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COMPARISON OF SOME PHARMACOLOGICAL PROPERTIES OF CHLORPROMAZINE, PROMETHAZINE, AND PETHIDINE

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The pharmacological actions of chlorpromazine have been described in detail by Courvoisier, Fournel, Ducrot, Kolsky, and Koetschet (1953). This substance was introduced into anaesthetic practice by Laborit and Huguenard (1951) and is given together with promethazine and pethidine, so that it is impossible to know what contribution each makes to the joint effect. We have therefore compared their pharmacological properties quantitatively as well as qualitatively.

The properties tested were the power to reduce body temperature; the effect on skeletal muscle stimulated directly and through the nerve; the chronic toxicity; the power to potentiate (*a*) pentobarbitone, (*b*) morphine; the anti-adrenaline action; the anti-acetylcholine action; the antihistamine action; and the local anaesthetic action.

METHODS

Body Temperature

Eight male mice were used in each experiment, their rectal temperatures being recorded by inserting a lubricated thermocouple into the rectum. This thermocouple was connected to a moving coil galvanometer and the cold junction thermocouple was placed in a constantly stirred water bath at 25° C. The mice were held in position by fastening the tail with adhesive tape to one end of a wire and turning the other end into a loop round the chest. Each mouse was placed in a small celluloid cage of hemispherical cross-section. After half an hour to an hour their temperatures remained steady, and then four mice were used as controls and were injected with saline, while the other four were injected with the substance being tested. The mean difference in temperature between the two groups of mice before the injections was taken as zero and allowance was always made for this difference in calculating the mean temperature-difference between the test mice and the controls recorded at 15-min. intervals.

Skeletal Muscle

The sciatic-gastrocnemius preparation of the cat was used as described by Dale and Gasser (1926). The muscle was stimulated indirectly through the sciatic nerve by rectangular voltage pulses and directly through the muscle by means of induction shocks from a Lewis rotary contact breaker. The rates of stimulation were adjusted so that they were both about 8 or 9/min., and the muscle was continuously stimulated by each method alternately at 1 min. intervals. Injections were made into the right iliac artery close to the bifurcation of the abdominal aorta.

The phrenic nerve-diaphragm preparation of the rat was also used. The experimental procedure was the same as that described by Bülbring (1946), the nerve being stimulated by a pair of platinum electrodes submerged in the organ bath (50 ml.).

Anti-adrenaline Action

The anti-adrenaline actions of chlorpromazine, promethazine and pethidine were compared on three preparations—the vessels of the rabbit ear, the blood pressure of the spinal cat, and the smooth muscle of the rabbit uterus.

(a) *Vessels of Rabbit Ear.*—The central artery of the rabbit ear was cannulated and injections were made into it by means of the device described by Gaddum and Kwiatkowski (1938). A Gaddum drop-timer was used to record the changes in vascular tone, and single injections of the substance being tested were made. A dose of each substance was found which reduced the effect of adrenaline to one-tenth of the initial effect, so that after an injection of the anti-adrenaline substance a dose of adrenaline 10 times greater than the initial dose was required to produce the same constriction.

(b) *Blood Pressure of Spinal Cat.*—A dose of adrenaline (about 10 μg.) was found which produced a reasonably large rise in blood pressure. The anti-adrenaline actions of chlorpromazine, promethazine and pethidine were then compared by finding the dose of each drug which reduced the effect of adrenaline to about one-third of its initial value. There were difficulties in an accurate estimation of chlorpromazine, since the vessels were rapidly desensitized to its action and since this desensitization lasted for several hours.

(c) *Rabbit Uterus.*—The anti-adrenaline actions of the three drugs were compared by finding the dose of each substance which reduced the effect of adrenaline to one-half of the initial effect.

Anti-acetylcholine Action

The anti-ACh actions of chlorpromazine, promethazine and pethidine were compared on two preparations, the guinea-pig ileum and the pupil of the mouse eye. The action of chlorpromazine on salivary secretion was also studied.

(a) *On Ileum.*—A piece of guinea-pig ileum was suspended in oxygenated Locke at 36° C. and a dose of ACh was found which produced reasonably large submaximal contractions. The anti-ACh actions of chlorpromazine, promethazine and pethidine were compared on this preparation by exposing the gut to a certain dose of each drug for 60 sec., and finding the dose such that twice the original dose of ACh then produced a contraction of equal height to the standard.

(b) *On Mouse Pupil.*—Chlorpromazine, promethazine and pethidine were tested on the mouse pupil for mydriatic activity by the method of Pulewka (1932). The mice (18–28 g.) were injected intraperitoneally with 0.2 ml. of the solution being tested and the effect on the size of the pupil was determined under a binocular microscope fitted with a scale in one eyepiece. The diameter was measured before and 20 min. after injections of chlorpromazine, promethazine and pethidine, by which time the optimal mydriatic effect had been reached.

(c) *On Salivary Secretion.*—The anti-ACh action of chlorpromazine was compared with that of atropine on salivary secretion. The method used was that described by Bülbring and Dawes (1945). A steady flow of saliva was usually produced by an intravenous infusion of a solution containing adrenaline (5–10 μg./ml. depending on the blood pressure of the cat) and carbachol (5–10 μg./ml.) at a rate of about 0.5 ml./min.

Antihistamine Action

The antihistamine actions of chlorpromazine, promethazine and pethidine were compared on two preparations, the guinea-pig ileum and the guinea-pig bronchioles.

(a) *On Ileum.*—Their antihistamine actions on the ileum were compared in exactly the same way as the anti-ACh actions. The dose of each substance was found which reduced the effect of histamine to one-half of the initial effect.

(b) *On Bronchioles.*—The bronchial tone was recorded by the method described by Konzett and Rössler (1940). A guinea-pig was anaesthetized with a 25% solution of urethane and the lungs were artificially respired by a Starling pump, which drove air into the trachea. The excess air which did not enter the trachea operated a float-recorder which recorded a vertical line on a kymograph. When the bronchioles constricted the lever rose, so that the length of the vertical line was a measure of the constriction. A dose of histamine, which caused a reasonably large bronchoconstriction, was injected intravenously at regular intervals until a uniform response was obtained. The antihistamine actions of chlorpromazine, promethazine and pethidine were then compared by finding the doses which caused about a 50% reduction in the response to the standard dose of histamine.

Local Anaesthetic Action

The local anaesthetic activities of chlorpromazine, promethazine and pethidine in 0.3%, 0.1% and 0.05% (w/v) concentrations were compared by the intracutaneous weal method described by Bülbring and Wajda (1945). Four injections were made into shaven areas on the back of a group of guinea-pigs, two at the front and two at the back, and, since the sensitivity of the different areas on the back of a pig varies considerably, all three concentrations of the three drugs were tested on each area. The reaction to six pin-pricks was determined at each site every 5 min. and the number of failures to respond to 36 pricks was a measure of the degree of anaesthesia.

RESULTS

Body Temperature

The effects of subcutaneous injections of chlorpromazine (1 mg./kg.), promethazine and pethidine (30 mg./kg.), and hexamethonium (5 mg./kg.) on body temperature were compared and the results are shown in Fig. 1. Observations were also made

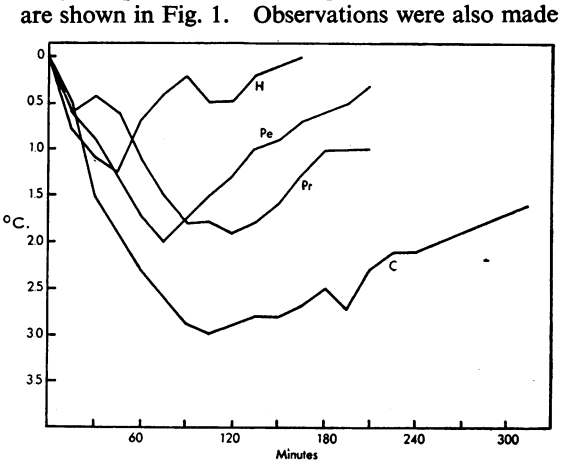

FIG. 1.—Effect of drugs on the body temperature of mice. Abscissae: time in min.; ordinates: mean temperature difference between test mice and controls. The results for each drug are the means of experiments with 12 control and 12 test mice, except hexamethonium, where 4 control and 4 test mice were used. H = hexamethonium, 5 mg./kg.; Pe = pethidine, 30 mg./kg.; Pr = promethazine, 30 mg./kg.; C = chlorpromazine, 1 mg./kg.

with a higher dose of chlorpromazine (3 mg./kg.) when the mean temperature-difference between the injected mice and controls was as much as 5.7° C. after 3 hr. and still 2° C. after 7 hr. from the time of injection. Promethazine in a dose of 3 mg./kg. had virtually no effect on body temperature.

Action on Striated Muscle

In the sciatic-gastrocnemius preparation of the cat, chlorpromazine caused a slight initial increase

in the size of contractions, both to direct and indirect stimulation, followed by a gradual decrease. The size of the contractions to direct stimulation always fell away more slowly than those to indirect stimulation. These effects are shown in Fig. 2, where it is seen that a dose of 4.6 mg./kg. eliminated completely the response to indirect stimulation after 75 min.

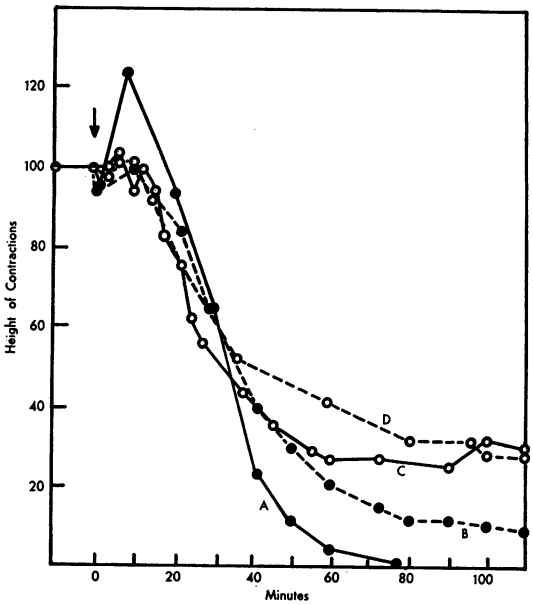

FIG. 2.—Effect of chlorpromazine (injected into the aortic bifurcation) on the twitch tension of the cat gastrocnemius to direct and indirect stimulation. Abscissae: time in min.; ordinates: height of contractions expressed as a percentage of the initial height. Injections of chlorpromazine made at arrow. The full lines indicate the response to indirect stimulation and the broken lines to direct stimulation. A and B are the responses after 4.6 mg./kg., and C and D after 3.1 mg./kg.

Similar effects were observed with promethazine, which had about 50% of the action of chlorpromazine, and pethidine, which had only about 10%. These figures are approximations, since there were wide variations in the 9 different animals used. The effects were not due to failure of the circulation, for in several experiments where the blood pressure was raised from a rather low level to about the original height by an infusion of pituitary extract (10 u./50 ml.) no alteration in the gradual decline of the contractions was observed. Furthermore, the effects were not due to fatigue, since in one experiment the gastrocnemius muscle was stimulated for 3 hr. before any injection was made and throughout this time always gave about the same response to the electrical stimuli (Fig. 3). Between (*b*) and (*c*) an injection of pethidine (20 mg./kg.) was made, and thereafter the picture obtained was exactly the

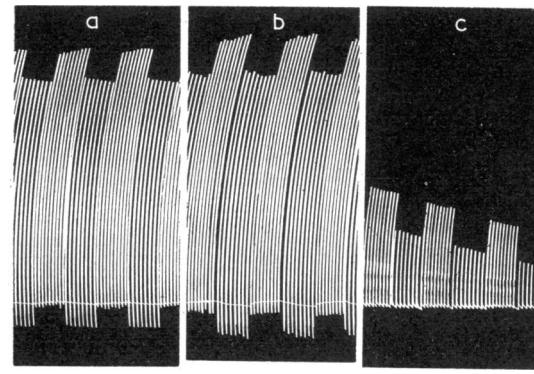

FIG. 3.—Contractions of the cat gastrocnemius. Single supramaximal shocks, 8 or 9 per min.; 0.7 millisecond duration. (*a*) Direct and indirect stimulation. (*b*) The same after 3 hr. continuous stimulation. (Note that there is no sign of fatigue.) (*c*) 40 min. after injection of pethidine (20 mg./kg.) into the iliac artery.

same as in other experiments. In one or two experiments it became necessary to apply artificial respiration.

The effect of nalorphine on this paralysing action of pethidine was investigated, but in only one experiment out of three was a moderate degree of recovery observed. In others the nalorphine had no effect. All attempts to counteract the action of chlorpromazine with nalorphine were unsuccessful.

In the phrenic nerve-diaphragm preparation similar results were obtained. In experiments with indirect stimulation alone, chlorpromazine in doses of about 100 μg. caused a slight increase in the muscle contractions. In doses of about 200 μg., there was a very rapid decrease and the contractions were abolished within 20 min. Promethazine behaved in a similar way except that a rather higher dose (400 μg.) was required to abolish the contractions (Fig. 4). Very much larger doses of pethidine were necessary to produce these effects; 2 mg. produced an increase in the contractions and about 10 mg. produced a decrease. These figures for pethidine agree closely with those of Dutta (1949). The contractions usually recovered after washing, showing that the effects of the chlorpromazine, promethazine, and pethidine were reversible. This was of particular interest, since the contractions in the cat sciatic-gastrocnemius preparation were never found to recover within 6 hr. of observation. Tests were made in 8 preparations.

Chronic Toxicity

The acute toxicity of chlorpromazine in mice has been studied by several workers, but very few details are available concerning chronic toxicity. The effect of chlorpromazine, promethazine, and pethidine on the growth of young rats was therefore studied. In each experiment, rats (35–55 g.) were

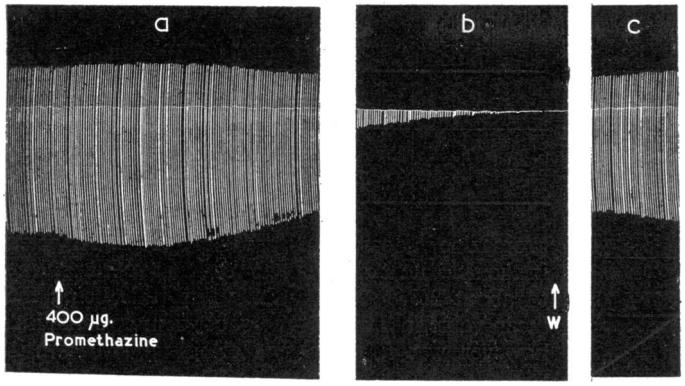

FIG. 4.—Rat phrenic nerve-diaphragm preparation in Tyrode solution, 37° C., 50 ml. bath. Single supramaximal shocks (7 per min., 0.7 msec. duration) through the phrenic nerve. (*a*) 400 µg. promethazine at arrow. (*b*) Response to stimuli abolished after 50 min. Change of bath fluid at W. (*c*) 25 min. later. The size of contractions had returned almost to their original height.

injected subcutaneously twice daily and their rate of growth, in comparison with control rats which received saline injections, was followed for at least a week. For the first 2 or 3 days the rats receiving chlorpromazine, promethazine, or pethidine in sufficiently low doses were unaffected and gained in weight by an amount approximately equal to that of the control group. In rather higher doses their mean weight remained constant or even fell. After 3 days the mean weight usually increased at the same rate as the controls (Fig. 5). There were occasional deaths after the third day, however, when the general condition of the rats was apparently improving and the typical drowsiness observed after the first few injections of chlorpromazine and promethazine was getting less and less. Pethidine produced an increase in excitability rather than drowsiness.

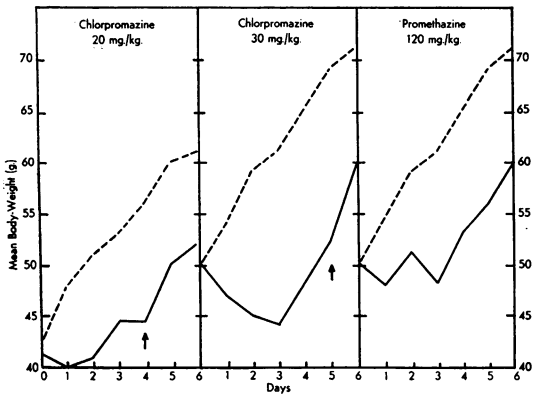

FIG. 5.—Effects on growth of rats. Abscissae: time in days; ordinates: mean body weight in g. Broken lines indicate the growth rate of controls and full lines the growth rate of test rats. At the arrows one test rat was found dead in its cage. Note that the inhibition of growth lasted for only 2 or 3 days.

From Table I it is seen that a dose of 30 mg./kg. of chlorpromazine for the first 4 days caused a retardation in growth similar to that produced by a dose of 150 mg./kg. of promethazine or pethidine. Thereafter all 3 substances had no further retarding action. It therefore appeared that chlorpromazine was about 5 times more toxic than promethazine or pethidine. Although 40 mg./kg. of chlorpromazine killed 3 out of 4 rats when given as a single or as a divided dose, this higher dose was tolerated by a group of 8 rats which had previously received a daily dose of 20 mg./kg. for one week. This fact, together with the decrease in drowsiness in the course of the injections, suggested that the rats acquired tolerance towards these drugs.

TABLE I

EFFECT ON GROWTH OF RATS (35–55 G. INITIAL WEIGHT)

Drug	Total Daily Dose (mg./kg.)	Mean Difference in Weight from Controls (g.)		No. of Deaths
		0–4 Days	0–6 Days	
Chlorpromazine ..	10	−2	−2	0/8
	20	−11	−8	1/15
	30	−19	−14	1/4
	40			6/8
	40*			
	40†	−6	−10	0/8
Promethazine ..	40*	0	0	0/4
	120	−12	−11	0/4
	150	−11	−12	3/8
Pethidine	100*	+6		0/4
	150	−8	−11	4/8
	200	−11		3/4

* One injection daily.
† These received a daily dose of 20 mg./kg. for one week previously.

Potentiation of Morphine and Pentobarbitone

The effect of chlorpromazine, promethazine, and pethidine on the action of morphine and of pentobarbitone was compared.

Morphine.—The analgesic action of morphine (1.5 mg./kg.), chlorpromazine, promethazine, and pethidine (all 10 mg./kg.), and then of morphine together with each of the above three drugs in the same doses, was tested by the application of electrical stimulation to the mouse tail (Grewal, 1952). All injections were given subcutaneously. The results are shown in Table II, from which it is seen that by this method the analgesic action of morphine was not potentiated by either chlorpromazine, promethazine, or pethidine. Nor indeed did the

TABLE II
ACTION ON MORPHINE ANALGESIA

Drug	No. of Mice	% Showing Analgesia
Morphine (1·5 mg./kg.)	20	10
Chlorpromazine (10 mg./kg.)	40	70
,, +morphine	40	40 (80)
Promethazine (10 mg./kg.)	40	25
,, +morphine	40	37·5 (35)
Pethidine (10 mg./kg.)	40	40
,, +morphine	40	35 (50)

The figures in brackets are those to be expected for an additive effect.

effect, except with promethazine, seem to be additive. The results quoted in Table II are for observations 15 min. after the injection of the substances. By this time the optimum effect had apparently been reached, for even after 30 or 60 min. the percentage of mice showing analgesia was not significantly different.

Pentobarbitone.—A group of 40 mice was injected intraperitoneally with pentobarbitone (50 mg./kg.), and the mean duration of sleep in minutes was observed. The mice were placed on a warm table and were considered to be asleep as long as they remained lying on their sides. Observations were also made on further groups of mice which were given chlorpromazine (10 mg./kg. and 3 mg./kg.), promethazine and pethidine (both 10 mg./kg.) in addition to the pentobarbitone. The drugs were all given subcutaneously, except pentobarbitone, which was given intraperitoneally. This was done because a precipitate was formed when the solutions were mixed. The results are shown in Table III.

TABLE III
ACTION ON PENTOBARBITONE HYPNOSIS

Drug	No. of Mice	Mean Duration of Sleep (min.)
Pentobarbitone (50 mg./kg.)	40	28·3
Chlorpromazine (3 mg./kg.)+pentobarbitone	80	39·5
,, (10 ,,)+ ,,	40	154
Promethazine (10 mg./kg.)+pentobarbitone	40	40·2
Pethidine (10 mg./kg.)+pentobarbitone ..	40	39·5

Chlorpromazine in a dose of 10 mg./kg. had a potentiating action on pentobarbitone and produced a nearly fivefold increase in the duration of sleep.

Anti-adrenaline Action

The approximate equipotent ratios on the three preparations used are shown in Table IV. Chlor-

TABLE IV
ANTI-ADRENALINE ACTION

Drug	Vessels of Rabbit Ear	Blood Pressure of Spinal Cat	Smooth Muscle of Rabbit Uterus
Chlorpromazine	1	1	1
Promethazine..	4	33	10
Pethidine ..	32	41	10,000

promazine in doses of the order of 1–10 mg. injected in the spinal cat reduced the response to adrenaline to about 25% of the initial value, this being the mean value in 7 cats. The effect of noradrenaline, however, was only slightly diminished, as shown in Fig. 6.

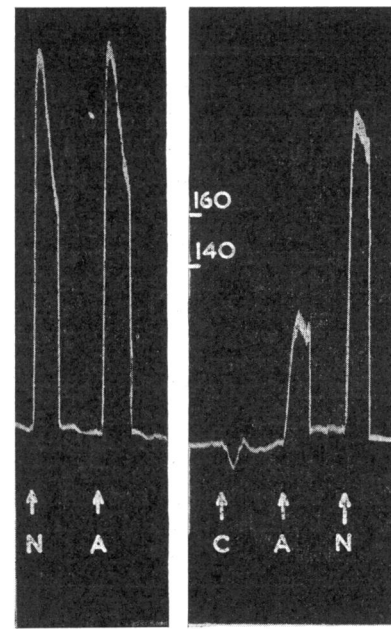

FIG. 6.—Effect of chlorpromazine on the adrenaline and noradrenaline blood-pressure rise in the spinal cat. N=8 μg. noradrenaline, A=15 μg. adrenaline, and C=10 mg. chlorpromazine. It can be seen that chlorpromazine in a dose which greatly reduces the effect of adrenaline has scarcely any effect on an equipotent dose of noradrenaline.

The effect of chlorpromazine on the blood-pressure rise after splanchnic stimulation was investigated before and after adrenalectomy. Before adrenalectomy there was the usual initial rapid rise due to constriction of vessels in the viscera, followed by a secondary less rapid rise due to liberation of adrenaline from the adrenal glands. After 5 mg. of chlorpromazine the blood-pressure rise was reduced by nearly 50% and the secondary rise was abolished, because of the anti-adrenaline action of the chlorpromazine. After about an hour, however, the blood-pressure rise had returned to its original

level. After adrenalectomy two doses of 5 mg. of chlorpromazine (given within 10 min.) then had virtually no effect; indeed, a slightly larger rise in blood pressure was observed.

In further experiments chlorpromazine was found to reduce the rise of blood pressure following nicotine in the spinal cat, when the adrenal glands were present.

Anti-acetylcholine Action

The approximate equipotent ratios are shown in Table V—for the guinea-pig ileum in terms of chlorpromazine=1, and for the mouse pupil in terms of atropine=1. On the mouse pupil chlorpromazine in doses as high as 20 mg./kg. (400 μg./mouse) showed no mydriatic activity whatsoever.

TABLE V
ANTI-ACETYLCHOLINE ACTION

Drug	Guinea-pig Ileum	Mouse Pupil
Chlorpromazine	1	No action
Promethazine	0·13	60
Pethidine	2·7	120
Atropine	Not tested	1

In experiments on the salivary flow, chlorpromazine produced a fall of blood pressure and showed an atropine-like action in inhibiting the salivary flow. This inhibition was not due to the blood-pressure fall, since after a minute or two the salivary flow returned to its original level, while the blood pressure did not recover. In 4 observations on 2 cats chlorpromazine appeared to be about one-thirtieth as active as atropine. We did not test promethazine and pethidine for ability to inhibit salivary secretion, but Schaumann (1940) reports that pethidine is more than 200 times weaker than atropine.

Antihistamine Action

The approximate equipotent ratios of the three drugs on the bronchioles and on the ileum are shown in Table VI. Promethazine is more potent on both preparations, particularly the bronchioles, than either chlorpromazine or pethidine, and its action also lasts very much longer.

TABLE VI
ANTIHISTAMINE ACTION

Drug	Guinea-pig Ileum	Guinea-pig Bronchioles
Chlorpromazine	1	1
Promethazine	0·33	0·01
Pethidine	40	150

Comparison of Antihistamine and Anti-acetylcholine Actions

The relative antihistamine and anti-acetylcholine actions of each substance on the guinea-pig ileum were compared by finding the dose required to reduce the response to histamine and acetylcholine by nearly 100%. The results are shown in Table VII. The antihistamine action of chlorpromazine is seen to be much stronger than its anti-acetylcholine action (Fig. 7).

TABLE VII
WEAKNESS OF ANTI-ACETYLCHOLINE ACTION, RELATIVE TO ANTIHISTAMINE ACTION TAKEN AS=1

Chlorpromazine	1 : 33
Promethazine	1 : 4
Pethidine	1 : 1·5

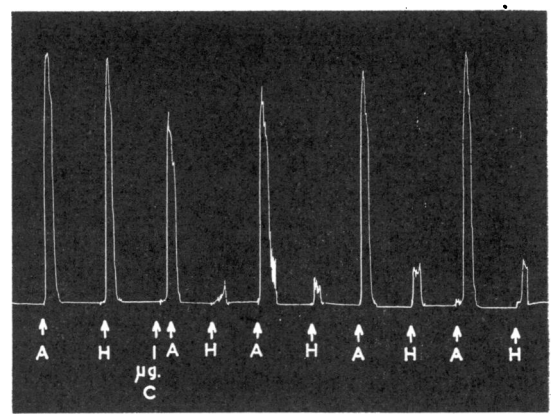

FIG. 7.—The antihistamine and anti-acetylcholine action of chlorpromazine on the guinea-pig ileum. A=0.1 μg. acetylcholine, H=0.4 μg. histamine, and C=chlorpromazine. Note that the antihistamine action of chlorpromazine is much greater and longer-lasting than the anti-acetylcholine action.

Local Anaesthetic Action

The activity of chlorpromazine was found to be 1.2 times greater than that of promethazine and 2.1 times greater than that of pethidine. Their relative local anaesthetic activities are shown in Fig. 8. Chlorpromazine, promethazine, and pethidine were tested for ability to induce plexus anaesthesia in frogs by the method of Bülbring and Wajda (1945). All three were active in concentrations of about 0.1–0.2%, chlorpromazine again being more active than promethazine or pethidine.

DISCUSSION

Chlorpromazine, promethazine, and pethidine were all found to lower the body temperature of mice, chlorpromazine being more than 30 times as effective as promethazine or pethidine. A similar

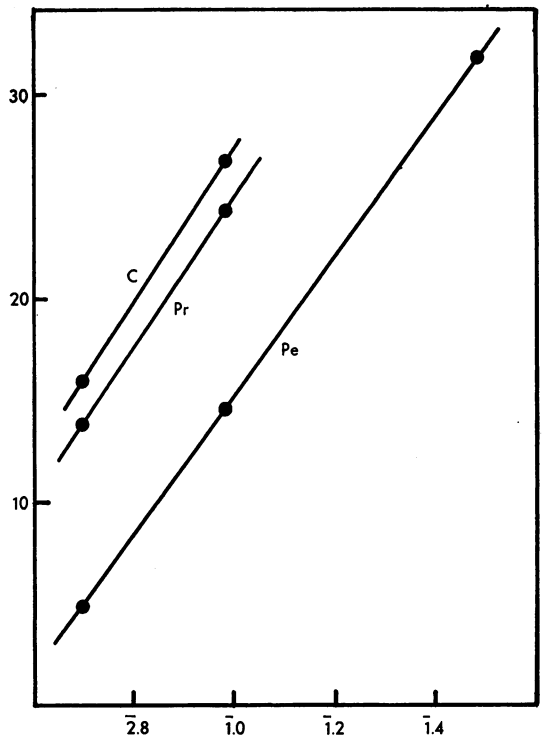

FIG. 8.—Local anaesthetic activity. Abscissae: log concn.; ordinates: degree of anaesthesia expressed as the mean failure to respond to 36 pricks in 30 min. The points represent the mean of observations on 15 guinea-pigs. C=chlorpromazine, Pr=promethazine, Pe=pethidine.

result was obtained by Courvoisier *et al.* (1953) comparing chlorpromazine and promethazine.

When the gastrocnemius muscle of the cat was stimulated, either directly or indirectly through the sciatic nerve, all three drugs depressed the response of the muscle. The doses required to produce these effects varied, but chlorpromazine was always the most effective. From the fact that both direct and indirect stimulation failed to have any appreciable effect after the muscle was paralysed, it was evident that the action was not curare-like but was a direct action on the muscle.

Since body temperature is maintained to a large extent by the normal tonus of skeletal muscles, any interference with the power to contract will affect heat production as well as the tonus. Our findings clearly show that chlorpromazine, promethazine, and pethidine have a depressant effect on skeletal muscles, and we therefore suppose that this action is at least partly responsible for the lowering of body temperature. There is also the possibility that these substances influence the chief centres for the integration of temperature control in the hypothalamus, although, as yet, there is no experimental evidence to support this view. It may appear surprising that none of the authors describing the action of chlorpromazine, promethazine, and pethidine in human subjects mentioned an effect on the skeletal muscles. It must be remembered, however, that in clinical practice the usual reduction in body temperature by these drugs, without external cooling, is not more than 1–2° C., so that the effect on skeletal muscles is presumably not great enough to be detected by routine clinical methods. Although the doses we used in our experiments on the cat were not very much higher than those used clinically, they were injected intra-arterially close to the muscle, and it is also likely that there may be considerable variation in species sensitivity. Paralysing effects on skeletal muscles, sufficient to be noticed by the clinician, may therefore be obtained only with much higher doses.

It has been stated by some anaesthetists that chlorpromazine owes its action on body temperature to a ganglion-blocking effect. We tested hexamethonium for power to reduce body temperature in a dose of 5 mg./kg., and found that it produced only a slight fall, much less than that caused by 1 mg./kg. chlorpromazine.

Our experiments showed that all the three substances investigated when given in sufficiently high doses inhibited the growth of young rats during the first three days. After this time the rate of growth was not affected, but during the period of our observations the mean weight of the test groups never reached that of the controls. These results can be interpreted in two ways: either the rats lost weight through loss of appetite as a consequence of drowsiness, or they lost weight because of an inhibitory effect on the metabolic rate. The first possibility is ruled out for pethidine, since pethidine produced excitability in the rats rather than drowsiness. If the second possibility is correct this might throw some light on the much-discussed problem as to whether chlorpromazine has a depressant action on metabolism or not.

Some authors, Courvoisier *et al.* (1953), Ducuing and Rieunau-Serra (1953), Irmer and Koss (1953), Peruzzo and Forni (1953), Staehelin and Kielholz (1953), Zettler (1953) and Laborit (1954), state that a reduction in the metabolic rate occurs in tissue slices as well as in whole organisms. Another group, Decourt (1953), Grosse-Brockhoff (1954), Peters and Lehr (1954), and Willems (1954), in experiments on plants, animals, normal and hyperthyroid human subjects, find that within the range of therapeutic doses no reduction in metabolism can be observed. Filk, Ritter, Stürmer, and

Loeser (1954) found in their experiments on rats a decrease in O_2 consumption during the first fourteen hours, but after continuous administration of chlorpromazine for several days the O_2 consumption of the animals returned to its normal level and remained unchanged. Our results seem to confirm these observations. Staehelin and Kielholz (1953) and Dundee, Gray, Mesham, and Scott (1953) also found a small reduction in the basal metabolic rate in human subjects. That Grosse-Brockhoff (1953) and Willems (1953) did not find any depression was probably because they used very much smaller doses.

Decourt (1953) and Peters and Lehr (1954) observed irreversible damage to plant cells, bacteria, moulds and infusoria only in very high concentrations. Weaker solutions never seemed to affect the cells directly. A " histoplegic " action, i.e. a depressant effect on every individual cell (Decourt, 1953, and Laborit, 1953), is therefore not very likely so far as therapeutic doses are concerned. From observations that the metabolism of brain sections is depressed by chlorpromazine (Peruzzo and Forni, 1953) it cannot be concluded that the metabolism of the whole body is also reduced.

Furthermore, the assumption that an effect on metabolism is the consequence of the fall in body temperature does not seem to be correct, since Juvenelle, Lind, and Wegelius (1952) have found that a pronounced inhibition of metabolic processes is only achieved when the temperature is reduced to below 25° C. So great a fall of temperature is not known to have been produced by these drugs alone when patients have survived.

In previous papers it has been reported that chlorpromazine potentiates the analgesic action of morphine both in animals and in human subjects (Courvoisier *et al.*, 1953; Wirth, 1954; Zettler, 1953; and Reckless, 1954), and we have studied the relative power of chlorpromazine, promethazine and pethidine in potentiating this effect. We followed the method of Grewal (1952) and were unable to detect an action of this kind, although the number of animals used in these experiments was certainly great enough to show any potentiating effect. Not even an additive effect was observed, however, except with promethazine. The property of potentiating the action of anaesthetics has been described in many publications (Courvoisier *et al.*, 1953; Dietmann, 1954; Dundee *et al.*, 1953; Staehelin and Kielholz, 1953; Zettler, 1953; and Zipf and Alstaedter, 1954), and all authors agree that the amount of anaesthetic required to produce surgical anaesthesia is considerably reduced. We investigated this potentiating action on pentobarbitone, and in the doses used promethazine and pethidine showed a slight potentiation but very much less than that of chlorpromazine.

On all three preparations (vessels of the rabbit ear, blood pressure of the spinal cat, and smooth muscle of the uterus) an anti-adrenaline action of chlorpromazine, promethazine, and pethidine was found, chlorpromazine always being the most potent, followed by promethazine and pethidine. There is a considerable variation between the equipotent ratios found by the three methods, but this is hardly surprising in view of the widely differing preparations.

Chlorpromazine itself causes a fall of blood pressure. This has been described by all workers who have used it experimentally or clinically. Our experiments on the cat's blood pressure with noradrenaline injections and stimulation of the splanchnic nerve before and after adrenalectomy provide further evidence that chlorpromazine possesses an anti-adrenaline action but very little anti-noradrenaline action. We never succeeded in producing a clear reversal of the adrenaline pressor effect, yet with sufficiently high doses of chlorpromazine it was possible to abolish almost completely the adrenaline rise of blood pressure. At this stage noradrenaline still showed a pressor effect in doses previously equipotent to adrenaline. It should therefore be possible by injecting noradrenaline to raise the blood pressure in patients when the fall is the result of chlorpromazine action.

Courvoisier *et al.* (1953) and others have described the anti-acetylcholine action of chlorpromazine. We studied the action of the three substances individually, and found that on the gut promethazine was about 8 times more active than chlorpromazine, which was about twice as active as pethidine. On the mouse pupil our results were similar to those of Friebel, Flick, and Reichle (1954), promethazine again being more potent than pethidine, whereas chlorpromazine showed no mydriatic activity at all. Nieschulz, Popendiker, and Sack (1954), who worked with a substance structurally related to chlorpromazine (P.391), made similar observations; there was an anti-acetylcholine action on the blood pressure, salivation, and peristalsis of the gut, but only a very weak one on the mouse pupil.

The effect of chlorpromazine, promethazine, and pethidine on bronchial and salivary secretion is recognized as an advantage by all surgeons (Zettler, 1953; Irmer and Koss, 1953; Koss, 1954; and Dundee *et al.*, 1953), since it reduces the number of postoperative pulmonary complications. In psychiatry, however, this side-effect is rather troublesome, producing dryness of the mouth and a burning sensation (Segerath, 1954). We tried to verify this

action and compared it quantitatively with atropine by the method of Bülbring and Dawes. Chlorpromazine only was tested, and, although about 30 times weaker than atropine, a definite inhibitory effect on the salivary flow of the cat, produced by a carbachol infusion, was always observed.

Promethazine has been known since 1946 as a powerful antihistaminic (Halpern and Ducrot, 1946; Viaud, 1947), and was used in conjunction with chlorpromazine and pethidine mainly on account of this property, since some authors believe that neither chlorpromazine nor pethidine possesses any antihistaminic activity (Irmer and Koss, 1953; Smith and Fairer, 1953). We therefore made a quantitative comparison of the antihistamine activity of the three substances, all of which were found to be antihistaminics, the most potent being promethazine, then chlorpromazine and finally pethidine, which is very weak indeed. This order is the same in the experiments on the gut as on the guinea-pig bronchioles, although there is a considerable difference in the actual ratios obtained by the two methods. On the gut, promethazine is 3 times stronger than chlorpromazine, which is 40 times stronger than pethidine, whereas on the bronchioles promethazine is 100 times stronger than chlorpromazine, which is 150 times stronger than pethidine.

The comparison of the antihistamine and anti-ACh actions of chlorpromazine, promethazine, and pethidine on the guinea-pig ileum reveals that all three are stronger antihistaminics than anti-ACh substances—chlorpromazine by more than 30 times, promethazine by 4 times, and pethidine by 1.5 times.

The local anaesthetic actions of chlorpromazine, promethazine, and pethidine were compared. By the intracutaneous weal method in guinea-pigs and measurement of the plexus anaesthesia in frogs, chlorpromazine was the most active and promethazine more active than pethidine. Our results therefore agree with those of Courvoisier *et al.* (1953).

In conclusion, it appears that chlorpromazine possesses some actions in greater degree than promethazine or pethidine, but that all three substances may be regarded as sharing the same type of pharmacological action (Dutta, 1948, 1949).

Summary

1. The following pharmacological properties of chlorpromazine, promethazine, and pethidine were compared:

(1) Action in causing a fall of body temperature.
(2) Action in causing paralysis of striated muscle.
(3) Chronic toxicity.
(4) Potentiation of morphine and pentobarbitone.
(5) Anti-adrenaline action.
(6) Anti-acetylcholine action.
(7) Antihistamine action.
(8) Local anaesthetic action.

2. Chlorpromazine always proved to be more active than promethazine or pethidine, except in its anti-acetylcholine and antihistamine actions.

3. Promethazine was the most active anti-acetylcholine and antihistamine compound; pethidine, on all the preparations tested, was consistently the weakest.

4. Chlorpromazine alone was tested for its anti-noradrenaline action and its effect on salivary flow. It was found to have only a very slight anti-noradrenaline action and it exerted an atropine-like action on salivary flow.

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