Few drugs have attracted so much attention in recent years as Chlorpromazine. With a wide range of pharmacological properties, this drug is rapidly being put to newer uses. Though it is a new drug, amine derivatives of phenothiazine have been of interest to pharmacologists for some years now. French and American workers took up the study of these compounds almost simultaneously. Goodman reported on some compounds in 1944; Charpentier, cut off by the war from American developments, prepared some others (Charpentier, 1947). These compounds were prepared by amine-substitution in phenothiazine; an obvious parallel is the amine-substituted antimalarials. However, unlike the parent compound, the substitution compounds had no antimalarial, trypanocidal or anthelmintic activity (Reid et al., 1948; Wright et al., 1950). The American Workers left the trail, and the next phase of development was chiefly in France, where RP 3015 and 3277 were developed, both possessing antihistaminic and central depressant properties. The Rhone-Poulenc-Special Laboratories at Vitry-Sur-Seine carried out a systematic study of phenothiazine derivatives with a view to finding out an analogue possessing the greatest central depressant activity. In the course of these investigations, chlorpromazine was synthesized by Charpentier in December 1950. Within the next few years it was used for “artificial hibernation” and “potentiation of anaesthesia” (Laborit and Huguenard, 1951; Laborit, 1952; Huguenard, 1953a). In 1952 Delay and Deniker presented its uses in psychiatry. Of all publications on the pharmacology of chlorpromazine so far, that of Courvoisier et al. (1953) is easily the most comprehensive.

The chemical structure of chlorpromazine hydrochloride is given below:

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\text{Chemical Structure of Chlorpromazine Hydrochloride}
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It is a greyish white substance with a slightly pungent odour. It is very soluble in water (1 gm./2.5 ml.) methanol, ethanol and chloroform, but insoluble in benzene. The pH of a 5 per cent solution is between 4.0 and 5.0.
Both powder and solution become discoloured in bright light. A large number of drugs, when mixed with chlorpromazine form a precipitate. These are the clinically used thiobarbiturates, hexamethonium bitartrate, atropine sulphate, a certain proprietary form of succinylcholine chloride, sodium bicarbonate (1.4 per cent.), saline (10 per cent.), dextrose (30 per cent), and Ringer’s solution. A precipitate forms with gallamine triethiodide, but this dissolves if excess of gallamine triethiodide is added. If chlorpromazine is diluted with polyvidone, a faintly cloudy solution might occur (Dundee, 1954).


PHARMACODYNAMICS

CENTRAL NERVOUS SYSTEM EFFECTS

Sedation and Hypnosis. The drug has a sedative and hypnotic effect. The central depressant action was unaffected by amphetamine or caffeine (Dobkin et al., 1954). Das et al., (1954) investigated the somnolent effect on animals. An intravenous dose of 0.7-2.0 mg./kg. administered to intact rhesus monkeys which were normally very fierce, changed their behaviour dramatically. They became quiet, permitted handling, and responded to nociceptive stimuli only by the withdrawal reflex. Corneal, tendon, and postural reflexes were present. The action lasted 3-8 hours, and in higher doses, sleep was induced (Das et al., 1954). These observations were confirmed by Hendley et al., (1956). Das et al., (1954) have not explained why the only monkey which was (unusually) timid became aggressive after the drug, though they have stressed upon the reversal of the behaviour pattern. In rats chlorpromazine depressed the stimulation of chronic electrodes in the amygdaloid nucleus by the animals themselves; the rats had been trained to stimulate themselves by reward (Killiam et al., 1956).

In toxic doses, animals showed locomotor disturbance, hypothermia, drowsiness and anaesthesia.

In conscious man, with 0.3-2.0 mg./kg. doses, drowsiness appeared (Conthier, 1953; Dobkin, Gilbert and Lamoureux, 1954). With an intramuscular dose of 25-50 mg., sedation occurred in 50 per cent of patients in about half an hour (Ratschow, 1953; Anton-Stephens, 1954; Kent, Knight, Morris, Dizon and Moyer, 1954; Lehman and Hanrohan, 1954). With large doses, motor retardation, unsteady gait and Parkinsonian facies were seen (Lehman and Hanrohan, 1954). On chronic administration, tolerance to sedative effect appeared early (Ratschow, 1953).

Potentiation of anesthetics and hypnotics. Like some other phenothiazine bodies, chlorpromazine, when combined with general anaesthetics, rendered the nerve cell more sensitive to the anaesthetic drug; anaesthesia was easier to induce, duration and depth of anaesthesia was increased, and to produce any given degree of anaesthesia a smaller amount of the anaesthetic agent sufficed. (Courvoisier et al., 1953). The last effect is of importance, because with a smaller amount of the anaesthetic, toxic features are less likely to be encountered. Hexobarbitone and ether were found to be potentiated in rats, guinea-pigs and dogs (Courvoisier et al., 1953).

Terzian (1954) basing his findings on EEG, offered an explanation for
the anaesthetic potentiation. Barbiturate narcosis arose secondarily from arrest of the continuous bombardment of the reticular formation by impulses from the cortex, or interruption of the afferent cortical pathways. The sleep induced by chlorpromazine, however, was primary effect due to a direct depressant action on the reticular formation which controlled wakefulness. Clinical impressions of potentiation of thiopentene by chlorpromazine have appeared, though precise estimations seem to be lacking. (Bariety et al., 1950, Laba, 1953; Dechene, 1954; Dobkin et al., 1954; Rizzi, 1954).

Both in the mouse and the rabbit chlorpromazine potentiated the properties of hypnotics like butobarbitone. In the rabbit 50 mg./kg. butobarbitone produced sleep for only about an hour. When butobarbitone was preceded by 25 mg. chlorpromazine, the rabbit slept for over five hours.

Chlorpromazine potentiated the action of alcohol. The phase of psychomotor excitement was suppressed and sometimes sudden collapse occurred (Courvoisier et al., 1953):

Anticonvulsant action. As with diethazine, the central depressant action suggested an anticonvulsant property. Good protection was found against nikethamide convulsions in rats and nicotine convulsions in rabbits. Even with toxic doses, no protection was obtained against strychnine convulsions in rats showing that the seat of anticonvulsant action was probably not in the medulla, but at a higher level of the central nervous system (Courvoisier et al., 1953). Protection against electroshock seizure was found to be rather poor. The ED50 were 23.75 and 4.68 mg./kg. with chlorpromazine and dilantin sodium respectively. The effect of dilantin sodium was potentiated with low doses of chlorpromazine, though with high doses antagonism was evinced (Gujral et al., 1956). The present authors wonder whether there is any connection between this antagonism and "confusion, hyperactivity and disorganized behaviour" found with high doses of chlorpromazine.

Effect on analgesia. Chlorpromazine has little analgesic action of its own. The analgesic action of drugs like morphine and pethidine was found to be potentiated by chlorpromazine (Courvoisier et al., 1953). These authors have remarked that morphine analgesia was characterised in rat by disappearance of pain sensation when awake. The apparent potentiation might have been due to the muscle tone lowered by the drug, thus diminishing the range of response to painful stimuli. On combination with morphine or pethidine, potentiation occurred. Onset of analgesia was earlier, and its intensity and duration were increased. Morphine produced analgesia even when given in non-analgesic doses, when combined with chlorpromazine. If 10 mg./kg., 15 mg./kg., and 20 mg./kg. of chlorpromazine were combined with an analgesic, hypotonia, general depression and drowsiness were produced, respectively. Potentiation was seen also with weaker analgesics like aspirin or salicylamide (Courvoisier et al., 1953; Gujral et al., 1956). Greater potentiation was produced with chlorpromazine than with promethazine (Courvoisier et al., 1953). Some workers have not been able to confirm this potentiating action (Wien, 1953; Kopera and Armitage, 1954).

Effect on body temperature. The well known association of hypothermic, antipyretic and antihistaminic activity (Wood, 1950) suggested enquiries in this direction. Courvoisier et al. (1953) found chlorpromazine to have a remarkable hypothermic activity in dogs and mice. It inhibited pyrexia produced by Ducrey's vaccine in rabbits (Courvoisier et al., 1953). Chlorpromazine was found by these workers to be a better hypothermic and anti-
pyretic agent than amidopyrine or aspirin. Several other workers have confirmed the hypothermic action of chlorpromazine in animal and man (Dundee et al., 1953; Dundee et al., 1954; Friebel et al., 1954; Ripstein et al., 1954; Ratschow, 1954). Scurr (1954) has reported that with 100 mg. of chlorpromazine, the body temperature of one of his patients went down to 29°C.

The hypothermia was ascribed partly to vasodilatation, the effect being similar to that produced on sympathetic blockade (Dubkin, Gilbert et al., 1954). Others have pointed out that vasodilatation alone cannot explain the hypothermia since chlorpromazine produced greater hypothermia than other vasodilator drugs like hexamethonium. A suppression of shivering with the incident decrease in formation of body heat was pointed out (Dundee, Mescam and Scott, 1954).

Laborit (1951) advanced an attractive hypothesis with regard to the effect of chlorpromazine on thermoregulation. He suggested that when the organism is in a “state of aggression”, the drug blocks the autonomic nervous system. This in turn prevents the homeostatic mechanism. This increase in body metabolism may bring about a state of shock depending on the grade and severity of the stress. Courvoisier et al. (1953) investigated this hypothesis by noting the oxygen consumption of intact and adrenalectomized rats at 28°C and 4°C. Chlorpromazine was found to prevent the animals from responding to the stress of cold, as the control animals did, by an increase in oxygen consumption. Or in other words, the “homeotherm” had become a “poikilotherm”. It is interesting to note that thermoregulation in adrenalectomised and chlorpromazine—treated rats was similar. In this, chlorpromazine resembled promethazine.

Decourt, Brunaud and Brunaud (1954) pointed out that the change of the homeothermic organism into a poikilothermic organism was not the only mode of action. Even when placed in an environment with a temperature higher than that of the body, animals responded to chlorpromazine with relative hypothermia. These workers and others (Decourt, 1953; Decourt, Gastel and Grenat, 1953) advanced the view that the hypothermia was due to reversible inhibition of cellular metabolism.

Anti-emetic activity. Following Chen and Ensor’s (1950) investigation Ducrot and Decourt (1951) noticed that many antihistaminic substances were also antiemetic agents. The antiemetic activity, however, ran parallel to the central activity rather than the antihistaminic activity. Courvoisier et al. (1953) found that in 2 mg./kg. doses chlorpromazine protected dogs markedly against apomorphine-induced vomiting. The drug was more effective when given subcutaneously rather than rectally. It was effective against morphine-and hydergine-induced vomiting. The drug was presumed to act by its action on the chemoreceptor trigger zone (CTZ) of Borison and Wang (1953), (Courvoisier et al., 1953; Brand et al., 1954; Boyd et al., 1954; Cook et al., 1954; Glaviano et al., 1954).

Brand et al. (1954) suggested that the drug did not act solely through the CTZ. The emetic response of intravenous copper sulphate and lanatoside C were not appreciably altered. They suggested that there may be different specific types of receptors in the chemoreceptor trigger zone, all of which may not be sensitive to chlorpromazine. Glaviano and Wang (1954) suggested that the antiemetic activity of chlorpromazine in low doses (up to 2.0 mg./kg.) in dog was due to a competitive blocking action by chlorpromazine. In high doses, it acted as a direct depressant of the vomiting centre.
They have shown that chlorpromazine (4 mg./kg.) stopped vomiting induced by oral copper sulphate. The seat of action, however, may be other regions beside the CTZ-vomiting centre complex. Pilocarpine-induced vomiting in cats was stopped by chlorpromazine, though the locus of action of the vomiting was the forebrain (Brand et al., 1954).

**Effect on reticular formation and muscle tone.** Hiebel et al., (1954) have described the action of chlorpromazine on reticular formation:

1. It suppressed the disturbances activated through the reticular formation by nociceptive stimuli. Promethazine and low doses of barbiturates also produced this effect. The optimum effect occurred with the dose of 1 mg./kg.

2. Bonvallet et al. (1953, 1954) showed that an injection of a small dose of adrenaline or a peripheral sympathetic discharge produced a central activating effect. Chlorpromazine suppressed this central activation perhaps through its anti-adrenaline action.

Distension of carotid sinus inhibits the reticular formation; chlorpromazine unmasked this inhibition (Bonvalet, 1954). The reduction of muscle tone with chlorpromazine was central in nature. The motor inhibitor action of chlorpromazine resembled a typical interneurone-blocking drug, myanesin. In this respectDasgupta and Werner (1954) found chlorpromazine to be 20-40 times as potent as myanesin except for crossed extensor reflex in spinal cat and motor activity due to pyramidal tract stimulation. The brain stem reticular formation is the major intermediate station in postural effects produced by cerebellar action; also single stimulations lead to widespread activation of reticular formation and so to the visible motor activity. It was under these circumstances that chlorpromazine showed best activity in inhibiting motor reflexes. On the above grounds Dasgupta and Werner (1951) suggested that the interference of motor activity by chlorpromazine was primarily brought about through its action on brain stem reticular formation.

In African green monkeys, 20 mg./kg. chlorpromazine was shown to produce first hypokinesia and somolence, followed by fine tremor (in 40 minutes) and then by coarse tremor in 1 hour (Windle et al., 1956). Investigating the transient parkinsonism, Baker et al., (1956) noticed that with 5.0-10.0 mg./kg. doses of chlorpromazine spike discharges appeared in the pallidum and sometimes in the caudate nucleus. The potentials evoked in the striopallidum by stimulating the various thalamic nuclei were not modified by the drug. Hence these authors suggested that the increased pallidal activity was not directly linked to the effect of chlorpromazine on the thalamus and that aside from the lower part of the brain stem, chlorpromazine affected the brain stem as far cranially as the basal ganglia.

**Effect on the phenomena of Reilly and syndrome of irritation.** The synthesis of chlorpromazine was also the culmination of a long search for compounds effective in what has been known to French workers as the phenomenon of Reilly and syndrome of irritation. These phenomena refer to the effects of irritation, as opposed to either simple section or stimulation of sympathetic nerves. Reilly et al. (1934) described the condition first as "haemorrhages, vascular and lymphatic lesions of the alimentary tract" produced by perisplanchnic injection of various noxious substances. Reilly's experiments showed that though the organs affected varied according to the nerve irritated, the nature of macroscopic and microscopic lesions were more or less the same. Suprarenal haemorrhage was a constant finding. In the syndrome of irritation the lesions were widespread and often far from the site of irritation. For example, if the splanchnic nerves were severely irritated, not only visceral
but also cerebral lesions appeared e. g., intense congestion, perivascular and pericellular oedema. Reilly and Tournier (1954) showed that the visceral and cerebral manifestations may be reproduced by violent irritation of any mucosa rich in autonomic innervation. The observations of Reilly (1934) were confirmed by others (Pham, 1935; Gastinel, 1936). Tardieu (1954) produced a typical typhoid state by means of intraventricular injection of typhoid antigen in dog. From the similarity of autopsy findings in fulminating infections, and lesions produced experimentally in the syndrome of irritation, Marquezy (1938) concluded that the lesions produced by acute txaemia were due to the effect of bacterial toxins, on the autonomic nerve endings rather than on the capillaries. Decourt (1951) compared the phenomenon of Reilly and syndrome of irritation with Selye’s reaction of alarm, and pointed out that though the chronic lesions produced were more or less the same, there is one important difference. Whereas the noxious stimuli employed by Selye were widespread and general, the stimuli employed by Reilly were either in contact with or in the proximity of autonomic nerves. This difference reflects their different opinions about the aetiology. Reilly and Selye have laid stress mainly on the autonomic and endocrinal responses respectively.

With 5.0 mg./kg. doses, chlorpromazine was found to protect 70 per cent of guineapigs in whom splanchnic nerves were irritated. 95 per cent of the control animals died. Addition of agents producing hypothermia, ganglionic blockade, or antihistaminic action did not confer any advantage. However, with high doses of chlorpromazine, the condition was aggravated (Reilly et al., 1953; Reilly and Tournier, 1954). The action of chlorpromazine was essentially preventive and not curative.

**Electroencephalographic changes.** The drug changed the electroencephalographic record “dramatically”. Alpha-wave voltage increased, and in 2 minutes time delta waves appeared with sudden and spiky discharges. Sleep spindles appeared with doses beyond 3 mg./kg. (Das et al., 1954). Longe et al. (1954) reported that spindle bursts in normal tracing (3-4 c/min.) became more sustained and frequent. The number of slow waves increased, and there was less response to external stimuli. Blocking reaction was not produced by auditory or tactile stimulation, and nociceptive stimuli only inhibited spindles, but not 4-5 c/sec. waves, which were characteristic of activation pattern. In the thalamic animal, arousal reaction waves were not seen.

Terzain (1952) showed that the overall EEG effects resemble normal sleep tracings. Barbiturate made the rhythm rapid irrespective of the state of consciousness; if the state of consciousness did not change the EEG did not change. In the state of disinterestedness Theta elements were accentuated. The clinical improvement of anxiety neurosis patients undergoing chlorpromazine therapy ran parallel with the changes in EEG. DeMaar et al. (1956) found that chlorpromazine blocked sometimes the activation in EEG by adrenaline.

**Local anaesthesia.** Apart from a local anaesthetic action of its own, chlorpromazine potentiated the local anaesthetic action of other drugs like procaine. Contact with 0.1 per cent solution produced no changes in the histological structure of the nerve cells. With higher concentrations, some cytoplasm degeneration and loss of myelin continuity appeared temporarily; these changes disappeared in a week. With a concentration of 1 per cent there was some damage to muscle fibres. Whereas the local anaesthetic concentration was half of the toxic concentration in many other drugs, it was
only one-tenth of the toxic concentration of chlorpromazine (Courvoisier et al., 1953).

**AUTONOMIC NERVOUS SYSTEM EFFECTS**

*Parasympathetic.* Chlorpromazine inhibited the bradycardia, hypotension and cardiac arrest induced by stimulation of the cut ends of the vagus. Acetylcholine-induced hypotension was not modified with 1.0-5.0 mg./kg. doses, but some inhibition was produced by 10.0 mg./kg. doses. Employing Shay's technique, chlorpromazine was found to diminish gastric juice secretion by 40 per cent as well as the incidence and severity of peptic ulcers. The inhibition of gastric juice secretion was less than with ethopropazine (Courvoisier et al., 1953). On Warburg manometry, horse pseudocholinesterase activity was found to be diminished by 10.0 mg./litre of chlorpromazine (Courvoisier et al., 1953; Jourdan et al., 1955). The effect on human anticholinesterase activity has been investigated quantitatively by Erdos et al. (1956).

*Sympathetic.* In 0.5-1.0 mg./kg. doses, the pressor response to adrenaline was inhibited. After 5.0 mg./kg. of chlorpromazine, adrenaline produced a depressor response (Courvoisier et al., 1953). In duration and degree of anti-adrenaline action, these authors have compared chlorpromazine with dibenamine. The pressor response to noradrenaline was diminished but not reversed; the duration of the noradrenaline pressor response was prolonged (Martin, 1956). The pressor response to amphetamine was antagonised completely (Courvoisier et al., 1953; Burn, 1954; Huidboro, 1954). The inhibitory properties of adrenaline and the adrenergic mediator, as seen from the tonus and contraction of the urinary bladder and uterus, were not antagonised (Courvoisier et al., 1953). Though the pressor action of isopropylnoradrenaline remained after the administration of chlorpromazine the response to adrenaline following isopropylnoradrenaline was pressor instead of depressor (Huidboro, 1954). Donnet and Zurrin (1954) pointed out that chlorpromazine was adrenolytic, but not sympatholytic, and that it acted very little on the adrenaline secretory centre. Holzbauer and Vogt (1954) found that the drug did not inhibit the stimulation of the sympathetic centre in the cat by morphine. There was a fall in the hypothalamic noradrenaline and the amount of medullary amine in the innervated animal. During certain periods of their experiments the medullary amine liberated in the circulation was sufficient to dilate the pupil (innervated and denervated) and was thus sufficient to overcome the adrenolytic action of chlorpromazine. In contrast nalorphine inhibited all manifestations of morphine poisoning including the stimulation of sympathetic centres (Hozbauer and Vogt, 1954).

*Ganglia.* Courvoisier et al. (1933) claimed at first that the drug was gangliolytic, but the claim was disproved (Decourt, 1954. Huidboro, 1954; Holzbauer-and Vogt, 1954). The changes in nictitating membrane contractions are fallacious in this regard as the drug has a peripheral relaxant effect on the nictitating membrane itself. Huidboro (1954) found no modifications to the response to stimulation of the left superior mesenteric ganglion. No gangliolytic activity was found on the left superior cervical ganglion of the cat by Holzbauer and Vogt, (1954).
Anti-shock action. Wiggers et al. (1948) showed that the organism reacts hyperactively to stressor agents through the agency of the suprarenals, and the adrenergic blocking agents were found to give protection in shock. Courvoisier et al. (1953) found prolongation of survival time of dogs with chlorpromazine (mg./kg. I. V.) while 82 per cent of the control series died within a few hours. This was repeated in rats also Employing the method of Noble and Collip (1942), a dose of 2.5-5.0 mg./kg. gave a protection of over 50 per cent. Chlorpromazine was more potent than promethazine with regard to its antishock property. Decortis and Lecomte (1953) have reported that chlorpromazine provided protection against peptone shock comparable to the antihistaminic-atropine combination (Halpern, 1942; Bennati, 1948; Davis et al., 1949; Parrot et al., 1942, 1950). Chlorpromazine did not prevent the initial drop of blood pressure but it reduced the duration of shock. The protective effect of shock has been confirmed by others (Laborit, 1952; Jaulme, 1952; Fournel, 1953). The protection was not connected with the effects on the autonomic nervous system. It was found to give protection against tourniquet shock in rats (Millican, 1956; Gujral et al., 1956; Ravenstein et al., 1956). Cier and Tanche (1954), however, have found very little protection with chlorpromazine against shock produced by muscle crushing in dogs. The use of hypothermia concurrently with chlorpromazine was found to give good protection against shock. The allied concept of artificial hibernation has been mentioned later.

CARDIOVASCULAR EFFECTS

Myocardium. The general effect is one of depression (Courvoisier et al., 1953). Using the cat heart papillary muscle, chlorpromazine in concentrations of 0.1—0.5 mg./100 ml. of bathing fluid produced a negative inotropic action, resulting in experimental 40-60 per cent reduction of the contractile action. In such contractions of the heart, irritability was diminished as demonstrated by a rise of the threshold voltage required to drive the muscle. Depression of automaticity also followed (Finkelsstein and Hammen, 1955).

Using the intracellular electrode implantation technique, Coraboeuf et al., (1954) showed that there was slowing in the fibres of Purkinje. With a concentration of 1:25,000 on isolated dog heart-lung preparation infused by Tyrode solution, there was a progressive lowering of the membrane potential and change in the shape of the action potential. Once established, this change was not reversed by repeated washings during the experiment. These authors concluded that chlorpromazine has its own depressant action quite different from the reaction produced by simple cooling of the heart.

Courvoisier et al. (1953) reported the prevention of local aconitine-induced arrhythmia by chlorpromazine. An intravenous dose of 2.5-5.0 mg./kg. prevented chloroform-adrenaline induced ventricular extrasystoles and fibrillation. Arora et al. (1955) have confirmed the effect of chlorpromazine as an antifibrillatory agent in experimental auricular fibrillation by local use of acetylcholine and aconitine and petrolatum ether-adrenaline technique. Similar results were-obtained by these workers in experimental auricular flutter (Arora et al., 1956). The antiarrhythmic property of chlorpromazine is shared with other adrenolytic phenothiazine derivatives (Bowet, Fourneau, Trefouel and Strickler, 1939; Shen, 1939; Huggins, Morse, Handley and Laforge, 1949; Meimsman-Roobroek, 1950). Intravenous chlorpromazine brought back to normal the cardiac arrhythmia produced by injection of tryptamine-stropanthidine in the cerebral ventricle. The mode
CHLORPROMAZINE: A REVIEW

of this action did not appear to be central, since a direct administration of chlorpromazine into the cerebral ventricle had a much weaker effect (Pocidalo, 1954).

Tachycardia occurred and there was no change in cardiac output with chlorpromazine (Moyer et al., 1955; Gujral and Lahiri, 1956).

Arterial blood pressure. There is considerable difference in the degree of hypotension reported by various workers. Courvoisier et al., (1953) found only 'negligent or transitory' decrease of blood pressure with 1.0-5.0 mg./kg. doses in dogs under chloralose anaesthesia. The extent of "sharp fall of blood pressure" appeared to be 20-30 mm. from the diagrams of Huidoro (1954). Following intraperitoneal administration, this hypotension persisted for over 24 hours. With 10.0 mg./kg. doses "a fairly constant fall" was seen by Moyer et al. (1954). Kalkoff (1954) reported a considerable fall of blood pressure in vagotomised dogs under morphine-urethane anaesthesia with even 0.05 mg./kg. I. V. This dose did not produce hypotension in the normally innervated animal though the pressor response to carotid occlusion was diminished (Kalkoff, 1954; Morin and Corriol, 1954). The bradycardia and hypotension following the stimulation of the central end of the cut vagus was temporarily diminished with 1.0-2.0 mg./kg. and completely inhibited with doses of over 10.0 mg./kg. (Morin and Corriol, 1954; Pocidalo et al., 1954). In nembutalized dog, a dose of 5.0 mg./kg. produced a fall of varying magnitude (60-80 mm.) and varying duration (3-5 minutes). The fall of blood pressure was accentuated by injecting the drug over a period of over 20 minutes (Decortis and Lecomte, 1955). The variations in the above reports were probably due to differences in experimental techniques and particularly to anaesthesia. Gujral and Lahiri (1956) tried to avoid this source of error by employing unanaesthetized rats, and they have established dose-effect relationships. They found the blood pressure fall to be 9.0-27.2 mm. with intraperitoneal doses from 0.5 to 10.0 mg./kg.

Chlorpromazine with pethidine and promethazine produced an increase in the peripheral blood flow, an increase in the pulse rate, a fall in the blood pressure, a higher cardiac output, and a decrease in the calculated overall systemic resistance in surgical patients, who had been administered "lytic cocktails" (Sheckman, 1954). Foster et al. (1954) reported a hypotensive response to chlorpromazine in man. A single dose of 25.0 mg. given by rapid I. V. injection to an anaesthetized subject produced a momentary fall of systolic blood pressure to 50 per cent of the original. In elderly patients of over 60 years, even with a single dose of 5.0-10.0 mg., the reduction was about 75 per cent. The average blood pressure fall was about 12.7 per cent and 14.5 per cent, in anaesthetized and unanaesthetized subjects, respectively. Couthier (1953) reported that the chlorpromazine-induced hypotension was "greater than hitherto reported". He also found that even with intravenous injection it took 20 minutes for the hypotension to appear in most of his patients.

Barcoft et al. (1954) reported an increase in peripheral blood flow, and increased warmth of extremeties. In patients with peripheral vascular disease, there was little or no increase in the cutaneous blood flow. This has been confirmed by Duff (1956). Lehman et al. (1954) have reported hypotension as a side effect. Burstein and Samson (1954) reported a case of severe hypotensive reaction. Winkelrnann (1955) observed in neuropsychiatric patients a systolic blood pressure fall of 5-60 mm. with 50 mg. of intramuscular chlorpromazine. Dobkin et al. (1955) have made similar clinical reports.
As regards the effect of chlorpromazine on high blood pressure, Gujral and Lahiri (1956) found that the drug lowered blood pressure much more effectively in hypertensive rats than in normotensive rats. Clinically, Couthier (1953) found that chlorpromazine had a "more definite effect" on hypertensive human. Winkelman (1955) has remarked that it appeared to have had a greater hypotensive effect in those of his neuropsychiatric patients who happened to be hypertensive. Lehman and Hanrohan (1955) have also reported that in two neuropsychiatric patients, severe hypotensive reactions were seen. Stevenson and Sjoerdsema have (1954) reported on its hypotensive action in nine hypertensive patients.

The hypotension produced by chlorpromazine is due to more than one factor. Adrenergic blockade (Courvoisier et al. 1953), metabolic depression, and selective depressant action on the vasomotor centre in the ascending reticular formation have so far been ascertained (Dasgupta and Werner, 1954). Decourt (1954) has suggested that the depression of the vasomotor centre was really a part of the generalized "narcobiotic" action. A reflex rise in the threshold of the pressoreceptors has been shown (Kalkoff, 1954).

Gujral and Lahiri (1956) found that chlorpromazine potentiated the hypotensive action of hexamethonium and reserpine in normotensive and hypertensive rats. Some antagonism occurred in normotensive rats with high doses of hydergine. Further investigation of hypotensive properties of combinations of chlorpromazine with other hypotensive drugs in experimental hypertension would be desirable.

**Cerebral haemodynamics.** It has been shown both by Kety's nitrous oxide technique and bubble flowmeter method in the human and the macaque monkey (Baruk et al., 1954; Moyer, 1954; Shotter, 1955) that cerebral blood flow is definitely increased. Fazekas et al. (1955) did not confirm this. They state that in man, over 200-300 mg. of chlorpromazine did not produce an increase in the cerebral blood flow. Brain tissue homogenate oxygen consumption was decreased (Baruk et al., 1955; Ganshirt et al., 1956). Pocidalo and Tardieu (1954) demonstrated a protective action of intravenous chlorpromazine against cerebral vascular accidents (with pulmonary lesions and gastrointestinal haemorrhages) evoked by injection of irritant substances like croton oil etc. These lesions were due to the damage to the cerebral peduncle.

**Coronary circulation.** In the Langendorff isolated heart preparation, the coronary blood flow increased (Courvoisier et al., 1953; Melville, 1954). Budde and Witzleb (1955) observed with the denervated heart-lung preparation that the dog coronary blood flow increased by 150% of the maximal flow; with "therapeutic doses" of 0.5-2.0 mg./kg., the increase was of the order of 50 per cent.

**Renal haemodynamics.** As observed from the glomerular plasma flow in man, the renal blood flow did not change much with chlorpromazine; if anything, it was "on the side of being raised." (Moyer, 1954, 1955).

**Peripheral blood vessels.** Chlorpromazine has a direct peripheral vasodilator action (Barcroft, 1952; Courvoisier et al, 1953; Dobkin et al., 1954; Dundee, 1954; Moyer et al., 1954). In concentrations of 0.1-1.0 gm./litre it produced a vasodilatation of vessels with 50-100 per cent increase of outflow (Courvoisier et al., 1953).

Chlorpromazine diminished capillary permeability in the rat. If a solution of trypan blue was injected intravenously, the blue colour appeared in the skin wherever a local irritant like xylol or chloroform was applied, or at the muzzle or extremeties when oedema appeared after an injection of egg albumin in sensitized rats or dextran in normal rats. This has been suggested
to be due to an increase in the capillary permeability. Chlorpromazine, in doses of 5.0-20.0 mg./kg. prevented the deposition of the dye under these circumstances (Courvoisier et al., 1953, 1955; Dundee, 1954).

Venous Pressure. Couthier (1953) reported a drop in venous pressure in man. Circulation time was unchanged. No experimental work seems to have been done in this regard.

Recently, chlorpromazine has been shown to have an anti-serotonin property (Dumke, 1956).

Tolerance. On chronic administration, tolerance to the cardiovascular response appears. This has been shown both experimentally and clinically (Moyer, 1955; Gujral and Lahiri, 1956). The latter workers found that if the drug was stopped for two weeks, the tolerance disappeared, only to return 3—4 weeks after the drug was resumed. Masson et al. (1955) showed in DOCA—hypertensive rats that chlorpromazine inhibited development of DOCA hypertension.

Electrocardiographic studies. In unanesthetized rabbits, 1 ml.-10.0 mg./kg. I. V. produced no E. C. G. changes. In "subtoxic doses" given at ten-minute intervals there was progressive bradycardia and an increase in the auriculoventricular and intraventricular conduction time shown by an increase in the P—R interval and the QRS complex. There was no disturbance of rhythm. With lethal doses such as 70.0 mg./kg. given in 7 different divided doses, electrocardiography showed bundle-branch block, myocardial infarction, and finally, auricular fibrillation. Moyer (1955) has reported occasional flattening of T—waves in dogs with a dose of 10.0 mg./kg. One dog showed a splitting of R—wave with a widening of the QRS and the Q—T interval. 75—85 mg./kg. given over a period of over 1—2 hours produced ventricular tachycardia. In hypertensive rats, 0.5-1.0 mg./kg. produced no abnormalities (Gujral and Lahiri, 1956). In the human, electrocardiography showed only an increased heart rate with therapeutic doses (Cauthier, 1953; Dobkin et al., 1954; Moyer et al., 1954, 1955). However, Boyd et al. (1955) have reported sinus arrhythmia in doses as low as 1.0-2.0 mg./kg. and occasional flattening of T—waves has been reported (Laborit, Iluguenard and Allaume, 1952; Dechene, 1954).

EFFECTS ON BLOOD

Chlorpromazine produced an increase in the clotting time of blood (Courvoisier et all., 1953). It lowered the total count of granulocytes and lymphocytes in intact and adrenalectomised rats (Kucher and Koch, 1955).

EFFECTS ON RESPIRATION

Chlorpromazine acted as a respiratory stimulant. With a dose of 5. ml.-10.0 mg./kg., Courvoisier et al. (1953) found a 20-40 percent increase in respiratory output. It was shown to have an antagonistic effect on nikethamide. With large doses, there was a prolonged apnoea producing death. In man, the respiratory stimulation has been confirmed by several workers (Laborit, 1951; Allaume 1952; Laborit, Huguenard and Allaume, 1952; Huguenard, 1953; Laborit and Huguenard, 1954). Reckless (1954) found that combination of chlorpromazine with morphine enhanced the analgesia, but the respiratory depression was reversed. Reckless has suggested the term "paradoxical potentiation" for this phenomenon.

Only one report seems to have been published on the actual changes in respiratory rate and volume in man by chlorpromazine. In anaesthetized
man, the respiratory rate was variably affected. Following 0.3-2.0 mg/kg dose I.V., respiration was depressed. With higher doses, unanaesthetized patients complained of conscious respiratory effort. Prolonged administration produced drying of the secretions (Broglie et al., 1953; Anton-Stephens, 1951; Kent et al., 1954). Hence in cases where prolonged therapy is intended, oral sepsis and minor respiratory complaints should be borne in mind. There are no reports on the effects of the drug on the lumen of the respiratory tract but beneficial effects have been reported in bronchial asthma (Broglie et al., 1954; Robinson and Zuck, 1954), though there can be some doubt whether the bronchial relaxation might have been due to the pethidine and promethazine given concurrently.

It is not sure whether it is a hepatotoxic agent. Observations on the serum bilirubin level, bromsulfalein excretion test and thymol turbidity test showed no abnormality in 25 patients (Dundee, 1954). Lehman and Hanrohan (1954), however, found abnormal cephalin-cholesterol tests in about half of their patients. Fall of blood pressure, with resulting anoxia may influence hepatic function adversely (Rich and Resnick, 1926; Schmidt, Unruh and Chesky, 1942; Davison, Lewis, Tagnon and Adams, 1946). The blood pressure changes have been considered to be the cause of involvement following spinal analgesia (Boyce and MacFetridge, 1938; Morrison, 1943; Engstrom and Frieberg, 1945). It is interesting to note that abnormalities of liver function tests were found only after prolonged use, as in psychotic disorders. Whether the prolonged hypotension was a cause is not known. The author feels that properly designed subacute and chronic experiments should be carried out to evaluate the effects of chlorpromazine on liver function tests. This would be of value in view of the clinical reports of jaundice following chlorpromazine therapy. The changes in the renal blood flow have already been mentioned earlier in the review. No changes were seen in electrolyte excretion (Moyer et al., 1954).

**PLAIN MUSCLE EFFECTS**

Chlorpromazine has a direct relaxant effect on rabbit intestine where it antagonized barium-induced spasm (Courvoisier et al., 1953).

**SKELETAL MUSCLE EFFECTS**

It has some skeletal muscle relaxant properties of its own (Courvoisier et al., 1953; Burn, 1954). It potentiated the properties of gallamine triethiodide (Courvoisier et al., 1953).

**ABSORPTION, FATE AND EXCRETION**

Dubost and Pascal (1954) found that the maximum blood concentration occurred in the dog and the rabbit 1.5 hours after subcutaneous and 3 hours after oral dosage. Irrespective of the route of administration there was a close correlation between the dose given and the blood concentration. Presumably the drug was well absorbed from the alimentary tract. In rabbits 24 hours after the large oral doses (200-500 mg./kg.) there was an appreciable amount left in blood (1.7-2.5 mg./100 ml.). At the end of 24 hours after subcutaneous injection only a negligible amount was found in blood (Dubost and Pascal, 1954). The drug was found in the maximum concentration in kidney (300 mg./G. tissue), lung, liver and brain, in the order mentioned. (Dubost and Pascal, 1954; Kok, 1955). Moyer et al., (1954) found that the drug was more effective in, and the sedation was greater after, oral administration in patients with liver dysfunction. Lehman and Hanrchan (1954) found that half of their 71 patients who were given
chlorpromazine daily showed some changes in cephalin-cholesterol flocculation changes. One third showed changes in serum protein and albumin-globulin ratio. Three cases developed jaundice. It therefore appears that the liver is probably responsible for at least part of its breakdown. It would be interesting to know the effect of the various liver enzymes on the drug. A series of liver biopsies of patients undergoing long-term chlorpromazine therapy would give valuable information.

**DETECTION IN THE BODY**

Dubost and Pascal (1954) described a method of estimation of chlorpromazine, in free and conjugated form, in biological fluids, based on the fairly sensitive reaction occurring between chlorpromazine and sulphuric acid (S.G. 1.83). The chlorpromazine base was extracted with ether in alkaline medium; a salt was reformed, which, in the presence of sulphuric acid gives a carmine-red reaction. This was very stable and sensitive, and determination of quantities in 1:800,000 concentration was possible, (Dubost and Pascal, 1953; Berti and Cima, 1955).

**MISCELLANEOUS**

Chlorpromazine gave protection to mice against an otherwise fatal dose of Salmonella typhi endotoxin. This was assumed to be connected with the adrenal glands in some way, since the protection did not exist in adrenalectomised mice (Chedid, 1954; Reilly and Tourpier, 1954).

**TOXICITY**

The LD50 varies from animal to animal. Given intravenously, the LD50 was (per kg.) 50 mg. for mice, 15 mg. for rabbits, and 25 mg. for rats. Given orally it is 75 mg. for mice. These figures are similar to those of promethazine.

With acute lethal doses the animals died of convulsions and respiratory arrest. No structural changes in the liver were found. In the kidney only small areas of congestion were found (Courvoisier et al., 1953).

With chronic administration to growing rats, retardation of growth occurred (Barn, 1954). Dogs administered 2 mg./kg. of chlorpromazine daily, showed some dilatation of the convoluted tubules and glomeruli. These changes were found only when the drug was given parenterally and not orally. Some thickening of lung tissue and atelectasis occurred at the end of one month in some animals. Even with 20 mg./kg. doses daily for a month there was no fatality in dogs. The only change in blood was a slight rise in blood sugar.

The toxic effects on the liver in man have already been considered. It should be remembered that the hepatotoxic feature of the parent compound, phenothiazine, has long been known (Hubble, 1941), a not unexpected feature in a benzene-containing structure.

**CLINICAL USES**

**Anaesthesia.** This drug is now being widely used in anaesthesia. The main anaesthetic uses can be mainly divided in three groups:

1. Given alone before anaesthesia in place of the routine premedication. Dobkin et al. (1954) employed chlorpromazine on the night before and on the morning of the operation. It lessened apprehension; induction of anaesthesia was easier, and a smaller amount of anaesthetic was necessary. If the usual amount of anaesthetic was employed, the anaesthesia was unduly prolonged.
2. Given prior to anaesthesia, though actually as a part of anaesthetic technique. This includes the so-called "potentiated anaesthesia and artificial hibernation". Laborit (1950) first described potentiated anaesthesia by phenothiazine derivatives—promethazine and diethazine at that time. It was postulated that these drugs, by blocking the autonomic nervous system partially, prevent the unfavourable reactions of the body to surgical trauma (Goldblatt, 1951). Chlorpromazine having similar properties was later employed for this purpose. Huguenard (1953c) described this method as "a pharmacodynamic technique, which by using autonomicolytic drugs, aims at establishing a controlled inhibition of the autonomic nervous system, a neuroplegia of homeostasis and as a consequence an attenuation of regulatory reactions. It amounts to an economical state of living with a state of hypometabolism, muscular relaxation and twilight sleep". He has mentioned that in France "artificial hibernation" is understood as a state in which there is "a deconnection as complete as possible of the autonomic nervous system, and consequently, of the endocrinal system". In his opinion the proper description would be "a stable physiobiological state" ("Un etat physiobiologique"). The term "artificial hibernation" is being objected to by many workers as being without justification (Kayser and Hiebel, 1952; Javenelle, 1954). The British technique for producing this state is the combination of chlorpromazine with pethidine before operation. Different workers have claimed that with this method apprehension, haemorrhage and shock were less and a smaller amount of anaesthetic was required (Smith and Fairer, 1953; Baxter, Bolster and McKethnie, 1954; Beard, 1954). The French and continental workers employ a more complicated technique; a number of drugs are employed together and hypothermia is sometimes combined (Dundee, 1954).

3. Before anesthesia to produce hypothermia.

As already mentioned it has little analgesic property of its own. In doses of 25 mg. 3-4 times a day, it was found to potentiate the action of analgesics such as morphine and methomorphinan and was reported to be effective in patients with inoperable malignant disease (Dundee, 1954; Howell et al., 1954; Sadove et al.; 1954). These data were not confirmed by Houde and Wallenstein (1955) who carried out well-designed experiments employing the double-blind technique to determine its status in analgesia.

Vomiting. Apart from the antiemetic action found in apomorphine-vomiting in man (Isaacs and MacArthur, 1954) it was found to give protection against vomiting in a large number of conditions, such as carcinomatosis, labyrinthitis, lymphomatosis, uraemia and in nausea and vomiting induced by man by drugs such as morphine, pethidine, methadone, codeine, nitrogen mustard, tetracyclines, and disulfiram in alcoholics. (Friend and Cummins, 1953). Good results were found in vomiting during labour, pregnancy, acute gastritis, and post-operative stages. Several workers have reported good results in vomiting due to the cardiac glycosides and nitrogen mustard (Kent et al., 1954; Albert and Coakley, 1954; Benaron et al., 1954; Feller, 1954; Donovan, 1955). However, the drug should not be employed before the cause of vomiting has been diagnosed, since it masks the condition by stopping vomiting. Marks (1954) reported on its efficacy in controlling vomiting due to radiotherapy. In motion sickness, it was found to be inferior to diphenyldramine and meclizine (Dundee, 1954).

Given intravenously, it was found very suitable in controlling intractable hiccough (Friedgood and Ripstein, 1955).

The dosage for antiemetic action of chlorpromazine has been variously
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mentioned as 25 mg., i. m., every 3-4 hours; single oral dose of 50 mg., and 10 mg. (Albert and Coakley, 194; Friend and Commins, 1954; Kent et al., 1954; Mark, 1654).

Pregnancy and labour. The use of this drug in the vomiting of pregnancy has already been mentioned. It has been used successfully in combination with pethidine in labour for analgesia (Lacomme et al., 1952; Quivy, 1954). It has been used for analgesia-amnesia in labour in combination with other drugs like pethidine, atropine etc. (Hershenson et al., 1954; Karp et al., 1955; Brown and Mannion, 1955; Donovan, 1955). The duration of labour has been variously reported to be shortened, lengthened and unaffected (Lacomme et al., 1952; Karp et al., 1955; Brown and Mannion, 1955). The drug did not appear to produce any adverse effect on the newborn (Barth, 1954; Hershenson, 1954; Lacomme et al., 1955; Quivy et al., 1954; Karp et al., 1955; Brown and Mannion, 1955; Benaron et al., 1955).

In eclampsia and pregnancy toxaeamias, chlorpromazine, combined with other drugs, has been tried successfully. (Labour, 1952; Rouchy and Creze, 1952). Recently eclampsia has been treated with some degree of success by hibernation therapy with the help of chlorpromazine (Aoustin, 1953; Baccaglini, 1953; Centaro, 1253; Pigeaud et al., 1954; O'Keefe et al., 1955).

Psychiatry. Chlorpromazine has been widely used in psychiatric practice. The interested reader is referred to the proceedings of the symposium held in 1955. Only the more important features will be touched upon here.

Chlorpromazine produces a state of psychic indifference. This is the basis of its action in severe psychomotor excitement (maniac states) and anxiety neuroses. To quote Winkelman (1954), it is a drug with "definite indications and is particularly outstanding in that it can reduce severe activity, diminish phobias and obsessions, reverse or modify paranoid psychoses, quieten maniac or extremely agitated patients, and make hostile agitated senile patients quiet and easily manageable." The results resembled prefrontal leucotomy. Ingrained thought disorders, however, were not changed (Elkes and Elkes, 1954). Patients became more co-operative and psychotherapy was easier to institute. The use of chlorpromazine, singly and in combination, has been recommended by various authors (Tchekoff and Bouchard-Tournier, 1952; Delay, Deniker and Tardieu, 1953; Deschamps and Coderet, 1953; Molle and Nickory 1953; Ratschow, 1953; Anton-Stephens, 1954; Azima and Ogle, 1954; Delay and Deniker, 1954; Elkes and Elkes, 1954; Garmany et al., 1954; Lehman and Hanrohan, 1954; Winkelman, 1954; Moyer et al., 1955). The doses employed for psychiatric use by different authors varied considerably, ranging from 15 mg. to 8 gm. a day. The duration of treatment varied from days to months. Obsessional symptoms, depression and hysteria were not much benefited. It has been recommended for use in alcoholism and drug addiction (Friend and Cummins, 1954; Mitchell, 1955; Friedgood and Ripstein, 1955).

Miscellaneous. It has been reported to be of use in diverse conditions like diagnosis and anaesthetic management of phaeochromocytoma (Emlet et al., 1951). It has also been tried in duodenal ulcer and peripheral vascular disease (Dobkin, Gilbert and Lamoureanx, 1954). In combination with other drugs it has been tried in various conditions like scarlet fever, bronchopneumonia, carbon monoxide poisoning, gunshot wounds, "neurotoxicosis" in children (Sorel et al., 1953) and experimental and clinical tetanus (Cole and Robertson, 1954; Kelly and Laurence, 1956).
Side effects. The acute side-effects may take the shape of faintness and dizziness due to postural hypotension, dry mouth, nasal congestion, palpitation and drowsiness (Lehman et al., 1954; Robson and Keele, 1955). Prolonged administration has been followed by nausea, anorexia and gastric distress (Lomas, 1955; Moyer, 1955). Liver damage was sometimes produced and the jaundice appeared to be obstructive in type. There was occasional inflammatory cell infiltration in the lobule, but without damage to the liver cell. In some cases liver function tests gave abnormal results though there was no actual jaundice (Lemire and Mitchell, 1955). The jaundice was somewhat like that produced by methyltestosterone (Van ommen and Brown, 1955). Sensitization reactions sometimes appeared after a week (Garmany, 1954), and were manifested in the form of maculopapular skin rash (Azima and Ofle, 1954); Photosensitivity to the exposed parts of the body (Lomas et al., 1954); and contact dermatitis (Dundee, 1954; Lewis and Sawicky, 1954). Withdrawal of the drug usually caused a reversal of these conditions. Leucopenia has been reported (Giacobini and Lassenius, 1954; Goldman, 1955; Lomas, 1955; Tasker, 1955). Oversedation occasionally occurred. Large doses sometimes produced confusion and disorientation or even Parkinsonism which disappeared on withdrawal (Moyer, 1955). In some cases, epileptic fits were increased.

CONCLUSION

Chlorpromazine is still a new drug, and only time will show how much the present enthusiasm about it is justified. But it appears that it is a valuable addition to a new group of tranquilizers; it is one of the most powerful antiemetics and is a useful anaesthetic adjuvant. The intimate mechanism of action of many of its pharmacological properties has not yet been elucidated, and considerable progress will have to be made in this field.

BIBLIOGRAPHY


