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Abstracts

1. Some Electroencephalographic Observations in Yogis

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This paper describes the E. E. G. observations in the following 4 categories of Yogis :—

(i) Those who tried to stop their heart voluntarily, (ii) Those who had increased threshold for pain produced by immersion in cold water, (iii) Yogis doing Bhu Samadhi (underground meditation) and, (iv) Yogis during the act of meditation.

(i) During the act of stoppage of circulation, the alpha-activity was considerably diminished.

(ii) The E. E. G. patterns of the persons having raised pain - threshold showed several runs of hump activity in the parietal zones. The occipital zones of these individuals showed bizzare activity which became more marked with hyperventilation. The possibility of some voluntary control on the thalamic and upper brain stem in these practitioners of Yoga is suggested.

(iii) One Bhu-Samadhi expert, who was studied in an air-tight box, showed an electroencephalographic sleep pattern interspersed with extraordinarily well marked alpha-activity here and there, during the experiment. He also exhibited persistant fast activity almost like beta activity from the occipital regions. The latter type of activity appeared after about the 4th hour and persisted till the end of the experiment without any change.

(iv) An increase in the alpha-activity of the meditative Yogis was noticed during meditation, and this activity was not influenced by "Bhang". Only one Yogi showed few runs of activity indicating drowsiness and hump stage of sleep during meditation, although he professed to be awake. The concentration by the Yogi on the different regions of the vault of head in succession causes eye movements, but concentration on one point increases alpha-activity. One Yogi had a paroxysmal discharge of high voltage and bizzare slow waves during concentration. Even when not in meditation, these Yogis usually had a prominent alpha-activity.

Even these few studies indicate a definite relationship between prominent alpha-activity and the yogic practices, especially of a meditative type. If corroborated by later work, this observation will have an important bearing on the problem.

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2. Electroencephalographic studies of spontaneous and activated patterns in the cerebellum and its projections.

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Cerebellum–"the head ganglion of the proprioceptive system" (Sherrington) has been the subject of immense interest during the recent years both from experimental and clinical aspects.

Though much is known about the role of cerebellum on the somatic functions of the body, much more remains to be elucidated about its autonomic activity. Previous evoked potential studies have demonstrated extensive projections from the posterior part of the paleo-cerebellum to most of the limbic system structures, which are intimately concerned with the control of autonomic activity.

Present studies were conducted to further elucidate this relationship. Electroencephalographic recordings were taken from different regions of the brain and cerebellum

(i) to study the spontaneous activity of these regions,

(ii) to study the modifications in this activity under the influence of stimulation of any of these regions.

Electrodes were implanted stereotaxically in cerebellum, anterior reticular formation of the brain stem, thalamus, hypothalamus, amygdala, hippocampus, caudate, orbital surface of frontal lobes, and parietal cortex, of 6 cats, 1 monkey and 1 dog. The spontaneous electrical activity of these regions was recorded on an E. E. G. machine 24-36 hrs. after implantation of the electrodes. The cerebellum on one side was stimulated with the help of a square-wave stimulator and the changes produced in the electrical activity of the above mentioned regions observed. The brain regions were also stimulated in turn and the effects produced on cerebellum were observed. Stimulation of cerebellum leads to desynchronization (increase in frequency and fall in amplitude) of the other brain regions, while stimulation of brain regions in turn also had the same effect on the cerebellum as well as other brain regions.

This brings out a most significant observation that the cerebellum and the other higher nervous regions mentioned above have reciprocal integrated functional activity. This study also supports the observations of workers who have demonstrated inverse relationship between the electroencephalographic activity of the hippocampus and the neocortex.

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3. The Spinal Cord—A possible site of action of Vasomotor Drugs

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The spinal cord has autonomous vasomotor loci, yet it is commonly neglected as a possible site of action of hypotensive drugs. Reproducible vasomotor responses are elicitable over a long period (suitable for an average acute experiment) by repeated compression of the spinal cord (ligated at C-7, while still enclosed in the meninges). A spinal fluid compression with 100-150 mm Hg pressure for a period of 10-15 secs. excites vasoactive neurones in the spinal cord and the vasomotor response is expressed by a sympatho–adrenal discharge. The technic of eliciting the spinal compression vasomotor response (SCVR) is simple and can be employed in any pharmacological laboratory. For purposes of analysis the SCVR has been divided into four components (a) *Latent period*–the period which elapsed between the application of the pressure stimulus and the onset of the response, (b) *Pre-primary phase*-an occasional rise in the blood pressure which occurred prior to the main blood pressure rise, (c) *Primary phase*–the characteristic blood pressure response, consisting of a sharp rise, a peak and a quick downward phase, (d) *Secondary phase*-the slow downward return of the blood pressure at the end of the primary phase often chracterised by small waves on the tracing.

The latent period decreased when the primary phase was increased in its amplitude and this was considered as a potentiated SCVR. Similarly, the latent period increased when the primary phase was decreased in its amplitude, and this was considered as a depressed SCVR. C. N. S. stimulants (metrazol, strychnine) potentiated the SCVR and the C. N. S. depressants (mephenesin and barbiturates) depressed the SCVR. The pre-primary phase was occasionally elicited with neostigmine and has been shown to be due to a skeletal muscle effect. The SCVR has a quick neurogenic component (primary phase) and a slow humoral component (secondary phase). The secondary phase was abolished by bilateral adrenalectomy. The SCVR was blocked by ganglionic or adrenergic blockade.

4. Isolation of a Hypoglycemic principle from the bark of Ficus bengalensis Linn.—Chemical and Biological studies.

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The bark of Ficus bengalensis Linn. was subjected to chemical analysis for organic and inorganic constituents. Successive extraction with various solvents was also carried out. A hypoglycemic substance, suspected to be a glycoside was separated. It is soluble in water and alcohol and has a melting point 160°C. On oral administration in normal rabbits and dogs, it produced a fall in fasting blood-sugar. In alloxan - diabetic rabbits and dogs and in depancreatised dogs it had no such action.

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5. Observations on apomorphine induced pecking in pigeons

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Administration of even minute amounts of apomorphine induces a persistant pecking behaviour in pigeons. The effect comes on very quickly (latent period 3-4 minutes) and lasts for 1/2-1 hour depending upon the dose employed. The ED 50 by the intramuscular roote was found to be 78·1± 11.1 μg/kg. On chronic administration of apomorphine there is a significant decrease in the latent period and weight which quickly recovers on stopping the drug. There is no conditioning and no tolerance. Ten other centrally acting agents tested (caffeine, cocaine 5-HT,LSD-25, methamphetamine, morphine, nalorphine, metrazol, strychnine and yohimbine) fail to produce a similar effect.

Thirty five drugs were tested for their capability to prevent pecking induced by 250 μg/kg. apomorphine given intramuscularly. The groups of drugs tested included C. N. S. stimulants, tranquilisers, hypnotics, analgesics, anticonvulsants, muscle-relaxants, adrenergic blocking agents, antiemetics and antihistaminics. Protection was afforded by caffeine(ED50,16.4. $\pm$ 1.2 mg/kg.), chlorpromazine (4.1 $\pm$ 0.13), cocaine (6.9 $\pm$ 1.3), cyclizine, LSD-25 (0.25 $\pm$ 0.001), morphine (17.2 $\pm$ 0.2), prochlorperazine, rauwolscine (0.5 $\pm$ 0.01), tigan and yohimbine (0.33 $\pm$ 0.1).

This pecking appears to be a feeding hallucination and may be identical with chewing movements produced by apomorphine in rat and rabbit. It has not been possible to demonstrate any consistent relation between anti-pecking activity and C. N. S. stimulant, C. N. S. depressant, sympatholytic parasympatholytic, or antihistaminic effects of a drug. However, most of the agents influence the pecking and emetic response to apomorphine in an identical manner.

6. Some further observations on LSD-25 morphine antagonism

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Dhawan and Gupta (1959) have reported antagonism of morphine and amidone analgesia in rats by LSD-25. The work has been extended to see if the drugs show antagonism in other effects also. In the present investigation the effect of morphine and related drugs on LSD-25 pyrexia and the effect of LSD-25 on morphine and apomorphine vomiting have been studied.

Pyrexia was produced in albino rabbits by (i) intramuscular injection of 50 μg/kg LSD-25, (ii) intravenous injection of 0.1 ml. TAB Vaccine or (iii) intraperitoneal injection of 10 mg/kg dinitropherol (DNP). Morphine or related drugs were given at the same time and rectal temperature recorded hourly for 5 hours. The pyretic action of LSD-25 was blocked by morphine, dihydromorphinan and dihydrohydroxycodeinone, while nalorphine, apomorphine, amidone and levorphan were ineffective. Morphine was the most potent blocking agent and the effect on LSD-25 pyrexia was more marked than on pyrexia induced by TAB or DNP. Tolerance developed to this effect of morphine.

The antiemetic effect was studied in mongrel dogs fed immediately before use. Emesis was produced by apomorphine (50 μg/kg intravenously), morphine (1 mg/kg intramuscularly) or emetine (3 mg/kg intravenously). Graded doses of LSD-25 were given intravenously 15 minutes before the emetic challenge. LSD-25 antagonised the emetic effect of apomorphine and morphine (ED50 being 12.7 $\pm$ 5.7 μg/kg and 25.8 $\pm$ μg/kg. respectively) but was ineffective against emetine emesis.

These observations strongly suggest a specific antagonism between central effects of LSD-25 and morphine. It would be interesting to investigate the effects of morphine on LSD-25 induced model psychoses in man.

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7. Effect of drugs on reserpine induced vomiting in pigeons.

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The emetic response in pigeons has been described to be a sensitive and reliable criterion for evaluation of reserpine like activity (Earl *et al.*, 1955). The present investigation was taken up to see if antagonism of this emesis could be used as a criterion of anti-reserpine effect of drugs. Emesis was induced by intramuscular injection of 0.5 mg./kg. reserpine.

The emesis was blocked by C. N. S. stimultants—caffeine (ED 50, 4.0 ± 1.8 mg./kg.), LSD-25 (0.23 ± 0.1), metamphetamine (5.8 ± 2.0) and methylphenidate and by morphine (0.45 ± 0.16) while two other C. N. S. depressants, pentobarbitone and diphenyl hydantoin, were ineffective. Five antiemetic agents—cyclizine, chlorpromazine, hyoscine butyl bromide, prochlorperazine and tigan-and four anticholinergic drugs-atropine, artane, benactyzine and hyoscine butyl bromide-were also ineffective. The hypothesis of Earl *et al.* that the emesis is probably a central parasympathetic effect appears to be untenable in view of these findings with the anticholinergic drugs. Further the inability of known antiemetic drugs to check it strongly suggests that the mechanism of reserpine emesis is different from that of other emetic agents. The vomiting could also be blocked by two indoles, yohimbine (0.068 ± 0.01) and its isomer rauwolscine (0.055 ± 0.003) and by iproniazid (144.4. ± 44.0). The blockade by iproniazid probably is the result of 5-HT preservation since parenterally administered 5-HT is known to antagonise reserpine emesis (Schneider, 1957). Most of the drugs found effective in the present investigation are known to antagonise effects of reserpine at other sites. Blockade of this emesis may be used as a convenient method for investigating anti-reserpine activity of drugs.

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8. Modification of morphine analgesia by ganglioplegic drugs and protoveratrine.

G. P. GUPTA AND B. N. DHAWAN

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A large number of agents are known to modify analgesic effect of morphine. Most of these agents are drugs acting on the central nervous system or on the autonomic effector cells. No attention has been paid, however, to the effect of drugs acting on the afferent sensory pathways. Hence in the present investigation, the effect of protoveratrine and ganglioplegics, some of which are known to act on afferent structures, has been studied on morphine analgesia.

The analgesic effect was studied in albino rats (35-55 gm. body weight) by the hot plate method of Eddy *et al.* The temperature of the plate was maintained at 56.5°C and the first licking of hind paws was taken as the end point. At least four dose levels of each drug or each combination were tested between limits of 100% analgesia and no analgesia. The data were analysed by log dose probit response method.

Protoveratrine (25 and 50 μg/kg), TEA (50 mg/kg) and hexamethonium (10 mg/kg) did not produce any significant alteration in the analgesic activity of morphine. A significant potentiation was, however, observed with pentolinium (2 and 10 mg/kg) and mecamylamine (1,5 and 10 mg/kg) which are not so far known to possess any sensory effects. These findings indicate that it is not possible to modify morphine analgesia by agents influencing afferent mechanisms.

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9. Gastric Vagal Projections into the Hypothalamus

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(Department of Physiology, All India Institute of Medical Sciences, New Delhi).

The role of afferents from the stomach in the regulation of hunger and appetite has been recognised for long. But the course of these afferents in the brain stem and higher nervous regions remains largely obscure. The present study has been taken up to map out the projections of these gastric impulses to the hypothalamus.

Cats immobilised with Flaxedil and put on artificial respiration were used for study. After implanting electrodes stereotaxically in the different regions of the hypothalamus, spinal cord was transected between cervical 2 and 3. Single shock stimuli were delivered to the gastric branches of vagus nerve through a square-wave stimulator and responses through the implanted electrodes in the hypothalamus recorded oscilloscopically. Stimulation of gastric vagal branches evoked short latency spikes from medial ("satiety" center) and supra-optic regions of the hypothalamus and spikes with longer latency from posterior hypothalamus. Responses recorded from "feeding" centers have been variable. Distension of intragastric balloons (rubber tube with attached balloon passed through the mouth into the stomach) also evoked potentials from the "satiety" regions of the hypothalamus. Well marked potential changes in the hypothalamic regions coincident with chewing and swallowing movements of the animal have also been observed. It is, therefore, suggested that the afferents from the stomach and the oro-pharyngeal regions modify feeding behaviour through reflex mechanisms operating through the hypothalamic centres.

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10. Differential metabolism of various regions in the limbic and neocortical system of the Brain—Respiratory activities.

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The phylogenetically old cortex and related structures making up the so called rhinencephalon were given the name 'Limbic System' by Broca in 1878. It encircles the old brain stem. In course of development from Amphibian Reptilian Lower mammalian Higher mammalian forms, the neocortex has increased in size. The limbic system and its immediately associated nuclear structures have been seen to provide the anatomical substratum for emotional behaviour. Maclean has further postulated a dichotomy in the function of the phylogenetically old and new cortex, to account for the differences between the emotional and intellectual behaviour.

QO_2 for the following seven regions have been found out by Warburg techniques using glucose as substrate. The regions are: (1) Temporal tip (2) Lateral Frontal Cortex (3) Anterior Cingulate (4) Orbital Cortex (Postero-medial) (5) Hippocampus (Ammon's Horn), (6) Hypothalamus (7) Cerebellum (medial part of right middle cerebellar lobe.) The values for QO_2 have been found both on the basis of the weight of tissues as well as on the DNA content. The latter gives an idea of the activity on the basis of the number of cells present in the fraction.

It has been established that the QO_2 for temporal tip, lateral frontal cortex, anterior cingulate and orbital cortex has almost the same value (0.87 to 0.89 micro liters of O_2 per mg. fresh weight per hour). The QO_2 of hypothalamus and cerebellum on the other hand is significantly lower than of the regions cited above. QO_2 of hippocampus lies in between that of the areas in the neocortex and that of the hypothalamus.

Results are discussed in light of the number of neurons and non-neuronal cells present in each of this area.

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11. The central vasomotor effects of two new ganglion blocking agents

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Two new orally effective long acting hypotensive agents, mecamylamine and pempidine, were studied for their central vasomotor effects independant

of their ganglion blocking property. These agents are known to cross the blood brain barrier and are concentrated in the brain (Harrington *et al.*, 1958, Lancet, 2,6.).

The study was done in 13 dogs and 17 cats. The animals were routinely anaesthetized with pentobarbital, bilaterally vagotomized and maintained on artificial respiration. The blood pressure was recorded from the left common carotid artery. An indwelling polythene tube was left in a femoral vein for intravenous injection of drug solutions.

The independant central action of the drugs was studied (i) by localizing the agents in the central nervous system (viz. by injection into lateral cerebral ventricle, vertebral artery or theca of the spinal cord) or (ii) by intravenous injection in doses which were inadequate to produce ganglionic blockade. The supraspinal vasomotor reactivity was assessed (a) by reflex pressor responses evoked by electrical stimulation of the afferent vagus or by occlusion of the carotid artery and (b) by direct pressor responses evoked by electrical stimulation of medullary vasomotor center. The spinal vasomotor reactivity was assessed by the vasomotor responses evoked by compression of the cord ligated at C-7. For detecting a peripheral ganglionic action of the drugs either nictitating membrane contractions to preganglionic stimulation or "nicotinic" response to acetylcholine were employed throughout the study.

That mecamylamine depressed the central vasomotor loci is indicated by inhibition of supraspinally mediated vasomotor reflexes and hypotension in doses which did not show ganglionic blockade. The spinal vasomotor loci were also inhibited. Thus mecamylamine was shown to possess a central hypotensive action independant of the ganglion blocking action. On the contrary, pempidine stimulated the central vasomotor loci. There was potentiation of the supraspinal (both reflex and direct) vasomotor responses. There was also facilitation of the spinal vasomotor responses. These effects could be demonstrated with a dose of pempidine which was inadequate to produce ganglionic blockade.

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12. Rat Diaphragm Method for the Study of Indigenous Antidiabetic Drugs.

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Many indigenous drugs are reputed antidiabetic remedies. Their alleged effectiveness in diabetes must be proved by subjecting them to scientific study. Reduction in animal blood sugar has been extensively used as a criterion of antidiabetic activity. Since the defect in diabetes lies in the tissue utilisation

of glucose mere hypoglycemia producing drug is unlikely to replace insulin adequately in the treatment of diabetes. If we were to look for a drug which enhances the tissue utilisation of glucose, the rat diaphragm method can be conveniently used. Following is the report of the study of the glycosidal fraction of Ficus bengalensis by the rat diaphragm method. The experiments were carried out in two parts. In the first part the drug was added in vitro to the incubation medium to test its effect on the glucose uptake of the rat diaphragm in presence and in absence of added insulin. In the second part the drug was fed orally to rats and glucose uptake of their diaphragms compared with that of the untreated rats. The result indicate that hot water extract of F. benga lensis when added *in vitro* did not increase glucose uptake of the rat diaphragm. Insulin caused a marked increase in the glucose uptake. Hot water extract of F. bengalensis significantly diminished this insulin effect. The glycosidal fraction of F. bengalensis did not affect the glucose uptake of the rat diaphragm nor did it affect insulin effect. On feeding the glycosidal fraction orally to rats the blood sugar of the rats diminished by an average of 24mg% but the glucose uptake of their diaphragms was not significantly different from that of the untreated rats.

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13. Changes in Histamine Metabolism induced by superficial burn

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In has been reported that after superficial skin burn, there is a 200-300% rise in skin histamine in both mice and rats in 3 weeks time (Ballani, Sinha & Sanyal, 1959; Ballani, Jha & Sanyal, 1959). The mechanism of this rise has now been studied in the rat.

The rise is shared by both the mast cell and non-mast cell fractions of skin histamine. The histamine content of the blood and urine is raised about 4 times the levels obtained in control rats. *In vitro* enzyme studies according to the method of Waton (1956) did not reveal any significant change in tissue histidine decarboxylase activity though the tissue histminase activity was considerably reduced.

Though it is possible that other factors are also involved, the results obtained so far indicate that diminished detoxication of histamine, leads to a rise in the blood level, increased excretion in urine and to a rise in the tissue content.

It was also seen that there is a rise in the eosinophil content of the blood 3 weeks after burn as has been noted in clinical practice (Sevitt, 1951).

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14. Effect of cooking on Amino-acids contents of foods cooked by different methods.

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More and more of the need is now being felt to be able to express the nutritive value of the different proteins rather than to think of all proteins as being equal. The biological value of proteins may be related not only to their content of indispensable amino-acids but to the relative rates of their release in and absorption from the intestinal tract. The release of amino-acids during the digestive changes in the gastro-intestinal tract may be, to certain exctent, dependable on the changes in the amino-acids composition of foods during predigestive processes, to which foods are subjected, like that of cooking etc.

The articles of foods were analysed for their amino-acids contents in the pre-cooked conditions. The foods were prepared, as described in the earlier communications (Pai, 1954, 1957 & 1958), in the laboratory under the controlled conditions of temperature, of adding water in a definite volume during washing, number of washings, adding water in a definite quantity during cooking etc. The amino-acids contents were determined quantitatively by filter-paper chromatographic technique and with the help of densitometer. The food material was subjected to two different types of cooking, namely, by direct application of heat on one hand and by steam-cooking in an ordinary cooker, on the other. There was a little loss of amino-acids during cooking, by either of the methods. The loss by the direct application of heat method was more than by the cooker method. The significance of the results obtained has been discussed in the paper.

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15. 5-Hydroxytryptamine content of Edible plants.

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It has been shown recently that banana pulp and skin contain 5-Hydroxytryptamine (Serotonin; West, 1958). Since 5-HT stimulates the smooth muscles in many species and may be involved in peristalsis (Hendrix, *et. al.* 1957; Bulbring & Lin, 1958), it was of interest to study the 5-HT content of common edible plants.

Edible parts of plants of several natural orders were studied. The extraction and bio-assay of 5-HT was done according to the method of Parratt & West (1957), the specificity of the reaction being checked by the 5-HT antagoinst drug, BOL-148. Further identification for both 5-Hydroxytryptamine and tryptamine was done chromatographically (Collier, 1958).

The maximum amount of 5-HT was detected in bananas. Tomatoes and brinjal, members of the natural order Solanaceae, contained moderate amounts. Small amounts were detected in fruits of plants belonging to natural order, Cucurbitaceae and Malvaceae. Potato, though a member of the natural order Solanaceae, only contained a trace.

West (*loc cit*) suggested that the ingested tryptamines along with food may lead to increased urinary excretion and thereby to an erroneous diagnosis of carcinoid tumours.

In view of the smooth muscle stimulating activity of 5-HT and it's known effect in antagonizing histamine induced gastric secretion in mammals (Black, Fisher and Smith, 1956) it will be of interest to study, if the foods studied as above can influence these mechanism.

Such a study is in progress and will be reported later.

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16. Hexokinase activity in different brain regions.

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The hexokinase reaction occupies a position of special importance, since it represents the initial step in the metabolism of carbohydrates. Long (1952) reported high hexokinase activity in the rat brain. Of all the tissues studied he found the highest activity of this enzyme in the brain. Similar observations were reported by Utter (1950), Weil-Malherbe *et al* (1951) and Crane *et al.*, (1953). Wiebelhaus and Lardy (1949) noticed that brain preparations

phosphorylated glucose, fructose and mannose but not galactose, ribose or gluconic acid. Kerby and Lecback (1957) have ascribed the hexokinase of brain as a non-specific enzyme which phosphorylates both glucose and fructose. Intracellular distribution of this enzyme has been worked out by Lowry *et al.*, (1956) by microtechniques.

The hexokinase activity has been found in the following regions of the dog's brain :—Hypothalamus, lateral parietal cortex, lateral frontal cortex, hippocampus, temporal tip, corpus callosum and cerebellum. The values range from 8.619 enzyme units to 11.90 enzyme units per μgm DNA of the brain tissue in the first four regions cited above. Hexokinase activity in corpus callosum was found to be 4.88 units per mg DNA and in cerebellum it was seen to be 2.004 enzyme units. A few experiments for hexokinase activity were done with the monkey's brain too. The distribution of activity was more or less similar to that found in the dog's brain except the figures for hypothalamus. Cerebellum has the lowest hexokinase activity of all areas studied.

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17. Nucleic acids and Nucleotides composition of various areas of the brain.

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From the numerous recent publications it has been seen that the nitrogen containing noncorbohydrate constituents of the nerve cell undergo a rapid change with neuronal activity. This fraction is labile in character and responds promptly with nervous activity. In biology it is also known that the templates concerned with the preservation of "information" in the cell are complexes between nucleic acids and proteins. As our object was to understand the metabolic differences between the limbic and neocortical systems of the brain and as the two regions of the brain differ in their physiological function we felt it worthwhile to investigate the RNA, DNA, total acid soluble phosphorous fraction, delta 7 nucleotides and lipid content in the various areas of the brain. The composition of the following 13 regions has been investigated and is reported. The regions are:—(1) Frontal Tip (2) Temporal Tip (3) Lateral Frontal Cortex (4) Lateral Parietal Cortex (5) Orbital Cortex (6) Lateral Occipital Cortex (7) Hippocampus (8) Amygdala (9) Anterior Cingulate Gyrus (10) Hypothalamus (11) Corpus Callosum (12) Cerebellum (13) Midbrain (14) Thalamus. The cerebellum has a high RNA and DNA content. The concentration of nucleotides and labile phosphate contents increases significantly under hypothermia.

18. Influence of variation in environmental temperature on the acute toxicity of reserpine and chlorpromazine in mice.

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The acute toxicity of chlorpromazine in mice is 18 times higher under cold environmental temperature of 4°c than at thermoneutrality (30°c). Under similar conditions the acute toxicity of reserpine increases more than 900 times. These findings confirm the earlier suggestion that these drugs cause hypothermia by different mechanisms of action. Increased acute toxicity was also noticed due to these drugs at a higher temperature (36°c).

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19. Restoration of pressor response to sympathomimetic amines, following adrenergic blockade.

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Since 1914 when Dale first showed the so called 'vaso-motor reversal' to adrenaline following ergot, attempts to analyse the mechanism of this depressor response have been continuing without much success. Ahlquist (1947) put fourth the theory of 'alpha' and 'beta' receptors and suggested that the depressor response was due to exclusive stimulation of the beta receptors. More recent attempts to analyse the mechanism are those of Levy and Ahlquist (1957); Maxwell *et al.* (1959) and Slater *et al.* (1959).

Recently there has been work to show that anti-histamines sensitize tissues to stimulant responses of adrenaline (Kuriaki and Uchidae, 1955 and Innes, 1958). There is no work to show the effect of anti-histaminics on depressor responses to adrenaline.

This work was undertaken to study the effect of anti-histaminic drugs on the depressor responses to adrenaline following adrenergic blockade, the hypothesis being that if the depressor response to adrenaline following adrenergic blockade could be restored to pressor response by drugs, it may help to elucidate the mechanism of this depressor response. It may also help to throw some more light on Ahlquist's hypothesis of 'alpha' and 'beta'–receptors.

Dogs of both sexes were used. Carotid blood pressure and tracheal respiration was recorded under phenobarbitone anaesthesia (150 mg/kg. I.P.) After obtaining standard responses to epinephrine, reversal was produced by injecting either dihydroergotamine, priscol, or chlorpromazine, When good reversal was repeatedly elicited, a slow infusion of one of the antihistaminic

drugs—Antistine or Anthisan was started. Within three to five minutes of the injection of the antihistaminic drug epinephrine injections were again repeated to see if the depressor response has been modified.

At least five experiments were done for each group of drugs, and the experiments were randomized.

Three control experiments were done with each adrenergic blocking drug to study the duration of the block, when no other drug is given after the blocking drug. The block persisted for at least three hours in all cases.

The following dosage was used :—

Priscol :	10 mg/kg
Largactil :	6 mg/kg
Dihydro-Ergotamine :	1 mg/kg
Antistine :	10-20 mg/kg
Anthisan :	10-20 mg/kg

Effect of Antistine and Anthisan on blockade produced by Priscol was studied. Similarly effect of Antistine and Anthisan on blockades produced by Ergot and Largactil were studied. Thus there were six groups of experiments. In the seventh group of experiment the effect of Antistine and Anthisan combined on Priscol blockade was studied.

It was noted that Antistine had no effect in restoring the pressor response to epinephrine after Largactil blockade. Anthisan however restored the pressor response to epinephrine in all experiments after Largactil blockade.

Priscol induced blockade was abolished and pressor response restored in three of the five experiments by Antistine and in four of the five experiments with Anthisan.

Ergot induced blockade was abolished and pressor response restored by Antistine in three of the five experiments. In one experiment the depressor response was abolished but the pressor response was not restored. Anthisan succeeded in restoring pressor response in all cases.

It was noted that a combination of Antistine and Anthisan, was more consistently effective in restoring the pressor response than any one drug alone. Very often the restored response was greater than the control response.

The demonstration of a method of abolishing the depressor response and restoring the pressor response to epinephrine may pave the way to analyse the mechanism of the depressor response and the possible composition of the adrenotropic receptors.

20. Studies on bile secretion—Influence of vagal stimulation and acetylcholine on the secretion of bile in dogs.

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In our earlier studies on the physiology of bile secretion, it was noticed that the chemical mediators of the sympathetic nervous system, nor-adrenalin and adrenalin decreased the flow of bile and altered the composition of the bile secreted. Further studies on the parasympathetic effect both by vagal stimulation and acetylcholine administration, under varying physiological conditions have now been carried out. The quantitative and qualitative responses noticed are reported in this communication.

The stimulation of the peripheral end of the cut vagus (right) caused a decrease in bile secretion which persisted for about an hour. The stimulation of the central end, with the left vagus intact increased the flow of bile. After severance of both vagi, artificial respiration by itself caused an increased flow. The qualitative changes noticed in all these cases were a decrease in the content of total solids, fatty acids, bile salts and pigments.

The nature of changes seen after the administration of acetylcholine, in single doses and during continuous infusion were similar to those observed after stimulation of the peripheral end of the severed vagal nerve.

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21. Central component of Hypotensive action of 1-Hydrazinophthalazine (Hydralazine)

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The mode of hypotensive action of 1-hydrazinophthalazine (Hydralazine) is not clearly understood. In addition to a definite adrenergic blocking action, depressant action on the medullary vasomotor centre has only been suggested. The purpose of the present investigation was to study the central vasomotor depressant action of this agent independant of the peripheral adrenergic block, by the use of suitable techniques.

The study was carried out on 20 dogs and 2 cats. The peripheral adrenergic blockade was avoided by either administering hydralazine intravenously in doses inadequate to produce adrenergic blockade, or the agent was

given in such a manner that it was localized in the central nervous system viz. by intracerebroventricular route, intra-carotid injection and by cross-circulation technique. The central vasomotor activity was assessed by observing the effect of the drug on centrally mediated vasomotor responses elicited by carotid occlusion, electrical stimulation of the central cut end of vagus and to direct stimulation of medullary vasomotor centre employing the stereotaxic technique.

A definite central component of hypotensive action of hydralazine was observed in the present study. In the dog, intracerebroventricular injection of hydralazine (10 mg) induced hypotension and the centrally mediated vasomotor reflexes were blocked. At the same time peripheral nor-epinephrine pressor response, which served as control for adrenergic blockade, remained unaltered. The hypotension produced by this agent was more marked in a neurogenic hypertensive dog. Injection of the agent (5 mg) into the internal carotid artery also induced hypotension and inhibition of vasomotor response to centripetal vagal stimulation. In the cat, intravenous injection of a non-adrenergic blocking dose of hydralazine (0.5 mg/kg) inhibited the vasomotor response evoked by electrical stimulation of the medullary vasomotor centre. Similarly, hydralazine (2 mg/kg) produced hypotension in the body of a receipient dog when it was limited only to the head circulation by the cross-circulation technique, the nervous connections between the head and the body were intact.

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22. Role of Ions in Experimental Auricular Arrhythmias

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Study was undertaken to elucidate the role of ions in the production and maintenance of experimental cardiac arrhythmias in the intact dog since no findings on this have been reported so far. 123 mongrel dogs anesthetized with pentobarbitone and heparinised were used. Venous blood was drawn from the coronary sinus through a Morawitz cannula and arterial sample from near the ostia of the coronary arteries using a polyethlene catheter through the left carotidy artery. Auricular arrhythmias were produced by the 3 standard techniques representing the 3 different theories of atrial flutter and fibrillation. (1) Acetylcholine-induced auricular fibrillation (Schalek) (2) Aconitine induced atrial fibrillation (Scherf) and (3) Injury stimulation-induced atrial flutter (Rosenblueth and Garcia Ramos). Samples were drawn before and after the arrhythmias. Plasma ionic concentration of Na^+, K^+, and Ca^{++}, were read on a Coleman flame photometer and Mg^{++} from the the protein-freed plasma

was precipitated as ammonium magnesium phosphate and phosphate concentration read on a Hilger Colorimeter. In all the 3 arrhythmias, there was a nonspecific rise of Na^+, K^+ and Ca^{++} in both venous and arterial blood. But there was a specific efflux of Mg^{++} from the heart in aconitine and acetylcholine-induced fibrillation but not injury stimulation induced flutter, indicating that experimental auricular arrhythmias produced by different techniques may have different mechanisms. Study of arteriovenous differences from cardiac catheterisation of 3 adult males with auricular fibrillation revealed a similar Mg^{++} efflux.

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23. Blood-pressure changes during superficial burn in experimental animals.

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Dogs of either sex weighing 2–5 kg. were employed for this study. Animals were anaesthetized with chloralose (80 mg/kg) and carotid blood pressure recorded. Superficial skin burn was produced by pouring hot water at 80° C on the ventral aspect of the abdomen.

There was a transient fall in blood pressure which was followed by a transient rise. Following these two phases, the blood pressure became normotensive. In next three hours only a gradual slight fall of 10 mm of systolic pressure was noticed. Mast cells showed degranulation and there was erythema of the burnt skin.

In animals pretreated with mepyramine, the initial hypotensive phase was absent and erythema was minimal though rupture of mast cells occurred. The hypertensive phase became prolonged in these cases.

The hypertensive phase was annulled by (a) infiltration of the area to be burnt with local anaesthetic drug; (b) decerebration; (c) ganglion blockade and (d) by administration of adrenergic blocking drugs.

Erythema and mast cell rupture was seen to occur in all such animals. The hypotensive phase became prolonged in these cases.

Thus it appears that the 3rd normotensive phase represents a balance between the factors causing hypotension and hypertension. The blood pressure changes were not affected by deep anaesthesia, injections of atropine or Bol-148 (a specific antagonist of 5-HT).

The hypotensive phase is thus likely to be mediated through release of histamine, whereas it is suggested that the hypertensive phase is due to reflex,

the impulses originating from the burnt area, and mediated through the vasomotor centre, the efferent impulses travelling along the vasoconstrictor sympathetic nerves.

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24. Further observations on hypotensive and chronic toxicity effects of Withania Somnifera Dunal (Aswagandha).

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The dried roots of Withania somnifera were powdered and subjected to 24 hours cold extraction in different solvents i.e. Water, Alcohol, Petroleum ether and Chloroform. An aqueous fraction of the alcoholic extract free from nicotine was prepared and subjected to pharmacological and toxicological studies.

A. Dogs Pharmacological investigations of A/W fraction showed marked and sustained hypotensive action in normotensive anaesthetised and acute hypertensive dogs. This effect was not blocked by atropine and antihistaminics. It slightly reduced the carotid baroreceptor reflex response and enhanced the vasopressor response of injected adrenaline. It showed some depressant action on heart in situ and vasodilating effect in limb perfusion experiments.

B. Frogs It has marked depressant action on isolated frog's heart which was not blocked by atropine.

C. Rats (C.N.S.) 1. Intraperitoneal injection produced mild sedative effects.

2. Chronic toxicological studies in rats did not show any significant untowards toxic effects.

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25. Effect of Ficus religiosa on smooth muscles.

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Dried bark of Ficus religiosa (Hindi: Pipal) was exhausted with hot alcohol. Watery suspension of the alcohol free extract was used for pharmacological investigations.

The extract decreased the tone and diminished the amplitude of movements of isolated instestines of rabbit, guinea pig and albino rat, and intestine *in situ* of dog. It also depressed the contractions of isolated uterus of rat.

The extract showed varying degree of spasmolytic activity against various spasmogens as tested on isolated intestines of rabbit, guinea pig and rat, and uterus of rat. The approximate spasmolytic ED_{50} of the extract on guinea pig ileum were—0.065 mg./ml. for acetycholine (0.2 μg/ml.), 0.29 mg./ml. for histamine (0.2 μg/ml.) and 0.78 mg./ml. for barium chloride (0.1 mg./ml.), and against Serotonin (0.4 μg/ml.) on rat uterus was 1.2 mg./ml. Atropine sulphate was found to show similar type of antispasmodic activity.

The extract had antiacetylcholine but no antihistamine action on isolated guinea pig heart. On the blood pressure of anaesthetised dog it had vagolytic and antiacetylcholine actions but showed no antagonism to histamine. In some of the experiments on dogs it reversed the depressor response of acetylcholine. The extract relaxed the bronchial musculature of spinal dog and also antagonised acetylcholine spasm in tracheal chain of dog. The extract, given intraperitoneally prevented asthma produced in guinea pigs by acetylcholine aerosol, in doses of 300 mg./kg. and by histamine aerosol, in doses of 450 mg./kg.

It had no antiacetylcholine action on frog's rectus.

The investigations showed that the extract of F. religiosa has atropine like properties.

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26. The male factor in fertility and infertility.

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It is only in recent years that the fertility of the husband has been given much consideration in the study and treatment of the infertile couple. Even now the study of the husband is often the final procedure in the management of the barren couple and quite frequently this study is inadequate.

The present investigation has been carried out to evaluate the male factor in fertility and infertility, where the study of semen quality has been undertaken in 500 consecutive unselected men whose wives complained of atleast 1 year's infertility. The semen analysis has been done with particular reference to active motile spermatozoa count diluting the sample with Ringer Locke's saline. The potential degree of fertility of the individual has been assessed on the theory that only active sperms are capable of reaching and fertilizing the ovum. The absolute motility of the sperms (expressed in millions of active sperms per ejaculate) has been employed as the measure of the individual's degree of fertility viz. highly fertile male is one who has a total of 185,000,000 or more active sperms; relatively fertile male 80,000,000

to 184,000,000 ; a subfertile male 1 sperm to 80,000,000 ; and sterile male, whose specimen is either necrospermatic or azoospermatic.

It has been observed that 332 or 66 percent of these men had an absolute motility of 80,000,000 or more sperms, and were potentially fertile, whereas 168 or 34 percent were potentially subfertile and sterile.

In the present study 51 percent of the men fall into the category of highly fertile individuals ; whereas it is seen that 49 percent of the men are either a contributory or an absolute factor for the sterile unions. As far as an absolute factor is concerned, 8 percent of these men are clinically sterile, being necrospermatic (1%) or azoospermatic (7%).

The changes in the average values of the semen between different groups are characteristically significant. The average volume of the ejaculate shows a decrease by about 1 cubic-centimeter inorder from highly fertile to sterile group. The active sperms per cubic-centimeter decrease in a geometrical progression as one passes from highly fertile group to subfertile group. The speed drive in highly fertile and relatively fertile group shows significant high values than that of subfertile group. The morphology of the sperm is found to vary closely with the potential degree of fertility.

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27. Calophyllolide: An Indigenous Anticoagulant.

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Calophyllolide, a pure, crystalline, active principle with a coumarin ring was isolated from the seeds of Calophyllum inophyllum (N. O. Guttiferae). Because of its coumarin structure it was investigated for anticoagulant properties. Dissolved in 95% alcohol, and diluted in distilled water, it was administered as a 1% solution orally to rabbits, and the prothrombin time estimated by the Quick's one-stage method. Its anticoagulant property was comparable to dicoumarol. This drug was further investigated for antiarrhythmic properties, for its ability to suppress ventricular ectopic beats in dogs, after an experimental myocardial infarction produced by a two-stage ligation of the anterior descending branch of the left coronary artery. Its antiarrhythmic property in the unanaesthetised coronary ligated dog was comparable with quinidine, while dicoumarol and tromexan had no antiarrhythmic properties. This combination of anticoagulant and antiarrhythmic properties in a single drug should prove immensely valuable, in view of the fact that the fatal outcome in myocardial infarction, is due to the extension of the clot in the coronary arteries or due to the development of ominous ventricular rhythms.