of sleep is problematical. Two reported studies on prolonged sleep deprivation (81/2-9 days) report normal (Poland et al, 1972) and abnormal periodicity (Slater et al, 1967). The secretory pattern of cortisol in narcoleptic patient is not different from that of normal subjects. A normal periodicity based on two sampling points has been reported on schizophrenic subjects (Kallio et al, 1961).

(6) **In Cushing's Disease**: The absence of a circadian periodicity of plasma corticosteroid levels (as determined by relatively in frequent sampling) in Cushing's disease and syndrome is well known (Doe et al, 1960). Corticosteroid levels are depicted as being essentially unchanged over the 24 hour period. In half hourly sampling studies on patients with Cushing's disease (Krieger et al, 1971), it has been demonstrated that these levels are not constant, but instead show continuous irregular oscillatory patterns. These patients in contrast to normal subjects, also do not display a greater proportion of peaks during the early morning hours. Such abnormal periodicity is present in patients with Cushing's disease when both clinically active and when in remission (Krieger and Glick, 1972), a normal pattern was seen in a patient with Cushing's syndrome following removal of an adrenal adenoma, the absence of a clearly defined circadian surge, and the presence of an abnormal corticosteroid
periodicity even when these patients are in clinical remission, together with
evidence of altered sleep EEG stages and periodicity of growth hormone release
in patients with both active disease and in remission, would suggest a mal-
function of central nervous system locus as being entiological in this disease.

(7) **Effect of Light-dark**

Effect of light and dark on the circadian pattern in general
and on diurnal rhythmicity of corticosteroids has been studied in details.
It was found that the normal early morning circadian rise still occurred in
normal subjects exposed to either 21 days constant light (Krieger et al,
1969) or 4 (Aschoff et al, 1971) or 10 days (Orth et al, 1969) of constant
darkness. (In the later instance there was a 1 hour period of light from 18°
in the constant light studies even though the same intensity of illumination
was present during the time when the subject was awake or asleep, eye-lid
closure may have diminished the amount of light impinging on retina). These
studies would indicate a minor role of light dark influences on the circadian
corticosteroid rise unlike the animal studies.

There are other studies, however, which indicate some
role for light-dark. Normal awake subjects after 13 days of light-dark reversal
(but not sleep-wake reversal) also showed a corticosteroid rise following light
on at 18° in addition to the early morning circadian rise (Orth & Island,1969).
In further studies by these investigators, it was noted that when the period
of dark was prolonged for 4 hours after morning awakening, although the
early morning circadian rise began during sleep, its time of peaking was
delayed until light onset. This might indicate as suggested above, a role for
light merely in entrainment of the rhythm.

These studies point out the difficulty of describing the parameter that influence the neurochemical and neuroanatomical substrate involved in the regulation of corticosteroid circadian periodicity or should be noted that individuals vary greatly in the time required and their ability to make phase adjustments, although a phase shift of plasma corticosteroid periodicity usually occurs within 8 days of light-dark, wake-sleep, phase shift (Sharp et al, 1961; Flink, 1959 and Doe, 1960). On the basis of available evidences it would appear that there is an endogenous 24 hour periodicity of corticosteroid levels, basically related to sleep-wake, in which light can act either as an entraining agent, or independently (outside of the period of major circadian rise), cause elevation of corticosteroid levels.

(8) **Response of CNS - Pituitary - Adrenal axis to stimuli at different points in Circadian Cycle**

There have been several studies reporting greater pituitary adrenal responsiveness to metyrapone (Martin and Hellman, 1964), vasopressin (Clayton et al, 1963) and pyrogen (Takebe et al, 1966) when these are administered in a period temporally proximal to the time of the beginning of the circadian rise (i.e. 23°00' - 04°00' ) than when they are administered subsequent to this time (i.e. 06°00' - 09°00' ). This could be explained by an increased amount of ACTH or CRF being available for discharge by these stimuli at this former time.

(9) **Physiological Significance of Corticosteroid Circadian Periodicity :**

Although periodicity of function is apparent at a cellular
level with increasing functional complexity of an organism, the necessity of hierarchical regulation of such periodicity becomes evident. There are a multiplicity of periodic functions described in the organism. Some of these may merely be an expression of regulation by a more fundamental oscillator. Pittendrigh (1960) has said "for instance the known physiological links between adrenal activity and virtually every other aspect of mammalian metabolism could be the basis for regarding whole complexes of rhythm as only forced by the rhythmic activity of these endocrines". It is apparent, however, from all of the foregoing evidences that the substrate for the genesis of corticosteroid circadian periodicity resides within the central nervous system.

**PLASMA CORTISOL AND DISEASE INCLUDED IN THIS STUDY**

Patients of (i) Breast cancer (ii) Pulmonary tuberculosis and (iii) Tropical Pulmonary Eosinophilia were included in the present study. So far little is known about the circadian nature and the role of pathophysiological stress of above diseases on the adrenocortical secretory and excretory pattern therefore, the present study was planned.

(i) **Plasma Cortisol and Breast Cancer** :-

The significance of the breast cancer problem is obvious with over one million cases of breast cancer in women reported world-wide each year. Incidences of breast cancer continue to increase globally, especially in western countries and in developing countries (Caulter et al, 1976). It has long been recognized that the female reproductive organs have a role in the genesis of breast cancer, Ramazzini (1713) commented on the mysterious
sympathy that exists between the female genital organs and the breast over
two centuries ago. A century later, Rigoni Stern noted that the Catholic
Sisters of Verona Italy had an increased risk of breast cancer compared
with non-monastic women (Clammensen, 1951). Recent epidemiologic studies
have focused on the potential effect of endogenous and exogenous hormonal
factors on the risk of developing breast cancer. Several hormonal factors
have been identified that appear to alter a woman's risk of developing breast
cancer. Breast cancer has been found to be more common in single than
in married women, occur more frequently in non-parous than parous women
and to be correlated with age of first pregnancy (Logan, 1953, Mac Mahon
demonstrated the single most important factor relating pregnancy to breast
cancer is the age of the mother at first birth. Pregnancy is characterized
by a vast change in a variety of hormones. The protective effect of early
pregnancy may be related to changes included in the breast by these hormones
rendering breast tissue less susceptible to carcinogenesis. Prolonged exposure
to endogenous estrogens may increase the risk of breast cancer. Women
with early menarche and with late age of menopause appear to be at increased
On the other hand, those women with early menopause appear to be afforded
It has been suggested that estrogen may be particularly effective in increasing
risk when exposed by progesterone as in the follicular phase of the menstrual
cycle or in cycles with a deficient luteal phase (Shermann & Korermann,
1974 and Sherman et al 1982). There appears to be a firm relationship between
obesity and risk for breast cancer (Hankin et al, 1978, de Weard et al, 1977). In postmenopausal women, the major source of estrogens is from the extra-glandular conversion of androstenedione to estrone, a principal site for this conversion is fat cells. Thus heavy women would be expected to have elevated estrogen levels. The evidence for the association of estrogens and oral contraceptives in the development of breast cancer has been extensively detailed (Drill, 1981 and Thomas, 1982). As breast cancer rarely occurs in the undeveloped breast, it is at least clear that these hormones are necessary for mammary gland growth. The presence of estrogens and progesterone serve to prepare the background for the action of genetic factors, viral and environmental factors in the initiation of malignancy. Schinzinger (1889) and Beatson (1896) were first to observe tumour regression with endocrine manipulations almost a century ago. Systematic exploitation of surgical ablative procedure was pursued in this century, but the disappointing results of prophylactic ablative measures led to their application in advanced disease (Taylor, 1939, Huggins & Bergenstal, 1951, Huggins & Dao, 1954, Nissen Meyer, 1964 and Kennedy et al, 1964). Surgical ablation of endocrine organs was found to produce clinical response in less than a third of patients, more commonly in postmenopausal women and in women with a long disease free interval after primary surgery. The clinical criteria used to select patients for hormonal therapy in this studies were (and still are) imprecise. The discovery of the ER provided an improved understanding of which tumours would respond to hormonal therapies (Mc Guire et al, 1975). When planning appropriate endocrine therapy of breast cancer, certain observations are now accepted as basic. Less than 10% of women with ER negative tumours will respond to hormonal therapy.
Conversely only 50-60% of patients with Er positive tumours will respond to endocrine manipulation (Forbes, 1986). The changes in the ratio of urinary 11-deoxy-17-oxosteroids and 17-OHCS have been found to be valuable in predicting the progress after adrenalectomy or hypophysectomy in these patients (Stern et al, 1964).

Alterations in corticosteroids metabolism have been reported in patients with breast cancer (Allen et al, 1957, Bulbrook et al, 1962, Beck et al, 1966 and Singh & Udupa, 1977). Deshpande et al, (1969) observed elevated levels of plasma 17-OHCS in advanced stages of the disease. An increased concentration of Plasma 17-OHCS was observed in all patients with breast cancer, irrespective of the stage of the disease by Udupa et al, (1973) and Singh et al, (1976) who further noted a consistent increase in the levels as the stress associated with the disease increased. Similarly urinary corticosteroids have also been reported to be altered in breast cancer patients (Allen et al, 1957, Bulbrook et al, 1962 and Miller et al, 1967).

**Plasma Cortisol And Pulmonary Tuberculosis**

Very few studies have so far been done on the estimation of the plasma cortisol level in pulmonary tuberculosis. Raised plasma cortisol levels particularly in acute cases of pulmonary tuberculosis (Brahul et al, 1963) have been reported. The increase in plasma cortisol level became more prominent as the disease processes progressed. A significantly higher Plasma cortisol level was also observed by Srivastva et al (1980). The rise in the level of plasma cortisol is not peculiar to tuberculosis because high cortisol
level has been reported in acute and chronic infections (Bayliss, 1955; Goncharov, 1969; Melby and Spink, 1958; Nabarro, 1967). That way tuberculous infection does not appear to be much different from other infections.

In a study done by Srivastva et al. (1980) a definite correlation was obtained with duration of illness and evidence of tuberculotoxaemia characterised by fever, sputum status and severity of disease. Several explanation have been given to account for the rise of plasma cortisol in pulmonary tuberculosis (Bayliss, 1955; Nabarro, 1967) such as -

1. Pyrexia
2. Reduction in tissue utilization of cortisol
3. Impaired metabolism of cortisol by the liver
4. Stress

Tuberculous involvement of adrenal cortex has been reported in 14% of cases (Daven-Port et al, 1951). The involvement may lead to mild to severe adrenocortical insufficiency which may produce symptoms of its own. A study of plasma cortisol levels and its rhythm, undoubtedly, will help us in the detection of this insufficiency.

(iii) **PLASMA CORTISOL AND TROPICAL PULMONARY EOSINOPHILIA**

Amoury Coulinho (1956) mentioned that steroids had equivocal results. In 3 cases of TPE he administered cortisone orally over a 10 days period, giving 200 mg 1st day, 200 mg second day, 100 mg daily thereafter soon after treatment stopped, there was a moderate falls in the eosinophil levels, accompanies by some clinical improvement, however, the respiratory symptoms and eosinophilia returned to their former levels with in a few days.
Herbert de Vries and Rose (1950) compared the results of ACTH in a case of Loeffler syndrome and a case of TPE. In each case, the dosage consisted of 2 inj.; 60 mg each with an interval of 5 hrs between the injections. In the patient with Loeffler syndrome, the eosinophil count fall from 2865/cmm to 54 with a concomitant disappearance of pul. infiltration, whereas in the patient with TPE, the fall in eosinophil was only from 39136/cmm to 25700/cmm (83.9% - 54.6%) without any alteration in the radiological mottling aspect. This difference in the efficacy of the drug led the authors to conclude that the two diseases are separate entities. Deschiens and Mauze (1956) arrived at similar results. When they administered cortisone (50-150mg) to 10 patients with TPE, over a period of 10-20 days. The fall in eosinophil count varied from 30% and 76% 8 hours after the end of treatment.

Dias Rivera (1954) obtained in one patient a striking reduction in the number of eosinophils from 31779/cmm to 2140 cell/cmm on 5th day of L/M ACT treatment. The fall in eosinophil level was accompanied by slight clinical improvement but no X-ray change. The duration of treatment was 9 days and the mean daily dose was 50 mg. 10 days after the end of treatment, the eosinophil count returned to previous level.

More remarkable results were published by Sanjivi et al (1952). They administered ACTH treatment I/V (20 mg dissolved in physiologic saline) over a 10 days period in 15 cases of TPE. Between the 3rd and 6th day, they observed a decrease in the eosinophil count from more than 5000 to 0 - 400/cmm in 12 pH and to 1000 to 1800/cmm in 3 patients with simultaneous clinical improvement. But symptoms and blood eosinophilia returned
to the previous levels a few weeks later.

All the investigations seem to indicate a non-specific action of ACTH treatment and cortisone in TPE comparable to their effect in other hypereosinophilic states such as Trichinosis and other parasitic diseases (Davis et al. 1951; Luongo et al. 1951; Morales, et al. 1950)