CENTRAL ACTIONS OF CHLORPROMAZINE

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(*Received March, 20 1961*)

The story of Chlorpromazine (CPZ) is already old. Having opened the door of a new arena, having made a very successful inroad into the domain of the mind, so long a close preserve of the philosophers, it has given place to newer compounds.

It was synthesized by M/s Rhone Poulence Laboratories of Paris, to meet the demand for a drug that will be effective in the prevention and/or treatment of surgical shock. This was sought to be achieved by damping out the homeostatic regulating reactions including those under the control of the hypothalamus, by the use of a suitable pharmacodynamic agent, supplemented by induced hypothermia. CPZ was introduced to meet these pharmacodynamic requirements.

Chlorpromazine was synthesised with a view to produce a central neuroplegia. It was reported by Laborit *et al.* (1952) that intravenous doses of 50-100 mg. of CPZ in man caused some sleepiness and a feeling of dissociation but no loss of consciousness. Courvoisier (1953) who made exhaustive studies with CPZ, provided evidences suggesting a probable central action for the drug. It potentiated the effect of general anesthetics, hypnotics and analgesics in a very significant manner. CPZ was found to potentiate the narcotic effect of alcohol and to suppress the psychomotor exitement of intoxication. It was also shown to antagonise the convulsant effects of nikethamide and nicotine, but had failed to suppress convulsions produced in rats by strychnine indicating perhaps its low activity on the spinal cord. From these findings Courvoisier *et al* (1953) inferred that the action of CPZ was not on medullary centres but should be at a higher level.

CPZ was also found to facilitate hypothermia. Further evidence of its central action was suggested by its capacity to suppress vomiting induced by

centrally acting emetics while failing to prevent vomiting of peripheral orign, such as that induced by copper sulphate (Brand *et al.*, 1954).

There was some direct experimental evidence in support of central action. Thus Cathala and Pocidelo (1952), injected CPZ directly into the ventricles, causing profound narcosis, hypothermia and complete absence of hypertensive response to electrical stimulation of the central end of the vagus and the carotid sinus reflex. Courvoisier *et al* (1953) also showed a loss of hypertensive response to electrical stimulation of the central cut end of the vagus and the caroid sinus reflex on intravenous injection They also shown by *in vitro* studies that CPZ caused a decrease in oxygen consumption by the cerebral cells, the degree of depression being in proportion to the concentration of the drug. This effect, however, was a part of a general depressant action on metabolism and did not give the least indication of the site of action of CPZ.

By applying the drug directly to the floor of the 4th ventricle, Donnet *et al* (1954) in later years obtained many of the results observed by Cathala and Pocidelo (1952). They noted that the effect of CPZ was of the same nature as that of cocaine applied locally, and thought that the findings of Cathala and Pocidelo were partly at least, due to a local anesthetic action of CPZ. It may be noted that the effect of intraventricular CPZ may be quite non-specific, depending on the dose in which it was administred. Thus, there was very scanty directly experimental evidence in support of central action of CPZ.

On the other hand there were indirect evidences to show that a definite central action for CPZ, with some preference for the diencephalon. Dasgupta, Werner and their associates undertook a comprehensive study on this aspect. A considerable amount of evidence, significant in nature, in support of central action of CPZ was the outcome of these studies. These studies also helped in the demarcation of the central site of action for CPZ. The main finding may be briefly stated here :-

(i) Blocking of vasopressor response to occlusion of both common carotid arteries following intracisternal administration of minute amounts of CPZ, which had no peripheral action (Dasgupta and Werner, 1954 a).

(ii) A suppression of Sham rage of decorticate cats with CPZ (as little as 250 μg/kg) given intravenously (Dasgupta *et al.*, 1954).

(iii) An inhibition of the hypothalamic and medullary pressor centres, stimulated reflexly or directly (drug given i. v.) (Dasgupta and Werner, 1954, a, b).

(iv) An inhibition of the condition reflexes (drug given i. p.) (Guha *et al*, 1954).

(v) A suppression of the natural oestrus in the rat (drug given i. p.) (Dasgupta, 1955).

(vi) A failure to prevent the liberation of ADH in response to nicotine (drug given i. p.) (Dasgupta and Hausler, 1955 a).

(vii) A failure to prevent the liberation of ACTH following stress—emotional and surgical (drug given i. p.) (Dasgupta, 1957).

(viii) A characteristic and simultaneous change in the behaviour and in the EEG in the rhesus monkey (drug given i. v.) (Das *et al.*, 1954).

(ix) A blocking effect on the intercalary neurones of the spinal cord and those portions of the formatio reticularis of the brain stem that activate or inhibit the reflexes of the spinal cord (Dasgupta and Werner, 1955).

(x) A depressant effect on the respiratory centre in conscious rabbits (drug given i. p., in a comparatively larger dose) (Dasgupta and Hausler 1955 b).

(xi) An abolition of the thalamocortical synergism on isolated brain specimen (drug given I. V.) (Das *et al*, 1955).

CPZ and hypothalamus.—Some of the above results, it will be noticed, indicate a hypothalamic activity for CPZ.

Sham rage.—The drug very effectively suppressed the 'Sham rage', in acutely decorticate and diencephalic cats in such small doses that would be devoid of any peripheral action. On the other hand, it could not suppress the rage pattern elicited only by bilaterl preoptical incisions at the base of the frontal lobes. But after an additional incision bilaterally of the lateral dorsal surfaces of the frontal lobes or tips of the temporal lobes, increased sensitivity to the drug became evident.

Philip Bard (1928) showed that the structure absolutely essential for the production of Sham rage was the caudal hypothalamus. For the drug to be effective in Sham rage, it appears plausible, therefore, that dissolution of some of the corticofugal pathways is necessary, rendering the hypothalamus hypersensitive to the action of the drug.

It was found that in anesthetised animals with an intact CNS, considerably higher doses of CPZ (0.5-1 mg/kg.) were required to block pressor responses

to electrical stimulation of the posterior hypothalamus, the lateral, caudal medullary reticular formation, or the sciatic nerve, but as little as 50 to 100 μg/kg uniformly abolished the same responses in decorticate cats. It seems that, normally, corticofugal pathways reinforce the upward and downward direct facilitatory functions of the R.F. and thereby provide a relative resistance to the depressant action of CPZ. The internuncial spread of impulses, in other words, will conceivably be more susceptible to suppression by hypnotic drug (e.g. thiopentone, etc) if its natural reinforcement from the celebral cortex is interfered with as a consequence of cortical ablation. The caudal hypothalamus, in the case of 'Sham rage' has been rendered highly susceptible to the action of CPZ because of the ablation of the rostral structures. These experiments also showed, that structures lower than the cortex play a very important role in producing integrated pattern of activity, the posterior hypothalamus being the lowest area from which integrated rage pattern could be evoked. CPZ is thus shown to have a profound activity on tbe subcortical areas capable of producing integrated behavior patterns. Thiopentone in proportionately higher doses produces similar but milder effects.

Hypothalamic pressor response.—Reference has already been made to the suppressive effect of CPZ on the hypothalamic vasomotor response to direct electrical stimulation in decorticated cats and also that in animals with an intact brain, even under anesthesia, the pressor response is not significantly affected by CPZ.

The pressor nuclei are situated in the posterior hypothalamus, the area concerned with adrenergic (sympathetic) activity. Therefore, the suppression of the pressor responses elecited on direct electrical stimulation of the hypothalamus by CPZ, provides the most direct evidence of the action of the drug on the hypothalamus and, more precisely, on the posterior hypothalamus.

CPZ and gonadotrophic hormones.—CPZ completely suppressed the natural oestrus cycle in virgin female rats in doses of 10 mg/kg/ day given intraperitoneally. Normal cyles reappeared at varying intervals after CPZ withdrawal. However, continuous oestrus induced by oestradiol benzoate in ovariectomised and normal rats was not suppressed by CPZ even at 40 mg/kg/ day, indicating that the suppression of natural oestrus was not peripheral in nature (Dasgupta and Hausler, 1955a). Suppression of gonadotrophic activity by CPZ was observed by various other workers (Krais *et al*, 1954), Werner (1955) Sulman and Winnik (1956). Barraclough and Sawyer (1957), from electrophysiological studies, reported that CPZ blocked the release of pituitary ovulating hormone in the rat.

These findings are contrary to the earlier findings of Courvoisier and Ducrot (1954). This difference may possibly be explained by the considerably smaller dose (1-5 mg/kg) and also by the different route of administration (subcutaneous) in their experiments.

The hypothalamic nuclei in the control of gonadotrophic hormones appear to exhibit species difference in its location. The overall picture that is taking shape from the works of various workers in this field, namely, Mcann (1953), Bogdanov and Halmi (1953) and Harris (1955) and others is that the nuclei occupy the area situated medially and extending backwards from the tubercinerium to the premammillary nuclei situated in the mammillary region of the hypothalamus, close to the n. mammilaris medialis. The area thus involves the posterior hypothalamus, and the suppression of oestrus activity by CPZ lends further support to the posterior hypothalamic activity of the drug.

CPZ and condition reflex —The interference by CPZ in subhypnotic doses, with the conditioning of rats to various stimuli as observed by Guha *et al*, (1954) also point towards an action on the hypothalamus of the drug. In these experiments the prominent action of the drug was the complete loss of ability to slove the problem successfully, irrespective of the reward or punishment. That the indifference of the animals towards the reward, in this case food to starving rats, was not due to the effect of CPZ on hunger was proved by subsequent experiments with cats and rats, when it was found that animals under comparable doses, pertook food, if presented to them, in quantity which was not significantly different from the control amount (Dasgupta, unpublished). Reserpine, on the other hand, in subhypnotic doses (1 mg/kg or less) did not affect the CR. Courvoisier *et al.* (1953) and Archer (1954) have also noted the ability of CPZ interfering with conditioned behaviors.

CPZ and hypothermia—Though there is a considerable difference of opinion about the actual mode of production of hypothermia (by CPZ), it is generally conceded that the effect is, at least partially, central. According to Mover (1955) the drug appears to inhibit the thermal regulatory centre. According to Binet and Decaud (1954), CPZ inhibited in animal, defence against heat in the same way that it inhibits defence against cold. They concluded that the animals after CPZ were converted into poikilothermic animals. Rats under CPZ recorded a fall of temperature if kept in a cooler enviroment. But, on the otherhand, if kept in an enviroment of higher temperature e.g. 45-55°C these rats reached a lethal temperature more rapidly than untreated controls. This finding is important because it effectively counteracts the hypothesis that the reduction in temperature was chiefly due to muscular relaxation with decreased heat production, CPZ having no particular effect on the heat regulation centres. Loss of muscular activity along with muscular

relaxation might be concieved to account, at least in part, for the fall of temperature after CPZ, but it could not explain the rise of body temperature in rats with CPZ kept in a higher enviromental temperature. A central action for CPZ is called for to explain these findings.

On the otherhand, in anaesthetised dogs covered with ice bags, 2 mg/kg of CPZ intramuscularly, prevented shivering and lowered body temperature by 10°C compared to 5.4°C in control dogs (Dundee *et al.* 1954). In human subjects Ripstien *et al* (1954) could bring down the body temperature to 26.5°C within 15-45 minutes without shivering by means of CPZ assisted by refrigerating blanket.

The general trend of findings, both clinical and experimental, has been that hypothermia or a tendency to hypothermia, prevailed after the administration of CPZ. The centre controlling the response to falling temperature is situated in the posterior hypothalamus, and it can therefore be inferred that CPZ acts on these posterior hypothalamic centres in producing hypothermia.

CPZ and antidiuretic hormone (ADH):—The foregoing experimental results are indicative of a strong hypothalamic activity for CPZ. But on the other hand evidences testifying to the failure of CPZ to depress different groups of hypothalamic nuclei are also available.

It has been shown (Dasgupta and Hausler, 1955a) that CPZ could not prevent the liberation of the antidiuretic hormone (ADH) in response to nicotine given intraperitoneally to rats. Failure of CPZ to interfere with the liberation of ADH in response to osmotic salt stimuli has been observed by Werner and his associates (1955).

The liberation of the ADH is under the control of the supraoptic nuclei and the contiguous areas of the anterior hypothalamus. The failure of CPZ to affect ADH liberation is therefore interesting in view of its activity on the hypothalamus described before and demonstrates that CPZ does not possess a depressant effect over the whole of the hypothalamus.

It should be added here that not only did CPZ fail to prevent ADH liberation, it actually increased the antidiuretic action of nicotine. In another experiment CPZ was found to enhance the antidiuretic action of posterior pituitary extract in rats (Dasgupta, 1957).

CPZ and thyrotrophic hormone.—CPZ failed to prevent the hyperplasia of the thyroid glands following the administration of thiouracil (Werner, 1955). Thiouracil induces thyroid hyperplasia through thyrotropin (Wright, 1952).

Hypothalamic nuclei controlling thyrotrophic activity is situated in the anterior hypothalamus (Geer, 1952 ; Bogdanove and Halmi, 1953 ; Ganong *et al*, 1955). Failure of CPZ to prevent thyrotrophic activity is then another example of its having no depressant effect on the anterior hypothalamus. These findings considered together lead one to the conclusion that CPZ is not effective as a depressant of the anterior hypothalamus.

C Z and adrenocorticotrophic hormone (ACTH).—Dasgupta (1957) has shown that CPZ failed completely to prevent the lymphocytopenia of stress both emotional and traumatic, even in diencephalic cats. The results recorded a complete failure of CPZ to prevent lymphocytopenia as a result of ACTH liberation. These findings are supported by Halzbaur and Vogt (1954) and also those of Naysmith (1955).

The above findings are in variance with the earlier findings of Aron *et al* (1953) and Castigne (1954) and also that of Sulman and Winnik (1956). Aron *et al* (1953) were so confident of their findings that they advocated the use of CPZ to perform a functional hypophysectomy in rats instead of surgical operation, for biological determination of cortiocotrophic hormones. Holzbaur and Vogt (1954 , however, thought that the different findings of Aron *et al* (1953) were probably due to the use of a very small number of rats and the lack of unoperated controls treated with the drug only. Castigne (1954) on the other hand used a dose of 50 mg/kg. in anesthetised rats. The very high dose of CPZ together with the anesthetic agent was likely to produce a profound generalised depression which may explain his findings. Sulman and Winnik (1956) relied on the reduction of weight of the adrenals. A loss of ascorbic acid follows administration of CPZ, while Filk and Loesser (1954) reported a loss of adrenal lipids. These may explain the reduction of weight that Sulman and Winnik (1956) recorded.

CPZ and radioactive iodine.—The uptake of radioactive iodine by the thyroid may be considered in this connection. Brena and Marocco (1953) found that surgical trauma produced a big reduction in the iodine uptakly but with surgical trauma following 50 mg/kg of CPZ given intraperitoneale, to guineapigs, the reduction of iodine uptake was greater still. Thus it will be evident that not only CPZ could not protect the animal against the effect of stress but it appeared to have added to the drug action in some way.

The liberation of ACTH is under the control of the hypothalamus. There is now general agreement that the hypothalamus is capable of stimulating the anterior pituitary gland to secrete ACTH, whenever the individual is exposed to a stressing agent.

The interesting works of Anand and Dua (1954) and that of Anand *et al* (1955), confirmed later by Laqueur *et al* (1955) have demarcated the medial part of the anterior hypothalamus and the antero-medial region of the median eminence of the tubercinerium to be the area concerned with ACTH secretion. From this it becomes evident that the effects consequent to stress (in the form of ACTH liberation) is mostly under the control of the middle hypothalamic region. The failure of CPZ, to inhibt the liberation of ACTH in response to stress shows, therefore, that the anterior and middle regions of the hypothalamus are not depressed by it.

It appears resonable to infer that so far as the hypothalamus is concerned, it is only the posterior hypothalamus which is sensitive to the depressant effect of CPZ, where as the anterior and even the middle hypothalamic regions are refractory to the depressant action of the drug. Moreover, the sensitiveness of the caudal hypothalamus is markedly enhanced if it is freed from the rostral (cortical) influences.

The area of the hypothalamus thus affected, it should be noted, is the area from where all normal coordinated autonomic sympathetic, i.e. ergotropic activity, is controlled and carried out.

It also appears, on the basis of available evidences, that the depressant effect of CPZ does not extend rostrally beyond the limits of the posterior hypothalamus. Though Sulman and Winink (1956) reported a stunted growth in rats which received 10 mg/kg, subcutaneously, and suggest an effect on the hypothalamic STH, this work could not be confirmed (Dasgupta, unpublished).

CPZ and meso-diencephalic R. F—Proceeding caudally from the hypothalamus down the axis of the brain, CPZ is found to have profound depressant action on the midbrain reticular formation, as evidenced by the findings, namely (i) the simultaneous changes in behavior of the animal and the resting patterns of the EEG, following the administration of the drug (Das *et al*, 1954) (ii) the inhibitory effects on the facilitatory influences in spinal cord reflexes originating from the brain stem RF, as well as posturae reaction resulting from cerebellar stimulation which according to Snider (1952) apparently take place via the brain stem RF as a major intermediet station (Dasgupta and Werner, 1955) and (iii) the effect on medullary pressor responses (Dasgupta and Werner, 1954, a, b.)

The antiemetic effect of CPZ brought about by its action on the CTZ (Brand *et al*, 1954) lends additional strong support. This is further supported

by the action of CPZ on the medullary respiratory centre (Dasgupta and Hausler, 1955).

Destruction of the cephalic part of the formatio reticularis leaving the classical sensory pathways as far as the cortex suppresses all waking activity and gives rise to EEG tracing similar to that of sleep. The EEG shows charactristic changes. The 'alpha' waves and other waves of greater frequency are replaced by slow waves of high voltage—delta waves (of 0.5 to 3C/S)-although the spindles of 12 to 14 C/S are occasionally found. The change in EEG is accompanied by a characteristic change in the behavior of the animal. Although not truly asleep the animal becomes completely akinetic and is profoundly somnolent.

Following the intravenous injection of CPZ in doses of 0.7-2 mg/kg there was drastic changes in the behavior of the rhesus monkeys. They were to start with aggressive and alert, ready to escape, and difficult to handle. Following the injection, they became peaceful, easy to handle and could be left unrestrained outside the cage. They maintained the posture in which they were placed by the observer. Their reaction to nociceptive stimuli of various intensity was limited to simple withdrawl of the affected extremity. Although not truly asleep, the behavior of those animals was characterised by complete akinesia and profound somnolence. The akinesia was; however, quite different from adynamia produced by a lesion in the hypothalamus. They differed from the akinetic animals following CPZ in that whereas the akinetic animals could be roused comparatively easily, the adynamic animals were completely unrousable. The monkeys, in other words, appeared to be completely changed in personality. It will be of interest to note here that, a monkey very timid to start with became extremely ferocious after CPZ. The change in the EEG was also very striking. Following the injection, there was first an increase in the voltage of alpha waves ($8\frac{1}{2}$-$9\frac{1}{2}$/sec.). Within 2 to 3 minutes, delta waves ($2\frac{1}{2}$-3/sec. 200-300 mv.) began to appear in single, double, and serial bursts which were interrupted by ocassional spindle bursts. The hypersynchrony could be temporarily desynchronised, however, by optic, acoustic or tactile stimuli. These two charactertic changes i.e. in behaviour and in the EEG, resembled strikingly the findings of Magoun (1951), subsequent to surgical interruption of the ascending influences from the centrally placed RF. It was concluded, therefore, in producing similar effects chlorpromazine also acted by suppressing the ascending influences of the RF.

Terzian (1952) was the first to observe changes in the EEG following CPZ in human beings. He inferred that the action of CPZ was perhaps

exerted on the afferent ascending portions of the RF. He did not, however, notice any effect on motor activity.

Professor Dell with his associates in later years, studied the effects of CPZ on EEG of the curarized cat or cats with pre-bulbar section of the brain stem (Hiebal *et al*, 1954) With doses of 0.5 to 1 mg/kg, the typical tracing showing fast waves was replaced by one showing irregular slow waves. The sleep spindles (characteristic of normal sleep and barbiturate effect), however, were absent. Auditory or olfactory stimuli provoked desynchronisation for a short period only. This, they concluded, suggested that CPZ was depressing the reticular arousal system. Electrical stimulation of this area in the normal animal produced a marked activation of the EEG and a peripheral sympathetic discharge. After CPZ the threshold was considerably raised. They also found that the injection of small doses of adrenaline in untreated animals produced an arousal reaction and CPZ prevented it. Lastly, these authors found that after CPZ, they were able to demonstrate readily, that sensory impulses from the baroreceptors in the carotid sinus inhibited the RF, producing slow waves in the electrocorticogram In the normal animal this effect was demonstrable only with difficulty. They concluded that CPZ depressed the spontaneous activity of the RF, and reduced its sensitivity to afferent sensory stimuli. It also inhibited stimulant effect of adrenaline on that formation and unmasked or accentuated the depressant effects of sensory stimuli from the carotid sinus. Longo *et al* (1954) using intact or encephale isole preparation of rabbit noted that CPZ given intravenously in doses of 2-5 mg/kg increased the frequency of spindle bursts from 3 to 5 per minute to 7 to 10 per minute ; duration of each burst was also increased. They also found that the effect of direct stimulation of the cephalic end of the RF was completely inhibited by CPZ in doses of 3 mg/kg.

It was found (Martin *et al*. 1958) that CPZ depressed the activating responses evoked by auditory stimulation, by direct stimulation of the RF or by intravenous adrenaline.It was further reported that CPZ was more effective on the rostral portion of the brain stem than the caudal part.

Rinaldi and Himwich (1955) using rabbits, recorded changes in the EEG produced by alerting stimuli and also by direct electrical stimulation of the activating system before and after the intravenous injection in increasing doses of CPZ. In the course of action of the drug, three stages of activity were observed - (i) absence of an alert response to sound and the shortening of the duration of the alert pattern after other types of stimulation ; (ii) absence of the alert responses to all the types of peripheral stimulation used and a significant increase in the threshold to direct electrical stimulation of

the RF and also a marked reduction in duration of the result and EEG effect with a dose of 3-5 mg/kg. (iii) a dose of 15-20 mg/kg was found to reverse the effect producing signs of excitement.

Bradley and associates have made exhaustive study of the subject extending over several years (1957, 1958, 1959). They found that with a dose of 2-4 mg/kg. there was a slight rise in threshold for both electrocortial and behavioral arousal in cats. Large doses caused no further change in threshold. An extremly interesting observation by Bradley and his colleagues was that very small dose of CPZ (0.1 to 0.5 mg/kg.) caused a slight fall in the behavioral and electrocorticographic thresholds. Killam and Killam (1956, 1957) with whom the present author was associated have reported a similar finding.

In contrast to the rather feeble effect of chlorpromazine on the arousal and behavioral thresholds of RF itself, Bradly *et al* found the effect of CPZ on the arousal response produced by sensory stimulation to be quite marked.

He, therefore, concludes that CPZ has rather mild effect on the RF itself, but it has a strong depressant effect whereby it blocks sensory inputs into the RF.

Thus all the evidences presented so far, obtained cheifly from animal experiments, acute and chronic, point to a very powerful depressant action of CPZ on the posterior hypothalamus and the mesodiencephalic RF.

The depressant effect on the RF is further supported by a number of other findings namely, (i) inhibition of motor activity induced by cortical stimulation, (ii) suppression of postural responses elicated by the stimulation of the cerebellar cortex, cerebellar nuclei and the RF itself. (iii) complete abolition of medullary pressor response to electrical stimulation, in doses which possessed no peripheral action, (iv) prevention of vomiting in non-depresant dose (Brand *et al*, 1954), and in larger doses directly affecting the vomiting centre itself (Glavianno and Wang, 1955) (v) depression in large doses of the medullary respiratory centr e.

CPZ and Spinal cord-When one proceeds further down the axis into the spinal cord, beyond the limit of the reticular formation, the effects of CPZ are found to be gradually waning off, as evidenced by the findings on the descending medullary tracts and also on the cross extensor reflex of the spinal cat (transection at C_1) (Dasgupta and Werner, 1955)

All these findings, mostly experimental, some clinical, lead one to the conclusion that CPZ has a pronounced depressant action, on the bulbo-mesodiencephalic reticular formation, particularly on its cephalic end.

Relation between caudal hypothalamus and the cephalic end of RF.—The posterior hypothalamus and the cephalic end of the brain stem reticular formation are situated in intimate close anatomial proximity. In fact, there is no definite cleavage between the hypothalamic nuclei and the tegmentum of the mesencephalon (Lindsley *et al*, 1950). It has recently been shown that the cephalic end of the RF branches to enter the posterior hypothalamus (Nauta and Kuypers 1957, Schibels, 1957). It may be expected then that lesions in either of the two structures, will bring about similar types of changes. Some recent vidences tend to throw some light on the nature of functional relationship between the posterior hypothalamus and the rostral end of the brain stem RF . Rinaldi and Himwich (1955) interpreted the beneficial effect of CPZ in anxiety states not due to the direct action of the drug on the hypothalamic neclei as was the case with reserpine, but as a result of depression of the ascending RF, whereby, flood of impulses impinging upon the hypothalamus are greatly reduced. Sawyer *et al* (1955) while studying the mechanism of action of the blocking of neurogenic stimulation of release of the pituitary ovulating hormone in the rat with drugs such as atropine and morphine, observed changes in the EEG and in the electrohypothalamogram (EHG) characteristic of inhibition of the cephalic end of the RF. On the basis of their observations, they made the assumption that an active reticular activating system was necessary for an afferent stimulation to excite the hypothalamic centre. They concluded that drugs which raised the threshold of arousal may be found to block pituitary activation.

It would appear, therefore, that the chief site of the inhibitory action of CPZ was the facilitatory mesodiencephalic reticular formation and its sphere of influence.

These formations control the waking state of all the telecephalon, thus without giving rise to anesthesia, without producing acutal sleep, chlorpromazine markedly diminishes the level of waking state, abolishes or diminishes the effect of any exteroceptive or nociceptive stimulation. By its action on the posterior hypothalamus, which is the lowest area necessary for integrated behavioral patterns, CPZ brings about some of the changes that follow its administration in a conscious animal.

CPZ effect on adrenaline sensitive sites in the RF.—There is a distinct difference in the nature of the depressant effect on the RF produced by CPZ and

the barbiturates. It must be noted that true sleep is not produced by CPZ where as barbiturates puts an animal to profound sleep. It is also comparatively easier to rouse an animal under CPZ accompained by short lasting EEG arousal, where as it is quite difficult to awake an animal under barbiturates either behaviorally or electroencephalographically. This may be explained in the following way. One specific difference in the EEG changes following barbiturates and CPZ is that while in the former sleep spindles predominate and a true sleep is the result, in the latter sleep spindles are indeed a rarity and at no time sleep ensues. Dell and his coworkers (1954) reported that in cats with prebulbar sections, the delayed activating of electrocortical activity produced by epinephrine was abolished by 2 mg/kg of CPZ. In dogs 0.5 mg/kg. of CPZ produced an inversion of the effects of epinephrine. On the basis of these findings, it was concluded that CPZ reduces the activating functions of the ascending reticular system by three mechanisms (i) blocking of sensory excitation, (ii) blocking of delayed excitation produced by epinephrine and (iii) "unmasking" of the carotid sinus inhibitory mechanism. Wilker (1957) puts this anti-adrenaline effect in the following terms "in therapeutic doses, the actions of chlorpromazine on the nervous system are predominantly central and appear to be exerted primarily on the reticular system, perhaps more markedly on the bulbar component, and possibly more in blocking the excitant actions of circulating epinephrine (and acetylcholine ?) upon than in blocking synaptic conduction within it. While these effects are shared by the barbiturates, the effects of these compounds on the entire reticular system appear to be more powerful, and they also effect synaptic transmission, more diffusely at all levels of the nervous system. The difference between tranquilization and narcosis is therefore reflected in the difference in the patterns of the neurophysiological actions of chlorpromazine and the barbiturates."

Dasgupta and Werner did not get any evidence in favour of depressant effect of CPZ in areas rostral to the posterior hypothalamus In fact, the meagre evidence would suggest a stimulating type of activity. Moreover, in the 'Cervou isole' preparation, following doses of CPZ (0.5 mg/kg, i. v.). they noted changes in the EEG, characteristic of petitmal epilepsy. In the 'Pyramidal cat', actual convulsions were found to develop. All these, they thought, were indicative of an abolition of thalamocortical synargism (Das *et al*, 1955).

Killam and Killam (1956) reported that CPZ markedly depressed the arousal responses within the limbic system, the normal rythmic, high voltage slow wave response of limbic arousal often being replaced by low fast voltage activity. Also, in contrast to barbiturates there was an absence of any effect

of CPZ on thalamic recovery time. The significance of these findings has yet to be fully evaluated.

These findings were comfirmed by Preston (1956). He also found that whereas, in curarized intact cats, 40-60 mg/kg. of CPZ produced synchroniz-, ed spike seizure discharges in the cerebral cortex (as also found by Das *et al*- 1955) the "Spontaneous burst" activity of the isolated cerebral cortex remained unaltered after injection of upto 50 mg/kg of CPZ, and there was net change in threshold for evoking burst discharge in this preparation. These findings indicated two likely but important conclusions, (i) CPZ does not a directly on the cerebral cortex and (ii) that the seizure activity produced by it in intact animal was subcortical in orign. Preston also noted the effect of CPZ on the spontaneous electrical activity of the "Limbic system". In doses of 20 mg/kg CPZ, isolated spikes and after 35 mg/kg, burst of spikes, appeared in the amygdaloid nuclear complex. Noting that in doses sufficient to produce behavioral change in the unanesthetized, uncurarized cat, CPZ produced only minimal or even no changes in the specific or the diffusely projecting sensory system, but did produce marked changes indicative of excitatory action in the amygdaloid nuclear complex, Preston concluded that the tranquilizing effect of CPZ may be due to augmentation of the inhibitory influences normally exerted by the amygdaloidal nuclear complex upon the structures involved in the execution of various forms of emotional behavors (rage, hypersexuality). This attractive hypothesis invites some comminte. Firstly, the doses used by Preston, to say the least, are heroic. As low a dose as 0.7 mg/kg in intact unanesthetized monkey has been observed to fully tranquilize where as such low doses do not produce any change in the amygdaloid complex. Secondly, if as he suggests that CPZ increases the inhibitory influences of the amygdala on emotional behavior including rage, then in preparations where a rage pattern was elicited by simply making bilateral incisions in the orbital surface of the frontal lobe, when the whole amygdaloid complex was left uninjured and intact, CPZ ought to have suppressed 'Sham rage' acting through the amygdala, which of course it failed to do.

Killam and Killam (1956, 1957) have also noted changes in the limbic system similar to those observed by Preston. But the dose required to produce these effects was considered to be too big by them. They were on the other hand more interested in the effect produced by very small doses of CPZ on the RF, namely a fall in RF threshold for electrical stimulation. Similar effects were observed by Bradley and his associates (1958). Killam and his associate (1957), found that potentials recorded directly from the RF itself showed after 1 mg/kg of CPZ a marked increment following either a stimula-

tion of a peripheral nerve (sciatic nerve) or at a point in the RF itself situated some distance behind the recording electrode. There was a marked increment in the intrareticular conduction. This finding implied an increased activity of the RF neurones in addition to the earlier observed fall in threshold for EEG arousal and behavioral change. Their next observation was that a stimulation of the cephalic end of the RF applied immediately before or simultaneously was capable of reducing the evoked potentials in response to clicks recorded from the cochlear and geniculate nuclei. After 1 mg/kg of CPZ, both cochlear and geniculate responses were inhibited at a lower threshold (6 volts) as compared to the control (10 volts) while at control voltage there was almost complete obliteration of the both cochlear and geniculate responses, and also recovery took muck longer time. In contrast, pentobarbital depressed the effectiveness of the RF, when administered alone or even after CPZ as in these experiments. These findings indicated a capacity for the RF to block sensory inputs from various modalities, suggesting a selective and-or filtering activity for the RF.

On the basis of these observations a hypothesis has been advanced to explain the tranquilising action of CPZ, in disturbed patients without the severe depression or heavy sedation characteristic of barbiturates. "The hyper-reactivity characteristic of such patients may be due to excessive transmission of sensory information along classical pathways without effective selection or control. Chlorpromazine, by increasing reticular input and conduction thus enhancing filtering mechanism originating from the reticular formation, may act to reduce the inflow of information lacking in importance to the organism", as is believed to be the function of a normally acting reticular formation.

SUMMARY

From the experimental evidence so far accumulated on the central action of Chlorpromazine (CPZ), it may be said that :—

(i) It has a pronounced depressant action on the posterior hypothalamus and the facilitatory mesodiencephalic reticular formation, especially the cephalic portion.

(ii) The posterior hypothalamus and the rostral end of the midbrain reticular formation appear to act as one functional unit. The depressant activity of CPZ on the central nervous system appears to be limited to the meso-diencephalic reticular formation and its sphere of influence.

(iii) Subcortical structures play an important role in producing integrated pattern of activity. The cortex also seems to stabilise the lower centres by keeping it facilitated against the action of CPZ.

(iv) Depressant effect of CPZ weakens as one proceeds down the axis and practically disappears in the spinal cord.

(v) The posterior hypothalmaus and the cephalic RF are the structures responsible for the ergotropic activity (HESS). By depressing these structures, CPZ suppresses all ergotropic activity and converts the animal into a trophotrope, whereby, it will be organised for, prevention or repair of wear and tear and for maintenance.

vi) In the areas rostral to the posterior hypothalamus, CPZ does not appear to possess any depressant action. Moreover, in the "Cerveau isole" preparation, changes in the EEG characteristic of petitmal epilepsy have been recorded. In "Pyramidal cats" epileptiform convulsions developed following CPZ. All these indicated an abolition of thalamocortical synergism.

(vii) A hypothesis to explain the tranquilising action of CPZ on disturbed patients, has been brought out.

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