Introduction

It is now well known that people of modern age suffer greatly from disorders of stress. In fact, they are the major causes of morbidity and mortality all over the world. Even now infective disorders take a great toll of lives in developing countries. But the disorders of stress and injuries are responsible for a large number of human tragedies in developed countries. Many of the accidental injuries are known to occur as a result of excess of stress and strain in life. Further, people undergoing too much of stress and strain are more liable to be affected by different types of infections than others because of poor immunological responses. If one considers all these matters together, one becomes convinced that the study of the causes and effects of stress would be one of the most important subjects of investigation for a modern medical man. Yet comparatively very few scientists and medical men have taken any interest in this subject. Hans Selye brought to the notice of the world about four decades ago cases of stress causing marked changes in the entire body in experimental animals, but very few attempts were made to apply this knowledge in solving the problems of human sufferings.

Selye, originally suggested that all the non-specific responses of stress such as hypertrophy of adrenal cortex, lymphopenia and gastro-intestinal ulcerations occurred as a result of excessive secretion of adrenocortical hormones. He further confirmed that such a response was mostly due to stimulation of anterior pituitary gland which regulated the function of the adrenal cortex through its secretion, adrenocorticotropic hormone (ACTH). However, this was not fully accepted by most of the other physiologists. Walter Cannon had postulated earlier that adrenal medulla and its hormone adrenaline were responsible for the appearance of various
physiological changes in the body after any type of psychosomatic stimulation. As a result of these two divergent views on the subject, not much progress could be made in the initial period.

Role of Neuroendocrines

In the meantime the extensive studies of the hypothalamus by Harris and also by Hess showed that it was the hypothalamus which regulated the functions of the anterior pituitary gland. Therefore, one could say that stress caused the stimulation of the hypothalamus which through its corticotrophic releasing factors stimulated the anterior pituitary gland to secrete more of ACTH. This in turn stimulated the adrenal cortex to pour out excess of cortisol. It is this that caused all the bodily changes in stress, which Selye called General Adaptation Syndrome. The hypothalamus is also connected with sympathetic nervous system which also becomes activated simultaneously with the changes taking place in the neuroendocrine apparatus. The stimulation of sympathetic nervous system essentially causes excess of liberation of noradrenaline. Along with this, the excessive stimulation of adrenal medulla causes an outpouring of adrenaline.

It is said that initially the adrenal medulla pours out sufficient amount of adrenaline and also some amount of noradrenaline on receipt of stressful stimuli through the neural pathways. However, for the outpouring of both of them for a prolonged period, the presence of excess quantity of plasma cortisol is also essential. Thus, there is a close correlation between the secretion of catecholamines (adrenaline and noradrenaline) and cortisol in the appearance of the effects of stress in the peripheral organs and tissues.

Even after the full knowledge of the functions of hypothalamus, pituitary gland, adrenal cortex and medulla, it was not clear how the stressful situations could stimulate the hypothalamus specifically leaving out the rest of the cerebral cortex in a normal state.
Role of Cerebral Cortex

In the meantime the Russian Schools of Physiology proposed that all these bodily changes following stress originate in the cerebral cortex. From there the stimuli reach the hypothalamic region through limbic system to produce the changes in the autonomic nervous system and in the neuroendocrine apparatus. The cerebral cortex receives environmental stressful stimuli through the normal channels of sense organs (exteroceptors) and also from the viscera, blood vessels, endocrine glands and muscles through interoceptors. All these stimuli ultimately converge at the psychic centres in the frontal lobe, from where messages are transmitted to produce various specific responses based on the earlier experiences of environmental stimuli and the genetic factors. From this, one can say that any stressful stimuli which are received by the cerebral cortex ultimately lead to some integrated physiological responses of the whole body. However, it was not at all clear as to how such a stress could produce many of the pathological lesions. It is here that our recent study of neurohumors greatly helped us to understand the pathogenesis of different stress disorders.

GENETIC FACTORS

It has been stated that all stress disorders are caused by multifactorial responses. Amongst them genetic factor is the most important one. It is known that some sort of susceptibility to get a particular disease such as diabetes mellitus, hypertension or coronary artery disease runs in families for several generations. How such a susceptibility is transmitted from parents to children is still a matter of conjecture. After studying the catecholamine degrading enzyme Monoamine Oxidase (MAO) in the platelets it is now postulated that the deficiency of this particular enzyme in the body might predispose a person to have a prolonged and excessive action of catecholamines leading to many harmful effects. Similarly, the deficiency of the acetylcholine degrading enzyme cholinesterasases may lead to the harmful effect of excessive action of acetylcholine in different organs and tissues. Although all these matters need
further study and confirmation, one can certainly understand how possibly the genetic factors play their role in causing various disorders of stress.

In addition, the psychosomatic constitution of an individual can also become a genetically transmitted trait which can also predispose a person to certain stress disorders. Physical anthropologists have divided human physiques into three broad categories: Ectomorphs, Mesomorphs and Endomorphs. We have in our earlier studies observed that even the physical body constitutions have a neurohumoral basis and their susceptibility to certain diseases also has a biochemical explanation.

Similarly, psychologists have also observed that there are mainly two types of personalities which are genetically transmitted, Introverts and Extroverts. It was also noted that introverts were more susceptible to stress disorders than extroverts. Friedman and his colleagues divided personalities into two types, A and B. Type A personalities are more ambitious, hard working and restless. They are more liable to get stress disease than the others (Type B) who are relatively quiet, contented and satisfied with whatever they attain in their lives without much struggle.

It seems that all these genetically transmitted psychic and psychosomatic constitutions also have a neurohumoral basis and hence the subsequent development of different stress disorders also has a certain neurohumoral pattern.

ENVIRONMENTAL FACTORS

In addition to the genetic susceptibilities, various environmental factors such as age, sex, marital status, family circumstances, childhood experiences, dietetic factors, nature and amount of daily work load, etc. may also play an important role in the causation of stress disorders. Normally, any type of stress and strain would lead to a series of changes in the body so as to make the person adapt himself efficiently to the changed environment. It is in the process of adaptation that various nonspecific changes described by Selye, namely alarm reac-
tion, stage of resistance and stage of recovery or exhaustion take place. If proper adaptation leading to full recovery does not take place, the person goes into a stage of exhaustion leading to the development of one of the diseases of adaptation or stress disorder.

There has been considerable discussion as to whether there is any relationship between the types of stressful situation and the nature of disease process. For example, breakdown of love affair in girls would lead to thyrotoxicosis, too much of frustration in life would lead to peptic ulcer or excessive marital tension or worry in life would lead to hypertension etc. However, recent studies have indicated that no such correlations can be established between the nature of stress and develop-ment of a particular type of disease.

STAGES OF DISEASE

It has now been observed that once a favorable stage has been set in for the development of a stress disease, a series of neurohumoral changes takes place leading at first to psychic changes, and then to psychosomatic changes, followed by somatic changes before it settles down to any one of the susceptible organs. Here, in the organ also at first the functional changes occur followed gradually by organic changes leading to the development of disease in the form known to modern pathology. It is now well established that these pathological changes occur as a result of disturbances in the microcirculation in that organ caused by local neurohumoral disturbance. This is especially so with regard to catecholamines leading to excessive vasoconstriction for a prolonged period which would trigger off the development of autoimmune phenomenon in that organ. This usually gives rise to variable amount of chronic inflammatory process in that organ as we see in thyrotoxicosis which ultimately heals by fibrosis in favourable circumstances. On the other hand, if the circumstances are adverse, there is a breakdown of inflammatory process causing ulceration such as we see in peptic ulcer, which may deteriorate further causing haemorrhage or perforation or it may heal up if circumstances are found favourable.
From these observations, one can understand how the changes in the microcirculation which occur as a result of local neurohumoral changes, can cause the entire pathological phenomenon in a given organ. In short it is these neuro-vascular changes occurring in a given organ which are responsible for the production of the diseases. These are primarily brought about by the effect of stress on the cerebral cortex especially its psychic centre. This psychic centre regulates these neuro-vascular changes in a given organ by arranging to liberate appropriate neurohumors such as acetylcholine, catecholamines, histamine etc. and transmitting them to that particular organ through limbic system, hypothalamus, and the autonomic nervous system. Surprisingly, such unified theory for the causation of various disorders had been conceived centuries ago by the sages of ancient Indian medicine who postulated the presence of three humors for the production of various psychosomatic changes in health and disease. The importance of such unified neurohumoral theory is that it greatly helps to plan effective therapeutic measures from the point of view of prevention and also that of cure.

YOGA THERAPY

Apart from the various specific psychotropic drugs which may directly act on the cerebral cortex either to reduce the activity or to increase it, there is one method whose sole purpose is to restore the function of the cerebral cortex to normalcy either by reducing its activity or by enhancing it. That method is Yoga which was well conceived and described by ancient Indian authors about 2500 years ago and which proves to be of great value even today. Its unique contribution is that it directly affects the brain, especially the psychic centre from where all the psychosomatic stress disorders are initiated. Hence, one can say that the practice of yoga can be a specific measure for the prevention and control of stress diseases.

Our studies have enabled us to demonstrate that these yogic measures produce their expected beneficial results by directly acting on the production of neurohumors. Hence, it seems that it is one of the most efficient and scientific methods for the
management of stress diseases. It is this fact which made us study this problem in great detail and we are happy that not only we could establish a therapeutic regimen for all the stress diseases on scientific lines, but also could advance adequate scientific explanations for all the phenomenon that occur in the disorders of stress. We, therefore, initiated our studies both in experimental animals and clinical cases with stress disorders. It is the results of these studies which have become the basis of this monograph wherein yoga exercises are discussed in detail for the benefit of all those interested in this field.
CHAPTER 1

Historical Background

Humoral Theory in Ancient Indian Medicine

The Ancient Indian Medicine—Ayurveda is considered to be the Science of Life by ancient Indian authors. According to them it stands for a total concept of life which includes both man and his environment. It emphasises that the well-being of man does not consist in the maintenance of good physical health alone, but also includes the mental and spiritual health.

Life is never static; it continuously undergoes changes to adapt itself to the environmental changes. Such a continuous activity of the body and its psychosomatic constitution is brought about by three essential humors of life known as Vata, Pitta and Kapha. Amongst them, Vata seems to be closely related to central nervous system and is the most important humor which moves fast and controls the other two humors. Pitta resembles the sympathetic nervous system and Kapha to the histamine and its derivatives such as kinin. Thus, life is more dependent upon Vata than anything else in the body. It helps to receive message from the environment and then transmit it to different centres of brain and to other parts of the body, whereas, the other two humors become disturbed after the Vata has become deranged.

If the organism fails to adjust or adapt to the environment, it succumbs to disease. But, it has been observed that reaction to same type of adverse environment differs from individual to individual. This is because of differences in body constitutions inherited genetically. Therefore the changes in the environment and differences in body constitution both should be considered jointly in assessing the life of an individual.
PSYCHOSOMATIC CONSTITUTION

Such a constitution is inherited genetically by every person and it remains constant throughout his life. In each individual one of the humors i.e. Vata, Pitta or Kapha predominates. In some cases a combination of any two may predominate whereas in others all the three humors may become equilibrated.

People with Vata predominance have small thin bodies and are always restless. They usually talk much and undertake every work very quickly. They are quickly affected by fears, likes and dislikes. They are intolerant of cold. They have rough hair on the head and face. Persons with Pitta constitution are intolerant of heat and have excessive hunger and thirst. They usually have scanty soft hair and are liable to become bald at an early age. They are highly intelligent and active in their life. Persons with Kapha constitution have a pleasant well knit body. They are slow in action and speech. They are slow in undertaking any work. They usually have comparatively less hunger and thirst. They have very soft hair which remains black for a considerably long time.

THE ENVIRONMENTAL CHANGES

If all the environmental factors remained homogeneous and congenial to an individual, he would maintain a good physical, mental and spiritual health. However, if there occurs some erroneous, inadequate or excessive interaction between sense objects, senses, body and mind, then gradually the humors become vitiated and diseases set in such a body. The vitiating factors can be climatic change, misuse of sense organs or unfavourable psychological environments.

In case these changes are mild and of a short duration, there occurs only a slight imbalance of the body humors which gradually subsides and then regains its normal state. However, if the vitiating factors are strong and extend over a longer period, then one may contract any one of the following pathological states, depending upon the strength of etiological factors, power of the bodily humors and the results of their interactions. Thus,
Historical Background

(i) The vitiating process may spread and affect the entire body which offers no resistance. It may lead to acute generalised disorder.

(ii) The vitiating process may be strong, but the bodily response also may become equally strong and this will result in a prolonged interaction of waxing and waning. The ultimate result depends upon which side wins the struggle.

(iii) In some situations the vitiating process does not affect the whole body but becomes localized to some system, organ or tissue. Here again, the vitiating process spreads quickly, but the body tissue tries to localize it leading to the development of acute inflammatory response.

(iv) If the vitiating process is slow and the body resistance is strong, a chronic inflammatory response develops. Sushruta described six definite stages of this vitiating process. These are nothing but pathological changes in the humoral functions and are as follows:

1. Excess accumulation of humors at their own sites of production.
2. Provocation or peridodical spillover of humors into circulation.
3. Diffusion of excess humors into the whole body through blood.
4. Localization of humoral disturbances in a particular organ or tissue.
5. Manifestation of such localized disturbances.
6. Termination of the humoral disturbances by different types of sequelae.

1. Stage of excess accumulation

At this stage, there occurs an excessive accumulation of humors and also of the different materials required for producing more humors at their own place. The symptomatology of this state includes lethargy, low grade temperature, digestive
disturbances, irritability, nervousness etc. If appropriate measures are taken at this stage these disturbances can be overcome without much difficulty.

2. Stage of provocation

The vitiated humors are poured out from the site of origin into blood periodically, and are then allowed to circulate in the whole body. Because of these excess humors circulating in the body there appear generalised symptoms of malaise, fever and restlessness.

3. Stage of diffusion

The excess humors circulating in the blood infiltrate and then try to settle down in all the organs and tissues of the body. However, if the vitiating factors are too strong then the whole body may be affected and a generalised disease may start manifesting. If the vitiating factors are not so strong and the body has developed a good resistance, the humor may continue to circulate in the blood till it settles at one place.

4. Stage of localization

The localization of the disease occurs in some organ or tissue by accumulation of the vitiating humors at the susceptible sites. Thus these circulating humors having attained some foot-hold in some organ, gradually get themselves fully established and start producing symptoms which are indicative not only of vitiated humors, but also of the disturbed function of that organ. These combined symptoms help in recognising the disease in its early stage.

5. Stage of manifestation

The disease fully manifests itself with all its clinical symptoms. It can be a generalised one, systemic one, or of one organ or limb, depending upon the location of the vitiated humors. This is the beginning of the organic manifestation of the disease, which can be generalized or localized depending upon the
susceptibility of the individual. Further, it can be acute or chronic depending upon the amount of vitiated humors circulating in blood.

6. Stage of termination

This stage is the end of the vitiating process of humors. In this, either the person completely recovers from illness or there occurs a dissolution of the affected part, if the vitiating process is too strong and the resistance of the organ is too poor. In dissolution, there can be suppuration or necrosis of the part leading to ulceration and elimination of the vitiated humors. When such elimination does not take place, a chronic inflammatory reaction may continue for a long time till it subsides either by medical or surgical measures.

The understanding of these different stages of pathogenesis may be of great value in the diagnosis of the disease in its prodromal stage and also in adopting prompt preventive and curative methods of management. Hence, it appears that the Ayurvedic concept of the development of diseases may help physicians to adopt various preventive measures against different individual diseases much more effectively than the modern methods. Therefore, it is high time that intensive studies are conducted to understand these problems more scientifically for quick adoption throughout the world.

Humoral Theory in Greek Medicine

Historically, there had been a good parallelism in the development of the Greek and Indian medicine probably because of the common origin of the Aryan people. It is said that in the early period one set of these Aryan people migrated to Indus valley to settle down in India and the other set went to Greece. Thus, in Greece and India scientific thinking and philosophical speculation started very early. Because of this, both Greeks and Indians acquired much more profound knowledge of medical sciences than the others. From Greek medicine, gradually modern Western medicine developed. However, in India, med-
icin gradually developed more along psychosomatic lines and treatment was conceived in terms of Yoga and other psychotherapeutic measures. Since both these systems, namely Greek and Indian, originated initially from the same culture, there are great similarities in various theories including the humoral theory of both systems. They flourished almost at the same time around 5th century B.C. The well known author of Greek medicine was Hippocrates and those of Indian medicine were Charaka and Sushruta.

In the Hippocratic medicine four humors were described: their balance meant good health and their imbalance caused disease. These humors were phlegm, blood, bile and water. These are transmitted from parents to offsprings through the sperms and ova; hence children have the same humors as their parents. During life, these humors are continuously renewed and maintained properly from the food and drink that we take every day. A surplus or deficiency of any one of these humors may be the cause of physical or mental disturbances. In fact, excess accumulation of any of these humors was thought to be one of the main causes of the development of disease at that time. The disturbed atmospheric condition was considered as another cause and physical and emotional injuries as still other causes of disease. All these factors were believed to act on the bodily humors to make them vitiated. Such vitiated humors were supposed to travel in the whole body and then ultimately attach themselves to some part or organ of the body, and the resulting disease was named after the organ affected.

In the Hippocratic theory, these four cardinal humors were held responsible not only for producing diseases, but also were thought to be the normal constituent parts of the human system. Such a humoral theory was commonly accepted and it dominated the Western medical science for many centuries.

At that time it was known that many diseases had seasonal characters and for this, different behaviour of the humors in different seasons was thought to be responsible. Similarly, other variations in the human constitution such as tallness and shortness, leanness and fatness, intelligence and stupidity etc. were also considered as predisposing factors. It was also
observed that certain bodily qualities were frequently associated with definite mental qualities. Thus, fatty people are usually benevolent. The devil is pictured as lean. In short it was found that there were different types of psychosomatic constitutions of men. Every individual is unique and no two have the same fingerprint. Therefore, different people can react quite differently to the same stimulus. This is because of the fact that in each individual one of the humors predominates over the others.

Hippocrates also emphasized that each disease has a natural course. Thus common cold lasts for one week, Pneumonia for ten days and Typhoid for 3 weeks. This was because of the fact that it took so much time to discharge and excrete the vitiated humors from the site of lesion such as nose, bronchi or small bowel respectively. As already stated, to start with, it is usually one of the humors which goes out of order due to faulty diet or other ways of life. Unless the vitiated humor is eliminated fully and brought in balance with others, health cannot be restored to normalcy. Summarizing all these views, Segerist says, “In every case the disease was due to an upset balance of the constitutional elements of the body, such as for instance the humors and the humors were everywhere in the body. This explained why in every case of illness the whole individual was sick and not just one of his organs, although the faulty humor frequently attached itself to an organ or region of the body. Treatment, therefore, was to be not only local, but also general, and the importance of psychological element in every case of illness not overlooked”.

From the above it becomes clear that there was a close similarity between the views of ancient Greek physicians and the ancient physicians of India during the fifth century B.C. Both the groups believed in the humors dominating the body constitution and then becoming responsible for causing disease. Both held that these humors became vitiated due to a variety of external or internal causes in the entire body at first and then settled down in one of the organs or regions of the body. Disease is cured only when the vitiated humor is eliminated either in a natural way or by medical treatment. The only
difference between Greek and Indian medicine was that the Greek physicians recognized four humors, including blood as the fourth one, whereas, ancient Indian physicians recognized only three humors. The details of the humoral theories of ancient Indian physicians have already been given. Suffice it to say here that there existed a close similarity between the humoral theories of diseases described by the ancient authors both Greek and Indian and the present day neurohumoral theories. Therefore, what the ancient physicians have described by their clinical observations can be confirmed now by the present day laboratory investigations. There is a great need for studying the ancient treatises written 2500 years ago for a better understanding of the entire problem.

Evolution of Humoral Theory in Medical Sciences

The concept of control of body functions by humors prevailed well over two thousand five hundred years. In fact from the time of Hippocrates (460-370 B.C.), Aristotle (384-322 B.C.) and Galen (130-200 A.D.) the humoral theory played a dominant role until the early part of the 19th century. In the 16th and 17th centuries this theory was questioned seriously, but there was nothing to replace it. The discovery of bioelectricity by Galvani in 1792 showed that during muscle contraction there occurred a flow of electric current sufficient to excite adjacent tissues. This led to the development of new ideas. Then the people thought that the transmission of excitation and control of body function were dependent upon the electrical rather than humoral phenomenon. From then onwards until the middle of the 20th century, there accumulated a large amount of data to show that predominantly it was the electrical process that controlled the function of nervous system and the activities of peripheral organs. Before the discovery of bioelectricity humors were thought to be responsible for causing muscle contractions and also for producing emotional and behavioural changes. At that time it was felt that nerves were involved in the transport of these humors to the target organs or tissues. Now when it was realized that nerves were not tubes
Historical Background

through which fluids might flow as does blood in the artery, the entire humoral concept receded into the background and it gave way to the more recent theory of electrical conduction controlling every organic function. The theory of electrical energy as the only source of excitation of organs and tissues remained in vogue for about two centuries. However, towards the middle of this century it became apparent by various studies that different chemical agents are required for conducting the excitation from neuron to neuron and from neuron to various target organs and tissues. As a result, the humoral or neurohumoral theory regained its importance in the regulation of the entire body function. Although electrical processes are even now thought to play some important role, they are no longer considered as primary factors in body functions.

However, it should be noted that current ideas about the nature of humors or neurohumoral agents released from the nerve endings appear to be somewhat different from the ancient ones, though, in principle, they can be easily compared with each other. It is now well known that the proof for the existence of chemical mediation and neural control of smooth and skeletal muscles was put forward only during the last four decades or so. Earlier it was thought that some such chemical mediation existed, but its exact nature could be determined only recently. Thus, the chemical transmission of nerve impulses to the affected cells can certainly be called a humoral agent controlling body function. Amongst all the humors, acetylcholine which is liberated by most of the cells of the central nervous system seems to be the most important primary humoral agent. The other neurohumoral agents will be discussed later on. Release of many hormones is triggered as a result of stimulation of these neurohumors. These hormones, therefore, can also influence the turnover of the neurohumors to a certain extent. However, it is primarily the brain which controls all the body activities by liberating various neurohumors directly and also indirectly by activating the autonomic nerves and the neuro-endocrine apparatus. Most of these changes are adaptive in nature. These adaptive changes occur
to maintain a constancy of body states which is known as 'homeostasis'. Which neurohumor initiates action in the brain is the subject of some controversy. It is agreed by many neurophysiologists that acetylcholine is the principal mediator of central synaptic transmission. However, they feel that there are other neurohumors, especially the aminoacids which not only initiate the action, but also modify the excitability of these nerve cells. All these cells synthetize the neurohumors and transmit them through their axons till they reach the junction of the target cells. Then, they are stored as quanta in case of acetylcholine or vesicles in the case of catecholamines and are released whenever a stimulus reaches the site. This in brief is the present concept regarding functions of neurohumors.
CHAPTER 2

The Brain and its Subcortical Centres

In the West there were initially two parallel theories, one proposed by Pavlov asserting the higher nervous activity of the cerebral cortex and and the other by Langley asserting the dominance of autonomic nervous system. These theories were of considerable significance in preventive and curative clinical medicine. However, later on these two theories were merged as it was observed that under certain special circumstances the cerebral cortex could modify the activity of the autonomic nervous system including functions of the heart, lungs, stomach and intestines. Thus, it could ultimately be asserted that all the functions of the body systems including those regulated by the autonomic nervous system are under the authority of the higher division of the central nervous system. It was found that all the internal organs and the blood vessels which supply them are richly supplied with various receptors such as Chemo-, Thermo- or Osmo-receptors which directly connect these organs with the sensory apparatus of the brain. When the brain receives excessive stimuli, it may undergo various changes leading to the development of neurosis, which in turn produce changes in the autonomic nervous system and the viscera supplied by it to produce psychosomatic disorders. Thus, the development of neurosis appears to be a precondition for the initiation of psychosomatic disorders and the clinician must remember this fact while managing these cases. Therefore, let us now discuss the various mechanisms involved in cortico-subcortical interrelationships.
Fig. 1. Shows the area of the brain comprising the limbic system.

**Limbic System:**

It is now well established that the limbic system is deeply involved in the behavioural, emotional and olfactory reactions of the body and also in the regulation of autonomic visceral activity. It mainly consists of cingulate gyrus, orbital areas of cerebral cortex, the hippocampus, amygdaloid nucleus, olfactory bulb, fornix, thalamus and hypothalamus (Fig. 1). Why such heterogeneous structures are grouped together as limbic system is because they help to maintain the homeostasis or constancy of internal environment of the organism, and play an important part in the formation of emotional and behavioural reactions. Thus, any excitation of the limbic system would produce behavioural and emotional reactions leading to changes in the cardiovascular, respiratory and digestive systems. In addition, significant endocrine changes are also observed particularly in the pituitary and adrenals, the hormones of which play an important part in the reaction to stress. Besides this, there is striapallidial system which plays most intimate and active part in the cortico-subcortical integration.
It consists of two corpora straita, the caudate nucleus and lenticular nucleus. Its main function seems to be inhibiting the autonomic and visceral activity probably mediated through the cholinergic and adrenergic innervations.

The thalamus also plays an important part since it is the main subcortical sensory centre in which almost all the afferent pathways of the cerebral cortex terminate. Through these pathways only, the thalamus is connected with all parts of the cerebral cortex. The thalamus is also well connected with the frontal lobe (psychic centre) both by afferent and efferent pathways.

The Reticular formation

The cerebral cortex is also connected with various subcortical centres by diffuse projection system called ascending reticular formation. They connect the cortex with reticular nuclei of

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Fig. 2. Shows the reticular formation and their connection showing sensory pathway below and various centres of cerebral cortex above.
medulla oblongata, pons, hypothalamus and the reticular nuclei of the thalamus. These connections have a diffuse activating influence over the cerebral cortex (Fig. 2). On the other hand, these connections also enable the cerebral cortex to regulate the activity of the autonomic nervous system. Since the reticular formation system receives multiple collaterals from all the specific regions of the brain, it plays an important part in the integration of various activities of the cerebral cortex.

**Hypothalamus**

The hypothalamus plays a central role in controlling the activities of various internal organs. It is closely connected with the structures of cerebral cortex, thalamus, limbic system and the brain stem and in that manner it acts as a railroad junction (Fig. 3). Through this the brain regulates the autonomic, endocrinal and metabolic functions. In fact, it is the highest centre of the activities of the autonomic nervous system, and it maintains homeostatic balance of the body by the process of adaptation. There are three major groups of nuclei—anterior, medial and posterior, but all of them are closely interlinked amongst themselves and with other centres of the brain.

The main functions of the hypothalamus are:

1. Regulation of blood circulation, digestion, respiration, urine formation and body temperature.
2. Control of metabolism of carbohydrates, fats and protein.
3. Regulation of ionic environment (electrolytes) within the body through neurohumoral secretions (Homeostasis).
4. Autonomic integration of all the bodily activities.
5. Regulation of all the activities of the endocrine system which plays an important role in the cellular and tissue activity. In addition, it also exerts its stimulatory influence on the cerebral cortex. Similarly, the cerebral cortex, especially the frontal lobe, exerts its influence on the hypothalamus directly and also through the limbic system. Considering the above mentioned functions of
hypothalamus, one can say that in all the problems of stress and its disorders hypothalamus plays a most significant role.

*Cerebellum*

The cerebellum is also well connected with the reticular formation and also with various nuclei in the thalamus. Through these structures it is also well connected with the cerebral cortex. Because of these connections, the cerebellum also participates in the regulation of autonomic nervous system. Electrical stimulation of certain areas of the cerebellum produces inhibitory response whereas stimulation of other areas produces excitatory response. All these stimulations are transmitted to autonomic nerves and viscera through the cerebral cortex and its limbic system.
Interaction of Cerebral Cortex with Subcortical Structures

Cortex and Hypothalamus

Recently, there has been a tendency to attach too much importance to the reticular formation, hypothalamus or to the autonomic nervous system on the basis of various animal experiments alone. Accordingly, the cerebral cortex is considered to play a secondary role in the normal functioning of a person as a whole. Even amongst the various subcortical structures more importance has been given to hypothalamus as the main centre for all the autonomic, visceral and metabolic functions of the body. The researchers have failed to produce any convincing evidence for the claim that in man the hypothalamus alone would be capable of achieving a high degree of adaptation without a normally functioning cerebral cortex. Several recent studies have indicated that there are direct connections between the cerebral cortex, especially the frontal lobe and the hypothalamus. These direct nervous connections connect the frontal lobe with mammillary bodies and also lateral and posterior hypothalamus (Fig. 4). Further, there are also projections from certain areas of frontal and orbital lobe to the supraoptic and and paraventricular nuclei of the hypothalamus. Most of these connections between the cerebral cortex and the hypothalamus are two way and bilateral. Moreover, such nervous connections are not only confined to direct pathways. There are also indirect functional connections between the cerebral cortex and the hypothalamus through various subcortical structures especially the thalamus in the form of cortico-thalamic and thalamohypothalamic fibres. Apart from this, there is physiological evidence to show that hypothalamic centres regulating autonomic activity are under the direct control of the cerebral cortex. For example, the frontal lobe exerts an inhibitory effect on the hypothalamic excitation of the salivary and gastric secretions. Such inhibitory influences of the cortex are blocked by various emotional excitements which ultimately lead to intensification of the autonomic reactions of the hypothalamus. Thus, the cerebral cortex makes an extensive use of the hypothalamus in order to
regulate the functions of internal organs, endocrine glands and also emotional reactions. Apart from this, the cerebral cortex, especially the frontal lobe, also exerts an inhibitory influence on the hypothalamus and through it on various behavioural reactions. In this regard, Kurtsin states, “Thus, in our opinion all claims that the hypothalamus is independent of cortical influence and plays the leading role in the control of autonomic visceral activity are unfounded since it has been shown that though the hypothalamus centres are very important biologically, in higher animals and man they are regulated, coordinated and generally controlled by the higher cerebral centres at the level of the cerebral cortex.” From this one can say that the hypothalamus is an important part of the corticollimbic, reticular hypothalamic complex which helps to adapt the autonomic and visceral functions in response to some external and internal environmental stimuli.
CORTEX AND RETICULAR FORMATION

Now it has become obvious that the reticular formation of the brain stem plays an important role in the activity of the cerebral cortex and the maintenance of its tone. At the same time it functions as subordinate to the cerebral cortex which utilizes the nuclei of reticular formation in regulating the function of autonomic and visceral system. Further, the cerebral cortex can also exert a blocking influence on these nuclei when they are activated by the afferent stimuli. In fact, the reticular formation acts as an intermediate station in the complex adaptive reactions of the cerebral cortex in which the hypothalamus also plays a significant role. In this connection Kurtsin observes, "Cortical impulses originating mainly in the frontal area either inhibit or promote the activity of the reticular formation depending on whether they arrive via direct or indirect pathways. As a result of the interplay between the excitatory and inhibitory mechanisms this activity is either intensified or blocked.... The frontal areas of the cerebral cortex are thought by some to play the decisive part in the integration of both behavioural acts and autonomic reactions. It is they which are able to inhibit the subcortical neural structures down to and including the reticular formation as well as the spinal conducting paths and autonomic centres". Further, he continues, "At the same time the reticular formation generates new bio-potentials which did not previously exist, indicating inhibition of the pathways conducting visceral impulses which do not function when the cortico-reticular connections are intact. In man this activating function of the reticular formation is dependent on influences from the limbic area of the cerebral cortex".

It is said that from the limbic cortex the efferent pathways also proceed to the anterior hypothalamus via supra-optic and paraventricular nuclei and mammillary bodies. From here these fibres continue through nuclei in the medulla oblongata and then through the vagus and sympathetic nerves into various affected organs such as heart, stomach etc. In short the reticular formation, like all other subcortical centres, is func-
tionally subordinate to the cerebral cortex and the cortical centres utilize the reticular formation whenever necessary for the maintenance of its power and also for its connection with the autonomic and viscerosomatic activities. Because of these extensive neurological connections which regulate various functions, the cerebral cortex has the unique position for integrating the activities of the entire body systems. It is this concept which makes the holistic approach of medicine really scientific with the cerebral cortex at its apex which initiates every activity, normal or abnormal, during health and disease respectively in response to various environmental stimuli. Though, various subcortical centres such as the hypothalamus and reticular formation are important for regulating the functions of endocrines and other vital organs, in human beings they are subordinate to the cortical centres, especially to the frontal cortex. To quote Kurtsin, "It means that one ignores the enormous body of evidence testifying that the human cerebral cortex is not only the organ of mental activity but also the supreme nervous centre for analysis and synthesis which integrates, coordinates and regulates the condition and activity of all the internal organs, endocrine glands, and blood vessels and somatic autonomic activity". In the same vein Kurtsin observes: "This is why it is impossible to agree with those who assign the cerebral cortex a secondary, auxiliary role in the mechanism of integration and control of autonomic visceral activity and in the regulation of such biological states as thirst, hunger and libido. While this point emphasized the dominant role of the cerebral cortex in the central mechanisms regulating autonomic visceral activity, it by no means detracts from the importance of the subcortical stem formations which constitute a 'functional unit' of the cerebral cortex". From this it becomes clear that the cerebral cortex has the pre-eminent position in all the activities of the body during health and disease with various subcortical centres as the functionally independent units which work under the overall control of the cerebral cortex. These facts are of great significance for the Indian science of Yoga which is stated to improve the power of the cerebral cortex in order to have a control over the auto-
nomic and visceral functions of the body. Thus, it seems, “Yoga” helps to develop better integration of various cerebral centres with the subcortical autonomic centres. It is the development of this vital power which ultimately makes a better man in the evolutionary sense since he would be able to control all the activities of the body by his sheer will power which would enable him to live a longer and happier life than what it is at present.

RELATIONSHIP OF CEREBRAL CORTEX WITH INTERNAL ORGANS

In the evolutionary process, the neocortex consisting of the cerebral cortex does not actually replace the ancient and older structures of the brain, such as brain stem centres. In fact, cerebral cortex only co-exists with them, though acquiring functionally a more dominant position. Thus, the brain stem portion which from the view point of evolution is an ancient part of the brain, has direct connections with all the internal organs through medulla oblongata and spinal cord. But the most advanced and developed part of the brain, namely the cerebral cortex, does not have a direct connection with internal organs and it makes its contact with these organs only through various subcortical structures. The cerebral cortex is a highly developed structure, yet highly integrated. In higher mammals it becomes the most dominant part of the brain and it is endowed with higher mental functions. It takes over the function of all the earlier parts of the brain seen in lower animals by integrating, coordinating and regulating the functions of the central nervous system, and also of the autonomic nervous system which were previously carried out in a primitive manner by the lower cerebral centres.

Developmentally also, in the early stages of postnatal life, only the subcortical connections, such as thalamic and hypothalamic connections, are found in the first few weeks. The cortico-pyramidal connections and the cortico-extra-pyramidal connection develop only after 4th to 6th month. The verbal connections develop still later. Gradually as the age advances the cerebral cortex acting through the subcortical
and other lower centres integrates the entire external and internal activity of the body and brings it into equilibrium with the external environment, thus providing optimum conditions for existence.

Thus, it is obvious that the cerebral cortex has a regulatory influence on the function of all the internal organs. These regulatory influences of the cerebral cortex do not occur by direct neural connections between the cortex and these organs. But it regulates the functions of internal organs by various neural and humoral chain reactions. Such reactions include numerous short and long reflex arcs, feedback systems, hormonal influences and metabolic interactions. Thus the cortico-visceral response occurs as a result of external or internal stimuli by both direct and indirect means of communication. The influence of the cerebral cortex on the subcortical centres and thereby on the internal organs can be stimulatory or inhibitory. An inhibitory response in the central nervous system occurs as a result of an excessive production of gamma-aminobutyric acid, which is the inhibitory mediator. This substance when formed causes a blocking reaction on the post-synaptic membrane and raises the excitation threshold leading to inhibitory response. Thus the ultimate effect is the result of a highly complex cortical-subcortical integration in which a significant part is played not only by the stimulatory mechanisms, but also by the inhibitory mechanisms of the cerebral cortex which are conveyed to the internal organs through various means.

What are the means through which the cerebral cortex controls the functions of internal organs? A large number of studies have indicated that the means could be direct or indirect. In the direct control, the cortical excitation is transmitted through one neuron to the other through the mediators like acetylcholine or noradrenaline, and from the terminal neuron to the affected cell which is further influenced by the second messenger in the cell membrane, namely, cyclic AMP or GMP.

The indirect control of the cerebral cortex over the functions of internal organs can be through the autonomic ner-
vous system which would influence the vascular system by way of vasodilatation or vasoconstriction. Through such a mechanism, vasodilatation would influence the capillary permeability and thereby the osmotic properties of blood. In this way it can influence the formation of hormones and their passage into blood. In the same way the vascular response influences many other cellular activities, such as tissue respiration, absorption and elimination of nutritional products, production and secretion of various hormonal substances. Therefore, the influence of the cerebral cortex not only produces stimulation and inhibition of internal organs, but also actively takes part in the cell metabolism and other cellular activities including permeability of cell and subcellular membranes and also other activities of various cellular enzyme systems.

One of the main functions of all these controlling systems is to maintain the constancy of internal environment, which is mostly done by the autonomic nervous system under the overall control of the cerebral cortex (Fig. 5). Any deviation in the normal internal environment is automatically followed by stimulation of the controlling system regulated by the nervous and humoral feedback mechanism. This immediately activates the neural integrator, namely, autonomic nervous system and also the humoral integrator, the endocrine glands to produce defence—adaptation response which restores the normal activity of the cells, organs, and various systems of the body. Such a self-regulatory mechanism exists not only at the organ level, but also at the cellular, subcellular and possibly even at the molecular level as seen in tissue culture studies. Even then in the intact animals, all these activities are regulated by the cerebral cortex as discussed earlier. In this connection Kurtsin states, “At the level of man and higher animals the central controlling organ is the cerebral cortex and the adjacent subcortex which through the main ‘switch board’ represented by the limbic system, the thalamohypothalamic region and the reticular formation exert their regulatory influence on the ‘nervous’ and ‘humoral’ integrators and
Fig. 5. Shows the sympathetic and parasympathetic nerve connections to different organs.
through them on all the autonomic processes in the cells and tissues. It seems that one must also recognize the principle that the level of activity rises from the lowest molecular and possibly submolecular level to the highest level of the cortex throughout the entire organism, the lower level becomes subordinate to the higher one”. From this it becomes clear that the cerebral cortex controls all the activities of various internal organs through the nerves and vessels supplying them.

MECHANISM OF CORTICO-VISCERAL DISTURBANCES

Whenever the cerebral cortex is subjected to too much of stress and strain for a prolonged period, it leads to the development of neurosis which further produces abnormal functions of internal organs. If the cerebral cortex is subjected to any of the following stimuli, it usually causes neurosis: (1) An extremely powerful stimulus; (2) Successive positive and negative stimuli; (3) Repeated low stimuli for a prolonged period; and (4) Stimuli of too many varieties acting simultaneously. All these stimuli ultimately lead to great strain on the excitatory and inhibitory processes of the cells of the cerebral cortex. This ultimately produces exhaustion of the cortex which would manifest itself in the form of neurosis as a result of chronic disturbance of the normal cortical and subcortical relationships. As a result, the excitatory and inhibitory processes not only of the cells of the cerebral cortex, but also of the cells of subcortical nerve centres regulating the autonomic nervous system, internal organs, vascular tone, hormonal activity and cellular metabolism are overtaxed. Because of the lack of control of the cerebral cortex which is a result of its reaching a state of exhaustion, the subcortical centres behave erratically on receipt of excessive stimuli causing much disturbance in all the bodily functions. Thus, the various manifestations of psychogenic stress depend not only upon the amount of exhaustion of the cerebral cortex, but also upon the amount and depth of involvement of various subcortical structures in the neurotic process such as reticular formation, brain stem, thalamus, hypothalamus and cerebellum. Such a
disturbance does not remain confined to these subcortical centres alone but spreads also to neuroendocrine apparatus which may lead to disorders of the endocrine glands including the catecholamine metabolism, and also to the disturbances of protein, fat, carbohydrate, water and salt metabolism. Thus, the main starting point of all these disturbances is the breakdown of all the activities of the cerebral cortex which interfere with its close relationship with various subcortical centres. It seems that these disturbances in the cortical and subcortical centres are mediated through the liberation of various neurohumors, such as acetylcholine, noradrenaline, adrenaline, 5 hydroxytryptamine, histamine and GABA.

MAJOR AREAS OF DISTURBANCE

As a result of excessive stress, both the cerebral cortex and the subcortical areas become disturbed. Even amongst them, the frontal and temporal areas of the cerebral cortex play a major role. Similarly in the subcortical areas, the limbic system and the hypothalamic centres play a major role in producing emotional disturbances in these cases. These emotional disturbances ultimately lead to behavioural and personality changes in addition to changes in the functions of the autonomic nervous system and the different internal organs. Recently importance has also been attached to the changes in the reticular formation which also contributes to a great extent in causing disturbances in the emotional pattern.
CHAPTER 3

Neurohumors

It is now well established that psychological and all other types of stress produce a series of neurohumoral changes leading to endocrinial, metabolic and other systemic changes. Therefore, a basic knowledge of neurohumors is essential to understand the whole problem.

The nerve cells have two important properties: (1) Electrical transmission, and (2) Chemical transmission. Both are very much interrelated and by assessing one, the other can be roughly quantitated. The nature of chemical transmission can be studied at the synaptic junction where the transmitters which are also known as neurohumors, are released by the presynaptic nerve terminals into the synaptic cleft and are then taken up by the post-synaptic cell membrane. Thus, whenever there is an excitatory impulse at the presynaptic nerve terminal, there occurs a physical change in the state of the membranes which increases the permeability to small cations. After the receipt of the impulse, at first the affinity of the excitable cell membrane for calcium ions is decreased. This displacement of calcium ions causes a conformational change in the cell membrane which permits transiently the sodium ion to enter and the potassium to leave the cell. The excitatory effects are usually attributed to a depolarization of the cell membrane produced by the inward movement of sodium. This transient change is restored to normalcy as soon as excitory impulse stops. On the other hand, increase in potassium causes acceleration of the rate of return to normalcy of the resting potential of all the depolarized membranes and would decrease the sensitivity of the membrane to stimulation. It is by these ion exchanges that the stimulation or inhibition of the neurohumors is brought into action at the synaptic cleft.
Neurohumors

It is postulated that the bulk of neurotransmitter synthesis occurs in the presynaptic terminal. However, some of the transmitters may also be synthetized in the main body of the nerve cell in almost the same way as synthesis of protein occurs in all other functionary cells. These newly synthetized neurohumors are deposited in small vesicles which would then travel along the axons to their nerve terminals. Whenever the stimuli reach the nerve terminal, there occurs a fusion between the presynaptic membrane and the vesicles and the contents of the vesicles are extruded by exocytosis into the synaptic cleft filled with glycoprotein materials. This produces changes in the post-synaptic membrane of the receiving cell leading to the excitation of that cell. Soon the neurohumor is inactivated by the respective enzymes both in the synaptic cleft and also in the post-synaptic cell itself. However, some amount of neurohumor is reabsorbed and deposited in the presynaptic nerve endings. In addition, a small quantity may even leak into the extracellular space which is absorbed into blood capillaries present in the region.

After the secretion, each neurohumor binds to specific receptors on the post-synaptic membrane and produces its post-synaptic effect on the cell. In case of acetylcholine, the broken down choline may also be taken up by the neuron and resynthetized into acetylcholine. The nature of the post-synaptic activity may differ from one neurohumor to the other. Many of them, such as acetylcholine, catecholamines, etc. are excitatory, whereas others, such as GABA (Gamma aminobutyric acid) or glycine may have inhibitory effect on the post-synaptic nerve cells. These are some of the general properties of neurohumors. Let us now discuss the characteristics of individual neurohumors briefly.

Acetylcholine

Recently, much work has been done on the role of acetylcholine in cholinergic transmission in the central nervous system. It is being studied extensively by using various chemical methods and by correlating these findings with the functional
disturbance of the brain. Acetylcholine is present in significant amount in all mammalian brains. However, it is not uniformly distributed within the brain. The highest concentration of acetylcholine is found in the caudate nucleus and the lowest in the cerebellum. There is normally a good correlation between the amounts of acetylcholine and its synthetizing enzyme “Choline acetylase” and its degrading enzyme “Cholinesterase” in any region of the brain.

The acetylcholine content of the brain does not remain constant. It varies inversely with the degree of functional activity of the brain. Thus, it remains normal or above normal during sleep or when the subjects are kept under anaesthesia. It is found considerably reduced during emotional excitement, electrical stimulation or during convulsions. This is because of the fact that during increased nervous activity or psychosomatic stress there occurs increased liberation of acetylcholine from the nerve endings of the brain followed by its destruction by cholinesterases.

METHODS OF MEASUREMENT

One of the most sensitive methods to measure acetylcholine in the tissues is the bioassay method in which frog’s rectus abdominus muscle, dorsal wall of the leech, cat’s blood pressure or guinea pig ileum are frequently used in a descending order as test objects. Some of these assays are most sensitive and under properly controlled conditions, the most specific procedure for determining acetylcholine. In recent years, many attempts have been made to devise various chemical methods with relatively higher sensitivity for determination of acetylcholine. Amongst them Radio-Isotopic, fluorometric and gas chromatographic methods have received more attention. For details of these techniques one may refer to the original papers of the authors.

METABOLISM OF BRAIN ACETYLCHOLINE

Synthesis:

Acetylcholine in the nervous system is synthetized from choline and acetylcoenzyme-A, which is catalysed by enzyme
choline acetylase in the following:

$$\text{Choline} + \text{Acetyl-Co A} \rightarrow \text{Choline Acetylase}$$

$$\rightarrow \text{Acetylcholine} + \text{Co A}.$$  

The main sources of choline for synthesis of acetylcholine are (1) Dietary choline which reaches the brain through the blood, (2) Reuptake of free choline after the catabolism of acetylcholines, and (3) Phospholipids of the brain tissue. The choline received from each of these three sources can be used for the synthesis of acetylcholine. If radioactive C\(^{14}\) choline is injected intravenously into animals about half of the same is converted into C\(^{14}\) acetylcholine. Thus, there is a definite evidence to indicate that much of the dietary or injected choline is utilized for the formation of acetylcholine.

The main source of acetyl CoA for the synthesis of acetylcholine within the brain cell is the oxidative metabolism of glucose via pyruvate. The oxidative conversion of pyruvate to acetyl CoA takes place in mitochondria. From here it comes out at the nerve endings and acts on choline to form acetylcholine.

The properties of enzyme choline acetylase, which help in synthetizing acetylcholine have not yet been fully established. Its molecular weight is approximately 65000 and it is mostly attached to the cell membrane.

SYNAPTIC NERVE TERMINALS

Regulation

The regulation of acetylcholine synthesis occurs through negative feedback mechanism as it occurs in the case of other hormones. There is definitely a limit to accumulating acetylcholine in the brain beyond which it does not increase further. Thus, if acetylcholine is present in adequate quantity, no more of this neurohumor will be formed. Similarly, if excess of acetylcholine is released from the brain, more synthesis of acetylcholine would occur with the operation of feedback system.
Storage

It had been shown by Whittaker and his colleagues that most of the acetylcholine present in the brain can be recovered from the presynaptic portion of the nerve terminals called synaptosomes. In the synaptosome, acetylcholine can be isolated mostly from the synaptic vesicles, though it can also be isolated from other components such as cell cytoplasm membrane and mitochondria to a lesser extent. The studies conducted after injection of H³ choline revealed that acetylcholine is synthetized in the cell cytoplasm and then eventually transferred to the vesicles which, thus, act as a storehouse for acetylcholine within the nerve endings.

Release

It is now well established that acetylcholine is released from the brain tissue in a large quantity whenever there is stimulation of the brain by excessive psychosomatic stress, electrical stimulation, or by the administration of certain psychotropic drugs. On receipt of any such stimulation, the vesicular acetylcholine is released as quanta through exocytosis. Thus, synaptic vesicles would fuse with the presynaptic membrane, open to the synaptic cleft and extrude their acetylcholine content outside the nerve terminals.

Enzymatic destruction

The most important means of inactivation of this neurohumor in the central nervous system is by hydrolysis of acetylcholine into choline and acetate by the enzyme cholinesterase. Acetylcholine + H₂O = choline + acetate. This enzyme is present in abundance and mainly attached to the particles of pre- and post-synaptic membranes. The regional distribution of cholinesterase in the brain is similar to that of acetylcholine and its synthetizing enzyme choline acetylase. The cerebellum is an exception where cholinesterase is found proportionately much more than the acetylcholine. The reason for such a change is not yet clear.
Reuptake

It is now well established that a part of the acetylcholine secreted into the synaptic cleft escapes the action of cholinesterase and is reabsorbed into the presynaptic nerve terminals. This process can be further aggravated by the administration of anticholinesterase drugs. It seems that this process of reuptake is another method of inactivating acetylcholine within the brain which works in addition to the action of cholinesterase in terminating its action.

Influence of Drugs

Various drugs may regulate the activities of this neurohumor, (1) by influencing the synthesis of acetylcholine by acting on the synthetizing enzyme or on choline, (2) by interfering with the release of the neurohumor, and (3) by interfering with the inactivation of this neurohumor by the enzyme cholinesterase.

General effects of drugs

It has been observed that all the central nervous system depressant drugs, such as barbiturates and opium derivatives, cause elevation of the total acetylcholine content of the brain. These drugs produce depression of the brain activity by interfering with the release of acetylcholine even on receipt of stimulation. On the other hand, in various excited conditions like tremors and convulsions there occurs a significant decrease in the brain acetylcholine. All cholinergic drugs such as pilocarpine increase the brain acetylcholine and the anticholinergic drugs such as atropine cause a reduction in the acetylcholine content of the brain. All the CNS stimulants such as nicotine decrease the acetylcholine content, whereas the cholinesterase inhibitors like eserine increase the acetylcholine content of the brain. The drugs which increase the acetylcholine content of the brain produce slow EEG waves, and those which decrease the acetylcholine content produce enhanced EEG waves.
Acetylcholine receptors

Pharmacologists have recognized two types of cholinergic receptors viz. nicotinic and muscarinic cholinergic receptors. The former may be stimulated by the direct application of acetylcholine or nicotine, and this activity is not blocked by atropine. Various viscera supplied by parasympathetic nerves possess muscarinic cholinergic receptors. They can be stimulated by acetylcholine or muscarine, but not by nicotine. This activity is antagonized by atropine which is a specific muscarinic blocker. The autonomic ganglia and cortical and subcortical regions of the brain contain mostly the muscarinic receptors. The acetylcholine binding properties of the receptor are similar to those of acetylcholinesterases.

In Myasthenia gravis, which is characterized by severe muscle weakness of the body, there occurs a low content of acetylcholine receptors in the affected muscles, which in due course would lead to low acetylcholine release at the nerve endings. This condition can be relieved by giving synthetic cholinergic preparations like prostigmine (Fig. 6). In all the stressful situations as will be discussed later, the liberation of

![Graph showing neurohumoral status](image-url)

Fig. 6. Shows neurohumoral status in Myasthenia gravis before and after treatment with Prostigmine. Note that before treatment there was a marked deficiency in acetylcholine and a high content of cholinesterase in the blood. However, after the treatment with Prostigmine the acetylcholine content increases with a marked decrease in the cholinesterase.
acetylcholine is increased from the cerebral cortex which in turn circulates in the whole body to excite its metabolic activities. In that respect one can say that acetylcholine is the initiator of all the changes that take place in the stressful situations.

**Catecholamines**

During the last two decades a rapid increase in our understanding of catecholamines has taken place and it is difficult to touch upon all these aspects in this short review. Therefore, those who want to know more about these important biogenic amines, may refer to the original papers of Julius Axelrod, and Von Euler. There are three important catecholamines in our body and they are noradrenaline, adrenaline and dopamine. Noradrenaline is primarily localized in the sympathetic nerves of the peripheral organs and tissues and in some nerve tracts of the brain. These noradrenergic nerve tracts originate in the brain stem and branch off to the hypothalamus, hippocampus, cerebral cortex and cerebellum. The adrenaline is produced mainly in the adrenal medulla. It is from here that it is released through stimulation of the splanchnic nerves. Recent work has, however, shown the presence of adrenergic tracts in the midbrain. From here the cell bodies send off their axons into parts of the hypothalamus.

Dopamine was once thought to be only the precursor of noradrenaline, but now it has been shown that it has its own function. It is localized mainly in the nerve tracts in the brain. Its cell bodies originate in the substantia nigra in the midbrain where it also contributes to the formation of melanin (black) pigment. Its axons course through the lateral hypothalamus and terminate in the caudate nucleus and putamen of the corpus striatum.

Recent studies with fluorescent microscope have shown that the catecholamine secreting nerves consist of a cell body, a long axon, and highly branched nerve terminals. The catecholamines are stored in dense vesicles present in their nerve terminals. In the adrenal medulla the adrenaline is stored in the chromaffin granules.
Fig. 7. Shows the mechanism of synthesis of noradrenaline in the sympathetic ganglia, its release and reuptake and also the method of degradation in the target cell. Such degraded products are ultimately excreted through kidneys and liver.

Catecholamine synthetization consists of the following steps: The aminoacid tyrosine is converted into DOPA by the enzyme tyrosine hydroxylase. Dopa is changed into dopamine by the enzyme Dopa decarboxylase. Dopamine is converted into noradrenaline with the help of the enzyme dopamine-B-hydroxylase (DBH). The noradrenaline is changed into adrenaline in the adrenal medulla with the help of the enzyme, Phenylethanolamine-N-Methyl Transferase. All these enzymes are present in the sympathetic nerve terminals and also in the adrenal medulla. These catecholamines act as neuro-humors at the synaptic junctions and produce quick changes in the post-synaptic cells by acting through their receptors. Further, adrenaline and noradrenaline secreted by the adrenal medulla circulate in the blood and produce changes in the distant target organs in the same way.

The catecholamines are degraded by four mechanisms: (1) O-Methylation by catechol-O-Methyl Transferase, (2) Deamination by Monoamine oxidase, (3) Absorption into the blood
stream through capillaries leading to metabolic degradation in liver and kidneys, and (4) Re-uptake into the nerve terminals (Fig. 7).

The catecholamine levels in the blood are constantly changing as they are being continuously synthetized, released and metabolized in various organs and tissues. However, through various regulatory mechanisms they normally remain within permissible limits. One of the important regulatory systems is the rate limiting enzyme—Tyrosine Hydroxylase whose excess production is prevented by the presence of adequate amount of catecholamines. When the level of catecholamine falls the activity of the tyrosine hydroxylase increases. This leads to more production of Dopa, Dopamine and noradrenaline. In addition, a few other mechanisms which play a minor role in the regulation of catecholamines are: (1) Inhibitory role of adrenergic receptors located presynaptically and (2) Formation of Dopamine-B-Hydroxylase in the sympathetic nerves and adrenal gland.

In addition, the conversion of noradrenaline into adrenaline is closely controlled by the adrenocorticoids secreted by the adrenal cortex. These corticoids control the formation of adrenaline by regulating the formation of PNMT. If hypophysectomy is done, PNMT falls in the adrenal medulla and it can be restored to normal either by injecting ACTH or by giving Dexamethasone. All these findings indicate that conversion of noradrenaline into adrenaline is controlled by the glucocorticoids secretion from the adrenal cortex perfusing the adrenal medulla through the cortical blood vessels draining into the medullary ones. In addition, hypophysectomy also produces decrease in the tyrosine hydroxylase and also the enzyme DBH within 2 to 3 weeks which can be restored to normalcy by injecting ACTH.

CATECHOLAMINES IN HYPOTHALAMUS

It has been well established that catecholamine containing cell bodies and nerve terminals exist in various regions of anterior hypothalamus and median eminence. Here the maximum quantity of Dopaminergic and Noradrenergic fibres are
found in the neighbourhood of median eminence indicating that these amines play an important role in this part of the hypothalamus. The ventromedial aspect of the hypothalamus contains the least amount of noradrenergic fibres. In addition to the above, the pineal gland which secretes the hormone “Melatonin” is heavily innervated by noradrenergic nerve terminals whose cell bodies are located in the superior cervical ganglion. It is through these noradrenergic nerve fibres that the body tries to regulate the synthesis and release of Melatonin which in turn influences the reproductive cycle of the animals.

METHOD OF ESTIMATION

Bioassay procedure still remains one of the most sensitive methods for the estimation of adrenaline and noradrenaline in the tissue extracts and biological fluids. However, the main disadvantage of this method is the lack of specificity. Because of this, the method is gradually being replaced by the chemical ones.

The development of sensitive fluorometric techniques has been the major factor in the rapid advancement of knowledge in the field of catecholamines. There are at present two well established chemical procedures for the estimation of catecholamines after their conversion into fluorescent derivatives, the ethylene diamine condensation method and trihydroxyindole method. For further details readers are requested to refer to original papers of the authors. Suffice it to say here that these techniques have greatly facilitated the studies of catecholamines in the body tissues and fluids. In addition, recently few methods have also been described in which Gas Chromatographic techniques and Radio-Isotopic methods have been used.

In recent years, Hillarp and Falck have developed a histochemical fluorescent technique to demonstrate the presence of catecholamines in adrenergic nerve endings and other tissues. This method is essentially based on conversion of catecholamines and their respective aminoacids to highly fluorescent derivatives in the presence of relatively dry formaldehyde vapor at 66 to 80°C. By this procedure it is now possible to localize catecholamines and their precursors within the histo-
logically recognizable microscopic structure when examined under the fluorescent microscope. The use of this fluorescent histo-chemical technique in the study of central nervous system has revealed the entire catecholaminergic neural pathway and its cell bodies and also has enabled us to map out the extensive monoaminergic pathways in the brain. Further, by using various monoamine inhibitors we can also assess the action of these drugs on different parts of the brain. It seems that the entire catecholamines in the brain are contained within the enlargement of nerve terminals instead of cell bodies or their axons. Therefore, it seems that these amines which are present in the presynaptic nerve terminals are mainly involved in the storage, release, reuptake and synthesis. The quantitative distribution of catecholamine in various parts of the body depends upon the amount of sympathetic nerve terminals present in each organ. They are present in larger quantity in the cardiovascular system, spleen and vas deferens. In the brain noradrenaline is present in a large quantity in the hypothalamic region while dopamine is present in a large quantity in the substantia nigra and caudate nucleus.

EFFECT OF DRUGS

It was at first observed that reserpine which is a potent hypotensive and tranquillizing agent caused a depletion of brain catecholamine. On the other hand, the use of various monoamine oxidase inhibitors, which increase the catecholamine content of the brain, stimulated the depressed brains. Thus, all the tranquillizers such as diazepam and its derivatives reduced the catecholamines of the brain especially of the hypothalamic region. On the other hand, various psychomotor stimulants such as amphetamine, and other similar drugs increase the catecholamine content of the brain. From these findings of drug actions one can also deduce that just as catecholamines act on the peripheral organs during stress and strain, they may also play significant role in the stressful situation of the central nervous system. Thus, now it is being established that behavioural depression is associated with defi-
ciency of catecholamines (usually noradrenaline) at various functionally important nerve centres. On the other hand, it is markedly increased in stressful and psychically excited situations. It has also been ascertained that by the use of drugs mentioned earlier these abnormal situations can be reversed towards normalcy. However, there is a great scope for further elaboration of all these actions of catecholamines in the brain.

CATECHOLAMINE RECEPTORS

There are two types of receptors for catecholamines in the peripheral system—alpha receptors and beta receptors. These receptors are pharmacologically defined by their ability to block these receptors by two classes of drugs. The most commonly used alpha blockers are phenoxybenzamine, the ergot alkaloids and phentolamine. The most widely used beta blocker is propranalol. Both types of receptors are stimulated by the catecholamines themselves and by the sympathomimetic drugs to different extent, whereas the blocking agents generally affect one type of receptor exclusively. These receptors can be recognized by the pharmacological means only and their biochemical characteristics are not yet clear. Further, it is also now realized that the brain catecholamines do not exactly follow the receptor mechanisms found in the peripheral organs.

In addition to these blocking agents, one should also know two important drugs which modulate catecholamines in the body viz. L-dopa and 6-Hydroxy dopamine. L-dopa is particularly effective in alleviating the symptoms of Parkinson's disease. In this disease there is loss of catecholaminergic neurons which originate in the substantia nigra in the midbrain. These neurons use dopamine as their neurohumors. In such cases with deficiency of dopamine the drug L-dopa increases the activity of these neurons in the substantia nigra and alleviates many of the symptoms of Parkinsonism.

The injection of 6-Hydroxy dopamine into the body causes selective destruction of catecholamine containing neurons, thus, causing chemical sympathectomy. This drug does not
cross the blood brain barrier and hence it is injected locally into the brain to destroy selectively the catecholamine producing neurons. These are some of the properties of catecholamines, a detailed knowledge of which is essential to the study of stress disorders.

**QUANTITATION OF STRESS BY CATECHOLAMINE ANALYSIS**

It is now well established that there exists a good correlation between various kinds of physical and mental stresses and the activity of the sympatho-adrenal system. In general, it may be stated that release of adrenaline from the adrenal medulla is the most common response to various stressful situations which involves certain degree of emotional disturbance. The activation of noradrenergic system in the sympathetic nerve endings usually occurs mostly after physical stimuli causing increased blood pressure. This can be measured by estimating these catecholamines in blood or urine. However, it has been observed by many that the determination of plasma catecholamine may not be the sole representative of the sympatho-adrenal system of the body since it may alter even on slight physical or mental disturbance. Hence, estimation of urinary excretion of adrenaline and noradrenaline has been found to be a more reliable indication of the status of sympatho-adrenal system. Even urinary excretion of VMA, a metabolite of catecholamine may not be the real indication of stress, since it does not differentiate adrenaline or noradrenaline in the urine.

As already stated, noradrenaline release is less affected by emotional stimuli than adrenaline. However, marked increase of noradrenaline occurs when stress is given to the animal in the form of excessive cooling or heating. Normally, adrenaline excretion in the urine comes to about 2 to 3 nanogram per minute and that of noradrenaline 6 to 10 nanograms. It is also known that various conditions of mental stress are accompanied by markedly increased excretion of adrenaline with relatively moderate increase of noradrenaline. Such an investigation can enable us to assess quantitatively the degree of stress by knowing the amount of adrenaline excretion in the
urine. In all cases of physical stress involving bodily discomforts, such as exposure to heat, cold, pain and bodily distress, it is the noradrenaline that is increased in the urine and its severity can also be quantitatively assessed by the degree of increase in the noradrenaline excretion. All these problems will be discussed again along with the problems of different types of stressful situations.

**Histamine**

There was some doubt whether histamine could be called neurohumor, though it is found in significant concentration in the brain and in other nerve tracts. It is produced from histidine by a specific enzyme histidine decarboxylase which is present in the brain in abundance and is metabolized into imidazolacetaldehyde by the enzyme histaminase. However, the doubt has now been dispelled as a result of extensive work of several workers in the field. It is found in abundance in the hypothalamus-hypophyseal region and in moderate quantity in midbrain and least in the cerebral cortex. It is suggested that apart from its own action it also potentiates the action of acetylcholine and in higher quantity it may inhibit the synaptic transmission of acetylcholine. In all other parts of the body the main source of histamine is the granules present in mast cells. However, such mast cells are absent in the central nervous system and hence the source of CNS histamine must be some other cellular component. Such subcellular distribution of brain histamines is consistent with the hypothesis that it is contained in the nerve endings. It is also interesting to note that the general distribution of histamine in the brain is quite like that of other biogenic amines such as noradrenaline and 5-Hydroxy-tryptamine.

Histamine is formed from histidine with the help of histidine decarboxylase and then it can be converted into methyl histamine and methylimidazole acetic acid. The methylating enzyme required for this purpose is the imidazole-N-methyl transferase, an enzyme which can be isolated from the brain. Histamine metabolism can be influenced by various drugs. For example, reserpine reduces the concentration of histamine in
Fig. 8. Shows the blood histamine and histaminase levels in different ages. It should be noted that as age advances histamine and histaminase become less and less.

the hypothalamus and thalamus just as it reduces the concentration of other amines. Tremorine also decreases brain histamine. Chloropromazine which inhibits N-methyl transferase increases the histamine concentration. But, all these findings do not exactly explain the function of histamine in the central nervous system. However, from their close association with the catecholamines, one can say that histamine by its vasodilating effect may be modulating the action of catecholamines. Thus, histamine may be functioning as a safety measure, which would prevent the excessive or prolonged vasoconstrictive action of catecholamines especially of noradrenaline in the brain. In this way, it may be said that histamine takes an active part in maintaining an efficient microcirculation in the brain as it does in other parts of the body. Normally it takes active part in growth and regeneration (Fig. 8). Pathologically it is increased in all allergic conditions (Fig. 9).
HISTAMINASE AND HISTAMINE IN PATIENTS OF TROPICAL PULMONARY EOSINOPHILIA

Fig. 9. Shows high histamine level in pulmonary eosinophilia. It also increases in all allergic conditions.

Serotonin (5-Hydroxytryptamine):

Serotonin occurs widely in nature. It is found in many types of fruits such as bananas and pineapples in large quantity. In mammals, the highest concentration of this material occurs in the pineal gland and in the enterochromaffin cells of the intestinal tract. In human beings, it is estimated that about 90% of Serotonin occurs in gastrointestinal tract; about 8 percent in platelets and only 2% within the central nervous system. Its synthesis occurs in various parts of the body by absorption of dietary tryptophan from plasma. Thereafter, in the presence of tryptophan hydroxylase this aminoacid is converted into 5-Hydroxytryptophan (5-HTP). This reaction can be blocked by p-chlorophenylalanine. After the synthesis of 5-HTP it is immediately decarboxylated to serotonin by the enzyme decarboxylases. Once serotonin is formed it may remain deposited at the place of synthesis or it may be catabolized by its deamination by the enzyme monoamine oxidase to ultimately form 5-Hydroxyindoleacetic acid (5-HIAA). In general, the rate of formation of serotonin is controlled by its rate limiting enzyme tryptophan hydroxylase.
In the brain, the histochemical and fluorescent microscopy showed that almost all the serotonin containing cell bodies are found in the group of neurons known as Raphe nuclei lying in the midportion of the Pons and upper part of the brain stem from where nerve fibres radiate to the forebrain above and the spinal cord below.

**PHYSIOLOGICAL ROLE**

The main function of serotonin in the brain consist in the regulation of (1) sleep, (2) perception and (3) temperature.

(1) It is now well established that 5HT in the brain is intimately related to the mechanism of sleep (Fig. 10). Thus, by electrical ablation of the Raphe nuclei which act as depository of cell bodies of serotoninergic neurons, or by pretreatment with p-chlorophenylalanine one can induce a marked reduction in sleep. It has also been observed that relative loss of sleep time appears proportional to the extent of serotonin loss. On the other hand, an intraventricular injection of serotonin or parenteral administration of 5-HT causes increase in sleeping time. However, acetylcholine and catecholamines may also play some role in modulating the sleep mechanism through Raphe nuclei.

**DIURNAL VARIATION OF PLASMA AND BRAIN 5-HT IN RATS**

![Graph showing diurnal variation of plasma and brain 5-HT in rats.](image)

Fig. 10. Shows the diurnal variation of plasma and brain 5-HT in rats. Note that at the time of sleep the brain 5-HT remains lowest while the Plasma 5-HT remains at the highest level.
In addition, serotonin injection into the ventricles causes profound rise of body temperature. However, if the serotonin content of brain is depleted, this elevation of body temperature does not take place. It does not automatically cause hypothermia.

The sensory perception mechanism is also disturbed if the serotonin content of brain is reduced by drugs. Thus, following the reduction of serotonin content of Raphe nuclei, animals exhibit decreased motor activity, decreased emotional reactivity and increased sensitivity to painful stimuli.

**Method of Assay**

Serotonin in the tissue extracts and biological fluids including plasma is best estimated by spectrophotofluorometry. This is a very sensitive technique. Fluorescence microscopy can also be adopted to detect 5-HT in histological preparations. By this one can visualize serotonin containing neurons in the Raphe nuclei present in the pons and brain stem.

**PINEAL GLAND**

Pineal is a very small gland in the brain, dorsal to the thalamus. It is innervated only by sympathetic nerves from superior cervical ganglion. The Pineal gland contains the highest concentration of serotonin among all the tissues of the body and in rats, pineal serotonin is 200 times more than that seen in the brain. In this gland serotonin is further converted by acetylation and methyl transfer into melatonin. The activity of melatonin synthesis seems to be controlled by the sympathetic nervous system and the light-dark cycle. Increased sympathetic activity or light increases the concentration of 5-HT, but decreases that of melatonin. The denervation or darkness suppresses this activity. Similarly, the activities of both acetylating and methylating enzymes are increased by darkness and rapidly decreased by light. Cyclic AMP stimulates the overall rate of 5-HT and melatonin synthesis. Sympathetic stimulation produces a similar reaction possibly mediated through
adenyl cyclase of adrenal gland. Skin colour is controlled by
the pituitary melanocyte stimulating hormone (MSH) and
melatonin. In many other species, it is also important in sexual
development as it suppresses the formation of female gonads
and the size of seminal vesicles. It is related to the development
of oestrus cycle in animals. However, its definite role in the
reproductive physiology needs further study.

**Gamma-aminobutyric Acid (GABA)**

The first report about the presence of GABA in the central
nervous system was made in 1950. A number of investigations
have now established that it is an inhibitory transmitter in the
vertebrate central nervous system (CNS). It is formed to a
large extent, if not entirely, from L-GLutamic acid. Its conver-
sion into GABA is catalyzed by L-glutamic acid decarboxylase
(GAD), an enzyme present only in mammalian CNS. It is
degraded by the enzyme GABA transaminase present in those
areas of the CNS where the concentration of GABA is also
found in excess. GABA is intimately related to the oxidative
metabolism of the carbohydrates in the central nervous
system.

The neurotransmitting action of GABA has been studied
extensively. At present, there is sufficient evidence regarding
the production, storage and pharmacological activity of
GABA which demonstrates its role as an inhibitory transmi-
ter. However, inhibitory pathway of GABA in the cerebral
cortex has not yet been clearly demonstrated. It is well estab-
lished that there is a spontaneous release of GABA from the
surface of the brain and also from the deeply seated nuclei of
the brain such as amygdala, caudate nucleus etc. GABA is also
known to be concentrated in the Purkinje cells in the cerebel-
lum which have inhibitory effects on various subcortical nuclei
of the cerebellum adjacent to fourth ventricle. Various investi-
gations, appear to support the hypothesis that GABA is an
inhibitory transmitter (Fig. 11). Further, there seems to be no
pharmacologically sensitive mechanism for the rapid destro-
duction of GABA similar to cholinesterase mechanism for the
destruction of acetylcholine. Similarly, there is no definite
Fig. 11. Shows the Gamma-aminobutyric acid (GABA) content of rat brain. Here one can see that after the acute and chronic electric shock there was a marked rise of GABA in the rat brain which is just opposite to the action of brain acetylcholine.

evidence to indicate how the action of GABA is terminated. However, it seems that some uptake mechanism works in the brain for recycling GABA and terminating its action. Thus, the development of any new technique which could help in assessing the turnover of GABA in vivo would greatly add to a better understanding of the functional importance of GABA in the central nervous system.

In Huntington's Chorea there occurs continuous extensive involuntary movement along with low concentration of GABA in the substantia nigra, putamen, globus pallidus and caudate nucleus. This is associated with the deficiency of the enzyme GAD and may indicate degeneration of the GABA containing cells in these tracts. This also suggests that in all the diseases with involuntary movements or convulsions GABA might be playing some important role. However, this needs further investigation.
GLYCINE

Quite a number of observations tend to suggest that the amino-acid glycine may play the role of inhibitory transmitter in the mammalian spinal cord. These indications are based on the fact that this amino-acid is found in relatively high concentration in the spinal cord as compared to other amino-acids. Further, glycine is found concentrated more in the spinal grey matter, especially in the ventral horn, than in the white matter suggesting that it may be associated with inhibitory interneurons. However, glycine is quite ineffective as an inhibitor of cerebral cortex, unlike GABA which acts as an inhibitory agent both for cortex and spinal cord. The uptake of glycine may be related to sodium, through which its action is possibly terminated. However, the mechanism of its release and its pathway is still not very clearly known. Strychnine is known to block the action of glycine. Thus, strychnine acts as a convulsant by blocking the post-synaptic membrane of the inhibitory neurons leading to incoordination of motor activity.

GLUTAMIC ACID AND ASPARTIC ACID

Glutamic acid and aspartic acid stimulate the central nervous system and are found in abundance in these regions. It is difficult to say at present whether or not they act as transmitters in the central nervous system. However, when the CNS is stimulated there occurs an excess outpouring of these amino-acids. Whether they come from blood or they are put out by the neurons of the cerebral cortex, it is difficult to ascertain. In the spinal cord, these act as excitants of the interneurons, motor neurons and also of the sensory nerve endings at the dorsal region of the spinal cord. Both glutamate and aspartate are common intermediary metabolites of neural tissue and hence, they can become available in all parts of the CNS. These findings tend to suggest that the response to these amino-acids represents a nonspecific activity of the neurons to these agents and is, not indicative of any transmitter function. However, they may serve as final excitatory agents in the synaptic transmission. The studies so far conducted indicate that glutamic
and aspartic acids function as excitatory agents and GABA and glycine act as inhibitory agents.

PROSTAGLANDINS

Prostaglandin is an active acidic lipid with a specific property of stimulating or depressing the smooth muscles. There are a number of naturally occurring prostaglandins, but two of them viz. prostaglandin E and prostaglandin F are important. Although, it is known that they have many roles to play in the body, here we will discuss only the neurohumoral role of prostaglandins. The stimulation of the splanchnic nerve in dogs and cats causes an output of large amount of prostaglandin E\textsuperscript{2}. However, if the organism is pretreated with alpha adrenergic agents such responses are abolished. This indicates that PGE might be having a modulatory antagonistic action.

PROSTAGLANDIN-LIKE ACTIVITY IN ESSENTIAL HYPERTENSION AND ISCHAEMIC HEART DISEASE

![Prostaglandin-like activity chart]

Fig. 12. Shows the prostaglandin-like activity in certain cardiovascular diseases. In hypertension it is reduced by about 40%, whereas in Ischaemic Heart disease it is about 60% less than the normal.
on the catecholamines (Fig. 12). In addition, it was found that both PGE and PGF series of prostaglandins are found in the central nervous system and exhibit a series of actions. However, there is not enough evidence to indicate definitely that they act as neurohumors of the central nervous system. There is some indirect evidence to support the view that prostaglandins may be playing a role in the transmission process in the CNS.

(a) PGE appears to be concentrated in sufficient quantity in the synaptosome fractions of the brain.
(b) They are the natural constituents and are synthetized and released on direct or indirect stimulation of the brain.
(c) When administered intraventricularly they produce gross physiological changes.

A number of pharmacological stimulants can induce release of prostaglandins from CNS. Amongst them Picrotoxin and strychnine are important ones. They are released from the surface of the sensory cortex and the release can be increased by direct or indirect stimulation of the cortex. Such a release from the cortex can also be increased if different nerves are stimulated. Thus, there is a considerable amount of evidence to indicate the role of prostaglandin in the central nervous system. However, their exact role in different areas of the brain needs further study.

ADENOSINE 3',5'-MONOPHOSPHATE (CYCLIC AMP)

It is now well established after the work of Sutherland, that actions of many of the hormones are mediated through cyclic AMP present in the cells. Thus, adrenaline stimulates glycogenolysis in the muscles, lipolysis in fat cells and release of many of the hormones from endocrine glands. All this appears to be under the control of the cyclic AMP (Fig. 13). It is possible that hormones and neurohumors might also be acting on the brain through the cyclic AMP which is present in abundance in the brain. In fact, of all the mammalian tissues, the brain has the
**Stress and its Management by Yoga**

**Fig. 13.** Mechanism of action of cyclic AMP on the cell membrane. The hormone first acts on the receptor which stimulates adenylyl cyclase enzyme present in the cell membrane to reduce ATP into 3' - 5' cyclic AMP and liberate energy for hormonal action like lipolysis etc.

**URINARY CYCLIC-AMP LEVELS IN CASES OF BRONCHIAL ASTHMA AND THYROTOXICOSIS**

![Bar graph showing urinary cyclic-AMP levels in normal, bronchial asthma, and thyrotoxicosis]

**Fig. 14.** Shows that in some stress disorders such as thyrotoxicosis, the urinary excretion of the cyclic AMP is increased whereas in bronchial asthma the cyclic AMP excretion is reduced.
highest concentration of the enzyme adenyl cyclase which catalyzes the synthesis of cyclic AMP and the phosphodiesterase which hydrolyzes the cyclic AMP. Caffeine and Theophylline stimulate central nervous system inhibiting phosphodiesterase which leads to increase in the concentration of cyclic AMP. From all these evidences one can say that cyclic AMP plays an important role in modulating the action of different neurohumors at the cellular and molecular level and hence one should know the details of its action in relation to different neurohumors already described. Recently, in certain clinical conditions, such as in bronchial asthma, it was found much decreased whereas in other conditions, such as thyrotoxicosis, it was found much increased (Fig. 14). From these observations one can say that cyclic AMP also plays an important role in mediating the activities of all the neurohumors in health as well as disease.
CHAPTER 4

Neurohumoral Response to Stress

Visceral Sensation

Broadly there are five types of sense qualities in the external environment which are perceived by the five sense-organs located in the body. The sensory receptors involved therein are called exteroceptors. Some receptors are imbedded in the internal organs, such as all the viscera, endocrine glands and blood vessels. These are called interoceptors which have three parts viz. (a) peripheral division containing sensitive nerve endings, (b) intermediate division or conducting pathways upto subcortical level, and (c) central division consisting of nuclei in the cerebral cortex. The interoceptors are either capsulated or uncapsulated. They are highly specialized and are capable of reacting to specific mechanical, thermal, osmotic and other stimuli promptly. Chemo-receptors readily respond to internal chemical changes. In the process of transformation of chemical stimulation into nerve impulse, acetylcholine released from nerve endings plays an important role. The presence of interoceptors in the blood vessels enables the cerebral cortex to regulate and maintain adequate blood supply to each organ. Thus, the main function of interoceptors is to keep the cerebral cortex informed about the activities of the organs supplied by it. Although, these receptors are present throughout the system, they are located in large numbers in certain areas like G.I. tract, Pyloric antrum, Ibocarcal region and rectum. In the cardiovascular system such a function is performed by carotid sinus and aortic arch. The main function of interoceptors is to regulate digestion, circulation, respiration, urine formation and all other autonomic processes. The func-
tions of these interoceptors can be modified either by the various stimulating agents at the visceral level or by the excitation or inhibition of the cerebral cortical centres. As already stated, in the intermediate division of the visceral sensory apparatus, afferent impulses travel along autonomic nerves, especially sympathetic nerves, as well as spinal nerves. In this way, the pathways from the receptors in the heart, lungs, stomach, iliocarcal region, rectum and bladder have been fairly well established through various segments of spinal cord. These pathways further pass through the spinal cord, medulla oblongata, subcortical regions, especially the reticular formation, hypothalamus and thalamus till they reach the cerebral cortex. In the cerebral cortex the messages are received especially by the limbic, premotor, orbital and other adjacent areas. In this way, the centres especially responsible for receiving visceral sensations are scattered all over cerebral cortex, especially in the anterior part. The final and accurate analysis of stimuli is done in association with other cortical centres (Fig. 15). In case of any pathological changes in the viscera messages from interoceptive apparatus reach the cerebral cortex from where the efferent impulses pass through hypothalamus and limbic system and produce various changes in the functioning of these organs through autonomic nervous system. In this connection Kurtsin states: “It was quite evident that the cerebral cortex is also greatly influenced by the nervous impulses arising in the receptors of the viscera, vessels and endocrine glands. These impulses reach the cerebral cortex via the nerves and provide nerve centres governing autonomic activity with information regarding state and performance of the internal structures. The information is then compared with the one which the cerebral centres received from the external environment. Only after a most complicated and detailed analysis of both these sources of information the cortical response is produced which determines not only the subsequent performance of the internal organ from which information was received but also the general behaviour of the body as a whole”.

From this it is clear that there is a need for complete reappraisal of the relationship of the cerebral cortex and inter-
Fig. 15. Shows how different sensations from the sense-organs, viscera and muscles reach the respective areas of the cerebral cortex which ultimately integrates all of them at the Psychic centre to produce the appropriate response.

...nal organs, which greatly influences the functioning not only of the autonomic nervous system but also of the emotions and behaviour of a person as a whole.

CLINICAL CONSIDERATIONS

It is now well established that many Psychosomatic stress disorders are caused by repeated and chronic exteroceptive stimuli especially through the auditory and visual organs
which ultimately stimulate the cerebral cortex to produce the necessary changes in the internal organs. However, it is not always realized by the clinician that any changes in the internal organs such as gastritis transmitted through interoceptors will also lead to disturbance in the higher nervous activity. Thus, it has been realized recently, that neurosis or psychosis can be caused by the presence of such disturbance in any one of the affected viscera. Further, occurrence of neurosis as a result of some disturbance in the cerebral cortex can also cause secondary visceral changes leading to a vicious circle. This has been confirmed by the experimental studies, whereby pathological changes in the internal organs were found to be accompanied by neurotic changes in higher nervous activity. The mechanism by which such a change happens was not known till intensive studies of interoceptive factors were carried out. Thus, the disturbance of higher nervous activity occurring in the presence of some pathological changes in the internal organs may be due to the shifting of interoceptive stimuli from the organ to the cerebral cortex. The resultant disturbances of higher nervous activity followed by disturbances of autonomic activity differed very little from the disorders caused by external environmental stress. In both cases, features depend upon the amount and degree of involvement of cortical and subcortical structures rather than the type of stimuli. Prolonged disturbances in an organ such as stomach, leading to gastritis or gastric ulcer induce functional or bio-electrical changes in the hypothalamus, reticular formation or limbic areas which may produce changes not only in the same organs, but also the other neighbouring organs, such as chronic hepatitis which can be associated with gastric ulcer. Thus, one can fully realize that for the development of psychosomatic stress disorders not only the external environmental stress factors operate on these patients, but sometimes the internal environmental changes in any organ can also initiate changes in the cerebral cortex which may in turn produce disturbances in that and other neighbouring organs by developing functional changes in both these Viscero-Cortical centres. On the basis of experimental studies of Kurtsin one can say that when these disturbances ultimately
settle down in an organ, one can hardly find out any change in
the manifestation of these disorders. Hence, while considering
the pathogenesis and pathology of stress disorder one should
take into account all these factors before finalizing the manage-
ment of these disorders.

DEVELOPMENT OF PSYCHOGENIC STRESS

Now, one would like to question as to how an extremely
powerful stimulus either auditory or visual can produce patho-
logical reaction and what the initial features of the same are.
Why the same type of stress produces different diseases in
different people and why it manifests quickly in some after
stress, whereas in others there is a long latent period before the
disease manifests itself? In man, psychic trauma caused by
emotional disturbances resulting from spoken or written word
is the most common stressful situation. The effect of such
psychic trauma can be greater than that of any type of physical
trauma. Thus, a common stress disease like hypertension can
be caused as a result of repeated minor mental trauma occur-
ing in everyday life. Although, we now know that such dis-
eases are caused by mental stress, we do not know exactly how
the disease actually develops and what are the changes that
occur in the body before the features of a particular disease
make their appearance. It is now known, that, most of the
stress diseases such as peptic ulcer, hypertension, thyrotoxico-
sis etc. are all preceded by some type of mental trauma and
nervous strain induced by emotional disturbances. In some,
the history of such psychic trauma is easy to trace, whereas in
others it may be difficult since many a time the patients do not
attach much importance to the mental strain as a causative
factor for the subsequent development of the disease. It is a
well known fact that during and immediately after the World
War II the incidence of peptic ulcer and hypertension increased
enormously in people living in war affected areas. Same is the
case in areas effected by floods and earthquakes. However, all
the people living in such areas did not develop stress disorders
and only a certain percentage of them got the effects.
Neurohumoral Response to Stress

It is now clinically observed that variation in the development of such stress diseases depends upon specific physical and mental constitution. Thus, persons of ectomorphic type of physical constitution and cerebrotonic type of mental constitution are more liable to develop stress diseases than others. However, these stress diseases can also occur in persons of mesomorphic and endomorphic constitution with somatonic and viscerotonic types of psychic constitution provided the degree of stressful situation is strong and exists for a prolonged period. Thus, mental trauma in a person with sensitive nervous system for a shorter or longer period is the root cause of all stress disorders. In addition, the nature of a mental trauma and the circumstances under which it is produced may also influence the nature, course and severity of these disorders. There is evidence to support the idea that usually situations causing excessive mental conflict are likely to cause cardiovascular diseases. Similarly, psychological maladjustment in food intake may cause peptic ulcer, and sexual maladjustment may lead to one of the endocrine diseases like thyrotoxicosis, amenorrhoea etc.

It is interesting to note that many a time some patients suddenly get the disease after psychic trauma and later on by treatment quickly return to normal, whereas others get the disease after a prolonged exposure to stress and such patients do not regain their normal health for a long period. All these peculiarities appear to be due to varying psychosomatic constitution and also the type of stressful state one is exposed to.

Physiological and Biochemical Changes Following Stress

We have already observed that there is a considerable time interval between the occurrence of mental trauma and the onset of the disease. Sometimes it takes even six months or a year to develop the disease. This is probably due to the fact that the capacity to adjust to such disturbed situations varies from person to person. Some persons remain adjusted to such a situation for a long period and when their defence mechanism
fails, they develop the disease. Such a defence mechanism exists in the cells of the psychic centre of the cerebral cortex and when it fails, it interferes with the basic excitation and inhibition mechanisms of the brain. More usually it is the inhibitory mechanism which is upset by stressful situations leading to a continuous stimulation of centres of subcortical region by the cerebral cortex, especially the psychic centre of the frontal lobe. Such a prolonged stimulation of subcortical centres, i.e. those of the limbic system, hypothalamus with its autonomic nervous centres and reticular formation ultimately leads to excessive stimulation of various internal organs causing a disease in any one of the susceptible organs or organ systems. However, before the onset of disease in any organ or system, there is a clear latent period when signs of anxiety neurosis persist for a variable period of time. During the period of this "neurosis" several types of biochemical, physiological and morphological changes are seen. Bykov and his colleagues who had done considerable amount of work in this field, observed that histological changes occur not only in the size and shape of various structures in the neurons, but also in the various structural components of synapses. Further, they also observed changes in the capillaries surrounding the affected neuron not only of the cerebral cortex but also of the organs affected by the various stressful stimuli. Extensive investigations have been carried out on experimental animals and human beings after giving repeated acoustic stimuli. Such repeated acoustic stimuli produced marked changes not only in the higher nervous activity of the cerebral cortex, but also in the activities of the cardiovascular, respiratory, digestive, urinary, endocrine and other systems both in men and animals. Marked changes were also seen in the metabolism of carbohydrate, protein, fat, water and salts.

Biochemical studies of the brain tissue have indicated decreased activity of various enzymes such as cholinesterases, histaminase and mono-amine oxidase. As a result of it, there occurs an excessive accumulation of acetylcholine, histamine, catecholamine and serotonin in the various centres of brain causing disturbances in their activities. In addition, there
occurs an excess of cyclic AMP and a fall in ATP and creatine phosphate in the brain. From all these findings, it appears that, the nature and duration of anxiety neurosis preceding the development of stress disease depends upon the degree of biochemical, physiological and structural changes that occur in the cerebral cortex. It has been shown that soon after the stress exposure, there is a sudden release of acetylcholine from the cerebral cortex which activates all subcortical centres to initiate the adaptive response. This is soon followed by an increase in the activity of adrenergic and noradrenergic nerve endings in the subcortical centres especially in the hypothalamus. Subsequently, the activity of the neuroendocrine systems especially of the pituitary and the adrenal glands is enhanced. The main substance responsible for the production of stress reaction is the ACTH from the pituitary and cortisol from the adrenal cortex. These hormones affect the whole body including the cerebral cortex and induce a number of metabolic alterations.

BIOCHEMISTRY OF INITIAL RESPONSE TO NEUROSES

Even after having all the above discussion we have not yet identified the main factor that actually triggers off the change in the cortical and other centres. It has now been well established from various physiological investigations and also from our own studies that psychologic stress, like any other type of stress produces excitation in certain specific cells of the cerebral cortex as a result of liberation of acetylcholine which causes nervous excitation in various cortical synapses and in the post-ganglionic endings of cholinergic fibres (Fig. 16). Normally, whenever acetylcholine is released into the synaptic cleft it is rapidly broken down by the enzyme cholinesterase. However, if the stimulus is very strong or if it is repetitive in nature, there is always a decrease in the formation of cholinesterase present at the synapses. Because of this, the excess acetylcholine is not destroyed. Such an excessive activation and liberation of acetylcholine in the cerebral cortex appears to be the main triggering factor in the genesis of all the changes
ACETYLCHOLINE RESPONSE TO PSYCHIC STRESS

![Graph showing the response to psychic stress in the acetylcholine content of brain and blood in rats.](image)

Fig. 16. Shows the response to psychic stress in the acetylcholine content of brain and blood in rats. Here one can see that stress causes marked reduction of acetylcholine in the brain coinciding with an increase in the acetylcholine content of blood. However, at later stages of stress both are found decreased.

that occur after psychologic stress. This biochemical change causes exhaustion of the inherent excitatory and inhibitory functions of the cerebral cortex. In case such a state is allowed to continue, it produces after a shorter or longer latent period, a neurotic condition of the cells of the cerebral cortex which disturbs the functional relationship between the cortical and subcortical brain centres. As already discussed, the cerebral cortex through its excitatory and inhibitory functions especially through the latter, controls the subcortical centres. If the inhibitory function is suspended and the subcortical centres are allowed to receive only excitation, the latter become hyperactive and produce not only marked excitation in their own function, but also in all linked systems such as the neuroendocrine system, the autonomic nervous system etc. Both these systems would ultimately excite all the internal organs and also all the other tissues leading to marked changes in the body.

The hypothesis regarding acetylcholine as the main initiating factor in the cerebral cortex has been studied by several investigators. Mitchel was the first person to observe through
Neurohumoral Response to Stress

PATTERN OF RBC ACETYLCHOLINE LEVEL IN DIFFERENT STRESSES DISORDERS

Fig. 17 Shows the changes in the acetylcholine content of blood in various common stress disorders. As one can see, anxiety neurosis has the maximum acetylcholine content followed by other common stress disorders like Hypertension, Myocardial infarction, Thyrotoxicosis, etc.

the Cup method that whenever there is an excitation of the cerebral cortex, there occurs a liberation of acetylcholine in abundance. Similarly, Kurtsin has reported that if acetylcholine is injected into the limbic cortex in the dosage of 2000 gamma through a previously prepared window in the skull, one could see the changes in the various activities of cortex and other centers after a lapse of 1 to 3 days which persisted for some weeks. We have also observed that acetylcholine is the first neurohumor which is liberated in an excessive quantity in the cortex following exposure to strong stimuli. In this connection Kurtsin states, "Hence, acetylcholine and no other mediator is the chemical agent which triggers the development of neurosis and cortico-visceral pathology while it is the limbic cortex that in psychic or some other cortical stress (emotional or interoceptive) overtaxes the nervous processes. The power of the 'Blow' produces severe disturbances of cerebral and visceral activity. Further, it also causes a prolonged after-effect lasting for weeks or even months (Fig. 17). This apparently contributes to the fact, that the strong stimulus entering the
brain 'smashes' the complex yet fragile structures made up of the neurons and their circulatory system and at the same time 'disorganises' the equally complex and fragile enzyme system'. Thus, for example, the cholinesterase activity is markedly reduced, while ribonuclease activity is increased. From this, one can realize how a strong psychological stress causes chain reaction of responses starting from the limbic and frontal cortex of the brain leading to changes in the rest of the body systems.

Although, it is true beyond doubt that acetylcholine is the main neurohumor which initiates the chain reaction, its subsequent course of action also depends upon the intact adrenergic and noradrenergic nerve endings in the subcortical centres. If these nerve centres are blocked by chlorpromazine administration, not many changes of the neurotic type can be seen in the rest of the body. Therefore, in order to induce chain reaction in all the subcortical centres and their ramifications such as autonomic nervous system and neuro-endocrine system, not only does it need intact adrenergic and noradrenergic mechanisms,

![Graph showing catecholamine response in the brain and blood of rats.](image)

**Fig. 18.** Shows the catecholamine response in the brain and blood of rats. Here one can observe an increase in catecholamine content in the brain throughout the period of stress. However, in the blood at first there was reduction, then a rise followed by its normalization possibly due to the process of adaptation.
(Fig. 18) but also other neurohumors, such as serotonin, histamine, gamma-aminobutyric acid (GABA) besides cyclic nucleotides. Apart from an excessive production of these neuro-humors, inadequacy of enzymes responsible for degrading the above mentioned neurohumors can also be considered an important factor responsible for causing various manifestations of neurosis in these subjects. Such changes in brain functions are always followed by alterations in the visceral activity which ultimately leads to the development of the disease at a later stage. In every organ, first there occur functional changes as a result of neurocirculatory overactivity, which are followed by organic changes leading to the appearance of the disease process.